| | |
|---|---|
| *Document title* | **Clinical Study Report Synopsis** |
| *Study title* | **Effects of ivabradine on cardiovascular events in patients with stable coronary artery disease and left ventricular systolic dysfunction. A three-year randomised double-blind placebo-controlled international multicentre study** |
| *Study drug* | **Ivabradine (S 16257)** |
| *Indication* | **Reduction of cardiovascular events in patients with coronary artery disease and left ventricular systolic dysfunction** |
| *Development phase* | **Phase III** |
| *Protocol code* | **CL3-16257-056** |
| *Study initiation date* | **20 December 2004** |
| *Study completion date* | **28 February 2008** |
| *Main coordinator* | [redacted] **United Kingdom** |
| *Sponsors* | **Institut de Recherches Internationales Servier (I.R.I.S.)**<br>**50 Rue Carnot**<br>**92284 Suresnes Cedex - France**<br><br>**Servier Canada Inc.**<br>**235 Armand-Frappier Blvd**<br>**Laval, Quebec H7H 4A7 - Canada**<br><br>**Servier Research and Development**<br>**Gallions, Wexham Springs, Framewood Road Wexham**<br>**Slough SL3 6RJ - 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* | **Final version of 9 March 2009** |

**~~CONFIDENTIAL~~**

## 2. SYNOPSIS

| | | |
|---|---|---|
| **Name of Company:**<br>**I.R.I.S.**<br>**6 place des Pleiades**<br>**92415 Courbevoie - FRANCE** | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

**Title of study:**
Effects of ivabradine on cardiovascular events in patients with stable coronary artery disease and left ventricular systolic dysfunction. A three-year randomised double-blind placebo-controlled international multicentre study – The BEAUTIFUL study.
Protocol No.: **CL3-16257-056**

**International Coordinators:** [redacted]
United Kingdom.
Assisted by 36 National Coordinators (2 from China, Bulgaria and Russia).

**Study centres:**
757 active centres in 33 countries included at least one patient: Argentina: (29 centres – 613 included patients), Australia (28 centres – 158 included patients), Austria (4 centres – 22 included patients), Belgium (9 centres – 48 included patients), Bulgaria (17 centres – 578 included patients), Canada (33 centres – 352 included patients), China / Hong Kong (12 centres – 118 included patients), Czech Republic (27 centres – 601 included patients), Denmark (27 centres – 360 included patients), Estonia (6 centres – 83 included patients), Finland (4 centres – 13 included patients), France (60 centres – 320 included patients), Germany (64 centres – 537 included patients), Greece (20 centres – 155 included patients), Hungary (35 centres – 449 included patients), Ireland (4 centres- 12 included patients), Italy (39 centres – 269 included patients), Latvia (8 centres – 167 included patients), Lithuania (9 centres – 254 included patients), Netherlands (48 centres – 694 included patients), Norway (3 centres – 25 included patients), Poland (48 centres – 1091 included patients), Portugal (10 centres – 46 included patients), Romania (36 centres – 710 included patients), Russia (52 centres – 1362 included patients), Slovakia (10 centres – 202 included patients), Slovenia (6 centres - 50 included patients), Spain (25 centres – 196 included patients), Sweden (6 centres – 60 included patients), Switzerland (7 centres – 27 included patients), Turkey (7 centres – 101 included patients), Ukraine (47 centres – 1162 included patients), United Kingdom (17 centres – 82 included patients).

**Publications:** Am Heart J 2006, 152:860-866 (study design); Cardiology 2008, 110:271-282 (baseline data); Lancet 2008, 372:807-816 (main study results); Lancet 2008, 372:817-821 (heart rate as prognostic risk factor).

| **Studied period:** | | **Phase of development of the study:** |
|---|---|---|
| Initiation date: | 20 December 2004 | Phase III |
| Defined completion date: | 15 January 2008 | |
| Last visit, last patient: | 28 February 2008 | |

**Objectives:** The primary objective was to demonstrate the superiority of ivabradine over placebo in the reduction of incidence of the composite endpoint: cardiovascular (CV) mortality, hospital admissions for acute myocardial infarction (MI), hospital admissions for new onset or worsening heart failure (HF).
The secondary objectives were to assess the effect of ivabradine:

- On hospital admissions for acute coronary syndrome (ACS; MI or unstable angina).
- On hospital admissions for ACS, new onset or worsening HF, coronary revascularisations (composite endpoint).
- On each endpoint of the previously mentioned composite endpoints.
- On mortality related to coronary artery disease (CAD), all-cause mortality.

The tertiary objectives were to assess the effect of ivabradine:

- On the development of diabetes and metabolic syndrome.
- On the evolution of left ventricular ejection fraction (LVEF), fractional shortening and end-diastolic dimension (investigator assessment).
- On the evolution of NYHA classification.

| **Name of Company:**<br>**I.R.I.S.**<br>**6 place des Pleiades**<br>**92415 Courbevoie - FRANCE** | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

**Methodology:**
This was a randomised, double blind, placebo-controlled, multi-centre, international morbidity-mortality study, with two parallel and balanced treatment arms. Randomisation was stratified on beta-blocker intake at randomisation and centre.

**Number of patients:**
Planned: 9650 patients (4825 patients in each treatment arm).
Randomised Set: 10,917 patients (5479 to ivabradine, 5438 to placebo).

**Diagnosis and main criteria for inclusion:**
Patients aged ≥ 55 years (if no history of diabetes) or ≥ 18 years (if a history of diabetes), with documented history of CAD, associated with LV systolic dysfunction (LVSD; ≤ 39% LV ejection fraction), LV dilation, in sinus rhythm with resting HR ≥ 60 bpm. Angina and/or HF symptoms should have been stable for ≥ 3 months, and patients should have been receiving optimal conventional cardiovascular medication on appropriate stable doses for at least one month.

**Study drug:** Oral ivabradine, twice daily (target dose 7.5 mg b.i.d. based on HR and clinical criteria):
All patients were prescribed the 5 mg b.i.d. dose (ivabradine or placebo) at D0. At D15, the dose was either maintained or increased to 7.5 mg b.i.d., depending on resting heart rate and signs/symptoms related to bradycardia. Subsequently, if bradycardia was evidenced (either asymptomatic or symptomatic), the treatment dose was either decreased to 5 mg b.i.d. in patients receiving 7.5 mg b.i.d., or the treatment was stopped in patients receiving 5 mg b.i.d.
5 mg tablet batches: L0002436; L0002520; L0003806; L0004300; L0004705; L0004707; L0004879; L0007525; L0007531; L0007537; L0008911; L0011281; L0012452; L0013977; L0017875; L0018142.
7.5 mg tablet batches: L0002607; L0002671; L0003819; L0004703; L0004706; L0004709; L0004960; L0004982; L0008910; L0011230; L0012453; L0013975; L0018137; L0013987.

**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.

**Criteria for evaluation:**
EFFICACY: An independent "Endpoint Evaluation Committee" 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 first event among: cardiovascular (CV) death (including sudden death of unknown cause), hospitalisation for acute MI (fatal or not) or hospitalisation for new onset or worsening heart failure (fatal or not).
Secondary criteria:
(i) Non-composite endpoints: all-cause mortality, death related to CAD, the components of the previously mentioned composite endpoint, hospitalisation for unstable angina, coronary revascularisation (percutaneous coronary intervention or coronary artery bypass graft; PCI/CABG).
(ii) Composite endpoints: first event among: CV death or hospitalisation for new onset or worsening HF; CV death or hospitalisation for acute MI; hospitalisation for ACS; hospitalisation for ACS or coronary revascularisation; ACS, hospitalisation for new onset or worsening HF or coronary revascularisation.
(iii) Cause of death, Mode of CV death and death of unknown cause (sudden/non-sudden) type of coronary revascularisation, change in heart rate.

Tertiary criteria: Occurrence of newly diagnosed diabetes; occurrence of newly diagnosed metabolic syndrome; change in echocardiographic criteria (LVEF, end-diastolic dimension and fractional shortening); change in New York Heart Association (NYHA) classification.

SAFETY: General safety appraisals were performed throughout the study. At the end of the study, a detailed safety appraisal was conducted on adverse events, on the evolution of blood pressure and on abnormalities observed from the electrocardiographic recordings (reported as adverse events).

| **Name of Company:**<br>**I.R.I.S.**<br>**6 place des Pleiades**<br>**92415 Courbevoie - FRANCE** | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

**Statistical methods:**

EFFICACY

The analyses took account of all endpoints identified during the study period (intent-to-treat approach) and analyses were carried out on the Randomised Set (RS), on the randomised patients with baseline resting HR ≥ 70 bpm (RS-HR70) and on subgroups defined in the final statistical analyses plan before study unblinding, based on 11 criteria of demographics (age, sex), disease severity (baseline HR, baseline beta-blocker intake, NYHA class, LVEF) or coexisting medical conditions (history of diabetes, history of metabolic syndrome, previous MI, previous revascularisation, history of hypertension) (primary composite endpoint and all-cause mortality).

The time to occurrence of the primary composite endpoint was compared between treatment groups using a Log-rank test stratified on beta-blocker intake at randomisation. The treatment effect was estimated using an adjusted Cox proportional hazards model with beta-blocker intake at randomisation as a covariate. Kaplan-Meier survival curves were estimated. The treatment effect was also estimated using an unadjusted approach, as a sensitivity analysis.

The same analyses were performed on each component of the primary composite endpoint and on the secondary endpoints.

Descriptive statistics and estimate (adjusted on baseline value) of the between-group difference were used for the analysis of heart rate.

Descriptive statistics were used for the analysis of tertiary outcomes.

Post hoc analyses (main elements of efficacy and safety) were made on the subgroups based on baseline beta-blocker intake and on the subgroup of patients closest to the population for which ivabradine has an approved European indication, i.e. chronic stable angina pectoris (defined as patients with NYHA class II or III, having anginal pain at baseline as limiting factor for physical activity). Complementary analyses were made in the group of patients with baseline HR < 70 bpm.

SAFETY

Adverse events and blood pressure were studied using descriptive statistics. The analyses were performed 'on-treatment' as well as 'during the study period', since patients could remain in the study following treatment withdrawal. Analysed separately from other adverse events were the emergent clinical events related to CAD and LV dysfunction (LVD), since they were considered as "foreseeable" in this population (the patients were at high risk for such events by design). The analyses of CAD/LVD events and all-cause hospitalisation were performed using descriptive statistics on data for 'during the study period'.

**SUMMARY - CONCLUSIONS**

STUDY POPULATION AND OUTCOME

A total of 12,473 patients with CAD and LVSD were screened and 10,917 were randomised: 5479 to ivabradine and 5438 to placebo. Patient status during the study is indicated in Table 1. In the prespecified subgroup of patients with baseline HR ≥ 70 bpm (RS-HR70) patient status was proportionally the same as in the Randomised Set (RS). Ten patients were excluded from the Safety Set, since they had taken no study treatment.

**Main baseline characteristics**

The main demographic and baseline characteristics in the RS revealed no relevant between-group difference. The mean age (± SD) was 65.2 ± 8.5 years (51.0% ≥ 65 year-old), 82.9% were men and 98.1% were Caucasian. CAD was documented by previous MI in 88.4% of patients, by positive coronary angiography in 64.7% and by PCI and/or CABG in about 30% each. In most patients (57.4%) CAD had been diagnosed for ≥ 5 years (mean 8.2 ± 7.0 years). Resting mean HR was 71.6 ± 9.9 bpm (median 69 bpm). Mean LVEF was 32.4 ± 5.5% (with 99.9% of patients having LVEF ≤ 39%). Most patients were of NYHA class II (61.4%) or class III (23.2%), with less class I patients (15.4%), but none of class IV. Associated risk factors were frequent, particularly dyslipidaemia (78.5%), hypertension (70.7%) and diabetes (37.0%).

| Name of Company:<br>I.R.I.S.<br>6 place des Pleiades<br>92415 Courbevoie - FRANCE | Individual Study Table Referring to Part of the Dossier | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

STUDY POPULATION AND OUTCOME (Cont'd)

The main CV concomitant treatments taken at randomisation were beta-blockers (86.9%), aspirin (84.8%), ACE-inhibitors (79.9%), statins (74.2%), diuretics (excluding anti-aldosterone agents: 58.9%; anti-aldosterones: 27.1%), and organic nitrates (43.4%). No relevant between-group differences in the baseline characteristics were observed.

**Table 1: Disposition of patients**

| | Ivabradine | | Placebo | | All | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **Randomised (RS)** | **5479** | **100.0** | **5438** | **100.0** | **10,917** | **100.0** |
| Died before completion | 572 | 10.4 | 547 | 10.1 | 1119 | 10.3 |
| Consent withdrawal | 114 | 2.1 | 102 | 1.9 | 216 | 2.0 |
| Withdrawn by sponsor's decision* | - | - | 3 | 0.1 | 3 | < 0.1 |
| Lost to follow-up | 1 | < 0.1 | - | - | 1 | < 0.1 |
| Completed | 4792 | 87.5 | 4786 | 88.0 | 9578 | 87.7 |
| **Patients analysed** | **5479** | **100.0** | **5438** | **100.0** | **10,917** | **100.0** |
| **RS-HR70** | **2699** | **49.3** | **2693** | **49.5** | **5392** | **49.4** |
| **Safety Set (SS)** | **5477** | **100.0** | **5430** | **99.9** | **10,907** | **99.9** |

** The "sponsor's decision" was to withdraw the 3 patients who had presented themselves for a second inclusion into the study, since the suspicion remained that they had provided false information to investigators.*
*N Total number of patients in the treatment group*
*% = (n / N) x 100*

The baseline characteristics of the SS were considered as being the same as those in the RS. The baseline characteristics in the RS-HR70 were similar to those in the RS, except for HR (mean 79.2 ± 8.6 bpm) and slightly higher frequencies of diabetes (42.4%), NYHA class III (26.7%) and diuretics (excluding anti-aldosterone agents: 63.0%) and a slightly lower incidence of baseline beta-blockers intake (83.6%). There were no relevant between-group differences in the RS-HR70 for any parameter.

The main baseline characteristics of the subgroup of patients with baseline anginal pain (N = 1507, 13.8% of RS; post-hoc) were comparable to those in the RS, except for the following parameters: patients with a history of hypertension (79.8% *versus* 69.3% in the complementary subgroup); prescriptions of organic nitrates (73.5% *versus* 38.5%), diuretics (49.0% *versus* 60.5%) anti-aldosterones (18.4% *versus* 28.4%) and statins (65.6% *versus* 75.5%); patients having previously undergone a positive coronary angiography (49.4% *versus* 67.2%), a CABG (19.2% *versus* 29.6%), or a PCI (21.2% *versus* 31.5%). In the patients with anginal pain, 74.5% were of NYHA class II and 25.5% of class III. No relevant between-group differences were evidenced.

**Study duration, study treatment duration and dose**

During the study, it was noted that event rate in the blinded study population was higher than expected (*e.g.* the expected incidence of the primary composite endpoint was 11% at 2.25 years and the observed was about 15% at 19 months in the overall population); the minimal 18 months follow-up period of the last included patients was therefore reduced to 12 months by Amendment No. 6.

The median duration of study follow-up in the RS was 19 months in both groups (mean ± SD = 19.5 ± 6.1 months). The mean duration of treatment was slightly shorter in the ivabradine group (15.8 ± 8.6 months) than in the placebo group (17.9 ± 7.3 months), in relation with the higher rate of treatment withdrawals in the first 3 months (protocol-directed withdrawal for asymptomatic or symptomatic bradycardia). The proportions of patients treated for minimum durations (months) were: on ivabradine 71.2% for ≥ 12, 43.6% for ≥ 18 and 18.6% for ≥ 24, *versus* on placebo: 82.1% ≥ 12, 50.6% ≥ 18 and 21.2% ≥ 24.

In the ivabradine group of the RS, 46.7% of patients were up-titrated to the 7.5 mg b.i.d. dose and 6.4% were later down-titrated to the 5 mg b.i.d. dose. In the placebo group, 77.0% of patients were up-titrated and 2.2% were later down-titrated. Mean compliance was satisfactory and similar between groups.

The mean dose of ivabradine at one month was 6.18 mg b.i.d. in the RS, and 6.64 mg b.i.d. in the RS-HR70.

| Name of Company:<br>I.R.I.S.<br>6 place des Pleiades<br>92415 Courbevoie - FRANCE | Individual Study Table Referring to Part of the Dossier | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

STUDY POPULATION AND OUTCOME (Cont'd)

**Permanent study withdrawal**

The study treatment was permanently withdrawn before study completion in 1528 ivabradine-treated patients (27.9%) *versus* 856 placebo-treated patients (15.7%), mainly for asymptomatic bradycardia (HR < 50 bpm) (10.2% *versus* 0.8%), symptomatic bradycardia (2.7% *versus* 0.6%) and atrial fibrillation (2.2% *versus* 1.9%). Treatment withdrawal for an emergent event related to visual symptoms was infrequent (0.5% *versus* 0.2%). In the predefined RS-HR70 subgroup and in the subgroup of patients with baseline anginal pain (post hoc analysis), the study follow-up duration, treatment duration and compliance were comparable to the RS, although in the RS-HR70 there were slightly lower rate of permanent study drug withdrawals in this subgroup (23.2% *versus* 16.0%) with fewer withdrawals for asymptomatic bradycardia (4.3% *versus* 0.5%) and symptomatic bradycardia (1.3% *versus* 0.3%), whereas the withdrawal rates for visual symptoms or atrial fibrillation were similar.

**Association of baseline resting HR with CV outcomes**

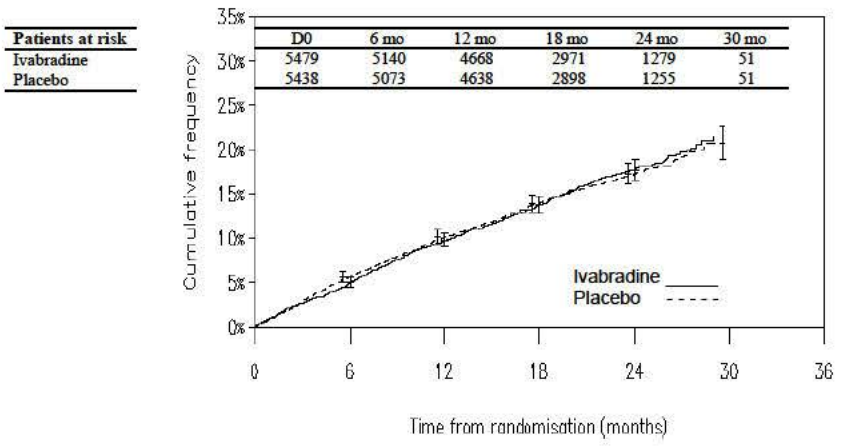
The predictive value of baseline HR as a risk marker for subsequent CV death and morbidity was studied in patients randomised to placebo, using Cox proportional hazard models for groups with a baseline HR ≥ 70 bpm (2693 patients) *versus* < 70 bpm (2745 patients). After adjustment for baseline characteristics, patients with HR ≥ 70 bpm had increased risk for CV death (34%, p = 0.004), hospitalisation for HF (53%, p < 0.001) and hospitalisation for MI (46%, p = 0.007).

EFFICACY RESULTS

- **Primary composite endpoints and selected secondary endpoints (monocomponents of the primary endpoint):**

***In the RS***, a total of 844 patients (15.40%) in the ivabradine group *versus* 832 (15.30%) in the placebo group reached the primary composite endpoint (first event among CV death, hospitalisation for acute MI, or hospitalisation for new onset or worsening HF), with annual incidence rates of 9.92%PY *versus* 9.87%PY, respectively. The estimated Hazard Ratio (HzR) was 1.00 (95% CI = [0.91 ; 1.10]; p = 0.945, stratified Log-rank test). The Kaplan-Meier time to event curve is shown in Figure 1 below. The predefined subgroup analyses showed a significant interaction between treatment effects and baseline HR (≥ or < 70 bpm): p = 0.030. Treatment effect did not reach statistical significance within the corresponding subgroups. Other predefined subgroups according to relevant baseline characteristics had a non-significant influence on the between-group comparison.

**Figure 1: Time to primary composite endpoint in the Randomised Set (N = 10,917)**



| Name of Company:<br>I.R.I.S.<br>6 place des Pleiades<br>92415 Courbevoie - FRANCE | Individual Study Table Referring to Part of the Dossier | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

EFFICACY RESULTS (Cont'd)

The secondary analysis performed on monocomponents of the primary endpoint is presented in Table 2.

No treatment effect was evidenced for any component. Although not statistically significant there were numerically more CV adjudicated deaths ($\Delta$ = 34) in the ivabradine group than in the placebo group. For almost half of the CV deaths, the cause was unknown but sudden and therefore suspected of CV origin (214 deaths in the ivabradine group *versus* 190 deaths in the placebo group). The CV deaths of known cause were mostly related to CAD (mainly HF or acute MI) or presumed arrhythmia.

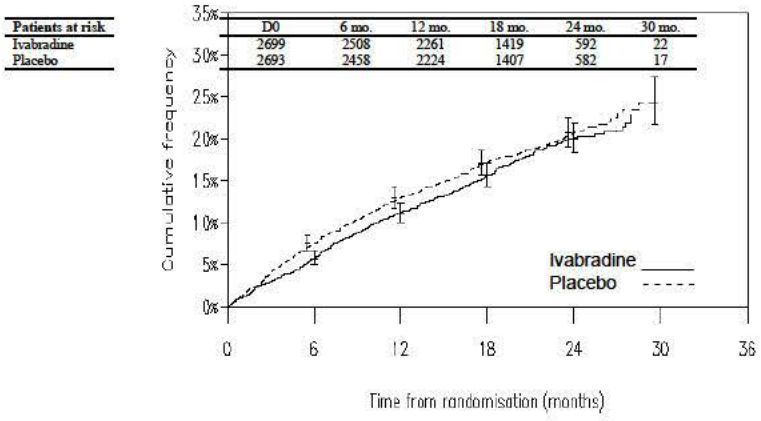
**Table 2: Incidence of the primary composite endpoint and selected secondary endpoints in the RS (N = 10 917)**

| | Ivabradine (N = 5479) n (%) [%PY] | Placebo (N = 5438) n (%) [%PY] | Hazard ratio E [95% CI] | p-value |
|---|---|---|---|---|
| **Primary composite endpoint** | **844 (15.40) [9.92]** | **832 (15.30) [9.87]** | **1.00 [0.91 ; 1.10]** | **0.945** |
| **Secondary endpoints:** | | | | |
| - CV death | 469 (8.56) [5.27] | 435 (8.00) [4.92] | 1.07 [0.94 ; 1.22] | 0.316 |
| - Hospitalisation for acute MI | 199 (3.63) [2.27] | 226 (4.16) [2.60] | 0.87 [0.72 ; 1.06] | 0.159 |
| - Hospitalisation for new onset or worsening HF | 426 (7.78) [4.96] | 427 (7.85) [5.01] | 0.99 [0.86 ; 1.13] | 0.850 |

*E [95% CI] Estimate of the hazard ratio between treatment groups [two-sided 95% confidence interval of estimate] based on an adjusted Cox proportional hazards model with beta-blocker intake as a covariate*
*p-value Log-rank test stratified on beta-blocker intake factor*
*N Number of patients in treatment group; n Number of patients reaching endpoint; % = (n / N) x 100*
*%PY = (n / number of patient years at risk in treatment group) x 100*

***In the predefined RS-HR70 subgroup***, 463 patients (17.15%) reached the primary composite endpoint *versus* 498 (18.49%) in the placebo group. The corresponding estimated HzR was 0.91 ([0.81 ; 1.04]; p = 0.166, stratified Log-rank test). The Kaplan-Meier time to event curve is shown in Figure 2 below. The pre-defined subgroups according to other relevant baseline characteristics (other than HR) had a non-statistically significant influence on the between-group comparison.

**Figure 2: Time to primary composite endpoint in the RS-HR70 (N = 5392)**



| Name of Company:<br>I.R.I.S.<br>6 place des Pleiades<br>92415 Courbevoie - FRANCE | Individual Study Table Referring to Part of the Dossier | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

EFFICACY RESULTS (Cont'd)

The secondary analysis performed on monocomponents of the primary endpoint is reported in Table 3. There was a significant treatment effect in favour of ivabradine on the hospitalisation for acute MI (fatal and non-fatal: 85 *versus* 131, HzR = 0.64 [0.49; 0.84], p = 0.001, RRR = 36%). (See Figure 3, below).

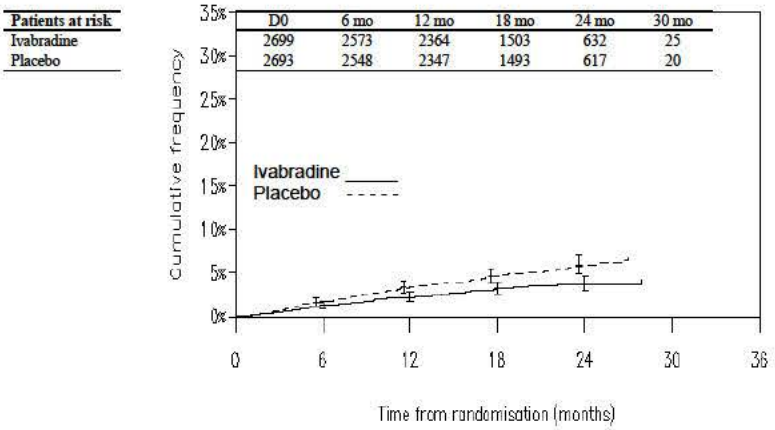
There was a small difference in CV adjudicated deaths with 6 more in the ivabradine group than in the placebo group. Sudden death of unknown cause (but suspected of CV origin) accounted for 113 deaths in the ivabradine group *versus* 118 in the placebo group. The CV deaths of known cause were mostly related to HF or presumed arrhythmia.

**Table 3: Incidence of the primary composite endpoint and selected secondary endpoints in the RS-HR70 (N = 5392)**

| | **Ivabradine (N = 2699) n (%) [%PY]** | **Placebo (N = 2693) n (%) [%PY]** | **Hazard ratio E [95% CI]** | **p-value** |
|---|---|---|---|---|
| **Primary composite endpoint** | **463 (17.15) [11.26]** | **498 (18.49) [12.26]** | **0.91 [0.81 ; 1.04]** | **0.166** |
| **Secondary endpoints:** | | | | |
| - CV death | 269 (9.97) [6.23] | 263 (9.77) [6.09] | 1.02 [0.86 ; 1.21] | 0.821 |
| - Hospitalisation for acute MI | 85 (3.15) [1.99] | 131 (4.86) [3.09] | 0.64 [0.49 ; 0.84] | **0.001** |
| - Hospitalisation for new onset or worsening HF | 268 (9.93) [6.47] | 271 (10.06) [6.59] | 0.97 [0.82 ; 1.15] | 0.759 |

*E [95% CI] Estimate of the hazard ratio between treatment groups [two-sided 95% confidence interval of estimate] based on an adjusted Cox proportional hazards model with beta-blocker intake as a covariate*
*p-value Log-rank test stratified on beta-blocker intake factor*
*N Number of patients in treatment group; n Number of patients reaching endpoint; % = (n / N) x 100*
*%PY = (n / number of patient years at risk in treatment group) x 100*

**Figure 3: Time to hospitalisation for acute myocardial infarction (fatal and non fatal) in the RS-HR70 (N = 5392)**



| Name of Company:<br>I.R.I.S.<br>6 place des Pleiades<br>92415 Courbevoie - FRANCE | Individual Study Table Referring to Part of the Dossier | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

EFFICACY RESULTS (Cont'd)

***In the subgroup of patients with anginal pain at baseline,*** the primary composite endpoint was reported by 11.99% of the patients in the ivabradine group *versus* 15.52% in the placebo group (post hoc analysis). Thus, treatment with ivabradine was associated with a relative risk reduction (RRR) for the primary composite endpoint by 24% (HzR = 0.76 [0.58 ; 1.00]; p = 0.050). The Kaplan-Meier curve is shown below (Figure 4). This benefit was mainly driven by hospitalisation for acute MI (HzR = 0.58 [0.37 ; 0.92], p = 0.021, RRR = 42%; see Table 4), although the incidence of CV death was also lower in the ivabradine group: 54 deaths *versus* 64 (*i.e.* 7.36% *versus* 8.28%).

**Figure 4: Time to primary composite endpoint in the subgroup of patients with anginal pain at baseline (N = 1507)**

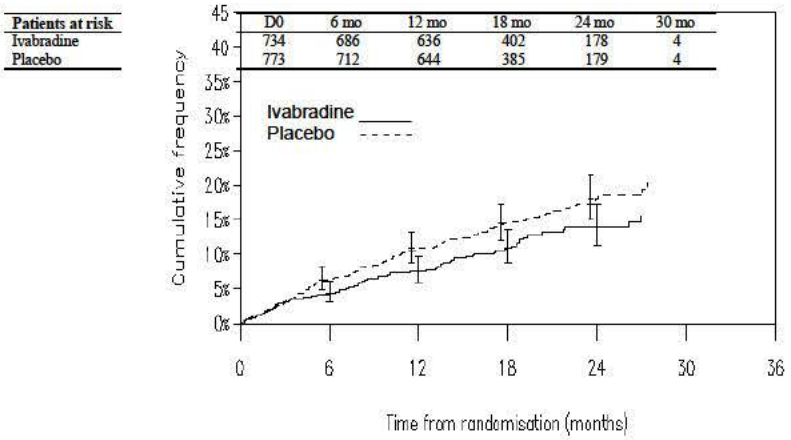



**Table 4: Incidence of the primary composite endpoint and selected secondary endpoints in the subgroup of patients with anginal pain at baseline (N = 1507)**

| | Ivabradine (N = 734) n (%) [%PY] | Placebo (N = 773) n (%) [%PY] | Hazard ratio E [95% CI] | p-value |
|---|---|---|---|---|
| **Primary composite endpoint** | **88 (11.99) [7.72]** | **120 (15.52) [10.23]** | **0.76 [0.58 ; 1.00]** | **0.050** |
| **Secondary endpoints:** | | | | |
| - CV death | 54 (7.36) [4.59] | 64 (8.28) [5.22] | 0.88 [0.62 ; 1.27] | 0.511 |
| - Hospitalisation for acute MI | 28 (3.81) [2.43] | 50 (6.47) [4.19] | 0.58 [0.37 ; 0.92] | **0.021** |
| - Hospitalisation for new onset or worsening HF | 33 (4.50) [2.85] | 41 (5.30) [3.43] | 0.84 [0.53 ; 1.33] | 0.454 |

*E [95% CI] Estimate of the hazard ratio between treatment groups [two-sided 95% confidence interval of estimate] based on an adjusted Cox proportional hazards model with beta-blocker intake as a covariate*
*p-value Log-rank test stratified on beta-blocker intake factor*
*N Number of patients in treatment group. n Number of patients reaching endpoint; % = (n / N) x 100*
*%PY = (n / number of patient years at risk in treatment group) x 100*

- **Other secondary endpoints (Table 5)**

***In the RS,*** a total of 1119 adjudicated deaths were analysed. All-cause mortality was 10.44% (572 deaths) in the ivabradine group *versus* 10.06% (547 deaths) in the placebo group. Most of these were of CV origin, with 469/572 in the ivabradine group *versus* 435/547 in the placebo group (*i.e.* 82.0% *versus* 79.5% of all deaths, respectively). No statistically significant between-group differences were evidenced in the secondary individual or composite endpoints.

| Name of Company:<br>I.R.I.S.<br>6 place des Pleiades<br>92415 Courbevoie - FRANCE | Individual Study Table Referring to Part of the Dossier | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

EFFICACY RESULTS (Cont'd)

***In the predefined RS-HR70 subgroup,*** all-cause mortality was 12.26% (331 deaths) in the ivabradine group *versus* 12.03% (324 deaths) in the placebo group. Most of these were of CV origin (*i.e.* 81.3% *versus* 81.2% of all deaths, respectively). CAD-related deaths were relatively fewer in the ivabradine group compared to the placebo group (3.04% *versus* 3.60%). There were relatively more presumed arrhythmic deaths in the ivabradine group as compared to placebo (1.93% *versus* 1.30%) and in deaths of other cardiac causes (0.26% *versus* 0.07%). In terms of the secondary endpoints of hospitalisation for acute MI, coronary revascularisation, hospitalisation for ACS, hospitalisation for ACS or coronary revascularisation, the incidences were statistically significantly lower in the ivabradine group with respective RRRs of 36% (p = 0.001), 30% (p = 0.016), 22% (p = 0.023) and 23% (p = 0.009).

**Table 5: Incidence of other secondary study endpoints in the RS and RS-HR70**

| | **RS (N = 10,917)** | | **RS-HR70 (N = 5392)** | |
|---|---|---|---|---|
| | **Ivabradine n %** | **Placebo n %** | **Ivabradine n %** | **Placebo n %** |
| ***Secondary individual study endpoints*** | | | | |
| **All-cause mortality** | **572 (10.44)** | **547 (10.06)** | **331 (12.26)** | **324 (12.03)** |
| **Cardiovascular death*** | **469 (8.56)** | **435 (8.00)** | **269 (9.97)** | **263 (9.77)** |
| • CV death of known cause | 255 (4.65) | 245 (4.51) | 156 (5.78) | 145 (5.38) |
| - CAD-related | 136 (2.48) | 151 (2.78) | 82 (3.04) | 97 (3.60) |
| ▪ Heart failure | 75 (1.37) | 82 (1.51) | 48 (1.78) | 52 (1.93) |
| ▪ Acute MI | 51 (0.93) | 63 (1.16) | 28 (1.04) | 41 (1.52) |
| ▪ Cardiac procedure | 10 (0.18) | 6 (0.11) | 6 (0.22) | 4 (0.15) |
| - Presumed arrhythmia | 86 (1.57) | 74 (1.36) | 52 (1.93) | 35 (1.30) |
| - Stroke | 19 (0.35) | 17 (0.31) | 14 (0.52) | 11 (0.41) |
| - Vascular procedure | 1 (0.02) | - | 1 (0.04) | - |
| - Other | 13 (0.24) | 3 (0.06) | 7 (0.26) | 2 (0.07) |
| • Sudden death of unknown cause | 214 (3.91) | 190 (3.49) | 113 (4.19) | 118 (4.38) |
| **Non cardiovascular death** | **81 (1.48)** | **101 (1.86)** | **49 (1.82)** | **55 (2.04)** |
| **Death of unclassifiable cause** | **22 (0.40)** | **11 (0.20)** | **13 (0.48)** | **6 (0.22)** |
| | **% [%PY]** | **% [%PY]** | **% [%PY]** | **% [%PY]** |
| **Hospitalisation for:** | | | | |
| New onset or worsening HF | 7.78 [4.96] | 7.85 [5.01] | 9.93 [6.47] | 10.06 [6.59] |
| Acute MI | 3.63 [2.27] | 4.16 [2.60] | **3.15 [1.99][1]** | **4.86 [3.09]** |
| Coronary revascularisation | 2.83 [1.77] | 3.42 [2.14] | **2.82 [1.78][2]** | **4.01 [2.55]** |
| Unstable angina | 2.08 [1.30] | 1.93 [1.20] | 2.26 [1.43] | 2.23 [1.41] |
| ***Secondary composite endpoints*** | | | | |
| **Hospitalisation for ACS (unstable angina or acute MI)** | 5.53 [3.50] | 5.83 [3.68] | **5.30 [3.39][3]** | **6.76 [4.34]** |
| **Hospitalisation for ACS, or coronary revascularisation** | 6.64 [4.23] | 7.37 [4.70] | **6.52 [4.20][4]** | **8.39 [5.45]** |
| **Hospitalisation for ACS, new/worsening HF or coronary revascularisation** | 12.43 [8.13] | 12.95 [8.49] | 14.26 [9.53] | 15.48 [10.4] |
| **CV death*, or hospitalisation for new or worsening HF** | 13.82 [8.81] | 13.30 [8.48] | 16.15 [10.5] | 16.41 [10.7] |
| **CV death*, or hospitalisation for acute MI** | 11.06 [6.92] | 10.90 [6.82] | 11.78 [7.45] | 12.96 [8.24] |

** Including sudden death from unknown cause*
*The results in bold indicate statistically significant between-group difference*
*N Number of patients in treatment group*
*n Number of patients reaching endpoint; % = (n / N) x 100*
*%PY = (n / number of patient years at risk in treatment group) x 100*
*p-value Log-rank test stratified on beta-blocker intake factor*

*[1] Relative risk reduction = 36%, p = 0.001*
*[2] Relative risk reduction = 30%, p = 0.016*
*[3] Relative risk reduction = 22%, p = 0.023*
*[4] Relative risk reduction = 23%, p = 0.009*

| **Name of Company:**<br>**I.R.I.S.**<br>**6 place des Pleiades**<br>**92415 Courbevoie - FRANCE** | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

EFFICACY RESULTS (Cont'd)

***In the subgroup of patients receiving baseline beta-blockers,*** all-cause mortality was 9.69% (460/4749) *versus* 9.60% (455/4738) in the ivabradine and placebo groups respectively, and in the subgroup of patients who did not take baseline beta-blockers the incidences were 15.34% (112/730) *versus* 13.14% (92/700), respectively.

***In the subgroup of patients with baseline anginal pain***, all-cause mortality was 8.72% (64/734) in the ivabradine group *versus* 9.96% (77/773) in the placebo group. Fewer deaths in the ivabradine group were reported for presumed arrhythmia than in the placebo group (1.63% *versus* 1.94%, respectively).

***In male patients***, all-cause mortality was 10.37% in the ivabradine group *versus* 10.58% in the placebo group, whereas ***in female patients***, there was an excess of all-cause mortality in the ivabradine group (10.76%) as compared to the placebo group (7.52%). This difference in the women patients was due mainly to the incidence of sudden death of unknown cause (4.69% *versus* 2.26%) and presumed arrhythmic death (0.75% *versus* 0.21%).

***In the subgroup of patients with LVEF < 35%***, all-cause mortality was 13.58% in the ivabradine group *versus* 12.15% in the placebo group (with an excess of CV death: 11.27% *versus* 9.79%), whereas ***in the subgroup of patients with LVEF ≥ 35%***, it was 6.88% *versus* 7.70% (with less CV deaths in the ivabradine group than in the placebo group: 5.52% *versus* 5.97%, including CAD death: 1.44% *versus* 2.12%).

- **Heart rate**

  In the RS, heart rate was decreased from baseline by ivabradine treatment whereas no clinically relevant change observed in the placebo group. At 12 months after randomisation, the change in the ivabradine group was -8.06 ± 10.74 bpm *versus* -1.77 ± 10.50 bpm in the placebo group**.** The mean difference between the treatment groups on HR change at 1 year (ivabradine - placebo) was -6.37 [-6.75 ; -5.98] bpm. In the RS-HR70, the within-group changes at 1 year were -12.40 ± 11.31 bpm *versus* -4.56 ± 11.34 bpm; the between-group difference at 1 year on HR change was -7.91 [-8.51 ; -7.31] bpm.

  The mean difference between the treatment groups (ivabradine minus placebo) in change from baseline HR was similar irrespective of background beta-blocker treatment: -6.37 [-6.78 ; -5.96] bpm at 1 year in patients with beta-blocker treatment *versus* -6.33 [-7.43 ; -5.23] bpm in patients without beta-blocker treatment.

SAFETY RESULTS

The main results concerning ***on-treatment emergent adverse events (EAEs)*** are summarised in Table 6. An overall total of 6064 patients (55.60%) reported at least one on-treatment EAE (excluding clinical events related to CAD or LVD): 55.65% (42.10%PY) of patients in the ivabradine group *versus* 55.54% (37.03%PY) in the placebo group.

The on-treatment EAEs in the ivabradine group concerned mostly events already described in the European Summary of Product Characteristics (SmPC) for ivabradine, including symptomatic bradycardia (3.76%, 2.85%PY *versus* 1.03%, 0.69%PY, ivabradine *versus* placebo groups respectively), asymptomatic bradycardia (preferred term *heart rate decreased*: 3.12%, 2.36%PY *versus* 0.63%, 0.42%PY), phosphenes (3.76%, 2.85%PY *versus* 0.85%, 0.56%PY) and ventricular extrasystoles (1.95%, 1.48%PY *versus* 1.88%, 1.25%PY). The most frequent EAE (in both groups) was atrial fibrillation (5.22%, 3.95%PY *versus* 4.86%, 3.24%PY).

| **Name of Company:**<br>**I.R.I.S.**<br>**6 place des Pleiades**<br>**92415 Courbevoie - FRANCE** | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

SAFETY RESULTS (Cont'd)

**Table 6: Summary of on-treatment EAEs - Safety Set**

| | **Ivabradine (N = 5477) NPY = 7239.85** | | | | **Placebo (N = 5430) NPY = 8144.08** | | | |
|---|---|---|---|---|---|---|---|---|
| **Patients having reported** | NEAE | n | % | %PY | NEAE | n | % | %PY |
| **at least one EAE** | 7474 | 3048 | 55.65 | 42.10 | 7586 | 3016 | 55.54 | 37.03 |
| **at least one drug-related EAE** | 1142 | 891 | 16.27 | 12.31 | 559 | 429 | 7.90 | 5.27 |
| **at least one EAE leading to study drug withdrawal** | 695 | 667 | 12.18 | 9.21 | 418 | 402 | 7.40 | 4.94 |
| **at least one emergent severe AE** | 589 | 478 | 8.73 | 6.60 | 629 | 499 | 9.19 | 6.13 |
| **at least one emergent SAE** | 1440 | 1030 | 18.81 | 14.23 | 1632 | 1136 | 20.92 | 13.95 |

*NEAE number of emergent adverse events*
*N total number of exposed patients in the treatment group*
*NPY total number of patient-years in treatment group*
*n number of affected patients; % = (n/N) x 100; %PY = (n/NPY) x 100*

***EAEs leading to permanent study drug discontinuation*** were observed in 12.18% (9.21%PY) in the ivabradine group *versus* 7.40% (4.94%PY) in the placebo group. The most frequent EAEs that lead to discontinuation in the ivabradine group were asymptomatic or symptomatic bradycardia in 2.68% and 2.08% ivabradine patients respectively, *versus* 0.63% and 0.26% placebo patients. Atrial fibrillation led to study drug withdrawal in 2.14% *versus* 1.90% (ivabradine *versus* placebo) and visual symptoms in 0.51% *versus* 0.17%, respectively.

***Severe EAEs on treatment*** were reported in 8.73% of the patients (6.60%PY) in the ivabradine group *versus* 9.19% (6.13%PY) in the placebo group. The most frequent severe events, which occurred at roughly similar rates in the two treatment groups were: atrial fibrillation (0.46%, 0.35%PY *versus* 0.44%, 0.29%PY), ischaemic stroke (0.40%, 0.30%PY *versus* 0.28%, 0.18%PY) and symptomatic bradycardia (0.31%, 0.23%PY *versus* 0.04%, 0.02%PY).

At least one ***on-treatment serious emergent adverse event*** was experienced by 18.81% (14.23%PY) of patients in the ivabradine group *versus* 20.92% (13.95%PY) in the placebo group. These concerned mostly cardiac disorders, particularly atrial fibrillation (2.32%, 1.75%PY *versus* 2.47%, 1.65%PY), atrial flutter (0.64%, 0.48%PY *versus* 0.52%, 0.34%PY), ventricular tachycardia (0.51%, 0.39%PY *versus* 0.98%, 0.65%PY) and bradycardia (0.40%, 0.30%PY *versus* 0.11%, 0.07%PY).

In the SS, the incidence of investigator-reported ***clinical events related to CAD/LVD*** during-the-study period was 26.97% (16.61%PY) in the ivabradine group *versus* 27.35% (16.82%PY) in the placebo group. Most events (45.15%) were related to an emergent heart failure (13.20%, 8.13%PY *versus* 12.84%, 7.89%PY) or were events related to CAD (10.15%, 6.25%PY *versus* 11.12%, 6.84%PY), as could be expected in this population.

***All-cause hospitalisations*** were reported for broadly similar reasons in the two treatment groups. In the ivabradine group a total of 1636 patients (29.87%, 18.40%PY) required hospitalisation during the study *versus* 1670 patients (30.76%, 18.92%PY) in the placebo group. More patients were hospitalised in the placebo group due to angina pectoris: 52 patients in the ivabradine group (0.95%, 0.58%PY) *versus* 73 in the placebo group (1.34%, 0.83%PY).

In ***patients with baseline HR ≥ 70 bpm***, ivabradine treatment was associated with higher rates of treatment-related EAEs (14.53%, 10.50%PY *versus* 7.88%, 5.31%PY in placebo) and EAEs leading to treatment discontinuation (10.86%, 7.85%PY *versus* 6.95%, 4.68%PY in placebo), although the incidences were lower than those observed in ivabradine-treated patients with baseline HR < 70 bpm.

| **Name of Company:**<br>**I.R.I.S.**<br>**6 place des Pleiades**<br>**92415 Courbevoie - FRANCE** | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
|---|---|---|
| **Name of Finished Product:**<br>Procoralan® (EU) | **Volume:** | |
| **Name of Active Ingredient:**<br>Ivabradine (S 16257) | **Page:** | |

SAFETY RESULTS (Cont'd)

The incidence of emergent adverse events was slightly lower in ***patients receiving beta-blocker treatment*** *versus* those who were not and the nature of events in either treatment group was not affected by the beta-blocker therapy. The incidence of symptomatic bradycardia in ivabradine-treated patients was 3.67% in patients receiving beta-blockers *versus* 4.38% in those without concomitant beta-blockers.

No particular safety concerns were identified in the subgroup of ***patients with anginal pain***.

Similar incidences of EAEs (severe or not) were observed in subgroups of *patients with NYHA class I or II*.

In ***male patients***, ivabradine treatment was associated with similar incidences of EAEs (severe or not) and serious EAEs as in the placebo group. In ***female patients*** in contrast, overall EAEs were more frequent in the ivabradine group than in the placebo group (60.92%, 47.54%PY *versus* 55.11%, 36.87%PY) and this trend was observed for all categories. Noticeably higher in ivabradine-treated women was atrial fibrillation (6.50%, 5.07%PY *versus*, on placebo, 3.88%, 2.59%PY). The difference in incidence of bradycardia (ivabradine *versus* placebo) was also higher in women +4.14% (+3.31%PY) than in men +1.67% (+1.60%PY).

***Elderly patients*** (≥ 75 years old) reported more EAEs, severe EAEs and SEAEs than patients aged < 75 years and the between-group differences in annual incidences, which showed an excess of events in the ivabradine arm, widened in the older age group.

**CONCLUSIONS**

**This international morbidity-mortality outcome study enrolled a patient population with coronary artery disease and LV dysfunction who were in sinus rhythm with resting HR ≥ 60 bpm. The Randomised Set (N = 10,917) had mean LVEF of 32.4%, were of NYHA class I (15.4%), II (61.4%), or III (23.2%) – there were no class IV – and a history of MI (in 88.4%). Patients were nearly optimally treated with respect to current therapeutic guidelines: beta-blockers (86.9%), aspirin (84.8%), ACE-inhibitors (79.9%), statins (74.2%), diuretics - excluding anti-aldosterone agents (58.9%) and anti-aldosterone agents (27.1%). The median follow-up time was 19 months (with only one patient lost to follow-up).**

**Analysis of the unblinded population revealed that there was at higher risk of primary outcomes than expected. Analysis of the placebo arm showed that an elevated HR at baseline (≥ 70 bpm) was statistically significantly associated with a greater risk of CV death and hospitalisation for cardiac events.**

**Ivabradine treatment was associated with significant HR reduction; the between group difference in HR change at 1 year was -6.37 bpm in the RS, smaller than in the high-risk patients (RS-HR70; -7.91 bpm).**

**The analysis of the primary composite endpoint (CV death, hospitalisation for acute MI, or new onset/worsening HF) revealed no difference in the incidence between the two treatment groups (ivabradine *versus* placebo) in the Randomised Set. The same result was observed for the secondary endpoints. In the key prespecified subgroup of high-risk patients (baseline HR ≥ 70 bpm; 49.4% of RS), statistically significant improvements of therapeutic interest were observed, with decreased risk in the ivabradine group for the secondary endpoints: hospitalisation for acute MI (RRR = 36%; p = 0.001), hospitalisation for coronary revascularisation (RRR = 30%; p = 0.016), hospitalisation for ACS (RRR = 22%; p = 0.023) and hospitalisation for ACS or revascularisation (RRR = 23%; p = 0.009).**

**The beneficial results on clinical outcomes evidenced in the high HR patients suggests that the limited effect on outcome incidence in the RS could have been due to the high proportion of patients with relatively low baseline HR, but it remains possible that insufficient overall HR reduction was achieved. In the overall population, a higher incidence of suspected CV death was reported in the ivabradine group. The between-group difference was greatest in the subgroups of female patients and of patients with baseline HR < 70 bpm. Overall, the emergent adverse events observed in ivabradine-treated patients presented no new signal to the known safety profile. Ivabradine was shown to be well tolerated in patients receiving background beta-blocker therapy. No particular safety concerns, especially in terms of CV death were identified in patients with baseline anginal pain - the subgroup closest to population indicated in the European SmPC for ivabradine.**

**Date of the report: 09 March 2009**