Clinical trial results:
Calcium for Out-of-Hospital Cardiac Arrest – A Randomized, Double-Blind, Placebo-Controlled trial

Summary

EudraCT number	2019-003387-46
Trial protocol	DK
Global end of trial date	16 April 2021

Results information

Result version number	v1 (current)
This version publication date	10 September 2022
First version publication date	10 September 2022

Trial information

Trial identification

Sponsor protocol code	COCA2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04153435
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Prehospital Emergency Medical Services: Central Denmark Region
Sponsor organisation address	Olof Palmes Allé 34, 1., Aarhus N, Denmark, DK-8200
Public contact	Lars Wiuff Andersen, Research Center for Emergency Medicine Department of Clinical Medicine Aarhus University, 0045 51781511, lwandersen@clin.au.dk
Scientific contact	Lars Wiuff Andersen, 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	Final
Date of interim/final analysis	30 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2021
Global end of trial reached?	Yes
Global end of trial date	16 April 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether calcium administration during adult OHCA will improve 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	20 January 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Ethical reason, Scientific research, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 391
Worldwide total number of subjects	391
EEA total number of subjects	391

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)	131
From 65 to 84 years	231
85 years and over	29

Subject disposition

Recruitment

Recruitment details:

Patients were screened through dispatch logs, prehospital journals, and clinican reports
Patients were included by the prehospital personnel by administrating at least one dose of the trial drug when the patient met the criteria for inclusion

Pre-assignment

Screening details:

1221 patients had an out-of-hospital cardiac arrest in the Central Denmark Region during the inclusion time frame
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830 Excluded
578 Did not meet inclusion criteria
63 Met exclusion criteria
189 Excluded for other reasons

Period 1

Period 1 title	Jan 20, 2020 - Apr 16, 2021 (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	Intervention

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Calciumchlorid ”SAD” injektionsvæske, opløsning
Investigational medicinal product code	A 12 AA 07
Other name	Calcium chloride
Pharmaceutical forms	Solution for injection
Routes of administration	Intraosseous use, Intravenous use

Dosage and administration details:

Calcium chloride (0.5 mmol/mL) 10 mL per dose - maximum of two doses

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Sodium chloride 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraosseous use, Intravenous use

Dosage and administration details:

Sodium Chloride 0.9% - 10 mL per dose - maximum of 2 doses

Number of subjects in period 1	Intervention	Placebo
Started	193	198
Completed	193	198

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Intervention	Placebo	Total
Number of subjects	193	198	391
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	67	69	
standard deviation	± 14	± 14	-
Gender categorical Units: Subjects			
Female	62	52	114
Male	131	146	277

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Return of spontaneous circulation

End point title	Return of spontaneous circulation
End point description:	
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 type	Primary
End point timeframe:	
Patient either achieved the primary outcome or died	

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	198		
Units: events	37	53		

Statistical analyses

Statistical analysis title	Return of spontaneous circulation
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	-7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	0.8

Secondary: Survival at 30 days

End point title	Survival at 30 days

End point description:

End point type	Secondary

End point timeframe:

30 days after the cardiac arrest occurred

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	198		
Units: events	10	18		

Statistical analyses

Statistical analysis title	Survival at 30 days
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.4
upper limit	1.3

Secondary: Survival at 30 days with a favorable neurological outcome

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

End point description:

End point type	Secondary

End point timeframe:

30 days after the cardiac arrest occurred

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	198		
Units: events	7	15		

Statistical analyses

Statistical analysis title	Survival at 30 days with a favorable neurological
Comparison groups	Intervention v Placebo
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9
upper limit	0.7

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Jan 20, 2020 - Apr 16, 2021	
Assessment type	Systematic
Dictionary used	
Dictionary name	Data Dictionary
Dictionary version	1.4
Reporting groups	
Reporting group title	Intervention (achieved ROSC)
Reporting group description: Specific adverse events were only entered for patients who achieved ROSC - please see protocol for details	
Reporting group title	Placebo (achieved ROSC)
Reporting group description: Specific adverse events were only entered for patients who achieved ROSC - please see protocol for details	

Serious adverse events	Intervention (achieved ROSC)	Placebo (achieved ROSC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)	0 / 53 (0.00%)	
number of deaths (all causes)	27	35	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Intervention (achieved ROSC)	Placebo (achieved ROSC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 37 (75.68%)	17 / 53 (32.08%)	
Cardiac disorders			
Tachyarrhythmia			
subjects affected / exposed	8 / 37 (21.62%)	14 / 53 (26.42%)	
occurrences (all)	8	14	
Gastrointestinal disorders			
Ulcer			
subjects affected / exposed	1 / 37 (2.70%)	0 / 53 (0.00%)	
occurrences (all)	1	0	
Pancreatitis acute			

subjects affected / exposed	3 / 37 (8.11%)	1 / 53 (1.89%)	
occurrences (all)	3	1	
Renal and urinary disorders			
Acute kidney failure requiring dialysis			
subjects affected / exposed	7 / 37 (18.92%)	3 / 53 (5.66%)	
occurrences (all)	7	3	
Endocrine disorders			
Hypercalcemia			
subjects affected / exposed	26 / 37 (70.27%)	1 / 53 (1.89%)	
occurrences (all)	26	1	

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? Yes

Date	Interruption	Restart date
16 April 2021	On April 15, 2021, the independent data and safety monitoring committee recommended that the trial be stopped due to a signal of harm in the calcium group. This was based on unblinded data from 383 patients included in the trial between January 20, 2020, and April 6, 2021. Based on this recommendation, the steering committee immediately stopped the trial.	-

Notes:

Limitations and caveats

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

1) Trial was stopped early leading to risk of overestimating effect size, 2) The trial only tested one dosing regime and timing, 3) The generalizability to the in-hospital setting is unclear

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35917866

http://www.ncbi.nlm.nih.gov/pubmed/34847226