Clinical trial results:
Long-term (3 years) ophthalmic safety and cardiac efficacy and safety of ivabradine administered orally at the therapeutic doses (2.5/5/7.5 mg b.i. d.) on top of anti-anginal background therapy, to patients with chronic stable angina pectoris.
An international, double-blind placebo controlled study.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2006-005475-17
Trial protocol	IE PT BE FI GB HU SE DE
Global end of trial date	12 February 2015

Results information

Result version number	v1 (current)
This version publication date	02 March 2016
First version publication date	02 March 2016

Trial information

Trial identification

Sponsor protocol code	CL3-16257-067

Additional study identifiers

ISRCTN number	ISRCTN99185656
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,
Public contact	ITP (Innovative Therapeutic Pole), Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com
Scientific contact	ITP (Innovative Therapeutic Pole), Institut de Recherches Internationales Servier, +33 1 55 72 43 66, clinicaltrials@servier.com

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 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2015
Global end of trial reached?	Yes
Global end of trial date	12 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To document the absence of retinal toxicity of ivabradine versus placebo in chronic stable angina patients after treatment cessation in the subset of patients with emergent bilateral relevant ERG abnormalities observed at 36 months under treatment. Consequently, the main endpoint of the study was a safety endpoint.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, 1964, as revised in Seoul 2008.

Mandatory withdrawal from the study if study drug not tolerated, prolonged loss of sinus rhythm, occurence of condition preventing the assessment of visual function or morphology , condition or treatment of the visual system which irreversibly reduced visual function beyond that reasonably attributable to age and/or established underlying condition such as diabetes, pregnancy.
Other criteria for premature withdrawal of the study: adverse event requiring discontinuation of study drug and/or administration of an unauthorized concomitant treatment.

Background therapy:

Standard anti-anginal therapies.

Evidence for comparator:

Not applicable

Actual start date of recruitment	29 April 2008
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	Portugal: 16
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Argentina: 28

Worldwide total number of subjects	97
EEA total number of subjects	51

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)	45
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study population was male or female with chronic stable angina pectoris, with reliable baseline electroretinogram and visual fields (static and kinetic), in stable condition regarding the angina symptoms and related treatments, in sinus rhythm and with a resting HR ≥ 60 bpm.

Period 1

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

Blinding implementation details:

Treatment randomisation and allocation centralized (interactive system response).
Study products of identical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ivabradine

Arm description: -

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

Dosage and administration details:

Starting dose of 5 mg twice daily or 2.5 mg twice daily (patients > 75 years and/or with concomitant treatment with moderate CYP3A4 inhibitors). During this period, highest dose was 7.5 mg twice daily and lowest dose 2.5 mg twice daily.

Arm title	Placebo

Arm description: -

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:

One placebo tablet (matching ivabradine tablet) twice daily.

Number of subjects in period 1	Ivabradine	Placebo
Started	50	47
Completed	39	37
Not completed	11	10
Adverse event, serious fatal	1	1
Consent withdrawn by subject	5	4
Adverse event, non-fatal	5	4
Lost to follow-up	-	1

Period 2	
Period 2 title	Run-out
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

All patients who completed the double blind treatment period (3-years) entered in the run-out period (2 months) during which they received placebo.

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:

One placebo tablet (matching ivabradine tablet) twice daily.

Arm title	Placebo

Arm description:

All patients who completed the double blind treatment period (3-years) entered in the run-out period (2 months) during which they received placebo.

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:

One placebo tablet (matching ivabradine tablet) twice daily.

Number of subjects in period 2	Placebo	Placebo
Started	39	37
Completed	39	37

Baseline characteristics

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

Reporting group values	Ivabradine	Placebo	Total
Number of subjects	50	47	97
Age categorical Units: Subjects			
Adults (18-64 years)	24	21	45
From 65-84 years	26	26	52
Age continuous Units: years			
arithmetic mean	63.4	63.6	
standard deviation	± 7.8	± 8.2	-
Gender categorical Units: Subjects			
Female	21	19	40
Male	29	28	57

End points

End points reporting groups

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

Reporting group description:

All patients who completed the double blind treatment period (3-years) entered in the run-out period (2 months) during which they received placebo.

Reporting group title	Placebo

Reporting group description:

All patients who completed the double blind treatment period (3-years) entered in the run-out period (2 months) during which they received placebo.

Subject analysis set title	Sub-Safety Ophthalmic Set
Subject analysis set type	Safety analysis

Subject analysis set description:

For the ophthalmic (OPH) safety analyses, a Safety Ophthalmic Set (SOS) was defined as all patients having received at least one dose of study drug and with at least one evaluation from at least one reliable OPH test (ERG, visual field ...) for each eye at baseline and at M36 (after 3-years of treatment) under treatment or at M38 (i.e. two months after treatment cessation). The SSOS was defined as all patients of the SOS with a bilateral relevant ERG abnormality at M36 under treatment on at least one of the four main ERG criteria (composite endpoint) and a reliable ERG test at M36 under treatment for each eye and at M38.

Primary: Bilateral relevant ERG abnormality

End point title	Bilateral relevant ERG abnormality

End point description:

Four main ERG criteria were defined as following:
Standard combined rod/cone response (3RC) a- and b-waves, amplitude.
-Standard combined rod/cone response (3RC) a- and b-waves, implicit time.
Single flash cone response (SFC) a- and b-waves, amplitude.
Single flash cone response (SFC) a- and b-waves, implicit time.

End point type	Primary

End point timeframe:

In patients with at least one bilateral relevant abnormality at M36 under treatment (SSOS, N = 5), presence (yes/no) of a bilateral relevant abnormality at M38 on at least one of the four main ERG criteria.

End point values	Ivabradine	Placebo	Sub-Safety Ophthalmic Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	2[1]	3[2]	5	
Units: number of patients	0	1	1	

Notes:

[1] - Both patients had a single ERG response affected at M36.

[2] - Each of these 3 patients had several ERG responses/components affected at M36.

Statistical analyses

Statistical analysis title	Primary composite safety endpoint

Statistical analysis description:

Estimate of the diffference between the two groups was given using 95% CI based on the Wilson score method .

Comparison groups	Ivabradine v Placebo
Number of subjects included in analysis	5
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Risk difference (RD)
Point estimate	-33.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-87.69
upper limit	52.87

Notes:

[3] - To estimate the difference between ivrabradine anbd placebo on an incidence rate (bilateral relevant ERG abnormality after treatment cessation at M36) using a non-parametric approach.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported all over the study. Adverse events reported over the 3-year double-blind treatment period in patients who received at least one dose of study drug are presented here as it was the only period when patients received ivabradine.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

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

Reporting group description: -

Serious adverse events	Ivabradine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 50 (42.00%)	19 / 47 (40.43%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial stromal sarcoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Gastric banding			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 50 (2.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 50 (0.00%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenomyosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 50 (2.00%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			

subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (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			
Alcohol poisoning			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Angina unstable			
subjects affected / exposed	2 / 50 (4.00%)	6 / 47 (12.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 50 (4.00%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 50 (0.00%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 50 (2.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
aortic valve stenosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			

subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sick sinus syndrome			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (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			
syncope			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
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 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
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			
Anaemia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
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	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			

subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
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			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 50 (2.00%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (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	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 50 (4.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 50 (2.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex encephalitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 50 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Septic shock			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (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			
Lactic acidosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 47 (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: 4 %

Non-serious adverse events	Ivabradine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 50 (80.00%)	37 / 47 (78.72%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 50 (12.00%)	9 / 47 (19.15%)	
occurrences (all)	7	10	
Hypotension			
subjects affected / exposed	2 / 50 (4.00%)	2 / 47 (4.26%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 50 (2.00%)	2 / 47 (4.26%)	
occurrences (all)	1	2	
Oedema peripheral			
subjects affected / exposed	3 / 50 (6.00%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Cough			
subjects affected / exposed	0 / 50 (0.00%)	2 / 47 (4.26%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 50 (2.00%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Depression			
subjects affected / exposed	0 / 50 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Insomnia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Investigations			
Heart rate decreased			
subjects affected / exposed	5 / 50 (10.00%)	2 / 47 (4.26%)	
occurrences (all)	5	2	
Blood pressure increased			
subjects affected / exposed	1 / 50 (2.00%)	2 / 47 (4.26%)	
occurrences (all)	2	4	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 50 (4.00%)	2 / 47 (4.26%)	
occurrences (all)	2	4	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	6 / 50 (12.00%)	6 / 47 (12.77%)	
occurrences (all)	6	7	
Atrial fibrillation			
subjects affected / exposed	1 / 50 (2.00%)	3 / 47 (6.38%)	
occurrences (all)	2	3	
Cardiac failure			

