



<i>Document title</i>	Clinical Study Report Synopsis
<i>Study title</i>	Evaluation of the effects of oral administration of ivabradine 5 mg and 7.5 mg b.i.d. in patients with heart failure and arterial hypertension insufficiently controlled by oral perindopril 4 mg per day. An open-label multicentre study.
<i>Study drug</i>	S 16257
<i>Studied indication</i>	Heart failure
<i>Development phase</i>	Phase II
<i>Protocol code</i>	CL2-16257-073
<i>Study initiation date</i>	13 December 2007
<i>Study completion date</i>	07 May 2009
<i>Main coordinator</i>	[REDACTED] France
<i>Company / Sponsor</i>	Institut de Recherches Internationales Servier (I.R.I.S.) 50 Rue Carnot 92284 Suresnes Cedex - France
<i>Responsible medical officer</i>	[REDACTED]
<i>GCP</i>	This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.
<i>Date of the report</i>	Final version of 10 August 2010

CONFIDENTIAL

Name of Company: I.R.I.S. 6 place des Pleiades 92415 Courbevoie - FRANCE	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>														
Name of Finished Product: Procoralan	Volume:															
Name of Active Ingredient: Ivabradine (S 16257)	Page:															
<p>Criteria for evaluation:</p> <p>Efficacy Measurements: Blood pressure, heart rate and NYHA classification. All efficacy parameters were assessed at each visit from J-30 to J120.</p> <p>Safety Measurements: Adverse events, standard 12-lead ECG at each visit from J-30 to J120 and laboratory parameters assessed at J-30 and J90 visits.</p>																
<p>Statistical methods: Considering the exploratory nature of this study and low number of patients included, the analyses were essentially descriptive on all included patients (Included Set). No formal statistical analysis plan was drafted.</p> <p>EFFICACY ANALYSIS:</p> <p>Primary criterion The <i>primary efficacy criterion</i> was change in Systolic Blood Pressure (SBP) at J90 compared to J0 and J-30 values.</p> <p>Secondary criteria The <i>secondary efficacy criteria</i> were:</p> <ul style="list-style-type: none"> - Diastolic blood pressure (DBP) value at J90 compared to J0 and J-30 values. - Systolic and diastolic blood pressure values at J30 and J60 compared to J0 value. - Heart rate values at J30, J60 and J90 compared to J0 and J-30 values. - NYHA classification at J30, J60 and J90 compared to J0 value. <p>SAFETY ANALYSIS: Descriptive statistics were provided on adverse events, standard 12-lead ECG and laboratory parameters.</p>																
<p>SUMMARY - CONCLUSIONS</p> <p>STUDY POPULATION AND OUTCOME</p> <p style="text-align: center;">Disposition of patients</p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="text-align: left;">Patient Status</th> <th style="text-align: center;">All</th> </tr> </thead> <tbody> <tr> <td>Selected</td> <td style="text-align: center;">13</td> </tr> <tr> <td>Included</td> <td style="text-align: center;">11</td> </tr> <tr> <td style="padding-left: 20px;">Lost to follow-up</td> <td style="text-align: center;">-</td> </tr> <tr> <td style="padding-left: 20px;">Withdrawn due to non medical reason</td> <td style="text-align: center;">1</td> </tr> <tr> <td>Completed</td> <td style="text-align: center;">10</td> </tr> <tr> <td>Run out visit</td> <td style="text-align: center;">10</td> </tr> </tbody> </table> <p>A total of 13 patients were selected and 11 were included in the study. There was no withdrawal during the ivabradine treatment period. 1 patient did not attend the run-out visit due to non-medical reason. The Included Set was only considered for the descriptive analysis. No protocol deviations were defined for this study.</p> <p>At selection, patients were 56.7 ± 10.9 years old on average. Most of them were men (8 men <i>versus</i> 3 women). The 11 included patients all had documented stable heart failure for at least 6 months. 8 patients were in NYHA class II at selection and 3 patients in NYHA class III. The origin of heart failure was dilated cardiomyopathy in 7 patients, ischaemia in 5 patients and/or hypertension in 4 patients (5 patients with 2 reasons). Essential hypertension was known in 4 patients between up to 3 years and in more than 3 years for the remaining 7 patients.</p>			Patient Status	All	Selected	13	Included	11	Lost to follow-up	-	Withdrawn due to non medical reason	1	Completed	10	Run out visit	10
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<p>SUMMARY – CONCLUSIONS (Cont'd) STUDY POPULATION AND OUTCOME (Cont'd) Nine patients received antihypertensive treatments (diuretics or agents acting on the renin-angiotensin system). As per protocol, previous renin-angiotensin system treatments were stopped (unless perindopril) except in 2 patients. Nine patients received anti-thrombotic agents (clopidogrel, aspirin or fluindione) and 8 patients received other cardiac agents (calcium channel blockers, beta-blockers, anti-arythmics, anti-ischaemics). The most frequently reported concomitant diseases were diabetes in 5 patients and hypercholesterolemia in 4 patients with respective use of diabetes related drugs and lipid modifying agents, continued during the study. At inclusion, mean SBP and DBP were 158 ± 12 mmHg and 94 ± 5 mmHg respectively. Heart rate when measured with the automatic device was 76 ± 7 bpm on average and 77 ± 7 bpm when measured on ECG. There were 10 patients with NYHA grade II and 1 patient with NYHA grade III at inclusion. The mean treatment duration was 90 ± 4 days for ivabradine and 151 ± 13 days for perindopril with a global compliance of $90 \pm 4\%$ and $99 \pm 3\%$ respectively. 6 patients had an ivabradine dose increased at J30 visit and 4 patients at J60 visit. 1 patient remained at the starting dose of 5 mg for 60 days followed by an up-titration to 7.5 mg for 30 days.</p>		
<p>EFFICACY RESULTS</p> <p>- Primary criterion:</p> <ul style="list-style-type: none"> Compared to baseline (J0), SBP decreased after 3 months (J90) of ivabradine treatment in 7 of the 11 included patients; overall, the mean change was -4 ± 13 mmHg. The mean SBP at J90 was 154 ± 16 mmHg. <p>- Secondary criteria: Compared to baseline (J0):</p> <ul style="list-style-type: none"> DBP at J90 decreased in 8 patients ; overall, the mean change was -11 ± 9 mmHg. Mean DBP at J90 was 83 ± 8 mmHg. SBP and DBP at J30 and J60 decreased. The mean change in SBP at J30 was -8 ± 11 mmHg and at J60 was -5 ± 21 mmHg. Mean change in DBP at J30 was -11 ± 9 mmHg and at J60 was -9 ± 13 mmHg. HR at J90 decreased in 9 patients ; overall, the mean change was -10 ± 14 bpm. Mean HR at J90 was 66 ± 12 bpm. NYHA classification at J90 was reduced by 1 class in 6 patients and by 2 classes in 1 patient. 		

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SUMMARY – CONCLUSIONS (Cont'd) SAFETY RESULTS		
Overall summary of safety results		
Included patients		N = 11
Patients having reported		
at least one emergent adverse event		4
at least one treatment-related emergent adverse event		1
Patients having experienced		
at least one serious adverse event (no death)		1
<p>4 patients reported a total of 6 emergent adverse events during the ivabradine treatment period. These were cardiac failure, blood pressure inadequately controlled, anaemia, dental abscess, rash and gastric ulcer. 5 events recovered and 1 event (moderate anaemia) was recovering at the study end. None of these events induced either an interruption of the ivabradine treatment or dose modification. No death was reported during the study.</p> <p>One emergent adverse event was rated as serious (cardiac failure, but resulted in no change of NYHA class, rated as II) and one emergent adverse event (rash) was considered possibly related to ivabradine according to investigator's opinion.</p> <p>No significant or medically important changes were observed in terms of clinical laboratory results, or in the vital signs of body weight.</p> <p>In addition, the assessment of ECG abnormalities and parameters revealed that no relevant changes occurred under treatment.</p>		
CONCLUSION		
In this open-label study in 11 heart failure patients with hypertension insufficiently controlled by perindopril 4 mg, oral ivabradine was well tolerated and a decrease in SBP and DBP was observed. An improvement in NYHA class was also observed in the majority of patients.		
Date of the report: 10 August 2010		