Safety of oral chronic administration of ivabradine modified release formulation compared to ivabradine immediate release formulation, in patients with stable coronary artery disease. A 6 to 12-month randomised double blind parallel groups multicentre study.

Published: 30-08-2012
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The purpose of this study is to assess the safety of the new modified release (MR) formulation of ivabradine administered orally, at titrated doses if necessary, in patients with stable coronary artery disease (CAD) with or without angina pectoris.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON36887

Source
ToetsingOnline

Brief title
CL3-16257-097: Safety of ivabradine modified release

Condition

- Coronary artery disorders
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym

Atherosclerosis/ hardening of the coronary arteries

Research involving
Human

Sponsors and support

Primary sponsor: Servier R&D Benelux
Source(s) of monetary or material Support: Institut de Recherches Internationales Servier (IRIS)

Intervention

Keyword: chronic administration, Ivabradine, Modified Release, safety

Outcome measures

Primary outcome

Safety endpoint: occurrence of emergent adverse events over 6 months (including

clinically significant 12-lead ECG abnormalities).

Secondary outcome

Safety endpoints:

-Occurrence of emergent adverse events over 12 months (including clinically

significant 12-lead ECG abnormalities),

-Other safety criteria over 6 and 12 months:

*Blood pressure,

*Laboratory test parameters.

Efficacy endpoints:

- HR change from baseline on resting 12-lead ECG over 6 and 12 months,

- Change in CCS (Canadian Cardiovascular Society) class, number of angina

attacks and short acting nitrates consumption

over 6 and 12 months for angina patients.

Safety and efficacy endpoints for switch:

-Occurrence of emergent adverse events after switch over 3 months,

-Blood pressure change,

-HR change on resting 12-lead ECG after switch over 3 months,

-Change in CCS class, number of angina attacks and short acting nitrates

consumption after switch over 3 months for angina patients.

Study description

Background summary

A MR formulation of ivabradine has been developed to ensure better patient compliance with a once daily administration scheme and to reduce the fluctuations in plasma concentrations of ivabradine, thereby achieving a steadier HR reduction over 24 hours. A line extension application is foreseen to apply for the registration of this MR formulation in the same indications as granted and/or foreseen for the IR tablet.

Study objective

The purpose of this study is to assess the safety of the new modified release (MR) formulation of ivabradine administered orally, at titrated doses if necessary, in patients with stable coronary artery disease (CAD) with or without angina pectoris.

Study design

This study is a phase III, international, multicentre, double blind, randomised, comparative study with two parallel groups (ivabradine MR versus IR formulation).
A total of 700 patients (350 in each group) will be included.120 of them will participate in the 24-hour Holter ECG assessment and 120 will participate in the PK assessments. The patients of the centres in the Netherlands will not participate in the Holter and PK assessments.

schedule of the visits:
-The pre-randomisation period from the selection visit to the inclusion visit (dedicated to confirm the eligibility of patients and their clinical stability, maximum duration is from 3 to 15 days). Patients will be randomly assigned to

ivabradine MR or ivabradine IR.
-The post-randomisation period (follow-up period):
-A First 6-month follow-up period, from D000 to M006, with visits at D014, M001, M002, M004 and M006
-A Second 6-month follow-up period, from M006 to M012, with visits at M009 and M012;
-A 3-month Switch period, from M006 to M009, with visits at M007 and M009.

Patient*s follow-up will last from 6 to 12 months depending on the time of the patient*s enrolment and the follow-up of the other participants.
-The first patients having completed a first 6-month follow-up period either on ivabradine MR or ivabradine IR will enter a second 6-month follow-up period on the same double-blind treatment (total study duration of 12 months) until at least 130 patients in each treatment group have entered this second 6-month follow-up period.
-The following 120 patients having completed the first 6-month follow-up period either on ivabradine MR or ivabradine IR will enter a 3-month switch period on the other ivabradine formulation, always in double-blind (total study duration of 9 months).
-The last randomised patients will stop the study after the first 6-month follow-up period (total study duration of 6 months).

Intervention

12 lead ECG and physical examination at each visit.
Blood sampling at ASSE, M006 and M012 for haematology and biochemistry.(for details cfr protocol)

Study burden and risks

cfr. E2 and E9

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

selection criteria:
-Women or men,
-Age *18 years (or having reached majority if the legal age of majority is over 18 years).
-obtained informed consent
-Documented stable CAD with or without chronic stable angina pectoris:
*CAD documented by:
.Prior myocardial infarction *3 months before selection,
.or prior coronary revascularisation *3 months before selection,
.or angiographically proven significant coronary atherosclerosis (*50% lumen diameter reduction of any major coronary artery),
.or reliable non-invasive evidence of myocardial ischaemia (i.e. myocardial perfusion scintigraphy, stress echography, stress MRI).
*In stable condition for at least 1 month before selection with regards to clinical symptoms and
cardiovascular treatments.
-In case of history of chronic stable angina pectoris:
*At least one angina attack within the 2 months preceding the selection visit, defined as chest
pain or discomfort, typically elicited by exertion or emotional stress and relieved by rest or short
acting nitrates.
*CCS class I to IV.
*Clinical stability within 1 month preceding selection (no significant change in frequency, duration, precipitating causes or ease to relief of angina).
-Normal sinus rhythm.

-Resting heart rate * 60bpm (measured on 12-lead ECG recording in supine position after a 10-minute rest).;Inclusion criteria:
-Documented sinus rhythm and HR * 60 bpm on 12-lead ECG recording in supine position after a 10-minute rest.

Exclusion criteria

Non-selection criteria:
-Women who are pregnant, breast-feeding or women of childbearing potential not using estro-progestative oral or intra-uterine contraception or implants, or women using estro-progestative or intra-uterine contraception or implants but who consider stopping it during the planned duration of the study.
-Participation in another interventional study within the previous 30 days or within a prior time of 5 half-lives of the investigational drug.
-Contra-indication to ivabradine, ivabradine not recommended or not effective, or requirement for a not recommended concomitant treatment (cf ivabradine SmPC):
*Resting heart rate below 60 bpm prior to ivabradine treatment.
*Hypersensitivity to the active substance or to any of the excipients, galactose intolerance, Lapp
lactase deficiency or glucose-galactose malabsorption.
*Cardiogenic shock.
*Severe hypotension (< 90/50 mmHg).
*Acute myocardial infarction or coronary revascularisation within less than 3 months.
*Unstable angina within less than 1 month.
*Recent stroke (within less than 1month).
*Hepatic insufficiency (child-pugh score >7).
*Severe renal insufficiency (creatinine clearance <15ml/min).
*Sick sinus syndrome.
*Sino-atrial block, 2nd or 3rd degree atrio-ventricular block.
*Pacemaker dependent more than 40% of the time or with a stimulation threshold *60bpm.
*Permanent atrial fibrillation or flutter or other cardiac arrhythmia that interfere with sinus node
function.
*Congenital long QT syndrome or patient requiring treatment with QT prolonging products.
*Patient requiring treatment with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin per
os, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone.
*Patient requiring treatment with heart rate reducing agents, which are moderate CYP3A4 inhibitors (e.g: diltiazem or verapamil).
-Heart failure patients with NYHA functional classification II, III or IV.
-Patient treated with ivabradine in the month preceding the selection.
-Known alcohol or drug abuse.
-Known carriers of hepatitis B surface antigen or human immunodeficiency virus antibodies or hepatitis C virus antibodies.;Non-inclusion criteria:

-Creatinine clearance <15ml/min.
-ALT or AST > 3 times the laboratory upper limit of normal (ULN).
-Late discovery of any condition not in accordance with selection/non-selection criteria.
-Other ECG or laboratory abnormalities or clinical deterioration excluding the patient from this study according to the investigator.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-11-2012
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Procoralan
Generic name:	Ivabradine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	30-08-2012

Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	26-09-2012
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	12-06-2013
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	30-04-2014
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-001668-31-NL
CCMO	NL41320.096.12