EU Clinical Trials Register

Clinical trial results:
Evaluating the effectiveness of intravenous ciclosporin on reducing reperfusion injury in patients undergoing primary percutaneous coronary intervention: a double-blind, phase II, randomised controlled trial (CAPRI)

Summary

EudraCT number	2014-002628-29
Trial protocol	GB
Global end of trial date	11 November 2017

Results information

Result version number	v1 (current)
This version publication date	12 July 2019
First version publication date	12 July 2019

Trial information

Trial identification

Sponsor protocol code	R&D6327

Additional study identifiers

ISRCTN number	ISRCTN27767229
ClinicalTrials.gov id (NCT number)	NCT02390674
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference: 13/NE/1070

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Freeman Hospital, Freeman Road, Newcastle upon Tyne, United Kingdom, NE7 7DN
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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	15 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2017
Global end of trial reached?	Yes
Global end of trial date	11 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of ciclosporin treatment prior to primary percutaneous coronary intervention on infarct size at 12 weeks relative to placebo treatment.

Protection of trial subjects:

No action required.

Background therapy:

All patients received a loading dose of two antiplatelet drugs and heparin before primary PCI. Use of thrombus aspiration and/or glycoprotein IIb/IIIa inhibition was left to the discretion of the treating physician.

Evidence for comparator:

This was a placebo controlled trial.

Actual start date of recruitment	16 March 2015
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	United Kingdom: 52
Worldwide total number of subjects	52
EEA total number of subjects	52

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)	26
From 65 to 84 years	24

85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants, all of whom had capacity, were recruited from patients with acute myocardial infarction (STEMI) as an emergency at the Freeman Hospital, (Newcastle upon Tyne Hospitals NHS Foundation Trust,) who agreed to undergo treatment by primary percutaneous coronary intervention. Participants were recruited between 05 March 2015 and 21 Dec 2016.

Pre-assignment

Screening details:

Potential participants were identified following emergency admission for acute myocardial infarction and agreement to undergo a primary percutaneous intervention (PPCI) procedure. The pregnancy exclusion criterion was assessed verbally due to the emergency nature of myocardial infarction and the need not to delay the standard PPCI procedure.

Period 1

Period 1 title	Randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Carer, Assessor

Blinding implementation details:

Randomisation was conducted by the Newcastle Clinical Trials Unit web system on a 1:1 ratio (ciclosporin:placebo) using random-permuted blocks with random block length. Assignment to either ciclosporin or placebo arm was blinded to both the patient and cardiologist in the cathlab. Preparation of the IMP infusion (ciclosporin or placebo) and randomisation of the patient was performed by unblinded nurses. The infusion bag was placed into a coloured bag to mask any colouration of the solution.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ciclosporin

Arm description:

Ciclosporin intravenous infusion of 2.5mg per kilogram of body weight through a catheter positioned within a peripheral vein. Ciclosporin was dissolved in saline (maximum concentration 2.5mg per millilitre).

Arm type	Experimental
Investigational medicinal product name	Ciclosporin
Investigational medicinal product code	
Other name	Sandimmun (concentrate for solution for infusion 50mg/ml), cyclosporin A, cyclosporine
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

Single bolus dose of ciclosporin (2.5mg per kg body weight dissolved in saline, maximum concentration 2.5mg/mL) over 4 minutes immediately prior to reperfusion.

Arm title	Placebo

Arm description:

Placebo (saline) infusion

Arm type	Placebo
Investigational medicinal product name	Not applicable
Investigational medicinal product code	
Other name	Sodium chloride solution
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single infusion over 4 minutes immediately prior to reperfusion (volume to match experimental IMP solution).

Number of subjects in period 1	Ciclosporin	Placebo
Started	26	26
Completed	26	26

Period 2

Period 2 title	Randomisation to 2 week assessment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ciclosporin

Arm description:

Ciclosporin intravenous infusion of 2.5mg per kilogram of body weight through a catheter positioned within a peripheral vein. Ciclosporin was dissolved in saline (maximum concentration 2.5mg per millilitre).

Arm type	Experimental
Investigational medicinal product name	Ciclosporin
Investigational medicinal product code	
Other name	Sandimmun (concentrate for solution for infusion 50mg/ml), cyclosporin A, cyclosporine
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

Single bolus dose of ciclosporin (2.5mg per kg body weight dissolved in saline, maximum concentration 2.5mg/mL) over 4 minutes immediately prior to reperfusion.

Arm title	Placebo

Arm description:

Placebo (saline) infusion

Arm type	Placebo

Investigational medicinal product name	Not applicable
Investigational medicinal product code	
Other name	Sodium chloride solution
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single infusion over 4 minutes immediately prior to reperfusion (volume to match experimental IMP solution).

Number of subjects in period 2	Ciclosporin	Placebo
Started	26	26
Completed	26	26

Period 3

Period 3 title	2 week assessment to 12 week assessment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ciclosporin

Arm description:

Ciclosporin intravenous infusion of 2.5mg per kilogram of body weight through a catheter positioned within a peripheral vein. Ciclosporin was dissolved in saline (maximum concentration 2.5mg per millilitre).

Arm type	Experimental
Investigational medicinal product name	Ciclosporin
Investigational medicinal product code	
Other name	Sandimmun (concentrate for solution for infusion 50mg/ml), cyclosporin A, cyclosporine
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

Single bolus dose of ciclosporin (2.5mg per kg body weight dissolved in saline, maximum concentration 2.5mg/mL) over 4 minutes immediately prior to reperfusion.

Arm title	Placebo

Arm description:

Placebo (saline) infusion

Arm type	Placebo

Investigational medicinal product name	Not applicable
Investigational medicinal product code	
Other name	Sodium chloride solution
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single infusion over 4 minutes immediately prior to reperfusion (volume to match experimental IMP solution).

Number of subjects in period 3	Ciclosporin	Placebo
Started	26	26
Completed	26	26

Baseline characteristics

Reporting groups

Reporting group title	Ciclosporin
Reporting group description:	
Ciclosporin intravenous infusion of 2.5mg per kilogram of body weight through a catheter positioned within a peripheral vein. Ciclosporin was dissolved in saline (maximum concentration 2.5mg per millilitre).	
Reporting group title	Placebo
Reporting group description:	
Placebo (saline) infusion	

Reporting group values	Ciclosporin	Placebo	Total
Number of subjects	26	26	52
Age categorical			
Patients who have been admitted as an emergency for acute myocardial infarction and agreed to undergo a primary percutaneous coronary intervention procedure			
Units: Subjects			
Adults (18-64 years)	16	10	26
From 65-84 years	8	16	24
85 years and over	2	0	2
Gender categorical			
Units: Subjects			
Female	2	6	8
Male	24	20	44
Diabetes			
Number of participants with diabetes			
Units: Subjects			
Yes	2	2	4
No	24	24	48
Smoking status			
Units: Subjects			
Never	9	9	18
Past	9	12	21
Current	8	5	13
Medical History: IHD			
Units: Subjects			
Yes	3	0	3
No	23	26	49
Medical History: COPD			
Units: Subjects			
Yes	0	2	2
No	26	24	50
Medical history: PVD			
Units: Subjects			
Yes	0	1	1
No	26	25	51
Other relevant medical history			
No previous history of MI, CVA/TIA, PCI was recorded in either group			

Units: Subjects			
Yes	11	6	17
No	15	20	35
Medication pre-admission - Aspirin			
Units: Subjects			
Yes	1	4	5
No	25	22	47
Medication pre-admission - Betablocker			
Units: Subjects			
Yes	2	1	3
No	24	25	49
Medication pre-admission - ACEi or ARB			
Units: Subjects			
Yes	6	2	8
No	20	24	44
Medication pre-admission - Diuretic			
Units: Subjects			
Yes	1	3	4
No	25	23	48
Medication pre-admission - Statin			
Units: Subjects			
Yes	6	6	12
No	20	20	40
Medication pre-admission - Ca Blocker			
Units: Subjects			
Yes	3	4	7
No	23	22	45
Medication pre-admission - Nitrates			
Units: Subjects			
Yes	1	0	1
No	25	26	51
Medication pre-admission - Nicorandil			
Units: Subjects			
Yes	1	0	1
No	25	26	51
ECG - infarct location			
Units: Subjects			
Non-anterior	18	18	36
Anterior	8	8	16
Pre-interventional medication - Aspirin			
Units: Subjects			
Yes	26	26	52
No	0	0	0
Pre-interventional medication - Clopidogrel			
Units: Subjects			
Yes	4	1	5
No	22	25	47
Pre-interventional medication - Prasugrel			
Units: Subjects			

Yes	19	21	40
No	7	5	12
Pre-interventional medication - Ticagrelor Units: Subjects			
Yes	3	4	7
No	23	22	45
Pre-interventional medication - Abciximab Units: Subjects			
Yes	1	0	1
No	25	26	51
Pre-interventional medication - Tirofiban Units: Subjects			
Yes	19	15	34
No	7	11	18
Pre-interventional medication - Bivalirudin Units: Subjects			
Yes	0	0	0
No	26	26	52
Pre-interventional medication - Heparin Units: Subjects			
Yes	26	26	52
No	0	0	0
Heparin units <=5000 Units: Subjects			
Yes	19	17	36
No	7	9	16
Pre-interventional medication - Heparin units >5000 Units: Subjects			
Yes	7	9	16
No	19	17	36
PCI-related parameters - Culprit lesion Units: Subjects			
Culprit Lesion - LAD	8	7	15
Culprit Lesion - LCx	7	4	11
Culprit Lesion - RCA	11	15	26
PCI-related parameters - TIMI flow before Units: Subjects			
TIMI flow before = 0	25	18	43
TIMI flow before = 1	1	8	9
TIMI flow before = 2	0	0	0
TIMI flow before = 3	0	0	0
PCI-related parameters - TIMI flow post Units: Subjects			
TIMI flow post = 0	0	0	0
TIMI flow post = 1	0	2	2
TIMI flow post = 2	0	0	0
TIMI flow post = 3	26	24	50

BMI			
Units: Score			
median	28.7	28.2	
inter-quartile range (Q1-Q3)	24 to 31	24.1 to 31.7	-
PCI procedure = onset to balloon			
Units: minutes			
arithmetic mean	202	179.8	
standard deviation	± 98.6	± 85.5	-
PCI procedure - call to balloon			
Units: minutes			
arithmetic mean	74.2	74.1	
standard deviation	± 26.2	± 37	-
PCI procedure - Door to balloon			
Units: minutes			
arithmetic mean	29.3	30.8	
standard deviation	± 10.4	± 15.5	-
PCI procedure - onset of symptoms to reperfusion			
Units: minutes			
arithmetic mean	204.8	187.1	
standard deviation	± 98.8	± 80.0	-
PCI procedure - Target vessel diameter			
Units: mm			
arithmetic mean	3.7	3.5	
standard deviation	± 0.4	± 0.5	-
PCI procedure - Target vessel stent length			
Units: mm			
arithmetic mean	41.9	40.0	
standard deviation	± 24.2	± 22.8	-
PCI procedure - Troponin at admission (0 hrs)			
Units: ng/L			
arithmetic mean	124.6	123.7	
standard deviation	± 210.5	± 206.1	-
Renal function - Glomerular filtration rate			
Units: mL/min			
arithmetic mean	87.3	87.0	
standard deviation	± 24.9	± 25.1	-
Renal function - Contrast volume per GFR (ml)			
Units: mL			
arithmetic mean	154.2	132.9	
standard deviation	± 58.6	± 51.9	-
Renal function - Urea at day 0			
Units: mmol/L			
arithmetic mean	5.7	5.9	
standard deviation	± 1.4	± 2.9	-
Renal function - creatinine at day 0			
Units: umol/L			
arithmetic mean	85.2	83.7	
standard deviation	± 17.7	± 25.6	-

T Lymphocyte count at baseline (0 minutes) total (CD45) Units: Count			
arithmetic mean	2068	1842	
standard deviation	± 691	± 935	-
T Lymphocyte count at baseline (0 minutes) B-cells (CD-19) Units: Count			
arithmetic mean	201	239	
standard deviation	± 107	± 332	-
T Lymphocyte count at baseline (0 minutes) Natural Killer Cells Units: Count			
arithmetic mean	500	423	
standard deviation	± 295	± 275	-
T Lymphocyte count at baseline (0 minutes) T-cells (CD3) Units: Count			
arithmetic mean	1350	1169	
standard deviation	± 540	± 688	-
T Lymphocyte count at baseline (0 minutes) CD4 Units: Count			
arithmetic mean	785	785	
standard deviation	± 294	± 532	-
T Lymphocyte count at baseline (0 mins) CD8 Units: Count			
arithmetic mean	504	357	
standard deviation	± 392	± 267	-
Time from symptom onset to randomisation Units: Minutes			
median	162	164	
inter-quartile range (Q1-Q3)	94 to 272	120 to 277	-

End points

End points reporting groups

Reporting group title	Ciclosporin
Reporting group description:	
Ciclosporin intravenous infusion of 2.5mg per kilogram of body weight through a catheter positioned within a peripheral vein. Ciclosporin was dissolved in saline (maximum concentration 2.5mg per millilitre).	
Reporting group title	Placebo
Reporting group description:	
Placebo (saline) infusion	
Reporting group title	Ciclosporin
Reporting group description:	
Ciclosporin intravenous infusion of 2.5mg per kilogram of body weight through a catheter positioned within a peripheral vein. Ciclosporin was dissolved in saline (maximum concentration 2.5mg per millilitre).	
Reporting group title	Placebo
Reporting group description:	
Placebo (saline) infusion	
Reporting group title	Ciclosporin
Reporting group description:	
Ciclosporin intravenous infusion of 2.5mg per kilogram of body weight through a catheter positioned within a peripheral vein. Ciclosporin was dissolved in saline (maximum concentration 2.5mg per millilitre).	
Reporting group title	Placebo
Reporting group description:	
Placebo (saline) infusion	

Primary: Infarct size at 12 weeks post-PPCI

End point title	Infarct size at 12 weeks post-PPCI
End point description:	
Infarct size at 12 weeks post-PPCI as measured by cardiac magnetic resonance imaging (MRI). Infarct size will be calculated as the percent of infarcted myocardium per left ventricular (LV) mass. Patients with two analysable MRI scans (technical problems with either the MRI scanner or insufficient image quality, meant some MRI scans were not analysable at either 0 or 12 weeks).	
End point type	Primary
End point timeframe:	
12 weeks post-PPCI	

End point values	Ciclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: % of infarcted myocardium per LVM				
arithmetic mean (standard deviation)	9.1 (± 7.0)	9.1 (± 7.0)		

Statistical analyses

Statistical analysis title	Percentage infarct size post-PPCI at 12 weeks

Statistical analysis description:

Multiple linear regression showing difference in mean infarct size post-PPCI at 12 weeks.

Comparison groups	Ciclosporin v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.45
upper limit	2.24

Secondary: Microvascular obstruction after 2-7 days as measured by a single cardiac MRI scan

End point title	Microvascular obstruction after 2-7 days as measured by a single cardiac MRI scan

End point description:

Patients with analysable MRI scan at 2-7 days (technical problems with either the MRI scanner or insufficient image quality, meant some MRI scans were not analysable).

End point type	Secondary

End point timeframe:

2-7 days post-PPCI

End point values	Ciclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	25		
Units: Microvascular obstruction (mL)				
arithmetic mean (standard deviation)	1.7 (± 6.4)	1.9 (± 4.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in T lymphocyte counts at 5 mins

End point title	Change in T lymphocyte counts at 5 mins
End point description:	
Change in T lymphocyte counts relative to baseline at 5 minutes post-reperfusion	
End point type	Secondary
End point timeframe:	
5 minutes post-reperfusion	

End point values	Ciclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: Counts				
arithmetic mean (standard deviation)				
Lymphocytes (total) (CD45)	2007 (± 734)	1497 (± 660)		
B-cells (CD3)	205 (± 109)	196 (± 231)		
NK-cells	542 (± 318)	329 (± 198)		
T-cells (CD3)	1248 (± 565)	963 (± 534)		
CD4	719 (± 308)	656 (± 415)		
CD8	471 (± 406)	285 (± 212)		

Statistical analyses

Statistical analysis title	Mean T lymphocyte counts (CD3) at 5 mins
Statistical analysis description:	
Multiple linear regression showing difference in mean T lymphocyte counts (CD3) at 5 mins	
Comparison groups	Placebo v Ciclosporin
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	142.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.9
upper limit	260.9

Secondary: Change in T lymphocyte counts at 15 mins

End point title	Change in T lymphocyte counts at 15 mins

End point description:
Change in T lymphocyte counts relative to baseline at 15 minutes post-reperfusion

End point type	Secondary

End point timeframe:
15 minutes post reperfusion

End point values	Ciclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: Counts				
arithmetic mean (standard deviation)				
Lymphocytes (total) CD45	1923 (± 885)	1363 (± 625)		
B-cells (CD3)	197 (± 109)	195 (± 220)		
NK cells	525 (± 289)	273 (± 154)		
T-cells (CD3)	1190 (± 685)	888 (± 522)		
CD4	689 (± 418)	611 (± 413)		
CD8	449 (± 390)	258 (± 206)		

Statistical analyses

Statistical analysis title	Mean T lymphocyte counts (CD3) at 15 minutes

Statistical analysis description:
Multiple linear regression showing difference in T lymphocyte counts (CD3) at 15 mins

Comparison groups	Ciclosporin v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	150.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.6
upper limit	348.8

Secondary: Change in T lymphocyte counts at 30 minutes

End point title	Change in T lymphocyte counts at 30 minutes

End point description:
Change in T lymphocyte counts relative to baseline at 30 minutes post-reperfusion

End point type	Secondary

End point timeframe:

30 minutes post-reperfusion

End point values	Ciclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: Counts				
arithmetic mean (standard deviation)				
Lymphocytes (total) (CD45)	1609 (± 675)	1381 (± 798)		
B-cells (CD19)	209 (± 117)	218 (± 305)		
NK cells	386 (± 232)	266 (± 145)		
T-cells (CD3)	1006 (± 506)	886 (± 632)		
CD4	615 (± 316)	638 (± 518)		
CD8	350 (± 282)	233 (± 166)		

Statistical analyses

Statistical analysis title	Mean T lymphocyte counts (CD3) at 30 mins
Statistical analysis description:	
Multiple linear regression showing difference in mean T lymphocyte counts (CD3) at 30 mins	
Comparison groups	Placebo v Ciclosporin
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-23.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-192.3
upper limit	144.8

Secondary: Change in T lymphocyte counts at 90 mins

End point title	Change in T lymphocyte counts at 90 mins
End point description:	
Change in T lymphocyte counts relative to baseline at 90 minutes post-reperfusion	
End point type	Secondary
End point timeframe:	
90 minutes post-reperfusion	

End point values	Ciclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: Counts				
arithmetic mean (standard deviation)				
Lymphocytes (total) (CD45)	1302 (± 596)	1331 (± 742)		
B-cells (CD19)	202 (± 113)	210 (± 266)		
NK-cells	242 (± 171)	244 (± 188)		
T-cells (CD3)	852 (± 472)	867 (± 572)		
CD4	591 (± 326)	657 (± 473)		
CD8	241 (± 183)	199 (± 137)		

Statistical analyses

Statistical analysis title	mean T lymphocyte counts (CD3) at 90 mins
Statistical analysis description:	
Multiple linear regression showing difference in mean T lymphocyte counts (CD3) at 90 mins	
Comparison groups	Ciclosporin v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-106.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-331.4
upper limit	118.4

Secondary: Change in T lymphocyte counts at 24 hours	
End point title	Change in T lymphocyte counts at 24 hours
End point description:	
Change in T lymphocyte counts relative to baseline at 24 hours post-reperfusion	
End point type	Secondary
End point timeframe:	
24 hours post-reperfusion	

End point values	Ciclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: Counts				
arithmetic mean (standard deviation)				
Lymphocytes (total) (CD45)	2187 (± 717)	1997 (± 971)		
B-cells (CD19)	277 (± 139)	274 (± 235)		
NK cells	248 (± 144)	255 (± 126)		
T-cells (CD3)	1650 (± 569)	1454 (± 838)		
CD4	1111 (± 431)	1001 (± 667)		
CD8	497 (± 213)	415 (± 245)		

Statistical analyses

Statistical analysis title	Mean B-cell counts (CD19) at 24 hours
Statistical analysis description:	
Multiple linear regression showing difference in mean B-cell counts (CD19) at 24 hours	
Comparison groups	Ciclosporin v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	32.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.5
upper limit	86.7

Statistical analysis title	Mean NK-cell counts at 24 hours
Statistical analysis description:	
Multiple linear regression showing difference in mean NK-cell counts at 24 hours	
Comparison groups	Ciclosporin v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-29.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-103.5
upper limit	43.8

Statistical analysis title	Mean T lymphocyte counts (CD3) at 24 hours
Statistical analysis description:	
Multiple linear regression showing difference in mean T lymphocyte counts at 24 hours	
Comparison groups	Ciclosporin v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	57.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-264.3
upper limit	379

Statistical analysis title	Mean CD4 count at 24 hours
Statistical analysis description:	
Multiple linear regression showing difference in mean CD4 count at 24 hours	
Comparison groups	Ciclosporin v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	106.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.7
upper limit	273.2

Statistical analysis title	Mean CD8 count at 24 hours
Statistical analysis description:	
Multiple linear regression showing difference in mean CD8 count at 24 hours	
Comparison groups	Ciclosporin v Placebo

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-92.9
upper limit	156.9

Other pre-specified: Troponin at 12h post PPCI (ng/L)

End point title	Troponin at 12h post PPCI (ng/L)

End point description:

End point type	Other pre-specified

End point timeframe:

12 hours

End point values	Ciclosporin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: ng/L				
arithmetic mean (standard deviation)	4304 (± 3241)	3879 (± 2810)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE information for each patient was recorded for the 12 weeks of the RCT. An SAE occurring more than 2 weeks after the ciclosporin was administered will not be reported as CTIMP-related.

Adverse event reporting additional description:

Renal impairment (creatinine increase ≥25% or ≥0.5mg/dl relative to baseline) in the first 2 weeks can be an adverse event related to either the IMP used in the trial (ciclosporin) or the contrast dye used in the routine PCI procedure (iodixanol or ioversol).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	Ciclosporin

Reporting group description:

Ciclosporin intravenous infusion of 2.5mg per kilogram of body weight through a catheter positioned within a peripheral vein. Ciclosporin was dissolved in saline (maximum concentration 2.5mg per millilitre).

Reporting group title	Placebo

Reporting group description:

Placebo (saline) infusion

Serious adverse events	Ciclosporin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 26 (38.46%)	17 / 26 (65.38%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Chest pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial bleed			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Contrast induced nephropathy			

	Ciclosporin	Placebo		
subjects affected / exposed	8 / 26 (30.77%)	15 / 26 (57.69%)		
occurrences causally related to treatment / all	8 / 8	14 / 15		
deaths causally related to treatment / all	0 / 0	0 / 0		
Clot retention				
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Creatinine rose by more than 25% from baseline				
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Haematuria				
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Raised creatinine - drug induced	Additional description: within normal limits			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
MPO vasculitis and AKI				
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.1 %

Non-serious adverse events	Ciclosporin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 26 (15.38%)	5 / 26 (19.23%)	
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Nervous system disorders			

Chronic subdural haematoma			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Inner ear problem			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Non cardiac chest pain	Additional description: Felt to be due to gall bladder disease		
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Collapse	Additional description: Attributed to bladder problem		
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Increase in creatinine from baseline to d=1	Additional description: Patient had a contrast dose that was >4xGFR volume of contrast. Creatinine improved at d=2		
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Chest pain	Additional description: Chest pain deemed to be muscular skeletal in nature		
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Diarrhoea	Additional description: Diarrhoea and temperature, also strong cough		
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2014	Confirmation that the saline solution used is a UK marketed product. Clarification regarding the immediate reporting of SAEs, SARs and SUSARs by the investigator to the sponsor during drug treatment. Provision for emergency unblinding of the trial.
14 January 2016	Changes to design of study: – Change of phase from II/III to phase II to avoid potential issue with term 'pilot' and CONSORT reporting. – Change of one of the two stratification variables from 'gender' to 'time from symptom onset to randomisation' as it was felt the outcome would not be dependent on gender. Changes to the procedures undertaken by the patient: – Removal of 60 minute arterial blood sample as only one sample can be taken from sheath remaining from surgery. – Clarification 90 minute arterial blood sample taken on coronary care unit using sheath. – Possible home visit by clinical fellow on day 3 to obtain U&E monitoring sample if patient discharged from hospital prior to day 3 (safety visit). – Addition of optional research blood sample at 2 week visit. Revision of wording of two of the secondary objectives for clarity Definition of how infarct size will be calculated added to primary outcome Details added regarding acquisition of cardiac MRI images and how cardiac MRI images will be analysed Definitions added of clinical endpoints for clarity Contact details amended if problems experienced with randomisation system Removal of integrity of blind check at 12 month visit Definition added regarding resolution of renal SAEs Responsibility for reporting of SUSARs to REC changed from CI to sponsor in line with sponsor SOP Monitoring percent of source data to be verified and eligibility criteria to be reviewed amended to reflect sponsor approved monitoring plan Trial registration numbers added Addition of 'phase II' to title of study
20 October 2016	An update to the CAPRI protocol to reflect the current IMP administration procedure and provide additional details regarding blinding. In addition the wording in section 19.2 referring to the Reference Safety Information (RSI) has been amended for clarification purposes. The updated RSI, section 4.8 of the SmPC for Sandimmun Concentrate for Solution for Infusion 50mg/mL dated 09 May 2016, was been submitted as part of the Substantial Amendment to the MHRA for review.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported