Clinical trial results:
Trial on treatment with inhaled furosemide of preterm and term neonates with transient tachypnoea

Summary

EudraCT number	2011-003473-29
Trial protocol	DE
Global end of trial date	09 July 2015

Results information

Result version number	v1 (current)
This version publication date	26 December 2020
First version publication date	26 December 2020

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-1488

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01407848
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Cologne
Sponsor organisation address	Albertus-Magnus-Platz, Cologne, Germany, 50923
Public contact	Klinisches Studienzentrum Pädiatrie, University Hospital Cologne, +49 2214786831, kinderklinik-studiensekretariat@uk-koeln.de
Scientific contact	Klinisches Studienzentrum Pädiatrie, University Hospital Cologne, +49 2214786831, kinderklinik-studiensekretariat@uk-koeln.de

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	28 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2015
Global end of trial reached?	Yes
Global end of trial date	09 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary endpoint of the study is the reduction of the Silverman score as an indicator of respiratory distress of the infant.
Silverman Score is the standard score to describe the degree of respiratory distress of neonate.

Protection of trial subjects:

The trial was conducted according to Good Clinical Practice guidelines, the applicable local laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.
The competent authorities approved the trial as required by national regulations.
Regulatory authorities were notified of the trial and amendments as required by national regulations.
Given the pilot nature of the trial, no interim analyse and no DMSC is foreseen. An Advisory Committee will be established, whose task will be to objectively discuss the (safety) data collected in the trial at EOT.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 April 2013
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	Germany: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	14
Newborns (0-27 days)	6
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: -

Pre-assignment

Screening details:

Premature and newborn children with clinical symptoms of a transient tachpnoe (respiratory frequency more than 60/min for premature and more than 50/min for newborn childern) and other in-and exclusion 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, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Furosemid

Arm description:

Furosemid solution as inhalation

Arm type	Experimental
Investigational medicinal product name	Furosemid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

1ml/kg every 6 hours

Arm title	NaCl (0.9%)

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	NaCl (0,9%)
Investigational medicinal product code	
Other name	Easyflex N Iso NaCl 500ml
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Inhalation use

Dosage and administration details:

NaCl was used for inhalation (1ml/kg)

Number of subjects in period 1	Furosemid	NaCl (0.9%)
Started	10	10
Completed	10	10

Baseline characteristics

Reporting groups	
Reporting group title	Furosemid
Reporting group description: Furosemid solution as inhalation	
Reporting group title	NaCl (0.9%)
Reporting group description: Placebo	

Reporting group values	Furosemid	NaCl (0.9%)	Total
Number of subjects	10	10	20
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
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 65-84 years			0
85 years and over			0
Age continuous Units: weeks			
arithmetic mean	36.7	36.2	
standard deviation	± 1.4	± 1.0	-
Gender categorical Units: Subjects			
Female	6	1	7
Male	4	9	13

End points

End points reporting groups	
Reporting group title	Furosemid
Reporting group description: Furosemid solution as inhalation	
Reporting group title	NaCl (0.9%)
Reporting group description: Placebo	

Primary: Area unter the Curve (AUC) of Silverman-Score	
End point title	Area unter the Curve (AUC) of Silverman-Score
End point description: AUC Silverman-Score	
End point type	Primary
End point timeframe: 26 and 72 hours from baseline	

End point values	Furosemid	NaCl (0.9%)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: cm²				
arithmetic mean (standard deviation)				
26 hours	44.1 (± 32.2)	54.0 (± 36.4)		
72 hours	91.6 (± 85.2)	97.2 (± 71.8)		

Statistical analyses

Statistical analysis title	AUC Silvermann Score

Statistical analysis description:

The primary target was the AUC (area under the curve) of the modified Silverman score. The measurements of the first 26 hours and 72 h of treatment were measured linearly interpolated and basedn on this AUC calculated. In case of intubation or premature end of therapy the missing values for 26 or 72 hours were updated by the end of treatment value. The statistical analysis was performed with SAS (V 9.3; t-test, $p<0.05$). Safety parameters were evaluated descriptively

Comparison groups	Furosemid v NaCl (0.9%)
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	t-test, 2-sided

Secondary: CPAP

End point title	CPAP

End point description:

End point type	Secondary

End point timeframe:

Hours since start of IMP

End point values	Furosemid	NaCl (0.9%)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: hours				
arithmetic mean (standard deviation)	18.6 (± 16.6)	25.3 (± 21.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intubation

End point title	Intubation

End point description:

Number of intubated patients

End point type	Secondary

End point timeframe:

0h until 72h

End point values	Furosemid	NaCl (0.9%)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Patient	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Sodium

End point title	Sodium

End point description:

End point type	Secondary

End point timeframe:
0h-72h

End point values	Furosemid	NaCl (0.9%)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: mmol/L				
arithmetic mean (standard deviation)				
0 hours	136 (± 4.4)	137.1 (± 1.8)		
24 hours	141.6 (± 5.6)	140.4 (± 2.5)		
48 hours	146.0 (± 3.5)	142.0 (± 4.0)		
72 hours	146 (± 5.7)	142.0 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Potassium

End point title	Potassium

End point description:

End point type	Secondary

End point timeframe:
0h-72h

End point values	Furosemid	NaCl (0.9%)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: mmol/L				
arithmetic mean (standard deviation)				
0 hours	5.4 (± 0.8)	5.8 (± 0.6)		
24 hours	4.7 (± 0.6)	4.6 (± 0.7)		
48 hours	4.2 (± 0.5)	4.0 (± 0.5)		
72 hours	4.3 (± 0.1)	4.2 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: pH

End point title	pH

End point description:

End point type	Secondary

End point timeframe:

0h-72h

End point values	Furosemid	NaCl (0.9%)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: negative of the base log. H+ activity				
arithmetic mean (standard deviation)				
0 hours	7.3 (± 0.1)	7.3 (± 0.1)		
24 hours	7.3 (± 0.1)	7.3 (± 0.0)		
48 hours	7.4 (± 0.0)	7.3 (± 0.0)		
72 hours	7.4 (± 0.0)	7.4 (± 0.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under curve (AUC) additional FiO2

End point title	Area under curve (AUC) additional FiO2

End point description:

End point type	Secondary

End point timeframe:

26 and 72 Hours from baseline

End point values	Furosemid	NaCl (0.9%)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: cm2				
arithmetic mean (standard deviation)				
26 hours	0.5 (± 1.3)	1.5 (± 2.7)		
72 hours	0.7 (± 1.8)	2.7 (± 5.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from signature of informed consent form.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Furosemid
Reporting group description: -	
Reporting group title	NaCl (0.9%)
Reporting group description: -	

Serious adverse events	Furosemid	NaCl (0.9%)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
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: 0 %

Non-serious adverse events	Furosemid	NaCl (0.9%)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 10 (10.00%) 1	
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	 0 / 10 (0.00%) 0	 1 / 10 (10.00%) 1	
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1	 0 / 10 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported