Clinical trial results:
Effect of ivabradine versus placebo on cardiac function, exercise capacity, and neuroendocrine activation in patients with Chronic Heart Failure with Preserved left ventricular Ejection Fraction
An 8-month, randomised double-blind, placebo controlled, international, multicentre study.

Summary

EudraCT number	2012-002742-20
Trial protocol	HU PT IT DE BE GB NL ES CZ AT SI
Global end of trial date	29 February 2016

Results information

Result version number	v1 (current)
This version publication date	04 March 2017
First version publication date	04 March 2017

Trial information

Trial identification

Sponsor protocol code	CL2-16257-101

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50, rue Carnot, Suresnes, France, 92284
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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	29 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 February 2016
Global end of trial reached?	Yes
Global end of trial date	29 February 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of ivabradine compared to placebo on the cardiac function, the exercise capacity and the neuroendocrine activation in patients with chronic heart failure over an 8-month treatment period.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 18

Country: Number of subjects enrolled	Hungary: 20
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 7
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United Kingdom: 14
Worldwide total number of subjects	179
EEA total number of subjects	116

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)	34
From 65 to 84 years	136
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

The number of patients included was substantially less (45%) than the 400 proposed in the protocol because of the difficulties in meeting the strict selection criteria designed to ensure to select an appropriate HFPEF population.

Pre-assignment

Screening details:

Patients were men or women aged at least 50 years with Chronic HF and preserved Ejection Fraction (HF-PEF) and HR ≥ 70 bpm.

Period 1

Period 1 title	double-blind treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivabradine

Arm description:

Ivabradine 2.5 mg, 5 mg or 7.5 mg: oral administration twice daily (b.i.d.) of one tablet during meals.

Arm type	Experimental
Investigational medicinal product name	Ivabradine
Investigational medicinal product code	S 16257
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ivabradine tablets were administered twice daily (morning and evening) during meals with a starting dose of 5 mg twice daily.
The dose of ivabradine could be titrated depending on the patient's ECG resting HR and tolerability to a lower dose (2.5 mg) or a higher dose (7.5 mg b.i.d. then 10 mg b.i.d. before Amendment No. 8). This could be done at any visit and multiple titrations were permitted.

Arm title	Matching placebo

Arm description:

Matching placebo: oral administration twice daily (b.i.d.) of one tablet during meals.

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

Dosage and administration details:

Matching placebo tablets were administered twice daily (morning and evening) during meals with a starting dose of 5 mg twice daily.
The dose of placebo could be titrated depending on the patient's ECG resting HR and tolerability to a lower dose (2.5 mg) or a higher dose (7.5 mg b.i.d. then 10 mg b.i.d. before Amendment No. 8). This could be done at any visit and multiple titrations were permitted.

Number of subjects in period 1	Ivabradine	Matching placebo
Started	95	84
Completed	76	77
Not completed	19	7
Adverse event, serious fatal	3	-
Non medical reason	6	2
Adverse event, non-fatal	8	5
Other reason	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Ivabradine
Reporting group description:	
Ivabradine 2.5 mg, 5 mg or 7.5 mg: oral administration twice daily (b.i.d.) of one tablet during meals.	
Reporting group title	Matching placebo
Reporting group description:	
Matching placebo: oral administration twice daily (b.i.d.) of one tablet during meals.	

Reporting group values	Ivabradine	Matching placebo	Total
Number of subjects	95	84	179
Age categorical Units: Subjects			
Adults (18-64 years)	18	16	34
From 65-84 years	70	66	136
85 years and over	7	2	9
Age continuous Units: years			
arithmetic mean	71.4	71.8	
standard deviation	± 8.6	± 9.3	-
Gender categorical Units: Subjects			
Female	59	57	116
Male	36	27	63

Subject analysis sets	
Subject analysis set title	Randomized Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients to whom a therapeutic unit was randomly assigned	

Reporting group values	Randomized Set		
Number of subjects	179		
Age categorical Units: Subjects			
Adults (18-64 years)	34		
From 65-84 years	136		
85 years and over	9		
Age continuous Units: years			
arithmetic mean	71.6		
standard deviation	± 8.9		
Gender categorical Units: Subjects			
Female	116		
Male	63		

End points

End points reporting groups

Reporting group title	Ivabradine
Reporting group description:	
Ivabradine 2.5 mg, 5 mg or 7.5 mg: oral administration twice daily (b.i.d.) of one tablet during meals.	
Reporting group title	Matching placebo
Reporting group description:	
Matching placebo: oral administration twice daily (b.i.d.) of one tablet during meals.	
Subject analysis set title	Randomized Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients to whom a therapeutic unit was randomly assigned	

Primary: E/e' – Change from baseline to last post-baseline

End point title	E/e' – Change from baseline to last post-baseline
End point description:	
Co-primary endpoint: (E= early diastolic mitral flow velocity, e'= mean of mitral annular lateral and septal proto diastolic velocities) an estimate of LV filling pressures based on Echo-Doppler measures.	
End point type	Primary
End point timeframe:	
A comprehensive transthoracic echocardiography was performed at the ASSE, M2 and M8 visits. The E/e' ratio was described in terms of value at baseline, last post-baseline value and change from baseline to last post-baseline value	

End point values	Ivabradine	Matching placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	83		
Units: no unit				
arithmetic mean (standard deviation)	0.9 (± 3.8)	-0.9 (± 6.4)		

Statistical analyses

Statistical analysis title	Ivabradine versus placebo effect
Comparison groups	Ivabradine v Matching placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.135 [1]
Method	Ancova adj. on geogra. area and baseline
Parameter estimate	Arithmetic group means (final values)
Point estimate	1.37

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.25
upper limit	2.49
Variability estimate	Standard error of the mean
Dispersion value	0.68

Notes:

[1] - Adjusted p-value for Hommel procedure (to be compared to 0.10).

Primary: Total distance in 6MWT – Change from baseline to last post-baseline

End point title	Total distance in 6MWT – Change from baseline to last post-baseline

End point description:

Co-primary endpoint.

End point type	Primary

End point timeframe:

The total distance walked in 6 minutes was performed at ASSE, D000, M002, M004 and M008. The 6MWT was described in terms of value at baseline, last post baseline value and change from baseline to last post-baseline value.

End point values	Ivabradine	Matching placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	84		
Units: meter				
arithmetic mean (standard deviation)	4.3 (± 50)	7.9 (± 67.9)		

Statistical analyses

Statistical analysis title	Ivabradine versus placebo effect
Comparison groups	Ivabradine v Matching placebo
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.882 [2]
Method	Ancova adj. on geogra. area and baseline
Parameter estimate	Arithmetic group means (final values)
Point estimate	-3.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	-19.14
upper limit	11.64
Variability estimate	Standard error of the mean
Dispersion value	9.3

Notes:

[2] - Adjusted p-value for Hommel procedure (to be compared to 0.10).

Primary: NT-proBNP – Change from baseline to last post-baseline

End point title	NT-proBNP – Change from baseline to last post-baseline

End point description:

Co-primary endpoint: Plasma concentration of N Terminal-pro Beta type Natriuretic Peptide centrally measured using blood samples.

End point type	Primary

End point timeframe:

NT-proBNP samples collected at D000 (baseline value), M002, M004 and M008. Log-transformation of mean values at baseline and last post-baseline value; change calculated as ratio of baseline value to post-baseline value.

End point values	Ivabradine	Matching placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	82		
Units: pg/mL				
geometric mean (inter-quartile range (Q1-Q3))	1.1 (0.8 to 1.5)	1.1 (0.8 to 1.4)		

Statistical analyses

Statistical analysis title	Ivabradine versus placebo effect
Comparison groups	Ivabradine v Matching placebo
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.882 [3]
Method	Ancova adj. on geogra. area and baseline
Parameter estimate	Geometric group means (final values)
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.86
upper limit	1.19

Notes:

[3] - Adjusted p-value for Hommel procedure (to be compared to 0.10).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Emergent adverse events on treatment were defined as all adverse events that occurred or worsened (in terms of intensity) or became serious between the first IMP intake date and the last IMP intake date +2 days (both included)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Ivabradine

Reporting group description: -

Serious adverse events	Placebo	Ivabradine	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 84 (25.00%)	33 / 94 (35.11%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 84 (1.19%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 84 (1.19%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 84 (2.38%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
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 pulmonary oedema			

subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 84 (1.19%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 84 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	5 / 84 (5.95%)	5 / 94 (5.32%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 84 (1.19%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	5 / 84 (5.95%)	6 / 94 (6.38%)	
occurrences causally related to treatment / all	0 / 5	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			

subjects affected / exposed	1 / 84 (1.19%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 84 (1.19%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 84 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid valve incompetence			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			

subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Barrett's oesophagus			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 84 (2.38%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 84 (1.19%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lymph node tuberculosis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory tract infection			
subjects affected / exposed	1 / 84 (1.19%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 84 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Ivabradine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 84 (60.71%)	57 / 94 (60.64%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	0 / 84 (0.00%)	2 / 94 (2.13%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 84 (8.33%)	11 / 94 (11.70%)	
occurrences (all)	7	11	
Hypotension			
subjects affected / exposed	1 / 84 (1.19%)	2 / 94 (2.13%)	
occurrences (all)	1	2	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	2 / 84 (2.38%)	1 / 94 (1.06%)	
occurrences (all)	2	1	
Oedema peripheral			
subjects affected / exposed	0 / 84 (0.00%)	4 / 94 (4.26%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 84 (1.19%)	3 / 94 (3.19%)	
occurrences (all)	1	4	
Investigations			
Blood pressure increased			
subjects affected / exposed	2 / 84 (2.38%)	1 / 94 (1.06%)	
occurrences (all)	2	1	
Heart rate decreased			
subjects affected / exposed	1 / 84 (1.19%)	5 / 94 (5.32%)	
occurrences (all)	1	5	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 84 (2.38%)	2 / 94 (2.13%)	
occurrences (all)	2	2	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 84 (3.57%)	2 / 94 (2.13%)	
occurrences (all)	4	2	
Atrioventricular block first degree			
subjects affected / exposed	1 / 84 (1.19%)	2 / 94 (2.13%)	
occurrences (all)	1	2	
Bradycardia			
subjects affected / exposed	2 / 84 (2.38%)	3 / 94 (3.19%)	
occurrences (all)	2	3	
Cardiac failure			
subjects affected / exposed	5 / 84 (5.95%)	2 / 94 (2.13%)	
occurrences (all)	5	2	
Sinus tachycardia			

subjects affected / exposed	2 / 84 (2.38%)	0 / 94 (0.00%)	
occurrences (all)	2	0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 84 (0.00%)	2 / 94 (2.13%)	
occurrences (all)	0	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 84 (7.14%)	2 / 94 (2.13%)	
occurrences (all)	7	2	
Headache			
subjects affected / exposed	2 / 84 (2.38%)	0 / 94 (0.00%)	
occurrences (all)	2	0	
Neuropathy peripheral			
subjects affected / exposed	0 / 84 (0.00%)	2 / 94 (2.13%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 84 (1.19%)	4 / 94 (4.26%)	
occurrences (all)	1	4	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 84 (2.38%)	0 / 94 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Photopsia			
subjects affected / exposed	0 / 84 (0.00%)	3 / 94 (3.19%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 84 (1.19%)	2 / 94 (2.13%)	
occurrences (all)	1	2	
Diarrhoea			
subjects affected / exposed	2 / 84 (2.38%)	1 / 94 (1.06%)	
occurrences (all)	2	1	
Dental caries			
subjects affected / exposed	0 / 84 (0.00%)	2 / 94 (2.13%)	
occurrences (all)	0	2	

Dyspepsia			
subjects affected / exposed	0 / 84 (0.00%)	2 / 94 (2.13%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	2 / 84 (2.38%)	0 / 94 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	2 / 84 (2.38%)	0 / 94 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 84 (2.38%)	1 / 94 (1.06%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 84 (1.19%)	2 / 94 (2.13%)	
occurrences (all)	1	2	
Muscle spasms			
subjects affected / exposed	4 / 84 (4.76%)	0 / 94 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 84 (2.38%)	0 / 94 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			
subjects affected / exposed	0 / 84 (0.00%)	3 / 94 (3.19%)	
occurrences (all)	0	3	
Lower respiratory tract infection			
subjects affected / exposed	3 / 84 (3.57%)	0 / 94 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	2 / 84 (2.38%)	1 / 94 (1.06%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 84 (0.00%)	2 / 94 (2.13%)	
occurrences (all)	0	2	
Hyperuricaemia			
subjects affected / exposed	0 / 84 (0.00%)	2 / 94 (2.13%)	
occurrences (all)	0	2	
Hyperkalaemia			
subjects affected / exposed	2 / 84 (2.38%)	2 / 94 (2.13%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2013	Amendment No. 6, was applicable in all countries. The main changes were as following: - Measurement of pulse rate before the 6MWT, immediately at the end of the test, and at 1 and 10 minutes after the test. - Addition of the ventricular-arterial coupling defined by the ratio Ea/Ees as secondary efficacy criterion. - Fasting conditions for blood sampling were not required. - A dose margin of diuretics within 4 weeks prior to selection was accepted. - Addition of large mitral calcifications and of aortic or mitral valvular surgery as non-selection criteria. - Rehabilitation program was accepted only if it was started at least 3 months prior to selection, and provided that the patients were under maintenance phase of rehabilitation at selection. - Clarification on the biomarkers analysis. - Addition of Slovenia as participating country. - Planification of the cardiac MRI sub-study in UK. - Slight modification of the cut-off of the NT-proBNP and BNP levels as inclusion criteria (NT-proBNP > 300 pg/mL or BNP > 100 pg/mL replaced by ≥ 300 pg/mL or ≥ 100 pg/mL respectively). - Addition of a check at inclusion that the patient was still able to perform the 6MWT. - Atrio-ventricular block of 3rd degree was considered as a contra-indication of the IMP and was consequently a withdrawal criterion. - Clarification of the process of echocardiography's review and of the instructions for echocardiography. - BioStorage Technologies were named responsible for the long-term storage of non genomic and genomic analyses.
31 March 2014	Amendment No. 7 was applicable in all countries. The main changes were as following: - Extension of the enrolment period. - Study completion update. - Possibility to perform the blood sampling at selection before any other investigations. - Decrease of the cut-off of the NT-proBNP and BNP levels (NT-proBNP ≥ 220 pg/mL or BNP ≥ 80 pg/mL) as inclusion criteria. - The NT-proBNP or BNP values could be checked at the selection visit if the results were available. - Decrease of the cut-off of the LVEF (≥ 45% and < 50%) as selection criterion. - Previous aortic surgery or intervention allowed if at least 1 year before selection. - Previous treatment with ivabradine allowed if stopped since at least 6 months before selection. - Possibility for patients to be re-enrolled in the study. - Decrease of the cut-off of creatinine clearance (> 15 and < 30 mL/min/1.73m²) at selection and inclusion. - Setting-up of a Data Monitoring Committee.
19 June 2014	Amendment No. 8, was applicable in all countries. The main changes were as following: - The highest 10 mg dose was removed from the study. - Korea and Taiwan were added as participating countries.

14 January 2015	Amendment No. 10, was applicable in all countries. The main changes were as following: - Intake of the grapefruit juice should be avoided. - Change of the method of calculation of the TEI index and removal of the IVCT criterion. - The 6MWT could be performed before the echocardiography in exceptional circumstances. - The samples for NT-proBNP and other biomarkers analyses were sent on a regular basis to the central laboratory CDL Pharma
04 May 2015	Amendment No. 12, was applicable in all countries. An interim analysis was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 August 2015	The recruitment period was extended for 8 months by Amendment 7, but further prolongation was abandoned.	-

Notes:

Limitations and caveats

None reported