Document title	**Clinical Study Report Synopsis**
Study title	**Evaluation of the effects of 3 successive oral dosages (2.5; 5; 7.5 mg b.i.d.) of ivabradine in patients with stable moderate to severe systolic chronic heart failure treated with beta-blockers.** **A 9-week pilot, open-label, international multicenter study.**
Study drug	**S 16257 Ivabradine**
Indication	**Chronic Heart Failure**
Development phase	**Phase II**
Protocol code	**CL2-16257-062**
Study initiation date	**22 September 2005**
Study completion date	**31 January 2007**
Main coordinator	[redacted] **- France**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 Rue Carnot** **92284 Suresnes Cedex – France**
Responsible medical officer	[redacted] **(I.R.I.S.)**
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 7 May 2008**

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SYNOPSIS

Name of Company: I.R.I.S. 6 place des Pleiades 92415 Courbevoie - FRANCE	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
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Title of study:
Evaluation of the effects of 3 successive oral dosages (2.5; 5; 7.5 mg b.i.d.) of ivabradine in patients with stable moderate to severe systolic chronic heart failure treated with beta-blockers.
A 9-week pilot, open-label, international multicenter study.
Protocol No.: CL2-16257-062

Coordinator:
[redacted] – France

Study centres: 15 centres located in 4 countries were opened and 14 included at least one patient: France – 3 centres (15 patients), Italy – 3 centres (22 patients), Germany – 6 centres (47 patients), The Netherlands – 2 centres (3 patients).

Publication (reference): Not applicable.

Studied period: Initiation date: 22 September 2005 Completion date: 31 January 2007	Phase of development of the study: Phase II

Objectives:

- Primary objectives: To evaluate the effects on heart rate, systolic and diastolic blood pressure, left ventricular volumes and function of 3 successive oral doses (2.5, 5.0 & 7.5 mg b.i.d.) of ivabradine given over a period of 6 weeks to patients with stable moderate to severe systolic symptomatic chronic heart failure receiving a stable background beta-blocker therapy.
- Secondary objectives:
  - To assess in these patients the effects of ivabradine on functional capacity, evaluated with the NYHA classification, clinical symptoms (overall clinical assessment according to the patient and the investigator), neurohormones (BNP measurement).
  - To evaluate in these patients the safety of ivabradine.
  - To assess in these patients plasma pharmacokinetic parameters for ivabradine and its metabolite S 18982.

Methodology: Open-label pilot study with one treatment arm using 3 doses of ivabradine of identical appearance: 2 dose titrations at 2-week intervals.

Number of patients:
Planned: 60 to 80
Included: 87

Diagnosis and main criteria for inclusion:
Patients with symptomatic systolic chronic heart failure (class III or IV) diagnosed since at least 3 months, receiving stable beta-blocker therapy and in sinus rhythm with resting HR $\geq$ 60 bpm.

Study drug:
Ivabradine tablets of strengths 2.5, 5.0 and 7.5 mg, administered orally, twice a day.
Batch Nos. L0004475 (2.5 mg tablets), L0002842, L0005445 (5 mg tablets), L0002924, L0005446 (7.5 mg tablets).

Reference product: Not applicable.

Duration of treatment:
Following the 1-week run-in period, patients were administered (at W0) ivabradine 2.5 mg (b.i.d.) for 2 weeks then (at W2) 5.0 mg (b.i.d.) for 2 weeks then (at W4) 7.5 mg (b.i.d.) for 2 weeks. Patients who could not be up-titrated (on HR criteria) remained on the preceding dose. The study treatment ended at W6 and was followed by a 2-week follow-up period without treatment (until visit Wend).

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Criteria for evaluation:

Efficacy measurements:

- Heart rate (HR, bpm), using central and investigator readings of HR from the electrocardiogram (ECG) recording, at each visit.
- Doses titration (dosage, dose sequence due to titration and reasons of non-up titration).
- Echocardiography parameters (at inclusion and W6 only): Left ventricular (LV) end-systolic volume (LVESV, mL), LV end-diastolic volume (LVEDV, mL) and LV ejection fraction (LVEF, %).
- Plasma concentration of BNP (Brain Natriuretic Peptide, pg/mL).
- NYHA functional class (I, II, III or IV), assessment at each visit.
- Clinical assessment of change under treatment (visits W2, W4, W6) and after the end of treatment (Wend), made both by patient and investigator.

Safety measurements:

- 12-lead ECG at each visit. Central reading and investigator reported ECG abnormalities.
- 24-hour Holter ECG, performed starting the day before inclusion visit and the day before last study drug intake, which were read centrally.
- Vital signs and adverse events, at each visit.
- Clinical laboratory examination: prior to inclusion and just before last study drug intake.

Pharmacokinetic measurements:

- Blood samples (3 mL per sample) were collected from all patients for the measurement in plasma of S 16257 and its main active metabolite, S 18982, at inclusion (baseline value) and W6 (predose, then postdose 45-75 min, 2-3 h, 3-4 h, and 4-6 h). Optional predose and postdose collections on patient's leaving from the centre were made on W2 and W4. The analysis of these data is presented in a separate report.

Statistical methods:

- Study outcome was analysed using descriptive statistics on the Included Set.
- Efficacy analyses: descriptive analyses on values at each visit, last value over the 6-weeks treatment period and changes from baseline were performed on the Full Analysis Set (FAS) and the Per Protocol Set (PPS) for heart rate (central reading, from 12-lead ECG), echocardiographic parameters, plasma BNP, NYHA classification, and clinical assessment. Regarding change between last value over 6-week treatment period and baseline value, 95% confidence intervals were calculated using a parametric approach based on Student distribution and a non-parametric approach based on Walsh averages for heart rate, echocardiographic parameters and BNP values.
  Graphs of the changes in activity criteria over 6-week treatment period were provided on fully documented patients of the FAS and graphs crossing qualitative and quantitative parameters (such as NYHA and heart rate) were drawn.
  Activity criteria were also analysed for the pre-defined subgroups: Beta-blockers at target daily dose (Yes/No), Ischaemic origin of CHF (Yes/No) and HR $\geq$ 70 bpm at baseline (Yes/No) and for each dose sequence due to study drug titration. For some parameters additional subgroups were specially studied (such as patients with LVEF $\leq$ 25%, patients aged $\geq$ 75 years and patients of NYHA class IV at baseline).
- Safety analyses: emergent adverse events under treatment / during follow-up, vital signs and abnormalities related to ECG, Holter or biological parameters were studied on patients of the safety set using descriptive statistics and individual listings.

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SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

		Study population
Included (randomised)	n	87
Lost to Follow-up	n	-
Withdrawn due to adverse event	n (%)	12 (13.8)
Completed	n (%)	75 (86.2)
Full Analysis Set (FAS)	n (%)	87 (100)
Per Protocol Set (PPS)	n (%)	68 (78.2)
Safety Set	n (%)	87 (100)

The FAS consisted of all the 87 patients included. The PPS comprised 68 patients (i.e. 78.2% of the FAS).

In the FAS, patients had a mean age (± SD) of 62.3 ± 13.3 years (52.9% were < 65 years old and 18.4% were ≥ 75 years), 65 were men (i.e. 74.7%), and CHF had been diagnosed in the study population for a median of 16.0 months. In 38 cases (43.7%) the CHF had an ischaemic origin. Mean LVEF was 28.6 ± 5.4% and mean HR was 74.4 ± 10.8 bpm (≥ 70 bpm in 52 patients (59.8%)). 81 patients (93.1%) were NYHA class III and 6 (6.9%) were class IV. Most patients had concurrent medical conditions, with 83.9% having metabolism and nutrition disorders (mainly lipid disorders 62.1% and diabetes 39.1%) and 77.0% having vascular disorders (mainly hypertension, 69.0%). All patients were treated with beta-blockers at baseline: 15 (17.2%) were receiving the target daily dose and a total of 52 (59.8%) were receiving at least half the target daily dose. At selection, 74 patients (85.1%) were receiving ACE inhibitors, 15 patients (17.2%) were receiving angiotensin receptor II inhibitors (98.9% were receiving ACE inhibitors and/or angiotensin receptor II inhibitors), 82 patients (94.3%) were receiving diruretics, 22 (25.3%) were receiving digitalics, and 11 (12.6%) were receiving amiodarone. During the study, the mean treatment duration was 42 ± 10 days. Compliance to treatment was good, at 95.7 ± 8.6%.

EFFICACY RESULTS

In the FAS, the baseline HR of 74.5 ± 10.8 bpm (mean ± SD, ECG central reading) was significantly reduced by 10.0 ± 11.1 bpm at the last assessment over the 6-weeks treatment period (95% CI: [-12.5 ; -7.5]). Similar results were observed in the PPS and in the FAS using investigator readings. Following the cessation of treatment the mean HR returned to baseline value (73.4 ± 11.3 bpm) at Wend. Most patients (57/87; 65.5%) were up-titrated to the highest ivabradine dose (7.5 mg b.i.d.) and a further 15 (17.2%) attained the intermediate 5 mg b.i.d. dose.

LV volumes were markedly decreased (-18.5 ± 30.0 mL for LVESV, -8.2 ± 37.5 mL for LVEDV) and mean LVEF was significantly increased by 5.3 ± 6.1%. An increase in LVEF of 5% or more was evidenced in 43 patients (50.6%). These results were also observed in the PPS.

A greater reduction in HR was evidenced in patients with higher baseline HR values (Pearson's coefficient = -0.374; p = 0.001, central reading) and a greater reduction in HR was correlated with a greater increase in LVEF (Pearson coefficient = -0.247; p = 0.028, central reading).

Baseline BNP level showed a very high variability and no consistent change under treatment was observed in the FAS or PPS.

Baseline and change (baseline to last value under treatment) of the main efficacy criteria in the FAS

	n	Baseline (mean ± SD)	Change * (mean ± SD)	95% confidence intervals **
Heart rate (bpm)	81	74.5 ± 10.8	-10.0 ± 11.1	[-12.5 ; -7.5]
LVESV (mL)	80	161.7 ± 60.6	-18.5 ± 30.0	[-25.2 ; -11.8]
LVEDV (mL)	81	223.8 ± 81.5	-8.2 ± 37.5	[-16.5 ; 0.1]
LVEF (%)	85	28.6 ± 5.4	5.3 ± 6.1	[4.0 ; 6.6]
BNP (pg/mL)	42	283.4 ± 266.9	-0.1 ± 153.6	[-47.9 ; 47.8]

n: number of evaluable patients; * Change from baseline; ** Parametric approach based on Student distribution

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EFFICACY RESULTS (Cont'd)

The changes observed in HR from baseline to last value as well as the changes in echocardiographic parameters (of which LVEF is presented below) over the 6-week treatment period for the main FAS subgroups were similar to the overall population.

Baseline and change (baseline to last value under treatment) in HR and LVEF in the FAS subgroups

	Heart rate (ECG central reading; bpm)			LVEF (%)		
	n	Baseline (mean ± SD)	Change from baseline (mean ± SD)	n	Baseline (mean ± SD)	Change from baseline (mean ± SD)
β-blockers at target dose	14	71.4 ± 6.5	-11.9 ± 6.8	15	28.6 ± 5.2	5.9 ± 7.7
Ischaemic origin	37	72.7 ± 9.9	-11.0 ± 11.5	37	27.5 ± 5.3	4.5 ± 6.7
HR ≥ 70 bpm	51	80.7 ± 8.5	-12.7 ± 11.2	53	28.1 ± 5.6	5.9 ± 6.9

n: number of evaluable patient; * investigator reading of ECG

Improvements in NYHA class (a decrease of ≥ 1 class) and in clinical assessment were observed in both the FAS and PPS.

Functional and clinical assessment at last visit under treatment in the FAS

			FAS
Assessment of NYHA class (investigator)	Improvements	n/N (%)	45/87 (51.7)
Assessment of clinical symptoms (investigator):	Improvements	n/N (%)	58/87 (66.7)
Assessment of clinical symptoms (patient) :	Improvements	n/N (%)	54/84 (64.3)

SAFETY RESULTS

The safety results are summarised in the table below. A total of 35 patients (40.2%) reported 64 emergent adverse events, which were most frequently visual disturbances (11 patients, 12.6%); cardiac failure (5 patients, 5.7%); sinus bradycardia / heart rate decreased (5 patients, 5.7%); diarrhoea (3 patients, 3.4%), i.e. adverse events that are largely foreseeable in this patient population and with ivabradine treatment. Out of the 12 patients (13.8%) who withdrew from the study due to an AE, 5 (5.7%) were withdrawn for bradycardia (symptomatic or asymptomatic; but no cases of HR < 40 bpm), 2 for cardiac failure, and 1 each for visual disturbance, erythema, gastroenteritis, diarrhoea or inadequately controlled blood pressure.

Overall summary of events in the Safety Set (N = 87)

Patients having reported		Ivabradine
At least one emergent adverse event	n (%)	35 (40.2)
At least one treatment-related emergent adverse event	n (%)	22 (25.3)
At least one visual disturbance	n (%)	11 (12.6)
At least one bradycardia/HR decreased	n (%)	5 (5.7)
At least one serious adverse event	n (%)	8 (9.2)
At least one adverse event leading to study withdrawal	n (%)	12 (13.8)
At least one serious adverse event leading to study withdrawal	n (%)	-
An AE of bradycardia/HR decreased leading to study withdrawal	n (%)	5 (5.7)
Deaths	n (%)	-

Four patients experienced a serious adverse event (SAE) during the treatment period: cardiac failure (during a treatment interruption); ventricular tachycardia which occurred one day after the last ivabradine intake; planned hospitalisation for investigation of pleural effusion; and upper abdominal pain. No SAE was considered by the investigator as being related to ivabradine treatment and all patients recovered. No patient died during the study.

No clinically relevant changes were detected in laboratory parameters over time, in blood pressure, body weight or cardiac abnormalities (as assessed by ECG).

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SAFETY RESULTS (Cont'd)

The 24h Holter recordings showed that mean HR dropped under treatment by -9.1 ± 7.1 bpm, and that the effect on the lowest HR values was lower, with a mean change of about -5.7 bpm. The frequencies of reported cardiac abnormalities in the Holter recordings indicated a slight increase in bradycardia during the awake period (but not asleep) and in frequencies of accelerated idioventricular rhythm (AIVR). In the summary table below, the frequencies of abnormalities are presented for the fully documented patients, i.e. patients having an evaluable Holter recording both at baseline and at last value under treatment with a comparable duration. Similar results were observed in the analysis of all evaluable recordings under treatment.

Cardiac abnormalities on 24h Holter in fully documented patients of the Safety Set at baseline and last value under treatment

Parameter	Baseline (N = 41) n (%)	Last value (N = 41) n (%)
Bradycardia: awake period (< 40 bpm)	-	3 (7.3)
sleep period (< 30 bpm)	-	-
Pause (RR-interval > 2.5 s)	1 (2.4)	1 (2.4)
AV block: 2nd degree (Mobitz type I)	-	-
2nd degree (Mobitz II)	1 (2.4)	1 (2.4)
3rd degree	-	-
Accelerated idioventricular rhythm (AIVR)	6 (14.6)	12 (29.3)
Ventricular tachycardia	13 (31.7)	13 (31.7)
Supraventricular tachycardia	10 (24.4)	11 (26.8)
Atrial fibrillation	-	1 (2.4)
Atrial flutter	-	-
Ventricular premature depolarisation	40 (97.6)	39 (95.1)
Supraventricular premature depolarisation	40 (97.6)	39 (95.1)

n: Number of patients with indicated abnormality
N: Evaluable recordings
%: (n x 100)/N

CONCLUSION

The patients included in this 9-week phase II open-label exploratory study had stable and severe CHF (NYHA class III: 93.1%, class IV: 6.7%; with mean LVEF 28.6% and hospitalisation for heart failure within the preceding year). All were receiving stable background beta-blocker therapy, as well as concomitant treatments appropriate for this patient population. During the 6-week active treatment period, most patients (57/87; 65.5%) were up-titrated to the highest ivabradine dose (7.5 mg b.i.d.) and a further 15 (17.2%) attained the intermediate 5 mg b.i.d. dose.

Ivabradine treatment induced a clinically and statistically significant reduction in HR, decrease in LV volumes and increase in LV ejection fraction indicating a beneficial effect on cardiac haemodynamics. These changes were concomitant with clinically relevant improvements in functional assessment (NYHA classification) and clinical assessment of symptoms (by patient and investigator). Similar effects were observed in all patient subgroups examined, including in patients receiving the target dose of beta-blockers.

Ivabradine was well tolerated. The adverse drug reactions observed were mainly the one that are already in the Summary of Product Characteristics as being common, and at frequencies and degrees of severity that are consistent with the type of population.

In conclusion, in line with the principle objective of this open, exploratory study, the results confirm the acceptability of ivabradine in patients with severe heart failure receiving already beta-blockers. Furthermore, ivabradine may be beneficial in this group of patients.

Date of the report: 7 May 2008