Clinical trial results:
RANOLAZINE IN PATIENTS WITH SYMPTOMATIC HYPERTROPHIC CARDIOMYOPATHY: A PILOT STUDY ASSESSING THE EFFECTS ON EXERCISE CAPACITY, DIASTOLIC FUNCTION AND SYMPTOMATIC STATUS

Summary

EudraCT number	2011-004507-20
Trial protocol	ES DE IT
Global end of trial date	14 November 2014

Results information

Result version number	v1 (current)
This version publication date	25 May 2016
First version publication date	25 May 2016

Trial information

Trial identification

Sponsor protocol code	MEIN/11/RAN-HCM/001

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	Menarini International Operations Luxembourg S.A., Medical Scientific Management, +352 264976,
Scientific contact	Menarini Corporate Medical Department, Menarini Industrie Farmaceutiche Riunite, +39 055 56801,

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	12 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 November 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary study objective is to demonstrate the efficacy of ranolazine in improving the Exercise capacity in patients affected by symptomatic hypertrophic cardiomyopathy (SHCM) using the V02 peak technique

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 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: 13
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Italy: 53
Worldwide total number of subjects	80
EEA total number of subjects	80

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)	66
From 65 to 84 years	14

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Total recruitment period (first patient in to last patient in) : 02.07.2012-12.06.2014

Pre-assignment

Screening details:

Between 02 Jul 2012 and 12 Jun 2014, a total of 119 patients were screened for inclusion in the MEIN/11/RAN HCM/001 study. These included 39 patients (32.8%) who failed screening and were not included in the study.

Period 1

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

Blinding implementation details:

Patients were blinded to the study drug they received. The blinding was assured by using matching placebo to guarantee the maintenance of double-blind conditions.
The ranolazine PR tablets and the matching placebo tablets were manufactured with the same shape and attributes (appearance, colour, etc.) in order to maintain the blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ranolazine 500/750/1000

Arm description:

Ranolazine PR (prolonged release) was administered at the initial dose of 500 mg/ bid.
After 7 days, the dose was up-titrated to 750 mg bid, if the drug was well tolerated (Visit 2). One further titration up to 1000 mg bid was performed after another 7 days (Visit 3), if the drug was well tolerated. If the up-titration to 750 mg or 1000 mg bid was not advisable, patients continued with 500 or 750 mg bid, respectively, throughout the remainder of the study.
After the titration phase (2 weeks, Visits 2 and 3) the treatment phase was composed of 3 visits (Visits 4, 5, and 6) at Week 4, Week 12 and Week 20 respectively,

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

Dosage and administration details:

Ranolazine was provided as prolonged release (PR) tablets to be taken orally and to be swallowed whole, without breaking, chewing, or crushing. Study drug was taken twice daily (bid), in the morning and in the evening, at approximately the same time each day, with a glass of water and with or without food.

Ranolazine PR was administered at the initial dose of 500 mg/ bid. After 7 days, the dose was up-titrated to 750 mg bid, if the drug was well tolerated (Visit 2). One further titration up to 1000 mg bid was performed after another 7 days (Visit 3), if the drug was well tolerated. If the up-titration to 750 mg or 1000 mg bid was not advisable, patients continued with 500 or 750 mg bid, respectively, throughout the remainder of the study.
Ranolazine was provided in 3 dosage strengths:

- 500 mg tablet
- 750 mg tablet
- 1000 mg tablet

Arm title	Placebo 500/750/1000

Arm description:

The matching placebo tablets (Placebo to Match, PTM) were provided in the same manner as 3 solid dosage film-coated, biconvex tablets. The 3 placebo tablets included:
- 500 mg tablet
- 750 mg tablet
- 1000 mg tablet

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

Dosage and administration details:

The matching placebo tablets (Placebo to Match, PTM) were provided in the same manner as 3 solid dosage film-coated, biconvex tablets. The 3 placebo tablets included:
- 500 mg tablet
- 750 mg tablet
- 1000 mg tablet

Placebo was provided as prolonged release (PR) tablets to be taken orally and swallowed whole, without breaking, chewing, or crushing. It was taken twice daily (bid), in the morning and in the evening, at approximately the same time each day, with a glass of water and with or without food.
It was administered at the initial dose of 500 mg/ bid. After 7 days, the dose was up-titrated to 750 mg bid, if it was well tolerated (Visit 2). One further titration up to 1000 mg bid was performed after another 7 days (Visit 3) if well tolerated

Number of subjects in period 1	Ranolazine 500/750/1000	Placebo 500/750/1000
Started	40	40
Completed	35	34
Not completed	5	6
Consent withdrawn by subject	3	-
Adverse event, non-fatal	-	2
non compliance with study drug	1	1
Investigator decision	1	1
Lost to follow-up	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Ranolazine 500/750/1000

Reporting group description:

Ranolazine PR (prolonged release) was administered at the initial dose of 500 mg/ bid.
After 7 days, the dose was up-titrated to 750 mg bid, if the drug was well tolerated (Visit 2). One further titration up to 1000 mg bid was performed after another 7 days (Visit 3), if the drug was well tolerated.
If the up-titration to 750 mg or 1000 mg bid was not advisable, patients continued with 500 or 750 mg bid, respectively, throughout the remainder of the study.
After the titration phase (2 weeks, Visits 2 and 3) the treatment phase was composed of 3 visits (Visits 4, 5, and 6) at Week 4, Week 12 and Week 20 respectively,

Reporting group title	Placebo 500/750/1000

Reporting group description:

The matching placebo tablets (Placebo to Match, PTM) were provided in the same manner as 3 solid dosage film-coated, biconvex tablets. The 3 placebo tablets included:

- 500 mg tablet
- 750 mg tablet
- 1000 mg tablet

Reporting group values	Ranolazine 500/750/1000	Placebo 500/750/1000	Total
Number of subjects	40	40	80
Age categorical Units: Subjects			
Adults (18-64 years)	32	34	66
From 65-84 years	8	6	14
Age continuous Units: years			
arithmetic mean	53.7	52.1	
standard deviation	± 13.92	± 13.46	-
Gender categorical Units: Subjects			
Female	16	18	34
Male	24	22	46

Subject analysis sets

Subject analysis set title	Ranolazine ITT/Safety population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) population included all randomized patients. Patients erroneously registered twice or more into the study were accounted for only once. Patients were analyzed according to the treatment assigned at the end of the randomization procedure. For patients registered twice or more the first assigned treatment was taken as reference.
The safety population included all randomized patients who received at least 1 dose of the study drugs. Patients were analysed according to the treatment actually received. In this particular study the safety population corresponds to the ITT population where this latter is considered the population that included all randomized patients.

Subject analysis set title	Ranolazine PP population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population consisted of the randomized patients who:
i) did not have major deviations from inclusion and exclusion criteria;

ii) received at least 80% and not more than 120% of the expected amount of the treatment assigned at the end of the randomization procedure;
iii) completed all the planned study visits and were evaluated for the primary endpoint of the study at the final visit.
Patients were analyzed according to the treatment they actually received.

Subject analysis set title	Placebo ITT/Safety population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) population included all randomized patients. Patients erroneously registered twice or more into the study were accounted for only once. Patients were analyzed according to the treatment assigned at the end of the randomization procedure. For patients registered twice or more the first assigned treatment was taken as reference.
The safety population included all randomized patients who received at least 1 dose of the study drugs.
Patients were analysed according to the treatment actually received

Subject analysis set title	Placebo PP population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population consisted of the randomized patients who:
i) did not have major deviations from inclusion and exclusion criteria;
ii) received at least 80% and not more than 120% of the expected amount of the treatment assigned at the end of the randomization procedure;
iii) completed all the planned study visits and were evaluated for the primary endpoint of the study at the final visit.
Patients were analyzed according to the treatment they actually received.

Reporting group values	Ranolazine ITT/Safety population	Ranolazine PP population	Placebo ITT/Safety population
Number of subjects	40	31	40
Age categorical Units: Subjects			
Adults (18-64 years)	32	25	34
From 65-84 years	8	6	6
Age continuous Units: years			
arithmetic mean	53.7	53.8	52.1
standard deviation	± 13.92	± 14.65	± 13.46
Gender categorical Units: Subjects			
Female	16	12	18
Male	24	19	22

Reporting group values	Placebo PP population		
Number of subjects	29		
Age categorical Units: Subjects			
Adults (18-64 years)	25		
From 65-84 years	4		
Age continuous Units: years			
arithmetic mean	51.3		
standard deviation	± 13.48		
Gender categorical Units: Subjects			
Female	14		
Male	15		

End points

End points reporting groups

Reporting group title	Ranolazine 500/750/1000

Reporting group description:

Ranolazine PR (prolonged release) was administered at the initial dose of 500 mg/ bid.
After 7 days, the dose was up-titrated to 750 mg bid, if the drug was well tolerated (Visit 2). One further titration up to 1000 mg bid was performed after another 7 days (Visit 3), if the drug was well tolerated.
If the up-titration to 750 mg or 1000 mg bid was not advisable, patients continued with 500 or 750 mg bid, respectively, throughout the remainder of the study.
After the titration phase (2 weeks, Visits 2 and 3) the treatment phase was composed of 3 visits (Visits 4, 5, and 6) at Week 4, Week 12 and Week 20 respectively,

Reporting group title	Placebo 500/750/1000

Reporting group description:

The matching placebo tablets (Placebo to Match, PTM) were provided in the same manner as 3 solid dosage film-coated, biconvex tablets. The 3 placebo tablets included:

- 500 mg tablet
- 750 mg tablet
- 1000 mg tablet

Subject analysis set title	Ranolazine ITT/Safety population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) population included all randomized patients. Patients erroneously registered twice or more into the study were accounted for only once. Patients were analyzed according to the treatment assigned at the end of the randomization procedure. For patients registered twice or more the first assigned treatment was taken as reference.
The safety population included all randomized patients who received at least 1 dose of the study drugs. Patients were analysed according to the treatment actually received. In this particular study the safety population corresponds to the ITT population where this latter is considered the population that included all randomized patients.

Subject analysis set title	Ranolazine PP population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population consisted of the randomized patients who:
i) did not have major deviations from inclusion and exclusion criteria;
ii) received at least 80% and not more than 120% of the expected amount of the treatment assigned at the end of the randomization procedure;
iii) completed all the planned study visits and were evaluated for the primary endpoint of the study at the final visit.
Patients were analyzed according to the treatment they actually received.

Subject analysis set title	Placebo ITT/Safety population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intention-to-treat (ITT) population included all randomized patients. Patients erroneously registered twice or more into the study were accounted for only once. Patients were analyzed according to the treatment assigned at the end of the randomization procedure. For patients registered twice or more the first assigned treatment was taken as reference.
The safety population included all randomized patients who received at least 1 dose of the study drugs. Patients were analysed according to the treatment actually received

Subject analysis set title	Placebo PP population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population consisted of the randomized patients who:
i) did not have major deviations from inclusion and exclusion criteria;
ii) received at least 80% and not more than 120% of the expected amount of the treatment assigned at the end of the randomization procedure;
iii) completed all the planned study visits and were evaluated for the primary endpoint of the study at the final visit.
Patients were analyzed according to the treatment they actually received.

Primary: Change of VO2 peak after 5 months of treatment

End point title	Change of VO2 peak after 5 months of treatment

End point description:

The primary efficacy assessment was VO2 peak evaluation using the cardiorespiratory test technique, after5 months at the maximum reached dosage of ranolazine, or placebo.

End point type	Primary

End point timeframe:

After 20 weeks of treatment (visit 6)

End point values	Ranolazine PP population	Placebo PP population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	29		
Units: mL/Kg/min				
arithmetic mean (standard deviation)	-0.35 (± 3.917)	0.01 (± 4.579)		

Statistical analyses

Statistical analysis title	Ranolazine vs Placebo

Statistical analysis description:

This was a superiority study: the treatment with ranolazine would be considered superior to placebo if the comparison between treatments at the end of the study obtained statistical significance in the analysis of covariance (ANCOVA)

Comparison groups	Ranolazine PP population v Placebo PP population
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.746
Method	ANCOVA

Notes:

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

Secondary: Change in E/E’ ratio (lateral)

End point title	Change in E/E’ ratio (lateral)

End point description:

Evaluation of E/E’ ratio (ratio between the early mitral valve flow velocity and the early diastolic lengthening velocities) changes with treatment using the tissue Doppler (TD) technique at the lateral annulus

End point type	Secondary

End point timeframe:

After 20 weeks of treatment (visit 6)

End point values	Ranolazine PP population	Placebo PP population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	29		
Units: ratio				
arithmetic mean (standard deviation)	-0.32 (± 3.571)	-0.78 (± 4.564)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in concentration of prohormone brain natriuretic peptide (proBNP)

End point title	Change in concentration of prohormone brain natriuretic peptide (proBNP)

End point description:

The change in proBNP concentration after 5 months of treatment with ranolazine or placebo was a secondary efficacy endpoint.

End point type	Secondary

End point timeframe:

After 20 weeks of treatment (visit 6)

End point values	Ranolazine PP population	Placebo PP population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	29		
Units: pg/mL				
arithmetic mean (standard deviation)	-241.3 (± 1233.9)	-20.5 (± 515.26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MLWHFQ total score

End point title	Change in MLWHFQ total score

End point description:

The change in symptomatic status evaluation as determined with the Minnesota Living With Heart Failure Questionnaire (MLWHFQ) after 5 months of treatment with ranolazine or placebo was a secondary endpoint.

End point type	Secondary

End point timeframe:

After 20 weeks of treatment (visit 6)

End point values	Ranolazine PP population	Placebo PP population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	29		
Units: number				
arithmetic mean (standard deviation)	-8.71 (± 15.231)	6.63 (± 14.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in E/E’ ratio (septal)

End point title	Change in E/E’ ratio (septal)

End point description:

Evaluation of E/E’ ratio (ratio between the early mitral valve flow velocity and the early diastolic lengthening velocities) changes with treatment using the tissue Doppler (TD) technique at the septal annulus

End point type	Secondary

End point timeframe:

After 20 weeks of treatment (visit 6)

End point values	Ranolazine PP population	Placebo PP population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	31	29		
Units: ratio				
arithmetic mean (standard deviation)	-0.5 (± 3.271)	-1.54 (± 5.888)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety measurements are recorded at each visit from Visit 2 (-7 days) to Visit 6 (20 weeks; end of study) during the treatment phase

Adverse event reporting additional description:

At each visit the investigator assessed any occurring subjective or objective AE. Adverse events communicated by the patient or by the patient's relatives or delegates through phone calls, letters or e-mails were also recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Ranolazine 500/750/1000

Reporting group description:

Ranolazine PR (prolonged release) was administered at the initial dose of 500 mg/ bid.
After 7 days, the dose was up-titrated to 750 mg bid, if the drug was well tolerated (Visit 2). One further titration up to 1000 mg bid was performed after another 7 days (Visit 3), if the drug was well tolerated.
If the up-titration to 750 mg or 1000 mg bid was not advisable, patients continued with 500 or 750 mg bid, respectively, throughout the remainder of the study.
After the titration phase (2 weeks, Visits 2 and 3) the treatment phase was composed of 3 visits (Visits 4, 5, and 6) at Week 4, Week 12 and Week 20 respectively,

Reporting group title	Placebo 500/750/1000

Reporting group description:

The matching placebo tablets were provided in the same manner as 3 solid dosage film-coated, biconvex tablets. The 3 placebo tablets included:

- 500 mg tablet
- 750 mg tablet
- 1000 mg tablet

Serious adverse events	Ranolazine 500/750/1000	Placebo 500/750/1000	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 40 (10.00%)	5 / 40 (12.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Intraocular pressure test			

subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoperfusion			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Glaucoma surgery			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			

subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (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: 5 %

Non-serious adverse events	Ranolazine 500/750/1000	Placebo 500/750/1000	
Total subjects affected by non-serious adverse events subjects affected / exposed	27 / 40 (67.50%)	30 / 40 (75.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 40 (2.50%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Hypotension			
subjects affected / exposed	3 / 40 (7.50%)	1 / 40 (2.50%)	
occurrences (all)	3	1	
Orthostatic hypotension			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Cardiac failure chronic			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 40 (2.50%)	1 / 40 (2.50%)	
occurrences (all)	1	1	
Ventricular extrasystoles			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 40 (7.50%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	5 / 40 (12.50%)	0 / 40 (0.00%)	
occurrences (all)	5	0	
Nausea			
subjects affected / exposed	2 / 40 (5.00%)	3 / 40 (7.50%)	
occurrences (all)	4	3	
Vomiting			
subjects affected / exposed	4 / 40 (10.00%)	1 / 40 (2.50%)	
occurrences (all)	4	1	
Diarrhoea			
subjects affected / exposed	2 / 40 (5.00%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 40 (2.50%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 40 (10.00%)	0 / 40 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 40 (2.50%)	3 / 40 (7.50%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 40 (2.50%)	3 / 40 (7.50%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2011	This protocol amendment was implemented to provide contact details for the study pharmacovigilance representative at the CRO, and to add the name of the Study Medical Expert to the Investigator's Approval page. In addition, typographical errors were corrected, including an incorrect mathematical symbol in the description of the null hypothesis.
13 January 2012	This protocol amendment was implemented in order to implement changes requested by Ethics Committees and Health Authorities during the approval phase, and to increase compliance with the SmPC. Changes were made to the eligibility criteria, including exclusion of patients using CYP3A4 inducers and patients who were hypersensitive to ranolazine (or its excipients), modification of the definition of alcoholism, and introduction of mandatory GFR calculation as part of the assessment of renal impairment. The parameters to be assessed during clinical laboratory assessment were clarified. Prohibition of grapefruit juice and CYP3A4 inducers was added due to their capacity to affect ranolazine metabolism. The severity of newly developed renal sufficiency requiring dose reduction was changed from mild severe to mild-moderate. The description of adverse reactions was updated to reflect the description provided in the updated SmPC. Verification of eligibility criteria (including laboratory tests) within 3 days of screening was introduced prior to provision of the patients' drug supply. The description of the efficacy variables was clarified to indicate that efficacy variables should be assessed at the maximum dosage reached. The description of the Modified Bruce exercise treadmill test protocol was amended to clarify that testing was to be carried out by suitably qualified individuals with training in basic life support, and with the requirement of a written emergency plan. In addition, changes were made to reflect changes in the study team, to clarify text and correct typographical errors.
12 March 2012	This protocol amendment was implemented following the availability of new data on ranolazine drug interactions, and to change the cardiopulmonary assessment from a treadmill test to a cycle ergometer. In addition, the title of the study was modified to include the "RESTYLE-HCM" name. Based on recent data showing that ranolazine can increase plasma concentrations of metformin by 1.8-fold, a maximum daily dose of 1000 mg metformin was introduced. In addition, the dose of simvastatin was limited to 20 mg once daily, due to the involvement of CYP3A4 in its metabolism. Eligibility criteria were modified accordingly. The description of the procedure for unblinding was clarified. The schedule of events was modified to clarify that physical examinations, ECGs, and assessments of E/E' ratio and pro-BNP were to take place before the VO2 peak evaluation, and to add recording of concomitant diseases and medications to Visits 2 and 3. The cardiopulmonary test to be employed was changed from the Treadmill test (Bruce modified) to the Cyclo ergometer test, based on the majority of study sites being more familiar with this test; both techniques were considered to be equally appropriate and comparable with regard to the determination of VO2 peak. In addition, changes were made to clarify text and correct typographical errors.

03 December 2013	This PA was implemented in order to add details to text describing certain evaluations (Holter ECG monitoring, pro-BNP analysis, etc), to extend the enrolment period further, to update the protocol according to the updated ranolazine SmPC, and to describe administrative changes. The enrolment period was increased from 18 months to 24 months. Clarification was made in the exclusion criteria that QTc would be calculated according to the Bazets method (...). A central review was introduced for ECG parameters (...), whilst clarifying that local evaluations should also be maintained. Details were provided on the data to be collected during the cardiopulmonary exercise test and VO2 peak evaluation. The definition of SAE was amended to include medically important conditions, and clarification was made that hospitalizations planned at the time of obtaining informed consent would not be reported as SAEs. It was also clarified that assessments of expectedness of AEs were to be made based on the ranolazine SmPC rather than the IB, as the SmPC is updated more frequently. The definition of SUSAR was also updated to reflect the definition provided in CT3. Clarification was made that clinically significant abnormal laboratory findings were to be considered as AEs. In addition, the text describing SAE reporting and AE management was updated. Descriptions of 24-h Holter ECG monitoring and proBNP evaluation were added (...). (...)Text describing AR was updated according to the most recent version of the ranolazine SmPC. (...) In addition, atorvastatin was added to the list of drugs metabolised by CYP3A4 that could undergo a dose reduction when co-administered with ranolazine. (...) Details of the study team were updated. (...) The appendices were updated with the most recent version of the Declaration of Helsinki, and with a list of CROs and Consultants involved in the study conduct. Changes were made to clarify text and correct typographical errors.

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.

No limitations or caveats are applicable to this summary

Notes: