



Clinical trial results:

A Phase 2 Study to Assess the Antiarrhythmic and Symptomatic Effect of the Second Generation Antisense Oligonucleotide ISIS 329993 Targeting CRP in Patients with Paroxysmal Atrial Fibrillation

Summary

EudraCT number	2012-000833-38
Trial protocol	GB
Global end of trial date	31 March 2014

Results information

Result version number	v1 (current)
This version publication date	24 July 2019
First version publication date	24 July 2019

Trial information

Trial identification

Sponsor protocol code	ISIS329993-CS6
-----------------------	----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01710852
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Court, Carlsbad, United States, CA 92010
Public contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.com
Scientific contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.com

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	31 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate whether treatment with the antisense inhibitor of human C-reactive protein (CRP) (ISIS 329993) can reduce atrial fibrillation (AF) burden (percentage of time spent in AF as derived from continuous pacemaker monitoring) in subjects with paroxysmal AF.

Protection of trial subjects:

Subjects were evaluated to determine their capacity to sign an informed consent form which was in English and easily understood by the subjects. The subjects were encouraged to complete the early termination study procedures and observations at the time of withdrawal.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 February 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 7
Worldwide total number of subjects	7
EEA total number of subjects	7

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)	1
From 65 to 84 years	6

85 years and over	0
-------------------	---

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at a single centre in the United Kingdom.

Pre-assignment

Screening details:

26 subjects with paroxysmal atrial fibrillation (AF) were screened and 7 were randomised to receive the treatment.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo – ISIS 329993 400 mg

Arm description:

In Treatment Period 1, subjects received placebo subcutaneously (SC) followed by ISIS 329993 400 milligrams (mg) in Treatment Period 2.

Arm type	Experimental
Investigational medicinal product name	ISIS 329993
Investigational medicinal product code	
Other name	CRPRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 329993 400 mg was administered SC

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was administered SC

Arm title	ISIS 329993 400 mg – Placebo
------------------	------------------------------

Arm description:

In Treatment Period 1 subjects received ISIS 329993 400 mg SC, followed by placebo SC, in Treatment Period 2.

Arm type	Experimental
Investigational medicinal product name	ISIS 329993
Investigational medicinal product code	
Other name	CRPRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 329993 400 mg was administered SC

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Placebo was administered SC	

Number of subjects in period 1	Placebo – ISIS 329993 400 mg	ISIS 329993 400 mg – Placebo
Started	4	3
Completed	4	3

Period 2

Period 2 title	Treatment Period 2
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?	No
Arm title	Placebo – ISIS 329993 400 mg

Arm description:

In Treatment Period 1, subjects received placebo SC followed by ISIS 329993 400 mg SC in Treatment Period 2.

Arm type	Experimental
Investigational medicinal product name	ISIS 329993
Investigational medicinal product code	
Other name	CRPRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 329993 400 mg was administered SC

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was administered SC

Arm title	ISIS 329993 400 mg – Placebo
------------------	------------------------------

Arm description:

In Treatment Period 1, subjects received ISIS 329993 400 mg SC followed by placebo SC in Treatment Period 2.

Arm type	Experimental
Investigational medicinal product name	ISIS 329993
Investigational medicinal product code	
Other name	CRPRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 329993 400 mg was administered SC

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was administered SC

Number of subjects in period 2	Placebo – ISIS 329993 400 mg	ISIS 329993 400 mg – Placebo
Started	4	3
Completed	4	3

Baseline characteristics

Reporting groups

Reporting group title	Placebo – ISIS 329993 400 mg
Reporting group description: In Treatment Period 1, subjects received placebo subcutaneously (SC) followed by ISIS 329993 400 milligrams (mg) in Treatment Period 2.	
Reporting group title	ISIS 329993 400 mg – Placebo
Reporting group description: In Treatment Period 1 subjects received ISIS 329993 400 mg SC, followed by placebo SC, in Treatment Period 2.	

Reporting group values	Placebo – ISIS 329993 400 mg	ISIS 329993 400 mg – Placebo	Total
Number of subjects	4	3	7
Age categorical			
Units: Subjects			

Age continuous			
Intent to Treat (ITT) population included all subjects who were randomised into the study regardless of whether they received study drug and provided at least one post-baseline measure of outcome.			
Units: years			
arithmetic mean	76.50	70.67	
standard deviation	± 5.92	± 8.62	-
Gender categorical			
Intent to Treat (ITT) population included all subjects who were randomised into the study regardless of whether they received study drug and provided at least 1 post-baseline measure of outcome.			
Units: Subjects			
Female	2	3	5
Male	2	0	2

End points

End points reporting groups

Reporting group title	Placebo – ISIS 329993 400 mg
Reporting group description: In Treatment Period 1, subjects received placebo subcutaneously (SC) followed by ISIS 329993 400 milligrams (mg) in Treatment Period 2.	
Reporting group title	ISIS 329993 400 mg – Placebo
Reporting group description: In Treatment Period 1 subjects received ISIS 329993 400 mg SC, followed by placebo SC, in Treatment Period 2.	
Reporting group title	Placebo – ISIS 329993 400 mg
Reporting group description: In Treatment Period 1, subjects received placebo SC followed by ISIS 329993 400 mg SC in Treatment Period 2.	
Reporting group title	ISIS 329993 400 mg – Placebo
Reporting group description: In Treatment Period 1, subjects received ISIS 329993 400 mg SC followed by placebo SC in Treatment Period 2.	
Subject analysis set title	ISIS 329993 400 mg
Subject analysis set type	Per protocol
Subject analysis set description: Three subjects received ISIS 329993 400 mg SC in Treatment period 1 and four in Treatment period 2.	

Primary: Change from Baseline in Atrial Fibrillation (AF) Burden During Treatment with ISIS 329993 to End of Treatment

End point title	Change from Baseline in Atrial Fibrillation (AF) Burden During Treatment with ISIS 329993 to End of Treatment ^[1]
End point description: AF burden was defined as the percentage of time spent in AF as derived from continuous pacemaker monitoring. It was assessed using long-term, beat-to-beat pacemaker Holter monitoring. Per Protocol population included all subjects who were randomised and received at least 5 doses of ISIS 329993 and who did not have any clinically significant protocol deviations. Measurements were only compared from baseline and active treatment period.	
End point type	Primary
End point timeframe: Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)	

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: Descriptive statistics only.

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: percentage of time in AF				
arithmetic mean (standard deviation)				
Baseline	2.943 (± 3.752)			
Change at End of Treatment	1.600 (± 4.342)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Number of AF Episodes to the End of Treatment

End point title	Change from Baseline in Total Number of AF Episodes to the End of Treatment
-----------------	---

End point description:

AF episodes were derived from continuous pacemaker monitoring. Per Protocol population included all subjects who were randomised and received at least 5 doses of ISIS 329993 and who did not have any clinically significant protocol deviations. Measurements were only compared from baseline and active treatment period.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: number of AF episodes				
arithmetic mean (standard deviation)				
Baseline	19.57 (± 22.91)			
Change at End of Treatment	19.86 (± 36.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Average Duration of AF Per Episode to the End of Treatment

End point title	Change from Baseline in Average Duration of AF Per Episode to the End of Treatment
-----------------	--

End point description:

The duration of AF episodes was derived from continuous pacemaker monitoring. The negative value indicated the decrease in the average duration of AF per episode. Per Protocol population included all subjects who were randomised and received at least 5 doses of ISIS 329993 and who did not have any clinically significant protocol deviations. Measurements were only compared from baseline and active treatment period.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: minutes (min)				
arithmetic mean (standard deviation)				
Baseline	269.43 (\pm 506.99)			
Change at End of Treatment	-115.57 (\pm 473.06)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Average Sinus Rhythm Duration to the End of Treatment

End point title	Change from Baseline in Average Sinus Rhythm Duration to the End of Treatment
-----------------	---

End point description:

Sinus rhythm duration was derived from continuous pacemaker monitoring. Per Protocol population included all subjects who were randomised and received at least 5 doses of ISIS 329993 and who did not have any clinically significant protocol deviations. Measurements were only compared from baseline and active treatment period.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: min				
arithmetic mean (standard deviation)				
Baseline	7548.00 (\pm 6901.36)			
Change at End of Treatment (n=6)	3624.83 (\pm 9741.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Atrial and Ventricular Rate During AF episodes to the End of Treatment

End point title	Change from Baseline in Atrial and Ventricular Rate During AF episodes to the End of Treatment
-----------------	--

End point description:

The atrial and ventricular rate during AF episodes were derived from continuous pacemaker monitoring. Per Protocol population included all subjects who were randomised and received at least 5 doses of ISIS 329993 and who did not have any clinically significant protocol deviations. Measurements were only compared from baseline and active treatment period.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Baseline Atrial rate	263.43 (\pm 58.70)			
Change in Atrial Rate at End of Treatment (n=5)	17.00 (\pm 21.13)			
Baseline Ventricular Rate (VR)	94.00 (\pm 17.67)			
Change in VR at End of Treatment (n=5)	1.80 (\pm 8.20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Ventricular Rate During Sinus Rhythm to the End of Treatment

End point title	Change from Baseline in Ventricular Rate During Sinus Rhythm to the End of Treatment
-----------------	--

End point description:

Ventricular rate during sinus rhythm was derived from continuous pacemaker monitoring. Per Protocol population included all subjects who were randomised and received at least 5 doses of ISIS 329993 and who did not have any clinically significant protocol deviations. Measurements were only compared from baseline and active treatment period.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: bpm				
arithmetic mean (standard deviation)				
Baseline	64.29 (± 6.07)			
Change at End of Treatment	1.57 (± 3.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Measures of Health-Related Quality of Life as Assessed by Short-form (SF) 36 to the End of Treatment

End point title	Change from Baseline in Measures of Health-Related Quality of Life as Assessed by Short-form (SF) 36 to the End of Treatment
-----------------	--

End point description:

SF-36 investigates the standard of quality of life (QOL) through a general health assessment. It is a 36-item questionnaire measuring 8 domains (bodily pain [BP], general health [GH], mental health [MH], physical functioning [PF], role emotional [RE], role physical [RP], social functioning [SF], vitality [VT]). Two summary scale scores were computed based on weighted combinations of the 8 domain scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Each domain score ranges from 0 (worst) to 100 (best), with higher scores reflecting better health-related functional status. Per Protocol population included all subjects who were randomised and received at least 5 doses of ISIS 329993 and who did not have any clinically significant protocol deviations. Measurements were only compared from baseline and active treatment period.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: score on the scale				
arithmetic mean (standard deviation)				
Baseline PCS (n=6)	42.7850 (± 4.2489)			
Change in PCS at End of Treatment (n=6)	-0.4367 (± 3.7477)			
Baseline MCS (n=6)	52.8733 (± 10.2874)			
Change in MCS at End of Treatment (n=6)	2.4917 (± 4.1913)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Measures of Health-Related Quality of Life as Assessed by Visual Analogue Scale (VAS) to the End of Treatment

End point title	Change from Baseline in Measures of Health-Related Quality of Life as Assessed by Visual Analogue Scale (VAS) to the End of Treatment
-----------------	---

End point description:

VAS QOL measurements were composed of 3 questions regarding overall health, daily activities, and mood. Per Protocol population included all subjects who were randomised and received at least 5 doses of ISIS 329993 and who did not have any clinically significant protocol deviations. Measurements were only compared from baseline and active treatment period.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	319.714 (\pm 155.436)			
Change at End of Treatment	3.143 (\pm 69.722)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life as Assessed by European Heart Rhythm Association (EHRA) Grade to the End of Treatment

End point title	Health-Related Quality of Life as Assessed by European Heart Rhythm Association (EHRA) Grade to the End of Treatment
-----------------	--

End point description:

EHRA scores represented the severity of symptoms. The four levels reported were No symptoms (NS), Mild symptoms (MS), Severe symptoms (SS), Disabling symptoms (DS). Per Protocol population included all subjects who were randomised and received at least 5 doses of ISIS 329993 and who did not have any clinically significant protocol deviations. Measurements were only compared from baseline and active treatment period.

End point type	Secondary
----------------	-----------

End point timeframe:

Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: number of subjects				
Baseline NS	2			
End of Treatment NS	2			
Baseline MS	4			
End of Treatment MS	4			
Baseline SS	1			
End of Treatment SS	1			
Baseline DS	0			
End of Treatment DS	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Measures of Health-Related Quality of Life as Assessed by Atrial Fibrillation Severity Score (AFSS) Questionnaire to the End of Treatment

End point title	Change from Baseline in Measures of Health-Related Quality of Life as Assessed by Atrial Fibrillation Severity Score (AFSS) Questionnaire to the End of Treatment
End point description:	
0 indicates that the summary was not calculated and the data is no longer available to generate. Measurements were only compared from baseline and active treatment period.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)	

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: score on a scale				
arithmetic mean (standard deviation)	0 (\pm 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in High Sensitivity C-reactive Protein (hsCRP) in Subjects with Paroxysmal AF to the End of Treatment

End point title	Change from Baseline in High Sensitivity C-reactive Protein (hsCRP) in Subjects with Paroxysmal AF to the End of
-----------------	--

End point description:

A negative sign indicated a reduction in hsCRP level. Per Protocol population included all subjects who were randomised and received at least 5 doses of ISIS 329993 and who did not have any clinically significant protocol deviations. Measurements were only compared from baseline and active treatment period.

End point type

Secondary

End point timeframe:

Baseline (Day 1) to End of Treatment (Day 29 for 3 subjects and Day 57 for 4 subjects)

End point values	ISIS 329993 400 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: milligrams per litre (mg/L)				
arithmetic mean (standard deviation)				
Baseline	4.1342 (\pm 3.3122)			
Change at End of Treatment	-2.9442 (\pm 2.7445)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) to end of follow-up period (Day 113)

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	16
--------------------	----

Reporting groups

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Data from the placebo period (Study Days 1, 3, 5, 8, 15 and 22 for subjects who received placebo, SC in Treatment Period 1 and Study Days 29, 31, 33, 36, 43 and 50 for subjects who received placebo, SC in Treatment Period 2) are reported for this group,

Reporting group title	ISIS 329993 400 mg
-----------------------	--------------------

Reporting group description:

Data from the ISIS 329993 400 mg, SC in the treatment period (Study Days 1, 3, 5, 8, 15 and 22 for subjects who received ISIS 329993 400 mg, SC in Treatment Period 1 and Study Days 29, 31, 33, 36, 43 and 50 for subjects who received ISIS 329993 400 mg, SC in Treatment period 2) are reported for this group.

Serious adverse events	Placebo	ISIS 329993 400 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	ISIS 329993 400 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	7 / 7 (100.00%)	
Investigations			
Urine output increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
International normalised ratio increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

International normalised ratio decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
International normalised ratio abnormal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blood glucose decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nervous system disorders			
Hyperaesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	2 / 7 (28.57%)	3 / 7 (42.86%)	
occurrences (all)	6	8	
Injection site pain			

subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	6	
Injection site erythema			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	10	
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Injection site warmth			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Injection site swelling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Injection site pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Injection site papule			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Cyst			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 7 (28.57%) 2	
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 7 (14.29%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	
Skin and subcutaneous tissue disorders Dermal cyst subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 7 (14.29%) 1	
Infections and infestations Viral infection subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	
Infection subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 7 (0.00%) 0	
Cellulitis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2012	Clarification provided for the use of concomitant medication whereby warfarin is the only anticoagulant permitted for use on study.
30 May 2012	Since plasma hsCRP levels may be elevated as a consequence of infection Exclusion Criterion 3 was amended to state that subjects with an active infection should complete systemic antiviral or antimicrobial treatment prior to the Screening Period.
13 July 2012	The rule for early crossover was changed to include any intolerable symptoms rather than just intolerable symptoms as a consequence of their AF.
17 December 2012	Direct thrombin antagonist dabigatran (Pradaxa TM) was added to the list of allowed therapeutic anticoagulant medications and to Inclusion Criterion 8. Additional safety stopping rules for bleeding were added to the safety monitoring rules.
02 May 2013	Inclusion Criterion 8 was modified to clarify that the requirement for being on a stable dose of anticoagulant for ≥ 3 months was only applicable to subjects who received dabigatran and that the ≥ 3 -month period of stable dosing for dabigatran was relative to Study Day 1. Since smoking increases CRP and impairs endothelial function, carbon monoxide breath testing throughout the duration of the study was added to the required study procedures for subjects that had been abstinent from smoking for ≤ 6 months prior to screening. Modified the wording of Inclusion Criteria 4 and 5, and Exclusion Criteria 2b, 6, 11, 18, and 24.
16 October 2013	The maximum number of subjects enrolled was reduced from 20 to 25 subjects to 10 subjects because the target treatment effect had been increased from 35% to 50% reduction in AF burden. The interim safety analysis, which was to be performed after 10 subjects had completed the treatment period, was removed since the number of subjects required in the study had been reduced to 10 subjects. Inclusion Criterion 9, hsCRP ≥ 2 mg/L and ≤ 10 mg/L at Screening, was removed since there is no specific threshold for hsCRP at which subjects are deemed to be at increased risk for higher AF burden. Exclusion Criterion 24 was removed since there is no strong association between current smoking status and AF burden.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported