Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Effect of ivabradine in patients with stable coronary artery disease without clinical heart failure. A randomised double-blind placebo-controlled international multicentre study.** **Study assessInG the morbi-mortality beNefits of the I_f inhibitor ivabradine in patients with coronary arterY disease (SIGNIFY)**
Test drug code	**Ivabradine (S 16257)**
Indication	**Reduction of cardiovascular events in patients with coronary artery disease without clinical heart failure**
Development phase	**Phase III**
Protocol code	**CL3-16257-083**
Study initiation date	**25 September 2009**
Study completion date	**24 January 2014**
Main coordinators	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot, 92284 Suresnes Cedex - France** **Servier Canada Inc.** **235, Armand Frappier Blvd.** **Laval – Quebec, H7V 4A7 - Canada** **Servier Research and Development Ltd.** **Rowley, Wexham Springs, Framewood Road** **Wexham, Slough SL3 6PJ - United Kingdom** **Laboratorios Servier S.L.** **Avd de los Madronos 33, 28043 Madrid - Spain**
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	**21 August 2014**
Version of the report	**Final version**
	~~CONFIDENTIAL~~

2. SYNOPSIS

Names of Sponsors: **I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France** **Servier Canada Inc. Laval - Quebec, H7V 4A7 - Canada** **Servier R & D Ltd. Wexham, Slough SL3 6PJ - United Kingdom** **Laboratorios Servier S.L. Avd de los Madronos 33, 28043 Madrid - Spain**		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Procoralan®, Corlentor®, Coraxan®, Coralan® **Name of Active Ingredient:** Ivabradine (S 16257)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study:

Effects of ivabradine in patients with stable coronary artery disease without clinical heart failure. A randomised double-blind placebo-controlled international multicentre study.

Study assessInG the morbi-mortality beNefits of the I_f inhibitor ivabradine in patients with coronary arterY disease (SIGNIFY).

Protocol No.: CL3-16257-083

EudraCT No.: 2009-011360-10

The description of the study protocol given hereafter includes the modifications of the substantial amendments to the protocol of main study (amendments No. 1, 2, 4, 5, and 6).

International coordinator

[redacted]

Study centres:

The Randomised Set comprised 19 102 patients who were included in 1139 centres located in 51 countries: Argentina (49 centres – 954 patients), Armenia (8 centres – 239 patients), Australia (17 centres – 116 patients), Austria (4 centres – 19 patients), Belgium (9 centres – 52 patients), Brazil (44 centres – 853 patients), Bulgaria (32 centres – 1121 patients), Canada (36 centres – 254 patients), China / Hong Kong (60 centres – 975 patients), Croatia (12 centres – 197 patients), Czech Republic (40 centres – 539 patients), Denmark (15 centres – 76 patients), Estonia (16 centres – 387 patients), Finland (3 centres – 8 patients), France (16 centres – 99 patients), Georgia (8 centres – 102 patients), Germany (39 centres – 309 patients), Greece (9 centres – 77 patients), Hungary (31 centres – 981 patients), India (13 centres – 295 patients), Ireland (7 centres – 47 patients), Italy (34 centres – 384 patients), Kazakhstan (7 centres – 141 patients), Korea (29 centres – 446 patients), Latvia (9 centres – 440 patients), Lithuania (13 centres – 302 patients), Malaysia (9 centres – 74 patients), Macedonia-FYROM (7 centres – 224 patients), Mexico (31 centres – 559 patients), Netherlands (44 centres – 555 patients), Norway (4 centres – 56 patients), Philippines (6 centres – 30 patients), Poland (52 centres – 1157 patients), Portugal (7 centres – 27 patients), Romania (32 centres – 892 patients), Russia (98 centres – 2119 patients), Serbia (16 centres – 210 patients), Singapore (3 centres – 21 patients), Slovakia (24 centres – 379 patients), Slovenia (6 centres – 68 patients), South Africa (41 centres – 374 patients), Spain (25 centres – 235 patients), Sweden (13 centres – 57 patients), Switzerland (2 centres – 50 patients), Taiwan (14 centres – 198 patients), Thailand (9 centres – 96 patients), Turkey (6 centres – 96 patients), Ukraine (77 centres – 1894 patients), United Kingdom (39 centres – 118 patients), Uruguay (5 centres – 29 patients), Vietnam (9 centres – 171 patients).

Publication (reference): Study design and baseline characteristics: Am Heart J 2013; 166 (4): 654-661.

Studied period: Initiation date: 25 September 2009 (date of first visit first patient) Completion date: 24 January 2014 (date of last visit last patient)	**Phase of development of the study:** Phase III

Objectives:
The purpose of this study was to demonstrate that ivabradine reduced cardiovascular (CV) events in patients with stable coronary artery disease (CAD) without clinical heart failure (HF).
The primary objective was to demonstrate the superiority of ivabradine over placebo in the reduction of CV mortality or non-fatal myocardial infarction (MI) (composite endpoint).
The secondary objectives were to assess the effect of ivabradine compared to placebo in the reduction of the non-composite endpoints, including all-cause mortality, CV mortality, coronary death (*added by amendment No. 1*), non-fatal MI, coronary revascularisation (elective or not), elective coronary revascularisation, new onset or worsening heart failure; as well as on other composite endpoints.
Other objectives included the change in angina symptoms using the classification of the Canadian Cardiovascular Society (CCS) in patients with angina symptoms at baseline; change in heart rate; and the assessment of safety.

Three sub-studies were planned (in selected countries) and these are reported separately: Health-related quality of life (using the Seattle angina questionnaire and a visual analogue scale); biomarkers of coronary artery disease (assessing von Willebrand factor, high-sensitivity cardiac Troponin T, and other markers of CAD progression and endothelial function); and a pharmacogenomics sub-study.

Methodology:
The target population was adult patients with stable CAD without clinical HF, receiving all treatments appropriate to their cardiovascular condition.
This was a randomised, double-blind, placebo-controlled, multicentre, international, event-driven, morbidity-mortality study, with two parallel and balanced treatment arms. The randomisation was stratified by centre and on whether or not the patients were in CCS class II or higher at selection and inclusion visits. The study was designed to continue until at least 1070 primary events had occurred and the last patients included had been followed-up for 18 months.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned: 16 850 patients were to be randomised, with 8425 patients for each treatment arm (as modified by Amendment No. 2), with a target of 1070 primary composite endpoints needed to detect an 18% relative risk reduction with a 90% power and 5% type I error (as initially planned in the protocol). It was expected that the main subgroup of angina patients in CCS class II or higher at baseline would comprise 60% of the overall population.
Included and randomised: 19 102 patients, with 9550 patients in the ivabradine group and 9552 patients in the placebo group.

Diagnosis and main criteria for inclusion:
The main selection and inclusion criteria were:

- Male or female aged ≥ 55 years.
- Evidence of CAD by either:
  - A previous MI (> 3 months prior to selection); or
  - Evidence of multivessel disease, irrespective of the revascularisation status, *i.e.* either the presence of a significant stenosis (at least 50% narrowing of the luminal diameter), or a previous revascularisation at least 3 months prior to selection (percutaneous transluminal coronary angioplasty with or without stent, or coronary artery bypass grafting) in 2 or more major coronary arteries [Note: A disease affecting the left main coronary artery was considered as a 2-vessel disease]; or
  - Evidence of nonrevascularised single-vessel disease with the presence of angiographic evidence of at least 50% narrowing in one major coronary artery, *plus* either a positive non-invasive stress test, or a hospitalisation with a documented diagnosis of unstable angina (within 12 months prior to selection).
- Sinus rhythm and resting heart rate (HR) equal to or higher than 70 bpm on 2 consecutive resting 12-lead electrocardiograms (ECGs) performed at least 5 minutes apart.

Diagnosis and main criteria for inclusion (Cont'd):

- Preserved left ventricular (LV) systolic function, defined as LV ejection fraction of 41% or higher.
- Ambulatory and in stable condition with respect to angina and on appropriate and stable doses of conventional CV medications (≥ 1 month).
- Presence of additional CV risk factor(s):
  - At least one major CV risk factor:
    - Angina in CCS class II or higher (≥ 1 month):
      - Objective evidence of myocardial ischaemia induced by stress testing (≤ 12 months prior to selection in patients who did not undergo subsequent coronary revascularisation), either: by a positive exercise tolerance test, or evidence of inducible myocardial ischaemia with reversible abnormalities in any imaging technique.
      - Hospital discharge with a documented diagnosis of major coronary event (acute MI or unstable angina) ≤ 12 months prior to selection.
  - Or at least two minor CV risk factors:
    - Documented low HDL cholesterol (< 1 mmol/L or 40 mg/dL) and/or documented high LDL cholesterol (> 4 mmol/L or 160 mg/dL despite lipid lowering treatment).
    - Presence of type 1 or 2 diabetes mellitus treated with an oral hypoglycaemic drug or insulin.
    - Presence of documented peripheral artery disease (symptomatic or not); or angiographic evidence of significant (> 50%) peripheral artery stenosis in at least one limb; or evidence from a non-invasive measurement of significant peripheral artery stenosis in at least one limb.
    - Current smoker (10 cigarettes or more per day on average).
    - Age ≥ 70 years.
- Written informed consent obtained.

The main non-inclusion criteria were:

- Unstable cardiovascular condition.
- Clinical signs and/or symptoms of heart failure in New York Heart Association (NYHA) class II or higher, or hospitalisation for heart failure as a primary diagnosis within the last 12 months.
- Known hypersensitivity to ivabradine or current treatment with marketed ivabradine.

Study drug:
Ivabradine, 5-milligram (mg) tablets, 7.5 mg tablets and 10 mg tablets; *per os* administration, one tablet twice daily (*b.i.d.*) during meals.
At inclusion, patients received ivabradine 7.5 mg *b.i.d.* or matching placebo, except for patients aged ≥ 75 years at selection, who were initiated at 5 mg *b.i.d.* At M1 and every subsequent visit, resting HR was measured by 12-lead ECG (two consecutive recordings performed > 5 minutes apart) and the study treatment adjusted accordingly with a target heart rate of 50-60 bpm. Thus, patients with heart rates > 60 bpm received the next higher dosage (maximum 10 mg *b.i.d.* or matching placebo); patients with HR 50 to 60 bpm were maintained on the same dosage; and patients with HR < 50 bpm or with symptoms of bradycardia received the next lower dosage (minimum 5 mg *b.i.d.* or matching placebo). In patients already on 5 mg *b.i.d.*, study treatment was stopped if HR < 45 bpm or if there were symptoms of bradycardia. Patients with HR 45 – 50 bpm on 5 mg *b.i.d.* and no symptoms of bradycardia were invited for a control visit within 1 week and then stopped the study drug if HR remained < 50 bpm.

5 mg tablet batches: L0027232; L0028922; L0029816; L0033605; L0036727; L0038676; L0040468; L0040741; L0042554; L0043030.
7.5 mg tablet batches: L0027230; L0028920; L0029295; L0032018; L0033608; L0038024; L0038975; L0041708; L0042556; L0044386; L0044844.
10 mg tablet batches: L0028680; L0028682; L0028678; L0030097; L0030099; L0030401; L0030403; L0031063; L0031069; L0032040; L0030403; L0032042; L0034024; L0031069; L0035021; L0035111; L0035474; L0035993; L0036266; L0036629; L0036627; L0038042; L0038912; L0039703; L0040675; L0040679; L0040673; L0041666; L0040975; L0041927; L0042015; L0042017; L0042413; L0042419.

Comparator:
Matching placebo tablets, *per os* administration, one tablet twice daily during meals, with the same titration protocol as described above.

Duration of treatment:
Following a run-in period of 14 to 30 days during which placebo was dispensed to patients in a single-blind way; the active double-blind treatment period (ivabradine *versus* placebo) lasted from 18 months to 48 months.

Criteria for evaluation:

Efficacy
All the clinical Pre-Specified Events (PSEs: all deaths, suspected MIs, ischemic symptoms or evidence of myocardial ischemia leading to hospitalisation or prolongation of hospitalisation, suspected strokes, coronary revascularisations, and suspected new or worsening HFs leading to hospitalisation or prolongation of hospitalisation) occurring in the study population were adjudicated by the independent and blinded Endpoint Validation Committee (EVC). The results of these adjudications were used for the efficacy analyses.

Primary endpoint
Composite endpoint of the time to first event among CV death or non-fatal MI.

Secondary endpoints

- Non-composite endpoints: time to occurrence of all-cause mortality, CV mortality, coronary death, fatal MI, non-fatal MI, coronary revascularisation (elective or not), elective coronary revascularisation, new onset or worsening heart failure.
- Composite endpoints:
  - Fatal or non-fatal MI.
  - Fatal or non-fatal MI, coronary revascularisation.
  - Fatal or non-fatal MI, coronary revascularisation, unstable angina.
  - CV death, non-fatal MI, non-fatal stroke.
  - Coronary death, non-fatal MI.
  - Non-fatal MI, coronary revascularisation, unstable angina.

Other secondary criteria:

- Angina symptoms: The effect of ivabradine, compared to that of a placebo, was studied using the CCS classification of angina severity, in patients with angina symptoms at baseline (*i.e.* in CCS class I or higher at selection and inclusion visits).
- The effect of ivabradine on heart rate was studied.

Safety evaluation
During the progression of the study, the independent and unblinded Data Monitoring Committee performed periodic assessments of the safety data on the included population.
The sponsor reviewed the blinded data for important medical events (IME) which could be upgraded for seriousness according to an internal process. At the end of the study, a detailed safety appraisal was conducted on adverse events, ECG abnormalities, vital signs and NYHA class.

Statistical methods:
Efficacy analysis: The efficacy analysis was performed on the Randomised Set (RS) and on the RS_{ANG} (the pre-specified subgroup of patients in angina CCS class II or higher at baseline).
Primary criterion:
The superiority of ivabradine as compared to placebo was tested on the primary composite endpoint using main analysis of a Cox proportional hazard model adjusted for the presence of angina in CCS class II or higher at baseline (the analysis of RS_{ANG} was unadjusted). An estimate of the hazard ratio and its 95% confidence interval were also provided based on the same model. A two-sided p-value was provided and compared to a 5% type I error rate. Sensitivity analyses estimated treatment effect using an unadjusted approach (in the RS) and an approach adjusted for prognostic factors in stable CAD.
Secondary criteria:
The same analyses were performed on each component of the primary endpoint and on all-cause mortality. The main analysis planned for the primary endpoint and the analysis without adjustment were carried out on the other secondary endpoints.
In order to take into account the multiplicity of secondary endpoints, a sequential procedure was used for 2 major secondary outcomes starting with the composite endpoint (non-fatal or fatal MI) and followed by elective coronary revascularisation. Other secondary endpoints were considered as supportive or exploratory, and thus no adjustment for multiplicity was applied to these. For the other secondary criteria (grade of angina pain, heart rate), descriptive statistics were provided by treatment group.

Statistical methods (Cont'd):
Safety analysis: Descriptive statistics were provided.
Interim analyses: Two formal interim analyses were carried out by the DMC when the percentage of expected events for the primary composite endpoint reached 35% and 60%. There was no overwhelming evidence of benefit or harm and the recommendation was to continue the study as per protocol. There was no pre-established stopping rule for futility.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 23 164 patients were screened and 21 862 were selected. The Randomised Set (RS) comprised 19 102 patients: 9550 in the ivabradine group and 9552 in the placebo group. The disposition of patients and their status at the end of the study is presented in Table 1. Overall, 92.8% completed the study and 4.9% died.
The Safety Set comprised 99.9% of the RS: 19 patients (11 in the ivabradine group and 8 in the placebo group) were excluded from, because they took no study medication.
The RS_{ANG} comprised 63.1% of the RS. The safety set of this subgroup, SS_{ANG}, was smaller by 10 patients for the same reason as given above.

Table 1 - Disposition of patients

Status	Ivabradine		Placebo		All	
	n	%	n	%	n	%
Included and randomised	**9550**	**100**	**9552**	**100**	**19102**	**100**
Study completed	8830	92.5	8894	93.1	17724	92.8
Adverse event leading to death	485	5.1	458	4.8	943	4.9
Consent withdrawal	231	2.4	199	2.1	430	2.3
Withdrawn by sponsor's decision*	1	< 0.1	-	-	1	< 0.1
Lost to follow-up	3	< 0.1	1	< 0.1	4	< 0.1
Randomised Set (RS)	**9550**	**100**	**9552**	**100**	**19102**	**100**
Safety Set (SS)	9539	99.9	9544	99.9	19083	99.9
RS_{ANG}	6037	63.2	6012	62.9	12049	63.1
SS_{ANG}	6030	63.1	6009	62.9	12039	63.0

n: Total number of patients in the considered treatment group; % = % of total number of patients treatment group
** Upon request from a local ethics committee further to recent diagnosis of Alzheimers disease in this patient, during the study*

MAIN BASELINE CHARACTERISTICS

The analysis of the demographic data and baseline characteristics in the RS revealed 2 homogeneous treatment groups, without clinically relevant differences regarding their medical condition (Table 2). The mean age was 65.0 ± 7.2 years, they were mostly men (72.5%), of Caucasian origin (81.3%) and mean BMI of 28.8 kg/m² (a third were obese, BMI ≥ 30 kg/m²). The mean resting HR was 77.2 ± 7.0 bpm and mean SBP / DBP was 130.5 / 78.2 mmHg. CAD had been diagnosed for a mean of 6.2 ± 6.3 years and it was documented by a previous MI in 67.6% and/or multi-vessel disease in 60.0%. In terms of all relevant medical history (*i.e.* specifically documented disease or not), 73% of patients overall reported a previous MI and 68% reported a previous coronary revascularisation. Comorbidities were prevalent: hypertension (86.2%), dyslipidaemia (71.7%), diabetes (43.1%) and peripheral artery disease (21.0%). Background CV treatments were widely prescribed: antithrombotics (97.7%), beta-blockers (83.1%), statins (92.2%), ACE inhibitors or ARBs (81.3%) and nitrates (40.0%). Among the patients receiving a beta-blocker, a large percentage (73.0% overall) were not receiving a dose in the upper recommended daily target range for their condition; the main reasons for which were concomitant conditions such as hypotension (in 22.9%) and tiredness (22.1%).

The demographic data and baseline characteristics of the RS_{ANG} were fairly similar to those described for the RS and the 2 treatment groups showed no clinically relevant differences regarding their medical condition. In the comparison with the RS, some differences were however observed, such as the rates of multi-vessel disease (56.0% in the RS_{ANG} *versus* 60.0% in the RS), CAD duration (mean 6.5 years [median 4.5]; 28.1% of patients overall had a duration < 2 years (28.1% *versus* 33.1%), previous coronary revascularisation (61% *versus* 68%). In terms of all relevant medical history (*i.e.* specifically documented disease or not), 75% of patients overall reported a previous MI (versus 73% in RS) and 61% reported a previous coronary revascularisation (versus 68% in RS). In addition, the rates of some comorbid conditions were slightly different: diabetes mellitus (35.5% *versus* 43.1%), peripheral artery disease (16.9% *versus* 21.0%) and dyslipidaemia (67.2% *versus* 71.7%).

SUMMARY - CONCLUSIONS (Cont'd)

MAIN BASELINE CHARACTERISTICS (Cont'd)

The use of antithrombotic agents excluding aspirin was slightly lower in the RS_{ANG} than in the RS (35.0% *versus* 39.3%), as was the use of antidiabetic treatments (31.6% *versus* 39.7%). Organic nitrates were relatively more frequently used (49.5% *versus* 40.0%). Beta-blocker use at randomisation in the RS_{ANG} was 86.9% (*versus* 83.1% in the RS), with mean daily doses similar to those in the RS.

Table 2 - Demographics and baseline characteristics in the Randomised Set

	Ivabradine (N = 9550)	**Placebo (N = 9552)**	**All (N = 19102)**
Age (years)	65.0 ± 7.2	65.0 ± 7.3	65.0 ± 7.2
< 65	5109 (53.5)	5096 (53.4)	10205 (53.4)
≥ 70	2687 (28.1)	2746 (28.7)	5433 (28.4)
≥ 75	1088 (11.4)	1139 (11.9)	2227 (11.7)
BMI (kg/m^2)	28.8 ± 4.6	28.7 ± 4.7	28.8 ± 4.6
HR (bpm)	77.1 ± 6.9	77.2 ± 7.1	77.2 ± 7.0
Male	6949 (72.8)	6890 (72.1)	13839 (72.5)
Caucasian	7788 (81.6)	7745 (81.1)	15533 (81.3)
Asian	1262 (13.2)	1285 (13.5)	2547 (13.3)
Supine SBP (mmHg)	130.5 ± 13.5	130.4 ± 13.6	130.5 ± 13.6
Supine DBP (mmHg)	78.3 ± 8.2	78.2 ± 8.2	78.2 ± 8.2
CV risk factors & medical history			
CAD duration (years)	6.20 ± 6.32	6.14 ± 6.23	6.17 ± 6.28
Previous MI	7009 (73.4)	6993 (73.2)	14002 (73.3)
Previous coronary revascularisation	6453 (67.6)	6496 (68.0)	12949 (67.8)
Multi-vessel disease	5743 (60.1)	5716 (59.8)	11459 (60.0)
Angina status			
No angina symptoms	2400 (25.1)	2416 (25.3)	4816 (25.2)
Class I	1113 (11.7)	1124 (11.8)	2237 (11.7)
Class II to IV	6037 (63.2)	6012 (62.9)	12049 (63.1)
Dyslipidaemia	6844 (71.7)	6853 (71.7)	13697 (71.7)
Diabetes mellitus	4103 (43.0)	4127 (43.2)	8230 (43.1)
Peripheral artery disease	1974 (20.7)	2042 (21.4)	4016 (21.0)
Current smoker	2285 (23.9)	2320 (24.3)	4605 (24.1)
Hypertension	8275 (86.7)	8191 (85.8)	16466 (86.2)
LVEF (%)	56.4 ± 8.5	56.5 ± 8.6	56.5 ± 8.6
Stroke	634 (6.6)	631 (6.6)	1265 (6.6)
Concomitant treatments			
Antithrombotic agents	9329 (97.7)	9343 (97.8)	18672 (97.7)
Statins	8819 (92.4)	8791 (92.0)	17610 (92.2)
ACE inhibitors or ARBs	7796 (81.6)	7735 (81.0)	15531 (81.3)
ACE inhibitors	5719 (59.9)	5617 (58.8)	11336 (59.3)
Organic nitrates	3871 (40.5)	3770 (39.5)	7641 (40.0)
Diltiazem or verapamil	438 (4.6)	403 (4.2)	841 (4.4)
Antidiabetic treatments	3787 (39.7)	3799 (39.8)	7586 (39.7)
Beta-blockers	7934 (83.1)	7944 (83.2)	15878 (83.1)
Metoprolol succinate	1612 (20.3)	1644 (20.7)	3256 (20.5)
Metoprolol tartrate	1251 (15.8)	1193 (15.0)	2444 (15.4)
Bisoprolol	2603 (32.8)	2639 (33.2)	5242 (33.0)
Carvedilol	990 (12.5)	999 (12.6)	1989 (12.5)
Nebivolol	790 (10.0)	757 (9.5)	1547 (9.7)

n (%)

SUMMARY - CONCLUSIONS (Cont'd)

MAIN BASELINE CHARACTERISTICS (Cont'd)

In the RS, the overall mean duration of study follow-up was 27.7 ± 8.7 months (median = 27.8 months) with no relevant difference between groups. The mean treatment duration was 24.5 ± 11.0 months (median = 24.1 months) in the ivabradine group and 25.9 ± 10.0 months (median = 25.4 months) in the placebo group. The treatment compliance was between 70% and 130% in 98.3% of patients.

In patients < 75 years the titration to the higher dose of the study drug (*i.e.* 10 mg *b.i.d.*) and its maintenance until the end of the study occurred in almost half (46.6%) of patients in the ivabradine group (as well as the majority (88.5%) of patients in the placebo group). In older patients (≥ 75 years), the titration to the higher dose (10 mg *b.i.d.*) and its maintenance until the end of the study occurred in more than a third (39.1%) of ivabradine-treated patients. The mean ivabradine dose prescribed was 8.3 ± 1.7 mg twice daily in younger patients and 7.3 ± 1.9 mg twice daily in older patients. Similar mean doses prescribed and dose profiles were observed in patients of the RS_{ANG}.

EFFICACY RESULTS

- **Primary composite endpoint: RS**

In the RS, ivabradine did not significantly affect the PCE (CV death or non-fatal MI) (Table 3): the estimated hazard ratio was 1.08 (95%CI: 0.96 - 1.20, p = 0.1969), with incidences of 6.85% (3.03%PY) in the ivabradine group *versus* 6.40% (2.82%PY) in the placebo group. Similar results were observed for the components of the PCE: CV death (hazard ratio: 1.10, 95%CI: 0.94 - 1.28, p = 0.2493) and non-fatal MI (hazard ratio: 1.04, 95%CI: 0.90 - 1.21, p = 0.6024). Overall, the absolute risk of attaining the PCE was low at 2.8-3.0%PY (lower than initially hypothesised in the study protocol [4.5% in the placebo group]). The absolute difference in PCE incidence between the treatment groups of the RS (0.2%PY), represented an excess of 43 events in the ivabradine group observed on 19 102 patients followed over 2.3 years.

Table 3 - Incidence of the primary composite endpoint and its components in the RS

	Ivabradine (N = 9550)				**Placebo (N = 9552)**				**Hazard ratio**			
	NPY	n	%	%PY	NPY	n	%	%PY	E	SE	95% CI	p-value
Primary composite endpoint	21594	654	6.85	3.03	21699	611	6.40	2.82	1.08	0.06	[0.96-1.20]	0.1969
Secondary endpoints												
Cardiovascular death	22039	329	3.45	1.49	22129	301	3.15	1.36	1.10	0.09	[0.94-1.28]	0.2493
Non-fatal MI	21595	351	3.68	1.63	21699	339	3.55	1.56	1.04	0.08	[0.90-1.21]	0.6024

N: number of patients at risk; NPY: number of patient-years; n: number of patients having experienced the endpoint
%: global incidence rate; %PY: (n/NPY) x100; E: estimate of the hazard ratio between treatment groups (Ivabradine/Placebo) on adjusted Cox proportional hazards model; SE: standard error of the hazard ratio; 95% CI: 95% Confidence Interval of the estimate (two-sided); p-value: Wald test

- **Other secondary endpoints: RS**

On the all-cause mortality endpoint, the rate in the ivabradine group was 5.08% (2.20%PY) *versus* 4.79% (2.07%PY) in the placebo group (485 deaths *versus* 458, respectively). The estimated hazard ratio of 1.06 (95%CI: 0.94 - 1.21) was not statistically significant (p = 0.3461) and represented an absolute difference of 0.13%PY. Most deaths were of cardiovascular origin (*i.e.* 66-68% of all deaths) (Table 4). No excess in sudden death was observed suggesting no ventricular proarrhythmic effect of ivabradine.

No statistically significant effects of treatment were observed on either of the 2 major secondary endpoints identified in protocol: first event of myocardial infarction (fatal or non-fatal), 392 events *versus* 372, with a hazard ratio of 1.06 (95%CI: 0.92 - 1.22, p = 0.4299) or first event of elective coronary revascularisation, 270 events *versus* 305, with a hazard ratio of 0.89 (95%CI: 0.75 - 1.04, p = 0.1458).

The effect of treatment was tested on a variety of other composite endpoint combinations, but for each, the estimate of the hazard ratio was close to 1.0.

Table 4 - Estimate of treatment effect on adjudicated causes of death in the RS

	Ivabradine (N = 9550)			**Placebo (N = 9552)**			**Hazard ratio**		
	n	%	%PY	n	%	%PY	E	95% CI	p-value
All-cause mortality	485	5.08	2.20	458	4.79	2.07	1.06	[0.94-1.21]	0.3461
Cardiovascular death	329	3.45	1.49	301	3.15	1.36	1.10	[0.94-1.28]	0.2493
Coronary death	263	2.75	1.19	249	2.61	1.13	1.06	[0.89-1.26]	0.5162

E: estimate of the hazard ratio between treatment groups (Ivabradine/Placebo); adjusted Cox proportional hazards model; Two-sided type I error rate: 0.05; 95% CI : 95% Confidence Interval of the estimate (two-sided); p-value: Wald test

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

- **Primary composite endpoint: RS_{ANG}**

In the main pre-specified subgroup of angina CCS class ≥ II patients (RS_{ANG}) there was a higher incidence of the PCE in the ivabradine group *versus* the placebo group of 7.60% (3.37%PY) *versus* 6.49% (2.86%PY), respectively (Table 5), which led to a statistically significant increase in the hazard ratio 1.18 (95%CI: 1.03 - 1.35, p = 0.0176). Similar trends were observed on the components of the PCE: CV death (hazard ratio 1.16, 95%CI: 0.97 - 1.40, p = 0.1053) and non-fatal MI (hazard ratio: 1.18, 95%CI: 0.97 - 1.42, p = 0.0918).

The absolute difference in PCE incidence between the treatment groups of the RS_{ANG} (0.5%PY), represented an excess of 69 events in the ivabradine group observed on 12 049 patients followed over 2.3 years.

Table 5 - Incidence of the primary composite endpoint and its components in the RS_{ANG}

	Ivabradine (N = 6037)				**Placebo (N = 6012)**				**Hazard ratio**			
	NPY	n	%	%PY	NPY	n	%	%PY	E	SE	95% CI	p-value
Primary composite endpoint	13625	459	7.60	3.37	13633	390	6.49	2.86	1.18	0.08	[1.03-1.35]	0.0176
Secondary endpoints												
Cardiovascular death	13921	245	4.06	1.76	13898	210	3.49	1.51	1.16	0.11	[0.97-1.40]	0.1053
Non-fatal MI	13625	235	3.89	1.72	13633	200	3.33	1.47	1.18	0.11	[0.97-1.42]	0.0918

N: number of patients at risk; NPY: number of patient-years; n: number of patients having experienced the endpoint
%: global incidence rate; %PY: (n/NPY) x100; E: estimate of the hazard ratio between treatment groups (Ivabradine/Placebo) on unadjusted Cox proportional hazards model;; SE: standard error of the hazard ratio; 95% CI: 95% Confidence Interval of the estimate (two-sided); p-value: Wald test

In a post hoc analysis, the PCE was analysed in all angina patients, *i.e.* CCS class ≥ 1 at baseline (N = 14 286, 74.8% of the RS). The global incidence rates were 7.20% (3.19%PY) in the ivabradine group *versus* 6.53% (2.88%PY) in the placebo group. The hazard ratio, using an unadjusted Cox model, was 1.11 (95% CI [0.98 - 1.26], p = 0.1097); a result which indicated no statistically significant difference between the treatment groups.

- **Other secondary endpoints: RS_{ANG}**

On the all-cause mortality endpoint, there were 325 deaths in the ivabradine group *versus* 288 in the placebo group (5.38%, 2.33%PY *versus* 4.79%, 2.07%PY). This difference (0.26%PY) was not statistically significant (p = 0.1421) and the estimated hazard ratio was 1.13 (95%CI: 0.96 - 1.32). Most deaths were of CV origin (*i.e.* 73 -75% of all deaths) (Table 6).

There was a non-statistically significant trend towards a higher rate of events of MI (fatal or not) in the ivabradine group as compared with the placebo group: 265 events *versus* 222 (4.39%, 1.94%PY *versus* 3.69%, 1.63%PY): giving a hazard ratio of 1.19 (95%CI: 1.00 - 1.43, p = 0.0509). In contrast, there was a non-statistically significant trend favouring the ivabradine group for the incidence of elective coronary revascularisation events: 172 events *versus* 208 (2.85%, 1.25%PY *versus* 3.46%, 1.53%PY), giving a hazard ratio of 0.82 (95%CI: 0.67 - 1.01, p = 0.0581).

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

The effect of treatment was tested on a variety of other composite endpoints, with no statistical difference between the two groups.

Table 6 - Estimate of treatment effect on adjudicated causes of death in the RS_{ANG}

	Ivabradine (N = 6037)			Placebo (N = 6012)			Hazard ratio		
	n	%	%PY	n	%	%PY	E	95% CI	p-value
All-cause mortality	325	5.38	2.33	288	4.79	2.07	1.13	[0.96-1.32]	0.1421
Cardiovascular death	245	4.06	1.76	210	3.49	1.51	1.16	[0.97-1.40]	0.1053
Coronary death	199	3.30	1.43	182	3.03	1.31	1.09	[0.89-1.33]	0.3919

E: estimate of the hazard ratio between treatment groups (Ivabradine/Placebo); unadjusted Cox proportional hazards model; Two-sided type I error rate: 0.05; 95% CI : 95% Confidence Interval of the estimate (two-sided); p-value: Wald test

The HR reduction in the ivabradine group was robust, with a between-group difference in the RS at 1 month (visit M1) of -10.3 bpm (95%CI: -10.5 – -10.0). In the RS_{ANG}, the between-group difference at 1 month was -9.7 bpm (95%CI: -10.1 – -9.4). In both the RS and the RS_{ANG}, these between-group differences remained stable throughout the study from 1 month onwards.
The analyses of CCS class showed a trend towards improvement between baseline and the last visit in the ivabradine group *versus* placebo in the RS and the RS_{ANG}. The proportion of patients reporting an improvement in the RS was 27.6% in the ivabradine group *versus* 25.5% in the placebo group. In the RS_{ANG}, the rates were 39.5% *versus* 36.2%, respectively.

SAFETY RESULTS
The analysis of the emergent adverse events (EAEs) was performed on the clinical events that occurred on treatment (*i.e.* after first study drug intake until the last study drug intake + 2 days). An analysis was also performed on all deaths that occurred during the study (*i.e.* after first intake of the randomised study drug until database closure).

The summary of incidence of EAEs by category and seriousness is presented in Table 7.

Table 7 - Overall summary of safety results in the Safety Set

On-treatment events (unless stated)	Ivabradine (N = 9539)			Placebo (N = 9544)		
	n	%	%PY	n	%	%PY
Patients having reported at least one:						
Emergent adverse event	6920	72.5	35.3	6321	66.2	30.6
Severe emergent adverse event	1309	13.7	6.7	1300	13.6	6.3
Treatment-related emergent adverse event	2437	25.5	12.4	557	5.8	2.7
EAE of bradycardia (all forms)	1703	17.9	8.7	202	2.1	1.0
EAE of phosphenes	509	5.3	2.6	51	0.5	0.2
Patients having experienced at least one:						
Serious emergent adverse event (including death)	3379	35.4	17.3	3263	34.2	15.8
Serious treatment-related emergent adverse event	269	2.8	1.4	60	0.6	0.3
Patients with treatment withdrawal due to:						
Emergent adverse event	1247	13.1	6.4	699	7.3	3.4
EAE of bradycardia (all forms)	381	4.0	1.9	45	0.5	0.2
EAE of phosphenes	61	0.6	0.3	11	0.1	0.1
Serious emergent adverse event	629	6.6	3.2	475	5.0	2.3
Fatalities						
EAE with fatal outcome	363	3.8	1.9	356	3.7	1.7
All-cause mortality (during the study)	498	5.2	2.3	466	4.9	2.1

N: total number of patients in considered treatment group; NPY: 19582.7 in the ivabradine group; 20685.6 in the placebo group
n: number of affected patients; % = (n/N) x 100; %PY = (n/NPY) x 100

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Emergent adverse events on treatment**

In the Safety Set, at least one EAE on treatment was reported by 72.5% of patients (35.3%PY) in the ivabradine group and 66.2% (30.6%PY) in the placebo group. The most frequently reported preferred terms in the ivabradine group concerned mostly events already described in the European SmPC for ivabradine, notably (ivabradine *versus* placebo, respectively): hypertension (11.8%, 5.8%PY *versus* 9.7%, 4.5%PY), asymptomatic bradycardia (preferred term [PT] [HR decreased]: 10.8%, 5.3%PY *versus* 1.2%, 0.5%PY), symptomatic bradycardia (PT [Bradycardia]: 6.0%, 2.9%PY *versus* 0.8%, 0.4%PY and PT [Sinus bradycardia]: 2.0%, 1.0%PY *versus* 0.2, 0.1%PY%), phosphenes (PT [Photopsia]: 5.3%, 2.6%PY *versus* 0.5%, 0.2%PY), and atrial fibrillation (AF) (4.6%, 2.2%PY *versus* 3.3%, 1.5%PY). Otherwise, the most frequently reported emergent adverse events were angina pectoris (6.4%, 3.1%PY *versus* 7.3%, 3.3%PY, respectively) and cardiac failure (4.9%, 2.4%PY *versus* 4.9%, 2.2%PY, respectively).

At least one **severe EAE** was reported by 13.7% (6.7%PY) in the ivabradine group *versus* 13.6% (6.3%PY) in the placebo group. Severe EAEs accounted for 8.1% *versus* 9.2%, respectively, out of all EAEs that were reported. Most frequently, they were cardiac disorders (MI or unstable angina). There were no relevant differences between the 2 groups in the most frequently reported events in this category.

Treatment-related EAEs were more frequently reported in the ivabradine group than in the placebo group (25.5%, 12.4%PY *versus* 5.8%, 2.7%PY). The difference between the two groups were mainly due to known adverse events associated with ivabradine treatment, notably asymptomatic bradycardia (PT [HR decreased]: 9.9%, 4.8%PY *versus* 1.0%, 0.5%PY), symptomatic bradycardia (PT [Bradycardia]: 5.6%, 2.7%PY *versus* 0.7%, 0.3%PY) and PT [Sinus bradycardia]: 1.8%, 0.9%PY *versus* 0.2%, 0.1%PY) and phosphenes (PT [Photopsia]: 5.1%, 2.5%PY *versus* 0.5%, 0.2%PY).

Emergent events leading to drug withdrawal were more frequently reported in the ivabradine group than in the placebo group (13.1%, 6.4%PY *versus* 7.3%, 3.4%PY, respectively). These withdrawals were mainly related to bradycardia (PT [HR decreased]: 2.1%, 1.0%PY *versus* 0.2%, 0.1%PY); [Bradycardia]: 1.4%, 0.7%PY *versus* 0.3%, 0.1%PY); and [Sinus bradycardia]: 0.5%, 0.2%PY *versus* < 0.1%, < 0.1%PY). It should be noted that bradycardia could lead to a protocol-directed drug withdrawal when patients were treated with the lowest dose of study drug (5 mg *b.i.d.* in this study). AF led to treatment withdrawal in 2.0% (1.0%PY) *versus* 1.2% (0.6%PY).

EAEs of particular interest (defined as identified or potentially important risks mentioned in the Risk Management Plan of ivabradine): bradycardia (all forms: 17.9%, 8.7%PY *versus* 2.1%, 1.0%PY), phosphenes ([Photopsia] 5.3%, 2.6%PY *versus* 0.5%, 0.2%PY), blurred vision (1.2%, 0.6%PY *versus* 0.4%, 0.2%PY) and AF (4.6%, 2.2%PY *versus* 3.3%, 1.5%PY) were observed at higher rates (as expected) in the ivabradine group as compared to placebo. The rate of events related to an increase in blood pressure, in patients diagnosed with hypertension, was slightly higher in the ivabradine group as compared with the placebo group (14.5%, 7.1%PY *versus* 11.9%, 5.5%PY). Comparable rates in the 2 treatment groups were observed for atrioventricular block (2^{nd} degree or complete), severe ventricular arrhythmia, supraventricular tachyarrhythmia other than AF or immune system disorders.

The outcome of events was similar in the 2 treatment groups: bradycardia (all forms): 97% of cases were recovered in the ivabradine group *versus* 95% in the placebo group; phosphenes: 90% *versus* 89% recovered; blurred vision: 87% *versus* 92% recovered; atrial fibrillation 72% *versus* 73% recovered.

Serious EAEs on treatment were reported at a comparable frequency in the 2 groups (ivabradine *versus* placebo, respectively): 35.4% (17.3%PY) *versus* 34.2% (15.8%PY). The most frequently affected SOCs in both groups were *Cardiac disorders, Nervous system disorders* and *Vascular disorders*. The largest between-group differences (in order of decreasing difference, ivabradine *versus* placebo) were in the incidences of AF (3.5%, 1.7%PY *versus* 2.4%, 1.1%PY), symptomatic bradycardia (PTs [Bradycardia]: 1.1%, 0.5%PY *versus* 0.2%, 0.1%PY and [Sinus bradycardia]: 0.5%, 0.2%PY *versus* 0.1%, < 0.1%PY), hypertension (2.1%, 1.0%PY *versus* 1.5%, 0.7%PY) and asymptomatic bradycardia (PT [HR decreased]: 0.6%, 0.3%PY *versus* 0.1%, < 0.1%PY). A serious ventricular arrhythmia was reported in 54 ivabradine-treated patients (0.6%) *versus* 38 placebo-treated patients (0.4%); an event which was fatal in 2 *versus* 7 patients, respectively.
SEAEs more frequently led to study drug withdrawal in the ivabradine group than in the placebo group: 6.6%, 3.2%PY *versus* 5.0%, 2.3%PY respectively. Again, these mostly concerned *Cardiac disorders* (4.0%, 2%PY *versus* 2.6%, 1.2%PY respectively) and, in particular, AF (1.4%, 0.7%PY *versus* 1.0%, 0.4%PY) or bradycardia (0.6%, 0.3%PY *versus* 0.2%, 0.1%PY).

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Fatalities: The number of deaths due to an on-treatment EAE was evenly balanced in the 2 groups: 363 in the ivabradine group (3.8%, 1.9%PY) and 356 in the placebo group (3.7%, 1.7%PY). Most were fatal outcomes within the SOC *General disorders and administration site conditions* with incidence rates of 1.4% (0.7%PY) *versus* 1.4% (0.6%PY) in the ivabradine and placebo groups respectively (265 deaths in total; mainly 'sudden death' or 'sudden cardiac death'). Events within the SOC *Cardiac disorders*, accounted for a total of 173 deaths with comparable incidence rates of 1.0% (0.5%PY) *versus* 0.9% (0.4%PY) and these concerned coronary artery disorders and heart failures (high-level group terms). Overall during the study, a total of 964 patients died: 498 (5.2%, 2.3%PY) in the ivabradine group and 466 (4.9%, 2.1%PY) in the placebo group.

In the Safety Set Angina, the rates of EAE and SEAE were slightly lower than in the Safety Set while the between-group differences were similar (Table 8).

The number of fatalities due to an on-treatment EAE was 246 in the ivabradine group (4.1%, 2.0%PY) and 229 in the placebo group (3.8%, 1.8%PY). At the SOC level, the fatal events occurring under *Cardiac disorders* showed similar rates (1.1% *versus* 1.0%).The all-cause mortality rates, during the study, were (5.5%, 2.4%PY *versus* 4.8%, 2.1%PY, respectively). A serious ventricular arrhythmia was reported in 32 ivabradine-treated patients (0.5%) *versus* 25 placebo-treated patients (0.4%); an event which was fatal in 1 *versus* 4 patients, respectively.

The summary of incidence of EAEs by category and seriousness is presented in Table 8.

Table 8 - Overall summary of safety results in the Safety Set Angina

On-treatment events (unless stated)	Ivabradine (N = 6030)			Placebo (N = 6009)		
	n	%	%PY	n	%	%PY
Patients having reported at least one:						
Emergent adverse event	4213	69.9	33.8	3757	62.5	28.9
Severe emergent adverse event	783	13.0	6.3	743	12.4	5.7
Treatment-related emergent adverse event	1506	25.0	12.1	346	5.8	2.7
EAE of bradycardia (all forms)	1082	17.9	8.7	152	2.5	1.2
EAE of phosphenes	291	4.8	2.3	20	0.3	0.2
Patients having experienced at least one:						
Serious emergent adverse event (including death)	2048	34.0	16.4	1885	31.4	14.5
Serious treatment-related emergent adverse event	156	2.6	1.3	36	0.6	0.3
Patients with treatment withdrawal due to:						
Emergent adverse event	727	12.1	5.8	390	6.5	3.0
EAE of bradycardia (all forms)	220	3.6	1.8	30	0.5	0.2
EAE of phosphenes	32	0.5	0.3	6	0.1	< 0.1
Serious emergent adverse event	383	6.4	3.1	260	4.3	2.0
Fatalities						
EAE with fatal outcome	246	4.1	2.0	229	3.8	1.8
All-cause mortality (during the study)	332	5.5	2.4	290	4.8	2.1

N: total number of patients in considered treatment group; NPY = 12453.8 in the ivabradine group; 13007.9 in the placebo group
n: number of affected patients; % = (n/N) x 100; %PY = (n/NPY) x 100

- **Laboratory tests**

In the Safety Set, blood creatinine and potassium levels did not show any relevant mean changes over time or differences between groups. High emergent abnormal values for creatinine were detected with somewhat higher frequency in ivabradine group than in placebo group (16.2% of patients *versus* 12.8%, respectively) and at comparable emergent abnormal rates for potassium (14.8% *versus* 14.2%, respectively). Potentially clinically significant emergent abnormal values were infrequent and similar in each treatment group (< 2%). Similar results were observed in the SS_{ANG}.

SUMMARY - CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

- **Other safety evaluation**

Vital signs
In the Safety Set, the analysis over time of supine blood pressure showed minimal and comparable mean changes in SBP/DBP in the 2 groups. There was no relevant mean change in weight. Similar results were observed in the SS_{ANG}. As expected, cases of HR value < 50 bpm (on resting ECG) were more frequently reported in the ivabradine group (30.4% of patients) than in the placebo group (2.5%), but there were few cases (< 0.5%) of HR value < 40 bpm in either group.

NYHA class
During the study in the Safety Set, most patients remained without signs or symptoms of heart failure or, at the most, had signs of NYHA class II. There was no relevant difference between the 2 treatment groups in the NYHA profiles. The global rate of patients having degradation in NYHA class was comparable (2.10% in the ivabradine group *versus* 2.06% in the placebo group). Similar results were observed in the SS_{ANG}.

CONCLUSION

The SIGNIFY study was a large international, event-driven, parallel arm morbidity-mortality study, designed to investigate the effect of ivabradine *versus* placebo, on top of recommended cardiovascular therapy, on clinical outcomes. The target population was patients with coronary artery disease, without evidence of clinical heart failure and with resting HR ≥ 70 bpm. The starting dose was 7.5 mg *b.i.d.* (or 5 mg *b.i.d.*, if aged ≥ 75 years) and the maintenance dose, following optional titration could be 5, 7.5 or 10 mg *b.i.d.* No titration lower than 5 mg *b.i.d.* was possible and, if indicated, the study drug was withdrawn. These starting doses were higher than currently recommended for the stable angina indication, and the upper maintenance dose (10 mg *b.i.d.)* is not currently authorised.

In the Randomised Set (N = 19 102) the incidence of the primary efficacy criterion (a composite endpoint [PCE] of CV death and non-fatal MI) was 3.03%PY in the ivabradine group *versus* 2.82%PY in the placebo group, with a hazard ratio of 1.08 (p = 0.1969). Thus, ivabradine did not significantly change clinical outcome. The effect of treatment was also neutral on the two components endpoints: CV death (hazard ratio 1.10 (p = 0.2493; 1.49%PY *versus* 1.36%PY) and non-fatal MI (hazard ratio 1.04 (p = 0.6024); 1.63%PY *versus* 1.56%PY). The incidence of the PCE was lower than initially hypothesised. Concerning the other secondary endpoints, all-cause mortality showed low absolute rates (2.20%PY in the ivabradine group *versus* 2.07%PY in the placebo group), with a small (0.1%PY) between-group difference and a non-statistically significant hazard ratio (HR = 1.06, p = 0.3461). On the composite endpoint of MI (fatal or non-fatal), the hazard ratio was 1.06 (p = 0.4299; 1.82%PY *versus* 1.71%PY). The rate of sudden deaths was similar in the 2 groups, suggesting no ventricular proarrhythmic effect of ivabradine.

In the main pre-specified subgroup of patients with angina CCS Class II or more (RS_{ANG}; N = 12 049), a higher incidence of the PCE was observed in the ivabradine group (3.37%PY *versus* 2.86%PY) and there was statistically significant increase in the hazard ratio 1.18 (p = 0.0176). Similar trends were observed on the component endpoints: CV death (hazard ratio 1.16 (p = 0.1053); 1.76%PY *versus* 1.51%PY) and non-fatal MI (hazard ratio 1.18 (p = 0.0918); 1.72%PY *versus* 1.47%PY). There was no statistically significant difference in all-cause mortality (hazard ratio 1.13 (p = 0.1421); 2.33%PY *versus* 2.07%PY). On the composite MI endpoint (fatal or non-fatal), there was a trend towards a higher rate of events in the ivabradine group: hazard ratio 1.19 (p = 0.0509; 1.94%PY *versus* 1.63%PY).

The safety profile of ivabradine was largely dominated by adverse drug reactions already well described for this product, notably bradycardia (all forms: 17.9%, 8.7%PY) and phosphenes (5.3%, 2.6%PY), although the incidence of these events was higher than observed in previous studies. This observation is probably explained by the higher starting dose of ivabradine (7.5 mg *b.i.d.*) in this study, and the relatively high proportion of patients who were up-titrated to 10 mg *b.i.d* (almost half of the patients aged < 75 years were up-titrated and maintained on 10 mg *b.i.d.* until the end of the study). Hypertension occurred at somewhat higher rates in the ivabradine group (5.8%PY *versus* 4.5%PY).

The results of this study show that ivabradine, added to guideline recommended medical therapy does not improve outcome in patients with stable CAD and without clinical heart failure. The increase in cardiovascular events in patients with angina CCS class II or higher, with a posology higher than the approved one, resulted in a safety issue notified to Competent Health Authorities.

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