Clinical trial results:
Effect on Ranolazine in Heart Failure Patients with Preserved Ejection Fraction

Summary

EudraCT number	2011-000805-27
Trial protocol	GB ES IT
Global end of trial date	22 January 2014

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-Did/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	Donatella Bemporad, A. Menarini Farmaceutica Internazionale S.R.L., 0039 055 5680685, dbemporad@menarini.it
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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	22 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate that ranolazine treatment results in a placebo corrected improvement in the 6-minute walk test (6MWT) after 28 weeks of treatment

Protection of trial subjects:

This study has been carried out in compliance with the study protocol, the recommendations on biomedical research on human subjects of the declaration of Helsinki, International Conference of Harmonisation – Good Clinical Practice (ICH-GCP) Guidelines, EU-Directive 2001/20 of April 4, 2001, and national requirements of the participating countries.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 May 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: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	4
EEA total number of subjects	4

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)	0
From 65 to 84 years	4

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Due to the prematurely end of the trial it was conducted in 4 investigational study sites (2 sites in Italy, 1 in the United Kingdom and 1 in Spain).
First Patient First Visit: 30 May 2013
Early termination date: 22 January 2014
Phase 2 study

Pre-assignment

Screening details:

Screening visit (Visit 1, from day -7 to -1, +/- 3 days) patient eligibility was determined by inclusion/exclusion criteria.
Overall, 13 patients were screened. Eight patients did not meet the inclusion/exclusion criteria and were not eligible for randomization. Another patient withdrew the consent before the baseline visit (Visit 2).

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	Investigator, Monitor, Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Ranolazine

Arm description:

Ranolazine was administered at the initial dose of 500 mg BID. After 2 weeks, the dose was uptitrated to 750 mg BID in all patients (Visit 3). One further titration up to 1000 mg BID was to be performed after another 2 weeks (Visit 4), if the drug was well tolerated. If the up-titration to 750 mg or 1000 mg was not advisable because of safety or intolerability issues, patients had to continue with 500 or 750 mg, respectively, throughout the remain of the study.
Adjustments (down-titration) to the dose of study drug were to be made in case of conditions occurred during the study treatment period according to study protocol.

Arm type	Experimental
Investigational medicinal product name	Ranolazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Prolonged-release tablet
Routes of administration	Oral use

Dosage and administration details:

Titration of the study drug occurred according to the following schedule:
· Visit 2 (Day 1): 500 mg BID;
· Visit 3 (Week 2): 750 mg BID;
· Visit 4 (Week 4): 1000 mg BID.
If the up-titration to 750 mg or 1000 mg was not advisable because of safety or intolerability issues, patients had to continue with 500 or 750 mg, respectively, throughout the remain of the study.
Ranolazine was provided as a PR tablet to be taken orally and to be swallowed whole, without breaking, chewing, or crushing. Study drug was to be taken BID, in the morning and in the evening, at around the same time each day, with a glass of water and with or without food.

Arm title	Placebo

Arm description:

Matching placebo tablets were administered following the same route of Ranolazine with a virtual uptitration after 2 and 4 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:

Placebo was provided as a film-coated tablet to be taken orally and to be swallowed whole, without breaking, chewing, or crushing. Study drug was to be taken BID, in the morning and in the evening, at around the same time each day, with a glass of water and with or without food.

Number of subjects in period 1	Ranolazine	Placebo
Started	3	1
Completed	1	0
Not completed	2	1
Consent withdrawn by subject	1	-
Study Premature Ending	1	1

Baseline characteristics

End points

End points reporting groups

Reporting group title	Ranolazine

Reporting group description:

Ranolazine was administered at the initial dose of 500 mg BID. After 2 weeks, the dose was uptitrated to 750 mg BID in all patients (Visit 3). One further titration up to 1000 mg BID was to be performed after another 2 weeks (Visit 4), if the drug was well tolerated. If the up-titration to 750 mg or 1000 mg was not advisable because of safety or intolerability issues, patients had to continue with 500 or 750 mg, respectively, throughout the remain of the study.
Adjustments (down-titration) to the dose of study drug were to be made in case of conditions occurred during the study treatment period according to study protocol.

Reporting group title	Placebo

Reporting group description:

Matching placebo tablets were administered following the same route of Ranolazine with a virtual uptitration after 2 and 4 weeks.

Primary: six-minute walking test

End point title	six-minute walking test[1]

End point description:

The study plan included a screening phase (one week), a randomised titration phase (4 weeks) and a randomised treatment phase (24 weeks). There were 6 clinic visits: screening (Visit 1, Day -7 to -1), randomisation (Visit 2, Day 1), 2 study drug titration visits (Visit 3, Week 2 and Visit 4, Week 4), and 2 treatment visits (Visit 5, Week 16 and Visit 6, Week 28). Due to early termination of the study only one subject completed all planned visits.

End point type	Primary

End point timeframe:

The study plan included a randomised treatment phase of 24 weeks.

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: No statistical and descriptive analysis were made. Only one subject completed the study.

End point values	Ranolazine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: meter				
number (not applicable)				

Notes:

[2] - No statistical and descriptive analysis was made. Only one subject completed the study

[3] - No statistical and descriptive analysis was made. No subjects completed the study

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent at Visit -1 (from day -7 to -1 day before treatment) to two weeks after the administration of the last treatment dose (Visit 6, 28 weeks of treatment). Total timeframe for Adverse event reporting was of 31 weeks.

Adverse event reporting additional description:

Due to the premature closure of the study, data were not entered in a database and no coding of adverse events was performed. Therefore, the adverse events are reported as verbatim terms and narrative, without any coding as preferred term (PT) or system organ class (SOC).

Assessment type	Non-systematic

Dictionary used

Dictionary name	no dictionary
Dictionary version	NA

Reporting groups

Reporting group title	Ranolazine

Reporting group description:

Ranolazine was administered at the initial dose of 500 mg BID. After 2 weeks, the dose was uptitrated to 750 mg BID in all patients (Visit 3). One further titration up to 1000 mg BID was to be performed after another 2 weeks (Visit 4), if the drug was well tolerated. If the up-titration to 750 mg or 1000 mg was not advisable because of safety or intolerability issues, patients had to continue with 500 or 750 mg, respectively, throughout the remainder of the study.
Adjustments (down-titration) to the dose of study drug were to be made in case of conditions occurred during the study treatment period according to study protocol.

Reporting group title	Placebo

Reporting group description:

Matching placebo tablets were administered following the same route of Ranolazine with a virtual uptitration after 2 and 4 weeks.

Serious adverse events	Ranolazine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrioventricular dissociation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ranolazine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	1 / 1 (100.00%)	
Investigations			
Laboratory test abnormal			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Somnolence			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Gastric disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Rash			
subjects affected / exposed	0 / 3 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	0 / 3 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2013	Current amended protocol updated to incorporate all of the previous country specific changes into one global Protocol. The following were the main changes: * Section 16.2a included to incorporate the UK specific Informed consent in the Global Protocol. * Updated version of the Declaration Helsinki (2008) included. * Protocol amended to safely facilitate the enrollment of patients through the following changes : ** Inclusion criteria #2c and 2d combined to state that patients would qualify for inclusion if evidence of LV diastolic dysfunction or increased LV filling pressure were verified at screening by at least one of the following criteria: • NT-ProBNP> 200 pg/ml measured at the central laboratory • BNP> 80 pg/ml measured at the investigational site's local laboratory • Evidence of LV diastolic dysfunction or increased LV filling pressure in the last month (defined by at least one of the criteria listed further in the protocol) ** Exclusion criteria #6 adjusted allowing enrollment of patients with BMI > 35 kg/m2. ** Exclusion criteria #10 changed to reduce the time prior to screening that patients must have been on a stable cardiovascular medication from 4 weeks to 2 weeks. ** Screening period extended from 7 days to 14 days to allow more time for the completion of screening assessments. The 3-day window around Visit 1 has been removed. * Texts updated to clarify that no additional inclusion or exclusion criteria analysis will be performed at the Randomization visit (Visit 2). * Total duration of the study updated. * Allow dose reduction to 500 mg in case of intolerability of 750-mg dose. * Introduction of contraceptive methods in women of childbearing potential as enrollment criterion based on new reproductive toxicity information. * Record retention updated * Editorial changes made throughout the document to correct or clarify previously presented information for consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 January 2014	Due to unexpected difficulties in the screening activities, particularly with regard to very specific and unusual characterization requirements of Heart Failure patients with Preserved Ejection Fraction (the "HFpEF"), only four (4) patients were randomized to the assigned treatment by the end of November 2013. This delay of approximately two years, as compared to the original timelines, would have had significant consequences both in terms of the study feasibility and of its expected scientific value. For the above reasons, the study sponsor decided to stop enrolling patients and to terminate the study. The decision to prematurely terminate the study was not taken due to any safety or drug-related reasons.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No reliable conclusions on efficacy and safety can be made due to the premature study interruption. 4 patients (3 Ranolazine, 1 Placebo) were treated, only one completed the study. Averse Drug Reactions were in line with the profile of Ranolazine.

Notes: