# EU Clinical Trials Register

## Clinical trial results:
## Adenosine in initial cardioplegia
### Summary

| EudraCT number | 2014-001382-26 |
|---|---|
| Trial protocol | FI |
| Global end of trial date | 31 May 2020 |

### Results information

| Result version number | v1 (current) |
|---|---|
| This version publication date | 25 April 2022 |
| First version publication date | 25 April 2022 |
| Summary attachment (see zip file) | Preliminary results of CABG (Results for 2014-001382-26.pdf) |

### Trial information

### Trial identification

| Sponsor protocol code | HCS-2014-2 |
|---|---|

### Additional study identifiers

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

Notes:

### Sponsors

| Sponsor organisation name | Tampere University Hospital Heart Center |
|---|---|
| Sponsor organisation address | Elämänaukio 1, Tampere, Finland, 33520 |
| Public contact | Prof Jari Laurikka, Tays Sydänsairaala, +358 (0)3311 67669, jari.laurikka@sydansairaala.fi |
| Scientific contact | Prof Jari Laurikka, Tays Sydänsairaala, +358 (0)3311 67669, jari.laurikka@sydansairaala.fi |

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 | 07 April 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 May 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 May 2020 |
| Was the trial ended prematurely? | No |

Notes:


## General information about the trial

Main objective of the trial:

myocardial function after cardiac surgery

Protection of trial subjects:

Trial patients in both study comparison groups received high-quality medical procedures to alleviate any surgical pain or discomfort prior, during and after the procedures. Close monitoring of health (medical parameters e.g. hemodynamic, metabolic and respiratory function measurements) were used. The surgical procedures for their medical conditions (aortic, stenosis and/or coronary artery disease) were used based on a multidisciplinary team evaluation and were performed by experienced surgeons and anesthesiologists.

Background therapy:

Aortic valve replacement (AVR) in extracorporeal circulation (1st study group, 45 patients). Coronary artery bypass grafting (CABG) in extracorporeal circulation (2nd study group, 43 patients).

Evidence for comparator:

Adenosine 20 mg i.a. in the study medication group, same volume of saline i.a. in the control group in both procedure types (AVR, CABG) applied right after aortic cross-clamping (beginning of the shut off of the heart circulation) and followed by routine administration of potassium enriched blood cardioplegia (to stop and protect the heart).

| | |
|---|---|
| Actual start date of recruitment | 04 November 2015 |
| 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 | Finland: 88 |
| Worldwide total number of subjects | 88 |
| EEA total number of subjects | 88 |

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) | 27 |
| From 65 to 84 years | 61 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment time: 3.11.2015- 2.1.2018

### Pre-assignment

Screening details:

Inclusion criteria check, exclusion criteria check prior to individual study presentation (for informed consent) to the patient

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 88 |
| Number of subjects completed | 88 |

### Period 1

| | |
|---|---|
| Period 1 title | Baseline (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 |

Blinding implementation details:

Independent pharmacist provided adenosine and saline, independent anesthesia nurse provided the operative team with the drug in no-name sterile syringe

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Adenosine group |

Arm description:

Individuals receiving active drug based on a randomization code during either AVR or CABG procedure

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Adenosine |
| Investigational medicinal product code | C01EB10 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intraarterial use |

Dosage and administration details:

20 mg given intra-arterial to asc. aorta after aortic cross-clamping and followed by routine potassium enriched blood cardioplegia

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Equal amount 4 ml of saline given intra-arterial to asc. aorta after aortic cross-clamping and followed by routine potassium enriched blood cardioplegia

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intraarterial use |

Dosage and administration details:

4 ml given intra-arterial to asc. aorta after aortic cross-clamping and followed by routine potassium enriched blood cardioplegia

| Number of subjects in period 1 | Adenosine group | Placebo |
|---|---|---|
| Started | 44 | 44 |
| Completed | 44 | 44 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Adenosine group |
|---|---|
| Reporting group description: | |
| Individuals receiving active drug based on a randomization code during either AVR or CABG procedure | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Equal amount 4 ml of saline given intra-arterial to asc. aorta after aortic cross-clamping and followed by routine potassium enriched blood cardioplegia | |

| Reporting group values | Adenosine group | Placebo | Total |
|---|---|---|---|
| Number of subjects | 44 | 44 | 88 |
| 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 | | | |
| Age at operation | | | |
| Units: years | | | |
| arithmetic mean | 67.36 | 68.25 | |
| standard deviation | ± 7.32 | ± 9.43 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 13 | 9 | 22 |
| Male | 31 | 35 | 66 |

### Subject analysis sets

| Subject analysis set title | CABG |
|---|---|
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Recruited CABG patients | |
| Subject analysis set title | AVR |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Recruited AVR patients | |

| Reporting group values | CABG | AVR | |
|---|---|---|---|
| Number of subjects | 43 | 45 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Age at operation | | | |
| Units: years | | | |
| arithmetic mean | 68.5 | 67.1 | |
| standard deviation | ± 9.1 | ± 7.7 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | 20 | |
| Male | 41 | 25 | |

## End points

### End points reporting groups

| Reporting group title | Adenosine group |
|---|---|
| Reporting group description: | |
| Individuals receiving active drug based on a randomization code during either AVR or CABG procedure | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Equal amount 4 ml of saline given intra-arterial to asc. aorta after aortic cross-clamping and followed by routine potassium enriched blood cardioplegia | |
| Subject analysis set title | CABG |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Recruited CABG patients | |
| Subject analysis set title | AVR |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| Recruited AVR patients | |

### Primary: Time to asystole

| End point title | Time to asystole |
|---|---|
| End point description: | |
| myocardial electrical contraction cessation after active drug or placebo injection | |
| End point type | Primary |
| End point timeframe: | |
| At induction of cardioplegia | |

| End point values | Adenosine group | Placebo | CABG | AVR |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 44 | 44 | 43 | 45 |
| Units: seconds | | | | |
| arithmetic mean (standard deviation) | 29.7 (± 66.7) | 121.0 (± 75.5) | 70.3 (± 87.5) | 80.2 (± 81.9) |

### Statistical analyses

| Statistical analysis title | t-test |
|---|---|
| Statistical analysis description: | |
| t-test | |
| Comparison groups | Adenosine group v Placebo v AVR v CABG |

| | |
|---|---|
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -91.3 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | -121 |
|    upper limit | -61 |
| Variability estimate | Standard deviation |
| Dispersion value | 15.2 |

## Primary: Myocardial performance, cardiac indices

| | |
|---|---|
| End point title | Myocardial performance, cardiac indices |

End point description:

Cardiac index and Stroke work indices (SWI) from baseline to post-CPB and at @19 (post operatively), @06 (next morning) in the ICU. Here we report Cardiac Index @ post-CPB.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

from baseline to post-CPB and at @19, @06 ICU stay

| **End point values** | Adenosine group | Placebo | CABG | AVR |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 42[1] | 40[2] | 38[3] | 44[4] |
| Units: l/min/m2, and SWI units | | | | |
| arithmetic mean (confidence interval 95%) | 2.44 (2.23 to 2.65) | 2.62 (2.41 to 2.84) | 2.42 (2.20 to 2.65) | 2.62 (2.42 to 2.83) |

Notes:

[1] - n in repeated measures anova for 4 time points

[2] - n in repeated measures anova for 4 time points

[3] - n in repeated measures anova for 4 time points

[4] - n in repeated measures anova for 4 time points

## Statistical analyses

| **Statistical analysis title** | Repeated measures analysis of CI at 4 time points |
|---|---|

Statistical analysis description:

Repeated measures analysis of CI at 4 time points by Adenosine/Placebo

| | |
|---|---|
| Comparison groups | Adenosine group v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | ANOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.186 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -0.491 |
|     upper limit | 0.119 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.153 |

## Primary: Myocardial performance, echographic

| | |
|---|---|
| End point title | Myocardial performance, echographic |

End point description:

transesophageal echo was recorded into file in all patients and prespecified time points were used to collect data from left and right ventricular contractive activity. Data under analysis.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

from baseline to the end of surgical procedure

| End point values | Adenosine group | Placebo | CABG | AVR |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 44 | 44 | 43 | 45 |
| Units: change from baseline | | | | |
| arithmetic mean (standard deviation) | 0 (± 0) | 0 (± 0) | 0 (± 0) | 0 (± 0) |

## Statistical analyses

| Statistical analysis title | Analysis undergoing |
|---|---|

Statistical analysis description:

Analysis undergoing

| | |
|---|---|
| Comparison groups | Placebo v Adenosine group |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | < 0.05 |
| Method | Chi-squared corrected |
| Parameter estimate | Risk ratio (RR) |

Notes:

[5] - Analysis undergoing

## Secondary: Markers of inflammation and injury in the myocardium

| End point title | Markers of inflammation and injury in the myocardium |
|---|---|
| End point description: | |
| Myocardial markers (CK,CK-MBm,Troponin-T ) are measured from baseline to 1st postoperative day. Here reported CK-MB at 1st PODay. | |
| End point type | Secondary |
| End point timeframe: | |
| from baseline to 1st postoperative day | |

| End point values | Adenosine group | Placebo | CABG | AVR |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 44 | 44 | 43 | 45 |
| Units: mg/l | | | | |
| arithmetic mean (standard deviation) | 36.1 (± 30.9) | 38.3 (± 26.1) | 38.6 (± 36.5) | 35.9 (± 18.2) |

## Statistical analyses

| Statistical analysis title | Comparison between medication groups |
|---|---|
| Statistical analysis description: | |
| Analysis in all CABG and AVR patients combined, comparing adenosine and placebo groups | |
| Comparison groups | Placebo v Adenosine group |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.4 |
| upper limit | 10.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 6.2 |

## Other pre-specified: Intra- and postoperative ECG data

| End point title | Intra- and postoperative ECG data |
|---|---|
| End point description: | |
| ECG was recorded from baseline to the 3rd postoperative day into a computer (mostly 1 channel data) | |

| End point type | Other pre-specified |
|---|---|

End point timeframe:

from baseline to the 3rd postoperative day

| End point values | Adenosine group | Placebo | CABG | AVR |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 44 | 44 | 43 | 45 |
| Units: deviations from baseline | 0 | 0 | 0 | 0 |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Metabolic changes in the right atrial myocardial tissue

| End point title | Metabolic changes in the right atrial myocardial tissue |
|---|---|

End point description:

right atrial tissue was harvested prior and post-CPB during the RA cannulation procedure

| End point type | Other pre-specified |
|---|---|

End point timeframe:

right atrial tissue harvesting prior and post-CPB

| End point values | Adenosine group | Placebo | CABG | AVR |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 44 | 44 | 43 | 45 |
| Units: percentage change from baseline | | | | |
| arithmetic mean (standard deviation) | 0 (± 0) | 0 (± 0) | 0 (± 0) | 0 (± 0) |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Postoperative major complications

| End point title | Postoperative major complications |
|---|---|

End point description:

Recording all major surgical and medical complications (SAE, AE ) from time of induction of anesthesia to time of discharge from hospital.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

from time of induction of anesthesia to time of discharge from hospital.

| End point values | Adenosine group | Placebo | CABG | AVR |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 44 | 44 | 43 | 45 |
| Units: frequency | 0 | 0 | 0 | 0 |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information[1]

| | |
|---|---|
| Timeframe for reporting adverse events: | |
| from operation to discharge from hospital | |
| Adverse event reporting additional description: | |
| All major surgical adverse cardiovascular and cerebral complications | |
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: 1 SAE (stroke w/later death) in the CABG Adenosine group on postop.day 3 but unrelated to study medication

**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

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

The results are in the process of being published, 1st CABG (mid 2022) and then AVR related results (end 2022).

Notes: