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 chronic heart failure and left ventricular systolic dysfunction. A 6 to 12-month randomised double blind parallel groups multicentre study.**
Test drug code	**Ivabradine S 16257-2**
Indication	**Chronic Heart Failure**
Development phase	**Phase III**
Protocol code	**CL3-16257-098**
Study initiation date	**29 November 2012**
Study completion date	**15 May 2014**
Main coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot, 92284 Suresnes Cedex – France** **Laboratorios Servier, S.L.** **Avenida de los Madroños 33, 28043 Madrid - Spain** **Les Laboratoires Servier Representative Office** **Paveletskaya sq 2, bld 3, floor 3, Moscow 115 054 - Russia**
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	**06 Mayl 2015**
Version of the report	**Final version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsors: **I.R.I.S., 50 rue Carnot, 92284 Suresnes Cedex - France** **Laboratorios Servier, S.L., Avd de los Madroños 33, 28043 Madrid - Spain** **Laboratoires Servier Representative Office, Paveletskaya sq 2, Moscow-Russia**		*(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 chronic heart failure and left ventricular systolic dysfunction. A 6 to 12-month randomised double blind parallel groups multicentre study.Protocol No.: CL3-16257-098
EudraCT No.: 2012-001689-3
The description of the study protocol given hereafter includes the modifications of the four substantial amendments to the protocol (Amendments No. 1, 2, 3 and 4).

International coordinator:
[redacted]

Study centres:
119 centres located in 16 countries included 791 patients: Argentina (8 centres, 40 included patients), Brazil (8 centres, 36 included patients), Bulgaria (10 centres, 117 included patients), Czech Republic (6 centres, 19 included patients), Estonia (4 centres, 33 included patients), Germany (6 centres, 25 included patients), Hungary (12 centres, 127 included patients), Italy (6 centres, 18 included patients), Latvia (4 centres, 37 included patients), Lithuania (6 centres, 36 included patients), Malaysia (4 centres,13 included patients), Philippines (3 centres, 12 included patients), Russia (18 centres, 117 included patients), Spain (10 centres, 27 included patients), Ukraine (10 centres, 104 included patients), Vietnam (4 centres, 30 included patients).

Publication (reference): Not applicable

Studied period: Initiation date: 29 November 2012 (first visit first patient) Completion date: 15 May 2014 (last visit last patient)	**Phase of development of the study**: Phase III

Objectives:
The primary objective was to compare the safety profiles of the ivabradine modified release (MR) formulation and ivabradine immediate release (IR) formulation over a 6-month period in patients with symptomatic chronic heart failure (CHF), LVEF ≤ 35% and under stable cardiovascular condition and treatment.

The secondary objectives were:

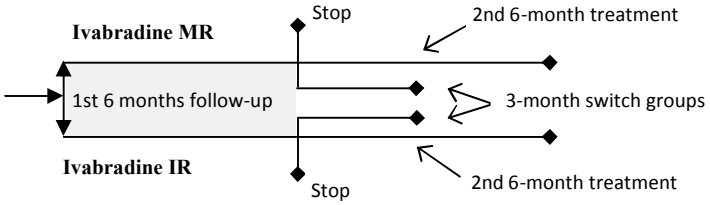
- To assess the safety profiles of the two formulations over a 12-month period.
- To assess the efficacy of the two formulations over 6 and 12-month periods:
  - On resting heart rate (HR) on 12-lead electrocardiogram (ECG).
  - On clinical symptoms: NYHA class.
- To assess the safety and efficacy of 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).

Diagnosis and main criteria for inclusion:
Male or female aged > 18 years, having signed an inform consent, those with symptomatic chronic heart failure NYHA class II, III or IV and LVEF ≤ 35%, at sinus rhythm with resting heart rate ≥ 75 bpm, in stable condition with regard to CHF symptoms and treatment and without contraindication or special warning and precautions for ivabradine use, or requirement for not recommended concomitant treatments.

