Document title	CLINICAL STUDY REPORT SYNOPSIS
Study title	**Effects of ivabradine on vascular function in individuals at increased risk of developing cardiovascular disease and with impaired endothelial function: IDENTIFY study** **An international, multicentre, randomised, double-blind, placebo-controlled study over 12 weeks.**
Test drug code	**Ivabradine (S 16257)**
Indication	**Cardiovascular Disease**
Development phase	**Phase II**
Protocol code	**CL2-16257-099**
Study initiation date	**06 December 2013**
Study completion date	**18 April 2014**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France** **Servier Research and Development Ltd,** **Rowley, Wexham Springs, Framewood Road** **Wexham, Slough SL3 6PJ – United Kingdom**
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	**07 November 2014**
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 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. Protocol No.: CL2-16257-099 EudraCT No.: 2012-000215-89		
International coordinator [redacted]		
Study centres: A total of 3 centres in 2 countries included at least one patient: 2 centres in Netherlands and 1 centre in Germany.		
Publication (reference): Not Applicable		
Studied period: Initiation date: 03 Dec 2013 Completion date: 18 Apr 2014	**Phase of development of the study:** Phase II	
Objectives: The purpose of this study was to demonstrate the beneficial effect of ivabradine on endothelial function in individuals with risk factors for cardiovascular disease and a resting HR ≥75 bpm. The primary objective was to demonstrate the beneficial effect of ivabradine compared with placebo on endothelial function as measured by Flow-mediated vasodilatation (FMD) of the brachial artery at 12 weeks of treatment. Secondary objectives were to investigate the effect of ivabradine compared with placebo on biomarkers of endothelial function and cardiovascular risk (including optional microRNA) and the effect on resting heart rate. Other objectives were to assess the intra-patient variability of FMD in a random subset of 20% of patients and evaluate the safety and tolerance profile of ivabradine compared to placebo. The study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents		
Methodology: Phase II international, multicentre, randomized, double-blind, placebo-controlled study with two parallel and balanced arms (ivabradine and placebo) in adult patients with at least 2 risk factors for atherosclerotic cardiovascular disease and with impaired endothelial function as measured by FMD. After selection and inclusion, the patient was randomized to receive ivabradine or placebo for 12 weeks. I.R.I.S., in agreement with the Scientific Board of the study, took the decision to prematurely terminate this study in view of the difficulties in the recruitment process and the strategic objectives for ivabradine.		
Number of patients: Planned: 340 patients (170 per group). Included: 4 patients (due to the premature termination of the study).		
Diagnosis and main criteria for inclusion: Men or postmenopausal women aged 21-74 years, in sinus rhythm with resting HR ≥ 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%), without previous diagnosis of coronary disease (acute coronary syndrome or coronary revascularization or stenosis ≥ 50% within the last 3 months, or positive stress test without revascularization), heart failure (NYHA functional classification class II or more), cerebrovascular disease or peripheral arterial disease affecting the upper extremities.		
Test drug: Ivabradine tablets: 5 mg, 7.5 mg or 10 mg tablets to be taken orally twice daily. Starting dose 7.5 mg twice daily, then after 2 weeks and 4 weeks dose up-titrated, down-titrated or maintained depending upon the resting heart rate and the presence or absence of symptoms or signs of bradycardia. Batch Nos.: L0043030 & L0045270 (5 mg); L0044844 (7.5 mg); L0044143 (10 mg)		
Comparator: Placebo tablets (matching those of ivabradine).		
Duration of treatment: Placebo run-in period: 1 to 2 weeks. Treatment period: 12 weeks.		

Criteria for evaluation:
Due to the premature termination of the study, the small number of included patients and the absence of any post-baseline FMD assessment, no efficacy analysis was performed.

Efficacy measurements: at Inclusion (W000) and Final Visit (W012):

- Flow mediated vasodilatation of the brachial artery in response to forearm occlusion (FMD).
- Blood biomarkers of endothelial function and cardiovascular risk.
- Resting HR on 12 lead ECG (at each visit).

Primary efficacy criterion: absolute change in FMD% from W000 to W012.
Secondary efficacy criteria:

- Change in biomarkers from W000 to W012.
- Change in resting HR over 12 weeks.

Other criteria: intrapatient variability in FMD (subgroup).

Safety measurements:

- Emergent adverse events including any clinically significant new abnormal findings at physical examination, on laboratory tests or on ECG recording over 12 weeks.
- Resting blood pressure, resting ECG (all visits).
- Routine laboratory tests (W000 and W012).

Statistical methods: No statistical analysis was carried out.

SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME

Disposition of patients

	Ivabradine	Placebo	All
Included	2	2	4
Withdrawn due to	2	2	4
premature study termination	2	2	4
Completed	-	-	-
Randomised Set (RS)	2	2	4

A total of 53 patients were screened for the study and 9 patients were selected. Among them, 4 patients were included and randomly assigned to one of the 2 groups: 2 patients in the ivabradine group and 2 in the placebo group.
All of the 4 included patients were withdrawn due to the premature study end.
Both of the patients randomized to ivabradine received the 7.5 mg (bid) posology of the IMP during the treatment period without titration. Their global compliance was satisfactory.

EFFICACY RESULTS
The primary endpoint was the absolute percentage change in FMD of the brachial artery from baseline to 12 weeks for ivabradine compared with placebo.
But due the premature study termination, only baseline FMD scans were performed. No FMD was performed under or after treatment intake.

Baseline Percentage in FMD of the brachial artery - Randomisation Set

	Ivabradine (N = 2)		Placebo (N = 2)	
	Patient No. 1008 00035	Patient No. 1008 00038	Patient No. 0101 00043	Patient No. 1001 00009
Percentage FMD (%)	1.41	1.72	4.55	2.99

SAFETY RESULTS
One emergent adverse event on treatment was reported, which was a case of fatigue in a placebo-treated patient. This mild event was reported as recovered at the W012 visit.
No other safety concern was identified.

CONCLUSION
The study was prematurely terminated in view of the difficulties in the recruitment process and the strategic objectives for ivabradine. Only 4 patients were included and no post-baseline FMD assessment was performed. No efficacy analysis was therefore carried out. No adverse events were reported in the active treatment group (ivabradine) and no unexpected safety concern was identified.

Date of the report: 07 November 2014

Version of the report: Final version