Clinical trial results:
Steroids in Cardiac Surgery (SIRS) trial

Summary

EudraCT number	2011-001495-18
Trial protocol	BE
Global end of trial date	01 July 2015

Results information

Result version number	v1 (current)
This version publication date	02 June 2022
First version publication date	02 June 2022
Summary attachment (see zip file)	SIRS Lancet Publication (SIRS_Lancet_2015-09-26.pdf)

Trial information

Trial identification

Sponsor protocol code	2010-04-23

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00427388
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT Austria: 2011-001099-21, EudraCT Ireland: 2011-000591-34-IE, EudraCT Belgium: 2011-001495-18-BE, EudraCT Italy: 2010-023093-39

Notes:

Sponsors

Sponsor organisation name	Population Health Research Institute
Sponsor organisation address	237 Barton Street East, Hamilton, ON, Canada, L8L 2X2
Public contact	SIRS Project Office, Population Health Research Institute, 905 522-1155 x40635, Sirs@phri.ca
Scientific contact	Dr. Richard Whitlock, Population Health Research Institute, 905 521-2100 x40306, Richard.Whitlock@phri.ca

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	26 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 August 2014
Global end of trial reached?	Yes
Global end of trial date	01 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Cardiopulmonary bypass (CPB) initiates a systemic inflammatory response syndrome that is associated with postoperative morbidity and mortality. Steroids suppress inflammatory responses and might improve outcomes in patients at high risk of morbidity and mortality undergoing cardiopulmonary bypass. The objective of this study is to assess the effects of steroids in patients at high risk of morbidity and mortality undergoing cardiopulmonary bypass. More specifically, this will be assessed by administering 500 mg of methylprednisolone divided into two intravenous doses of 250 mg each, one during anesthetic induction and the other on CPB initiation, or matching placebo.

Protection of trial subjects:

An independent data and safety monitoring board reviewed the interim analyses when 50% and 75% of the 30-day follow-up data were available. SAS version 9.1 was used for all analyses.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 June 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 18
Country: Number of subjects enrolled	Australia: 453
Country: Number of subjects enrolled	Belgium: 88
Country: Number of subjects enrolled	Brazil: 101
Country: Number of subjects enrolled	Canada: 2614
Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	China: 912
Country: Number of subjects enrolled	Colombia: 462
Country: Number of subjects enrolled	Czechia: 155
Country: Number of subjects enrolled	Greece: 150
Country: Number of subjects enrolled	India: 803
Country: Number of subjects enrolled	Iran, Islamic Republic of: 301
Country: Number of subjects enrolled	Ireland: 14
Country: Number of subjects enrolled	Hong Kong: 73
Country: Number of subjects enrolled	Italy: 420
Country: Number of subjects enrolled	Spain: 119
Country: Number of subjects enrolled	United States: 710

Country: Number of subjects enrolled	Austria: 100
Worldwide total number of subjects	7507
EEA total number of subjects	1046

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)	2514
From 65 to 84 years	3771
85 years and over	1222

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between June 21, 2007, and Dec 19, 2013. Complete 30-day data was available for all 7507 patients randomly assigned to methylprednisolone (n=3755) and to placebo (n=3752).

Pre-assignment

Screening details:

7507 enrolled and randomly assigned patients; 3755 patients allocated to receive methylprednisolone (146 did not receive allocated intervention) and 3752 patients allocated to placebo (154 did not receive allocated intervention)

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, Carer, Assessor

Blinding implementation details:

Patients were assigned by block randomization with random block sizes of 2, 4, or 6, stratified by centre. Methylprednisolone was obtained from the centre’s local pharmacy, and the study drug was prepared and masked by the local pharmacy following procedures described in a provided study manual. Patients, health-care providers, data collectors, and outcome adjudicators were masked to treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Methylprednisolone

Arm description:

Intravenous methylprednisolone, divided. 250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass.

Arm type	Experimental
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass

Arm title	Active Placebo

Arm description:

Intravenous placbeo, divided. 250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass

Number of subjects in period 1	Active Methylprednisolone	Active Placebo
Started	3755	3752
Completed	3755	3752

Baseline characteristics

Reporting groups	
Reporting group title	Active Methylprednisolone
Reporting group description:	
Intravenous methylprednisolone, divided. 250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass.	
Reporting group title	Active Placebo
Reporting group description:	
Intravenous placbeo, divided. 250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass.	

Reporting group values	Active Methylprednisolone	Active Placebo	Total
Number of subjects	3755	3752	7507
Age categorical Units: Subjects			
<65	1250	1264	2514
65-80	1897	1874	3771
>80	608	614	1222
Age continuous Units: years			
arithmetic mean	67.6	67.3	
standard deviation	± 13.6	± 13.8	-
Gender categorical Units: Subjects			
Female	1498	1472	2970
Male	2257	2280	4537
EuroSCORE Units: Subjects			
4-5	518	504	1022
6-8	2454	2495	4949
>8	400	398	798
Missing data	383	355	738
Receipt of at least one dose of study drug or placebo Units: Subjects			
Received at least 1 dose of study drug or placebo	3364	3353	6717
Did not receive at least 1 dose of study drug or p	146	154	300
Missing data	245	245	490
Operative Characteristics (Procedure) Units: Subjects			
Isolated cardiac valve	1209	1228	2437
Isolated coronary artery bypass	825	762	1587
Other	1721	1762	3483
Non-study Postoperative Steroids Units: Subjects			
Received non-study postoperative steroids	75	85	160

Did not receive non-study postoperative steroids	3680	3667	7347

Bypass time (min)			
Units: Minuntes			
median	108	110	
inter-quartile range (Q1-Q3)	82 to 144	84 to 142	-

End points

End points reporting groups

Reporting group title	Active Methylprednisolone
Reporting group description:	
Intravenous methylprednisolone, divided. 250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass.	
Reporting group title	Active Placebo
Reporting group description:	
Intravenous placbeo, divided. 250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass.	

Primary: Primary End Point

End point title	Primary End Point
End point description:	
End point type	Primary
End point timeframe:	
>	

End point values	Active Methylpredniso lone	Active Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3755	3752		
Units: Subjects				
Death	154	177		
Death, MI, Stroke, Renal/Resp. failure	909	885		
Myocardial injury	486	399		
Stroke	71	79		
New renal failure	139	160		
Respiratory failure	343	375		

Statistical analyses

Statistical analysis title	Co-primary outcome #1
Statistical analysis description:	
Effect of Methylprednisolone vs Placebo on Death	
Comparison groups	Active Methylprednisolone v Active Placebo

Number of subjects included in analysis	7507
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.07

Statistical analysis title	Co-primary outcome #2

Statistical analysis description:

Effect of Methylprednisolone vs Placebo on the composite of death, myocardial injury, stroke, new renal failure, or respiratory failure

Comparison groups	Active Methylprednisolone v Active Placebo
Number of subjects included in analysis	7507
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01 [1]
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.11

Notes:

[1] - First primary outcome of death @ 0.041 level of significance & second primary outcome @ 0.01. It maintained the overall type I error rate for both comparisons at 5%, under the assumption that the overlap between the two outcomes was at least 15%.

Secondary: Secondary End Point

End point title	Secondary End Point

End point description:

End point type	Secondary

End point timeframe:

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End point values	Active Methylprednisolone	Active Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3755	3752		
Units: subjects				
Death or myocardial injury	605	530		
New atrial fibrillation	821	846		
Transfusions	1832	1865		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Patients were followed up for 30 days for all outcomes and for 6 months for vital status.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Active Methylprednisolone

Reporting group description:

Intravenous methylprednisolone, divided. 250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass.

Reporting group title	Active Placebo

Reporting group description:

Intravenous placbeo, divided. 250 mg at anaesthetic induction and 250 mg at initiation of cardiopulmonary bypass.

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: Data not collected.

Serious adverse events	Active Methylprednisolone	Active Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	137 / 3755 (3.65%)	135 / 3752 (3.60%)	
number of deaths (all causes)	154	177	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	23 / 3755 (0.61%)	14 / 3752 (0.37%)	
occurrences causally related to treatment / all	0 / 24	1 / 14	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac disorders			
Cardiac tamponade			
subjects affected / exposed	28 / 3755 (0.75%)	37 / 3752 (0.99%)	
occurrences causally related to treatment / all	0 / 30	0 / 37	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	15 / 3755 (0.40%)	10 / 3752 (0.27%)	
occurrences causally related to treatment / all	0 / 16	0 / 10	
deaths causally related to treatment / all	0 / 5	0 / 2	

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	48 / 3755 (1.28%)	59 / 3752 (1.57%)	
occurrences causally related to treatment / all	0 / 49	0 / 59	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	23 / 3755 (0.61%)	15 / 3752 (0.40%)	
occurrences causally related to treatment / all	0 / 23	2 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active Methylprednisolone	Active Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 3755 (0.00%)	0 / 3752 (0.00%)	

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.

None reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26501386

http://www.ncbi.nlm.nih.gov/pubmed/24766975

http://www.ncbi.nlm.nih.gov/pubmed/30833491

http://www.ncbi.nlm.nih.gov/pubmed/26460660

http://www.ncbi.nlm.nih.gov/pubmed/27775998

http://www.ncbi.nlm.nih.gov/pubmed/28683994

http://www.ncbi.nlm.nih.gov/pubmed/24598306