Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Effect of ivabradine *versus* placebo on cardiac function, exercise capacity, and neuroendocrine activation in patients with chronic heart failure with preserved left ventricular ejection fraction.** **An 8-month, randomised double-blind, placebo controlled international, multicentre study.** **(EDIFY study)**
Test drug code	**Ivabradine (S 16257-2)**
Indication	**Heart Failure with Preserved left ventricular Ejection Fraction**
Development phase	**Phase II**
Protocol code	**CL2-16257-101**
Study initiation date	**25 June 2013**
Study completion date	**29 February 2016**
Main 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 sq 2, bld 3, floor 3, 115054 Moscow, Russia** **Laboratorios Servier, S.L. Depart. de Investigacion y Desarrollo, 33 av. de los Madroños, 28043 Madrid, Spain** **Servier Research and Development, Gallions, Wexham Springs, Framewood Road, Slough SL3 6RJ, UK**
Responsible medical officers	[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	**24 November 2016**
Version of the report	**Final version**
	~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(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: Effect of ivabradine *versus* placebo on cardiac function, exercise capacity, and neuroendocrine activation in patients with Chronic Heart Failure with Preserved left ventricular Ejection Fraction. An 8-month, randomised double-blind, placebo controlled international, multicentre study. Study acronym EDIFY Protocol No.: CL2-16257-101 EudraCT No.: 2012-002742-20 The description of the study protocol given hereafter includes the modifications of the 11 substantial amendments to the protocol.		
International coordinators [redacted]		
Study centres: 97 centres located in 20 countries were opened; 67 included at least one patient: 3 centres in Argentina (6 patients included), 3 centres in Australia (5 patients included), 2 centres in Belgium (2 patients included), 3 centres in Brazil (5 patients included), 4 centres in Czech Republic (10 patients included), 3 centres in France (3 patients included), 6 centres in Germany (18 patients included), 8 centres in Hungary (20 patients included), 1 centre in Ireland (1 patient included), 2 centres in Italy (5 patients included), 4 centres in Republic of Korea (7 patients included), 3 centres in the Netherlands (6 patients included), 1 centre in Poland (13 patients included), 3 centres in Portugal (3 patients included), 8 centres in Russian Federation (32 patients included), 1 centre in Slovenia (2 patients included), 7 centres in Spain (19 patients included), 3 centres in Taiwan (8 patients included) and 2 centres in United Kingdom (14 patients included).		
Publication (reference): Not applicable.		
Studied period: Initiation date: 25 June 2013 (date of first visit first patient) Completion date:29 February 2016 (date of last visit last patient)	**Phase of development of the study:** Phase II	

Objectives:

The **primary objective** of this study in patients with symptomatic chronic Heart Failure and Preserved left ventricular Ejection Fraction (HF-PEF) was to determine whether ivabradine compared to placebo could improve the diastolic function, the exercise capacity and the neuroendocrine activation, over an 8-month treatment period on:

- The ratio E/e' (E = early diastolic mitral flow velocity, e' = mean of mitral annular lateral and septal proto diastolic velocities), an estimate of LV filling pressures based on echo- Doppler measures. [The hypothesis was that ivabradine would have a positive effect on filling pressures, manifest by a decrease in the ratio E/e'].
- The 6-minute walk test (6MWT).
- NT-proBNP plasma level.

The **secondary objectives** were to evaluate:

- The effects of ivabradine compared to placebo on:
  - Cardiac function and structural parameters.
  - Quality of life.
  - NYHA classification.
  - Other biomarkers (the optional microRNA determination was not carried out).
- And the safety and tolerance profile of ivabradine compared to placebo.

In addition to the main study, 2 sub-studies were proposed: a spiroergometry and a Cardiovascular Magnetic Resonance (CMR) sub-studies. A specific protocol was provided separately for each sub-study. Results relative to the spiroergometry sub-study are presented in a separate clinical report, and due to the very low number of patients included in the CMR sub-study (4 patients), only the individual data are provided in the Appendix to the main study report.

Methodology:

This was a phase II, randomised, multicentre, international, double-blind, placebo-controlled proof-of-concept study with two parallel groups. The randomisation was stratified on centres.

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

Number of patients:

Planned: 400 patients, 200 patients in each group.
Included: a total of 179 patients were included due to difficulties in recruitment: 95 in the ivabradine group, 84 in the placebo group.

Diagnosis and main criteria for selection/inclusion:

- Male or female ≥ 50 years.
- Symptomatic chronic heart failure (NYHA class II or III) for at least 3 months.
- Stable clinical condition with regard to CHF symptoms for at least 4 weeks prior to selection.
- Unchanged CHF medications or dosages for at least 4 weeks (6 weeks for beta-blockers) prior to selection.
- ECG documented sinus rhythm and resting HR ≥ 70 bpm at selection and inclusion.
- NT-proBNP ≥ 220 pg/mL or BNP ≥ 80 pg/mL at selection (modified by Amendment No. 7).
- Results of selection echocardiography assessed and considered as valid for inclusion by the investigator, based on the following ESC (European Society for Cardiology) criteria:
  - LVEF ≥ 45% (modified by Amendment No. 7, from ≥ 50%) **and**
  - E/e' > 13 (E = early diastolic mitral flow velocity; e' = mean of mitral annular lateral and septal proto diastolic velocities), **or**
  - e' lateral < 10 cm/s and e' septal < 8 cm/s, **or**
  - LAVI > 34 mL/m².
- Ability to perform the 6MWT.

Main criteria for non-inclusion:

- Unstable condition within the previous 4 weeks (*e.g.* documented hospitalisation for worsening HF, unstable angina, cardiogenic shock).
- Significant valvular dysfunction.
- Primary hypertrophic or restrictive severe cardiomyopathy or systemic illness associated with infiltrative heart, disease (*e.g.* cardiac amyloidosis).
- Documented permanent or hospitalization within the last 3 months for atrial fibrillation or other cardiac arrhythmia that interfere with the sinus node function.
- Patients able to walk more than 450 meters within 6 minutes during the selection and the inclusion visits.

Investigational Medicinal Product (IMP):
Ivabradine 2.5 mg, 5 mg or 7.5 mg: oral administration twice daily (*b.i.d.*) of one tablet during meals.
Dose titration: starting dose of 5 mg *b.i.d.*, then up-titrated to 7.5 mg *b.i.d.* according to patient's HR on resting ECG and tolerability. During the study, the dose might be down-titrated to 2.5 mg *b.i.d.* or stopped.
(Note: the 10 mg ivabradine dose was suppressed by Amendment No. 8 [19 June 2014]).
Batch Nos. Ivabradine 2.5 mg: L0047727, L0050645, L0054975; 5 mg: L0043030, L0051386; 7.5 mg: L0045846, L0047809, L0054050, L0044844; 10 mg: L0044143, L0044706, L0050750, L0051037.

Comparator:
Matching placebo tablets, twice daily, in the same conditions as specified above for ivabradine.

Duration of treatment:
Pre-inclusion/Run-in period: single-blind placebo treatment during 2 weeks.
Post-inclusion period: double-blind IMP treatment during 8 months.

Criteria for evaluation:

Efficacy measurements:

Co-primary endpoints:
- Echocardiography (central reading): E / e' ratio (see above inclusion criteria for E and e' definition).
- Six-minute walk test: distance walked during 6 minutes.
- Neuroendocrine biomarker (central laboratory): plasma concentration of NT-proBNP.

Secondary endpoints:
Heart rate
- 12-lead ECG heart rate
- Pulse rate measured before the 6MWT, immediately at the end of the test, then 1 and 10 minutes later.

Echocardiography parameters:
A large number of secondary echocardiographic parameters were collected to assess cardiac structure and function.

Quality of life
Patient clinical status using the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Functional status
New-York Heart Association (NYHA) classification.

Other biomarkers
Cardiovascular biomarkers: cystatin-c, s-ST2, and hs-Troponin T.

Safety measurements:
- Adverse events
- Vital signs (blood pressure)
- Heart rate (12-lead ECG, pulse measurement at specific timepoints during the 6MWT)
- Blood laboratory parameters.

Statistical methods:

Analysis Sets:

The Full Analysis Set (FAS) was defined as all randomised patients having the studied disease, having taken at least one dose of IMP and with at least one evaluation of the primary efficacy criteria.

The Per Protocol Set (PPS) was defined as all patients of the FAS without relevant deviation(s), which could affect the evaluation of the efficacy at M008.

Efficacy analysis:

All efficacy analyses were carried out on patients of the FAS and on patients of the PPS as sensitivity analyses.

Co-primary criteria:

In order to demonstrate the superiority of ivabradine compared to placebo on improvement of the diastolic function [with the hypothesis that a positive effect of ivabradine on filling pressures would manifest by a decrease in the ratio E/e'], the exercise capacity and the neuroendocrine activation, ivabradine was tested on each of co-primary endpoints using an analysis of covariance (ANCOVA) model. This analysis included the fixed, categorical effects of treatment, and geographic area, as well as the continuous fixed covariate of baseline. An estimate of the between-group difference of change from baseline to last post baseline and its two-sided 90% confidence interval were provided. The type I error was set at $\alpha = 10\%$ (bilateral situation). And p-values were adjusted using Hommel procedure.

Secondary analyses were carried out on the co-primary endpoints using an analysis of variance (ANOVA) model and a non-parametric approach without adjustment based on the Hodges-Lehmann estimator.

Secondary criteria:

For all secondary efficacy criteria, including all echocardiography parameters, heart rate, pulse rate, KCCQ scores, NYHA classification, and cardiovascular biomarkers othe than BNP, descriptive statistics were provided.

For the main echocardiographic parameters of LV mass, stroke volume (SV), mean of lateral and septal e' (e') and Ea/Ees, and the heart rate, a parametric analysis of covariance with adjustment on geographic area and baseline value as a covariate (ANCOVA), and a non-parametric approach without adjustment based on the Hodges-Lehmann estimator for independent samples as sensitivity analysis, were provided. And for cardiovascular biomarkers, a non-parametric approach without adjustment based on the Hodges-Lehmann estimator for independent samples was carried out.

Study outcome and safety analysis: Descriptive statistics were provided.

An interim analysis was done in October 2015 on all the patients' data available.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 654 patients were screened for the study. Of them, 422 patients were selected and 179 patients were included and randomly assigned to one of the two groups: 95 patients in the ivabradine group *versus* 84 in the placebo group. 232 patients were not selected and 243 not included, with the main reason of non-compliance with selection / non-selection (207 patients) or inclusion / non-inclusion criteria (222 patients). 153 patients (85.5% of included) completed the study (Table 1). One patient in the ivabradine group was excluded from the SS due to no IMP intake and 8 patients were excluded from the FAS for no post baseline values of primary efficacy endpoints (all from ivabradine group). 44 patients (26 on ivabradine *versus* 18 on placebo) were excluded from the PPS, with 40 of them due to deviations affecting the efficacy evaluation at M008.

In the predefined subgroups, patients were evenly distributed by treatment between the subgroup pairs for those of LVEF, E/e' and NYHA; there was some imbalance (around 7%) for the other subgroups.

