



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 clinician reports

Patients were included by the prehospital personnel by administering 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

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