Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Safety of oral chronic administration of ivabradine modified release formulation compared to ivabradine immediate release formulation, in patients with stable coronary artery disease. A 6 to 12-month randomised double blind parallel groups multicentre study.**
Test drug code	**Ivabradine (S 16257-2)**
Indication	**Stable coronary artery disease**
Development phase	**Phase III**
Protocol code	**CL3-16257-097**
Study initiation date	**13 November 2012**
Study completion date	**14 April 2014**
International coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Les Laboratoires Servier Representative Office** **Paveletskaya square 2, Moscow 115 054 - Russia** **Servier Research and Development** **Rowley, Wexham Springs, Framewood Road** **Wexham, SL3 6PJ Slough - United Kingdom** **Laboratorios Servier, S.L.** **Departamento de Investigación y Desarrollo** **Avenida de los Madroños, 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	**13 April 2015**
Version of the report	**Final version**
	~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Sponsors: **I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France** **Laboratoires Servier Representative Office, Paveletskaya sq 2, Moscow - Russia** **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: Safety of oral chronic administration of ivabradine modified release formulation compared to ivabradine immediate release formulation, in patients with stable coronary artery disease. A 6 to 12-month randomised double blind parallel groups multicentre study.
Protocol No.: CL3-16257-097.
EudraCT No.: 2012-001668-31.
The description of the study protocol given hereafter includes the modifications of the two substantial amendments to the protocol (Amendments No. 1 and 2).

International coordinator
[redacted]

Study centres:
85 centres located in 11 countries included 842 patients: 9 centres in Bulgaria (117 included patients), 8 centres in Germany (59 included patients), 12 centres in Hungary (119 included patients), 5 centres in Italy (45 included patients), 6 centres in Korea (72 included patients), 10 centres in The Netherlands (91 included patients), 10 centres in Russia (83 included patients), 6 centres in Slovakia (51 included patients), 13 centres in Spain (107 included patients), 3 centres in United Kingdom (58 included patients) and 3 centres in Vietnam (40 included patients).

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 13 November 2012 (date of first visit first patient) Completion date: 14 April 2014 (date of last visit last patient)	Phase III

Objectives:
The primary objective was to compare the safety profiles of ivabradine modified release (MR) formulation and ivabradine immediate release (IR) formulation over a 6-month period in patients with coronary artery disease (CAD) with or without chronic stable angina pectoris and under stable cardiovascular condition and treatment.

Secondary objectives were:

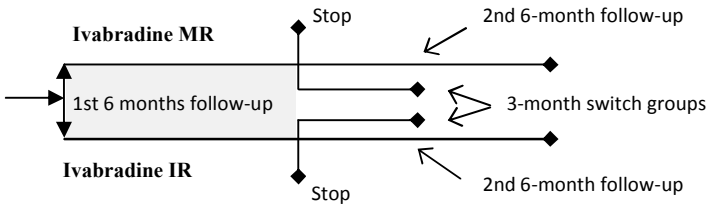
- To assess the safety of the two formulations over a 12-month period.
- To assess the efficacy of the two formulations over 6 and 12-month periods:
  - On resting heart rate (HR) decrease on 12-lead electrocardiogram (ECG).
  - On clinical symptoms for angina patients: Canadian Cardiovascular Society (CCS) class, number of angina attacks, short acting nitrates consumption.
- To assess the safety and efficacy of switching ivabradine formulations over a 3-month period.

Other objectives were to assess in a subgroup of patients from selected centres:

- The cardiac safety of the two formulations from 24-hour Holter ECG at 6 months.
- The pharmacokinetic profile of the two formulations over 24 hours (detailed in a separate PK report).

Methodology:
This was a phase III, international, randomised, double-blind, multicentre, comparative study with two parallel groups (ivabradine MR *versus* IR formulations). The non-adaptative randomisation was stratified on country and Holter assessment participation (yes/no). The first 6 months of treatment (main analysis) was followed by a blinded extension treatment period of 6 months for the early recruited eligible patients in each group. For later recruited patients, a blinded switch (cross-over) treatment period of 3 months was planned, during which they received the alternate formulation of equivalent dose. For the last recruited patients, study participation was terminated after the first 6 months.

Methodology (Cont'd):



In a subgroup of patients: two 24-hour Holter ECG recordings (inclusion visit, before first IMP intake, and just before the M6 visit). In a subgroup of patients: PK assessments were performed at D14 (6 samplings) and M6 visits (2 samplings) with HR measurement (supine ECG) before each sampling.

The study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:

Planned:

- First 6-month period: 700 patients (350 per group) of whom at least half with chronic stable angina pectoris (defined as *"patients having had at least one angina attack within the two months preceding the selection visit and being in CCS class I to IV")*. Amendment No. 2 increased the sample size to approximately 850 patients (425 per group). During this period, 120 patients (60 per group) were planned to participate to the 24-hour Holter ECG assessment and 120 patients to the PK assessment.
- Second 6-month treatment period: 260 patients (130 per group).
- 3-month switch period: 120 patients (60 per group). Amendment No. 2 increased the size of the switch group to 240 patients (120 per group).

Included:

- First 6-month period: 842 patients (421 in the ivabradine MR group and 421 in the ivabradine IR group), of whom 500 (255 and 245, respectively) with chronic stable angina. A total of 118 patients (58 and 60, respectively) were enrolled in the 24-hour Holter ECG assessment and 166 patients (73 and 93, respectively) in the PK assessment.
- Second 6-month treatment period: 270 patients (140 in the ivabradine MR group and 130 in the IR group).
- 252 patients (118 patients in the ivabradine MR group and 134 in the IR group).

Diagnosis and main criteria for inclusion:

Male or female aged >18 years having signed an inform consent, with documented stable CAD with or without chronic stable angina pectoris, those at sinus rhythm with resting HR ≥ 60 bpm, without heart failure in NYHA class II or higher, and without contraindication or special warning and precautions for ivabradine use, or requirement for not recommended concomitant treatments. A minimum of 50% of recruited patients were required to have chronic stable angina.

Investigational Medicinal Products (IMP):

Ivabradine MR once-a-day formulation: 7.5 mg, 15 mg, 22.5 mg or 30 mg, orally administered, one capsule in the morning. The starting dose was 15 mg once daily then, at each visit, dose up-titrated, maintained, down-titrated or stopped according to the tolerability and the HR on resting 12-lead ECG.
The ivabradine MR formulation consisted of pellet-filled capsules. The pellets, of identical size, were of a dense matrix formulation manufactured with hot melt extraction using Eudragit® RL PO and Eudragit® RSP O as excipients.

Batch numbers: L0047055 (7.5 mg capsules); L0045172, L0044904, L0047591 & L0044956 (15 mg capsules) L0047607 (22.5 mg capsules); L0047598 (30 mg capsules).

Ivabradine IR twice-a-day formulation **(reference product):** 2.5 mg, 5 mg, 7.5 mg or 10 mg, orally administered, one tablet in the morning and one tablet in the evening.
Starting dose of 5 mg twice daily then, at each visit, dose up-titrated, maintained, down-titrated or stopped according to the tolerability and the HR on resting 12-lead ECG.
Batch numbers: L0044336 (2.5 mg tablets); L0042554; L0044837 (5 mg tablets); L0042556 & L0045846 (7.5 mg tablets); L0044712 (10 mg tablets).

Investigational Medicinal Products (Cont'd):

Dose titration (both ivabradine formulations): the dose was adapted according to the tolerability and HR on resting 12-lead ECG at the D14 and M1 visits (and at later follow-up visits if necessary). If adverse HR-related symptoms or HR < 50 bpm, then down-titration to the next dose was recommended (if already on lowest dose then treatment discontinued). If resting HR > 60 bpm, then up-titration to next dose (if already on highest dose then dose maintained). If resting HR ≥ 50 and ≤ 60 bpm and no HR-related symptom, then dose maintained; if HR-related symptom observed, then down-titration to next dose. For patients who were randomized to switch their treatment formulations at M6 they had to stay at the same titration step; if any dose titration was indicated at M6, then the patient was not permitted to continue in the switch period.

Placebo capsules and tablets matching the active products for double blind masking.

Duration of treatment:
The pre-randomisation period (3 to 15 days) was without treatment.
The planned length of the treatment period depended on the time of recruitment into the study and could be 6 months (minimum), 9 months or 12 months (maximum).

Criteria for evaluation:
Efficacy criteria (secondary objective):

- Resting heart rate on 12-lead ECG.
- Symptomology of angina: CCS class, intake of short acting nitrates (SAN) and number of angina attacks.

Safety criteria (primary objective):

- Adverse events (primary endpoint): emergent adverse events (EAE) on treatment; serious adverse events during the study.
- Secondary endpoints: vital signs, clinical laboratory parameters, 24-hour Holter ECG parameters.

Pharmacokinetics:
Concentrations of ivabradine and its metabolite measured over an 18 hour period.

Statistical methods:
Efficacy analyses
The efficacy analyses were carried-out in 3 Full Analysis Sets (FAS): over the first 6-month treatment period (FAS_{6m}), over the 12-month treatment period (FAS_{12m}) and over the 3-month switch period (FAS_S), with in each, a subgroup analysis in the patients with stable angina at baseline. The FAS_{6m} was defined as: all patients of RS, having taken ≥ 1 dose of IMP during the first 6-month treatment period and with one baseline and ≥ 1 post-baseline 12-lead ECG HR measurement over the first 6-month treatment period.

Heart rate at rest: An estimate of the difference between the two formulations on the change from baseline to M6 was calculating using a parametric covariance analysis adjusted for country and baseline value. Standard error and 95% confidence interval (CI) were also provided. Sensitivity analyses were performed using a parametric variance analysis without adjustment as well as a non-parametric rank-based approach (Wilcoxon Score) with adjustment on country factor and baseline value.

Angina symptoms for patients with stable angina at selection: descriptive statistics on the change from baseline in the CCS angina class, number of angina attacks and SAN consumption were calculated. The difference between treatment groups was estimated on the change from baseline of angina symptomatology with two-sided 95% CI was calculated using a parametric analysis of variance without adjustment and a non-parametric approach without adjustment based on the Hodges and Lehman estimator.

Safety analyses
The safety analyses were carried-out in 4 Safety Sets (SS): over the first 6-month treatment period (SS_{6m}) (main analysis), over the 12-month treatment period (SS_{12m}), over the 3-month switch period (SS_S). In each set, a subgroup analysis was performed in the patients with stable angina at baseline.

- ***Main analysis*** (in the SS_{6m}): emergent adverse events (EAEs) were analysed using descriptive statistics. The estimate of the difference (95% CI) between treatment groups in the incidence of EAEs reported in the ivabradine Risk Management Plan (RMP) was calculated using Wilson score with continuity correction.
- ***Secondary analyses*** (SS_{6m}, SS_{12m} and SS_S): The same analysis described above was performed on SS_{12m} over the 12-months treatment period and on SS_S over the switch period, except for the analysis on the RMP events, for which only a descriptive analysis was done. Blood pressure, resting HR from 12-lead ECG and clinical laboratory parameters were analysed using descriptive statistics in all sets. EAEs were also described in the SS_{12m} and the SS_S.

Statistical methods (Cont'd):

Other secondary endpoints: From 24-hour Holter assessment: An estimate of the difference between the two formulations on change from baseline to M6 of HR from 24-hour Holter ECG was calculated in the SS_{Holter} using a covariance analysis adjusted for country and baseline value. Descriptive statistics were given on Holter ECG abnormalities.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 961 patients were screened for the study and 842 were included: 421 were randomised to ivabradine MR and 421 to ivabradine IR. A total of 500 patients at selection were reported with stable angina: 255 were allocated to ivabradine MR and 245 to ivabradine IR.

The first 6-month period of the study was completed by a total of 722 patients (85.7%), while 9.1% were prematurely withdrawn due to an adverse event, 3.6% due to a non-medical reason and 1.3% for protocol deviation. One patient in the ivabradine MR group was reported as lost to follow-up at the D14 visit.

Among patients who completed the first 6-month treatment period: 270 patients continued the study for the second 6-month treatment period (140 in the ivabradine MR group and 130 in the ivabradine IR group) and 254 patients entered the 3-month switch period (134 patients initially randomised on ivabradine IR switched to ivabradine MR at M6 and 120 patients initially on ivabradine MR switched to ivabradine IR). The remainder completed at M6. Patient status during the study is indicated in Table 1.

The number of patients in each analysis sets is presented in Table 2.

Table 1 - Disposition of randomised patients by group and by treatment period

Status		**Ivabradine MR**	**Ivabradine IR**	**All**
6-month treatment period in the RS				
Included (randomised)	**N**	**421**	**421**	**842**
in compliance with the protocol	n	368	371	739
with protocol deviation(s) before or at inclusion	n	53	50	103
Withdrawn due to	**n (%)**	**70 (16.6)**	**50 (11.9)**	**120 (14.3)**
adverse event	n (%)	41 (9.7)	36 (8.6)	77 (9.1)
non-medical reason	n (%)	19 (4.5)	11 (2.6)	30 (3.6)
protocol deviation	n (%)	9 (2.1)	2 (0.5)	11 (1.3)
lost to follow-up	n (%)	1 (0.2)	-	1 (0.1)
other protocol withdrawal criteria	n (%)	-	1 (0.2)	1 (0.1)
Completed	**n (%)**	**351 (83.4)**	**371 (88.1)**	**722 (85.7)**
in compliance with the protocol	n (%)	318 (75.5)	323 (76.7)	641 (76.1)
with a protocol deviation after inclusion	n (%)	33 (7.8)	48 (11.4)	81 (9.6)
12-month treatment period in the SS_{12M}				
Included	**N**	**140**	**130**	**270**
in compliance with the protocol	n	126	118	244
with protocol deviation(s) before or at inclusion	n	14	12	26
Withdrawn due to	**n (%)**	**11 (7.9)**	**10 (7.7)**	**21 (7.8)**
adverse event	n (%)	5 (3.6)	5 (3.8)	10 (3.7)
lack of efficacy	n (%)	1 (0.7)	-	1 (0.4)
non-medical reason	n (%)	4 (2.9)	5 (3.8)	9 (3.3)
other protocol withdrawal criteria	n (%)	1 (0.7)	-	1 (0.4)
Completed	**n (%)**	**129 (92.1)**	**120 (92.3)**	**249 (92.2)**
in compliance with the protocol	n (%)	108 (77.1)	101 (77.7)	209 (77.4)
with a protocol deviation after inclusion	n (%)	21 (15.0)	19 (14.6)	40 (14.8)
3-month switch period in the SS_S (following M6)		***MR to IR***	***IR to MR***	***All***
Included	**N**	**120**	**134**	**254**
in compliance with the protocol	n	110	117	227
with protocol deviation(s) before or at inclusion	n	10	17	27
Withdrawn due to	**n (%)**	**5 (4.2)**	**4 (3.0)**	**9 (3.5)**
adverse event	n (%)	2 (1.7)	3 (2.2)	5 (2.0)
non-medical reason	n (%)	3(2.5)	1 (0.7)	4 (1.6)
Completed	**n (%)**	**115 (97.5)**	**130 (97.0)**	**245 (97.2)**
in compliance with the protocol	n (%)	105 (89.0)	109 (81.3)	214 (84.9)
with a protocol deviation after inclusion	n (%)	10 (8.3)	21 (15.7)	31 (12.2)

SUMMARY - CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

Table 2 - Analysis Sets

Analysis sets		Ivabradine MR	Ivabradine IR	All
Randomised Set	**n**	**421**	**421**	**842**
Full Analysis Set 6 months (FAS_{6m})	**n (%)[1]**	**414 (98.3)**	**416 (98.8)**	**830 (98.6)**
Full Analysis Set 12 months (FAS_{12m})	n (%)[2]	140 (33.8)	129 (31.0)	269 (32.4)
Full Analysis Set Switch (FAS_S)	n (%)[2]	118 (28.5)[#]	134 (32.2)[##]	252 (30.4)
Safety Set 6 months (SS_{6m})	**n (%)[1]**	**419 (99.5)**	**421 (100)**	**840 (99.8)**
Safety Set 12 months (SS_{12m})	n (%)[3]	140 (33.4)	130 (30.9)	270 (32.1)
Safety Set Switch (SS_S)	n (%)[3]	120 (28.6)[#]	134 (31.8)[##]	254 (30.2)
Randomised Set Holter (RS_{Holter})	**n (%)[1]**	**73 (17.3)**	**75 (17.8)**	**148 (17.6)**
Safety Set Holter (SS_{Holter})	n (%)[4]	58 (79.5)	60 (80.0)	118 (79.7)

N: Total number of patients included (by period); n: number of patients in each category; % = (n/N) x 100
[1] % of the Randomised Set ; [2] % of the $FAS_{6m,}$; [3] % of the SS_{6m} [4] % of the RS Holter
[#] MR to IR; [##] IR to MR

Main baseline characteristics

The main demographic and baseline characteristics in the RS revealed no relevant between-group differences. The mean age (± SD) was 62.9 ± 9.5 years, 75.5% were men and 85.6% were Caucasian. CAD was documented by previous MI in 61.3% of patients, by prior coronary revascularisation in 81.2%, by angiographically proven significant coronary atherosclerosis in 70.6% and by non-invasive evidence of myocardial ischemia in 12.8%. The overall mean duration of CAD from diagnosis until selection was 74.3 ± 70.7 months (median: 52.0).

A total of 500 patients (255 in the ivabradine MR group and 245 in the ivabradine IR group) had chronic stable angina at baseline (*angina subgroup*). In this subgroup, the mean age was 62.6 ± 9.6 years, 71.6% were men and 83.6% were Caucasian. CAD was documented by previous MI in 56.4% of patients, by prior coronary revascularisation in 79.4%, by angiographically proven significant coronary atherosclerosis in 73.8% and by non-invasive evidence of myocardial ischemia in 13.8%. On average CAD had been diagnosed for 67.9 ± 67.1 months (median: 46.0) and angina pectoris diagnosed for 67.5 ± 68.9 months (median: 44.0). One third of this subgroup were CCS class I (32.6%) and nearly two thirds were class II (62.0%); the mean number of angina attacks per week was 2.5 ± 4.0.

The mean HR (on resting supine ECG) was 71.5 ± 8.4 bpm in the overall RS. Mean SBP and DBP were 131.8 ± 15.1 mmHg and 77.9 ± 8.9 mmHg, respectively, and mean BMI was 29.2 ± 4.7 kg/m^2. In the *angina subgroup*, values for blood pressure and HR were similar to those in the global population. No relevant between-group difference was observed for these parameters in either the overall population or the angina subgroup.

The main cardiovascular concomitant treatments taken at randomisation in the overall RS were antiplatelet agents (93.8%), lipid-lowering agents (92.9%), beta-blockers (82.3%) and ACE inhibitors (54.2%). In *angina subgroup*, the rates of these concomitant treatments were: antiplatelet agents (95.0%), lipid-lowering agents (92.4%), beta-blockers (86.8%), ACE inhibitors (54.8%) and organic nitrates (60.0%). No relevant between-group difference was observed in either the overall population or the angina subgroup.

For patients in the 12-month treatment period (SS_{12m}) the main baseline characteristics were similar to those in the RS, except for lower intake rates of beta-blockers and organic nitrates as compared to the RS (76.3% *versus* 82.3% and 33.7% *versus* 45.7%, respectively). Treatment groups were similar except for the proportion of males (82.1% on ivabradine MR *versus* 75.4% on ivabradine IR), the duration of CAD diagnosis (72.4 ± 66.2 months *versus* 81.3 ± 74.4 months, respectively) and the documentation of CAD by coronary atherosclerosis (70.7% *versus* 60.8%, respectively). In the *angina subgroup*, there was a lower proportion of patients in CCS class II in the ivabradine MR group (54.8%) than in the ivabradine IR group (63.6%).

SUMMARY - CONCLUSIONS (Cont'd)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

In patients who entered the switch period (SS_S), the main baseline characteristics were similar to those in the RS, although the patients with angina pectoris (about 2 thirds of each group) had, as compared to the RS, a longer mean duration of angina diagnosis (73.9 ± 71.8 months overall). Differences between the treatment groups were noted for the duration of CAD diagnosis (median: 49.5 months in the IR to MR group *versus* 57.5 months in the MR to IR group) and angina diagnosis (median: 47.0 *versus* 56.0 months) and the documentation of CAD by myocardial ischemia (16.4% *versus* 6.7%, respectively). At baseline switch (*i.e.* the last reliable value prior to the first study drug intake of switched treatment) the mean resting HR was 58.2 ± 7.7 bpm in the IR to MR group and 60.1 ± 8.4 bpm in the MR to IR group. Mean overall SBP and DBP were 131.4 ± 15.4 mmHg and 76.6 ± 9.3 mmHg, respectively, with no relevant between-group difference. Slight between-group differences were observed at baseline switch for the number of angina attacks per week (5.3 ± 5.1 in the IR to MR group *versus* 9.0 ± 13.6 attacks, in the MR to IR group; medians 3.5 *versus* 4.0) and for the proportion of patients with angina CCS class II (29.1% *versus* 35.4%, respectively).

In the RS_{Holter}, main baseline characteristics were similar to those described in the RS, except for a higher prevalence of ACE inhibitor intake at inclusion (62.8%) and a lower prevalence of organic nitrate intake (24.3%). Overall 83.1% of patients had an analysable Holter (*i.e.* recording performed, with a sufficient quality of recording and at least 18 hours of recording) at both D0 and M6 visits: 82.2% in the ivabradine MR group and 84.0% in the ivabradine IR group. Mean HR over the baseline 24-hour period was 73.7 ± 7.3 bpm and 73.4 ± 7.5 bpm in the ivabradine MR and IR groups, respectively.

Treatment duration and dose

Treatment duration was similar in the two groups with an overall mean duration (± SD) of 5.4 ± 1.6 months in the RS and 5.3 ± 1.6 months in angina patients. Overall study drug compliance was good with at least 95.0% of patients achieving a compliance between 70-130%. In the SS_{12m}, treatment duration was equal in the two groups with a mean duration of 11.6 ± 1.0 months. In the SS_S (during the switch period), the mean treatment duration was also equal in the two groups (2.9 ± 0.4 months). Compliance was good in both the SS_{12m} and the SS_S.

About a quarter of patients (23.9%) remained on starting dose: MR 15 mg o.d. or IR 5 mg b.i.d.; 20.0% were up-titrated once (MR 22.5 mg o.d. or IR 7.5 mg b.i.d.); 30.5% were up-titrated twice (MR 30 mg o.d. or IR 10 mg b.i.d.); and 14.4% were down-titrated (MR 7.5 mg o.d. or IR 2.5 mg b.i.d.). The titration profiles were similar between the treatment groups. In the angina subgroup, a slightly lower proportion of patients were uptitrated; 27.2% remained on the starting dose. In the SS_S, most patients (83.1%) needed no dose adaptation at M7, indicating that the equivalence between the formulations was good.

EFFICACY RESULTS (secondary objectives)

Statistical analyses are presented with imputation using a Last Observation Carried Forward (LOCF) approach. (Consistent results were observed using the complete case approach).

Heart rate on resting ECG

In the FAS_{6m} (N = 830) over the first 6-month treatment period, as expected, a relevant reduction in resting HR was observed in both groups. The mean HR decreased from baseline to M6 by 11.4 ± 9.8 bpm in the ivabradine MR group and by 12.4 ± 9.7 bpm in the ivabradine IR group. Mean HR at M6 was 60.2 ± 9.6 bpm in the MR group *versus* 59.1 ± 8.8 bpm in the IR group. In the *angina subgroup* of the FAS_{6m} (n = 492) the mean HR decreased from baseline to M6 by 10.7 ± 10.2 bpm in the MR group and by 12.2 ± 9.4 bpm in the IR group.

In patients who were treated over 12 months (FAS_{12m} N = 269) comparable reductions in resting HR were observed: mean HR decreased between baseline and M12 by 10.8 ± 8.7 bpm in the MR group and by 9.8 ± 11.4 bpm in the IR group. In the *angina subgroup* of the FAS_{12m} (n = 75), the mean HR decreased from baseline to M12 by 8.1 ± 9.2 bpm and by 9.2 ± 7.4 bpm, respectively. No relevant between-group differences were observed over the 12-months treatment period.

Results in the switch and Holter groups of patients are presented further below, following the M6/M12 safety results.

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

Symptomatology of angina
In the angina subgroup of the FAS_{6m}, 42.2% of patients in the MR group improved in CCS class between baseline and M6 *versus* 46.1% in the ivabradine IR group. In both groups, the intake of SAN decreased over the period: -1.0 ± 2.8 intakes/week in MR group *versus* -1.1 ± 6.7 intakes/week in the IR group, with no relevant between-group difference. Similarly, the mean number of angina attacks per week decreased: -2.4 ± 3.8 attacks/week in ivabradine MR group *versus* -1.8 ± 3.7 attacks/week in the ivabradine IR group, with no relevant between-group difference.
Similar results were observed in the angina subgroup of the FAS_{12m}, although the decrease in the mean number of SAN intake/week was not as marked: -0.5 ± 1.1 intakes/week in the MR group versus -0.2 ± 1.6 in the IR group. The reduction in the mean number of angina attacks was however more marked: -2.8 ± 3.1 attacks/week in ivabradine MR group *versus* -2.5 ± 3.7 attacks/week in the IR group. No important between-group differences were observed for angina symptoms in the FAS_{12m}.

SAFETY RESULTS (main objectives)

Primary endpoint (occurrence of emergent adverse events over first 6 months, evaluated in the SS_{6m})

In the SS_{6m} (N = 840), during the first 6-month treatment period, at least one EAE was reported by 240 patients (57.3%) in the ivabradine MR group *versus* 265 (62.9%) in the ivabradine IR group (Table 3). In the *angina subgroup* of the SS_{6m} (n = 498), at least one EAE was reported by 142 patients (56.1%) in the ivabradine MR group and 150 patients (61.2%) in the ivabradine IR group.

The most frequently affected SOCs in the SS_{6m} overall were cardiac disorders (11.9% in the MR group *versus* 15.4% in the IR group), infections and infestations (11.7% *versus* 14.3%, respectively), eye disorders (12.6% *versus* 13.1%, respectively), investigations (13.4% *versus* 11.9%, respectively) and vascular disorders (7.9% *versus* 10.9%, respectively). In the *angina subgroup* the profile was similar: cardiac disorders (14.2% *versus* 18.0%), infections and infestations (9.9% *versus* 12.7%, respectively), eye disorders (12.6% *versus* 12.2%, respectively), investigations (12.6% *versus* 11.8 %, respectively) and vascular disorders (8.7% *versus* 13.1%, respectively).

The most frequently reported EAEs were mostly events already described in the ivabradine RMP (potential or identified risks) and were reported with similar incidences in both treatment groups. In the SS_{6m} overall: bradycardia (symptomatic or asymptomatic): 11.5% *versus* 10.9%, respectively; phosphenes (photopsia): 10.5% *versus* 6.9%, respectively; increased blood pressure in hypertensive patients: 6.2% *versus* 8.6%, respectively. In the *angina subgroup* of the SS_{6m} the rates were bradycardia (11.5% *versus* 13.1%, respectively), phosphenes (9.9% *versus* 7.3%, respectively) and increase in blood pressure in hypertensive patients (7.1% *versus* 9.8%, respectively).

Treatment-related EAEs in the SS_{6m} were slightly more frequently reported in the ivabradine MR group (28.2% of patients) than in the ivabradine IR group (24.5%), but this difference was not evident in the *angina subgroup* (26.5% *versus* 26.1%, respectively).

Main safety results are summarised in Table 3.

Table 3 - Overall summary of safety results in the Safety Set_{6m} and angina subgroup

		All		Angina patients	
		Iva MR (N = 419)	**Iva IR (N = 421)**	**Iva MR (N = 253)**	**Iva IR (N = 245)**
Patients reporting at least one:					
EAE	n (%)	240 (57.3)	265 (62.9)	142 (56.1)	150 (61.2)
Treatment-related EAE	n (%)	118 (28.2)	103 (24.5)	67 (26.5)	64 (26.1)
Patients with treatment withdrawal due to :					
EAE	n (%)	42 (10.0)	38 (9.0)	31 (12.3)	23 (9.4)
EAE of bradycardia or sinus bradycardia	n (%)	6 (1.4)	5 (1.2)	6 (2.4)	3 (1.2)
EAE of HR decreased	n (%)	5 (1.2)	8 (1.9)	3 (1.2)	7 (2.9)
EAE of photopsia	n (%)	2 (0.5)	2 (0.5)	1 (0.4)	1 (0.4)
Patients reporting at least one:					
Serious EAE (including death)	n (%)	54 (12.9)	69 (16.4)	39 (15.4)	48 (19.6)
Serious treatment-related EAE	n (%)	7 (1.7)	6 (1.4)	5 (2.0)	4 (1.6)
Patients who died	**n (%)**	**3 (0.7)**	**3 (0.7)**	**3 (1.2)**	**3 (1.2)**

N: total number of exposed patients in the treatment group; n: number of affected patients; % = (n/N) x 100

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

EAEs leading to permanent study drug discontinuation were observed in 10.0% of patients in the ivabradine MR group *versus* 9.0% in the ivabradine IR group. In the *angina subgroup*, the rates were 12.3% *versus* 9.4%, respectively. The events most frequently concerned symptomatic bradycardia (1.4% *versus* 1.2%, respectively) or asymptomatic bradycardia [HR decreased] 1.2% *versus* 1.9%, respectively (as protocol-directed withdrawals during dose titration). In the *angina subgroup*, the slight imbalance between groups was due to cardiac disorders (4.7% *versus* 2.0%, respectively), mainly driven by symptomatic bradycardia (6 patients *versus* 3; 2.4% *versus* 1.2%, respectively) and atrial fibrillation (3 patients *versus* 0; 1.2% *versus* none, respectively).

At least one ***serious emergent adverse event*** was reported by 12.9% in the ivabradine MR group *versus* 16.4% in the ivabradine IR group. In the *angina subgroup*, the rates were 15.4% *versus* 19.6%, respectively. The most frequently affected SOCs in the SS_{6m} overall were cardiac disorders (4.3% *versus* 6.2%), nervous system disorders (1.0% *versus* 3.1%, respectively) and vascular disorders (1.0% versus 2.6%, respectively). More frequently reported preferred terms were: atrial fibrillation (3 patients *versus* 6 patients; 0.7% *versus* 1.4%), hypertension (1 patient *versus* 8; 0.2% *versus* 1.9%, respectively), angina pectoris and angina unstable (both 0.7% *versus* 1.2%).
In the *angina subgroup*: cardiac disorders (5.5% *versus* 6.9%), nervous system disorders (1.2% versus 2.4%, respectively) and surgical and medical procedures (2.0% versus 1.6%, respectively). In terms of events: angina pectoris (3 patients *versus* 5 patients; 1.2% *versus* 2.1%), atrial fibrillation (3 patients in each group; 1.2%) and angina unstable (0.4% *versus* 2.1%).

There were 6 deaths on-treatment, all of which occurred during the first 6-month period: 3 patients in the ivabradine MR group: two from sudden death and one from cardiac failure; and 3 patients in the ivabradine IR group: one from acute myocardial infarction and acute pulmonary oedema, one from gastric haemorrhage and one from cardiogenic shock. None of these deaths were considered as related to the study treatment. All 6 patients were diagnosed with angina at baseline.

In addition, 2 patients died more than 2 days after the last treatment intake: one from unknown cause (an 81 year old man randomised to ivabradine MR) and one following completed suicide (a 63 year old woman randomised to ivabradine IR).

Secondary endpoints
Emergent adverse events over the 12-month treatment period in the SS_{12m}
In the SS_{12m} (N = 270) over M0-M12 at least one EAE was reported by 93 patients (66.4%) in the ivabradine MR group and 97 patients (74.6%) in the ivabradine IR group. In the *angina subgroup* (n = 75), the rates were 64.3% *versus* 78.8%, respectively. The most frequently affected SOCs in the SS_{12m} were infections and infestations (18.6% *versus* 25.4%, respectively), investigations (16.4% *versus* 16.9%, respectively) and eye disorders (12.1% *versus* 21.5%, respectively). Vascular disorders were reported at 12.1% *versus* 14.6%, respectively and cardiac disorders at 10.7% *versus* 13.1%. In the *angina subgroup* the profile was comparable but since the group size was small further detail loses pertinence.
The most frequently reported EAEs (in the SS_{12m} overall) were phosphenes (photopsia) (10.0% *versus* 9.2%), hypertension (8.6% *versus* 11.5%), asymptomatic bradycardia (HR decreased) (8.6% *versus* 5.4%), and nasopharyngitis (6.4% *versus* 6.2%, respectively). The profiles of treatment-related EAEs, EAEs leading to IMP discontinuation and serious EAEs were similar to those observed over the first 6-month period in the SS_{6m}.

Blood pressure
In the SS_{6m} the analyses of BP over the first 6-month treatment period showed only minimal change in SBP but a trend toward a decrease in DBP in both groups. SBP: -0.9 ± 13.5 mmHg in the ivabradine MR group and -1.2 ± 15.4 in the ivabradine IR group; DBP: -3.2 ± 9.1 mmHg and -3.0 ± 9.3 bpm, respectively (median change = -2.0 mmHg in both groups). In the *angina subgroup,* SBP: -1.8 ± 13.0 mmHg and -0.6 ± 14.6 mmHg, MR and IR groups respectively; DBP: -3.4 ± 9.6 mmHg and -1.9 ± 8.9 mmHg, respectively (median change = -2.0 *versus* 0.0 mmHg).

In the SS_{12m} the analysis of SBP and DBP over 12 months of treatment, SBP: 0.6 ± 15.9 mmHg in the ivabradine MR group and 0.3 ± 15.6 in the ivabradine IR group; DBP: -2.3 ± 8.6 mmHg and -3.9 ± 9.6 bpm, respectively.

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

Laboratory examination
Emergent potentially clinically significant abnormal (PCSA) values of the biochemical and haematological parameters were infrequent in the SS_{6m} over the first 6-month treatment period. Only emergent high values for GGT in both groups were reported: 4 patients (1.2%) in the ivabradine MR group and 5 patients (1.4%) in the ivabradine IR group, but most of these occurred in patients with high out-of-reference-range values at baseline and in the absence of any significant change in ALT/AST levels.
In the SS_{12m} over the 12-month treatment period, few emergent PCSA were reported, with no relevant between-group differences.

Results in the switch set of patients (secondary objective)
In the SS_S (N = 254), EAEs were reported at similar rates in both groups (23.1% in the ivabradine IR to MR group and 20.8% in the ivabradine MR to IR group). EAEs were mostly related to cardiac disorders (6.7% *versus* 6.7%, respectively), with 8 patients overall (3.1%) reporting angina pectoris. At the end of the 3 month switch period, a slight increase in sitting SBP was observed in the IR to MR group (4.1 ± 14.0 mmHg), which was concomitant with a slight increase in HR (4.5 ± 8.9 bpm [in FAS_S]); changes that were not apparent at M7 and may have been related to modifications concomitant beta-blocker intake. In the MR to IR group no relevant change in SBP or HR was observed.

At baseline switch the mean resting HR in the FAS_S (N = 252) was 58.2 ± 7.7 bpm in the IR to MR group and 59.9 ± 8.2 bpm in the MR to IR group. At M9 the values were 62.6 ± 8.8 bpm *versus* 61.3 ± 9.4 bpm, respectively. Similar results were observed in *angina subgroup* of the FAS_S (N = 168).

In the *angina subgroup*, there was a higher proportion of asymptomatic patients in the ivabradine IR to MR group (30.2%) than in the ivabradine MR to IR group (22.0%). The mean number of angina attacks after treatment switch remained stable during the 3-month switch period in both groups (changes: 0.2 ± 0.9 in the ivabradine IR to MR group *versus* 0.0 ± 0.7 attacks/week in the ivabradine MR to IR group). Changes in the mean consumption of short-acting nitrates per week over the 3-month switch period were 0.2 ± 0.8 *versus* 0.1 ± 0.4 intakes/week, respectively. No statistically significant differences between groups were observed for angina symptoms in the FAS_S.

24-hour Holter
At baseline in the SS_{Holter} (N = 118), mean HR measured over 24 hours by Holter ECG was 73.7 ± 7.3 bpm in the ivabradine MR group and 73.4 ± 7.5 bpm in the ivabradine IR group. At M6, relevant HR reduction was evidenced in both groups: -12.1 ± 5.9 bpm in the ivabradine MR *versus* -11.3 ± 6.8 bpm in the ivabradine IR group. The estimate of the difference between the two formulations is slight (close to 1 bpm or less for each period). Similar between-group results were observed for lowest HR and highest HR, during the 24-hour, awake and sleep periods.

The main cardiac ECG abnormalities in the SS_{Holter} are presented in Table 4. The 2 treatment groups were very similar in the profile of abnormalities on treatment.

No patient in either treatment group reported HR < 30 bpm during awake or sleep.
One patient (ivabradine IR group) had a sustained SVT at M6, in addition to non-sustained episodes. A total of 16 patients (27.6%) in the MR group *versus* 9 (15.3%) in the IR group showed an increase in the number of SVT episodes between baseline and M6.

Seven patients (12.1%) in the MR group *versus* 4 (6.8%) in the IR group presented at least one episode of VT; all were non-sustained (< 30 seconds); 5 patients (8.6%) *versus* 4 (6.8%), respectively showed an increase in the number of VT episodes between baseline and M6, whereas 4 (6.9%) *versus* 3 (5.1%) showed a decrease.

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

Table 4 - Main cardiac abnormalities on 24h Holter at baseline and M6 on treatment - Safety Set$_{Holter}$

			Ivabradine MR (N = 58)		Ivabradine IR (N = 60)	
			Baseline	**M6**	**Baseline**	**M6**
Heart rate decrease						
over awake period	Lowest HR < 50 bpm	n (%)	3 (5.2)	37 (63.8)	5 (8.5)	31 (52.4)
	Lowest HR < 40 bpm	n (%)	-	2 (3.5)	-	-
	Lowest HR < 30 bpm	n (%)	-	-	-	-
over sleep period	Lowest HR < 50 bpm	n (%)	15 (25.9)	42 (72.4)	13 (22.0)	44 (74.6)
	Lowest HR < 40 bpm	n (%)	-	3 (5.2)	-	5 (8.5)
	Lowest HR < 30 bpm	n (%)	-	-	-	-
Supraventricular premature complexes		n (%)	55 (94.8)	58 (100)	57 (96.6)	59 (100)
Paired SVPC		n (%)	23 (39.7)	30 (51.7)	24 (40.7)	32 (54.2)
Supraventricular tachycardia (SVT)						
Non sustained (< 30 sec)		n (%)	18 (31.0)	21 (36.2)	20 (33.9)	16 (27.1)
Sustained (≥ 30 sec)		n (%)	-	-	-	1 (1.7)
Atrial fibrillation		n (%)	-	-	1 (1.7)	-
Atrial flutter		n (%)	-	-	1 (1.7)	-
Ventricular premature complexes		n (%)	56 (96.6)	55 (94.8)	56 (94.9)	5 (91.5)
Couplet		n (%)	18 (31.0)	16 (27.6)	19 (32.2)	18 (30.5)
Accelerated idioventricular rhythm		n (%)	2 (3.4)	8 (13.8)	2 (3.4)	7 (11.9)
Ventricular tachycardia (VT; all non-sustained**)**		n (%)	6 (10.3)	7 (12.1)	3 (5.1)	4 (6.8)
Monomorphic		n (%)	6 (10.3)	6 (10.3)	3 (5.1)	1 (1.7)
Polymorphic		n (%)	-	2 (3.5)	1 (1.7)	3 (5.1)
Torsade de pointe		n (%)	-	-	-	-
Atrioventricular block						
over awake period	AVB II Mobitz I	n (%)	-	-	1 (1.7)	-
over sleep period	AVB II Mobitz II	n (%)	-	1 (1.7)	-	-
Pathological pause on RR interval						
over awake period	> 2 sec	n (%)	-	1 (1.7)	-	1 (1.7)
	> 2.5 sec	n (%)	-	-	-	-
over sleep period	> 2 sec	n (%)	-	2 (3.4)	-	3 (5.0)
	> 2.5 sec	n (%)	-	1 (1.7)	-	-

*% = n/nobs*100 (nobs: number of patients with a value observed at baseline and at M6 on treatment)*

CONCLUSION

This was a phase III, randomised, double-blind comparison of ivabradine MR (modified release; once a day formulation) *versus* ivabradine IR (immediate release; twice a day formulation) in patients with CAD with or without chronic stable angina pectoris and under stable cardiovascular condition and treatment. The primary objective was the safety assessment over the first 6 months.

The randomised population conformed well to the target population with 59% of angina patients and the two treatment arms were well-balanced in terms of demographics, baseline characteristics, concomitant medication and study duration.

The two formulations were equally effective in reducing HR and, in patients with angina, a comparable anti-anginal effect was observed (reductions in angina attacks and intake of short-acting nitrates). These effects were first observed at the end of 6 months and confirmed in patients who continued treatment for a further 6 months and in patients who switched formulations after 6 months for a period of 3 months.

The safety assessment showed that MR and IR ivabradine formulations were very similar in terms of frequency of emergent adverse events as well as AE profile, showing a high consistency with the existing Summary of Product Characteristics of ivabradine. Over the first 6 month treatment period, as well as over 12 months, the most frequent drug related events were visual symptoms and symptomatic or asymptomatic bradycardia. In the patients who switched treatment formulations at M6, emergent AEs were infrequent and similar in the 2 treatment arms, with the most frequently reported events overall being angina pectoris (8 [3.1%]) and hypertension (8 [3.1%]). The Holter assessment revealed no unexpected emergent abnormalities in the MR group as compared with the IR group and the 2 groups were very similar. No new signals of concern were observed.

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