Clinical trial results:
Allopurinol as a possible new therapy for acute coronary syndromes: The Next Steps

Summary

EudraCT number	2011-004996-35
Trial protocol	GB
Global end of trial date	13 March 2015

Results information

Result version number	v1 (current)
This version publication date	10 July 2016
First version publication date	10 July 2016

Trial information

Trial identification

Sponsor protocol code	2010CV30

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01457820
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Dundee/NHS Tayside
Sponsor organisation address	Tayside Medical Science Centre, Dundee, United Kingdom, DD1 9SY
Public contact	Catrina Forde, University of Dundee, 44 1382 383890, c.forde@dundee.ac.uk
Scientific contact	Catrina Forde, University of Dundee, 44 1382 383890, c.forde@dundee.ac.uk
Sponsor organisation name	University of Dundee/NHS Tayside
Sponsor organisation address	Tayside Medical Science Centre, Dundee, United Kingdom, DD1 9SY
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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	21 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2015
Global end of trial reached?	Yes
Global end of trial date	13 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal research question is: To establish how quickly giving a dose of allopurinol alters the time it takes for exercise to produce ST depression in the ECG.
The overall design was to study patients with chronic stable angina (CSA) who develop ST depression on exercise, to examine time to exercise induced ST depression and in particular the change in this endpoint induced by various different loading doses of allopurinol.

Protection of trial subjects:

No measures specific to this trial.

Background therapy:

Standard approved drugs for ischaemic heart disease.

Evidence for comparator:

Previous evidence shows that allopurinol prolongs time to ST depression in patients with ischaemic heart disease. This effect agrees with experimental work where allopurinol clearly redcues oxygen consumption for any given stroke volume.

Actual start date of recruitment	01 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	5
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was active between May 2012 to August 2014.
A total of 133 participants were assessed for eligibility and consented for this study. 26 subjects were randomised from the 133 consented, 5 of this number dropped out prior to the end of the study.

Pre-assignment

Screening details:

Patients attended for ETT. Patients with ECG changes were invited back for a second ETT and if timing of ECG changes were within a given range they were recruited. If not, a 3rd ETT was performed and if changes consistent they could be recruited. patients without ECG changes or with changes not consistent in onset were not recruited.

Pre-assignment period milestones

Number of subjects started	26
Number of subjects completed	26

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, Data analyst

Blinding implementation details:

Double blind medication (allopurinol or placebo) was prepared and packaged by Tayside Pharmaceuticals. The medication was labeled as "participant 1", "participant 2", etc. and distributed to the participant by the research fellow according to their sequence number. randomization was carried out By Tayside Pharmaceuticals using block randomization in eleven groups of six (with three active/placebo in each block). They used a validated randomization program and this was securely backed up.

Arms

Are arms mutually exclusive?	No
Arm title	Arm 1

Arm description:

IMP/Placebo
Each treatment consisted of a single loading dose, either Placebo, 400mg Allopurinol or 800mg Allopurinol. This was followed by a reduced BD dose for a period of 5 days.

Arm type	either placebo or IMP
Investigational medicinal product name	Allopurinol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Loading dose either placebo, 400mg or 800mg.
If 400mg loading dose, followed by BD 300mg for 5 days
If 800mg loading dose, followed by BD 400mg for 5 days
Each treatment period followed by a 1 week washout period minimum.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

The placebo and active tablet were visually identical.

Arm title	Arm 2

Arm description:

IMP/Placebo Each treatment consisted of a single loading dose, either Placebo, 400mg Allopurinol or... more 800mg Allopurinol. This was followed by a reduced BD dose for a period of 5 days.

Arm type	IMP or placebo
Investigational medicinal product name	Allopurinol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Loading dose either placebo, 400mg or 800mg.
If 400mg loading dose, followed by BD 300mg for 5 days
If 800mg loading dose, followed by BD 400mg for 5 days
Each treatment period followed by a 1 week washout period minimum.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo and IMP were visually identical

Arm title	Arm 3

Arm description:

IMP/Placebo Each treatment consisted of a single loading dose, either Placebo, 400mg Allopurinol or... more 800mg Allopurinol. This was followed by a reduced BD dose for a period of 5 days.

Arm type	IMP/placebo
Investigational medicinal product name	Allopurinol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Loading dose either placebo, 400mg or 800mg.
If 400mg loading dose, followed by BD 300mg for 5 days
If 800mg loading dose, followed by BD 400mg for 5 days
Each treatment period followed by a 1 week washout period minimum.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo and IMP were visually identical

Number of subjects in period 1	Arm 1	Arm 2	Arm 3
Started	26	21	21
Completed	26	21	21

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	26	26	
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)	5	5	
From 65-84 years	21	21	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	6	6	
Male	20	20	

Subject analysis sets

Subject analysis set title	Intention -to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

If a subject is non compliant theyare encouraged to become compliant. If they persist it is intended to have them remain in the study , not on study medication, in order to do an "intention to treat" analysis.

Reporting group values	Intention -to-treat		
Number of subjects	26		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	5		
From 65-84 years	21		
85 years and over	0		

Gender categorical Units: Subjects			
Female	6		
Male	20		

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description:	
IMP/Placebo Each treatment consisted of a single loading dose, either Placebo, 400mg Allopurinol or 800mg Allopurinol. This was followed by a reduced BD dose for a period of 5 days.	
Reporting group title	Arm 2
Reporting group description:	
IMP/Placebo Each treatment consisted of a single loading dose, either Placebo, 400mg Allopurinol or... more 800mg Allopurinol. This was followed by a reduced BD dose for a period of 5 days.	
Reporting group title	Arm 3
Reporting group description:	
IMP/Placebo Each treatment consisted of a single loading dose, either Placebo, 400mg Allopurinol or... more 800mg Allopurinol. This was followed by a reduced BD dose for a period of 5 days.	
Subject analysis set title	Intention -to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
If a subject is non compliant theyare encouraged to become compliant. If they persist it is intended to have them remain in the study , not on study medication, in order to do an "intention to treat" analysis.	

Primary: Time to ST depression on ETT

End point title	Time to ST depression on ETT
End point description:	
Subject would start on the ETT using the Bruce protocol. ETT would finish either when subject asked to stop, Blood pressure became too elevated, clinician stopped the test.	
End point type	Primary
End point timeframe:	
From beginning of ETT	

End point values	Arm 1	Arm 2	Arm 3	Intention -to-treat
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	26	21	21	26
Units: seconds and minutes	331	353	358	331

Statistical analyses

Statistical analysis title	Multi level model
Statistical analysis description:	
A multi level model of Mills was used.	
Comparison groups	Arm 1 v Arm 2 v Arm 3

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority[1]
Parameter estimate	Multi level model
Point estimate	-4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.6
upper limit	13.4
Variability estimate	Standard error of the mean

Notes:

[1] - None

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Duration of time participant spent in study.

Adverse event reporting additional description:

Participants were instructed to contact the investigator at any time after consenting to join the study if any symptoms developed. All AEs were recorded in detail in the subject CRF and in an AE log. The investigator initiated appropriate treatment according to their medical judgment. Unresolved AEs at study end followed up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Hypotension	Additional description: Collapse (due to hypotension) post loading dose		
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 26 (30.77%)		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Dyspepsia			

subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in jaw subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1 1 / 26 (3.85%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2012	Consent form version change to V.3 Participation information sheet version change to V.3 Protocol version change to V.2
16 November 2012	Protocol version change to V.3
11 December 2012	Protocol version change to V.4
04 April 2013	Consent form version change to V.3
17 October 2013	Additional sites added

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.

Study terminated early due to difficulties recruiting .

Notes: