Clinical trial results:
A Randomised, Double-Blind, Double-Dummy, Placebo-Controlled, Dose-Ranging Phase II Study Assessing Ranolazine in the Maintenance of Sinus Rhythm after Electrical Cardioversion in Patients with Non-Permanent Atrial Fibrillation

Summary

EudraCT number	2011-002789-18
Trial protocol	DE ES GB IT
Global end of trial date	30 September 2013

Results information

Result version number	v1 (current)
This version publication date	20 August 2021
First version publication date	20 August 2021

Trial information

Trial identification

Sponsor protocol code	RAF-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01534962
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MENARINI RICERCHE S.P.A.
Sponsor organisation address	Via Sette Santi 1, Florence, Italy, 50131
Public contact	Corporate Clinical Sciences, MENARINI RICERCHE S.P.A., 0039 055-56809933, ACAPRIATI@MENARINI-RICERCHE.IT
Scientific contact	Corporate Clinical Sciences, MENARINI RICERCHE S.P.A., 0039 055-56809933, ACAPRIATI@MENARINI-RICERCHE.IT

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 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2013
Global end of trial reached?	Yes
Global end of trial date	30 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of Ranolazine administered as 3 different doses regimens versus placebo in the maintenance of sinus rhythm after electrical cardioversion in patients with non-permanent Atrial Fibrillation (defined as a continuous Atrial Fibrillation with a minimum duration of 7 days to a maximum of 6 months or requiring termination by cardioversion).

Protection of trial subjects:

If any event(s) related to the conduct of the study or the development of the IMP affects the safety of the study participants, the sponsor and the Investigator will take appropriate urgent safety measures to protect the patients against any immediate hazard. The CAs and IRB/ECs will be informed forthwith about these new events and the measures taken. For patients participating in the study, Menarini Ricerche S.p.A. has stipulated an insurance policy in accordance with local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 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	Spain: 73
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Germany: 100
Country: Number of subjects enrolled	Italy: 57
Worldwide total number of subjects	241
EEA total number of subjects	241

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)	103
From 65 to 84 years	135
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The first patient was screened on 18 Jan 2012. The last patient completed the study on 30 Sep 2013. The study was conducted at 45 investigational sites in 4 European countries.

Pre-assignment

Screening details:

A total of 310 patients were screened and underwent cardioversion (CV). Of these, 241 were still in sinus rhythm 2 hours post-CV and could be enrolled. Three patients were randomised but did not take study medication. Finally, a total of 238 patients were randomised and took at least one dose of study (ITT population).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ranolazine low dose

Arm description:

375 mg, oral administration, BID; for a maximum of 16 weeks

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

Dosage and administration details:

BID

Arm title	Ranolazine intermediate dose

Arm description:

500 mg, oral administration, BID; for a maximum of 16 weeks

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

Dosage and administration details:

BID

Arm title	Ranolazine high dose

Arm description:

750 mg, oral administration, BID; for a maximum of 16 weeks

Arm type	Experimental

Investigational medicinal product name	Ranolazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

BID

Arm title	Placebo

Arm description:

Placebo (sugar pill), oral administration, BID; for a maximum of 16 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

BID

Number of subjects in period 1[1]	Ranolazine low dose	Ranolazine intermediate dose	Ranolazine high dose
Started	65	60	58
Completed	30	34	34
Not completed	35	26	24
Discontinued at AF recurrence	35	26	24

Number of subjects in period 1[1]	Placebo
Started	55
Completed	24
Not completed	31
Discontinued at AF recurrence	31

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 310 patients were screened and underwent cardioversion. Of these, 241 were still in sinus rhythm 2 hours post-CV and could be enrolled. Three patients were randomised but did not take study medication. Finally, a total of 238 patients were randomised and took at least one dose of study, forming the ITT population and represent the baseline population.

Baseline characteristics

Reporting groups	
Reporting group title	Ranolazine low dose
Reporting group description:	
375 mg, oral administration, BID; for a maximum of 16 weeks	
Reporting group title	Ranolazine intermediate dose
Reporting group description:	
500 mg, oral administration, BID; for a maximum of 16 weeks	
Reporting group title	Ranolazine high dose
Reporting group description:	
750 mg, oral administration, BID; for a maximum of 16 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo (sugar pill), oral administration, BID; for a maximum of 16 weeks	

Reporting group values	Ranolazine low dose	Ranolazine intermediate dose	Ranolazine high dose
Number of subjects	65	60	58
Age categorical Units: Subjects			

Age continuous			
Arithmetic mean age per reporting group in years and related standard deviation			
Units: years			
arithmetic mean	66.9	65.6	63.6
standard deviation	± 11.8	± 8.5	± 11.3
Gender categorical			
Caterorical gender (female, male) per reporting group.			
Units: Subjects			
Female	19	9	12
Male	46	51	46
Time since first AF			
Mean time since first atrial fibrillation (AF) diagnosis and related standad deviation.			
Units: months			
arithmetic mean	10.5	7.2	15.5
standard deviation	± 24.0	± 12.9	± 28.2

Reporting group values	Placebo	Total	
Number of subjects	55	238	
Age categorical Units: Subjects			

Age continuous			
Arithmetic mean age per reporting group in years and related standard deviation			
Units: years			
arithmetic mean	65.2		
standard deviation	± 9.5	-	

Gender categorical			
Caterorical gender (female, male) per reporting group.			
Units: Subjects			
Female	14	54	
Male	41	184	
Time since first AF			
Mean time since first atrial fibrillation (AF) diagnosis and related standad deviation.			
Units: months			
arithmetic mean	6.9		
standard deviation	± 13.5	-	

Subject analysis sets

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

Subject analysis set description:

ITT-population (all randomised patients who received at least one dose of study medication)

Reporting group values	ITT population		
Number of subjects	238		
Age categorical			
Units: Subjects			

Age continuous			
Arithmetic mean age per reporting group in years and related standard deviation			
Units: years			
arithmetic mean	65.3		
standard deviation	± 10.4		
Gender categorical			
Caterorical gender (female, male) per reporting group.			
Units: Subjects			
Female	54		
Male	184		
Time since first AF			
Mean time since first atrial fibrillation (AF) diagnosis and related standad deviation.			
Units: months			
arithmetic mean	10		
standard deviation	± 20.7		

End points

End points reporting groups

Reporting group title	Ranolazine low dose
Reporting group description: 375 mg, oral administration, BID; for a maximum of 16 weeks	
Reporting group title	Ranolazine intermediate dose
Reporting group description: 500 mg, oral administration, BID; for a maximum of 16 weeks	
Reporting group title	Ranolazine high dose
Reporting group description: 750 mg, oral administration, BID; for a maximum of 16 weeks	
Reporting group title	Placebo
Reporting group description: Placebo (sugar pill), oral administration, BID; for a maximum of 16 weeks	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT-population (all randomised patients who received at least one dose of study medication)	

Primary: Number of Patients with AF Recurrence

End point title	Number of Patients with AF Recurrence
End point description: Number of patients with documented AF recurrence. Please note: The time to event related analysis, namely "Time to first documented AF recurrence" was hampered by a high variability of data that precluded the calculation of point estimates and confidence intervals and limited the capacity of this study to show unequivocal results.	
End point type	Primary
End point timeframe: 16 weeks (112 days)	

End point values	Ranolazine low dose	Ranolazine intermediate dose	Ranolazine high dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	60	58	55
Units: patients	37	25	23	31

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	238			
Units: patients	116			

Statistical analyses

Statistical analysis title	Descriptive statistics
Statistical analysis description:	
Descriptive statistics comparing verum groups vs placebo	
Comparison groups	Ranolazine low dose v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.47
Method	Chi-squared

Statistical analysis title	Descriptive statistics
Statistical analysis description:	
Descriptive statistics comparing verum groups vs placebo	
Comparison groups	Ranolazine intermediate dose v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.42
Method	Chi-squared

Statistical analysis title	Descriptive statistics
Statistical analysis description:	
Descriptive statistics comparing verum groups vs placebo	
Comparison groups	Ranolazine high dose v Placebo
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.28
Method	Chi-squared

Secondary: Number of AF recurrences

End point title	Number of AF recurrences
End point description:	
Number of Documented and Confirmed AF Recurrences. Please note: The time to event related analysis, namely "Time to first documented and confirmed AF recurrence" was hampered by a high variability of data that precluded the calculation of point estimates and confidence intervals and limited the capacity of this study to show unequivocal results.	
End point type	Secondary
End point timeframe:	
16 weeks (112 days)	

End point values	Ranolazine low dose	Ranolazine intermediate dose	Ranolazine high dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	60	58	55
Units: Events	31	19	16	24

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	238			
Units: Events	90			

Statistical analyses

No statistical analyses for this end point

Secondary: Documented AF Recurrence in Patients Still in Sinus Rhythm 2 Days After Cardioversion

End point title	Documented AF Recurrence in Patients Still in Sinus Rhythm 2 Days After Cardioversion

End point description:

Documented AF recurrences in those patients who did not experience early relapses (within 48 hours after cardioversion).

Please note: The time to event related analysis, namely "Time to first documented AF recurrence in patients still in sinus rhythm 2 days
post DCCV" was hampered by a high variability of data that precluded the calculation of point estimates and confidence intervals and limited the capacity of this study to show unequivocal results.

End point type	Secondary

End point timeframe:

16 weeks (112 days)

End point values	Ranolazine low dose	Ranolazine intermediate dose	Ranolazine high dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	60	58	55
Units: Events	32	19	21	27

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	238			
Units: Events	99			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 16 weeks (112 days)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1
Reporting groups	
Reporting group title	Ranolazine low dose
Reporting group description: 375 mg, oral administration, BID; for a maximum of 112 days	
Reporting group title	Ranolazine intermediate dose
Reporting group description: 500 mg, oral administration, BID; for a maximum of 112 days	
Reporting group title	Ranolazine high dose
Reporting group description: 750 mg, oral administration, BID; for a maximum of 112 days	
Reporting group title	Placebo
Reporting group description: Placebo (sugar pill), oral administration, BID; for a maximum of 112 days	

Serious adverse events	Ranolazine low dose	Ranolazine intermediate dose	Ranolazine high dose
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 65 (3.08%)	3 / 60 (5.00%)	3 / 58 (5.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 65 (1.54%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			

subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 65 (1.54%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 60 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 65 (0.00%)	0 / 60 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Psychotic disorder			
subjects affected / exposed	0 / 65 (0.00%)	1 / 60 (1.67%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 55 (7.27%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	0 / 55 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 55 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus node dysfunction				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Syncope				
subjects affected / exposed	0 / 55 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	0 / 55 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Sudden death				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			

Gastrointestinal disorders			
Pancreatitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ranolazine low dose	Ranolazine intermediate dose	Ranolazine high dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 65 (78.46%)	46 / 60 (76.67%)	42 / 58 (72.41%)
Investigations			
Blood creatine increased			
subjects affected / exposed	2 / 65 (3.08%)	3 / 60 (5.00%)	0 / 58 (0.00%)
occurrences (all)	2	3	0

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	29 / 65 (44.62%)	24 / 60 (40.00%)	23 / 58 (39.66%)
occurrences (all)	31	33	27
Atrial flutter			
subjects affected / exposed	2 / 65 (3.08%)	0 / 60 (0.00%)	3 / 58 (5.17%)
occurrences (all)	2	0	3
Palpitations			
subjects affected / exposed	9 / 65 (13.85%)	11 / 60 (18.33%)	11 / 58 (18.97%)
occurrences (all)	11	18	19
Tachycardia			
subjects affected / exposed	1 / 65 (1.54%)	1 / 60 (1.67%)	3 / 58 (5.17%)
occurrences (all)	1	1	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 65 (9.23%)	2 / 60 (3.33%)	14 / 58 (24.14%)
occurrences (all)	7	4	20
Headache			
subjects affected / exposed	2 / 65 (3.08%)	2 / 60 (3.33%)	5 / 58 (8.62%)
occurrences (all)	2	2	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 65 (6.15%)	1 / 60 (1.67%)	5 / 58 (8.62%)
occurrences (all)	4	2	5
Chest pain			
subjects affected / exposed	8 / 65 (12.31%)	7 / 60 (11.67%)	4 / 58 (6.90%)
occurrences (all)	9	16	4
Fatigue			
subjects affected / exposed	11 / 65 (16.92%)	10 / 60 (16.67%)	9 / 58 (15.52%)
occurrences (all)	13	14	10
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 65 (1.54%)	1 / 60 (1.67%)	4 / 58 (6.90%)
occurrences (all)	2	2	7
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	1 / 65 (1.54%)	2 / 60 (3.33%)	3 / 58 (5.17%)
occurrences (all)	1	2	3
Nausea			
subjects affected / exposed	5 / 65 (7.69%)	1 / 60 (1.67%)	4 / 58 (6.90%)
occurrences (all)	7	1	7
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 65 (7.69%)	7 / 60 (11.67%)	5 / 58 (8.62%)
occurrences (all)	6	11	5

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 55 (74.55%)		
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	27 / 55 (49.09%)		
occurrences (all)	28		
Atrial flutter			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Palpitations			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	7		
Tachycardia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	8		
Headache			

subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	 2 / 55 (3.64%) 2 6 / 55 (10.91%) 6 5 / 55 (9.09%) 5		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 2 / 55 (3.64%) 3		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 1 / 55 (1.82%) 1 0 / 55 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 6 / 55 (10.91%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 November 2011	Addition of one sentence in den patient information v.1.2 dated 05.10.2011 approved. Addition of 3 new sites.
14 March 2012	Change of sentence in the following study documents: study protocol, patient information and informed consent form and TT-ECG handling manual, Addition of a new site.
09 May 2012	Change in SmPC and related documents: study protocol, patient information and informed consent, letter to general practitioner and investigators' brochure.
03 August 2012	Amendment to the site clinical trail agreement and addition of 3 new sites.
07 December 2012	Addition of a new 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.

Analysis of time to events endpoints were hampered by a high variability of data that precluded the calculation of point estimates and
confidence intervals and limited the capacity of this study to show unequivocal results.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25602175