

**Clinical trial results:
CYCLOsporinE A in reperfused acute myocardial infarction (CYCLE)
Summary**

EudraCT number	2011-002876-18
Trial protocol	IT
Global end of trial date	30 January 2015

Results information

Result version number	v1 (current)
This version publication date	24 February 2019
First version publication date	24 February 2019
Summary attachment (see zip file)	Cyclosporine A in Reperfused Myocardial Infarction (Ms_CYCLE_JACC 2016.pdf)

Trial information**Trial identification**

Sponsor protocol code	2011-002876-18
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01650662
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Istituto di Ricerche Farmacologiche Mario Negri- IRCCS
Sponsor organisation address	Via Privata Giuseppe La Masa, 19, Milan, Italy, 20157
Public contact	Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche Mario Negri-IRCCS, +39 0239014454, cycle@marionegri.it
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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	Final
Date of interim/final analysis	31 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2014
Global end of trial reached?	Yes
Global end of trial date	30 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the present study is improvement of myocardial reperfusion, measured with ST-segment resolution $\geq 70\%$ 1 hour after PCI.

Protection of trial subjects:

It was run according to the Declaration of Helsinki of Good Clinical Practice. Regulatory agencies and local ethics committees approved the study protocol. All patients gave written informed consent.

Background therapy:

Recommended treatments according to STEMI European guidelines

Evidence for comparator: -

Actual start date of recruitment	01 September 2011
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	Italy: 410
Worldwide total number of subjects	410
EEA total number of subjects	410

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)	185
From 65 to 84 years	225
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 410 STEMI patients were enrolled from January 19, 2012, to April 30, 2014, in 31 Italian centers:

207 received an IV bolus of CsA, and 203, who served as controls, received conventional treatment.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	410
Number of subjects completed	410

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cyclosporine A

Arm description:

Cyclosporine A. The investigational active treatment is CsA, an immunosopressant indicated for the prevention of acute rejection after organ transplant, including cardiac transplantation. The preparation used in the trial will be Sandimmun IV, contening CsA 50 mg/ml, Cremophor EL and 94% ethyl alchool in a 5 ml vial. Patients will received Cyclosporine A on the top of recommend standard care of acute myocardial infarction.

Arm type	Experimental
Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	25300
Other name	Sandimmune IV, Novartis, Basel, Switzerland
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

The bolus of 2.5 mg/kg of cyclosporine A was injected over 20 to 30 s into an antecubital vein after coronary angiography, but just before passage of the wire into the culprit artery (thus avoiding any wire-related dissolution/fragmentation of the occlusive thrombus), and at least 5 min before PCI, to allow distribution of the drug.

Arm title	Control group
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Arm description:

The control group receveid on the top of recommended standared care of acute myocardial infarction.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Cyclosporine A	Control group
Started	207	203
Completed	207	203

Baseline characteristics

Reporting groups

Reporting group title	Cyclosporine A
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Reporting group description:

Cyclosporine A. The investigational active treatment is CsA, an immunosopressant indicated for the prevention of acute rejection after organ transplant, including cardiac transplantation. The preparation used in the trial will be Sandimmun IV, contening CsA 50 mg/ml, Cremophor EL and 94% ethyl alchool in a 5 ml vial. Patients will received Cyclosporine A on the top of recommend standard care of acute myocardial infarction.

Reporting group title	Control group
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Reporting group description:

The control group receveid on the top of recommended standard care of acute myocardial infarction.

Reporting group values	Cyclosporine A	Control group	Total
Number of subjects	207	203	410
Age categorical			
The study population comprised patients >18 years of age			
Units: Subjects			
adults =/>18 years	207	203	410
Age continuous			
Units: years			
arithmetic mean	62.5	63.2	
standard deviation	± 12.4	± 11.6	-
Gender categorical			
Femal and male			
Units: Subjects			
Female	40	43	83
Male	167	160	327

End points

End points reporting groups

Reporting group title	Cyclosporine A
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Reporting group description:

Cyclosporine A. The investigational active treatment is CsA, an immunosopressant indicated for the prevention of acute rejection after organ transplant, including cardiac transplantation.

The preparation used in the trial will be Sandimmun IV, contening CsA 50 mg/ml, Cremophor EL and 94% ethyl alchool in a 5 ml vial.

Patients will received Cyclosporine A on the top of recommend standard care of acute myocardial infarction.

Reporting group title	Control group
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Reporting group description:

The control group receveid on the top of recommended standared care of acute myocardial infarction.

Primary: Incidence ST-segment resolution of 70% or more

End point title	Incidence ST-segment resolution of 70% or more
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End point description:

The primary endpoint was incidence of $\geq 70\%$ ST-segment resolution 60 min after TIMI flow grade 3.

End point type	Primary
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End point timeframe:

One hour after PCI

End point values	Cyclosporine A	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	192		
Units: precision value				
incidence of $\geq 70\%$ ST-segment resolution	105	94		

Statistical analyses

Statistical analysis title	Logistic regression model
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Statistical analysis description:

The primary endpoint (complete ST-segment resolution [i.e., $\geq 70\%$, 60 min after PCI]) was analyzed with a logistic regression model. Adjustment was made by multivariable logistic regression for baseline characteristics (number of ECG leads with ST-segment deviation, ventricular tachycardia, and Rentrop score ≥ 2 unbalanced between the 2 groups).

Comparison groups	Cyclosporine A v Control group
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Number of subjects included in analysis	394
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox

Secondary: concentration of hs-cTnT

End point title	concentration of hs-cTnT
End point description:	
End point type	Secondary
End point timeframe: measured on day 4 after pPCI	

End point values	Cyclosporine A	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	175	171		
Units: ng/l				
median (inter-quartile range (Q1-Q3))	2160 (1087 to 3274)	2068 (1117 to 3690)		

Statistical analyses

Statistical analysis title	Wilcoxon non-parametric test
Comparison groups	Cyclosporine A v Control group
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	t-test, 2-sided

Secondary: All cause mortality or Heart Failure or cardiogenic shock

End point title	All cause mortality or Heart Failure or cardiogenic shock
End point description: Rehospitalization for cardiovascular reasons, all cause and cardiovascular death, heart failure, and cardiogenic shock	
End point type	Secondary
End point timeframe: From entry to 6 months follow-up	

End point values	Cyclosporine A	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: precision value	29	28		

Statistical analyses

Statistical analysis title	Kaplan-Meier method
Comparison groups	Cyclosporine A v Control group
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox

Secondary: Regional left ventricular function

End point title	Regional left ventricular function
End point description:	Left ventricular akinetic and dyskinetic segments were assessed by echocardiography.
End point type	Secondary
End point timeframe:	day 4 and 6 months

End point values	Cyclosporine A	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	184		
Units: percent				
arithmetic mean (standard deviation)	11.8 (± 14.7)	11.6 (± 13.3)		

Statistical analyses

Statistical analysis title	Student t-test
Comparison groups	Cyclosporine A v Control group

Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: Global left ventricular function

End point title	Global left ventricular function
End point description:	Left ventricular ejection fraction assessed by ecocardiography
End point type	Secondary
End point timeframe:	Day 4 and 6 months follow up

End point values	Cyclosporine A	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	184		
Units: percent				
arithmetic mean (standard deviation)	53.9 (± 9.8)	55.1 (± 9.3)		

Statistical analyses

Statistical analysis title	Student t test
Comparison groups	Control group v Cyclosporine A
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From entry to 6 months follow-up

Adverse event reporting additional description:

Only 1 serious adverse drug reaction was reported in the whole trial, a patient in the CsA group who died after surgery for myocardial rupture 23 days after the index MI

Assessment type Systematic

Dictionary used

Dictionary name MedDRA

Dictionary version 16.0

Reporting groups

Reporting group title Cyclosporine A group

Reporting group description: -

Serious adverse events	Cyclosporine A group		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 207 (0.48%)		
number of deaths (all causes)	18		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Myocardial rupture	Additional description: Only 1 serious adverse drug reaction was reported in the whole trial, a patient in the CsA group who died after surgery for myocardial rupture 23 days after the index MI.		
subjects affected / exposed	1 / 207 (0.48%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	Cyclosporine A group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 207 (1.45%)		
Skin and subcutaneous tissue disorders			
Allergic reaction			
subjects affected / exposed	3 / 207 (1.45%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2012	<p>DSMB composition: new composition of the DSMB</p> <p>Extension of the inclusion criteria for randomization: "All (male and female) patients, aged over 18, presenting with a large STEMI within 4 hours of onset (defined as angina pectoris or equivalent symptoms of more than 20 minutes duration within the last 4 hour..." was changed with: "All (male and female) patients, aged over 18, presenting with a large STEMI within 6 hours of onset (defined as angina pectoris or equivalent symptoms of more than 20 minutes duration within the last 6 hour..."</p> <p>Type of randomization: "Central randomization in a 1:1 ratio will be performed by telephone call to the National Coordinating Centre" was changed with: "Central randomization will be performed in a 1:1 ratio."</p> <p>Cyclosporine dosed:" 2.5mg of CsA" was changed with : " 2.5mg/kg of CsA"</p>
04 March 2013	<p>Steering Committee composition: two components were added</p> <p>Statistical and Data Management composition: 1 component was substituted</p> <p>Duration of the study: recruitment period "Start: September 1, 2011 End: February 28, 2013 The expected duration of the study for each subject is 6 months, for a total study duration of 24 months."was changed with: "Start: September 1, 2011 End: February 28, 2014 Study duration The expected duration of the study for each subject is 6 months, for a total study duration of 36 months."</p> <p>Time of second ECG recording "The primary end-point of ST resolution will be assessed by the ECG Core Lab. The core lab will receive from each Center an ECG tracing at randomization and another after 60 minutes for each patient enrolled to CYCLE." was changed with: "The primary end-point of ST resolution will be assessed by the ECG Core Lab. The core lab will receive from each Center an ECG tracing at randomization and another after 60 minutes after the antegrade flow was observed, for each patient enrolled to CYCLE."</p>
08 January 2014	<p>Duration of the study: recruitment period Recruitment period: "Start 1/09/2011 End 28/02/2014 End of follow-up: 30/08/2014 Data analysis: 30/10/2014" was changed with: Recruitment period: "Start 1/09/2011 End 30/04/2014 End of follow-up: 31/10/2014 Data analysis: 31/12/2014"</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26821623>