Clinical trial results:
A randomised, double-blind, placebo-controlled trial assessing the safety and efficacy of intracoronary nitrite infusion during acute myocardial infarction

Summary

EudraCT number	2011-000721-77
Trial protocol	GB
Global end of trial date	09 February 2017

Results information

Result version number	v1 (current)
This version publication date	22 February 2018
First version publication date	22 February 2018
Summary attachment (see zip file)	Nitrite AMI Circ publication (Nitrite AMI CIRC 2015.pdf) Nitrite AMI Heart publication (Nitrite AMI Heart 2017.pdf)

Trial information

Trial identification

Sponsor protocol code	NITRITE/AMI/4.1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01584453
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Barts and the London NHS Trust
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Professor Anthony Mathur, Barts and the London NHS Trust, 0044 20 8983 2216 , a.mathur@qmul.ac.uk
Scientific contact	Professor Anthony Mathur, Barts and the London NHS Trust, 0044 20 8983 2216 , a.mathur@qmul.ac.uk

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	30 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether the intracoronary delivery of nitrite in patients undergoing primary percutaneous coronary angioplasty (PPCI) for acute myocardial infarction (heart attack) decreases the amount of damage caused by the heart attack (as measured by levels of damage detected in blood tests)

Protection of trial subjects:

1). The risks from the IMP are low. Sodium and nitrite are endogenously- occurring ions with no immunological
potential, therefore there is no risk of an allergic reaction. The small volume of 1.8micromol in 10 ml of saline given
over 30 seconds is very unlikely to pose any problems.
2). Possible Delay in Door to Balloon inflation time. The delivery of the IMP (sodium nitrite) down the coronary artery
will lead to a small delay in balloon inflation. There are studies demonstrating that any delay in door-to-balloon time
for patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention is
associated with higher mortality, even among patients treated within 90 minutes of admission. Our institution sets
internal targets of <60 minutes for door to balloon time. Any possible delay has been minimised by
1). the wire will have already been passed down the coronary artery possibly restoring some epicardial flow
2). the nitrite infusion will be delivered down an over the wire balloon so that immediately after infusion the balloon
can be inflated restoring flow if necessary otherwise an export catheter will be used to aspirate thrombus first
3). the time of the infusion has been kept to 30 seconds meaning at most there should be a delay of 1-2 minutes in
the door to balloon time.
3). CMR scan − the CMR scan does not use radiation. There are no major known side effects or risks attached to
CMR although some patients may find it a little claustraphobic. The main issues are related to possible allergy to
contrast agent and the scanning process. Most CMR exams are painless, however, some patients find it uncomfortable t

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 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	United Kingdom: 82
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	54
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period: 10/04/2012 to 30/11/2012.
82 patients were recruited.

Pre-assignment

Screening details:

Screening period: 10/04/2012 to 30/11/2012.
patients presenting to the Heart Attack Centre with St Elevation Myocardial Infarction were screened ; A total of 430.

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

Blinding implementation details:

The IMP was allocated a specific number identifier, which only the manufacturer and pharmacy team knew. The study team and patient did not know which IMP contained the active ingredient. The master list for the IMP was securely stored in by the pharmacy team who were also responsible for unblinding the patients.
A independent randomisation algorithm was used to allocate the IMP identifier aiming for a 1:1 allocation in 82 patients.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active arm

Arm description:

Patients randomised to receiving the active IMP

Arm type	Active comparator
Investigational medicinal product name	Sodium Nitrite (1.8micromol in 10mls N/Saline)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intracoronary use

Dosage and administration details:

1.8micromols Sodium Nitrite in 10 mls N/Saline

Arm title	Control Arm

Arm description:

Patients randomised to placebo

Arm type	Placebo
Investigational medicinal product name	Placebo (10mls N/saline)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intracoronary use

Dosage and administration details:

10 mls of N/Saline

Number of subjects in period 1	Active arm	Control Arm
Started	40	42
Completed	40	40
Not completed	0	2
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
82 patients with STEMI undergoing primary PCI	

Reporting group values	Overall trial	Total	
Number of subjects	82	82	
Age categorical			
Between April 2012 and December 2012, 430 patients were hospitalized for management of AMI at The Barts Health Heart Attack Center. Of these patients, 353 underwent PCI. Among these 353 patients, 13 were not evaluated for enrollment because study personnel were not available. 82 were recruited to the study.The mean age of the trial participants was 57 years, with 84% male. The age range was from 34 years old to 81 years old.			
Units: Subjects			
Adults 18-85	82	82	
Gender categorical			
All consented patients 84% male, 16% female			
Units: Subjects			
Female	13	13	
Male	69	69	

End points

End points reporting groups

Reporting group title	Active arm
Reporting group description: Patients randomised to receiving the active IMP	
Reporting group title	Control Arm
Reporting group description: Patients randomised to placebo	

Primary: Infarct Size (AUC) over 48 hrs

End point title	Infarct Size (AUC) over 48 hrs
End point description:	
End point type	Primary
End point timeframe: Creatine Kinase AUC measured over 48 hours	

End point values	Active arm	Control Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	33		
Units: CK AUC	44608	55666		

Statistical analyses

Statistical analysis title	Non-Parametric testing
Statistical analysis description: This endpoint was assessed using the Wilcoxon Rank Sum test as non-paramteric data	
Comparison groups	Control Arm v Active arm
Number of subjects included in analysis	66
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported for all consented patients until the end of the study.
AE and SAE were reported to the sponsor within 24 hours of the site becoming aware of them.
Supporting documentation were provided as soon as possible

Adverse event reporting additional description:

Supporting documentation were provided as soon as possible.
The DSMB met every 3 months during the recruitment phase of the study and then twice yearly. The independent members were aware of the recruitment rate/AS and SAE. All events were assessed and adjudicated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Active arm

Reporting group description:

Patients randomised to receiving the active IMP

Reporting group title	Control Arm

Reporting group description:

Patients randomised to placebo

Serious adverse events	Active arm	Control Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 40 (10.00%)	12 / 42 (28.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 40 (2.50%)	5 / 42 (11.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Wound infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary			

disease			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active arm	Control Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 40 (7.50%)	2 / 42 (4.76%)	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences (all)	0	1	
Thrombosis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences (all)	0	0	
Percutaneous coronary intervention			
subjects affected / exposed	2 / 40 (5.00%)	1 / 42 (2.38%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2012	Altered timings of secondary endpoints and additon of safety endpoint
28 May 2012	Change of sponsor to Barts Health NHS Trust
12 November 2012	Updating age range for recruitment Clarifying Blood sample times
19 April 2013	Unbliding timings and SAE reporting
09 September 2013	Addition of CMR Sub-study
22 February 2016	Change of trial sponsor representative Change in end of trial definition

Notes:

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.

Reduction in infarct size seen in sub-group analysis (TIMI 0/1 subgroup), overall no reduction in infarct size seen in whole trial cohort (see Jones DA et al Circ Research 2015; 116:437-447

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25512434

http://www.ncbi.nlm.nih.gov/pubmed/27683405