Clinical trial results:
Prevention of early ventilator-associated pneumonia with antibiotic therapy in patients treated with mild therapeutic hypothermia after cardiac arrest.
Randomized, multicenter double-blind placebo-controlled trial.

Summary

EudraCT number	2014-000202-35
Trial protocol	FR
Global end of trial date	14 September 2017

Results information

Result version number	v1 (current)
This version publication date	27 May 2021
First version publication date	27 May 2021
Summary attachment (see zip file)	Summary results (RRF Anthartic v1.0 20191231.pdf)

Trial information

Trial identification

Sponsor protocol code	I13018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02186951
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Limoges University Hospital
Sponsor organisation address	2 avenue Martin Luther King, LIMOGES, France, 87042
Public contact	Directeur Recherche et innovation, CHU de LIMOGES, +33 555056349, drc@chu-limoges.fr
Scientific contact	Directeur Recherche et innovation, CHU de LIMOGES, +33 555056349, drc@chu-limoges.fr

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	Interim
Date of interim/final analysis	19 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2016
Global end of trial reached?	Yes
Global end of trial date	14 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Incidence reduction of early VAP with short term amoxicillin-clavulanic acid in patients treated with hypothermia after out-of-hospital cardiac arrest

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 August 2014
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	France: 194
Worldwide total number of subjects	194
EEA total number of subjects	194

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	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)	121
From 65 to 84 years	69
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

No pre-assignment period

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Augmentin

Arm description:

Amoxicillin-clavulanic acid 1g, three times a day during 2 days, started within one hour after randomization and before the beginning of hypothermia.

Arm type	Experimental
Investigational medicinal product name	Amoxicilline/Acide Clavulanique
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

6g total

Arm title	Placebo

Arm description:

Placebo 1g, three times a day during 2 days, started within one hour after randomization and before the beginning of hypothermia.

Arm type	Placebo
Investigational medicinal product name	Chlorure de sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The sodium chloride was prepared at the moment of the injection, or maximum 15 minutes before.
The sodium chloride was administered as a slow intravenous injection over a period of 3 to 4 minutes.

Number of subjects in period 1	Augmentin	Placebo
Started	99	95
Completed	99	95

Baseline characteristics

Reporting groups	
Reporting group title	Augmentin
Reporting group description:	
Amoxicillin-clavulanic acid 1g, three times a day during 2 days, started within one hour after randomization and before the beginning of hypothermia.	
Reporting group title	Placebo
Reporting group description:	
Placebo 1g, three times a day during 2 days, started within one hour after randomization and before the beginning of hypothermia.	

Reporting group values	Augmentin	Placebo	Total
Number of subjects	99	95	194
Age categorical Units: Subjects			
Adults (18-64 years)	61	60	121
From 65-84 years	37	32	69
85 years and over	1	3	4
Age continuous Units: years			
arithmetic mean	60.6	60.3	
standard deviation	± 14.3	± 14.6	-
Gender categorical Units: Subjects			
Female	76	80	156
Male	23	15	38

Subject analysis sets	
Subject analysis set title	all patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients randomized and treated	

Reporting group values	all patients		
Number of subjects	194		
Age categorical Units: Subjects			
Adults (18-64 years)	121		
From 65-84 years	69		
85 years and over	4		
Age continuous Units: years			
arithmetic mean	60.5		
standard deviation	± 14.4		
Gender categorical Units: Subjects			
Female	38		

Male	156		

End points

End points reporting groups

Reporting group title	Augmentin
Reporting group description:	
Amoxicillin-clavulanic acid 1g, three times a day during 2 days, started within one hour after randomization and before the beginning of hypothermia.	
Reporting group title	Placebo
Reporting group description:	
Placebo 1g, three times a day during 2 days, started within one hour after randomization and before the beginning of hypothermia.	
Subject analysis set title	all patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients randomized and treated	

Primary: Incidence reduction of early VAP

End point title	Incidence reduction of early VAP[1]
End point description:	
Incidence reduction of early VAP with short term amoxicillin-clavulanic acid in patients treated with hypothermia after out-of-hospital cardiac arrest	
End point type	Primary
End point timeframe:	
7 days	

Notes:

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

End point values	Augmentin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	95		
Units: number of early VAP				
number (not applicable)	19	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality

End point title	Mortality
End point description:	
Mortality	
End point type	Secondary
End point timeframe:	
28 days	

End point values	Augmentin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	95		
Units: number				
number (not applicable)	41	35		

Statistical analyses

No statistical analyses for this end point

Secondary: Infections nosocomiales autres que PAVM

End point title	Infections nosocomiales autres que PAVM

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	Augmentin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	95		
Units: number				
number (not applicable)	7	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Late PAVM

End point title	Late PAVM

End point description:

End point type	Secondary

End point timeframe:

28 days

End point values	Augmentin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	95		
Units: number				
number (not applicable)	4	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

overall study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	all patients

Reporting group description: -

Serious adverse events	all patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	93 / 194 (47.94%)		
number of deaths (all causes)	86		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
delayed waking-up			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
refractory shock			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Eventration repair			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	5 / 194 (2.58%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 4			
Cardio-respiratory arrest				
subjects affected / exposed	5 / 194 (2.58%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 3			
Sinus arrest				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiogenic shock				
subjects affected / exposed	5 / 194 (2.58%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 5			
Atrial fibrillation				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mitral insufficiency				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				

subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
brain damage				
subjects affected / exposed	2 / 194 (1.03%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Coma				
subjects affected / exposed	8 / 194 (4.12%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 8			
Encephalopathy				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
anoxic encephalopathy				
subjects affected / exposed	26 / 194 (13.40%)			
occurrences causally related to treatment / all	0 / 26			
deaths causally related to treatment / all	0 / 26			
Status epilepticus				
subjects affected / exposed	3 / 194 (1.55%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
hypoxia cerebral				
subjects affected / exposed	13 / 194 (6.70%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 13			
cerebral lesion				
subjects affected / exposed	1 / 194 (0.52%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
cerebral oedema				

subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Syncope			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Heparin-induced thrombocytopenia			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
multi-organ failure			
subjects affected / exposed	8 / 194 (4.12%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 8		
thoracic pain			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
cerebrel death			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			

subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
ventilator associated pneumonia			
subjects affected / exposed	5 / 194 (2.58%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 3		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Tracheobronchitis			
subjects affected / exposed	1 / 194 (0.52%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	2 / 194 (1.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	all patients		
Total subjects affected by non-serious adverse events subjects affected / exposed	49 / 194 (25.26%)		
Respiratory, thoracic and mediastinal disorders ventilator associated pneumonia subjects affected / exposed occurrences (all)	36 / 194 (18.56%) 38		
aspiration pneumonia subjects affected / exposed occurrences (all)	13 / 194 (6.70%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2014	Addition of e secondary objective, modification of patient participation duration, addition of supplementary analyses in microbiot study and addition of exclusion criteria
07 May 2015	prolongation of inclusion period for 12 months
22 September 2016	Increasing of inclusion number

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/31693806