SUMMARY – CONCLUSIONS (CONT'D)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (CONT'D)

Table 1 - Disposition of patients

	Ivabradine	Placebo	All
	n (%)	n (%)	n (%)
Included (randomised)	**95**	**84**	**179**
Withdrawn due to	**19 (20.0)**	**7 (8.3)**	**26 (14.5)**
adverse event	11 (11.6)	5 (6.0)	16 (8.9)
non-medical reason[1]	6 (6.3)	2 (2.4)	8 (4.5)
protocol violation[2]	1 (1.1)	-	1 (0.6)
other[3]	1 (1.1)	-	1 (0.6)
Completed	**76 (80.0)**	**77 (91.7)**	**153 (85.5)**
Full Analysis Set (FAS)	**87 (91.6)**	**84 (100)**	**171 (95.5)**
Per Protocol Set (PPS)	**61 (64.2)**	**66 (78.6)**	**127 (70.9)**
Safety set (SS)	**94 (98.9)**	**84 (100)**	**178 (99.4)**

n number of patients affected; % % of the Randomised Set

[1] These reasons were all consent withdrawal, except for one patient (placebo) withdrawn in error at M8.

[2] The patient was withdrawn at D015 due to haemoglobin level outside predefined limits (no IMP was taken).

[3] The patient was temporally withdrawn from treatment due to bradycardia, but subsequently the IMP was not re-started due to a concomitant antibiotic prescription and corresponding safety concern.

BASELINE CHARACTERISTICS

The demographic data and main baseline characteristics are presented in Table 2. The demographic data were comparable between the 2 treatment groups, with no relevant difference observed. The overall mean duration of CHF was 43.8 ± 54.8 months, ranging from 3 months to 30 years. Slight imbalances between groups were observed for the following risk factors: hypertension (93.7% in the ivabradine group *versus* 86.9% in the placebo group), coronary artery disease (50.5% *versus* 56.0%), and obesity (50.5% *versus* 45.2%). For specific concomitant treatments, some differences were observed (ivabradine *versus* placebo): diuretics excluding anti-aldosterone (58.9% *versus* 70.2%) and ACE inhibitors (52.6% *versus* 47.6%). About three quarters of the patients (74.3% overall) were prescribed beta-blockers.

For the co-primary criteria at baseline, the E/e' ratio and total distance in 6MWT were similar between groups, whereas the NT-proBNP tended to be higher in the ivabradine group mean than placebo group in the comparison of mean, median and geometric mean.

The key echocardiographic parameters assessed at baseline and read by the Core Lab were:

- The overall mean LVEF at baseline was 60.1 ± 9.4%.
- The overall mean E/e' ratio at baseline was 13.6 ± 5.8.
- The overall mean left atrium volume index (LAVI) at baseline was 41.9 ± 13.4 mL/m².

SUMMARY – CONCLUSIONS (CONT'D)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (CONT'D)

