Document title	**Clinical Study Report Synopsis**
Study title	**Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction: SHIFT study** **A three-year randomised double-blind placebo-controlled international multicentre study**
Study drug	**Ivabradine (S 16257)**
Studied indication	**Chronic heart failure**
Development phase	**Phase III**
Protocol code	**CL3-16257-063**
Study initiation date	**26 September 2006**
Study completion date	**19 April 2010**
International coordinators	[redacted] **France** [redacted] **Sweden**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **6 place des Pleiades** **92415 Courbevoie 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 21 October 2010**

~~CONFIDENTIAL~~

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

Title of study:

Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction: SHIFT study. A three-year randomised double-blind placebo controlled international multicentre study.

Protocol No.: **CL3-16257-063**

International Coordinators:

[redacted] rance.

[redacted] Sweden

[redacted] Sweden).

Study centres:

The Randomised Set comprised 6505 patients who were included in 625 centres in 37 countries: Argentina: (48 centres – 414 patients), Australia (5 centres – 10 patients), Austria (1 centre – 10 patients), Belgium (13 centres – 52 patients), Brazil (23 centres – 246 patients), Bulgaria (20 centres – 553 patients), Canada (10 centres – 30 patients), Chile (9 centres – 74 patients), China / Hong Kong (48 centres – 343 patients), Czech Republic (24 centres – 237 patients), Denmark (14 centres – 92 patients), Estonia (4 centres – 68 patients), Finland (4 centres – 18 patients), France (17 centres – 105 patients), Germany (29 centres – 168 patients), Greece (9 centres – 64 patients), Hungary (28 centres – 387 patients), India (12 centres – 92 patients), Ireland (4 centres – 10 patients), Italy (19 centres - 112 patients), Korea (16 centres – 64 patients), Latvia (8 centres – 199 patients), Lithuania (8 centres – 111 patients), Malaysia (3 centres – 21 patients), The Netherlands (26 centres – 83 patients), Norway (5 centres – 14 patients), Poland (41 centres – 480 patients), Portugal (6 centres – 36 patients), Romania (25 centres – 651 patients), Russia (47 centres – 728 patients), Slovakia (9 centres – 75 patients), Slovenia (6 centres – 44 patients), Spain (12 centres – 77 patients), Sweden (17 centres – 49 patients), Turkey (7 centres – 66 patients), Ukraine (42 centres – 710 patients), United Kingdom (6 centres – 12 patients).

Publication (reference): Study design: Eur J Heart Failure 2010; 12: 75-81.
Main results: Lancet 2010; 376:875-885.

Studied period:
First visit, first patient: 26 September 2006
Last visit, last patient: 19 April 2010

Phase of development of the study:
Phase III

Objectives:

The primary objective was to demonstrate the superiority of ivabradine over placebo in the reduction of cardiovascular mortality or hospitalisation for worsening heart failure (composite endpoint), in patients with moderate to severe symptoms of chronic heart failure (CHF), a reduced left ventricular ejection fraction (LVEF) and receiving currently recommended therapy for this disease.

The secondary objectives were to assess the effects of ivabradine compared to placebo on:

- The primary composite endpoint in patients receiving at least half of the target daily dose of beta-blockers at randomisation (RS_{BBdose}; specified in Amendment No. 5).
- Death from heart failure and overall mortality, morbidity, functional capacity and clinical symptoms of heart failure in both the RS and RS_{BBdose} analysis sets.

Other objectives were to assess in specific sub-studies in selected centres (see separate reports) the effects of ivabradine on known predictors of prognosis in CHF (left ventricular remodelling, NT-proBNP plasma concentration and heart rate variability) and quality of life. A pharmacokinetic sub-study was also carried out.

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

Methodology:
This was a randomised, double blind, placebo-controlled, multi-centre, international, event-driven, morbidity-mortality study, with two parallel and balanced treatment arms. Randomisation was stratified on beta-blocker intake (yes/no) at time of randomisation and on centre. The study was event driven and designed to terminate after at least 1600 (Amendment No. 5) primary composite endpoints had occurred.

Number of patients:
Planned: 6500 patients, with 3250 in each treatment arm. 1600 events were necessary to detect 15% relative risk reduction assuming 90% power and a significance level of 5%. The expected annual incidence rate of the primary composite endpoint (placebo group) was 14% and the mean follow-up was expected to be 2.25 years (following Amendments No. 5 and 6).
Included and randomised: 6505 patients, with 3241 in the ivabradine group and 3264 in the placebo group.

Diagnosis and main criteria for inclusion:
The target population was adult patients with stable, moderate to severe CHF and LV systolic dysfunction and receiving currently recommended therapy for this disease.
The main selection / inclusion criteria included: systolic CHF (all aetiologies of CHF included, except for congenital heart disease, severe aortic or mitral stenosis, severe aortic regurgitation, or severe primary mitral regurgitation), with NYHA class II, III or IV, and in stable clinical condition for ≥ 4 weeks, with optimal and unchanged CHF medications and dosages for ≥ 4 weeks, with documented hospital admission for worsening HF within 12 months before selection, in sinus rhythm at selection with resting heart rate ≥ 70 bpm (ECG documentation), documented LV systolic dysfunction (LVEF ≤ 35%) within 3 months before inclusion.

Study drug:
Oral ivabradine, twice daily.
All patients were prescribed the 5 mg b.i.d. dose (ivabradine or placebo) at D000. Then, the dose was either maintained, up-titrated to the target dose of 7.5 mg b.i.d., or down-titrated to 2.5 mg b.i.d. depending on resting heart rate and tolerability.
2.5 mg tablet batches: L0012211, L0012808, L0012217, L0014993, L0018448, L0020079, L0012802, L0013855, L0013861, L0013867, L0014987, L0016150, L0019530, L0020081, L0021598, L0023416.
5 mg tablet batches: L0008911, L0011281, L0012452, L0017875, L0018142, L0013977, L0020219, L0022041.
7.5 mg tablet batches: L0011230, L0012453, L0008910, L0017120, L0018137, L0013975, L0020220, L0022040.

Reference product:
Matching placebo tablets; orally, twice daily.

Duration of treatment:
Following a run-in period of 14 days during which no study treatment was dispensed to patients, the active double-blind treatment period (ivabradine *versus* placebo) lasted from 12 months to 36 months, extended by Amendments No. 5 and 6 up to a maximal duration of 52 months. After the month 4 visit (M004), follow-up visits were planned every 4 months thereafter until the end-of-study (TERM) visit.

Criteria for evaluation:
Efficacy
An independent Endpoint Validation Committee (EVC), blinded to treatment group and baseline HR, adjudicated the clinical Pre-Specified Events occurring in the study population. The results of these adjudications were used for the efficacy analyses.

Primary criterion
Composite endpoint of the time to first event among cardiovascular death (including death from unknown cause) or hospitalisation for worsening heart failure.

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

Criteria for evaluation (Cont'd):

Secondary criteria

(i) **Non-composite endpoints:** time to first event of all cause death, cardiovascular death, death from heart failure, all cause hospitalisation, any cardiovascular hospitalisation and hospitalisation for worsening heart failure.

(ii) **Composite endpoint**

Composite endpoint of the time to first event among cardiovascular death (including death from unknown cause), hospitalisation for worsening heart failure, or hospitalisation for non fatal myocardial infarction.

(iii) Change in functional capacity (NYHA class) and global assessment of heart condition (using patient and physician global assessment scores, PaGA and PhGA). Change in heart rate.

Safety

A general safety evaluation was performed throughout the study by the Data Monitoring Committee.

A detailed safety analysis was conducted after study completion on adverse events, evolution of blood pressure, ECG heart rate and laboratory exam.

Statistical methods:

Efficacy

Survival analyses based on time-to-first event were performed for all endpoints using the intention-to-treat principle. The same statistical analyses were carried-out on patients of the Randomised Set (RS) then on patients receiving at least half the target daily dose of beta-blockers at randomisation (RS_{BBdose}) based on a hierarchical procedure.

The superiority of ivabradine as compared to placebo was tested on the time to occurrence of the primary composite endpoint using a Cox proportional hazards model adjusted for beta-blocker intake at randomisation (stratification factor). An estimate of the hazards ratio and its 95% confidence interval (CI) were also provided based on the same model. Kaplan-Meier survival curves were estimated. The treatment effect (on the primary composite endpoint and its components) was also estimated using an unadjusted model (sensitivity analysis), and a model adjusted for baseline prognostic factors.

The treatment effect on the primary composite endpoint was also documented on pre-defined subgroups of the RS based on eight criteria of demographics (age, gender), beta-blocker intake at randomisation, disease severity (baseline NYHA class, baseline HR), aetiology of chronic heart failure and coexisting medical conditions (diabetes, hypertension) as well as on non pre-defined subgroup ≥ 75 years.

The main and sensitivity analyses were performed on each component of the primary endpoint and on secondary endpoints.

For the other secondary criteria (functional capacity, clinical symptoms, heart rate), descriptive statistics were provided by treatment group. The treatment effect was estimated on the change from baseline of heart rate using a covariance analysis adjusted for baseline.

Complementary statistical tests were performed on selected secondary endpoints and these are mentioned with the presentation of results.

Safety

The safety analyses were carried-out on patients of the Safety Set. Analyses were performed on emergent adverse events (EAEs) "on treatment" (*i.e.* after the first intake of study drug until the last study drug intake + 2 days included) as well as on those occurring "during the study" (*i.e.* after first intake of study drug until the database was closed). Emergent adverse events, blood pressures, laboratory test parameters and ECG heart rate were studied using descriptive statistics. For heart rate, counts were made of the patients having an emergent bradycardia on resting ECG of < 50 bpm and < 40 bpm.

Three planned interim efficacy analyses were carried out by the DMC. No modification to the conduct of the study was recommended.

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 7411 patients were screened, 7106 were selected and 6505 (91.5% of selected patients) were included and randomised in the study: 3241 in the ivabradine group and 3264 in the placebo group. Patient status at the end of the study is indicated in Table 1. A total of 14 patients were excluded from the Safety Set, because they never took any study medication and one included patient who received the study drug (placebo) without being randomised was included in the safety set in the placebo group.

Table 1 - Disposition of patients

		Ivabradine	**Placebo**	**All**
Included and randomised (RS)	**N**	**3241**	**3264**	**6505**
Died before completion	n (%)	503 (15.5)	553 (16.9)	1056 (16.2)
Consent withdrawal	n (%)	73 (2.3)	58 (1.8)	131 (2.0)
Lost to follow-up	n (%)	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)
Completed	n (%)	2663 (82.2)	2652 (81.3)	5315 (81.7)
Patients analysed	n (%)	**3241 (100.0)**	**3264 (100.0)**	**6505 (100.0)**
RS_{BBdose}	n (%)	**1581 (48.8)**	**1600 (49.0)**	**3181 (48.9)**
Safety Set	n (%)	**3232 (99.7)**	**3260 (99.9)**	**6492 (99.8)**

N Total number of patients in the randomised treatment group
n Number of patients concerned
% = (n / N) x 100

Main baseline characteristics

No clinically relevant differences between treatment groups were noted regarding the main demographic data or baseline characteristics.

The *Randomised Set* consisted of patients with a mean age (± SD) of 60.4 ± 11.4 years (range from 19 to 92 years), they were mostly men (76.4%) and of Caucasian origin (88.7%). Asian patients comprised 8.2% of the population. The mean heart rate (in patients with sinus rhythm) was 79.9 ± 9.6 bpm.