subjects affected / exposed	1 / 50 (2.00%)	2 / 47 (4.26%)	
occurrences (all)	1	3	
Palpitations			
subjects affected / exposed	0 / 50 (0.00%)	2 / 47 (4.26%)	
occurrences (all)	0	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 50 (8.00%)	3 / 47 (6.38%)	
occurrences (all)	5	3	
Headache			
subjects affected / exposed	1 / 50 (2.00%)	2 / 47 (4.26%)	
occurrences (all)	1	3	
Eye disorders			
Cataract			
subjects affected / exposed	6 / 50 (12.00%)	3 / 47 (6.38%)	
occurrences (all)	7	3	
Cataract nuclear			
subjects affected / exposed	3 / 50 (6.00%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Photopsia			
subjects affected / exposed	4 / 50 (8.00%)	2 / 47 (4.26%)	
occurrences (all)	4	2	
Conjunctivitis allergic			
subjects affected / exposed	0 / 50 (0.00%)	2 / 47 (4.26%)	
occurrences (all)	0	2	
Blepharitis			
subjects affected / exposed	2 / 50 (4.00%)	1 / 47 (2.13%)	
occurrences (all)	2	1	
Dry eye			
subjects affected / exposed	3 / 50 (6.00%)	1 / 47 (2.13%)	
occurrences (all)	3	2	
Eyelid disorder			
subjects affected / exposed	0 / 50 (0.00%)	2 / 47 (4.26%)	
occurrences (all)	0	2	
Gastrointestinal disorders			

Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 50 (4.00%)	1 / 47 (2.13%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	3 / 50 (6.00%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	0 / 50 (0.00%)	2 / 47 (4.26%)	
occurrences (all)	0	2	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 50 (0.00%)	4 / 47 (8.51%)	
occurrences (all)	0	4	
Myalgia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 47 (0.00%)	
occurrences (all)	3	0	
Arthralgia			
subjects affected / exposed	0 / 50 (0.00%)	2 / 47 (4.26%)	
occurrences (all)	0	2	
Musculoskeletal chest pain			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 50 (8.00%)	3 / 47 (6.38%)	
occurrences (all)	7	3	
Influenza			
subjects affected / exposed	3 / 50 (6.00%)	1 / 47 (2.13%)	
occurrences (all)	3	1	

Sinusitis			
subjects affected / exposed	1 / 50 (2.00%)	3 / 47 (6.38%)	
occurrences (all)	1	3	
Bronchitis			
subjects affected / exposed	2 / 50 (4.00%)	1 / 47 (2.13%)	
occurrences (all)	2	1	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 50 (2.00%)	2 / 47 (4.26%)	
occurrences (all)	1	3	
Upper respiratory tract infection			
subjects affected / exposed	0 / 50 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Urinary tract infection			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis			
subjects affected / exposed	2 / 50 (4.00%)	0 / 47 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 50 (4.00%)	2 / 47 (4.26%)	
occurrences (all)	2	2	
Dehydration			
subjects affected / exposed	1 / 50 (2.00%)	2 / 47 (4.26%)	
occurrences (all)	1	2	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 50 (2.00%)	2 / 47 (4.26%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2009	Extension of study completion date. Non-selection criteria: patients currently or having treated with not marketed (added) ivabradine. Time window between the last visit of double-blind treatment period and the visit of run-out period: 1 to 3 months allowed. Cyclosporine removed from unauthorised concomitant treatments.
23 December 2009	Extension of study completion date.
27 April 2012	Number of planned patients reduced from 300 to 100. Extension of study completion date.
10 September 2012	To comply with changes of the Summary of Products Characteristics for ivabradine product. Final threshold values for potential clinical concern related to the ERG responses were calculated taking in account the data of patients included in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported