Clinical trial results:
Isoprenaline infusion as a method of induction of Atrial Fibrillation; A randomised controlled trial investigating the use of Isoprenaline to induce an episode of atrial fibrillation

Summary

EudraCT number	2014-002290-11
Trial protocol	
Global end of trial date	30 March 2017

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	
Summary attachment (see zip file)	Iso-AF statement (IsoAF statement FINAL.pdf)

Trial information

Trial identification

Sponsor protocol code	Iso1

Additional study identifiers

ISRCTN number	ISRCTN17309312
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS ID: 138811, REC reference: 14/SC/1171

Notes:

Sponsors

Sponsor organisation name	Royal Bournemouth and Christchurch Hospitals NHS Trust
Sponsor organisation address	Castle Lane East, Bournemouth, United Kingdom, BH7 7DW
Public contact	Laura Purandare, Head of Research, Royal Bournemouth and Christchurch Hospitals NHS Trust, +44 300 019 8500, researchsponsorhip@uhd.nhs.uk
Scientific contact	Laura Purandare, Head of Research, Royal Bournemouth and Christchurch Hospitals NHS Trust, +44 300 019 8500, researchsponsorhip@uhd.nhs.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 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 March 2017
Global end of trial reached?	Yes
Global end of trial date	30 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principle objective of the study is to answer the question "can an infusion of the drug isoprenaline induce an episode of the abnormal heart rhythm atrial fibrillation?" To answer this question we will take a group of people with a past medical history of atrial fibrillation that comes and goes on its own and administer an infusion of isoprenaline to half of them and a dummy infusion to the other half. We will compare how many participants have an episode of atrial fibrillation whilst they are being given an isoprenaline infusion with how many have an episode whilst being given a dummy infusion. If significantly more episodes of atrial fibrillation occur in those being given the isoprenaline infusion, we will know it is the isoprenaline that is causing the rhythm disturbance.

Protection of trial subjects:

Participants will not experience any pain as a result of taking part in this study. By taking part in this study, participants undergoing an ablation procedure as part of their usual care will spend more time in the Cardiac Electrophysiology Laboratory (where we perform ablation procedures) around the time of their ablation procedure. It is noted that participants may not realise this however as the length of a standard ablation varies widely dependent on what is found at the time. In addition, subjects will be sedated as a standard part of the procedure. Participants may end up requiring additional sedation as the procedure will be longer, to some this may be considered a burden of the research involvement, to others a benefit. The additional sedation which may be required is not considered a source of potential harm. There are a number of specific potential risks to study subjects which have been considered. They relate to the administration of isoprenaline in specific populations, to the consequences of inducing an episode of atrial fibrillation and to the methods of restoration of sinus rhythm if required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2014
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: 188
Worldwide total number of subjects	188
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	157
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 188 participants were recruited across both participating sites.

Pre-assignment

Screening details:

Potential participants will be identified as being possible study candidates at the time of clinical review as part of their usual care.

Period 1

Period 1 title	Part A
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This part of the protocol was open label.

Arms

Arm title	Isoprenaline

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Isoprenaline
Investigational medicinal product code	MIA(IMP) 13079
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Injection

Dosage and administration details:

Infusions were drawn up by combining 80mls of 5% glucose with x2 10mls vials of Isoprenaline sulphate 10mcg/ml. The resulting solution thus contained 200mcg Isoprenaline Sulphate in 100mls. Infusions given via central or peripheral intravenous access using an infusion pump to control the rate of administration.

Number of subjects in period 1	Isoprenaline
Started	188
Completed	169
Not completed	19
Consent withdrawn by subject	19

Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator

Blinding implementation details:

Part B of the protocol was double blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Isoprenaline

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Isoprenaline
Investigational medicinal product code	MIA(IMP) 13079
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Injection

Dosage and administration details:

Infusions were drawn up by combining 80mls of 5% glucose with x2 10mls vials of Isoprenaline sulphate 10mcg/ml. The resulting solution thus contained 200mcg Isoprenaline Sulphate in 100mls. Infusions given via central or peripheral intravenous access using an infusion pump to control the rate of administration.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	0.9% Saline
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Injection

Dosage and administration details:

Infusions given via central or peripheral intravenous access using an infusion pump to control the rate of administration. 0.9% Saline for infusion was supplied by participating NHS trusts from the same supply used for clinical care.

Number of subjects in period 2	Isoprenaline	Placebo
Started	94	75
Completed	94	75

Baseline characteristics

Reporting groups

Reporting group title	Part A

Reporting group description: -

Reporting group values	Part A	Total	
Number of subjects	188	188	
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)	157	157	
From 65-84 years	31	31	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	0		
standard deviation	± 0	-	
Gender categorical Units: Subjects			
Female	62	62	
Male	126	126	

Subject analysis sets

Subject analysis set title	99999
Subject analysis set type	Per protocol

Subject analysis set description:
99999 - Analysis not completed

Reporting group values	99999		
Number of subjects	169		
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)	157		

From 65-84 years	31		
85 years and over	0		

Age continuous Units: years			
arithmetic mean	0		
standard deviation	± 0		
Gender categorical Units: Subjects			
Female	62		
Male	126		

End points

End points reporting groups

Reporting group title	Isoprenaline
Reporting group description: -	
Reporting group title	Isoprenaline
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	99999
Subject analysis set type	Per protocol
Subject analysis set description: 99999 - Analysis not completed	

Primary: Change in outcome between two administrations of the study drug infusion protocol

End point title	Change in outcome between two administrations of the study drug infusion protocol[1]
End point description:	
End point type	Primary
End point timeframe: N/A	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis not done

End point values	Isoprenaline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	75		
Units: N/A				
99999	99999	99999		

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of the occurrence of atrial fibrillation lasting greater than 30 seconds during study drug infusion protocol

End point title	Frequency of the occurrence of atrial fibrillation lasting greater than 30 seconds during study drug infusion protocol[2]
End point description:	
End point type	Primary
End point timeframe: N/A	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis not done

End point values	Isoprenaline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	75		
Units: N/A				
99999	99999	99999		

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of the occurrence of an arrhythmia other than atrial fibrillation, sinus tachycardia or junctional rhythm lasting greater than 30 seconds during study drug infusion protocol

End point title	Frequency of the occurrence of an arrhythmia other than atrial fibrillation, sinus tachycardia or junctional rhythm lasting greater than 30 seconds during study drug infusion protocol[3]

End point description:

End point type	Primary

End point timeframe:

N/A

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis not done

End point values	Isoprenaline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: N/A				
99999				

Notes:

[4] - Analysis not done

[5] - Analysis not done

Statistical analyses

No statistical analyses for this end point

Secondary: Change in time to outcome between two administrations of the study drug infusion protocol

End point title	Change in time to outcome between two administrations of the study drug infusion protocol

End point description:

End point type	Secondary

End point timeframe:

N/A

End point values	Isoprenaline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: N/A				
99999				

Notes:

[6] - Analysis not done

[7] - Analysis not done

Statistical analyses

No statistical analyses for this end point

Secondary: Change in maximum rate of infusion between two administrations of the study drug infusion protocol

End point title	Change in maximum rate of infusion between two administrations of the study drug infusion protocol

End point description:

End point type	Secondary

End point timeframe:

N/A

End point values	Isoprenaline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: N/A				
99999				

Notes:

[8] - Analysis not done

[9] - Analysis not done

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of the occurrence of atrial fibrillation lasting less than 30 seconds during study drug infusion protocol

End point title	Frequency of the occurrence of atrial fibrillation lasting less than 30 seconds during study drug infusion protocol

End point description:

End point type	Secondary

End point timeframe:

N/A

End point values	Isoprenaline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: N/A				
99999				

Notes:

[10] - Analysis not done

[11] - Analysis not done

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of the occurrenceof an arrhythmia other than atrial fibrillation,sinus tachycardia or junctional rhythmlasting less than 30 seconds during study drug infusion protocol

End point title	Frequency of the occurrenceof an arrhythmia other than atrial fibrillation,sinus tachycardia or junctional rhythmlasting less than 30 seconds during study drug infusion protocol

End point description:

End point type	Secondary

End point timeframe:

N/A

End point values	Isoprenaline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	75		
Units: N/A				
99999	99999	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from start of infusion protocol to occurrence of atrial fibrillation

End point title	Time from start of infusion protocol to occurrence of atrial fibrillation

End point description:

End point type	Secondary

End point timeframe:
N/A

End point values	Isoprenaline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	75		
Units: N/A				
99999	99999	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of infusion at time of occurrence of atrial fibrillation

End point title	Rate of infusion at time of occurrence of atrial fibrillation

End point description:

End point type	Secondary

End point timeframe:
N/A

End point values	Isoprenaline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: N/A				
99999				

Notes:
[12] - Analysis not done
[13] - Analysis not done

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum tolerated rate of study drug infusion prior to its cessation for any reason

End point title	Maximum tolerated rate of study drug infusion prior to its cessation for any reason

End point description:

End point type	Secondary

End point timeframe:
N/A

End point values	Isoprenaline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: N/A				
99999				

Notes:

[14] - Analysis not done

[15] - Analysis not done

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
From consent to study end	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Not available

Serious adverse events	Isoprenaline	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 94 (3.19%)	0 / 75 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Cardiac Arrest			
subjects affected / exposed	1 / 94 (1.06%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Cerebral vascular accident			
subjects affected / exposed	1 / 94 (1.06%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary Embolus			
subjects affected / exposed	1 / 94 (1.06%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Isoprenaline	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 94 (0.00%)	0 / 75 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2015	SA05: The amendment is applying for approval to use a site specific Participant Information Sheet (PiS) for those participants recruited from the John Radcliffe Hospital site in Oxford. Of note, we are yet to start recruiting at that site.

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.

The Research Sponsorship Group are concerned about the data obtained for the trial and do not believe it to be of sufficient quality to allow reporting of results to the regulatory bodies or the public.

Notes: