2. 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 on peripheral and central haemodynamics parameters, safety, and tolerance of 3-hour intravenous perfusion (0.1 mg/kg) of ivabradine given to severe congestive heart failure patients.
A pilot, open labelled, monocenter study.
Protocol No.: CL2-16257-053

Investigator:
[redacted]

Study centre: Monocentre study involving 10 patients.

Publication: DE FERRARI, GM *et al*. Ivabradine infusion in patients with severe heart failure is safe, reduces heart rate, and increases left ventricular stroke volume and systolic work. European Society of Cardiology - Barcelona 2006.

Studied period:	**Phase of development of the study:**
Initiation date: 7 September 2004 Completion date: 25 February 2006	Phase II

Objectives:

- *Primary objective*: to evaluate the effects of ivabradine on central and peripheral haemodynamics parameters in patients with severe congestive heart failure.
- *Secondary objective*: to assess safety of ivabradine in these patients.

Methodology: Monocentric, non-controlled, open, single-arm study.

Number of participants:
Planned: 12 (according to Amendment No. 1)
Included: 10

Diagnosis and main criteria for inclusion:
Males and females aged from 18 to 75, with severe systolic congestive heart failure as stated by LVEF < 35%, stabilised without acute cardiac failure, for whom an invasive haemodynamic procedure was indicated. Treatment by beta-blockers was authorised if dosage was stabilised since one month prior to selection.

Study drug: Ivabradine administered in a single 3-hour intravenous infusion at the following dose: 0.100 mg/kg over first 90 minutes then dose adaptation to 0.050 or 0.075 mg/kg over last 90 minutes, depending on heart rate - Batch No. L09825.

Reference product: Not applicable.

Duration of treatment: 3-hour infusion.

Criteria for evaluation:

- Activity measurements:
  - Haemodynamics parameters and blood pressure at pre-dosing baseline, H0:30, H1:00, H1:30, H2:00, H3:00, H4:00, H6:00, H8:00, H24:00.
  - Heart rate from 12-lead ECG at selection, pre-dosing baseline, H1:00, H3:00, H6:00, H24:00 and follow-up visits.
  - Echocardiographic parameters at pre-dosing baseline, H3:00, H24:00.
  - Neurohormones at pre-dosing baseline, H1:00, H3:00, H24:00.

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Criteria for evaluation (Cont'd):

- Safety measurements:
  - Adverse events during all the study.
  - 12-lead ECG at selection, pre-dosing baseline, H1:00, H3:00, H6:00, H24:00 and follow-up visits.
  - Vital signs at selection, pre-dosing baseline and follow-up visits.
  - Laboratory tests at selection and follow-up visits.
- Pharmacokinetic measurements: at pre-dosing baseline, at H0:30, H3:00 (or H1:30 if ivabradine infusion was stopped after 90 minutes) and H24:00.

Statistical methods:

- Activity analysis: descriptive statistics on values at each measurement time and change from baseline were performed on the Included Set for haemodynamics parameters and other activity criteria. Graphs plotting the mean evolution over 8 hours and 24 hours on fully documented patients and individual graphs over 24 hours were drawn. Descriptive statistics on the Per Protocol Set were provided on 4 relevant haemodynamics parameters (heart rate, pulmonary capillary wedge pressure, left ventricular stroke volume, and cardiac index) at H0:00, H3:00 and H24:00.
- Safety analysis: emergent adverse events, abnormalities related to ECG or biological parameters and vital signs parameters were studied on patients of the Safety set using descriptive statistics and individual listings.
- Pharmacokinetic analysis: Statistical methods used for pharmacokinetic assessment are described in the corresponding report in Appendix 16.3.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Ten patients were selected and included in the study. All included patients received the ivabradine infusion and completed the study. The Included Set and the Safety Set consisted of all included patients. One patient was excluded from the Per Protocol Set because of missing haemodynamics data at H24:00.

Patients, 8 males and 2 females, were aged from 23 to 67 years (mean ± SD = 50.4 ± 11.9 years). All had a documented history of congestive heart failure, due to dilated cardiomyopathy in 8 patients (3 with ischaemic cardiomyopathy, 2 with hypertensive cardiomyopathy, and 3 with idiopathic cardiomyopathy), toxic cardiomyopathy in one patient and myocarditis associated with hypereosinophilia in one patient. LVEF ranged from 11 to 32 %, and heart rate from 82 to 102 bpm.

All patients started the infusion at the dosage of 0.100 mg/kg. After 90 minutes the dosage was modified into 0.075 mg/kg in 5 patients and into 0.050 mg/kg in 5 others. In one patient infusion was prematurely interrupted after 150 minutes because of a heart rate reduction to 60 bpm.

Main baseline characteristics in the Included Set are summarised in the Table below.

Parameter (Unit)	**Mean ± SD** (N = 10)
Duration of disease (months)	39.7 ± 56.2
Left ventricular ejection fraction (%)	20.9 ± 6.8
Heart rate from haemodynamic procedure (bpm)	93.2 ± 7.6
PCWP (mmHg)	18.8 ± 4.4
Cardiac index (L/min/m²)	2.3 ± 0.6
Left ventricular stroke volume (mL)	43.9 ± 11.1

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SUMMARY - CONCLUSIONS (Cont'd)

ACTIVITY RESULTS

- **Haemodynamics parameters**

Peak of activity was observed at H4:00 for most haemodynamics parameters. Heart rate decreased, while left ventricular stroke volume and left ventricular work increased. Cardiac index and PCWP remained stable.
Main results in the Included Set are summarised in the Table below. The same trends were observed at H3:00 in the Per Protocol Set.

Main activity parameters - Included Set (N = 10)

Parameter (unit)	**Baseline**		**H4:00**		**Change from baseline**	
	Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median
Heart rate (bpm)	93.2 ± 7.6	96	68.3 ± 9.1	70	-24.9 ± 11.2	-24
Left ventricular stroke volume (mL)	43.9 ± 11.1	41.9	66.4 ± 17.3	61.0	22.5 ± 11.5	24.4
PCWP (mmHg)	18.8 ± 4.4	16	18.1 ± 5.0	16	-0.7 ± 3.0	-1
Cardiac index (L/min/m²)	2.3 ± 0.6	2.2	2.5 ± 0.5	2.7	0.2 ± 0.6	0.2
Cardiac output (L/min)	4.1 ± 1.2	3.8	4.5 ± 0.9	4.6	0.4 ± 1.1	0.2
Left ventricular work (g/m)	38.7 ± 12.9	36.3	57.6 ± 20.2	56.8	18.9 ± 11.4	21.2

Systemic artery resistance tended to decrease with mean change from baseline at H4:00 = -241.6 ± 488.1 dyne.sec/cm^5 (median change = -159 dyne.sec/cm^5).
Systolic pulmonary pressure slightly increased from baseline with maximum change from baseline at H4:00 (7.4 ± 8.2 mmHg, median change = 6 mmHg). No clinically relevant variation was observed for other haemodynamics parameters, especially for mean pulmonary pressure.

- **Other assessment criteria**
  - Heart rate measured from 12-lead ECG decreased under ivabradine infusion, with change from baseline = -21.9 ± 9.8 bpm at H3:00. Heart rate was still lower than at inclusion after 24 hours (mean change = -8.1 ± 9.0 bpm).
  - Systolic blood pressure remained stable during the study whereas diastolic blood pressure tended to decrease with mean change from baseline at H6:00 = -9.5 ± 6.3 mmHg (median change = -13 mmHg).
  - With regards to echocardiographic parameters, stroke volume increased from baseline (mean ± SD = 47.3 ± 18.1 mL) to H3:00 (mean ± SD = 54.6 ± 42.9 mL) with mean change = 7.3 ± 28.8 mL, in line with results from haemodynamic procedure. Mean left ventricular end systolic volume (LVESV) decreased from baseline to H3:00 (change = -10.7 ± 19.2 mL) while no relevant change was detected for other left ventricular function parameters.
  - BNP tended to decrease under ivabradine infusion. Epinephrine had also a trend to decrease but mean value was highly influenced by extreme values in patient No. 053 380 0001 00008. Considering median value, a trend toward a moderate decrease was observed. Lastly, norepinephrine did not increase under ivabradine infusion.

SAFETY RESULTS

- **Emergent adverse events**

  Four patients reported a total of 5 emergent adverse events. Three emergent adverse events were considered related to treatment by the investigator: 2 visual disturbances, and one heart rate decrease below 65 bpm. The latter one led to premature interruption of the ivabradine infusion (after 2h30). All adverse events recovered. No serious adverse event occurred.
  Emergent adverse events are described in the Table below.

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SAFETY RESULTS (Cont'd)

Emergent adverse events by patient - Safety Set

Patient No.	Sex, age	Preferred Term	Intensity	Action taken	Treatment-related
053 380 0001 00002	Male, 58 years	Ventricular tachycardia	Mild	No change	No
053 380 0001 00005	Male, 57 years	Visual disturbance	Mild	Not applicable	Possible
053 380 0001 00007	Male, 51 years	Visual disturbance	Mild	Not applicable	Probable
		Bacteraemia	Moderate	Additional therapy	No
053 380 0001 00009	Female, 46 years	Heart rate decreased	Mild	Infusion stopped	Probable

- **Laboratory tests**
  Few abnormal values were observed. None of them was considered clinically significant by the investigator.
- **Vital signs**
  No clinically relevant change between selection and follow-up was observed for mean values of weight, supine SBP and supine DBP. Supine heart rate tended to be lower at follow-up than at baseline.
- **12-lead ECG**
  Only one patient had an ECG abnormality not present at baseline (ventricular extrasystoles at follow-up in patient No. 053 380 0001 00006, considered not clinically significant by the investigator), but this patient had a medical history of ventricular arrhythmia. All other ECG abnormalities were already present at baseline.

CONCLUSION

Ivabradine infusion over 3 hours in patients with severe congestive heart failure was well tolerated, induced heart rate reduction, increased stroke volume and preserved cardiac index. These results suggest a potential role for ivabradine in the treatment of advanced heart failure.

Date of the report: 04 June 2007