



Clinical trial results:

Effects of oral administration of ivabradine (7.5 mg bid) on post-ischaemic stunning induced by exercise stress in patients with coronary artery disease and exercise inducible ischaemia.

Summary

EudraCT number	2011-000783-98
Trial protocol	IT
Global end of trial date	13 August 2014

Results information

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

Trial information

Trial identification

Sponsor protocol code	CL2-16257-095
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Additional study identifiers

ISRCTN number	ISRCTN90566768
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	Innovation Therapeutic Pole, Institut de Recherches Internationales Servier, +33 155724366, clinicaltrials@servier.com
Scientific contact	Innovation Therapeutic 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 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 August 2014
Global end of trial reached?	Yes
Global end of trial date	13 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of Ivabradine on post-ischaemic stunning induced by exercise stress in patients with stable coronary artery disease and exercise-inducible ischaemia

Protection of trial subjects:

The study treatment could be prematurely discontinued if it was not tolerated, no longer appropriate or considered as contra-indicated.

For the sake of safety, only patients presenting with a positive exercise at moderate or high workload were selected in the study, thus patients with low-effort inducible ischemia were not included.

Background therapy:

Previous cardiovascular medication were maintained except previous anti-angina treatments. Short acting nitrates were authorized during the study.

Evidence for comparator:

Not applicable

Actual start date of recruitment	27 March 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	Italy: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	5

From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was carried out under the supervision of Prof. P.G. Camici in a unique centre at Istituto Scientifico Universitario San Raffaele, Milan, Italy

Pre-assignment

Screening details:

Study population was male and female patients with proven Coronary Artery Disease, Left Ventricular Ejection Fraction $\geq 40\%$, sinus rhythm, resting heart rate ≥ 70 bpm and exercise-inducible myocardial ischaemia at moderate to high workload and subsequent stunning. 26 patients were screened; 25 patients pre-selected and 15 patients were included.

Pre-assignment period milestones

Number of subjects started	26 ^[1]
Number of subjects completed	15

Pre-assignment subject non-completion reasons

Reason: Number of subjects	non compliance to selection criteria: 11
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 11 patients showed non-compliance to selection criteria

Period 1

Period 1 title	Ivabradine (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ivabradine
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Arm description:

ivabradine 7.5 mg

Arm type	test drug
Investigational medicinal product name	ivabradine 7.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet twice daily during meals

Number of subjects in period 1	ivabradine
Started	15
Completed	15

Baseline characteristics

Reporting groups

Reporting group title	Ivabradine
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Reporting group description: -

Reporting group values	Ivabradine	Total	
Number of subjects	15	15	
Age categorical			
Units: Subjects			
Adults (18-64 years)	5	5	
From 65-84 years	10	10	
Age continuous			
Units: years			
arithmetic mean	65.8		
standard deviation	± 7.4	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	15	15	

End points

End points reporting groups

Reporting group title	ivabradine
Reporting group description: ivabradine 7.5 mg	
Subject analysis set title	Included Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: All included patients	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All included patients having received at least one study drug intake and having a strain value at baseline and at W2 visit, at each time point (at rest, at peak and at 3 minutes of recovery) for at least one segment showing exercise-inducible myocardial stunning at baseline.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All included patients having received at least one study drug intake.	

Primary: Post-ischaemic myocardial stunning

End point title	Post-ischaemic myocardial stunning ^[1]
End point description: By using bi-dimensional echocardiography at rest and at peak of exercise and during the recovery phase, a strain value (%) was measured for 16 segments of the LV myocardial wall. The segments showing post-ischaemic myocardial stunning at baseline were assessed for efficacy results.	
End point type	Primary
End point timeframe: The primary endpoint was the post-ischaemic myocardial stunning evaluating changes (%) in regional myocardial wall motion from rest to peak exercise and to recovery time points (3 min, 10 min, 20 min). Change from baseline to W2 was provided.	

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: only descriptive analyses were done

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: strain relative change from rest				
arithmetic mean (standard deviation)				
change from baseline at peak	23.1 (± 16.3)			
change from baseline at 3 min recovery	20.1 (± 12.3)			
change from baseline at 10 min recovery	10.3 (± 13.9)			
change from baseline at 20 min recovery	2.2 (± 10.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

All over the study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	ivabradine
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Reporting group description: -

Serious adverse events	ivabradine		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	ivabradine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Low number of patients receiving the study drug and short duration of the treatment period.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2012	To extend the enrolment period by one year from October 2012 to October 2013. -To update information on concomitant treatments and the list of adverse events for which specific information was requested and already collected, if any.
11 July 2013	-To extent the enrolment period by ten months from October 2013 to August 2014 To clarify a study procedure regarding the blood sampling results to be checked by the investigator before the inclusion of the patient

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported