Clinical trial results:
Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest – A Randomized, Double-Blind, Placebo-Controlled Trial

Summary

EudraCT number	2017-004773-13
Trial protocol	DK
Global end of trial date	21 January 2022

Results information

Result version number	v2 (current)
This version publication date	06 May 2022
First version publication date	17 November 2021
Version creation reason	• Correction of full data set final trial date added

Trial information

Trial identification

Sponsor protocol code	00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03640949
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul Jensens blvd 99, Aarhus, Denmark, 8200
Public contact	Research Center for Emergency Medic, Research Center for Emergency Medicine Department of Clinical Medicine Aarhus University , 0045 51781511, lwandersen@clin.au.dk
Scientific contact	Research Center for Emergency Medic, Research Center for Emergency Medicine Department of Clinical Medicine Aarhus University , 0045 51781511, lwandersen@clin.au.dk

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	22 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 April 2021
Global end of trial reached?	Yes
Global end of trial date	21 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine whether the combination of vasopressin and methylprednisolone, as compared to placebo, when administered during IHCA, will increase return of spontaneous circulation.

Protection of trial subjects:

The study was approved by the regional ethics committee and the Danish Medicines Agency. An independent data monitoring committee oversaw the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Ethical reason, Scientific research
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 501
Worldwide total number of subjects	501
EEA total number of subjects	501

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)	126
From 65 to 84 years	327

85 years and over	48

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

2362 Patients with in-hospital cardiac arrest were screened for enrollment
1850 Excluded
685 Did not meet inclusion criteria
110 Met exclusion criteria
1055 Excluded for other reasons

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo 9% saline

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

Placebo consisted of 9 mg/mL of sodium chloride from identical ampoules

Arm title	Metylprednisolone and vasopressin

Arm description:

metylprednisolone and vasopressin

Arm type	Experimental
Investigational medicinal product name	Empressin®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

20 IU of vasopressin (Empressin, Amomed Pharma GmbH) given as soon as possible after the first dose of epinephrine. Additional doses of vasopressin (20 IU) were administered after each epinephrine dose for a
maximum of 4 doses (80 IU).

Investigational medicinal product name	SOLU-MEDROL®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

Solu-medrol® will be administered as a single dose of 40mg as soon as possible after the first dose of adrenaline.

Number of subjects in period 1	Placebo	Metylprednisolone and vasopressin
Started	264	237
Completed	264	237

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo 9% saline	
Reporting group title	Metylprednisolone and vasopressin
Reporting group description: metylprednisolone and vasopressin	

Reporting group values	Placebo	Metylprednisolone and vasopressin	Total
Number of subjects	264	237	501
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: years			
arithmetic mean	70	71	
standard deviation	± 12	± 13	-
Gender categorical Units: Subjects			
Female	90	89	179
Male	174	148	322

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo 9% saline	
Reporting group title	Metylprednisolone and vasopressin
Reporting group description: metylprednisolone and vasopressin	

Primary: Return of spontaneous circulation	
End point title	Return of spontaneous circulation
End point description:	
End point type	Primary
End point timeframe: The primary outcome was return of spontaneous circulation, which was defined as spontaneous circulation with no further need for chest compressions sustained for at least 20 minutes	

End point values	Placebo	Metylprednisolone and vasopressin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	237		
Units: percentage	33	42		

Statistical analyses

Statistical analysis title	Fisher exact test
Comparison groups	Placebo v Metylprednisolone and vasopressin
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	18

Secondary: Survival at 30 days with a favorable neurologic outcome

End point title	Survival at 30 days with a favorable neurologic outcome

End point description:

favorable neurologic outcome, is defined as a Cerebral Performance Category score of 1 or 2. The Cerebral Performance Category score is a 5-point scale assessing neurologic outcomes after brain damage,
with higher scores indicating worse outcomes.

End point type	Secondary

End point timeframe:

30 days

End point values	Placebo	Metylprednisolone and vasopressin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	237		
Units: 1-5	20	18		

Statistical analyses

Statistical analysis title	Fisher exact test
Comparison groups	Metylprednisolone and vasopressin v Placebo
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.99
Method	Fisher exact

Secondary: Survival at 30 days

End point title	Survival at 30 days

End point description:

End point type	Secondary

End point timeframe:

Survival at 30 days

End point values	Placebo	Metylprednisolone and vasopressin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	237		
Units: percentages	31	23		

Statistical analyses

Statistical analysis title	Fisher exact test
Comparison groups	Placebo v Metylprednisolone and vasopressin
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During admission

Adverse event reporting additional description:

Definitions for adverse events are provided in the protocol. Hyperglycemia and hypernatremia were assessed within 48 hours after return of spontaneous circulation. The remainder of the adverse events were assessed until death or hospital discharge.

Assessment type	Systematic

Dictionary used

Dictionary name	Predefined in proto
Dictionary version	1

Reporting groups

Reporting group title	Vasopressin and methylprednisolone
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Vasopressin and methylprednisolone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)	0 / 86 (0.00%)	
number of deaths (all causes)	77	55	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Vasopressin and methylprednisolone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 100 (77.00%)	63 / 86 (73.26%)	
Endocrine disorders			
Hyperglycemia			
subjects affected / exposed	77 / 100 (77.00%)	63 / 86 (73.26%)	
occurrences (all)	77	63	
Hypernatremia			
subjects affected / exposed	20 / 100 (20.00%)	20 / 86 (23.26%)	
occurrences (all)	28	27	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34587236

http://www.ncbi.nlm.nih.gov/pubmed/34223347