Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Effects of oral administration of ivabradine (7.5 mg b.i.d.) on post-ischaemic stunning induced by exercise stress in patients with coronary artery disease and exercise inducible ischaemia.**
Test drug code	**Ivabradine (S 16257-2)**
Indication	**Coronary artery disease**
Development phase	**Phase II**
Protocol code	**CL2-16257-095**
Study initiation date	**27 March 2012**
Study completion date	**13 August 2014**
Investigator	[redacted]
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**08 June 2015**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Procoralan® **Name of Active Ingredient:** Ivabradine (S 16257-2)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Effects of oral administration of ivabradine (7.5 mg b.i.d.) on post-ischaemic stunning induced by exercise stress in patients with coronary artery disease and exercise inducible ischaemia.
Protocol No.: CL2-16257-095
EudraCT No.: 2011-000783-98
The description of the study protocol given hereafter includes the modifications of the two substantial amendments to the protocol.

Investigator: [redacted]

Study centre: [redacted]

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 27 March 2012 (date of first visit first patient) Completion date: 13 August 2014 (date of last visit last patient)	Phase II

Objectives:

Primary objective was to evaluate the effect of ivabradine on post-ischaemic stunning induced by exercise stress in patients with stable CAD and exercise-inducible ischaemia.
Secondary objectives were to investigate the effect of ivabradine on:
- Arterial elastance.
- Ventricular-arterial coupling.
- HR at rest (added to statistical analysis planned in the study protocol).
- Safety.

Methodology:

Phase II, monocentre, open label, non-controlled exploratory study.
The study was performed on male and female patients with proven CAD, LVEF ≥ 40%, sinus rhythm, resting HR ≥ 70 bpm and exercise-inducible myocardial ischaemia at moderate to high workload and subsequent stunning.
After a 1 to 2 weeks wash-out period of previous anti-anginal treatment and a 1 week run-in period on placebo with two exercise tests, inclusion was performed at Istituto Scientifico Universitario San Raffaele. The treatment period for each patient was two weeks.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:

Planned: 15 patients.
Included: 15 patients.

Diagnosis and main criteria for inclusion:

The main selection criteria were:
- Patients (male and female) 30-75 years.
- Evidence of CAD proven by clinical history (*e.g.* previous myocardial infarction, and/or positive non-invasive stress testing, and/or > 75% diameter narrowing in at least one major coronary artery at angiography).
- LVEF ≥ 40%.
- Sinus rhythm with resting HR ≥ 70 bpm.
- Exercise-inducible myocardial ischaemia defined as clear-cut horizontal on downsloping ST segment depression (≥ 0.1 mV).
- Myocardial stunning, assessed by echocardiography and defined by hypo or akinesis of ≥ 3 LV wall segments that were normally contracting or mildly hypokinetic in resting condition.
- Informed consent obtained.

The main inclusion criteria were:
- Sinus rhythm with resting HR ≥ 70 bpm.
- Second positive demonstration of exercise-inducible myocardial ischaemia and subsequent myocardial stunning.

The main non-inclusion criteria were:
- Angina present at rest or, if not, with angina symptoms class IV of the CCS classification.
- Unstable cardiovascular condition.
- Previously treated with any anti-anginal medication (short acting nitrates were allowed) within 1 week before inclusion.

Investigational Medicinal Product:

Ivabradine, 7.5 mg tablet; *per os* administration, one tablet twice daily during meals.

Batch numbers: L0038024 & L0047809

Comparator: a masked placebo was provided during the wash-out and run-in periods.

Duration of treatment: 4-5 weeks including
- Wash-out period of previous anti-anginal treatment during 1 to 2 weeks with placebo dispensation.
- Run-in period during 1 week with placebo dispensation.
- Treatment period (W0-W2) with patients receiving ivabradine during 2 weeks.

Criteria for evaluation:

Efficacy measurements:

Primary endpoint

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. 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 (basal, medium and apical segments) at baseline and after 2 weeks of treatment. Post-ischaemic myocardial stunning was defined by hypo or akinesis of segments that were normally contracting or mildly hypokinetic in resting condition.

Secondary endpoints

Arterial elastance measured at rest and at peak of exercise and during the recovery phase (mmHg/ml).
Ventricular-arterial coupling measured at rest and at peak of exercise and during the recovery phase.
HR at rest.

Safety measurements:

Secondary endpoints
- Adverse events.
- Vital signs at rest: blood pressure.
- ECG parameters at rest.

Statistical methods:

Efficacy analysis:
It was done in the Full Analysis Set (FAS) defined as all patients of the Included Set (IS) having taken at least one dose of IMP and having a strain value at baseline and at W2, at each time point (at rest, at peak and at 3 minutes of recovery) for at least one segment with deterioration at baseline.

Primary endpoint
The strain values were described in the Full Analysis Set (FAS) with graphical and numerical approach on myocardial wall segments showing exercise-inducible myocardial stunning at baseline:

- Individual patient graphs of strain evolution over time (*i.e.* at rest, at peak of exercise and during the recovery phase) were provided at baseline and W2.
- For each of these segments, the strain values at each time point (rest, peak ETT, recovery phase) and the relative change from rest were provided at baseline and W2, as well as the absolute change from baseline to W2.

Moreover, as subject reference values, the same analysis (graphical approach) was performed on the 16 segments for each patient.

Secondary endpoints
Arterial elastance and ventricular-arterial coupling measuring at rest and at peak of exercise and during the recovery phase were described using the same analyses (graphical and numerical approach) as for the primary efficacy endpoint.
Heart rate from 12-lead ECG at rest was also described at baseline and W2 and change from baseline to W2.

Study outcome and safety analysis: Descriptive statistics were provided in the IS and Safety Set (SS)

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS
25 patients were pre-selected. Of them, 15 patients were selected and included. All included patients completed the study. All analysis sets consisted in the same 15 included patients.

Main baseline characteristics
The mean (±SD) age was 65.8 ± 7.4 years. All patients were men. CAD was documented mainly by positive non-invasive stress testing (12 patients), > 75% narrowing at least one major coronary artery at angiography (10 patients), percutaneous coronary intervention (7 patients), prior myocardial infarction (5 patients) and coronary artery bypass graft (4 patients). The overall mean duration of CAD from diagnosis until selection 9.5 ± 8.5 years.
The mean heart rate from resting ECG was 75.9 ± 6.0 bpm. Mean values of supine SBP and DBP were 132.0 ± 16.0 mmHg and 76.0 ± 6.6 mmHg, respectively. The mean BMI was 25.8 ± 2.0 kg/m^2.
Within the two months before entry in the study, 13 patients stopped treatments for CAD which could interfere with the natural course of angina (beta-blockers in 9 patients, calcium channel blockers in 5 patients and long-acting organic nitrates in 2 patients). Concomitant treatments received at inclusion were mainly antithrombotic agents (14 patients), lipid modifying agents (13 patients), agents acting on renin-angiotensin system (9 patients), drugs for acid related disorders (5 patients), drugs used in diabetes (4 patients) and drugs used in benign prostatic hypertrophy (3 patients).

Treatment duration
All patients received 7.5 mg ivabradine b.i.d. during the treatment period. The mean treatment duration was 15.1 ± 0.6 days. The mean overall compliance was 100.7 ± 2.6% and ranged from 96% to 108%.

Characteristics of the exercise tolerance
Mean total exercise duration was 7.2 ± 2.2 min and workload achieved 10.3 ± 2.1 MET. These parameters were unchanged at W2.
As expected due to pharmacological effect of ivabradine, the mean HR at rest and at peak decreased from baseline (76.6 ± 6.1 and 135.8 ± 15.4 bpm, respectively) to W2 (change: -16.5 ± 7.3 and -18.5 ± 12.8 bpm, respectively).
The mean SBP at rest and at peak was quite unchanged after ivabradine treatment from baseline (130.7 ± 16.1 and 162.0 ± 17.3 mmHg respectively) to W2 (change: -1.3 ± 13.2 and -1.3 ± 11.4 mmHg, respectively). The mean DBP slightly decreased at rest and at peak after ivabradine treatment from baseline (76.0 ± 6.6 and 84.3 ± 10.3 mmHg respectively) to W2 (change: -4.7 ± 7.2 and -7.0 ± 8.6 mmHg, respectively).
Therefore, the mean rate pressure product (RPP) at rest and at peak decreased after ivabradine treatment from baseline (99.8 ± 11.5 and 220.0 ± 33.8 mmHg*bpm/100 respectively) to W2 (change: -22.4 ± 7.8 and -30.7 ± 17.9 mmHg*bpm/100).

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS

Primary endpoint

57 segments with induced post-ischaemic stunning at baseline were assessed. The individual patient graphs showed the effort-induced decrease in wall motion was strongly diminished or not present after 2 weeks of treatment. The strain relative changes from at rest to at peak ranged from -10% to 62% and was lower than 0% in only 2 segments (2 patients). In these overall segments (unplanned analysis), the strain relative change from rest decreased after 2 weeks of treatment by 23.1 ± 16.3% at peak ETT, by 20.1 ± 12.3% at 3 min recovery, by 10.3 ± 13.9% at 10 min recovery and by 2.2 ± 10.6% at 20 min recovery.

Secondary endpoints

Between baseline and W2, the arterial elastance relative change from rest was 4.2 ± 24.9% at peak ETT, -2.6 ± 38.1% at 3 min recovery, -0.3 ± 27.6% at 10 min recovery and -11.8 ± 27.1% at 20 min recovery.

Between baseline and W2, the ventricular-arterial coupling relative change from rest was -15.6 ± 54.3% at peak ETT, -23.8 ± 40.3% at 3 min recovery, 12.1 ± 47.0% at 10 min recovery and -13.4 ± 38.2% at 20 min recovery.

As expected with ivabradine, resting HR decreased from baseline (mean = 75.9 ± 6.0 bpm) to W2, with a mean reduction of 16.2 ± 6.8 bpm.

SAFETY RESULTS

No emergent adverse event was reported during the study.

No clinical laboratory evaluation was performed for safety purpose in the present study.

The analysis of supine blood pressure showed no significant change in mean SBP and DBP from baseline to W2: -2.0 ± 14.6 mmHg and -4.3 ± 7.3 mmHg, respectively.

Few emergent abnormal ECG values were reported: low HR in 2 patients (47 and 49 bpm) and high QRS duration (122 ms) with high PR interval (214 ms) in one patient. None of these abnormal values were considered as clinically significant by the investigator.

CONCLUSION

This was a phase II, monocenter, open label, non-controlled exploratory study of ivabradine in patients with stable CAD. The primary objective was to evaluate the effect of a two weeks ivabradine treatment on the post-ischaemic myocardial stunning induced by exercise stress.
The included population conformed well to the target population.
57 myocardial segments with post-ischaemic stunning at baseline in 15 patients were assessed. After two weeks of ivabradine 7.5 mg b.i.d., this effort-induced decrease in wall motion was strongly diminished or no more present. Ivabradine reduced the post-ischemic stunning in CAD patients with exercise induced ischemia.
The safety assessment showed no emergent adverse events and no other relevant finding.

Date of the report: 08 June 2015

Version of the report: Final version