



Clinical trial results: EFFICACY OF RANOLAZINE IN PATIENTS WITH CORONARY ARTERY DISEASE (CAD)

Summary

EudraCT number	2011-001278-24
Trial protocol	GR ES IE GB DE AT IT BG
Global end of trial date	06 January 2016

Results information

Result version number	v1 (current)
This version publication date	11 November 2018
First version publication date	11 November 2018

Trial information

Trial identification

Sponsor protocol code	MEIN/10/Ran-Cad/003
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Menarini International Operations Luxembourg S.A
Sponsor organisation address	1, Avenue de la Gare, Luxembourg, Luxembourg, L-1611
Public contact	Study Medical Expert (SME), Menarini International Operations Luxembourg SA, 0039 02516555236, dzava@lusofarmaco.it
Scientific contact	Study Medical Expert (SME), Menarini International Operations Luxembourg SA, 0039 02516555236, dzava@lusofarmaco.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	05 September 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary study objective will be to verify whether ranolazine 750 mg b.i.d. is effective in increasing exercise capacity (exercise treadmill time at peak).

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and local law requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2011
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: 68
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Bulgaria: 152
Country: Number of subjects enrolled	Germany: 78
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Ireland: 19
Country: Number of subjects enrolled	Italy: 116
Country: Number of subjects enrolled	Romania: 67
Country: Number of subjects enrolled	Russian Federation: 124
Worldwide total number of subjects	651
EEA total number of subjects	527

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	288
From 65 to 84 years	363
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1004 subjects have been screened at Visit 0.

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Treatment arm
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Arm description:

Ranolazine arm: ranolazine tablets 375 mg b.i.d for 2 weeks + ranolazine tablets 500 mg b.i.d for the next 2 weeks and finally ranolazine tablets 750 mg b.i.d for 24 weeks.

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

Dosage and administration details:

- Ranolazine 375 mg b.i.d for 2 weeks
- Ranolazine 500 mg b.i.d for 2 weeks
- Ranolazine 750 mg b.i.d for 24 weeks

Arm title	Placebo arm
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Arm description:

Placebo 1 tablet b.i.d. for 28 weeks

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

Dosage and administration details:

1 tablet b.i.d. for 28 weeks

Number of subjects in period 1	Treatment arm	Placebo arm
Started	324	327
Completed	302	299
Not completed	22	28
Protocol deviation	22	28

Baseline characteristics

Reporting groups

Reporting group title	Treatment arm
Reporting group description: Ranolazine arm: ranolazine tablets 375 mg b.i.d for 2 weeks + ranolazine tablets 500 mg b.i.d for the next 2 weeks and finally ranolazine tablets 750 mg b.i.d for 24 weeks.	
Reporting group title	Placebo arm
Reporting group description: Placebo 1 tablet b.i.d. for 28 weeks	

Reporting group values	Treatment arm	Placebo arm	Total
Number of subjects	324	327	651
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	140	148	288
From 65-84 years	184	179	363
85 years and over	0	0	0
Age continuous Units: years			
median	64.5	63.3	
standard deviation	± 9.22	± 9.33	-
Gender categorical Units: Subjects			
Female	75	76	151
Male	249	251	500

Subject analysis sets

Subject analysis set title	Ranolazine Therapy
Subject analysis set type	Intention-to-treat
Subject analysis set description: IIT population who have taken IMP	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: IIT population who have taken placebo	

Reporting group values	Ranolazine Therapy	Placebo	
Number of subjects	302	299	

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)	132	137	
From 65-84 years	167	165	
85 years and over	0	0	
Age continuous			
Units: years			
median	64.6	63.1	
standard deviation	± 9.08	± 9.12	
Gender categorical			
Units: Subjects			
Female	68	70	
Male	234	229	

End points

End points reporting groups

Reporting group title	Treatment arm
Reporting group description: Ranolazine arm: ranolazine tablets 375 mg b.i.d for 2 weeks + ranolazine tablets 500 mg b.i.d for the next 2 weeks and finally ranolazine tablets 750 mg b.i.d for 24 weeks.	
Reporting group title	Placebo arm
Reporting group description: Placebo 1 tablet b.i.d. for 28 weeks	
Subject analysis set title	Ranolazine Therapy
Subject analysis set type	Intention-to-treat
Subject analysis set description: IIT population who have taken IMP	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: IIT population who have taken placebo	

Primary: Change in treadmill total exercise duration

End point title	Change in treadmill total exercise duration
End point description: The study aim was to demonstrate the effect of ranolazine in patients with CAD characterized by angina and limited exercise capacity on treadmill test (3-9 min on modified Bruce protocol).	
End point type	Primary
End point timeframe: 28 weeks of treatment (from V1 to V8)	

End point values	Treatment arm	Placebo arm	Ranolazine Therapy	Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	324	327	302	299
Units: seconds	324	327	302	299

Statistical analyses

Statistical analysis title	Ranolazine vs Placebo in the TED after 28 weeks
Statistical analysis description: change from baseline in the Total Exercise Duration (TED) with ranolazine or placebo in the two study groups.	
Comparison groups	Ranolazine Therapy v Placebo

Number of subjects included in analysis	601
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.008
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	29.601
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.734
upper limit	51.467
Variability estimate	Standard error of the mean
Dispersion value	11.134

Notes:

[1] - H0: $\mu \text{ ranolazine} - \mu \text{ placebo} \leq 0 \text{ [mL} \cdot \text{Kg}^{-1} \cdot \text{min}^{-1}]$
versus
H1: $\mu \text{ ranolazine} - \mu \text{ placebo} > 0 \text{ [mL} \cdot \text{Kg}^{-1} \cdot \text{min}^{-1}]$

The hypothesis are tested using the F test (two-way ANCOVA, with treatment and baseline values as covariates), using a two-sided alpha level of 5%.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from Visit 1 to V8 (from Informed Consent signed to final visit).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Treatment arm
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Reporting group description:

Ranolazine arm: ranolazine tablets 375 mg b.i.d for 2 weeks + ranolazine tablets 500 mg b.i.d for the next 2 weeks and finally ranolazine tablets 750 mg b.i.d for 24 weeks.

Reporting group title	Placebo arm
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Reporting group description:

Placebo 1 tablet b.i.d. for 28 weeks

Serious adverse events	Treatment arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 324 (6.79%)	15 / 327 (4.59%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Vascular disorders			
Angina pectoris aggravated			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Arterial stenosis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Surgical and medical procedures			

Bypass surgery			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Percutaneous coronary intervention			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Thromboendarterectomy			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Chest pain non cardiac			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Concomitant disease aggravated			
subjects affected / exposed	2 / 324 (0.62%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	2 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Investigations			
Coronary angiograph			

subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Endoscopy			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Injury, poisoning and procedural complications			
Vertebral fracture			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences causally related to treatment / all	0 / 39	1 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Vertebral injury			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences causally related to treatment / all	0 / 39	1 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Angina pectoris			
subjects affected / exposed	2 / 324 (0.62%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	2 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Angina pectoris unstable			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences causally related to treatment / all	0 / 39	1 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Atrial fibrillation			
subjects affected / exposed	1 / 324 (0.31%)	4 / 327 (1.22%)	
occurrences causally related to treatment / all	1 / 39	4 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	

Cardiovascular disorder			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences causally related to treatment / all	0 / 39	1 / 20	
deaths causally related to treatment / all	0 / 0	1 / 2	
Left heart failure			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences causally related to treatment / all	0 / 39	1 / 20	
deaths causally related to treatment / all	0 / 0	1 / 2	
Non ST segment elevation myocardial infarction			
subjects affected / exposed	2 / 324 (0.62%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	2 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Paroxysmal atrial fibrillation			
subjects affected / exposed	2 / 324 (0.62%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	2 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Silent myocardial ischemia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Unstable angina			
subjects affected / exposed	3 / 324 (0.93%)	6 / 327 (1.83%)	
occurrences causally related to treatment / all	3 / 39	6 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Ventricular ectopic beats			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Ventricular tachycardia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Nervous system disorders			

Carotid artery stenosis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Middle cerebral artery stroke			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Syncope			
subjects affected / exposed	2 / 324 (0.62%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	2 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Transient ischemic attacks			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Vertigo			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences causally related to treatment / all	0 / 39	1 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Blood and lymphatic system disorders			
Anaemia aggravated			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Eye disorders			
Detached retina			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences causally related to treatment / all	0 / 39	1 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Gastrointestinal disorders			
Atrophic gastritis			

subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Epigastric pain			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hypersecretion gastric			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Reflux esophagitis			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Vomiting			
subjects affected / exposed	2 / 324 (0.62%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	2 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Musculoskeletal and connective tissue disorders			
Contusion of multiple site of trunk			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Infections and infestations			
Respiratory infection			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences causally related to treatment / all	0 / 39	1 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences causally related to treatment / all	1 / 39	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 2	

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

Non-serious adverse events	Treatment arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 324 (25.00%)	72 / 327 (22.02%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences (all)	200	135	
Blood pressure inadequately controlled			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences (all)	200	135	
hypertension aggravated			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences (all)	200	135	
Surgical and medical procedures			
Coronary angioplasty			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences (all)	200	135	
General disorders and administration site conditions			
General Body Pain			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences (all)	200	135	
Performance status decreased			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences (all)	200	135	
Sickness			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences (all)	200	135	
Oedema			
subjects affected / exposed	1 / 324 (0.31%)	1 / 327 (0.31%)	
occurrences (all)	200	135	

Asthenia subjects affected / exposed occurrences (all)	1 / 324 (0.31%) 200	0 / 327 (0.00%) 135	
Malaise subjects affected / exposed occurrences (all)	1 / 324 (0.31%) 200	0 / 327 (0.00%) 135	
Respiratory, thoracic and mediastinal disorders Dyspnea subjects affected / exposed occurrences (all)	1 / 324 (0.31%) 200	0 / 327 (0.00%) 135	
Increased shortness of breath subjects affected / exposed occurrences (all)	0 / 324 (0.00%) 200	1 / 327 (0.31%) 135	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 324 (0.62%) 200	0 / 327 (0.00%) 135	
Investigations Coronary Angiograph subjects affected / exposed occurrences (all)	2 / 324 (0.62%) 200	0 / 327 (0.00%) 135	
Weight increased subjects affected / exposed occurrences (all)	0 / 324 (0.00%) 200	1 / 327 (0.31%) 135	
Cardiac disorders Angina pectoris aggravated subjects affected / exposed occurrences (all)	2 / 324 (0.62%) 200	0 / 327 (0.00%) 135	
Atrial fibrillation paroxysmal subjects affected / exposed occurrences (all)	1 / 324 (0.31%) 200	0 / 327 (0.00%) 135	
Left bundle branch block subjects affected / exposed occurrences (all)	0 / 324 (0.00%) 200	1 / 327 (0.31%) 135	
Paroxysmal atrial fibrillation			

subjects affected / exposed occurrences (all)	1 / 324 (0.31%) 200	0 / 327 (0.00%) 135	
Tachycardia subjects affected / exposed occurrences (all)	1 / 324 (0.31%) 200	0 / 327 (0.00%) 135	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	2 / 324 (0.62%) 200	1 / 327 (0.31%) 135	
Headache subjects affected / exposed occurrences (all)	2 / 324 (0.62%) 200	2 / 327 (0.61%) 135	
Presyncope subjects affected / exposed occurrences (all)	1 / 324 (0.31%) 200	1 / 327 (0.31%) 135	
Parkinson's disease subjects affected / exposed occurrences (all)	2 / 324 (0.62%) 200	0 / 327 (0.00%) 135	
Ear and labyrinth disorders Hearing loss subjects affected / exposed occurrences (all)	0 / 324 (0.00%) 200	1 / 327 (0.31%) 135	
Otalgia subjects affected / exposed occurrences (all)	0 / 324 (0.00%) 200	1 / 327 (0.31%) 135	
Wax in ear subjects affected / exposed occurrences (all)	1 / 324 (0.31%) 200	0 / 327 (0.00%) 135	
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	0 / 324 (0.00%) 200	2 / 327 (0.61%) 135	
Cataract subjects affected / exposed occurrences (all)	1 / 324 (0.31%) 200	1 / 327 (0.31%) 135	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	4 / 324 (1.23%)	1 / 327 (0.31%)	
occurrences (all)	200	135	
Diarrhoea			
subjects affected / exposed	3 / 324 (0.93%)	1 / 327 (0.31%)	
occurrences (all)	200	135	
Gastrointestinal bleeding			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences (all)	200	135	
Inguinal hernia			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences (all)	200	135	
Nausea			
subjects affected / exposed	2 / 324 (0.62%)	3 / 327 (0.92%)	
occurrences (all)	200	135	
Obstipation			
subjects affected / exposed	3 / 324 (0.93%)	0 / 327 (0.00%)	
occurrences (all)	200	135	
Vomiting			
subjects affected / exposed	0 / 324 (0.00%)	1 / 327 (0.31%)	
occurrences (all)	200	135	
Odynophagia			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences (all)	200	135	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 324 (0.31%)	0 / 327 (0.00%)	
occurrences (all)	200	135	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 324 (0.31%)	2 / 327 (0.61%)	
occurrences (all)	200	135	
Erythema			
subjects affected / exposed	0 / 324 (0.00%)	2 / 327 (0.61%)	
occurrences (all)	200	135	
Exacerbation of psoriasis			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hair Loss</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 324 (0.00%)</p> <p>200</p> <p>0 / 324 (0.00%)</p> <p>200</p>	<p>1 / 327 (0.31%)</p> <p>135</p> <p>2 / 327 (0.61%)</p> <p>135</p>	
<p>Endocrine disorders</p> <p>Iodine hyperthyroidisms</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Secondary hyperthyroidism</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 324 (0.31%)</p> <p>200</p> <p>1 / 324 (0.31%)</p> <p>200</p>	<p>0 / 327 (0.00%)</p> <p>135</p> <p>0 / 327 (0.00%)</p> <p>135</p>	
<p>Musculoskeletal and connective tissue disorders</p> <p>Leg Pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Joint pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 324 (0.00%)</p> <p>200</p> <p>1 / 324 (0.31%)</p> <p>200</p>	<p>1 / 327 (0.31%)</p> <p>135</p> <p>0 / 327 (0.00%)</p> <p>135</p>	
<p>Infections and infestations</p> <p>Acute diverticulitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Acute gastroenteritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cold</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Flu</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>gastroenteritis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 324 (0.00%)</p> <p>200</p> <p>1 / 324 (0.31%)</p> <p>200</p> <p>1 / 324 (0.31%)</p> <p>200</p> <p>1 / 324 (0.31%)</p> <p>200</p> <p>1 / 324 (0.31%)</p> <p>200</p>	<p>1 / 327 (0.31%)</p> <p>135</p> <p>0 / 327 (0.00%)</p> <p>135</p> <p>0 / 327 (0.00%)</p> <p>135</p> <p>0 / 327 (0.00%)</p> <p>135</p> <p>0 / 327 (0.00%)</p> <p>135</p>	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2012	<ul style="list-style-type: none">- To better clarify the characteristics of patients to be included- To exclude inclusion of patients with already planned revascularization- To exclude inclusion of patients with implant of a pacemaker- To add in exclusion criteria the list of medication not permitted- To exclude patients who participated in other clinical trials in the previous three months before enrolment- To exclude patients who are prescribed and using off-label medications- To adapt paragraph of concomitant medications not permitted during the study according to the new updated version of SmPC (April 2012)
20 January 2014	<ul style="list-style-type: none">- Better clarify inclusion/exclusion criteria- How to notify new safety information- More details in paragraph "Methods"- More details in paragraph "Objective"- Changes in paragraph "Secondary Endpoint"

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 May 2015	<p>Menarini International Operations Luxembourg S.A. decided to early terminate the CAD study.</p> <p>Due to a higher than expected screening failure rate and to the clinical management changes driven by new guidelines with respect to these specific patients, although new Investigational Sites have been opened we have faced many difficulties in recruiting patients and only about half of the expected patients have been randomized.</p> <p>No safety or drug related reasons are related to the decision of study closure.</p>	-

Notes:

Limitations and caveats

None reported