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 follow-up (main analysis) was followed by a blinded extension treatment period of 6 months for the first 130 eligible patients in each group. For later recruited patients, 120 in each group a blinded switch (cross-over) treatment period of 3 months was planned, during which they received the alternate formulation of equivalent dose. For the late recruited patients in each group, after the first 6 month follow-up period was completed, their study participation was terminated.



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.

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

Number of patients:
Planned:

- First 6-month treatment period: 700 patients (350 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. Due to the slow recruitment for Holter ECG, the overall study recruitment continued over 700 patients until the target of 120 patients planned for Holter ECG had been reached.
- 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 treatment period: 791 patients (393 in the ivabradine MR group, 398 in the ivabradine IR group)**.** A total of 113 patients (55 in the ivabradine MR group and 58 in the ivabradine IR group) were enrolled in the 24-hour Holter ECG assessment and 156 patients (80 and 76, respectively) in the PK assessment.
- Second 6-month treatment period: 259 patients (130 in the ivabradine MR group, 129 in the IR group)
- 3-month switch period: 253 patients (134 in the ivabradine MR group, 119 in the ivabradine IR group).

Investigational Medicinal Products (IMP):
Ivabradine MR once-a-day formulation: 7.5 mg, 15 mg or 22.5 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 in which the pellets are of identical size and of a dense matrix formulation manufactured with hot melt extraction using Eudragit® RL PO and Eudragit® RS PO as excipients.
Batch numbers: L0045423, L0047055 (7.5 mg capsules); L0044904 & L0047591 (15 mg capsules); L0044958, L0045177, L0047609 & L0047608 (22.5 mg capsules).

Ivabradine IR twice-a-day formulation **(reference product):** 2.5 mg, 5 mg or 7.5 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 & L0047727 (2.5 mg tablets); L0042554 & L0044837 (5 mg tablets); L0042556 & L0045846 (7.5 mg tablets).

Investigational Medicinal Products (IMP) (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 entered in switch their treatment formulations at M6 had to stay at the same titration step; if any dose titration was indicated at M6, 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 HR on 12-lead ECG.
- Chronic heart failure symptomatology: NYHA class.

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 at different times at days 13-14 and at 6 months.

Statistical methods:
Efficacy analyses
The efficacy analyses were carried-out on patients 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). 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 using a parametric variance analysis without adjustment as well as a non-parametric rank-based (Wilcoxon score) with adjustment on country factor and baseline value were performed.

Chronic heart failure symptomatology: descriptive statistics of NYHA class at baseline, at each post-baseline visit and on the change from baseline to M6 and M12, from baseline switch to M7 and M9 was given.

Safety analyses:
The safety analyses were carried-out on patients of the Safety Set 6 months (SS_{6m}) for analyses over the first 6-month treatment period, the Safety Set 12 months (SS_{12m}) for analyses over the 12 months follow-up period and the Safety Set switch (SS_S) for analyses over the 3-month switch period. 24-Hour Holter assessments were performed on the Safety Set Holter (SS_{Holter}).

- ***Main analysis*** (in the SS_{6m}): emergent adverse events (EAEs) were analysed using descriptive statistics. Moreover, the estimate of the difference between incidence rates of at least one event of the RMP of each treatment group and 95% CI was given using the Wilson's score approach with continuity correction.
- ***Secondary analyses*** (in the SS_{6m}, the SS_{12m} and the 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. Moreover, blood pressure, HR from resting 12-lead ECG and blood laboratory parameters were analysed using descriptive statistics.

Other secondary analyses: from 24-hour Holter assessment, an estimate of the difference between the two formulations on the change from baseline to M6 of heart rate from 24-hour Holter ECG was calculated in the SS_{Holter} using a parametric 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 905 patients were screened for the study, and 791 were included and randomised: 393 patients to ivabradine MR and 398 to ivabradine IR.

The first 6-month period of the study was completed by a total of 708 patients (89.5%), while 5.4% were prematurely withdrawn due to an adverse event, 3.3% due to a non-medical reason and 1.6% for protocol deviation. One patient in the ivabradine MR group was reported as lost to follow-up at the M1 visit.

Among patients having completed the first 6-month treatment period: 259 patients continued the study through the second 6-month treatment period (130 in the ivabradine MR group and 129 in the ivabradine IR group) and 253 patients continued the study through the 3-month switch period (134 patients initially randomised on ivabradine IR switched to ivabradine MR at M6 and 119 patients initially on ivabradine MR switched to ivabradine IR). Patient status during the study and number of patients in each analysis sets are presented in Table 1.

Table 1 - Disposition of patients

Status		**Ivabradine MR**	**Ivabradine IR**	**All**
First 6-month treatment period in the RS				
Included (randomised)	**N**	**393**	**398**	**791**
Withdrawn due to	**n (%)**	**44 (11.2)**	**39 (9.8)**	**83 (10.5)**
adverse event	n (%)	20 (5.1)	23 (5.8)	43 (5.4)
non-medical reason	n (%)	16 (4.1)	10 (2.5)	26 (3.3)
protocol deviation	n (%)	8 (2.0)	5 (1.2)	13 (1.6)
lost to follow-up	n (%)	-	1 (0.2)	1 (0.1)
Completed	**n (%)**	**349 (88.8)**	**359 (90.2)**	**708 (89.5)**
12-month treatment period in the SS_{12M}				
Included	**N**	**130**	**129**	**259**
Withdrawn due to	**n (%)**	**9 (6.9)**	**7 (5.4)**	**16 (6.2)**
adverse event	n (%)	8 (6.1)	6 (4.6)	14 (5.4)
non-medical reason	n (%)	1 (0.8)	1 (0.8)	2 (0.8)
Completed	**n (%)**	**121 (93.1)**	**122 (94.6)**	**243 (93.8)**
3-month switch period in the SS_S		**MR to IR**	**IR to MR**	**All**
Included	**N**	**119**	**134**	**253**
Withdrawn due to	**n (%)**	**3 (2.5)**	**5 (3.7)**	**8 (3.2)**
adverse event	n (%)	2 (1.7)	3 (2.2)	5 (2.0)
non-medical reason	n (%)	1 (0.8)	2 (1.5)	3 (1.2)
Completed	**n (%)**	**116 (97.5)**	**129 (96.3)**	**245 (96.8)**
Analysis sets		**Ivabradine MR**	**Ivabradine IR**	**All**
Randomised Set	**n**	**393**	**398**	**791**
Full Analysis Set 6 months (FAS_{6m})[1]	**n (%)**	**387 (98.5)**	**395 (99.2)**	**782 (98.9)**
Full Analysis Set 12 months (FAS_{12m})[2]	n (%)	127 (32.8)	126 (31.9)	253 (32.4)
Full Analysis Set Switch (FAS_S) [2]	n (%)	119 (30.7)	133 (33.7)	252(32.2)
Safety Set 6 months (SS_{6m})[1]	**n (%)**	**393 (100)**	**398 (100)**	**791 (100)**
Safety Set 12 months (SS_{12m})[3]	n (%)	130 (33.1)	129 (32.4)	259 (32.7)
Safety Set Switch (SS_S)[3]	n (%)	119 (30.3)	134 (33.7)	253 (32.0)
Randomised Set Holter (RS_{Holter})[1]	**n (%)**	**65 (16.5)**	**64 (16.1)**	**129 (16.3)**
Safety Set Holter (SS_{Holter})[4]	n (%)	55 (84.6)	58 (90.6)	113 (87.6)

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

SUMMARY - CONCLUSIONS (Cont'd)
DISPOSITION OF PATIENTS AND ANALYSIS SETS (Cont'd)

Main baseline characteristics
The main demographic and baseline characteristics in the RS revealed no relevant between-group differences.
The mean age ± SD was 60.5 ± 11.3 years, 74.3% were men and 90.8% were Caucasian. CHF had been diagnosed for a mean of 53.6 ± 53.2 months. The main origin of CHF was mostly ischaemic (65.2%), dilated cardiomyopathy (24.1%) or hypertension (7.8%). CHF symptoms were mostly in NYHA class II (55.6%) or class III (41.0%). The mean LVEF was 30.2 ± 4.7%.

The mean HR (on resting supine ECG) was 83.0 ± 7.9 bpm overall in the overall RS. Mean values of SBP and DBP were 125.9 ± 14.9 mmHg and 78.2 ± 9.3mmHg, respectively, and the mean BMI was 28.8 ± 5.4 kg/m^2.

The main cardiovascular concomitant treatments taken at randomisation were beta-blocker (90.6%), diuretics (excluding anti-aldosterone agents) (74.3%), ACE inhibitors (67.4%), anti-aldosterone agents (58.8%), angiotensin II antagonists (21.4%) and digoxin (9.7%). Treatments were comparable between groups, except for ACE inhibitors intake (63.6% *versus* 71.1%, ivabradine MR *versus* IR) and anti-aldosterone agents (63.4% *versus* 54.3%).

For patients in the 12-month treatment period (SS_{12m}), the main baseline characteristics were similar to those in the RS, except for mean duration since CHF diagnosis and ACE inhibitors intake that were higher compared to the RS (65.1 ± 57.3 *versus* 53.6 ± 53.2 months and 76.1% *versus* 67.4%, respectively) and for anti-aldosterone agents intake that was lower compared to the RS (49.0% versus 58.8%, respectively). Moreover, these characteristics were comparable between ivabradine MR and ivabradine IR groups at baseline except for the proportion of males (80.8% *versus* 66.7%, ivabradine MR *versus* IR), the duration from CHF diagnosis (69.3 ± 59.3 *versus* 60.8 ± 55.1 months), ACE inhibitors intake (63.6% *versus* 71.1%) and anti-aldosterone agents intake (63.4% *versus* 54.3%).

In patients who entered the switch period (SS_S), the main baseline characteristics were similar to those in the RS, although the mean duration since CHF diagnosis and proportion of patients in NYHA class III were lower compared to the RS (45.7 ± 48.8 *versus* 53.6 ± 53.2 months and 43.0% *versus* 51.0%, respectively). Moreover, these characteristics were comparable between ivabradine MR and ivabradine IR groups at baseline except for proportion of patients in NYHA class II (55.2% in the ivabradine IR to MR group *versus* 42.0% in the ivabradine IR to MR group) and those in NYHA class III (44.8% *versus* 58.0%, respectively), ACE inhibitor intake (28.4% *versus* 33.6%, respectively) and anti-aldosterone intake (58.2% *versus* 66.4%, respectively).

In the RS_{Holter}, main baseline characteristics were similar to those in the RS, except for mean duration since CHF diagnosis, proportion of patients in NYHA class II, implanted pacemaker, implanted cardioverter defibrillator and digoxin intake that were higher compared to the RS (59.7 ± 56.6 *versus* 53.6 ± 53.2 months, 71.3% *versus* 55.6%, 5.4% *versus* 1.1%, 10.1% *versus* 5.2%, 18.6% *versus* 9.7%, respectively). Overall 87.6% of patients had 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: 84.6% in the ivabradine MR group and 90.6% in the ivabradine IR group. For patients on treatment at M6 in the SS_{Holter}, mean HR over the baseline 24-hour period was 79.4 ± 10.3 bpm and 76.7 ± 9.4 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 5.6 ± 1.3 months in the SS_{6m}. Overall study drug compliance was good with 96.2% of patients achieving compliance between 70-130% for both tablets and capsules. In the SS_{12m}, treatment duration was equal in the two groups with a mean duration of 11.7 ± 1.0 months. In the SS_S, treatment duration (± SD) was equal in the two groups (3.0 ± 0.4 months *versus* 3.0 ± 0.3 months, ivabradine IR to MR *versus* MR to IR). Compliance was good in both the SS_{12m} and the SS_S.
Most of patients in RS (69.8% overall) were up-titrated once (MR 22.5 mg o.d. or IR 7.5 mg b.i.d.), 15.9% received no dose titration during the study (*i.e.* remained at the starting dose: MR 15 mg o.d. or IR 5 mg b.i.d.) and 4.8% 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 SS_S, most patients (88.5%) needed no dose adaptation at M7, indicating the equivalence between the formulations was good.

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (secondary objectives)

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

Heart rate on resting ECG

In the FAS_{6m} (N = 782) over the first 6-month treatment period, as expected, a relevant reduction in resting HR was observed in both groups. The mean decrease in HR from baseline to M6 was very similar in both groups (17.1 ± 12.6 bpm in the ivabradine MR group and 17.2 ± 10.9 bpm in the ivabradine IR group).
In patients who were treated over 12 months (FAS_{12m} N = 253), comparable reductions in resting HR were observed between baseline and M12 in both groups: mean HR was decreased by 15.7 ± 13.8 bpm and 16.8 ± 12.2 bpm, respectively for ivabradine MR and IR groups.

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

Symptomatology of chronic heart failure

At baseline most patients of the FAS_{6m} were in NYHA class II (53.2% and 58.7%, respectively in the ivabradine MR and ivabradine IR groups) and in class III (46.2% and 41.0%, respectively).
In the FAS_{6m} over the first 6-month treatment period, most patients were stable in NYHA class for each group (80.5% in ivabradine MR group and 81.2% in the ivabradine IR group. A similar proportion of patients in the two groups (18.9% *versus* 17.7%, respectively) showed an improvement in NYHA class at M6 in comparison with baseline. Similar results were observed over the 12-month treatment period in the FAS_{12m}.

SAFETY RESULTS (main objectives)

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

In the SS_{6m} (N = 791), during the first 6-month treatment period, at least one EAE was reported by 181 patients (46.1%) in the ivabradine MR group *versus* 192 (48.2%) in the ivabradine IR group (Table 2).

The most frequently affected SOCs in the SS_{6m} overall were cardiac disorders (18.6% *versus* 16.1%), investigations (7.6% *versus* 10.8%, respectively) and infections and infestations (7.6% *versus* 10.1%, respectively).
The most frequently reported EAEs were events already described in the ivabradine RMP (potential or identified risk) and were reported with similar incidences in both groups for increase blood pressure in hypertensive patients (4.6% *versus* 5.3%), phosphenes (3.6% *versus* 4.5%), atrial fibrillation (2.3% *versus* 1.5%), asymptomatic bradycardia [HR decreased] (1.8% in both groups), ECG QT prolongation (2.0% *versus* 1.8%) and symptomatic bradycardia (5.1% *versus* 2.5%).

Main safety results in the SS_{6m} are summarised in Table 2.

Table 2 - Overall summary of safety results in the Safety Set_{6m}

		Ivabradine MR (N = 393)	Ivabradine IR (N = 398)
Patients who reported at least one:			
EAE	n (%)	181 (46.1)	192 (48.2)
Treatment-related EAE	n (%)	67 (17.0)	57 (14.3)
Patients with treatment withdrawal due to:			
EAE	n (%)	21 (5.3)	17 (4.3)
EAE of bradycardia or sinus bradycardia	n (%)	1 (0.3)	1 (0.3)
EAE of atrial fibrillation	n (%)	5 (1.3)	4 (1.0)
Patients reporting at least one:			
Serious EAE (including death)	n (%)	48 (12.2)	64 (16.1)
Serious treatment-related EAE	n (%)	7 (1.8)	5 (1.3)
Serious EAE with fatal outcome	n (%)	2 (0.5)	9 (2.7)

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

Treatment-related EAEs were slightly more frequently reported in the ivabradine MR group (17.0% of patients) than in the ivabradine IR group (14.3%). The difference between the two groups was mainly due to symptomatic bradycardia (4.9% *versus* 2.5 %, respectively).

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

EAEs leading to study drug withdrawal were observed in 5.3% of patients in the ivabradine MR group *versus* 4.3% in the ivabradine IR group, including atrial fibrillation (1.3% *versus* 1.0%). Bradycardia led to study drug withdrawal in one patient in both groups (0.3%).

At least one ***serious EAE*** was experienced by 12.2% of patients in the ivabradine MR group *versus* 16.1% in the ivabradine IR group. Serious EAEs concerned mostly cardiac disorders (6.6% *versus* 7.0%, respectively) with between group differences for cardiac failure chronic (3 patients [0.8%] *versus* 6 patients [1.5%]), ventricular tachycardia (2 patients [0.5%] *versus* 4 patients [1.0%], which were sustained in 1 patient *versus* 2 patients) and ventricular fibrillation (none *versus* 2 patients [0.5%]).

There were 18 serious EAE leading to death during the study. It concerned 5 patients in the ivabradine MR group (after switch IR to MR in one patient) and 13 patients in the ivabradine IR group. None of these were considered as related to the study drug. 11 patients died on-treatment during the first 6-month period: 2 patients in the ivabradine MR group, one from cardiopulmonary failure and one from recurrent ischemic stroke, and 9 patients in the ivabradine IR group, 5 from sudden death, 2 from cardiac failure, 1 from ventricular fibrillation and 1 from mesenterial vessels acute thrombosis. There were 6 deaths during the second 6-month period (see below) and 1 during the 3-month switch period (see below). In addition, 3 patients who were not on treatment died: one (a 78 year old woman) from unknown cause before she was randomised, one (a 73 year old man) from worsening of heart failure and one (a 63 year old man) from sudden death, both with AE leading to death occurring more than 2 days after the last treatment intake.

Secondary endpoints

Emergent adverse events over the 12-month treatment period in the SS_{12m}

In the SS_{12m} (N = 259) over M0-M12 at least one EAE was reported by 70 patients (53.8%) in the ivabradine MR group and 72 patients (55.8%) in the ivabradine IR group. The most frequently reported SOCs were cardiac disorders (22.3%*versus* 21.7%, respectively), investigations (12.3% *versus* 10.1%, respectively) and vascular disorders (11.5% *versus* 12.4%, respectively). The most frequent EAE reported in both groups was hypertension (8.5% *versus* 7.0%, respectively).

The profile 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}.

During the second 6 month follow-up period, 6 patients died on-treatment: 2 patients in the ivabradine MR group, one from sudden death and the other from asphyxia due to gastric aspiration, and 4 patients in the ivabradine IR group, one from sudden death, one from acute heart failure, one from worsening heart failure and one from liver metastases.

Blood pressure

In the SS_{6m} the analysis of BP over the first 6-month treatment period showed a trend toward an increase in SBP but minimal changes in DBP in both groups. SBP change was 2.8 ± 14.7 mmHg in the ivabradine MR group and 1.9 ± 13.1 bpm in the ivabradine IR group; median change: 2.5 and 0.0, respectively. DBP change was -0.3± 8.8 mmHg and 0.0 ± 8.9 mmHg, respectively.

In the SS_{12m}, the analysis of BP over 12 months of follow-up showed similar result as in the SS_{6m}. The mean change in SBP was 2.7 ± 13.9 mmHg in the ivabradine MR group and 2.7 ± 14.8 mmHg in the ivabradine IR group (median: 1.0 and 0.5, respectively) and the mean change in DBP was -0.7 ± 8.6 mmHg and 0.3 ± 10.8 mmHg, respectively.

The slight SBP increase observed in both SS_{6m} and $SS_{12m}$was probably the reflection of an improvement in haemodynamics.

Laboratory examination

Emergent PCSA values for the biochemical and haematological parameters were infrequent in the SS_{6m} in both groups, except for high GGT values reported in 8 patients (2.2%) in both groups.

Similarly, over the 12-month treatment period in the SS_{12m}, few emergent PCSA were reported, without relevant between-group differences, except for GGT high values reported in 2 patients (1.5%) in the ivabradine MR group and 9 patients (7.0%) in the ivabradine IR group.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Results in the switch set of patients (secondary objective)

In the SS_S, the incidence of patients with EAEs was similar in both groups (17.2% in the ivabradine IR to MR group and 15.1% in the ivabradine MR to IR group). Few EAEs were reported after treatment switch and events were mostly related to cardiac disorders (5.2% *versus* 5.9%, respectively). No particular safety concern was found regarding the safety profile after treatment switch.

During the 3 month switch follow-up period, 2 patients died from sudden death. One (a 52 year old man) was in the ivabradine IR to MR group with death occurring on treatment. The other (a 63 year old man) was in the ivabradine MR to IR group with death occurring more than 2 days after the last treatment intake.

At baseline switch (*i.e.* the last reliable value prior to the first study drug intake of switched treatment) the mean resting HR in the FAS_S (N = 252) was 64.4 ± 10.4 bpm in the ivabradine IR to MR group and 65.9 ± 11.2 bpm in the ivabradine MR to IR group. Over the period from M6 to M9, mean HR was stable in both groups: 0.6 ± 8.9 bpm in ivabradine IR to MR group and -0.1 ± 10.2 bpm in ivabradine MR to IR group.

Over the switch period, the large majority of patients showed no change in NYHA class.

24-hour Holter

At baseline in the SS_{Holter} (N = 113), mean HR measured over 24 hours by Holter ECG was 79.4 ± 10.3 bpm in the ivabradine MR group and 76.7 ± 9.4 bpm in the ivabradine IR group. At M6, relevant mean HR reduction over 24-hour was evidenced in both groups: -12.8 ± 9.3 bpm in the ivabradine MR *versus* -11.7 ± 9.0 bpm in the ivabradine IR group. The estimate of the difference between the two formulations is slight (close to 1 bpm whatever the diurnal period). Similar estimate of the difference between the two groups for highest HR and for lowest HR (close to 1.5 bpm) was observed.

The main ECG Holter abnormalities at baseline and at M6 on treatment are presented in Table 3.

At M6, episodes of HR < 50 bpm were quite frequently observed in both groups, with a higher incidence reported during sleep (49.1% and 67.9% in the 2 groups respectively) than during awake (38.5% and 46.4%). Episodes of lowest HR < 40 bpm were reported during awake period in 1 patient (1.8%) of the ivabradine MR group and during sleep period in 2 patients (3.7%) of the ivabradine MR group and 3 patients (5.4%) of the ivabradine IR group. No patients in either treatment group reported HR < 30 bpm during awake or sleep.

One patient in the ivabradine MR group had both sustained and non-sustained supraventricular tachycardia (SVT) and one patient in the ivabradine IR group had sustained SVT at M6. The median number of SVT episodes did not increase in overall patients, while 28.3% of patients in the ivabradine MR group *versus* 23.2% in the ivabradine IR group had a number of episodes increased between baseline and M6. Ventricular tachycardia episodes were all non-sustained (< 30 seconds) and affected fewer patients on-treatment at M6 in both groups (47.2% in the MR group and 37.5% in the IR group) compared with baseline (54.7% in the MR group and 50.0% in the IR group).

Table 3 - Main ECG Holter abnormalities at baseline and M6 on treatment - SS_{Holter}

			Ivabradine MR (N = 55)		Ivabradine IR (N = 58)	
			Baseline	**M6**	**Baseline**	**M6**
Heart rate decrease		n_{obs}	53	53	56	56
over awake period	Lowest HR < 50 bpm	n (%)	3 (5.7)	19 (35.8)	7 (12.5)	26 (46.4)
	Lowest HR < 40 bpm	n (%)	-	-	1 (1.8)	1 (1.8)
	Lowest HR < 30 bpm	n (%)	-	-	-	-
over sleep period	Lowest HR < 50 bpm	n (%)	7 (12.7)	27 (49.1)	15 (26.8)	38 (67.9)
	Lowest HR < 40 bpm	n (%)	-	2 (3.6)	1 (1.8)	3 (5.4)
	Lowest HR < 30 bpm	n (%)	-	-	-	-
Supraventricular premature complexes (SVPC)		n (%)	51 (96.2)	53 (100)	54 (96.4)	53 (94.6)
Paired SVPC		n (%)	23 (43.4)	14 (26.4)	25 (44.6)	15 (26.8)
Supraventricular tachycardia		n (%)				
Non sustained (< 30s)		n (%)	19 (35.8)	20 (20.8)	21 (37.50)	23 (41.07)
Sustained (≥ 30s)		n (%)	-	1 (1.9)	-	1 (1.8)
Atrial fibrillation		n (%)	-	1 (1.9)	-	-
Atrial flutter		n (%)	-	-	-	-

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

(Continued)

Table 3 (Cont'd) - Main ECG Holter abnormalities at baseline and M6 on treatment - SS_{Holter}

			Ivabradine MR (N = 55)		Ivabradine IR (N = 58)	
			Baseline	**M6**	**Baseline**	**M6**
Ventricular premature complexes (VPC)		n (%)	52 (98.1)	52 (98.1)	54 (96.4)	56 (100)
Couplet		n (%)	41 (77.4)	36 (67.9)	36 (64.3)	33 (58.9)
Accelerated idioventricular rhythm (AIVR)		n (%)	14 (26.4)	10 (18.9)	11 (19.6)	8 (14.3)
Ventricular tachycardia (VT)* (all were non-sustained: < 30s)		n (%)	29 (54.7)	25 (47.2)	28 (50.0)	21 (37.5)
Monomorphic		n (%)	24 (43.6)	19 (34.5)	18 (32.1)	26 (46.4)
Polymorphic		n (%)	15 (27.3)	17 (30.9)	12 (21.4)	11 (19.6)
Torsade de pointe		n (%)	-	-	-	-
AV block						
over awake period	AVB II Mobitz I	n (%)	-	-	-	1 (1.8)
over sleep period	AVB II Mobitz II	n (%)	-	-	1 (1.8)	2 (3.6)
Pathological pause on RR interval						
over awake period	> 2s	n (%)	-	1 (1.9)	-	3 (5.4)
	> 2.5s	n (%)	-	-	-	-
over sleep period	> 2s	n (%)	1 (1.9)	1 (1.9)	1 (1.8)	5 (8.9)
	> 2.5s	n (%)	-	-	-	2 (3.6)
	> 3s	n (%)	-	-	-	2 (3.6)

*% = n/n_{obs}*100 (n_{obs}: number of patients with a value observed at baseline and at M6 on treatment); * ≥ 3 consecutive VPCs at HR >100 bpm*

CONCLUSION

This was a phase III, randomised, double-blind comparison study of ivabradine MR (modified release; once a day formulation) *versus* ivabradine IR (immediate release; twice a day formulation) in patients with CHF and under stable cardiovascular condition and treatment. The primary objective was the safety assessment over first 6 months.
The randomised population conformed well to the target population 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 had comparable favourable effects on CHF symptoms. These effects were 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 SmPC 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 hypertension (5 [2.0%]).

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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