CHF had been diagnosed for less than 5 years in 75.9% of patients (mean = 3.5 ± 4.2 years, median = 2.0 years). The primary cause of CHF was ischaemic in two-thirds of the population (67.9%). For patients having a non-ischaemic origin for their CHF (32.1%), the most frequent reason was an idiopathic dilated cardiomyopathy (20.7% of the RS). 48.7% of the study population was of NYHA class II at study entry, 51.3% was of class III or IV. The mean LVEF was 29.0 ± 5.2% (7 – 39%) with 24.8% of patients having an LVEF below or equal to 25%.

Coronary artery disease or myocardial infarction were reported as medical histories in 72.7% and 56.4% of patients, respectively. Hypertension was frequent at 66.3% of the population and diabetes was present in 30.4%.

All patients of the RS were receiving at least one concomitant treatment at randomisation. The background treatments at randomisation complied with ESC guideline recommendations, including agents acting on the renin-angiotensin system (91.1%) (an ACE inhibitor was used by 78.6% of patients), beta-blockers (89.5%) and anti-aldosterone agents (60.3%). Patients received also diuretics excluding anti-aldosterone agents (83.2%), antithrombotic agents (83.7%), lipid modifying agents (58.3%) and digitalis (21.8%).

Of the 5820 patients taking a beta-blocker at randomisation, 98.2% were taking an ESC recommended beta-blocker or metoprolol tartrate at randomisation; among these, 55.7% were receiving their beta-blocker at least half the target daily dose and 26.1% were at the target daily dose. The predominant reasons for not reaching the target doses of beta-blockers were hypotension (in 44.6% of patients not at target) or fatigue (in 31.9%). 10.5% of the RS did not receive a beta-blocker at randomisation, mainly because of concomitant conditions of COPD, hypotension or asthma. Overall, a total of 244 patients (3.8%) had at least one cardiac device, *i.e.* a pacemaker and/or a CRT and/or an ICD.

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

STUDY POPULATION AND OUTCOME (Cont'd)

In the RS_{BBdose} (48.9% of RS) the demographic and baseline characteristics were similar to those of the RS. The patients had a mean age (± SD) of 59.2 ± 11.1 years, were mostly male (76.0%) and of Caucasian origin (93.6% *versus* 88.7% in the RS). The mean HR was 79.0 ± 8.7 bpm. The overall mean duration of the CHF from the diagnosis was 3.7 ± 4.2 years with an ischaemic primary cause in 69.1% of patients. 49.8% of patients were of NYHA class II at study entry, 50.2% were of class III or IV. The mean LVEF was 29.3 ± 5.0% (7 – 37%). Approximately, half of the patients (46.8%) were taking the target daily dose of beta-blocker. Concerning the other specific concomitant treatments, patients were most frequently treated with an ACE inhibitor and/or ARB (92.8%), followed by use of a diuretic (excluding anti-aldosterone) with 81.9% of patients concerned. 59.3% of patients were receiving anti-aldosterone agents.

Follow-up duration, treatment duration and dose

The overall mean duration of the follow-up in the RS was 21.9 ± 8.0 months (median = 22.9 months) with 74.2% of the patients having a follow-up of at least 18 months; the overall mean treatment duration was 20.1 months (median = 21.6 months) with 65.5% of the patients having a treatment duration of at least 18 months. Compliance was good: 97.8% of patients had a compliance between 70% and 130%. No difference between treatment groups was noted concerning these parameters.

In the ivabradine group of the RS, 60.3% of patients were up-titrated to the higher dose of the study drug (*i.e.* 7.5 mg b.i.d) maintained during all the study, 7.2% of patients were down-titrated to the dose 2.5 mg b.i.d. (maintained during all the study) and 8.7% maintained at the 5 mg dose (during all the study). The remaining patients received several study drug doses during the study. The mean ivabradine doses prescribed according to treatment duration and follow-up duration were 6.4 ± 1.4 mg twice daily and 5.8 ± 2.1 mg twice daily, respectively.

In the placebo group, 90.6% of patients were up-titrated and maintained this dose during all the study.

Similar results were observed in the RS_{BBdose}.

Permanent treatment withdrawal

The study treatment was prematurely discontinued in a total of 1287 patients (19.8%): 682 patients (21.0%) in the ivabradine group *versus* 605 (18.5%) in the placebo group. (Note: Not counted in this analysis were treatment withdrawals for reason of death nor treatment withdrawals that were followed by death within 2 days). The treatment withdrawals were due to adverse events (64.0% of withdrawals), non-medical reason (31.0%), concomitant treatment(s) started during the study (3.0%) or HR < 50 bpm at the 2.5 mg b.i.d dose without symptoms of bradycardia (2.0%). The main between-group differences on the withdrawal study drug were events related to the mechanism of action of ivabradine, *i.e.* slowing of HR (including the category "HR < 50 bpm at the 2.5 mg b.i.d dose", and the adverse events, bradycardia and HR decreased) which led to treatment withdrawal in a total of 70 patients in the ivabradine group (2.2% of RS; 10.3% of withdrawals) *versus* 13 in the placebo group (0.4% of RS; 2.1% of withdrawals). It was noted that fewer patients in the ivabradine group were withdrawn by the investigator for cardiac failure than in the placebo group: 56 patients (8.2% of withdrawals) *versus* 65 (10.7% of withdrawals), respectively.

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

EFFICACY RESULTS

- **Primary composite endpoint**

In the RS (N = 6505), a total of 793 patients (24.5%) in the ivabradine group *versus* 937 (28.7%,) in the placebo group reached the primary composite endpoint (first event of CV death or hospitalisation for worsening HF), with annual incidence rates of 14.5%PY *versus* 17.7%PY, respectively (see Table 2). The estimate of the hazard ratio was 0.82 (95% CI [0.75 ; 0.90], p < 0.0001), with a clinically and statistically significant Relative Risk Reduction (RRR) of 18%.

The Kaplan-Meier curves of the time to first event of primary composite endpoint are presented in Figure 1.

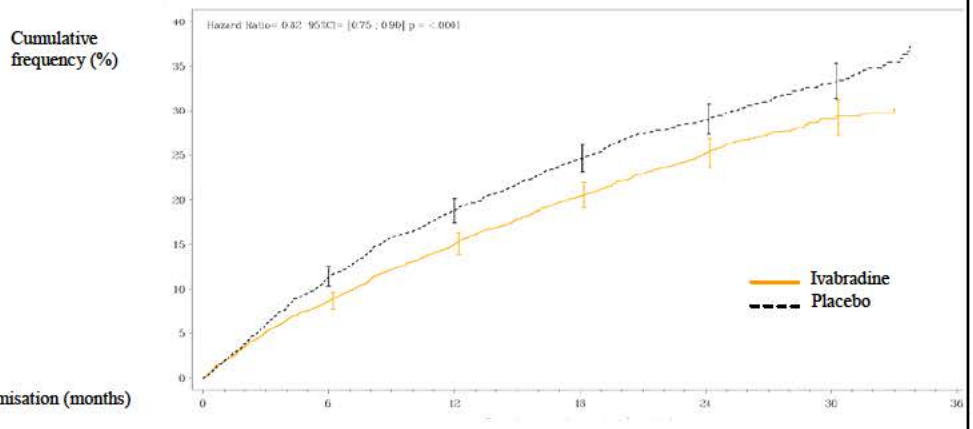
The results of the components of the composite as secondary endpoints are described on the following page.

Table 2 - Incidence of the primary composite endpoint and components (secondary endpoints) in the RS

	Ivabradine (N = 3241; NPY = 5478)			**Placebo (N = 3264; NPY = 5299)**			**Hazard ratio**	**p-value**
	n	**%**	**%PY**	**n**	**%**	**%PY**	**E [95% CI]**	
Primary composite endpoint	**793**	**24.5**	**14.5**	**937**	**28.7**	**17.7**	**0.82 [0.75 ; 0.90]**	**< 0.0001**
Secondary endpoints								
- Cardiovascular death	449	13.9	7.5	491	15.0	8.3	0.91 [0.80 ; 1.03]	0.128
- Hospitalisation for worsening HF	514	15.9	9.4	672	20.6	12.7	0.74 [0.66 ; 0.83]	**< 0.0001**

N number of patients at risk; NPY number of patient-years at risk for primary composite endpoint; n number of patients reaching the endpoint; % global incidence rate, (n/N) x 100; %PY annual incidence rate, = (n/NPY) x 100
E [95% CI] estimate of the hazard ratio between treatment groups [2-sided 95% Confidence Interval of the estimate] based on an adjusted Cox proportional hazards model with beta-blocker intake at randomisation as a covariate
p-value Wald test

Figure 1 - Time to first event of primary composite endpoint in the RS



Number of patients at risk (Ivabradine / Placebo)	3241 / 3264	2928 / 2868	2600 / 2489	2173 / 2061	1191 / 1089	477 / 439	16 / 17
Cumulative number of endpoints	-	276 / 366	477 / 604	638 / 775	745 / 876	788 / 922	793 / 937
Cumulative frequency (%)	-	8 57 / 11 27	14 93 / 18 74	20 42 / 24 58	25 17 / 28 92	29 03 / 33 15	30 26 / 37 26

The sensitivity analysis (without adjustment) and the prognostic factor analysis (with adjustment on beta-blocker intake at randomisation, NYHA class, LVEF, aetiology of CHF (ischaemic or not), age, systolic blood pressure, heart rate and estimated glomerular filtration rate, at baseline) confirmed these results: hazard ratio = 0.82 [0.75 ; 0.90] for the unadjusted analysis and hazard ratio = 0.83 [0.75 ; 0.91] for the analysis adjusted on prognostic factors.

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

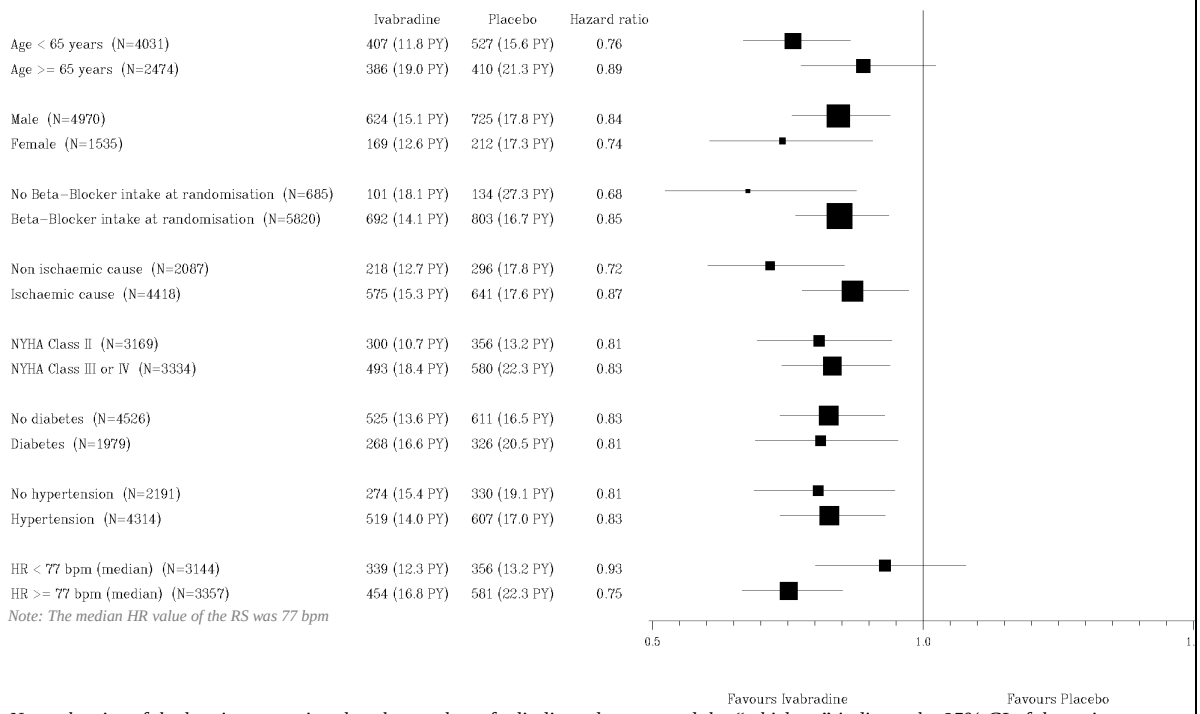
EFFICACY RESULTS (Cont'd)

The estimates of treatment effect on primary composite endpoint in the **predefined subgroups** of the RS according to baseline characteristics are summarised in Figure 2.

The incidence of the primary composite endpoint was consistently reduced with ivabradine *versus* placebo in all subgroups, although a greater effect of ivabradine was observed in patients with a baseline heart rate above the median (HR ≥ 77 bpm): hazard ratio = 0.75 in this subgroup *versus* 0.93 in the subgroup "HR < 77 bpm" (interaction test, p = 0.0288).

The results in the subgroup "age ≥ 75 years" (n = 722; complementary subgroup) were also in favour of ivabradine with a hazard ratio = 0.89, 95% CI [0.70 ; 1.14].

Figure 2 - Estimate of treatment effect on primary composite endpoint in pre-defined subgroups of the RS



Note: the size of the box is proportional to the number of adjudicated events and the "whiskers" indicate the 95% CI of the estimate

In the RS_{BBdose} (N = 3181 patients), a total of 330 patients (20.9%, 11.9%PY) in the ivabradine group *versus* 362 (22.6%, 13.3%PY) in the placebo group reached the primary composite endpoint. The estimate of the corresponding hazard ratio using an unadjusted Cox proportional hazards model, was 0.90 (95% CI [0.77 ; 1.04]), indicating a trend towards a risk reduction in the ivabradine group (p = 0.155).

- **Secondary endpoints**

Analysis of deaths

In the RS, a total of 1055 adjudicated deaths from any cause that occurred before or at the TERM visit were analysed as efficacy endpoints. Table 3 presents the causes of deaths by treatment group.

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

EFFICACY RESULTS (Cont'd)

The **all-cause mortality** tended to be lower in the ivabradine group than in the placebo group (15.5% *versus* 16.9%), corresponding to a 10% RRR (E = 0.90, 95% CI [0.80 ; 1.02], p = 0.092). Most of these were of cardiovascular origin and the global incidence rate of **cardiovascular death** was lower in the ivabradine group than in the placebo group (13.9% *versus* 15.0%, respectively) with a 9% RRR estimate (E = 0.91, 95% CI [0.80 ; 1.03], p = 0.128).

The cardiovascular deaths were mostly related to sudden cardiac death which occurred in 7.2% of patients in the ivabradine group *versus* 6.7% in the placebo group. Considering the ensemble "sudden cardiac death/sudden death of unknown cause", the incidence rate was 7.9% in both groups. **Deaths from heart failure** occurred less frequently in the ivabradine group (3.5% *versus* 4.6%), corresponding to a clinically and statistically significant RRR estimate of 26% (E = 0.74, 95% CI [0.58 ; 0.94], p = 0.0140).

Table 3 - Causes of deaths by treatment group in the RS

	Ivabradine (N = 3241; NPY = 5954)			**Placebo (N = 3264; NPY = 5917)**		
	n	**%**	**%PY**	**n**	**%**	**%PY**
Death from any cause	**503**	**15.5**	**8.5**	**552**	**16.9**	**9.3**
Cardiovascular death	**449**	**13.9**	**7.5**	**491**	**15.0**	**8.3**
Sudden cardiac death	232	7.2	3.9	220	6.7	3.7
Death from heart failure	113	3.5	1.9	151	4.6	2.6
Death from myocardial infarction	29	0.9	0.5	25	0.8	0.4
Death from other cardiovascular reason	42	1.3	0.7	48	1.5	0.8
Death of unknown cause	33	1.0	0.6	47	1.4	0.8
Sudden death of unknown cause	25	0.8	0.4	39	1.2	0.7
Non sudden death of unknown cause	8	0.3	0.1	8	0.3	0.1
Non-cardiovascular death	**54**	**1.7**	**0.9**	**61**	**1.9**	**1.0**

N number of patients at risk; NPY number of patient-years at risk; n number of patients reaching endpoint
% = (n/N) x 100; %PY annual incidence rate, = (n/NPY) x 100

In the RS_{BBdose}, a total of 401 deaths from any cause were adjudicated. No difference in the global incidence rate of **all-cause mortality** and **cardiovascular death** was shown between treatment groups although **death from heart failure** was non-statistically significantly reduced by 16% in the ivabradine group.

Analysis of hospitalisations

In the RS, a total of 2661 hospitalisations for any cause in 1231 patients in the ivabradine group were adjudicated *versus* 3110 in 1356 patients in the placebo group. The mean number (± SD) of hospitalisations per patient was similar in the 2 groups (overall, 2.2 ± 2.0).

Table 4 gives the number and percentage of patients in the RS having experienced at least one hospitalisation according to the different reasons. A total of 977 patients (30.2%, 19.8%PY) were hospitalised at least once for a CV reason in the ivabradine group *versus* 1122 patients (34.4%, 23.5%PY) in the placebo group) and 15.9% (9.4%PY) *versus* 20.6% (12.7%PY) respectively, for at least one event of worsening HF. The total number of hospitalisations for worsening HF was 902 in the ivabradine group *versus* 1211 in the placebo group.

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

EFFICACY RESULTS (Cont'd)

The global incidence rate of the **all-cause hospitalisation** was lower in the ivabradine group with 38.0% *versus* 41.5% in the placebo group, corresponding to a statistically significant RRR of 11% in the ivabradine group (E = 0.89, 95% CI [0.82 ; 0.96], p = 0.0027). **Hospitalisation for CV reason** occurred in 30.2% of patients in the ivabradine group *versus* 34.4% in the placebo group, mainly due to **worsening heart failure** (15.9% *versus* 20.6%). The incidence of hospitalisation for myocardial infarction was similar in both groups (2.6% *versus* 2.7%). A statistically significant treatment effect in favour of ivabradine was observed on hospitalisation for CV reason with a RRR of 15% (E = 0.85, 95% CI [0.78 ; 0.92], p = 0.0002) and on hospitalisation for worsening heart failure with a RRR of 26% (E = 0.74, 95% CI [0.66 ; 0.83], p < 0.0001).

Table 4 - Causes of hospitalisations by treatment group in the RS

Number of patients with at least one:	**Ivabradine (N = 3241; NPY = 4638)**			**Placebo (N = 3264; NPY = 4527)**		
	n	**(%)**	**%PY**	**n**	**(%)**	**%PY**
Hospitalisation for any cause*	**1231**	**38.0**	**26.5**	**1356**	**41.5**	**30.0**
Hospitalisation for cardiovascular reason	**977**	**30.2**	**19.8**	**1122**	**34.4**	**23.5**
Hospitalisation for worsening heart failure	514	15.9	9.4	672	20.6	12.7
Hospitalisation for myocardial infarction	84	2.6	1.4	87	2.7	1.5
Hospitalisation for other CV reason	577	17.8	10.8	635	19.5	12.0
Hospitalisation for undetermined cause	18	0.6	0.3	36	1.1	0.6
Hospitalisation for non-cardiovascular reason	**477**	**14.7**	**8.7**	**508**	**15.6**	**9.3**

** Patients were often hospitalised on more than one occasion and for different reasons the first admission for each analysed reason is counted in this analysis*
N number of patients at risk; NPY number of patient-years at risk for hospitalisation for any cause (the values for NPY for subordinate categories are not shown); n number of patients reaching endpoint
% = (n/N) x 100; %PY annual incidence rate, = (n/NPY) x 100

In the RS_{BBdose}, a total of 2461 **all-cause hospitalisations** were reported in 1155 patients, the global incidence rate tending to be lower in the ivabradine group with 34.9% than in the placebo group with 37.8% (p = 0.081). The main reason of hospitalisation was cardiovascular (27.6% of patients in the ivabradine group *versus* 30.7% in the placebo group), mostly related to worsening HF (13.5% of patients *versus* 16.3%, respectively). A statistically significant RRR of 12% for the **hospitalisation for CV reason** and of 19% for the **hospitalisation for worsening HF** was observed in the ivabradine group.

Secondary composite endpoint

In the RS, 825 patients (25.5%) in the ivabradine group and 979 (30.0%) in the placebo group reached the secondary composite endpoint (first event among cardiovascular death, hospitalisation for worsening heart failure or hospitalisation for non fatal myocardial infarction) (Table 5). The estimate of the hazard ratio was 0.82 (95% CI [0.74 ; 0.89], p < 0.0001), with a clinically and statistically significant relative risk reduction of 18%.

Table 5 - Incidence of the secondary composite endpoint and estimate of treatment effect in the RS

Ivabradine				**Placebo**				**Hazard ratio**	**p-value**
n/N	(%)	NPY	(%PY)	n/N	(%)	NPY	(%PY)	E [95% CI]	
825/3241	(25.5)	5432	(15.2)	979/3264	(30.0)	5250	(18.7)	0.82 [0.74 ; 0.89]	< **0.0001**

n number of patients having experienced the endpoint; N number of patients at risk; NPY number of patient-years at risk
% global incidence rate, (n/N) x 100; %PY annual incidence rate, (n/NPY) x 100
E [95% CI] estimate of hazard ratio between treatment groups [2-sided 95% Confidence Interval of estimate] based on adjusted Cox proportional hazards model with beta-blocker intake at randomisation as a covariate
p-value Wald test

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

EFFICACY RESULTS (Cont'd)

In the RS_{BBdose}, a trend towards a reduction on the **secondary composite endpoint** in the ivabradine group was observed, with a relative risk reduction of 11% (p = 0.124).

- Other secondary criteria

NYHA classes

The rate of patients in the RS having an improvement in NYHA class between baseline and last post-randomisation visit was slightly higher in the ivabradine group than in the placebo group (27.6% *versus* 24.0%, respectively; p = 0.0010, complementary test). In the RS_{BBdose}, the rates were similar in each group (25.9% *versus* 24.2%, respectively). In parallel, fewer patients registered a worsening in NYHA class in the ivabradine group than in the placebo group (4.9% *versus* 6.0%, respectively in the RS and 4.4% *versus* 5.1%, respectively in the RS_{BBdose}).

Global assessment of heart condition

The analyses of the patient and investigator reported **clinical global assessments** showed that more patients and physicians, respectively, accorded an improvement in heart condition under ivabradine at the last post randomisation visit (for PaGA: 71.8% in the ivabradine group *versus* 67.6% in the placebo group, p = 0.0005; for PhGA: 61.1% *versus* 57.0%, respectively, p = 0.0011, complementary tests).

Heart rate

The mean HR at baseline was similar in the RS and RS_{BBdose} and in the two treatment groups.
In the RS, there was a decrease of -15.4 ± 10.7 bpm in the ivabradine group between baseline and D028 *versus* -4.6 ± 10.6 bpm in the placebo group, corresponding to a statistically and clinically significant between-group difference of -10.9 bpm (95% CI [-11.4 ; -10.4]).
This heart rate lowering effect was sustained during the study; at the last post-randomisation visit, the HR decreased of -12.0 ± 13.3 bpm from baseline in the ivabradine group *versus* -4.1 ± 12.9 bpm in the placebo group, the between-group difference of -8.1 bpm being statistically significant (95% CI [-8.7 ; -7.5]).
Similar between-group differences were observed in the RS_{BBdose}.

SAFETY RESULTS

Overall during the study (first study drug intake until database closure) a total of 20,142 EAEs in 4862 patients (75.5%, 41.0%PY in the ivabradine group *versus* 74.3%, 41.0%PY in the placebo group) and 1074 deaths (16.5%, 9.1%PY) were reported. In the ivabradine group there were 510 (15.8%, 8.6%PY) deaths and in the placebo group there were 564 (17.3%, 9.5%PY).

Emergent adverse events (all clinical events) on treatment

The main focus of the presentation of EAEs was on the clinical events that occurred on treatment (adverse events which occurred, worsened or became serious between the first study drug intake and the last study drug intake + 2 days (included)).
Of the 828 (12.8%, 7.6%PY) on-treatment EAEs with a fatal outcome: 400 (12.4%, 7.4%PY) occurred in the ivabradine group *versus* 428 (13.1%, 7.8%PY) in the placebo group. The most frequently reported reasons (according to the investigator) for these fatal events were sudden death (3.4%, 2.1%PY *versus* 3.7%, 2.2%PY, respectively), sudden cardiac death (2.3%, 1.4%PY *versus* 2.1%, 1.2%PY, respectively), or due to cardiac failure (2.1%, 1.3%PY *versus* 2.8%, 1.7%PY, respectively).

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

SAFETY RESULTS (Cont'd)

The summary of incidence of EAE by category and seriousness is presented in Table 6.

At least one EAE on-treatment was reported in 74.7% of patients (44.7%PY) in the ivabradine group *versus* 73.4% (43.5%PY) in the placebo group. The most frequently affected System Organ Classes (SOCs) had fairly similar event rates in the 2 treatment groups. These SOCs were: *cardiac disorder*s (41.2%, 24.7%PY *versus* 41.6%, 24.7%PY, respectively), *infections and infestations* (19.6%, 11.7%PY *versus* 22.4%, 13.3%PY, respectively), *investigations* (14.0%, 8.4%PY *versus* 10.0%, 5.9%PY, respectively), *metabolism and nutrition disorders* (13.9%, 8.3%PY *versus* 14.7%, 8.7%PY, respectively) and *vascular disorders* (13.5%, 8.1%PY *versus* 13.0%, 7.7%PY, respectively).

Table 6 - Overall summary of safety results - All clinical events on treatment

Patients having reported at least one on-treatment event of:	**Ivabradine (N = 3232) (NPY = 5401.1)**			**Placebo (N = 3260) (NPY = 5495.3)**		
	n	%	%PY	n	%	%PY
Emergent adverse event	2414	74.7	44.7	2392	73.4	43.5
Severe emergent adverse event	773	23.9	14.3	820	25.2	14.9
Treatment-related emergent adverse event	574	17.8	10.6	271	8.3	4.9
EAE leading to study treatment withdrawal*	467	14.5	8.7	416	12.8	7.6
Serious adverse event (including death)	1369	42.4	25.4	1481	45.4	27.0
Serious treatment-related adverse event	66	2.0	1.2	42	1.3	0.8
SEAE leading to study treatment withdrawal*	270	8.4	5.0	279	8.6	5.1

N total number of patients in considered treatment group; NPY number of patient-years in considered treatment group
n number of affected patients; % = (n/N) x 100; %PY = (n/NPY) x 100
** including permanent drug withdrawals and temporary withdrawals without restart*

The most frequently reported EAEs in both groups were (ivabradine *versus* placebo):

- Cardiac failure: 21.7%, 13.0%PY *versus* 26.0%, 15.4%PY, respectively.
- Atrial fibrillation: 8.3%, 4.9%PY *versus* 6.7%, 4.0%PY, respectively.
- Blood pressure inadequately controlled: 7.1%, 4.2%PY *versus* 6.1%, 3.6%PY, respectively.

The EAEs more frequently reported in the ivabradine group than in the placebo group were generally those expected during ivabradine treatment, in particular:

- Asymptomatic bradycardia (HR decreased): 5.6%, 3.4%PY *versus* 1.4%, 0.8%PY, respectively.
- Symptomatic bradycardia: 4.6%, 2.7%PY *versus* 0.9%, 0.5%PY, respectively.
- Phosphenes: 2.8%, 1.7%PY *versus* 0.5%, 0.3%PY, respectively.

Severe EAEs: on-treatment severe EAEs were reported with similar incidences: 23.9% (14.3%PY) in the ivabradine group *versus* 25.2% (14.9%PY) in the placebo group.

Treatment-related EAEs were more frequently reported in the ivabradine group (17.8%, 10.6%PY) than in the placebo group (8.3%, 4.9%PY). The difference between the two groups was mainly due to known adverse drug reactions of ivabradine, notably asymptomatic bradycardia (HR decreased: 4.6%, 2.8%PY *versus* 1.0%, 0.6%PY, respectively), symptomatic bradycardia (3.7%, 2.2%PY *versus* 0.7%, 0.4%PY, respectively), and phosphenes (2.7%, 1.6%PY *versus* 0.5%, 0.3%PY, respectively).

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

SAFETY RESULTS (Cont'd)

EAEs leading to study treatment withdrawal occurred at incidences of 14.5% (8.7%PY) in the ivabradine group *versus* 12.8% (7.6%PY) in the placebo group. These events were most frequently related to *cardiac disorders* (9.4%, 5.6%PY *versus* 8.3%, 4.9%PY, respectively), mainly atrial fibrillation (4.2%, 2.5%PY *versus* 3.5%, 2.1%PY), in accordance with the protocol-directed withdrawal in case of sustained fibrillation; and also cardiac failure (2.0%, 1.2%PY *versus* 2.4%, 1.4%PY). Asymptomatic bradycardia (HR decreased) was relatively infrequent at 0.9% (0.5%PY) *versus* 0.2% (0.1%PY), respectively, as were symptomatic bradycardia at 0.6% (0.4%PY) *versus* 0.2% (0.1%PY) and eye disorders 0.3% (0.2%PY) *versus* 0.2% (0.1%PY).

Serious EAEs on treatment were reported at a slightly lower frequency in the ivabradine group: 42.4%, 25.4%PY *versus* 45.4%, 27.0%PY in the placebo group. The most frequently affected SOCs were *cardiac disorders* and *general disorders and administration site conditions*. The largest between-group difference was due to the incidence of cardiac failure (15.7%, 9.4%PY *versus* 20.4%, 12.1%PY, respectively). Only minor between-group differences were observed in the incidences of other preferred terms.
SEAEs that led to treatment withdrawal were reported with similar frequencies in each treatment group: 8.4%, 5.0%PY, in the ivabradine group *versus* 8.6%, 5.1%PY in the placebo group. They were mainly *cardiac disorders* (6.1%, 3.6%PY *versus* 5.8%, 3.4%PY, respectively).

As regards the analyses of adverse events in the subgroup of **elderly patients** (≥ 75 years old; n = 720; 11.1% of Safety Set; complementary analysis), ivabradine was relatively well tolerated *versus* placebo, with similar overall rates of EAE (78.8%, 50.3%PY *versus* 77.6%, 48.0%PY, respectively) and lower overall rates of SEAEs (50.1%, 32.0%PY *versus* 53.8%, 33.3%PY, respectively).

Clinical laboratory evaluation tests and vital signs

Biochemical and haematology parameters did not show any relevant changes over time or differences between groups.
Patients with emergent high abnormal values were detected with similar frequency in both treatment groups for creatinine (17.4% in the ivabradine group *versus* 16.4% in the placebo group), ALAT (14.7% *versus* 15.1%, respectively), ASAT (12.9% *versus* 13.1%, respectively) and potassium (13.0% *versus* 14.0%, respectively). Emergent values that exceeded the potentially clinically significant abnormal (PCSA) thresholds were infrequent and similar in both treatment groups (< 2%).
Low emergent abnormal values were detected for haemoglobin with similar frequency in each treatment group (14.3% *versus* 15.5%, respectively). Emergent low PCSA values occurred at rates of 0.4% *versus* 0.5%, respectively.
The analysis over time of sitting blood pressure showed in the ivabradine group a mean change of SBP/DBP of +4.1 ± 16.0/0.4 ± 10.2 mmHg *versus* in the placebo group +2.0 ± 16.2 /0.7 ± 10.3 mmHg. The slight SBP increase in the ivabradine group was probably the reflection of an improvement in haemodynamics. Mean weight slightly increased over time in each group (0.9 kg).

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)*
Name of Finished Product: Procoralan® EU	**Volume:**	
Name of Active Ingredient: Ivabradine (S 16257)	**Page:**	

CONCLUSION

Ivabradine significantly reduced, *versus* placebo, the incidence rate of CV death or hospitalisation for worsening HF (primary composite endpoint) in patients with moderate to severe chronic HF, having a reduced LVEF and receiving currently recommended therapy for this condition. The relative risk reduction (RRR) of 18% was clinically and statistically significant ($p < 0.0001$).

In the analysis of secondary endpoints, ivabradine treatment was associated with 26% lower risk of hospitalisation for worsening HF ($p < 0.0001$) and 26% lower risk of death for HF ($p = 0.0140$). There was a trend to fewer CV deaths (RRR of 9%, $p = 0.128$) and lower all-cause mortality (RRR of 10%, $p = 0.092$).

In patients receiving at least half of target daily dose of beta-blockers at randomisation (49% of RS), the incidence of the primary composite endpoint *versus* placebo tended to be lower in the ivabradine group (RRR = 10%; $p = 0.155$).

A significant improvement in NYHA class was reported in 27.6% of patients in the ivabradine group *versus* 24% in the placebo group ($p = 0.0010$); patient-reported global assessment improved in 71.8% *versus* 67.6%, respectively ($p = 0.0005$); and physician-reported assessment in 61.1% *versus* 57.0%, respectively ($p = 0.0011$)

After 4 weeks of treatment and from a baseline HR value of 80 bpm, the patients randomised to ivabradine had a mean HR reduction of 15 bpm; they maintained a marked reduction *versus* placebo throughout the study.

The safety profile of ivabradine remains similar to the one already known; it was in accordance with the mechanism of action and did not raise any new safety concerns in this population.

Overall, study CL3-063 demonstrated that oral ivabradine, when added to guideline-recommended treatment, reduces mortality and major morbidity associated with chronic heart failure in patients with elevated heart rate (≥ 70 bpm).

Date of the report: 21 October 2010