Table 2 - Demographics and baseline characteristics in the Randomised Set

			Ivabradine (N = 95)	Placebo (N = 84)	All (N = 179)
Age (years)		Mean ± SD	71.4 ± 8.6	71.8 ± 9.3	71.6 ± 8.9
		Median	72.0	73.0	73.0
	[18 ; 64]	n (%)	18 (19.0)	16 (19.1)	34 (19.0)
	[65 ; 84]	n (%)	70 (73.7)	66 (78.6)	136 (76.0)
	≥ 85	n (%)	7 (7.4)	2 (2.4)	9 (5.0)
Female		n (%)	59 (62.1)	57 (67.9)	116 (64.8)
Chronic heart failure history and related risk factors					
Disease duration of CHF (months)		Mean ± SD	42.9 ± 57.9	44.9 ± 51.4	43.8 ± 54.8
		Median	24.6	26.4	25.6
Hypertension		n (%)	89 (93.7)	73 (86.9)	162 (90.5)
Coronary artery disease		n (%)	48 (50.5)	47 (56.0)	95 (53.1)
Obesity		n (%)	48 (50.5)	38 (45.2)	86 (48.0)
Diabetes		n (%)	41 (43.2)	37 (44.1)	78 (43.6)
None of these conditions		n (%)	3 (3.2)	2 (2.4)	5 (2.8)
Specific concomitant treatments at inclusion					
Diuretics (excluding antialdosterone)		n (%)	56 (58.9)	59 (70.2)	115 (64.2)
Antialdosterone		n (%)	30 (31.6)	23 (27.4)	53 (29.6)
Beta-blockers		n (%)	71 (74.7)	62 (73.8)	133 (74.3)
ACE inhibitors		n (%)	50 (52.6)	40 (47.6)	90 (50.3)
Angiotensin II antagonists		n (%)	36 (37.9)	32 (38.1)	68 (38.0)
Calcium channel blockers		n (%)	36 (37.9)	30 (35.7)	66 (36.9)
Co-primary efficacy criteria					
E/e' ratio		n	94	83	177
		Mean ± SD	13.3 ± 4.6	13.9 ± 6.9	13.6 ± 5.8
		Median	12.7	12.9	12.8
Total distance in 6MWT		n	95	84	179
(m)		Mean ± SD	304.4 ± 92.1	308.7 ± 83.3	306.4 ± 87.9
		Median	320.0	321.0	320.0
NT-proBNP (pg/mL)		n	92	82	174
		Mean ± SD	687.9 ± 752.6	548.4 ± 579.5	622.2 ± 678.3
		Median	385.0	343.0	375.0
		Geometric Mean	440.8	390.1	416.2
Vital signs					
Resting heart rate on ECG (bpm)		Mean ± SD	76.2 ± 6.0	76.5 ± 7.5	76.3 ± 6.7
		Median	75.0	74.0	75.0
Sitting SBP (mmHg)		Mean ± SD	132.4 ± 15.3	132.8 ± 17.8	132.6 ± 16.4
		Median	132.0	132.5	132.0
Sitting DBP (mmHg)		Mean ± SD	75.6 ± 10.9	77.1 ± 9.8	76.3 ± 10.4
		Median	76.0	79.5	77.0

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

EXTENT OF EXPOSURE

In the RS the overall mean treatment duration was 221.8 ± 60.3 days (median at 241 days) and mean compliance was 92.8 ± 17.6%, both of which were slightly lower in the ivabradine group due to a higher withdrawal rate in this group, compared to placebo group. In the FAS, the treatment duration and compliance were similar between groups.

Almost half patients in the ivabradine group (48.4%) up-titrated to 7.5 mg *b.i.d.* and maintained on this dose during the study (*versus* 64.3% in the placebo group). The mean dose prescribed was slightly higher in the placebo group than in the ivabradine group.

EFFICACY RESULTS

- **Co-primary efficacy criteria**

The statistical analyses of co-primary criteria are summarised in Table 3. The mean E/e' in the ivabradine group was slightly increased by 0.88, *versus* a slight decrease of -0.91 in the placebo group, with an estimated difference between groups of 1.37 (90% CI [0.25 ; 2.49], p = 0.135) based on parametric ANCOVA, a result showing a tendency in favour of placebo.

The mean total distance in 6MWT was relatively stable in both groups, with no relevant difference between groups. Geometric mean of NT-proBNP increased slightly in both groups, while again showing no statistical significance between groups (estimate of the ratio between geometric group means: 1.01 (90%CI [-0.86 ; 1.19], p = 0.882).

Table 3 – Statistical analyses of co-primary efficacy criteria in the FAS

		E/e'		Total distance in 6MWT (m)		NT-proBNP (pg/ml)	
		Ivabradine (N = 87)	**Placebo (N = 84)**	**Ivabradine (N = 87)**	**Placebo (N = 84)**	**Ivabradine (N = 87)**	**Placebo (N = 84)**
Descriptive Statistics							
Baseline	n	84	83	84	84	83	82
	Mean ± SD	13.1 ± 4.66	13.9 ± 6.9	305.4 ± 92.2	308.7 ± 83.3	710.8 ± 780.9	548.4 ± 579.5
	Median	12.6	12 9	323.0	321.0	385.0	343.0
	Geometric Mean	-	-	-	-	447.7	390.1
Last post-baseline	Mean ± SD	14.0 ± 4.9	13.0 ± 5.4	309.7±102.8	316.6 ± 100.8	898.3 ± 1403.8	683.0 ± 934.0
	Median	14.0	11 9	327.5	330.5	490.0	369.0
	Geometric Mean	-	-	-	-	483.4	420.9
Change from Baseline	Mean ± SD	0.9 ± 3.8	-0.9 ± 6.4	4.3 ± 50.0	7.9 ± 67.9	187.5 ± 1028.0	134.6 ± 695.0
	Median	1.0	-0.6	0.0	11.0	19.0	16.5
	Ratio change[1]	-	-	-	-	1.1	1.1
Statistical analysis							
Parametric with adj.	E (SE)[2] / E[3]	1.37 (0.68)		-3.75 (9.30)		1.01	
	90% CI	[0.25;2.49]		[-19.14;11.64]		[0.86;1.19]	
	p-value	0.135		0.882		0.882	

[1] *Ratio of last postbaseline geometric mean/Baseline geometric mean.*

[2] *Estimate (standard error) of ivabradine versus placebo effect difference between group means based on a parametric analysis of covariance with adjustment on geographic area and baseline value as a covariate*

[2] *Estimate of ivabradine versus placebo effect ratio between geometric group means for NT-proBNP after logarithmic transformation*

Adj. Adjustment

90%CI Confidence interval of the estimate (two-sided)

p-value Adjusted p-value for Hommel procedure (to be compared to 0.10)

- **Secondary assessment criteria**

The mean change of **heart rate** from baseline to last post-baseline was -12.1 ± 8.9 bpm in the ivabradine group, *versus* -4.3 ± 9.8 bpm in the placebo group. The estimate of between-group difference was -7.7 bpm (90% CI:[-10.0 ; -5.4]).

No relevant effect of treatment was observed on other echocardiographic parameters such as LV mass, e' or on the ratio of arterial elastance to ventricular end-systolic elastance (Ea/Ees). However the decrease in heart rate in the ivabradine group was associated with a small increase in the ejection time and the volume of blood ejected at each systole. The small increase in left atrial volume index in the ivabradine group (in systole) (2.7 ± 11.9 mL/m² *versus* -1.7 ± 10.2 mL/m²) may be related to an increase in LA filling. The lengthening of the cardiac cycle induced by ivabradine was associated mainly with an increase in diastolic filling time which was of greater amplitude than the increase in the ejection time. This was also associated with an increase of the amount of blood passing through the mitral valve. This increase affected mainly the early diastolic filling (increase in the amplitude and the duration of E wave).

The **KCCQ scores**, after 8-month treatment period, was relatively stable in both groups, with changes of -0.14 ± 15.2 (ivabradine group) *versus* 3.03 ± 19.9 (placebo group) for overall summary score and -1.9 ± 16.6 *versus* 2.7 ± 17.2 for clinical summary score; small changes were without clinical relevance.

After the 8-month treatment, most patients (78.2% on ivabradine *versus* 83.3% on placebo) kept stable in CHF symptoms, with no change in **NYHA class**. 13 patients (14.9%) improved in the ivabradine group *versus* 7 (8.3%) in the placebo group and among them, 6 *versus* 2 were assessed as class I.

No relevant between-group changes were observed in the biomarkers of cystatin-c, s-ST2 or hs-Troponin T.

SAFETY RESULTS

Main safety results in the SS are summarised in the table 5.

Table 5 - Overall summary for adverse events in the Safety Set

		Ivabradine (N = 94)	Placebo (N = 84)
Patients having reported at least one:			
EAE	n (%)	65 (69.1)	55 (65.5)
Treatment-related EAE	n (%)	16 (17.0)	9 (10.7)
Heart rate decreased[1]	n (%)	5 (5.3)	1 (1.2)
Bradycardia[2]	n (%)	3 (3.2)	3 (3.6)
Photopsia[3]	n (%)	3 (3.2)	-
Patients having experienced at least one:			
SAE (including death)	n (%)	34 (36.2)	21 (25.0)
Serious EAE (including death)	n (%)	33 (35.1)	21 (25.0)
treatment-related SAE	n (%)	2 (2.1)	1 (1.2)
Patients with treatment withdrawal due to:			
EAE	n (%)	10 (10.6)	5 (6.0)
Serious EAE	n (%)	7 (7.4)	3 (3.6)
Treatment-related EAE	n (%)	2 (2.1)	3 (3.6)
Treatment-related serious EAE	n (%)	1 (1.1)	1 (1.2)
Patients who died*	n (%)	3 (3.2)	-

N Total number of patients in the considered group
n Number of patients concerned; % = (n/N) x 100
Preferred terms used to code [1] asymptomatic bradycardia; [2] symptomatic bradycardia; [3] phosphenes
[1 2 3] The most frequently reported adverse drug reactions mentioned in the European Risk Management Plan (RMP) for ivabradine
** Ischaemic stroke; acute pulmonary oedema; diffuse large B-cell lymphoma.*

- **Emergent adverse events**

A total of 214 EAEs were reported in 65 patients (69.1%) in the ivabradine group *versus* 158 EAEs in 55 patients (65.5%) in the placebo group. The most frequently affected system organ classes (SOCs) with a higher incidence in the ivabradine group than in the placebo group (≥ 5%) were: Cardiac disorders (28.7% *versus* 20.2%, respectively), Gastrointestinal disorders (17.0% *versus* 10.7%, respectively), Metabolism and nutrition disorders (10.6% *versus* 4.8%, respectively), Blood and lymphatic system disorders (10.6% *versus* 3.6%, respectively), Eye disorders (7.4% *versus* 2.4%) and Neoplasms benign, malignant and unspecified (7.4% *versus* 1.2%).

The most frequently reported EAEs were events related to the underlying pathology such as cardiac failure (8.5% *versus* 10.7%), or hypertension (13.8% *versus* 10.7%; where most cases were in patients with pre-existing hypertension). Concerning events noted in the ivabradine RMP (identified risks), they were observed at levels roughly consistent with previous studies (considering however that percentages are here based on a small number of events). At least one emergent severe event was reported by 10.6% of patients in the ivabradine group versus 3.6% in the placebo group.

Treatment-related EAEs were more frequently reported in the ivabradine group (17.0% of patients) than in the placebo group (10.7% of patients). The difference between the two groups was mainly due to asymptomatic bradycardia [HR decreased] (5.3% *versus* 1.2%, respectively) and eye disorders (SOC) (4.3% *versus* none).

The premature withdrawal of treatment due to adverse event was reported for 10 patients in the ivabradine group *versus* 5 in the placebo group), with the most affected SOC of cardiac disorders (5 patients *versus* 3 patients).

SAFETY RESULTS (CONT'D)

- **Emergent adverse events (Cont'd)**

Serious emergent adverse events (SEAEs) on treatment (including deaths) were reported in 33 patients (35.1%) in the ivabradine group (66 events) and 21 patients (25.0%) in the placebo group (37 events). These concerned mostly cardiac disorders (17.0% *versus* 11.9%, respectively; 9 patients *versus* 7). The second most frequently affected SOC was vascular disorders (5.3% *versus* 6.0%; 5 patients in each group), mainly concerning hypertension (3 *versus* 2). The events (PTs) in other affected SOCs were reported in no more than 1 patient in either group, except for dyspnoea (2 *versus* 1) and osteoarthritis (2 patients in each group).
Three serious events had a fatal outcome; none were considered as being related to the study treatment; all were emergent on ivabradine. One patient (male 57 years of age) had an ischaemic stroke after 37 days of treatment and died 4 days later. One patient (male 83 years of age) had an acute pulmonary oedema after 228 days of treatment and died 4 days later. One patient (female, 66 years of age) was diagnosed with diffuse large B-cell lymphoma after 63 days of treatment; she withdrew from the study and died 151 days after the last treatment intake.

Five serious emergent events in 3 patients were considered related to treatment according to the investigator: bradycardia, nausea and cardiac failure in the ivabradine group (2 patients) and bradycardia and dizziness in the placebo group (1 patient). All but one (cardiac failure) led to treatment withdrawal.
A serious emergent event led to the withdrawal of the study drug in 5 patients (5.3%) in the ivabradine group *versus* 3 patients (3.6%) in the placebo group

- **Laboratory tests**

The abnormal biochemical values were sparse in both groups. The only abnormal value with a slightly higher incidence in the ivabradine group was high creatinine (*versus* placebo): 9 patients (14.3%) *versus* 4 patients (6.3%). 2 high values of creatinine were emergent PCSA values, both in the ivabradine group, and one of them was considered clinically significant (a medical history of chronic kidney disease was reported for the patient). In addition, 4 emergent abnormal values (not PCSA) were considered clinically significant: 3 cases of potassium increased (1 on ivabradine *versus* 2 on placebo) and 1 case of creatinine increased on placebo.

As for the haematological results, 3 cases of low haemoglobin were considered clinically significant and reported as [anaemia]. No emergent PCSA haematological value was detected during the study.

- **Other safety evaluation**

The systolic blood pressure and diastolic blood pressure were relatively stable in both groups with no relevant between-group difference: 1.4 / -1.9 mmHg in the ivabradine group *versus* 0.0 / -0.8 mmHg in the placebo group. The weight decreased slightly in the ivabradine group (-1.0 ± 3.0 kg) whereas it tended to be stable in the placebo group (-0.1 ± 2.4 kg).

CONCLUSION

This was a proof-of-concept study which aimed to investigate whether HR reduction could result in the improvement of functional status, cardiac function and neuroendocrine activation in HF-PEF. Patients were randomised to either ivabradine or matching placebo that could be titrated up or down from the initial starting dose of 5 mg b.i.d., according to HR and tolerance criteria over a duration of 8 months. Three co-primary criteria were defined: E/e' (a ratio of echocardiographic measures that evaluates left ventricular filling pressures), a test of effort (the 6-minute walk test; 6MWT) and plasma NT-proBNP (a neuroendocrine biomarker of myocardial stress).

The included population conformed well to the target population, relatively severe HF-PEF patients, but comprised only 45% (179 patients) of the expected sample size (400 patients). The two treatment arms were well-balanced in terms of demographics, baseline characteristics, concomitant medication and study duration.

None of the 3 co-primary endpoints showed evidence of improvement on ivabradine treatment as compared to placebo. Mean E/e' ratio increased slightly in the ivabradine group and decreased slightly in the placebo group. The estimated between-group difference in change from baseline to last visit did not reach statistical significance (1.37 (90% CI [0.25 ; 2.49]; p = 0.135), using the parametric covariance model. There was no relevant difference between groups in 6MWT change (estimated between-group difference: -3.8 m (90% CI [-19.1 ; 11.6], p = 0.882) or in the change in the plasma concentration of NT-proBNP (estimate of the ratio between geometric group means: 1.01 (90%CI [0.86 ; 1.19], p = 0.882). Mean HR was lowered in the active group (estimated between group difference in the change at last value under treatment: -7.7 bpm (90% CI: -10.0 ; -5.4).

The safety profile of ivabradine was as expected and no new safety concern was identified.

In HF-PEF patients, the HR reduction with ivabradine added to usual background treatments does not improve LV filling pressure evaluated by E/e' and has no impact on patient clinical status, on exercise tolerance or on neuroendocrine activation.

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