Clinical trial results:
Effects of ivabradine on vascular function in individuals at increased risk of developing cardiovascular disease and with impaired endothelial function
An international, multicentre, randomised, double-blind, placebo-controlled study over 12 weeks.

Summary

EudraCT number	2012-000215-89
Trial protocol	IT GB NL
Global end of trial date	18 April 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	CL2-16257-099

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 (I.R.I.S.)
Sponsor organisation address	50, rue Carnot, Suresnes, France, 92284
Public contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com
Scientific contact	Therapeutic Innovation Pole, Institut de Recherches Internationales Servier, +33 155 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	18 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 April 2014
Global end of trial reached?	Yes
Global end of trial date	18 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

-To demonstrate the beneficial effect of ivabradine compared with placebo on endothelial function as measured by flow mediated dilation (FMD) of the brachial artery at 12 weeks of treatment

Protection of trial subjects:

Before randomisation, a patient was to be withdrawn from the study when the investigator was aware that a selection/non-selection criterion or an inclusion/non-inclusion criterion was not verified.
The IMP was prematurely discontinued in the following circumstances:
-IMP not tolerated: occurrence of any suspected adverse reaction that caused the patient discomfort and led to interruption of usual activities or in the case of a suspected adverse reaction that was considered by the investigator as a safety issue. An example of such a situation could be the occurrence or persistence of symptomatic bradycardia while the lower IMP dose-regimen (ivabradine 5 mg bid or matching placebo) was administered.
-IMP no longer appropriate: occurrence of prolonged loss of sinus rhythm (for example persistent atrial fibrillation).
-IMP considered as contra-indicated: e.g. sick sinus syndrome or sino-atrial block.
-Need of treatment not allowed during the study: e.g. strong CYP3A4 inhibitor.
-Major protocol deviation which, in the opinion of the investigator, made it unsafe for the patient to continue to take the test drug and to stay in the study.
-Non-medical reason: e.g. patient’s personal decision to stop treatment, withdrawal of consent etc…
-Lost to follow-up: when the investigator had no news of the participant, he/she made every effort to contact him/her, to establish the reason for the discontinuation of treatment, and to suggest the participant came to an end-of-study visit. If all these attempts to contact the participant failed, the investigator was to declare the participant “lost to follow-up”. The investigator documented all these attempts in the corresponding medical file.

Background therapy:

The treatment received by the study participants should be optimal according to the investigator’s judgement and in accordance to guidelines

Evidence for comparator:

Placebo

Actual start date of recruitment	06 December 2013
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	Netherlands: 1

Country: Number of subjects enrolled	Germany: 3
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)	3
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

15 centres were "opened" and trained. Only 10 centres in DEU and NLD screened patients (total of 53 patients) 9 patients were selected (5 in DEU and 4 in NLD). A total of 4 patients were included and randomly assigned: 2 in the ivabradine group and 2 in the placebo group. No patient completed the study since it was terminated prematurely

Pre-assignment

Screening details:

Men or postmenopausal women aged 21-74 years, in sinus rhythm with resting HR superior or equal to 75 bpm, at increased risk of subsequent cardiovascular disease (documented by the presence of at least two cardiovascular risk factors such as diabetes, hypertension, smoking, hypercholesterolemia) and impaired FMD (<5.0%), signed an informed consent

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

Arm description: -

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

Dosage and administration details:

During the treatment period after randomisation, the IMP (double-blind ivabradine or matching placebo) was taken orally twice daily, at 12-hour intervals in the morning and in the evening, during meals. Three doses were used: 5 mg, 7.5 mg or 10 mg tablets ivabradine or matching placebo.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
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Dosage and administration details:

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Number of subjects in period 1	Ivabradine	Placebo
Started	2	2
Completed	2	2

Baseline characteristics

Reporting groups

Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	4	4	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	3	3	
From 65-84 years	1	1	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	2	2	
Male	2	2	

Subject analysis sets

Subject analysis set title	Randomised Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

No statistical analysis plan was written because of the small sample size.

Reporting group values	Randomised Set		
Number of subjects	4		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	3		
From 65-84 years	1		
85 years and over	0		

Gender categorical Units: Subjects			
Female	2		
Male	2		

End points

End points reporting groups

Reporting group title	Ivabradine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Randomised Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

No statistical analysis plan was written because of the small sample size.

Primary: No primary endpoint

End point title	No primary endpoint[1]

End point description:

The primary endpoint was the absolute percentage change in FMD of the brachial artery from baseline to 12 weeks for ivabradine compared with placebo. However, because of the premature study termination, no FMD was performed under or after treatment intake.

End point type	Primary

End point timeframe:

The primary endpoint was the absolute percentage change in FMD of the brachial artery from baseline to 12 weeks for ivabradine compared with placebo. However, because of the premature study termination, no FMD was performed under or after treatment intake

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: The primary endpoint was the absolute percentage change in FMD of the brachial artery from baseline to 12 weeks for ivabradine compared with placebo. However, because of the premature study termination, no FMD was performed under or after treatment intake.

End point values	Ivabradine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: not applicable				

Notes:

[2] - Because of the premature study termination, no FMD was performed under or after treatment intake.
[3] - Because of the premature study termination, no FMD was performed under or after treatment intake.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: the overall study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
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	0 / 2 (0.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Ivabradine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2014	Amendment No. 1, dated 28 February 2014, was applicable in all countries. It concerned mainly: The modification of the study selection criteria to allow the inclusion of patients with "minor and stable cardiovascular disease" (the HR requirement of ≥ 75 bpm was left unchanged). The minimal time between selection and inclusion visits is reduced from 12 to 6 days. The amendment did not require any changes to the patient information sheet or informed consent form.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 April 2014	Decision to prematurely terminate the study The study investigators were informed by letter (dated 07-Apr-2014) of the decision to end the study. At the end of March 2014, I.R.I.S., in agreement with the Scientific Board, took the decision to prematurely discontinue this study in view of the difficulties in the recruitment process and the strategic objectives for ivabradine.	-

Notes:

Limitations and caveats

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

At the end of March 2014, I.R.I.S., in agreement with the Scientific Board, took the decision to prematurely discontinue this study in view of the difficulties in the recruitment process and the strategic objectives for ivabradine.

Notes: