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
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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 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 standard deviation	 68.5 ± 9.1	 67.1 ± 7.7	
Gender categorical Units: Subjects			
Female Male	2 41	20 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: