Clinical trial results:
Effects of oral chronic administration of ivabradine (7.5 mg b.i.d.) in comparison to placebo (b.i.d.) on top of beta-blockers, on central aortic blood pressure. Randomised, cross-over, double-blind, multicentre, study over 10 weeks in patients with stable coronary artery disease and a resting heart rate equal or superior to 70 bpm, already treated with beta-blockers.

Summary

EudraCT number	2011-004779-35
Trial protocol	IE IT
Global end of trial date	13 May 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	CL2-16257-096

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
Public contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, 33 155724366, clinicaltrials@servier.com
Scientific contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, 33 155724366, 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	13 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2014
Global end of trial reached?	Yes
Global end of trial date	13 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of ivabradine on central aortic systolic blood pressure (CASBP) in comparison to placebo in patients with stable coronary artery disease (CAD), and a resting heart rate (HR) ≥ 70 bpm, treated by beta-blockers (BBs).

Protection of trial subjects:

Non-selection criteria:
-Pregnant women, breast-feeding or women of childbearing potential not using, oestro-progestative or progestative or intra-uterine contraception or subcutaneous contraceptive implant, or using oestro-progestative or progestative or intra-uterine contraception or subcutaneous contraceptive implant but who consider stopping it during the duration of the study
-History of central neuropathy and/or of symptomatic orthostatic hypotension of nonmedicamentous etiology
-Severe hypotension at the time of selection (blood pressure < 90 / 50 mmHg)
-Patient currently or previously treated with ivabradine within the last 3 months before selection visit
-Patient currently or previously treated with nebivolol within the last 3 months before selection visit
-Patients with recent (less than 3 months) MI or coronary revascularisation
-Patients with recent (less than 3 months) stroke or cerebral transient ischemic attack
-Patients scheduled for coronary revascularisation procedures
-Patients with transplanted heart
-Implanted pacemaker, implantable cardioverter defibrillator, cardiac resynchronisation therapy
-Valvular disease likely to require surgery within the coming year
-Permanent atrial fibrillation or flutter
-Sick sinus syndrome, sino-atrial block, congenital long QT, 2nd degree and complete atrio-ventricular block
-Patients with angina at rest and angina of class IV
-Clinical signs and/or symptoms of heart failure in NYHA class II or higher
-Hospitalisation for heart failure as primary diagnosis within the last 12 months
-Known carriers of hepatitis B surface antigen or human immunodeficiency virus antibodies or hepatitis C virus antibodies
-Known alcohol or drug abuse
-Patients requiring treatments which are not allowed during the study
-Known hypersensitivity or contra-indication to the administration of ivabradine
-Known hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Background therapy:

Beta-blockers at doses estimated appropriate by the investigators.

Evidence for comparator: -

Actual start date of recruitment	05 June 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	Ireland: 3
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	9
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Males and females (at least 30 years old) with medical history of CAD, with sinus rhythm, stable and appropriate treatment by beta blockers at the exception of nebivolol and carvedilol, with sinus rhythm and 12-lead ECG HR ≥ 70 bpm at selection and at inclusion visit, with normal fasting laboratory results and informed consent obtained.

Period 1

Period 1 title	Overall study (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/Placebo

Arm description:

- 3-week double-blind active treatment period P1: patients received Ivabradine
- 2-week wash-out period: patients received no study treatment
- 3-week double-blind active treatment period P2: patients received Placebo

Arm type	Test drug
Investigational medicinal product name	Ivabradine
Investigational medicinal product code	S16257
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

7.5 mg tablets twice a day at 12-hour intervals during meals, at breakfast and dinner, starting the next morning at breakfast after the visit.

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

Dosage and administration details:

Matched tablets twice a day during meals, at breakfast and at dinner, starting the next morning after the visit.

Arm title	Placebo/Ivabradine

Arm description:

- 3-week double-blind active treatment period P1: patients received Placebo
- 2-week wash-out period: patients received no study treatment
- 3-week double-blind active treatment period P2: patients received Ivabradine

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:

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Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

7.5 mg tablets twice a day at 12-hour intervals during meals, at breakfast and dinner, starting the next morning at breakfast after the visit.

Number of subjects in period 1	Ivabradine/Placebo	Placebo/Ivabradine
Started	6	8
Completed	6	6
Not completed	0	2
Adverse event, non-fatal	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ivabradine/Placebo
Reporting group description:	
- 3-week double-blind active treatment period P1: patients received Ivabradine - 2-week wash-out period: patients received no study treatment - 3-week double-blind active treatment period P2: patients received Placebo	
Reporting group title	Placebo/Ivabradine
Reporting group description:	
- 3-week double-blind active treatment period P1: patients received Placebo - 2-week wash-out period: patients received no study treatment - 3-week double-blind active treatment period P2: patients received Ivabradine	

Reporting group values	Ivabradine/Placebo	Placebo/Ivabradine	Total
Number of subjects	6	8	14
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	7	9
From 65-84 years	4	1	5
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	69	58.4	
standard deviation	± 7.8	± 5.9	-
Gender categorical Units: Subjects			
Female	1	1	2
Male	5	7	12

End points

End points reporting groups

Reporting group title	Ivabradine/Placebo
Reporting group description:	
- 3-week double-blind active treatment period P1: patients received Ivabradine - 2-week wash-out period: patients received no study treatment - 3-week double-blind active treatment period P2: patients received Placebo	
Reporting group title	Placebo/Ivabradine
Reporting group description:	
- 3-week double-blind active treatment period P1: patients received Placebo - 2-week wash-out period: patients received no study treatment - 3-week double-blind active treatment period P2: patients received Ivabradine	
Subject analysis set title	Ivabradine
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set (PPS) consisted of 9 patients	
Subject analysis set title	Placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
The Per Protocol Set (PPS) consisted of 9 patients	

Primary: CASBP-change from baseline over 3-week treatment period

End point title	CASBP-change from baseline over 3-week treatment period[1]
End point description:	
Change of central aortic systolic blood pressure from baseline.	
End point type	Primary
End point timeframe:	
Change from baseline over 3-week treatment period	
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: Due to recruitment issues, the study was prematurely stopped after 14 patients were included. Therefore only descriptive statistics will be performed.	

End point values	Ivabradine	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: mmHg				
arithmetic mean (standard deviation)	-3.3 (± 10.2)	1 (± 9.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AE occuring during treatment periods only.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17

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	0 / 12 (0.00%)	1 / 14 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Coronary artery restenosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	
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: 5 %

Non-serious adverse events	Ivabradine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)	2 / 14 (14.29%)	
Injury, poisoning and procedural complications			
Coronary artery restenosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Photopsia			
subjects affected / exposed	4 / 12 (33.33%)	0 / 14 (0.00%)	
occurrences (all)	4	0	
Retinal disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2012	This amendment will apply to the centers in FRANCE, IRELAND and ITALY: - Precision on CAD and Type II diabetes documentation. - Addition of carvedilol to not allowed previous beta-blocker treatment. Addition of substance-induced long QT as medical and therapeutic non-selection criterion. - Addition of carvedilol to not allowed previous beta-blocker treatments. - Addition of potassium-depleting diuretics as treatment to be used with precautions in patients receiving ivabradine and having long QT interval. Addition of carvedilol and marketed ivabradine to not allowed concomitant treatments. - Precision on tonometry methods (dominant arm) - Precision on blood pressure measurement (dominant arm) - Update the list of adverse events for wich specific information is requested and already collected.
26 March 2013	This amendment will apply to the centers in FRANCE, IRELAND and ITALY: The main changes are: - The removal of the type II diabetes selection criteria. - The change of the planned date of Last Visit Last Patient - The addition of a non-inclusion criterion related to the quality of applanation tonometry at inclusion visit.
03 July 2013	This amendment will apply to the centers in FRANCE, IRELAND and ITALY: The main changes are: - The addition of a new participating Country/Centre in Italy and the possibility to set-up a new centre, not yet identified, in France - The modification of titles of sponsor signatories - The measurement of skin capillary density only in patients from centres equipped with the adequate material - The addition of non-selection and non-inclusion criteria related to the type and to the stability of diabetes before selection.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 May 2014	The study was prematurely stopped due to recruitment issue.	-

Notes:

Limitations and caveats

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

The section NSAE presented EAEs on treatment and included SEAEs. The causality and seriousness of reported SAE can be ultimately upgraded by the sponsor. The sponsor took these decisions to be compliant with the existing ICH E3 Clinical Study Report;

Notes: