Clinical trial results:
The Effects of Inorganic Nitrite on cardiac and skeletal muscle: Physiology, pharmacology and therapeutic potential in patients suffering from Angina

Summary

EudraCT number	2012-000196-17
Trial protocol	GB
Global end of trial date	19 December 2014

Results information

Result version number	v1 (current)
This version publication date	25 August 2018
First version publication date	25 August 2018

Trial information

Trial identification

Sponsor protocol code	3/077/11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02078921
WHO universal trial number (UTN)	-
Other trial identifiers	Michael Frenneaux: Angina

Notes:

Sponsors

Sponsor organisation name	University of Aberdeen
Sponsor organisation address	Research & Innovation, University Offices, Aberdeen, United Kingdom, AB24 3FX
Public contact	Professor Michael Frenneaux, University of Aberdeen , 01224 554362, m.p.frenneaux@abdn.ac.uk
Scientific contact	Dr Peter Nightingdale , University of Aberdeen , 01224 554362, researchgovernance@abdn.ac.uk
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Scientific contact	Dr Peter Nightingdale , University of Aberdeen, 01224 554362, resesearchgovernance@abdn.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	01 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 December 2014
Global end of trial reached?	Yes
Global end of trial date	19 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main outcome is to assess whether increasing plasma nitrate by dietary means increases the time to onset of angina using a Modified Bruce Exercise Test.

Protection of trial subjects:

This trial was approved by the Scotland A Research Ethics Committee, subject to Medicines and Healthcare products Regulatory Agency regulation, and run in accordance with the Declaration of Helsinki. All patients signed an informed consent form.

Background therapy:

Inorganic sodium nitrate will be made available through the manufacturers, Western Glasgow Infirmary Pharmacy, Dumbarton Road, Glasgow, G11 6NT and delivered to the Pharmacy at the study site packaged and labelled according to the manufacturers licence.

Evidence for comparator: -	
Actual start date of recruitment	02 October 2012
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: 70
Worldwide total number of subjects	70
EEA total number of subjects	70

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)	20
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male or female patients diagnosed with chronic stable angina of more than 2 months duration will be recruited and will be invited to read the information and consider if they wish to participate. Patients can be on background anti-anginal therapy, however this dose of background therapy has to ideally remain fixed during the trial.

Pre-assignment

Screening details:

Pts are identified while attend cardiology out-pt appts at study sites. Cardio techs performing routine exercise tolerance tests (usually as part of chest pain or follow-up clinic) will identify potential participants by virtue of positive exercise test. Pts with positive tests will be asked for permission to be contacted.

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, Carer, Assessor

Blinding implementation details:

An emergency unblinding procedure is in place through Aberdeen Royal Infirmary Pharmacy. Patient treatment may only be unblinded in the event of a clinical emergency when the medical treatment of the patient depends on knowing current drug therapy.

Arms

Are arms mutually exclusive?	Yes
Arm title	Inorganic Sodium Nitrate

Arm description:

Sodium Nitrate powder will be filled into size 1 opaque gelatine capsules using a semi-automated method. In process limits of +/- 7.5% will be applied.

Arm type	Experimental
Investigational medicinal product name	Sodium Nitrate
Investigational medicinal product code	TR483
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Sodium Nitrate powder will be filled into size 1 opaque gelatine capsules using a semi-automated method. In process limits of +/- 7.5% will be applied.

Arm title	Placebo

Arm description:

The placebo will be lactose filled hard gelatin capsules.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	TR483p
Other name	Lactose Monohydrate
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The placebo will be lactose filled hard gelatin capsules

Number of subjects in period 1	Inorganic Sodium Nitrate	Placebo
Started	36	34
Completed	36	34

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description:

Sodium Nitrate powder will be filled into size 1 opaque gelatine capsules using a semi-automated method. In process limits of +/- 7.5% will be applied.

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	70	70	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	20	
From 65-84 years	50	50	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	18	18	
Male	52	52	

End points

End points reporting groups

Reporting group title	Inorganic Sodium Nitrate
Reporting group description:	
Sodium Nitrate powder will be filled into size 1 opaque gelatine capsules using a semi-automated method. In process limits of +/- 7.5% will be applied.	
Reporting group title	Placebo
Reporting group description:	
The placebo will be lactose filled hard gelatin capsules.	

Primary: Primary outcome

End point title	Primary outcome
End point description:	

End point type	Primary
End point timeframe:	
The primary outcome is to assess whether increasing plasma nitrate by dietary means increases the time to onset of angina using a Modified Bruce Exercise Test.	

End point values	Inorganic Sodium Nitrate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	34		
Units: Electrocardiogram treadmill test	36	34		

Statistical analyses

Statistical analysis title	Time to 1mm ST depression
Comparison groups	Inorganic Sodium Nitrate v Placebo
Number of subjects included in analysis	70
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.1
Method	Linear Model

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Once the Investigator becomes aware that an SAE has occurred in a study participant, they will report the information to the Sponsor within 24hrs of becoming aware of the event as per the current UoA-NHSG-SOP-014.

Adverse event reporting additional description:

In general the treatment was tolerated well. Gastrointestinal side effects were more common in the nitrate arm.

Assessment type	Systematic

Dictionary used

Dictionary name	none
Dictionary version	00

Reporting groups

Reporting group title	Total AE

Reporting group description: -

Serious adverse events	Total AE		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Total AE		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)		
General disorders and administration site conditions			
Dry Mouth			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Tiredness			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Hot Flushes			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Loose stool			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 22 (40.91%)		
occurrences (all)	9		
Vomiting			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 May 2012	SA01 - Changes in interpretation of scientific documents/value of the trial and changes in conduct or management of the trial
16 October 2012	SA02 - Changes in conduct or management of the trial.
21 January 2013	SA03 - Changes in conduct or management of the trial.
19 June 2013	SA04 - Addition of a blood sample sub-study, request to participants for omission of Beta Blockers and Addition of Dietary Advice Sheet.
04 September 2013	Modified AM05 - Changes in conduct or management of the trial.
08 September 2013	SA05 - Replacement of dobutamine with exercise in the PET-CT sub-study.
18 November 2014	SA06 - Changes to washout period and reduction of sample size.

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.

None documented.

Notes: