Clinical trial results:
Does Cyclosporine ImpRove Clinical oUtcome in ST elevation myocardial infarction patients (CIRCUS study)

Summary

EudraCT number	2009-013713-99
Trial protocol	FR BE ES
Global end of trial date	28 June 2017

Results information

Result version number	v1 (current)
This version publication date	21 August 2019
First version publication date	21 August 2019

Trial information

Trial identification

Sponsor protocol code	2009-559

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01502774
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hospices Civils de Lyon
Sponsor organisation address	3 Quai des Célestins, Lyon, France,
Public contact	Valerie PLATTNER, Hospices Civils de Lyon, +33 4 72115213, valerie.plattner@chu-lyon.fr
Scientific contact	Valerie PLATTNER, Hospices Civils de Lyon, +33 4 72406840, valerie.plattner@chu-lyon.fr

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	17 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2015
Global end of trial reached?	Yes
Global end of trial date	28 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is to determine whether Cyclosporine A, administered immediately prior to PCI reperfusion improves clinical outcomes in STEMI patients at 12 months

Protection of trial subjects:

Quality of life questionnaire measuring pain and anxiety

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 April 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	Spain: 40
Country: Number of subjects enrolled	Belgium: 46
Country: Number of subjects enrolled	France: 884
Worldwide total number of subjects	970
EEA total number of subjects	970

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)	635
From 65 to 84 years	308
85 years and over	27

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Depending on each country and local procedures in the management of AMI, patients may be considered eligible by the local emergency units (SAMU in France, emergency rooms …) after verification of eligibility criteria and exclusion criteria (pre-screening). The pre-hospital MD briefly informed the patients about the study.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Cyclosporin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cyclosporine A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

All patients will receive an intravenous bolus of 2.5 mg/kg per day of cyclosporine A. The injection will be performed slowly over 2 to 3 minutes.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

All patients will receive an intravenous bolus of 2.5 mg/kg per day of cyclosporine A. The injection will be performed slowly over 2 to 3 minutes.

Number of subjects in period 1	Cyclosporin	Placebo
Started	475	495
Completed	420	433
Not completed	55	62
Adverse event, serious fatal	28	26
Consent withdrawn by subject	10	20
Adverse event, non-fatal	1	1
Lost to follow-up	4	3
Protocol deviation	12	12

Baseline characteristics

Reporting groups	
Reporting group title	Cyclosporin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Cyclosporin	Placebo	Total
Number of subjects	475	495	970
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	299	336	635
From 65-84 years	159	149	308
85 years and over	17	10	27
Gender categorical Units: Subjects			
Female	75	99	174
Male	400	396	796

End points

End points reporting groups

Reporting group title	Cyclosporin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
includes all patients who were randomized, have received the study treatment, except those without informed consent, or without any legal protection measure, or without any data post randomization.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
all patients randomized to a study treatment who received any amount of a planned study medication.	

Primary: combined incidence of "total mortality, hospitalization for heart failure, and LV remodelling

End point title	combined incidence of "total mortality, hospitalization for heart failure, and LV remodelling
End point description:	
End point type	Primary
End point timeframe:	
1 year	

End point values	Cyclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	395	396		
Units: events	233	230		

Statistical analyses

Statistical analysis title	Logistic mixted effect regression model
Comparison groups	Cyclosporin v Placebo
Number of subjects included in analysis	791
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.774
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.39
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: At 1, 3, 6 and 12 months	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	Cyclosporin A
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Cyclosporin A	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	255 / 472 (54.03%)	240 / 490 (48.98%)	
number of deaths (all causes)	28	26	
number of deaths resulting from adverse events	21	24	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	255 / 472 (54.03%)	240 / 490 (48.98%)	
occurrences causally related to treatment / all	0 / 475	0 / 514	
deaths causally related to treatment / all	0 / 27	0 / 27	

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

Non-serious adverse events	Cyclosporin A	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	369 / 472 (78.18%)	362 / 490 (73.88%)	
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	318 / 472 (67.37%)	302 / 490 (61.63%)	
occurrences (all)	482	536	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2010	Amendment n°1: Modification of IMP : CicloMulsion® instead of Sandimmun® Modification of the principal judgement criterion and of the statistical analysis plan
29 November 2010	Amendment n°2: Update of participating investigator sites Addition of one non eligibility criteria Revision of patient's information letter
14 April 2011	Amendment n°3: Update of participating investigator sites
27 June 2011	Amendment n°4: Update of participating investigator sites Addition of two blood samples
09 September 2011	Amendment n°5: Update of participating investigator sites
30 November 2011	Amendment n°6: Collection of informed consent according to emergency situations Revision of eligibility criteria Revision of secondary objectives and end points wording General information details
22 March 2012	Amendment n°7: Extension of the recruitment period Transfer from principal to sub-study of one secondary endpoint Modification of the stopping rules relative to the interim safety analysis Update of participating investigator sites General information details
12 September 2012	Amendment n°8: Modification of one non eligibility criteria Extension of time to perform the first echocardiogram Modification of the injection duration Update of participating investigator sites
15 July 2013	Amendment n°9: Extension of the recruitment period (1 year more) Modification of the delay for phone call (1 week to 2 weeks) Update of principal investigator in Montpellier General information details
28 January 2014	Amendment n°10: Follow-up extension during 2 additional years. Update of participating investigator sites. Update the investigator brochure version

11 March 2014	Amendment n°11: Modification of the quality of life questionnaire for the 3-year visit: EQ-5D-3L . Addition of a patient card. General information details in flowchart Update of principal investigator in Mulhouse
12 December 2014	Amendment n°12: Update of secondary objectives, secondary end-points, and statistical analysis according to SAP Update of the responsible team of the statistical analysis Delete Bourges and Hopital Georges Pompidou centres Update of principal investigator in Toulouse and Nancy Clarification of principal investigator in Brest, Compiègne, Rouen, Lyon General information details in flowchart Update contact information for the sponsor
22 January 2015	Amendment n°13: Correction of inclusion criteria #4: From "> 0.2 mV" to "≥ 0.2 mV" according to European Society of Cardiology and American Heart Association guidelines.
23 June 2015	Amendment n°14: Addition of a second addendum version: proposed to the patient by phone. Addendum modification: possibility to recover the data a posteriori in case of late addendum signature. Update of principal investigator in Massy

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported