16 March 2012

EMA/194513/2012

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procoralan

ivabradine

Procedure No.: EMEA/H/C/000597/II/0018

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Les Laboratoires Servier submitted to the European Medicines Agency on 11 November 2010 an application for a Type II variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Procoralan	ivabradine	See Annex A

The following variation was requested:

Variation(s) requested		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to add the treatment in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy, including beta-blocker therapy, or when beta-blockers are contraindicated or not tolerated. The MAH proposed the update of sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8 and 5.1 of the SmPC in order to extend the indication and to introduce new information following the results of the SHIFT study. The Package Leaflet was proposed to be updated in accordance.

In addition it was proposed to delete version of the RMP from Annex IIB.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Rapporteur: Pieter de Graeff (NL)

Co-Rapporteur: Jaane Komi (FI)

1.2. Steps taken for the assessment

Submission date:	11 November 2010
Start of procedure:	16 January 2011
Rapporteurs' preliminary assessment report circulated on:	11 March 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	14 April 2011
MAH's responses submitted to the CHMP on:	14 October 2011
Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	25 November 2011
Rapporteurs' updated assessment report circulated on:	8 December 2011
CHMP opinion:	15 December 2011

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/157/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/157/2010 was not yet completed as some measures were deferred.

2. Scientific discussion

2.1. Introduction

Procoralan was authorised through the Centralised Procedure in the EU in 2005 for the indication: *"Symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who have a contra-indication or intolerance for beta-blockers".*

The active ingredient, ivabradine, is a selective inhibitor of the cardiac pacemaker current I_f, that plays a key role during the early phase of spontaneous diastolic depolarisation in sinoatrial node cells. Inhibition of I_f reduces the slope of spontaneous diastolic depolarisation, thereby increasing the time required to reach the voltage threshold for action potential initiation and slowing the spontaneous firing and therefore heart rate. Ivabradine is the first agent of this type for which marketing approval was sought. Anti-anginal therapy is intended in patients with stable angina for: 1) symptom relief, where generally sublingual short-acting nitrates are used and 2) prophylaxis, for which beta-blockers are first-line agents. Calcium antagonists are mostly a second-line alternative when beta-blockers are contraindicated or ineffective (or in combination when beta-blockers alone are insufficient). Ivabradine belongs to a therapeutic class of anti-ischaemic agents with a different mode of action, being a specific

negative chronotropic action. This concept involves decreasing the heart rate and increasing the duration of diastole, to improve the balance between myocardial oxygen supply and demand as well as coronary perfusion.

Following the completion of the SHIFT study the MAH submitted this extension of indication application to include the following new indication: *Treatment of chronic heart failure: Reduction of cardiovascular events (cardiovascular mortality or hospitalisation for worsening heart failure) in adults in sinus rhythm with symptomatic chronic heart failure and with heart rate ≥ 70 bpm.*

2.2. Non-clinical aspects

2.2.1. Ecotoxicity/environmental risk assessment

At the end of the initial registration procedure for ivabradine, further investigation of the risk to the aquatic environment (Phase II Tier B) was requested by the CHMP when considering the PEC/PNEC ratio based on algae, in accordance with the then most recent *CPMP draft guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CPMP/SWP/4447/00/draft, 20 January 2005)*. Only a long-term toxicity study in fish (either OPPTS 850.1500 or OECD two generation test, or OECD210 ELS test) and a water/sediment study (OECD308) were requested by the CHMP. Consequently, the MAH committed itself to perform a fish ELS toxicity test (OECD210) and the aerobic water/sediment test (OECD308) and this is handled within post-marketing follow-up measure FUM 6. Based on the review of the outstanding issue for FUM 6, the CHMP considered that the aquatic risk assessment was not changed by the ELS fish outcome and the risk was considered acceptable, when referring to the final *Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CPMP/SWP/4447/00, 01 June 2006)*. To complete the environment risk assessment of ivabradine, a sediment toxicity study was requested by CHMP. The study protocol was further approved by the CHMP and the final study report of the sediment toxicity study has been used to update the ERA for ivabradine that was submitted within current application.

Table X: Summary of main study results

Substance (INN/Invented Name): Ivabradine			
CAS-number (if available): 155974-00-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD122	log K_{ow} = 2.1 (at pH 7.4)	Not PBT/vPvB
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$	0.53	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121	log K_{oc} = 1.34 (at pH 1.51); 4.00 (at pH 10.58)	List all values
Ready Biodegradability Test	OECD 301B	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = ND $DT_{50, sediment}$ = ND $DT_{50, whole\ system}$ = ND % shifting to sediment = > 10% in sediment at day 14	DT_{50} not calculated since the mineralisation rate at the end of the study was below 20% of applied TRR for all water-sediment systems
Phase IIa Effect studies			
Study type	**Test protocol**	**Results**	**Remarks**

Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.882	mg/ L	*Scenedesmus subspicatus* (NOEC based on specific growth rate)
Daphnia sp. Reproduction Test	OECD 211	NOEC		mg/ L	Study to be submitted
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	10	mg/ L	*Oncorhynchus mykiss* (rainbow trout)
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50}	> 1000	mg/ L	
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	464	mg/ kg	*Chironomus riparius*

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

a chronic Daphnia reproduction test (OECD211), in order to evaluate the risk for the groundwater compartment, in accordance with the current guideline on Environmental Risk Assessment.

There were no other new nonclinical studies submitted and assessed within this application.

2.3. Clinical aspects

2.3.1. Introduction

The MAH has conducted a three year randomized double-blind placebo-controlled international multicenter trial to evaluate the effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction (Study CL3-16257-063; SHIFT STUDY). The MAH provided a justification that heart rate (HR) and change in heart rate are predictors of the risk for death or hospitalisation for heart failure (HF). Beta-blockers (BB) have reduced morbidity and mortality beyond what is achieved with renin-angiotensin-aldosterone antagonists (RAAS) alone. Their benefits seem to be linked, at least in part, to their heart-rate-lowering properties. Heart-rate reduction could be particularly important in chronic heart failure (CHF), by attenuating the effect of energy starvation of the myocardium. In patients with coronary artery disease (CAD) and left-ventricular dysfunction (LVD), a heart rate of 70 beats per minute (bpm) or higher was associated with a 34% increased risk of cardiovascular death and a 53% increase in admission to hospital for heart failure compared with heart rate lower than 70 bpm. The MAH considered that HF patients treated with BB who are still at an elevated HR level would be eligible for inclusion in the SHIFT trial.

The CHMP agreed that the rationale presented by the MAH has its merits. Lowering HR is an important target for HF therapies. A meta-analysis by McAlister et al. [2009 Ann Int Med] indicates that increasing HR reduction by BB is associated with increased survival. However, whether this also applies to a non-betablocking drug with a different mechanism of action – pure HR lowering – needs to be established. In the BEAUTIFUL trial which evaluated morbidity-mortality of ivabradine in CAD and LVEF dysfunction patients, no effect on CV outcome was observed, but a significant effect was seen in a subgroup of patients with a HR ≥ 70 bpm (Fox et al, Lancet, 2008). This study was assessed for safety purposes and was included in section 5.1 of the SmPC. With current application the MAH submitted a single pivotal study to support the hypothesis based on the BEAUTIFUL trial in the targeted HF population. Given that only one pivotal study was submitted to support the new indication, data should be compelling and the trial impeccably performed and in line with the *EMA Points to Consider on application with 1. meta-analysis; 2. one pivotal study (CPMP/EWP/2330/99)*. With this application the

MAH provided also supportive data which provide insight in benefits and harms of the drug in an earlier stage (CAD) of the CV disease continuum.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

An inspection was conducted following a request of the CHMP in connection with the current type II variation. This was triggered because the clinical evidence was based on a single pivotal trial and the complexity of the trial with composite endpoints adjudicated by an independent Endpoint Validation Committee. In such context, the inspection was to focus on the systems implemented by the sponsor and the overview by the sponsor during the conduct of the trial. The inspection team qualifies the level of GCP compliance for the SHIFT study to be sufficient and therefore, they regard the data to be acceptable for evaluation in the context of a marketing authorisation application. However, the aspect of safety data (PSEs, SAEs, (re)-coding) and finally the information on Procoralan now available in the PhV database, especially the part of / based on the SHIFT study, is highlighted by the inspection team as a point of special attention.

2.3.2. Clinical efficacy

Main study

Study CL-3-16257-063; **SHIFT (Systolic heart failure treatment with I_f inhibitor ivabradine Trial).**

Methods

This was a three year randomized double-blind placebo-controlled international multicenter trial to evaluate the effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction.

Study Participants

The most important inclusion criteria at selection visit (2 weeks before randomisation) are listed below:

- Male or female adult patients;

- At least 4 weeks prior to selection, symptomatic chronic heart failure (CHF) *i.e.* New York Heart Association (NYHA) class II, III or IV; stable clinical condition with regards to CHF symptoms; optimal and unchanged CHF medications or dosages;

- Documented hospital admission for worsening heart failure within 12 months before selection;

- All aetiologies of CHF could be included, except for congenital heart disease and for severe aortic or mitral stenosis, or severe aortic regurgitation, or severe primary mitral regurgitation;

- Electrocardiographic documentation of sinus rhythm at selection, with a resting heart rate (HR) ≥ 70 bpm on standard 12-lead ECG;

- LV systolic dysfunction documented by echocardiography, radionuclide ventriculography, magnetic resonance imaging, cardiac angiography or computed tomography angiography;

The most important inclusion criteria at randomisation are listed below:

- Documented sinus rhythm and HR ≥ 70 bpm on a recent (within 24 hours) resting standard 12-lead ECG;

- LVEF ≤ 35% as measured and documented within the previous 3 months (in a stable clinical condition) by either echocardiography, radionuclide ventriculography, magnetic resonance imaging, cardiac angiography or computed tomography angiography;

The most important exclusion criteria are listed below:

- Recent (less than 2 months prior to selection) MI or coronary revascularisation;

- Scheduled coronary revascularisation (percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG));

- History of stroke or cerebral transient ischaemic attack within the previous 4 weeks;

- Severe aortic or mitral stenosis, or severe aortic regurgitation, or severe primary mitral regurgitation;

- Scheduled surgery for valvular heart disease;

- Active myocarditis;

- Congenital heart diseases;

- Previous cardiac transplantation or on list for cardiac transplantation;

- Cardiac resynchronisation therapy (CRT) started within the previous 6 months;

- Pacemaker with atrial or ventricular pacing (except bi-ventricular pacing) > 40% of the time, or with a stimulation threshold at the atrial or ventricular level ≥ 60 bpm;

- Permanent atrial fibrillation or flutter;

- Sick sinus syndrome, sinoatrial block, 2nd and 3rd degree atrio-ventricular block;

- History of symptomatic or sustained (≥ 30 sec) ventricular arrhythmia unless a cardioverter defibrillator was implanted;

- Any cardioverter defibrillator shock experienced within the previous 6 months;

- Patients with familial history or congenital long QT syndrome or treated with selected QT prolonging products;

- Severe or uncontrolled hypertension (sitting systolic blood pressure > 180 mmHg or sitting diastolic blood pressure > 110 mmHg);

- Sitting systolic blood pressure < 85 mmHg or current symptomatic hypotension;

- Known moderate or severe liver disease (Child-Pugh score > 7) or known severe renal disease (serum creatinine > 220 µmol/L) or known anaemia (blood haemoglobin < 110 g/L);

Treatments

The trial consisted of a pre-randomisation period of 2 weeks without study treatment to confirm eligibility and clinical stability, followed by a post-randomisation period of up to 42 months during which patients received either ivabradine or placebo in addition to their ongoing cardiovascular treatment. The starting dose of ivabradine was 5 mg b.i.d. which was increased to 7.5 mg b.i.d. at 2 weeks or subsequently at any time during the study unless heart rate was ≤ 60 bpm, or decreased to 2.5 mg b.i.d. if heart rate was < 50 bpm or the patient experienced signs or symptoms related to bradycardia. Study visits were scheduled at 2 weeks, 1 month, 4 months, and then every 4 months (see figure below).

Determining HR after 5 min rest from single ECG was not considered very reliable by the CHMP. The Committee believed that ambulatory ECG- recordings or at least repeated ECG-recordings would have been more reliable and the MAH provided further justifications also indicating that all patients had a resting HR measurement on ECG recording repeated twice, at Selection and Inclusion visits separated by a 14 days interval. ECG recording was said to be more precise than pulse palpation, and measurement after a period of 5 minutes rest has been recommended by a European Society of Hypertension consensus meeting.

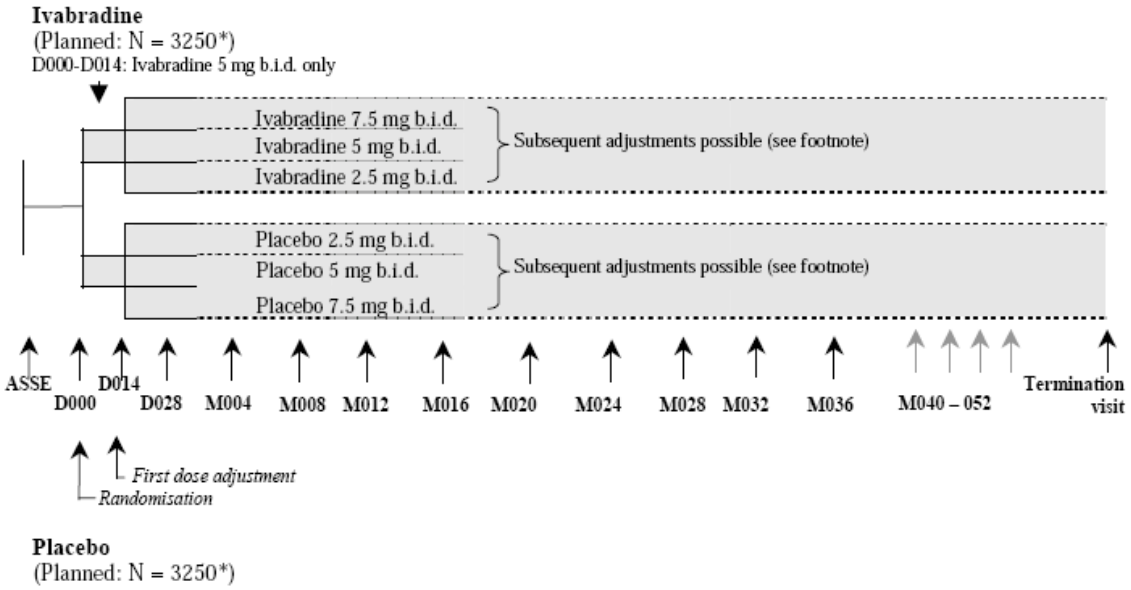


Figure 1: Study design of the SHIFT trial

Objectives

The primary objective was to demonstrate the *superiority* of ivabradine over placebo in the reduction of cardiovascular mortality or hospitalisation for worsening heart failure (composite endpoint), in patients with moderate to severe symptoms of chronic heart failure (CHF), a reduced left ventricular ejection fraction (LVEF) and receiving currently recommended therapy for this disease.

The secondary objectives were to assess the effects of ivabradine compared to placebo on:

- The primary composite endpoint in patients receiving at least half of the target daily dose of beta-blockers at randomisation.

- Death from heart failure and overall mortality, morbidity, functional capacity and clinical symptoms of heart failure in both the randomised set and randomised (at least half of the target dose) beta-blocker subset.

Outcomes / endpoints

The primary composite endpoint was the time to occurrence of the first event of cardiovascular death or hospitalization for worsening heart failure.

Choice of the primary endpoint

This trial has been conducted to reduce clinical endpoints associated with heart failure with treatment of ivabradine. Therefore the *EMA Guideline on Clinical investigation of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95 Rev. 1)* is applicable to the current submitted dossier. The duration of the trial was sufficiently long to identify long-term efficacy of ivabradine. Composite endpoints in heart failure trials have been subject for discussion, but the combination of cardiovascular morbidity and overall mortality is the recommended endpoint in the above mentioned EMA Guideline. According to the guideline overall mortality is of prime importance. A composite endpoint including cardiovascular death is increasingly recognized as acceptable and has been used in recent heart failure trials as long as no negative effect is observed on overall-death. In the current trial the combined endpoint of hospitalizations due to HF and CV death is used while the combined endpoint of hospitalizations due to HF and overall mortality has not been analysed as secondary endpoint. Therefore, the MAH was requested to provide information on the combined endpoint of hospitalisation for HF and overall mortality. The effect of ivabradine treatment evaluated with the heart failure guideline-preferred composite endpoint of overall death and hospitalisation for worsening heart failure was consistent with the effect on the SHIFT defined primary composite endpoint.

Secondary endpoints included:

Individual endpoints of all-cause death, cardiovascular death, all-cause hospitalisation, cardiovascular hospitalisation, hospitalisation for worsening heart failure and the composite of cardiovascular death, hospitalisation for worsening heart failure, or hospitalisation for non-fatal myocardial infarction.

In addition, an evaluation was made of changes in functional capacity (assessed by NYHA classification), and in clinical symptoms of heart failure (assessed by Patient Global Assessment and Physician Global Assessment questionnaires).

The MAH was asked to provide further explanation as to why more objective measurements to assess the clinical status of the patients were lacking (such as NT-pro-BNP measurements, 6 min tests, spiroergometries, or regular exercise tolerance tests). Explanation for not using objective tests to estimate physical capacity of the heart failure patients seem to be mainly practical in nature. It would have been a tedious task in the entire study population. Six min walking test may not have direct correlation with mortality, but it is largely used both clinically and in clinical research to assess the therapeutic response. Oxygen intake or consumption during spiroergometry were used to assess the suitability of the heart failure patients for major operations or, *e.g.*, their need for heart transplantation. The arguments the MAH presented can not be disputed, but opposite standpoints could be supported as well. NT-Pro-BNP results (in the Echo/BNP sub study of SHIFT, n=611) did not reach statistical significance, but this was understandable since ivabradine does not impact blood pressure or fluid overload significantly. Baseline pro-BNP levels appeared quite moderate (the patients belonged mainly to NYHA II to III classes) which makes large improvements due to ivabradine use unlikely to occur. In the subgroups of patients with non-ischaemic heart failure, reduction of BNP-levels reached statistical significance in favour of ivabradine, ratio 0.70, 95% CI 0.51 to 0.96, as well in patients not taking at least half of the target dose of beta blockers, ratio 0.78, 95% CI 0.62 to 0.99. The latter finding may be supportive of those patients who do not tolerate beta blockers, might benefit from ivabradine use. These explanations were considered by the CHMP as satisfactory.

Sample size

The efficacy analysis was based on 6505 patients, 3241 in the ivabradine group and 3264 in the placebo group.

Randomisation

Study treatments were allocated via an interactive response system (via telephone or internet) using a non-adaptive and balanced randomisation, with two stratification factors: study centre and whether treated or not with beta-blockers at randomisation.

Blinding (masking)

Treatment group allocation was blinded for patients and investigators, and ivabradine and placebo tablets were identical in taste and appearance. The dose level of study treatment (ivabradine and placebo) was not blinded. Slight problems in blinding were found, the patients and physicians could assess the HR affected by ivabradine (a decrease by 15 bpm in general). Adjudication of the hard endpoints by the Endpoint Committee blindly of the treatment or baseline HR was not affected by any investigator bias. Reduced heart rates (up to 15 bpm) were observed in 16% to 20% of the placebo patients whereas up to 14% to 18% of the ivabradine patients had a reduction less than 5 bpm.

Statistical methods

The efficacy analysis was performed on all randomised patients, on a time-to-first-event basis and according to the intention-to-treat principle (ICH E9, 1998). The main analysis was the superiority of ivabradine, relative to placebo, in the primary endpoint using a Cox's proportional hazards model, adjusted for the randomisation stratification factor of beta-blocker intake or not at randomisation (CPMP /EWP/2863/99, 2003), to estimate the treatment effect in terms of hazard ratio and its 95% confidence interval and p-value. The proportionality of hazard was checked by adding an interaction between log (time) and randomised treatment to the Cox model. The influence of other prognostic factors was also investigated using adjusted Cox model. Time-to-event curves were estimated using the Kaplan-Meier method. The main and sensitivity analyses were also applied to the main secondary endpoints. Treatment effects and 95% confidence intervals were also calculated for the primary endpoint in pre-specified subgroups using Cox models containing treatment effect, beta-blocker status at randomisation and subgroup status. P-values for interaction between randomised treatment and subgroup status were also obtained by adding treatment by subgroup interaction to the model.

The type I error rate was 5% (two-sided) for all statistical tests.

The independent Data Monitoring Committee performed two interim efficacy analyses. On the basis of the Peto procedure, the nominal significance level for evidence of benefit of ivabradine treatment was set at 0.001 at both interim analyses. This approach does not significantly affect the overall type I error rate used for the final analysis.

Results

Participant flow

A total of 7411 patients were screened, of whom 7106 were selected and entered the pre-randomisation run-in period. Of these, 547 patients were excluded; 68 due to adverse events, 125 due to withdrawal of consent, 349 due to non-compliance with study criteria, and 5 for unknown reasons. The main reasons for non-compliance with study criteria related to having heart rate < 70 bpm, LVEF

> 35%, or to biological exclusion criteria. The remaining 6558 patients were randomised, but 7 patients were finally not included and did not receive the study drug. Two study centres and their 46 patients were removed from the trial prior to unblinding, due to invalid data caused by misconduct detected during study audit. Excluded patients were evenly distributed among treatment groups. The efficacy analysis was therefore based on 6505 patients, 3241 in the ivabradine group and 3264 in the placebo group.

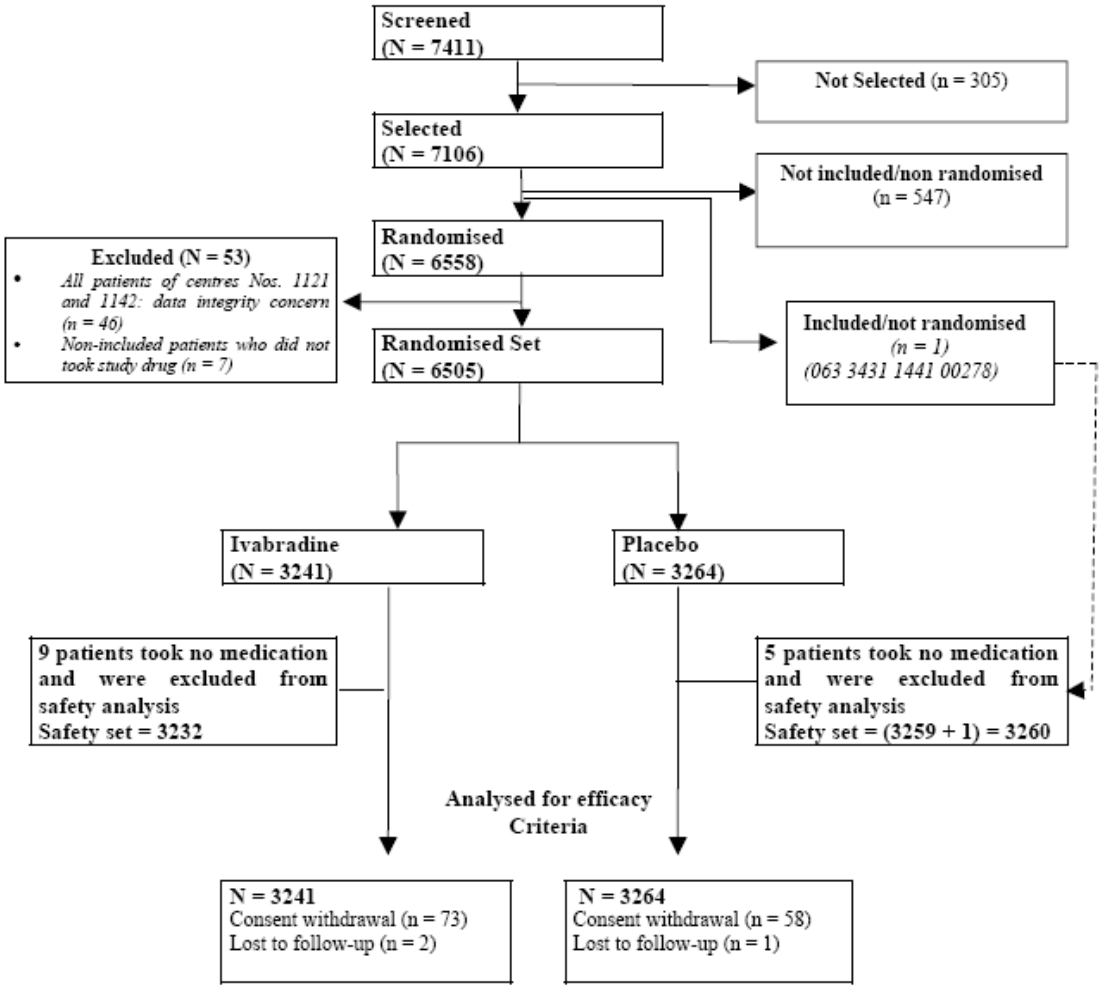


Figure 2: Participant flow of the SHIFT trial

The MAH stated that 53 randomised patients were excluded from the efficacy analyses (exclusion of two centres entirely accounting for 46 patients, and 7 patients not receiving study drugs due to exclusion criteria [6] or adverse event [1]). The MAH was asked to submit analysis including these patients. Inclusion of patients from the misconducting study centres did not affect the outcome of the study, thus it is safe to exclude those patients due to GCP violations. Definition of the study populations (ITT, no PP) is acceptable.

Conduct of the study

Patients eventually received study drug according to the dose titration schemes provided below.

Table 1: Study drug dose titration profiles

All doses taken twice daily	Ivabradine N = 3241	Placebo N = 3264
5 mg	8.7%	3.6%
5 mg, then 7.5 mg	60.3%	90.6%
5 mg, then 7.5 mg, then 5 mg	6.9%	1.8%
5 mg, then 2.5 mg	7.2%	0.7%
5 mg, then 2.5 mg, then 5 mg	2.9%	0.2%
Other dose profile	13.7%	3.0%
No study drug administered	0.3%	0.2%

The dosing scheme for ivabradine was essentially similar to the dosing scheme already described in the SmPC and used in clinical practice. Most patients adhered to the standard dose scheme of 5 mg to 7.5 mg uptitration without any back titration (60%). It was not surprising that more patients (90%) in the placebo group were without problems up titrated to 7.5 mg BID – as it is unlikely affecting HR. The MAH was asked whether any relation exists between reached target dose level of ivabradine and the effect on the primary endpoint.

Sixty percent of patients in SHIFT were able to follow the standard uptitration scheme, from a starting dose of 5 mg uptitrated to a maintenance dose of 7.5 mg. The 40% of patients who followed different titration schemes resulting in lower maintenance doses also had lower baseline heart rates. Both strategies resulted in considerable reductions in heart rate (14.9 and 12.6 bpm) resulting in on therapy mean heart rates (last recorded HR) that remained lower in low dose patients (61.2 bpm) than in high dose patients (68.8 bpm). Finally, no difference was observed in effect size for patients on lower maintenance doses, 2.5 or 5 mg, versus those on a 7.5 mg dose. These results are in line with the McAllister paper [2009 Ann Int Med] that showed that heart rate control may be more relevant than achieving target beta blocker dose. The data therefore supported the proposed flexible titration scheme. The CHMP agreed with this opinion.

Baseline data

Baseline data for the included patients is provided in the table below. The mean age of patients included in to the trial was about 60 years of age. Patients mostly had heart failure due to ischemic causes, had an ejection fraction of 29%, had NYHA class II or III and a heart rate of 80. The vast majority used a beta-blocker, RAAS blocker and diuretic.

Table 2: Demographic and clinical characteristics at baseline, expressed as n patients (%) unless stated otherwise.

	Ivabradine N = 3241	Placebo N = 3264
Age (years), mean ± SD	60.7 ± 11.2	60.1 ± 11.5
Male gender	2462 (76%)	2508 (77%)
Ethnic origin		
Caucasian	2879 (89%)	2892 (89%)
Asian	268 (8%)	264 (8%)
Other	94 (3%)	108 (3%)
Current smokers	541 (17%)	577 (18%)
Body mass index (kg/m^2), mean ± SD	28.0 ± 5.1	28.0 ± 5.0
Primary cause of heart failure		
Ischaemic	2215 (68%)	2203 (67%)
Non-ischaemic	1026 (32%)	1061 (33%)
Duration of heart failure (years), mean ± SD	3.5 ± 4.2	3.5 ± 4.2
LVEF (%), mean ± SD	29.0 ± 5.1	29.0 ± 5.2
NYHA class		
Class II	1585 (49%)	1584 (49%)
Class III	1605 (50%)	1618 (50%)
Class IV	50 (2%)	61 (2%)
Heart rate (bpm), mean ± SD	79.7 ± 9.5	80.1 ± 9.8
Systolic blood pressure (mmHg), mean ± SD	122.0 ± 16.1	121.4 ± 15.9
Diastolic blood pressure (mmHg). mean ± SD	75.7 ± 9.6	75.6 ± 9.4
Medical history		
Myocardial infarction	1829 (56%)	1837 (56%)
Hypertension	2162 (67%)	2152 (66%)
Diabetes	973 (30%)	1006 (31%)
Previous stroke	228 (7%)	295 (9%)
History of atrial fibrillation or flutter	263 (8%)	259 (8%)
Beta-blockers	2897 (89%)	2923 (90%)
Carvedilol	1323 (46%)	1281 (44%)
Bisoprolol	721 (25%)	765 (26%)
Metoprolol succinate	399 (14%)	416 (14%)
Metoprolol tartrate	303 (10%)	315 (11%)
Nebivolol	100 (3%)	98 (3%)
Other	55 (2%)	52 (2%)
ACE inhibitor and/or ARB	2963 (91%)	2960 (91%)
Diuretics (excluding antialdosterone agents)	2719 (84%)	2695 (83%)
Antialdosterone agents	1981 (61%)	1941 (59%)
Cardiac glycosides	706 (22%)	710 (22%)
Devices	110 (3%)	134 (4%)
Cardiac resynchronisation therapy	28 (1%)	44 (1%)
Implantable cardioverter/defibrillator	92 (3%)	115 (4%)

SD: standard deviation ; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

ACE: angiotensin-converting-enzyme; ARB: angiotensin II receptor blocker

Table 3: Specific information on CHF at baseline.

			Ivabradine (N = 3241)	Placebo (N = 3264)	All (N = 6505)
Duration since CHF diagnosis (years)		n	3241	3264	6505
		Mean ± SD	3.5 ± 4.2	3.5 ± 4.2	3.5 ± 4.2
		Median	2.0	2.0	2.0
		Q1 ; Q3	0.6 ; 4.8	0.6 ; 4.9	0.6 ; 4.8
		Min ; Max	0.1 ; 40.7	0.0 ; 35.8	0.0 ; 40.7
Duration class (years)	< 2	n (%)	1621 (50.0)	1646 (50.4)	3267 (50.2)
	[2 ; 5[	n (%)	845 (26.1)	827 (25.3)	1672 (25.7)
	[5 ; 15[	n (%)	691 (21.3)	709 (21.7)	1400 (21.5)
	≥ 15	n (%)	84 (2.6)	82 (2.5)	166 (2.6)
Primary cause of CHF	Ischaemic	n (%)	2215 (68.3)	2203 (67.5)	4418 (67.9)
	Non-ischaemic	n (%)	1026 (31.7)	1061 (32.5)	2087 (32.1)
Main non-ischaemic reasons:	Idiopathic dilated cardiomyopathy	n (%)	664 (20.5)	685 (21.0)	1349 (20.7)
	Hypertensive	n (%)	226 (7.0)	253 (7.8)	479 (7.4)
	Valvular	n (%)	14 (0.4)	18 (0.6)	32 (0.5)
	Other	n (%)	122 (3.8)	105 (3.2)	227 (3.5)
Documented hospitalisation for worsening HF within the previous 12 months	No	n (%)	42[#] (1.3)	37 (1.1)	79 (1.2)
	Yes	n (%)	3199 (98.7)	3227 (98.9)	6426 (98.8)
NYHA class		n	3241	3264	6505
	Class I	n (%)	1 (0.03)	1 (0.03)	2 (0.03)
	Class II	n (%)	1585 (48.9)	1584 (48.5)	3169 (48.7)
	Class III	n (%)	1605 (49.5)	1618 (49.6)	3223 (49.5)
	Class IV	n (%)	50 (1.5)	61 (1.9)	111 (1.7)
LVEF (%)		n	3241	3264	6505
		Mean ± SD	29.0 ± 5.1	29.0 ± 5.2	29.0 ± 5.2
		Median	30.0	30.0	30.0
		Min ; Max	9 ; 39	7 ; 37	7 ; 39
	≤ 20%	n (%)	299 (9.2)	316 (9.7)	615 (9.5)
	]20 ; 25]	n (%)	513 (15.8)	482 (14.8)	995 (15.3)
	]25 ; 30]	n (%)	894 (27.6)	939 (28.8)	1833 (28.2)
	]30 ; 35]	n (%)	1533 (47.3)	1524 (46.7)	3057 (47.0)
	> 35	n (%)	2 (0.1)	3 (0.1)	5 (0.1)

 # excluding 1 patient with a deviation for undocumented hospitalisation for worsening HF within previous 12 months who was confirmed as having a hospitalisation by the investigator
N: Total number of patients in the considered treatment group; n: Number of patients concerned
% = (n/N) x 100 ; %' = (n/n') x 100
SD: Standard deviation

The inclusion criteria resulted in the inclusion of 6505 HF patients across NYHA class II to IV with a LVEF of ≤35% with the aim of a claim of treatment with ivabradine in symptomatic HF patients.

However, only a very small proportion of patients with NYHA class IV were ultimately included in the trial (1-2% patients). Therefore, it was questioned by the CHMP whether the trial results also apply to these severe HF patients. It was also discussed whether specific recommendations should be included within the SmPC and whether the data suffice to lift the current contraindication in that patient population. The MAH clarified that 111 patients with NYHA class IV heart failure were included in the SHIFT trial. Approximately 20% of these patients used target doses of beta blockers, and 40% used at least 50% of the target dose of beta blockers. No significant differences were observed in the baseline characteristics of patients in the ivabradine (n=50) and placebo (n=61) groups. Compared to the general study population, these patients were slightly older (62.8 vs. 60.4 years), had higher baseline HR 84 bpm vs 79.9 bpm, and lower systolic BP 115.7 vs. 121.7 mmHg. They used less beta blockers at target dose 20.2% vs. 26.1% or at least 50% of the target dose 40.4% vs. 55.7%, but more digitalis 48.7% vs. 21.8%. The average decline in HR throughout the study was 10.4 to 13.2 bpm in the ivabradine group and 4.3 to 6.8 bpm in the placebo group. The decline in HR in the ivabradine-NYHA IV patients was slightly smaller than in the entire population of ivabradine patients. Improvement of NYHA class during the study was observed in 62% of the ivabradine patients and 44.3% of the placebo patients.

In the subgroup of NYHA IV patients with HR $\geq$ 75 at baseline (n=87), there was a statistically significant reduction in the primary composite endpoint, 42.5% in the ivabradine group vs. 68.1% in the placebo group, (hazard ratio 0.53, 95% CI 0.29 to 0.95, p=0.03). Positive trends were observed also in all secondary endpoints. Incidence of cardiac failure was smaller in the ivabradine group, 32.0% vs. 41.0%. Incidences of asymptomatic bradycardia, atrial fibrillation, *angina pectoris*, or myocardial infarctions did not differ between the groups. Sudden death was reported for 8% in the ivabradine group vs. 18% in the placebo group. Death from any cause during the study was reported in 36.0% in the ivabradine group vs. 49.2% in the placebo group. Similar observations were made in the subpopulations with baseline HR $\geq$ 75 bpm. In patients with LVEF < 20% (n=615) and LVEF < 15% (n=124): in the first population, primary endpoint was met in 34.8% of the ivabradine patients vs. 38.3% of the placebo patients, hazard ratio 0.87, 95% CI 0.75 to 0.90, and positive trends in secondary endpoints. If only the patients with baseline HR $\geq$ 75 bpm were taken into account, the respective figures were hazard ratio 0.80, 95% CI 0.59 to 1.09 – indicating that if the patient did have baseline heart rate control by *e.g.*, sufficient beta blockade - the efficacy of ivabradine became less evident.

In the LVEF < 15% population the respective figures were 30.9% in the ivabradine group vs. 34.8% in the placebo group, hazard ratio 0.88, 95% CI 0.75 to 0.90. And in patients with baseline HR $\geq$ 75 bpm the respective figures were hazard ratio 0.73, 95% CI 0.34 to 1.57. In the LVEF < 20% group there were 12 cases (4.0%) with "unstable angina" as emergent adverse event in the ivabradine group and 6 (1.9%) in the placebo group. There was however no correlation observed with mortality from the myocardial infarctions. Atrial fibrillation was reported in 9.4% of the ivabradine patients vs. 6.4% of the placebo patients, and sudden death in 5.0% of the ivabradine patients vs. 3.8% of the placebo patients. Asymptomatic or symptomatic bradycardia was observed more in the ivabradine group 5.4% vs. 1.6% in the placebo group. Overall mortality was smaller in the ivabradine group 21.4% vs. 26.8% in the placebo group. In the LVEF< 15% group, atrial fibrillation was reported in 10.9% of the ivabradine patients vs. 4.4% of the placebo patients, and sudden cardiac death in 3 (5.5%) of the ivabradine patients vs. 0 of the placebo patients. Asymptomatic or symptomatic bradycardia was again observed more in the ivabradine group. Overall mortality was smaller in the ivabradine group 12.7% vs. 29.4% in the placebo group.

The analyses indicate consistent treatment effects as compared to those in the overall population. Similar treatment effects were also observed in patients with very low ejection fractions; LVEF ≤ 20% and ≤ 15%, of which slightly more patients were included, 614 respectively 124 patients. A higher incidence of adverse events was reported in NYHA IV patients, however, in comparison to placebo, the safety profile was not different. This is reassuring, patients in NYHA IV often have high heart rates to compensate for poor ventricular function, and it would be this group that would stand to benefit most from a heart rate lowering therapy. The CHMP considered that following the results from the SHIFT study the removal from the section 4.3 (Contraindications) of the SmPC previous contraindication for patients in NYHA III and IV, and the modifications of the section 4.4 of the SmPC (Warnings) were justified. In section 4.4 of the SmPC the CHMP proposed to remove the warnings for NYHA I and II patients, and to include a cautioning statement for patients in NYHA IV. The study protocol specified that patients had to be in a stable clinical condition with regards to CHF symptoms. Therefore, none of the patients with NYHA IV were patients who were unstable or could be considered presenting with acute heart failure. A relevant contraindication for unstable or acute heart failure patients was introduced in the SmPC.

HF is a very heterogeneous disease, but the demographics of the study population indicate that various etiologies are evenly distributed across both treatment groups. The majority of patients had an ischemic event as primary cause of their heart failure. Overall, patient characteristics are evenly distributed over the treatment groups. Patients were relatively young (approx. 60 ± 11 years) with on

average 3.5 ± 4.2 years duration of their HF. Generally, inclusion criteria were met. However, approximately 1% of included patients had no documented hospitalisation for worsening heart failure in the previous 12 months before randomization but it is unlikely this affected the treatment outcome due to the low numbers. Patients received appropriate and state-of-the-art background therapy of beta-blocker, RAAS inhibitors, diuretics and aldosterone antagonists. 90% of the patients received an ACE-inhibitor and/or a beta-blocker. The MAH has demonstrated that this was evenly distributed during the trial. Inclusion of patients using amiodarone is of high clinical value. HF patients carry a high risk for atrial and ventricular arrhythmias and are often prescribed potent antiarrhytmics. The CHMP paid particular attention to the efficacy and safety aspects in this group of patients. Around 10% of the SHIFT-study population took potent anti-arrhythmics. 188 patients received amiodarone (class III) at randomisation and 415 patients started amiodarone during the study (total n=603). 52 patients received either propafenone (n=13, class Ic), mexiletine (n=5, class Ib), quinidine (n=4, class Ia), or procainamide (n=2, class Ia). Further 32 patients were at least once administered lidocaine (class Ib). In this subpopulation, the incidence of the PCE was 36.2% in the ivabradine group and 44.0% in the placebo group, RR 0.72, 95% CI 0.56 to 0.93, p=0.017. For hospitalisations from heart failure the figures were 21.6% vs. 30.8%, RR 0.60, 95% CI 0.44 to 0.82, p=0.0014, and for death from heart failure 8.5% vs. 13.2%, RR 0.59, 95% CI 0.36 to 0.97, p=0.038. Atrial fibrillation was more common in this subpopulation and use of ivabradine increased it further. No additional safety concerns could be observed. Thus, the benefit/risk ratio of ivabradine appears favourable in patients taking amiodarone or potent class I anti-arrhythmics.

Within initial submission the confounding effects of the concomitant medications (e.g., changes in the doses or use of beta blockers during the study) have not been fully investigated or reported (use of digitalis glycosides or other antiarrhytmics). This issue was further discussed within the responses to the CHMP Request for the Supplementary Information. The need to initiate a beta blocker or increase the beta blocker dose during the study was higher in patients taking placebo. The reasons for such actions were not elucidated individually, but they may have to do with optimal HR control. Assumption, that increasing the dose of beta blocker would improve the HR control and cause more benefit for the placebo patients than ivabradine patients, would only strengthen the idea of the efficacy of ivabradine in the primary and secondary efficacy outcomes.

Outcomes and estimation

Treatment duration

The median duration of follow-up was 22.9 months (mean 21.9 months); the median treatment duration was 21.6 months (mean 20.1 months) and was similar in both groups. 65.5% of patients had a treatment duration ≥ 18 months and 35.3% of ≥ 24 months. Three patients were lost to follow-up and they were censored at their last contact time.

Primary endpoint results

The incidence of the primary endpoint, the composite of cardiovascular death or hospitalisation for worsening heart failure, was significantly lower in the ivabradine group (24.5%) than with placebo (28.7%), corresponding to an 18% relative risk reduction (hazard ratio 0.82, 95% CI 0.75–0.90, p <0.0001; see table below) and a 4.2% absolute risk reduction in the primary endpoint.

Treatment with ivabradine for 1 year would prevent one cardiovascular death or hospital admission for heart failure for every 26 patients treated. The Corresponding numbers of patients needed to be treated for 1 year to prevent one hospitalisation for heart failure and one hospitalisation for any cardiovascular reason are 27 patients and 34 patients, respectively.

Table 4: Primary and main secondary endpoints

	Ivabradine N = 3241	Placebo N = 3264	Hazard ratio [95% CI]	p-value
Primary composite endpoint				
Cardiovascular death or hospitalisation for worsening heart failure	793 (24.5%)	937 (28.7%)	0.82 [0.75–0.90]	<0.0001
Heart failure endpoints				
Hospitalisation for worsening heart failure	514 (15.9%)	672 (20.6%)	0.74 [0.66–0.83]	<0.0001
Death from heart failure	113 (3.5%)	151 (4.6%)	0.74 [0.58–0.94]	0.014
Secondary composite endpoint				
Cardiovascular death, hospitalisation for heart failure, hospitalisation for non-fatal MI	825 (25.5%)	979 (30.4%)	0.82 [0.74–0.89]	<0.0001
Other secondary endpoints				
All-cause mortality	503 (15.5%)	552 (16.9%)	0.90 [0.80–1.02]	0.092
Cardiovascular death	449 (13.9%)	491 (15.0%)	0.91 [0.80–1.03]	0.128
All-cause hospitalisation	1231 (38.0%)	1356 (41.5%)	0.89 [0.82–0.96]	0.003
Any cardiovascular hospitalisation	977 (30.2%)	1122 (34.4%)	0.85 [0.78–0.92]	0.0002

MI: myocardial infarction

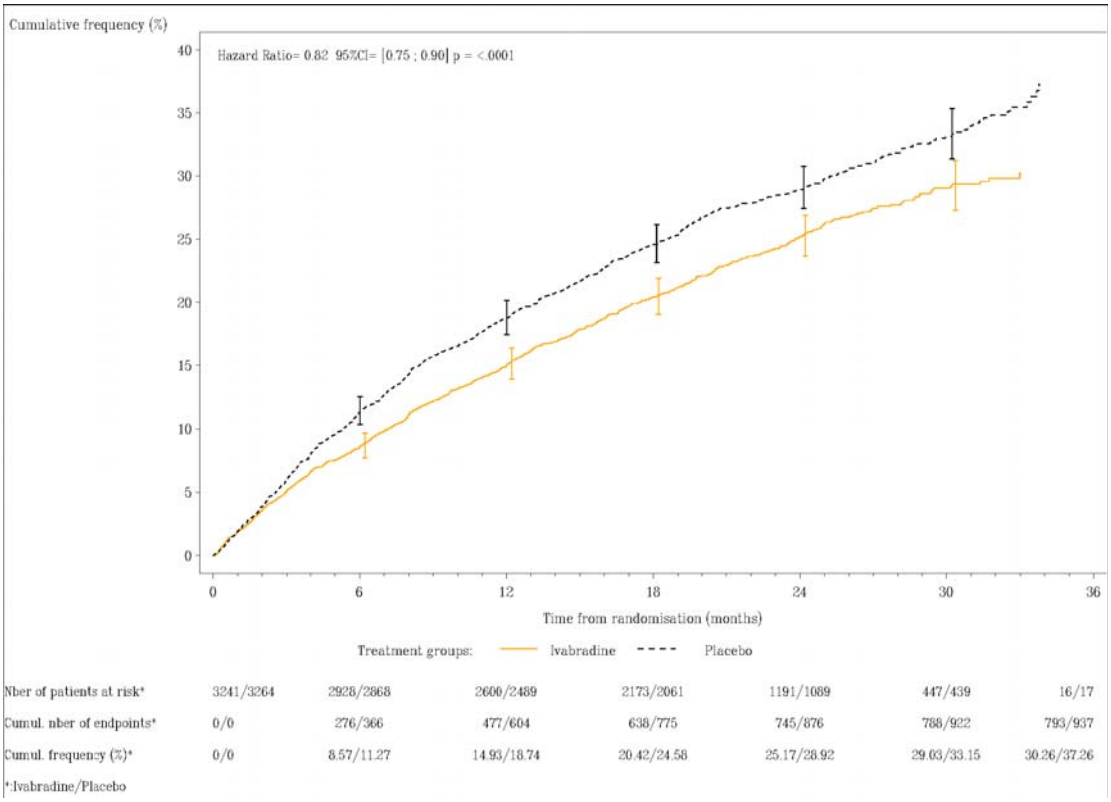


Figure 3: Kaplan-Meier survival curve of the primary composite endpoint

Endpoints of causes of hospitalisation showed consistent results of greater efficacy with ivabradine [see below].

Number of patients with at least one:	Ivabradine (N = 3241; NPY = 4638)			Placebo (N = 3264; NPY = 4527)		
	n	(%)	%PY	n	(%)	%PY
Hospitalisation for any cause	**1231**	**38.0**	**26.5**	**1356**	**41.5**	**30.0**
Hospitalisation for cardiovascular reason	**977**	**30.2**	**19.8**	**1122**	**34.4**	**23.5**
Hospitalisation for worsening heart failure	514	15.9	9.4	672	20.6	12.7
Hospitalisation for myocardial infarction	84	2.6	1.4	87	2.7	1.5
Hospitalisation for other CV reason	577	17.8	10.8	635	19.5	12.0
Hospitalisation for undetermined cause	18	0.6	0.3	36	1.1	0.6
Hospitalisation for non-cardiovascular reason	**477**	**14.7**	**8.7**	**508**	**15.6**	**9.3**
Unplanned hospitalisation for any cause	**1137**	**35.1**	**23.8**	**1264**	**38.7**	**27.3**
Unplanned hospitalisation for CV reason	**909**	**28.1**	**18.0**	**1047**	**32.1**	**21.5**

PY= patient years

Subgroup analyses

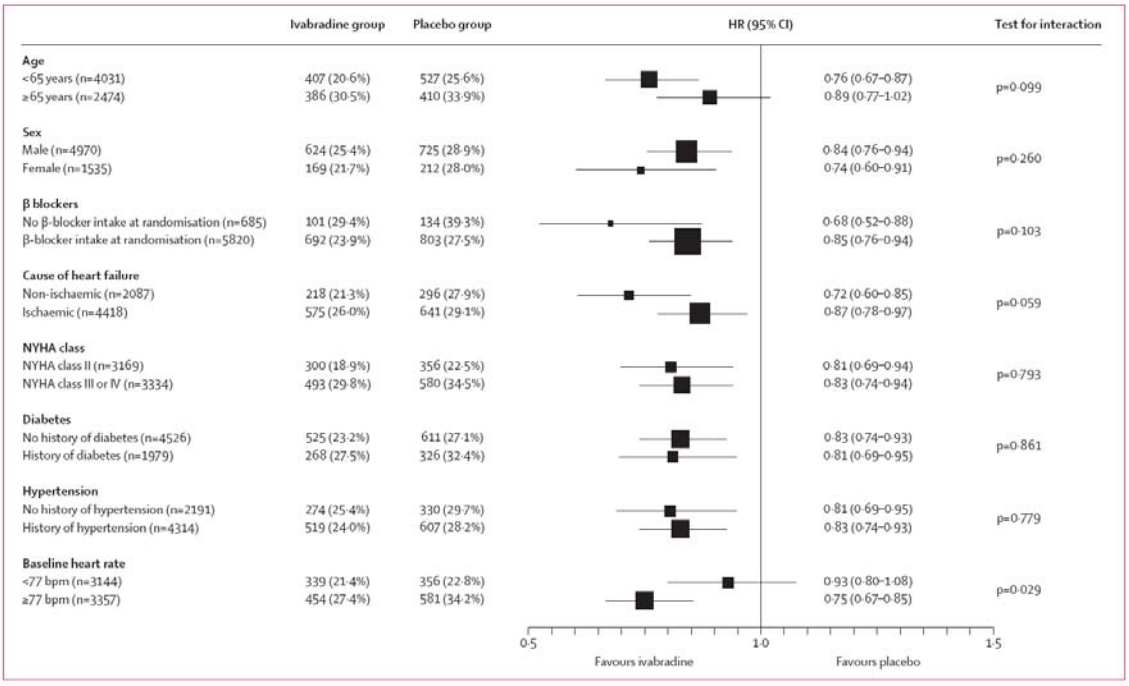


Figure 5: **Effect of treatment on primary composite endpoint in prespecified subgroups**
Data are number (%) of patients with first events. HR=hazard ratio. NYHA=New York Heart Association. bpm=beats per min.

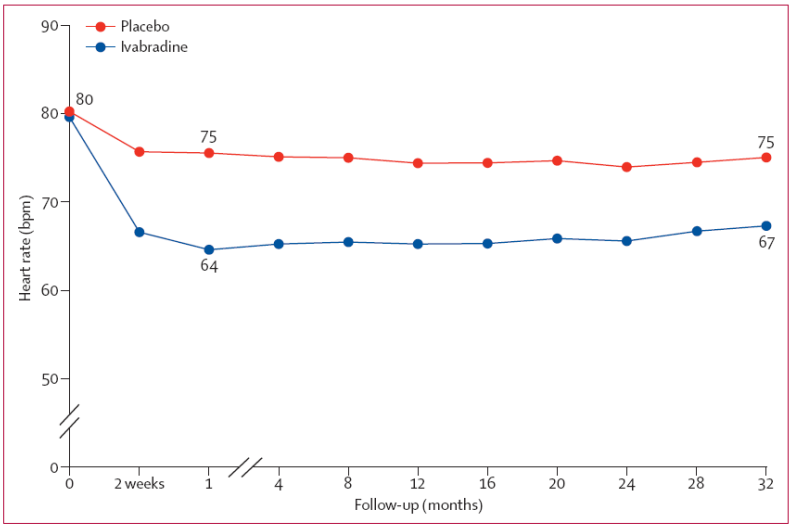
Figure 4: Treatment effects on the primary composite endpoint in pre-defined subgroups

The Heart Rate subgroup was the only subgroup with p for interaction reaching statistical significance (p=0.029).

<u>Short-term physical improvements</u>

Heart rate decrease

Between baseline and 28 days, heart rate decreased by 15.4 bpm in the ivabradine group compared with 4.6 bpm in the placebo group, a difference of -10.9 bpm (95%CI -11.4;-10.4).



NYHA class improvement

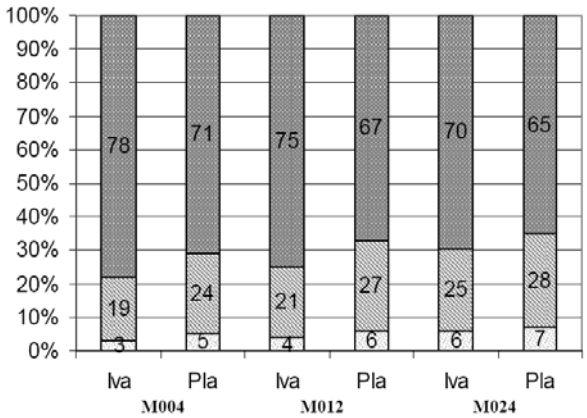
There was a modest but statistically significant improvement in NYHA class with ivabradine relative to placebo during the study; at the last recorded value, 28% of patients in the ivabradine group had improved by ≥ 1 NYHA class relative to baseline, compared with 24% with placebo (p = 0.001).

Table 5: Change in NYHA class between baseline and last visit.

		Randomised Set		Randomised Set-BB-dose	
		Ivabradine (N = 3241)	Placebo (N = 3264)	Ivabradine (N = 1581)	Placebo (N = 1600)
All	**n**	**3216**	**3234**	**1570**	**1585**
Improvement	n' (%)	887 (27.6)[1]	776 (24.0)[1]	407 (25.9)[2]	384 (24.2)[2]
Stability	n' (%)	2172 (67.5)	2265 (70.0)	1094 (69.7)	1120 (70.7)
Worsening	n' (%)	157 (4.9)	193 (6.0)	69 (4.4)	81 (5.1)

Symptom improvement

At the last recorded value, patient-reported global assessment improved in 72% of patients in the ivabradine group, compared with 68% in the placebo group (p = 0.0005), and physician-reported global assessment improved in 61% of patients in the ivabradine group and 57% with placebo (p = 0.0011). For month 4, 12 and 24 this is shown in the figure below.



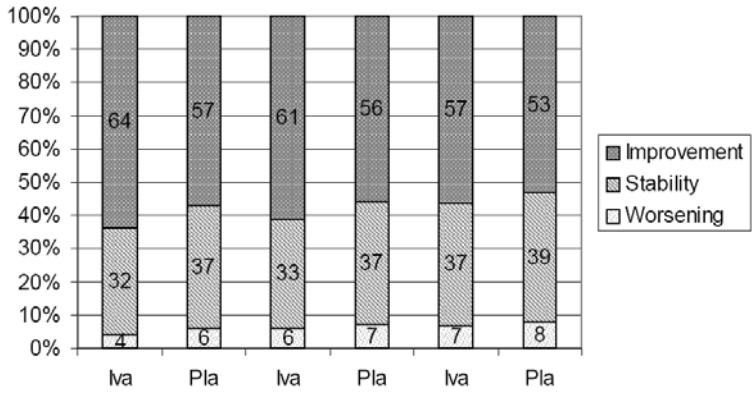


Figure 5: Global assessment questionnaire by study visit for patients (left panel) and physicians (right panel).

Beta-blocker use

The extent of concomitant beta-blocker use, reasons for not reaching target beta-blocker dose and impact on study outcome are described below.

Table 6: Daily doses of beta-blocker, and reasons for not receiving the target dose expressed as n patients (%), unless stated otherwise

	Ivabradine N = 3241	**Placebo N = 3264**
Patients receiving a beta-blocker at baseline	2897 (89%)	2923 (90%)
Daily dose of beta-blocker (mg), mean ± SD		
Carvedilol	25.0 ± 17.8	25.0 ± 17.7
Bisoprolol	6.2 ± 3.3	6.2 ± 3.4
Metoprolol succinate	90.2 ± 59.9	89.5 ± 60.0
Metoprolol tartrate	66.8 ± 47.4	71.2 ± 47.4
Nebivolol	5.9 ± 2.8	5.9 ± 3.0
Patients at target dose of beta-blocker*	743 (26%)	745 (26%)
Patients at ≥ 50% of target dose of beta-blocker*	1581 (56%)	1600 (56%)
Reasons for not receiving target dose of beta-blocker*,**		
Hypotension	933 (44%)	952 (45%)
Fatigue	676 (32%)	670 (32%)
Dyspnoea	284 (14%)	302 (14%)
Dizziness	267 (13%)	245 (12%)
Cardiac decompensation	180 (9%)	187 (9%)
Bradycardia	134 (6%)	125 (6%)
Other	199 (9%)	219 (10%)

**Analysis restricted to patients receiving carvedilol, bisoprolol, metoprolol succinate, metoprolol tartrate and nebivolol. Target doses: carvedilol = 50 mg, bisoprolol and nebivolol = 10 mg, metoprolol succinate = 190 mg, metoprolol tartrate = 150 mg*
*** more than one reason could be reported*
SD: standard deviation

MAH provides several analyses in the subgroup of patients receiving at least half of the target dose of a beta-blocker (N = 3181 patients). In this subgroup a total of 330 patients (20.9%, 11.9%PY) in the ivabradine group *versus* 362 (22.6%, 13.3%PY) in the placebo group reached the primary composite endpoint. The estimate of the corresponding hazard ratio using an unadjusted Cox proportional hazards model, was 0.90 (95% CI [0.77; 1.04]), indicating a trend towards a risk reduction in the ivabradine group (p = 0.155).

Table 7: Primary endpoint in the subgroup receiving at least half of the target dose of a beta-blocker

	Ivabradine (N = 1581)				**Placebo (N = 1600)**				**Hazard ratio**	**p-value**
	NPY	n	%	%PY	NPY	n	%	%PY	E [95% CI]	
Primary composite endpoint	**2778**	**330**	**20.9**	**11.9**	**2721**	**362**	**22.6**	**13.3**	**0.90 [0.77 ; 1.04]**	0.155
Secondary endpoints										
- Cardiovascular death	2982	176	11.1	5.9	2968	175	10.9	5.9	1.00 [0.81 ; 1.24]	0.986
- Hospitalisation for worsening HF	2778	213	13.5	7.7	2721	260	16.3	9.6	0.81 [0.67 ; 0.97]	**0.0211**

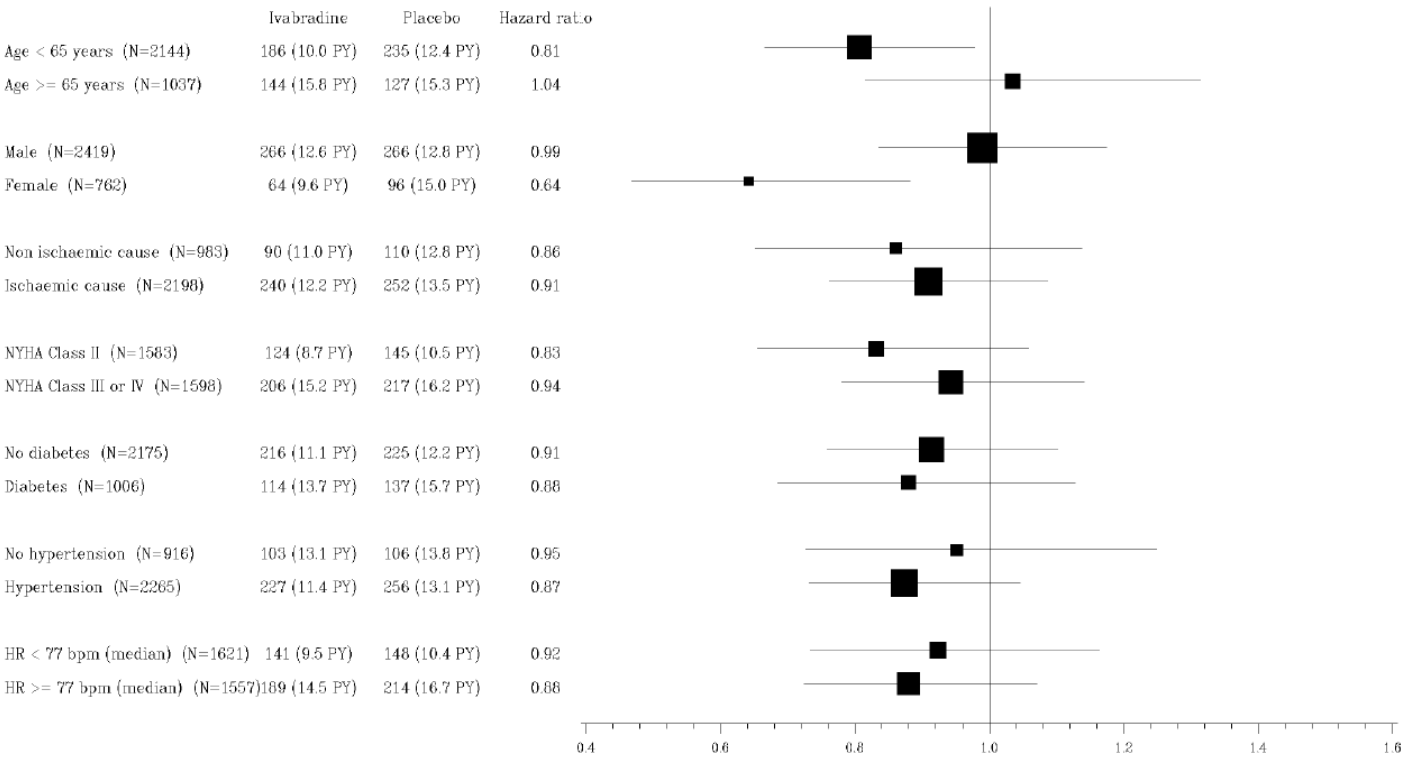


Figure 6: Treatment effects on the primary composite endpoint in pre-defined subgroups in the subgroup of patients receiving at least half of the target dose of beta-blocker.

Heart rate

The MAH has provided an analysis of treatment effect stratified for patients with baseline HR above and below 77 bpm on the primary endpoint (see figure 4). Additional analyses were also provided on the individual components of the primary endpoint and death from any cause (below):

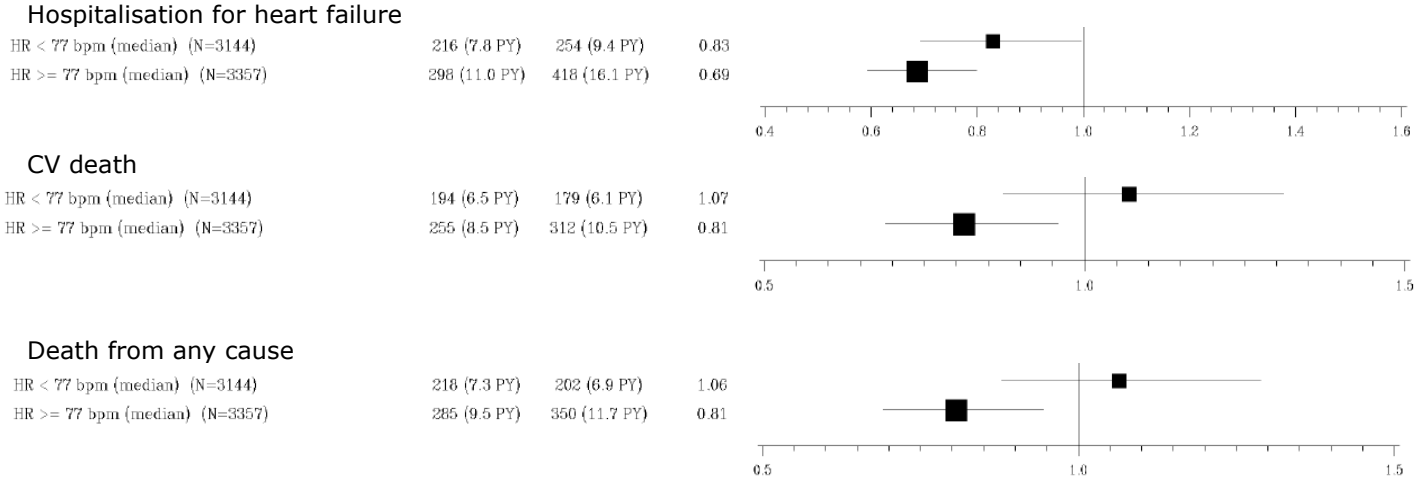


Figure 7: Individual components of the primary endpoint and death from any cause for the subgroup stratification of heart rate.

The CHMP concluded that subgroup analyses showed generally consistent effects. However, two principal interrelated issues remain. First, the observation that patients with the higher baseline HR (≥77 bpm) show the greatest benefit (p for interaction 0.029). This is in line with the proposed MoA, but leads to the question what baseline HR is the most appropriate cut-off. Second, concomitant use of

beta-blockers reduces the effect size, albeit that no statistical significant interaction was observed. The efficacy of ivabradine treatment seems to be inversely related to beta-blocker dose used in the SHIFT trial. The benefit of ivabradine was most pronounced in those patients not receiving beta-blocker [RR 0.68 95%CI 0.52 – 0.88], and was less [RR 0.82 95%CI: 0.76-0.94] in the overall population and lowest in the population at least half target BB dose [RR0.90 95%CI: 0.77-1.04]. It is therefore uncertain what the benefit of ivabradine will be when added to target beta-blocker dose.

Thus, the MAH was asked to discuss this apparent inverse relationship between % of target dose of beta-blocker and beneficial effects of ivabradine with respect to the overall impact on the benefit/risk balance in patients treated with (near) optimal beta-blocker doses and the implications of these findings for the indication. A separate analysis was asked for the patient groups that did achieve target dose (26%). Furthermore, it can be expected that patients using higher doses of beta-blocker have a lower baseline HR. The patients with the lowest baseline HR and the highest dose of beta-blocker probably benefit least when ivabradine is added to their HF therapy. In line with this hypothesis in the Böhm [2010 Lancet] paper fewer patients in the highest HR quintiles were prescribed beta-blockers at randomisation ($p<0.0001$). Beta-blockers were prescribed ranging from 93% in the lowest quintile (70 to 72 bpm) and 82% in the highest quintile (≥87 bpm) of patients in SHIFT. Therefore, the MAH was asked to discuss the implications on clinical efficacy of ivabradine of this finding. In the same article by Böhm the effect of ivabradine treatment increases with HR, in line with the subgroup analysis in the dossier on patients with baseline HF ≥ 77bpm. Up to a baseline rate of 75 bpm the point estimate is close to 1 indicating a null effect of adding ivabradine to 'optimal' baseline therapy [see figure below]. This finding supports the mechanism of action but questions whether the correct cut-off for initiating ivabradine treatment may be higher than 70, probably above 75.

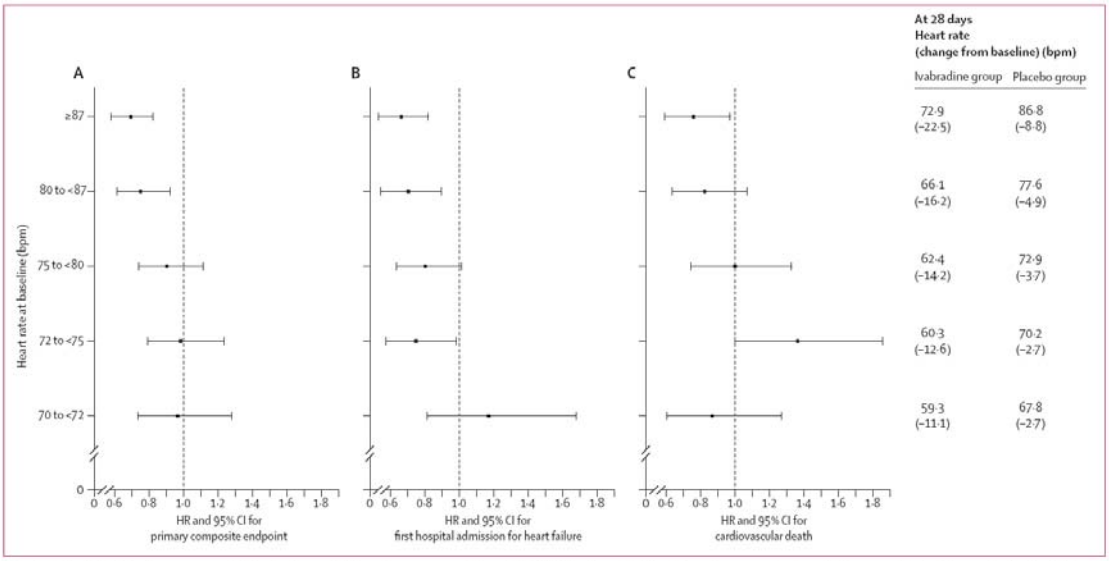


Figure 2: **Effect of ivabradine compared with placebo on (A) the primary composite endpoint, (B) first hospital admissions for worsening heart failure, and (C) cardiovascular deaths in the whole patient population, defined by quintiles of baseline heart-rate distribution**

Primary composite endpoint includes cardiovascular deaths and hospital admissions for worsening heart failure. Adjusted for β-blocker intake at randomisation, New York Heart Association class, left-ventricular ejection fraction, ischaemic cause, age, systolic blood pressure, and creatinine clearance at baseline. HR=hazard ratio. bpm=beats per min.

<u>Reasons for not reaching beta-blockers target dose</u>

In the response the MAH confirmed that only 26% of patients were on target dose and 49% of patients received at least 50% of the target beta blocker dose. This may be in line with clinical practice, despite efforts of the SHIFT investigators to optimize background therapy. Still, the MAH was asked to for further justifications. It was questioned whether patients were really on their maximum tolerated target dose. One reason could be that patients were slow CYP2D6 metabolisers, however, it is unknown whether any patients were genotyped and to what extent this may have played a role. Some

of the mentioned reasons for not increasing beta-blocker dose are not well understood. In almost half of the cases patients were not on their target dose of beta-blockers because of hypotension. Yet 'blood pressure not controlled' was one of the most reported adverse events, whereas hypotension was only reported in a small proportion of patients (1.9% see safety section). In addition, bradycardia was the reported reason for not receiving target beta-blocker dose only in 6% of patients.

The company provided the data for the subgroup of patients on target beta-blocker dose. Event rates (20.1% vs. 20.1%; ivabradine vs. placebo) in this subpopulation were lower than in the overall population (24.5% vs. 28.7%). No treatment effect was observed on the primary endpoint (HR 0.99; 0.79-1.24). Again, for the individual components of the primary endpoint no or a diminished treatment effect was observed for those on target BB dose versus the overall population (hospitalization for worsening HF 0.84 [0.63-1.11] vs HR 0.74 [0.66-0.83], and CV death 1.08 [0.78-1.48] vs 0.91 [0.80-1.03]). The MAH presented also data for the patients (n=938) on target BB dose but with baseline heart rate **≥** 75 bpm. In this relatively small subgroup there was still no effect on the primary endpoint (HR 0.97 [0.74-1.28]). However, hospitalization for worsening HF (HR 0.79 [0.56-1.10]) and death from HF (HR 0.69 [0.31-1.56]), although not statistically significant, showed protective effects. Other endpoints were inconclusive with hazard ratios close to one. In conclusion, treatment effects of ivabradine are attenuated when patients are on target beta blocker dose. Nevertheless, in the SHIFT trial patients on target beta-blocker dose, but with baseline heart rate ≥ 75 bpm demonstrated positive effect on specific heart failure endpoints.

Given that the CHMP questioned whether patients not on target dose of beta-blockers were optimally treated. The MAH has provided sufficient justification that all possible effort had been made to ascertain that patients were on their maximally tolerated BB dose. Specific attention was paid to this in the trial oversight as documented in eCRF and protocol. Investigators were explicitly asked to treat patients with optimal dose of beta-blocker according to the protocol. In SHIFT 26% of patients were on target BB dose, which is in the lower range when compared to reported CHF trials or clinical practice. However, when looking at baseline blood pressure across trials and clinical practice surveys, blood pressure was clearly lower in SHIFT. Hypotension was thus in SHIFT the main cause recorded in the eCRF why patients were not on target BB dose. The recorded reason for not being on target dose was corroborated by the finding that these patients not on target BB dose had lower BP (mean SBP/DBP 113/72 mmHg) than patients on target dose (mean SBP/DBP 122/76 mmHg). Other – sometimes overlapping – reasons were recorded for not being on target BB dose. The main other reasons were also in SHIFT: hypotension, older age, lower LVEF, NYHA III/IV similar to those reported in previous CHF trials and clinical practice surveys. The relation between a patient's CYP2D6 status and reaching target BB dose in an individual patient could not be fully established. Genotyping has not been performed; therefore it is not known whether patients were poor metabolisers. The MAH showed that across all beta blockers the ratio of achieved BB dose over target beta blocker dose was approximately 0.5. This was irrespective of the role of CYP2D6 in their metabolism. Taking these observations together, it seems unlikely that inhibition – drug induced or genetic – of the CYP2D6 isoenzyme played a major role in patients not reaching target BB dose.

Data previously reported suggest that 75 bpm might be a clinically useful threshold for defining patients who may benefit from ivabradine treatment (Böhm, 2010). Sixty-five percent of patients in SHIFT had a heart rate ≥ 75 bpm. This subpopulation benefitted clearly to a larger extent from ivabradine treatment, an increased benefit that was observed across all endpoints. Event rates were higher than in the overall population (26.6% vs. 32.8%; ivabradine vs. placebo) The safety profile is comparable to the overall safety profile. Therefore, the benefit for this subgroup seems demonstrated more clearly and the MAH has proposed to adopt the indication accordingly. The effects were attenuated in patients who were on target BB dose, but the number of patients in this subgroup of this subpopulation with heart rate ≥75 bpm is relatively small (n=938). Clear beneficial effects were still

observed on heart failure-related hospitalizations and deaths. Other differences were reported as well between patients in the lower quintiles versus high quintiles, where patients were less severely ill and received a different drug regimen. These factors may have contributed all to some extent that a heart rate lowering strategy, using ivabradine, in heart failure patients becomes beneficial only when patients present with an appropriately elevated heart rate, here ≥75 bpm. The MAH proposal to modify the new indication to patients with baseline heart rate over 75 bpm instead of 70bpm was supported by the CHMP. Beta-blocker dose was indeed somewhat lower in the higher heart rate quintile groups. In these quintiles hypotension was more frequently reported as a reason for not reaching target BB dose.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table X. Summary of Efficacy for trial **CL3-16257-063**

Title: **Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction: the SHIFT study**		
Study identifier	CL3-16257-063	
Design	A three-year, event-driven, phase III, randomised, double-blind placebo-controlled, two-balanced arm parallel, international, multicentre study	
	Duration of main phase:	Planned treatment duration : from 12 up to 52 months
	Duration of Run-in phase:	Planned duration : 14 days but duration 7 to 30 days accepted
	Duration of Extension phase:	not applicable
Hypothesis	To demonstrate the superiority of ivabradine over placebo in the reduction of cardiovascular mortality and hospitalisations for worsening heart failure (composite endpoint), in patients with moderate to severe symptoms of chronic heart failure and a reduced left ventricular ejection fraction receiving currently recommended therapy for this disease.	
Treatments groups	Ivabradine	Mean treatment duration = 20.0 ± 9.0 months, N= 3241 patients in the RS
	Placebo	Mean treatment duration = 20.2 ± 8.9 months, N= 3264 patients in the RS
Endpoints and definitions	Primary composite endpoint	Time to occurrence of the first event of one of the following: cardiovascular death or hospitalisation for worsening heart failure.
	Secondary endpoints	Time to occurrence of the first event of: -Cardiovascular death, -Hospitalisation for worsening heart failure, -All cause death, -Death from HF, -Hospitalisation for any cause, -Hospitalisation for CV reason.
Database lock	31st May 2010	

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Randomised patients (Intent to treat) Time to first event		
Descriptive statistics	Treatment group	Ivabradine	Placebo
	Number of subjects	3241	3264
	Primary composite endpoint n (%)	793 (24.5%)	937 (28.7%)
	Cardiovascular death n (%)	449 (13.9%)	491 (15.0%)
	Hospitalisation for worsening heart failure n (%)	514 (15.9%)	672 (20.6%)
	All cause death n (%)	503 (15.5%)	552 (16.9%)
	Death from HF n (%)	113 (3.5%)	151 (4.6%)
	Hospitalisation for any cause n (%)	1231 (38.0%)	1356 (41.5%)
	Hospitalisation for CV reason n (%)	977 (30.2%)	1122 (34.4%)
Effect estimate per comparison		Comparison groups	Ivabradine versus Placebo
	Statistic test	Cox's proportional hazards model adjusted for beta-blocker intake at randomization (Wald test)	
	Primary composite endpoint	Hazard ratio	0.82
		95%CI	[0.75;0.90]
		p-value	< 0.0001
	Cardiovascular death	Hazard ratio	0.91
		95%CI	[0.80;1.03]
		p-value	0.128
	Hospitalisation for worsening heart failure	Hazard ratio	0.74
		95%CI	[0.66;0.83]
		p-value	< 0.0001
	All cause death	Hazard ratio	0.90
		95%CI	[0.80;1.02]
		p-value	0.092
	Death from HF	Hazard ratio	0.74
		95%CI	[0.58;0.94]
		P-value	0.0140
	Hospitalisation for any cause	Hazard ratio	0.89
		95%CI	[0.82;0.96]

		p-value	0.0027
	Hospitalisation for CV reason	Hazard ratio	0.85
		95%CI	[0.78;0.92]
		p-value	0.0002
Notes	Efficacy of ivabradine increases with baseline heart rate. Patients with HR ≥ 75 bpm at baseline appear to be the population benefiting the most from the addition of ivabradine.		
Analysis description	**Sub-group of patients with HR ≥ 75 bpm at baseline**		
Analysis population and time point description	Randomised patients with HR ≥ 75bpm at baseline (Intent to treat) Time to first event		
Descriptive statistics	Treatment group	Ivabradine	Placebo
	Number of subjects	2052	2098
	Primary composite endpoint n (%)	545 (26.6%)	688 (32.8%)
	Cardiovascular death n (%)	304 (14.8%)	364 (17.4%)
	Hospitalisation for worsening heart failure n (%)	363 (17.7%)	503 (24.0%)
	All cause death n (%)	340 (16.6%)	407 (19.4%)
	Death from HF n (%)	78 (3.8%)	126 (6.0%)
	Hospitalisation for any cause n (%)	796 (38.8%)	932 (44.4%)
	Hospitalisation for CV reason n (%)	640 (31.2%)	779 (37.1%)
Effect estimate per comparison		Comparison groups	Ivabradine versus Placebo
	Statistic test	Cox's proportional hazards model adjusted for beta-blocker intake at randomization (Wald test)	
	Primary composite endpoint	Hazard ratio	0.76
		95%CI	[0.68;0.85]
		p-value	< 0.0001
	Cardiovascular death	Hazard ratio	0.83
		95%CI	[0.71;0.97]
		p-value	0.0166
	Hospitalisation for worsening heart failure	Hazard ratio	0.70
		95%CI	[0.61;0.80]
		p-value	< 0.0001
	All cause death	Hazard ratio	0.83
		95%CI	[0.72;0.96]
		p-value	0.0109

	Death from HF	Hazard ratio	0.61
		95%CI	[0.46;0.81]
		p-value	0.0006
	Hospitalisation for any cause	Hazard ratio	0.82
		95%CI	[0.75;0.90]
		p-value	< 0.0001
	Hospitalisation for CV reason	Hazard ratio	0.79
		95%CI	[0.71;0.88]
		p-value	< 0.0001

2.3.3. Discussion on clinical efficacy

Ivabradine is a heart rate lowering agent, acting by reducing the rate of pacemaker activity in the sinoatrial node. Ivabradine has been registered for treating chronic stable angina pectoris with coronary artery disease. The MAH proposes to extend the indication to patients with chronic heart failure and a heart rate above 70 bpm. This was based on the SHIFT trial including patients with stable heart failure NYHA class II to IV and LVEF ≤35%. The study is a complex study in design and performed worldwide across 677 centres in 37 countries. The primary composite outcome, as well as several important secondary endpoints were adjudicated by an Independent Endpoint Validation Committee to confirm that reported events are of equal relevance across all site.

Due to the complexity of this single pivotal trial for the benefit/risk assessment of ivabradine in heart failure, a GCP inspection was performed to evaluate the sponsor's oversight over the whole study and results of the inspection were considered positive.

The MAH demonstrated a significant and clinically relevant efficacy of ivabradine versus placebo in addition to current standard treatment on the chosen composite endpoint of cardiovascular death and hospitalization for worsening heart failure (HR 0.82 (95%CI 0.75-0.90), p<0.0001) with an absolute risk reduction of 4.2% during a 36 months of follow-up. A separation of effect appeared within the first 6 months. The effect is driven by the observed difference between treatment groups in the 'hospitalisation due to worsening heart failure' component of the composite endpoint. Cardiovascular death showed a numerical benefit, but this change did not reach statistical significance.

All other secondary endpoints showed consistent statistically significant beneficial effects of ivabradine compared to placebo, except for the – most robust -overall death endpoint where only a numerical advantage could be shown. Symptomatic improvements demonstrated similar absolute effects as the composite endpoint, although the relevance of an additional 4% of patients improving one NYHA class, or a similar proportion of physicians and patients reporting improved symptomatology appears small.

The *EMA Guideline on clinical investigation of medicinal products for the treatment of the heart failure [CPMP/EWP/235/95 Rev. 1]* preferred primary endpoint would have at least included all cause mortality. In this study all cause mortality was a secondary endpoint. All primary and secondary analyses were in the same – beneficial – direction, therefore a reanalysis of an endpoint including all cause mortality would not change conclusion of efficacy of ivabradine in the overall treatment population.

Given that the objective measurements to assess the clinical status of the patients were lacking (such as NT-pro-BNP measurements, 6 min. walking tests, spiroergometries, or regular exercise tolerance tests) the MAH provided additional explanations that were considered justified by the CHMP. Definitions of ITT and PP efficacy sets were also further discussed. The MAH provided also additional explanations regarding the determination of HR after 5 min rest from single ECG which were accepted by the CHMP. Slight problems in blinding were identified as the patients and physicians could assess the HR affected by ivabradine but this in the opinion of the CHMP did not affect the conduct of the study.

Despite the inclusion criteria aiming to include a broad range of symptomatic HF patients, NYHA HF class II to IV, only 1 to 2% of included patients were in NYHA class IV. However further explanations provided by the MAH reassured the CHMP that the results of this study apply as well to this population of patients and that the contraindication for this group of patients was deleted from section 4.3 of the SmPC.

The CHMP noted that relatively young patients (60±11 years) were included in the SHIFT trial. The MAH provided subgroup analyses of treatment effects for patients ≥65 years of age and ≥70 years of age. The results were essentially similar to those observed in the overall population of the SHIFT trial. Although the impact on the primary endpoint was slightly less, and not statistically significant, in patients ≥65 years it was somewhat larger and significant in the over 70 years old. In addition, when considering the subpopulation with baseline heart rate over 75 bpm, also in the ≥65 years beneficial effects were observed on the primary endpoint.

No specific safety concerns emerged, and similar rates of adverse events were reported in elderly patients in both ivabradine and placebo treatment groups. Furthermore, inclusion of patients using amiodarone was considered by the CHMP of high clinical value. HF patients carry a high risk for atrial and ventricular arrhythmias and are often prescribed potent antiarrhytmics. The efficacy and safety aspects in this group of patients were discussed by the MAH and considered in the SmPC and the RMP.

In SHIFT a similar dosing scheme as included in the SmPC was used, where patients were up- respectively down-titrated to 7.5 mg or 2.5 mg BID based on tolerability (especially HR<50 bpm or bradycardia). Any dose response relationship has not been presented. However, only 60% reached the maximal dose. Further explanations were provided by the MAH as to which patients did not tolerate the maximal doses and the analysis of the benefit-risk according to dose reached.

Prespecified subgroup analyses demonstrated consistent effects of ivabradine. However, the prespecified subgroup of patients with the higher baseline HR (≥77 bpm) showed the greatest benefit. This is in line with the proposed MoA, but leads to the question what baseline HR is the most appropriate cut-off. Concomitant use of beta-blockers reduces the effect size, albeit that no statistical significant interaction was observed in the prespecified subgroup analysis (yes/no beta-blocker use). Efficacy of ivabradine treatment seems to be inversely related to beta-blocker dose used in the SHIFT trial. The benefit of ivabradine was most pronounced in those patients not receiving beta-blocker [RR 0.68 95%CI 0.52 – 0.88], and was less [RR 0.82 95%CI:0.76-0.94] in the overall population and was lowest in the population at least half target BB dose [RR 0.90 95%CI: 0.77-1.04]. It is therefore uncertain what the benefit of ivabradine will be when added to target beta-blocker dose. In addition, only 26% of patients were on target dose and 56% of patients received 50% or more of target beta blocker dose. This may be in line with clinical practice and despite effort of SHIFT investigators to optimize background therapy.

However, the reasons for not achieving beta-blocker target dose were not fully clear. Hypotension was reported as reason for half of the patients not reaching target dose yet 'blood pressure not controlled' was one of the most reported adverse events but only few cases of hypotension were reported. In addition, bradycardia was for 6% of patients the reported reason for not receiving target BB dose, although these patients would likely not qualify for treatment with ivabradine or meet the HR inclusion criterion.

On the other hand, poor CYP2D6 metabolisers may be considered on optimal beta blocker dose despite not having reached target dose. In the published study of Böhm (Lancet 2010), HR was divided into quintiles to evaluate the relation of HR to clinical outcome in the SHIFT trial. Beta-blockers were prescribed more in the lowest quintile compared to the highest quintile, ranging from 93% in the lowest quintile (70 to 72 bpm) and 82% in the highest quintile (≥87 bpm) of patients. It can also be expected that patients with lower baseline HR use higher doses of beta-blocker at baseline. Therefore, the MAH was asked the implications on clinical efficacy of ivabradine of this finding. In the same paper it was stated that the effect of ivabradine treatment increased with HR, but does not improve from a null effect below a baseline HR of 75 questioning whether a higher baseline HR as cut off would be more appropriate before initiating therapy with ivabradine. In the response the MAH confirmed that only 26% of patients were on target dose and 56% of patients received at least 50% of the target beta

blocker dose. This may be in line with clinical practice, despite efforts of the SHIFT investigators to optimize background therapy. The company provided the data for the subgroup of patients on target beta-blocker dose. Event rates (20.1% vs. 20.1%; ivabradine vs. placebo) in this subpopulation were lower than in the overall population (24.5% vs. 28.7%). No treatment effect was observed on the primary endpoint (HR 0.99; 0.79-1.24). Again, for the individual components of the primary endpoint no or a diminished treatment effect was observed for those on target BB dose versus the overall population (hospitalization for worsening HF 0.84 [0.63-1.11] vs HR 0.74 [0.66-0.83], and CV death 1.08 [0.78-1.48] vs 0.91 [0.80-1.03]). The MAH presented also data for the patients (n=938) on target BB dose but with baseline heart rate **≥** 75 bpm. In this relatively small subgroup there was still no effect on the primary endpoint (HR 0.97 [0.74-1.28]). However, hospitalization for worsening HF (HR 0.79 [0.56-1.10]) and death from HF (HR 0.69 [0.31-1.56]), although not statistically significant, showed protective effects. In conclusion, treatment effects of ivabradine are attenuated when patients are on target beta blocker dose. Nevertheless, in the SHIFT trial patients on target beta-blocker dose, but with baseline heart rate ≥ 75 bpm demonstrated positive effect on specific heart failure endpoints. The MAH has provided also sufficient justification that all possible effort had been made to ascertain that patients were on their maximally tolerated BB dose. Specific attention was paid to this in the trial oversight as documented in eCRF and protocol. Investigators were explicitly asked to treat patients with optimal dose of beta-blocker according to the protocol.

Data previously reported suggest that 75 bpm might be a clinically useful threshold for defining patients who may benefit from ivabradine treatment. Sixty-five percent of patients in SHIFT had a heart rate ≥ 75 bpm. This subpopulation benefitted clearly to a larger extent from ivabradine treatment, an increased benefit that was observed across all endpoints. Event rates were higher than in the overall population (26.6% vs. 32.8%; ivabradine vs. placebo). The safety profile in this subgroup was comparable to the overall safety profile. Therefore, the benefit for this subgroup seemed to be demonstrated more clearly and the MAH has proposed to modify the indication accordingly. The CHMP agreed to this proposal.

2.3.4. Conclusions on the clinical efficacy

The CHMP considered that the MAH provided sufficient data to support the extension of indications to include the *Treatment of chronic heart failure: Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. (see section 5.1)*

2.4. Clinical safety

Patient exposure

Adverse events

Table 8: Overall summary of adverse events

	Ivabradine (N = 3232) (NPY = 5401)			Placebo (N = 3260) (NPY = 5495)		
	n	**%**	**%PY**	**n**	**%**	**%PY**
EAEs reported during the study						
All EAEs	**2439**	**75.5**	**41.0**	**2423**	**74.3**	**41.0**
Cardiac disorders	1390	43.0	23.4	1403	43.0	23.7
EAEs reported while on treatment						
All EAEs	**2414**	**74.7**	**44.7**	**2392**	**73.4**	**43.5**
Cardiac disorders	1332	41.2	24.7	1357	41.6	24.7
All EAEs leading to treatment withdrawal	**467**	**14.5**	**8.7**	**416**	**12.8**	**7.6**
All serious EAEs (fatal and non-fatal)	**1369**	**42.4**	**25.4**	**1481**	**45.4**	**27.0**
Cardiac disorders	853	26.4	15.8	939	28.8	17.1
All serious EAEs leading to treatment withdrawal	**270**	**8.4**	**5.0**	**279**	**8.6**	**5.1**

EAE: emergent adverse event; N: total number of exposed patients; NPY: number of patient-years
n: number of patients affected by at least one event in a given level
% = n/N x 100; %PY: number of patients with at least one event per 100 patient-years (n/NPY x 100)

Table 9: Most common adverse events reported on treatment (≥2% of patients in either treatment group)

	Ivabradine (N = 3232) (NPY = 5401)			Placebo (N = 3260) (NPY = 5495)		
	n	%	%PY	n	%	%PY
Cardiac failure	701	21.7	13.0	846	26.0	15.4
Atrial fibrillation	267	8.3	4.9	217	6.7	4.0
Blood pressure inadequately controlled	228	7.1	4.2	198	6.1	3.6
Heart rate decreased*	181	5.6	3.4	45	1.4	0.8
Bradycardia	148	4.6	2.7	28	0.9	0.5
Ventricular extrasystoles	144	4.5	2.7	138	4.2	2.5
Diabetes mellitus inadequate control	135	4.2	2.5	141	4.3	2.6
Angina pectoris	133	4.1	2.5	142	4.4	2.6
Pneumonia	120	3.7	2.2	132	4.1	2.4
Angina unstable	118	3.7	2.2	126	3.9	2.3
Sudden death	111	3.4	2.1	119	3.7	2.2
Anaemia	96	3.0	1.8	100	3.1	1.8
Phosphenes	89	2.8	1.7	16	0.5	0.3
Sudden cardiac death	73	2.3	1.4	68	2.1	1.2
Bronchitis acute	68	2.1	1.3	85	2.6	1.6
Influenza	67	2.1	1.2	70	2.2	1.3
Renal failure	63	2.0	1.2	83	2.6	1.5
Chronic obstructive pulmonary disease	65	2.0	1.2	78	2.4	1.4
Nasopharyngitis	66	2.0	1.2	70	2.2	1.3
Hypotension	62	1.9	1.2	87	2.7	1.6
Ventricular tachycardia	60	1.9	1.1	70	2.2	1.3
Sinus tachycardia	40	1.2	0.7	102	3.1	1.9

* Coding for asymptomatic bradycardia

Treatment related adverse events

Treatment-related AEs were more frequently reported in the ivabradine group (17.8%, 10.6%PY) than in the placebo group (8.3%, 4.9%PY). The difference between the two groups was mainly due to known adverse drug reactions of ivabradine, notably asymptomatic bradycardia (HR decreased: 4.6%, 2.8%PY *versus* 1.0%, 0.6%PY, respectively), symptomatic bradycardia (3.7%, 2.2%PY *versus* 0.7%, 0.4%PY, respectively), and phosphenes (2.7%, 1.6%PY *versus* 0.5%, 0.3%PY, respectively). Reported numbers of sudden death were less frequently (3.4%, 2.1%PY *versus* 3.7%, 2.2%PY) and sudden cardiac death events more frequently reported (2.3%, 1.4%PY *versus* 2.1%, 1.2%PY) for ivabradine versus placebo respectively.

Table 10: Treatment related adverse events on treatment in at least 5 patients in either patient group

System organ class Preferred term	Ivabradine (N = 3232) (NPY = 5401.1)				Placebo (N = 3260) (NPY = 5495.3)			
	NEAE	n	%	%PY	NEAE	n	%	%PY
All	**744**	**574**	**17.8**	**10.6**	**340**	**271**	**8.3**	**4.9**
Cardiac disorders	**228**	**196**	**6.1**	**3.6**	**100**	**83**	**2.6**	**1.5**
Bradycardia	128	121	3.7	2.2	25	23	0.7	0.4
Cardiac failure	22	20	0.6	0.4	13	13	0.4	0.2
Atrial fibrillation	10	9	0.3	0.2	3	3	0.1	<0.1
Ventricular extrasystoles	9	9	0.3	0.2	11	11	0.3	0.2
Ventricular tachycardia	6	6	0.2	0.1	8	7	0.2	0.1
Palpitations	8	6	0.2	0.1	6	6	0.2	0.1
Atrioventricular block second degree	5	5	0.2	0.1	5	5	0.2	0.1
Atrioventricular block first degree	6	5	0.2	0.1	2	2	0.1	< 0.1
Atrioventricular block complete	5	5	0.2	0.1	1	1	< 0.1	< 0.1
Supraventricular extrasystoles	3	3	0.1	0.1	5	5	0.2	0.1
Investigations	**188**	**171**	**5.3**	**3.2**	**54**	**53**	**1.6**	**1.0**
Heart rate decreased*	164	150	4.6	2.8	34	34	1.0	0.6
Transaminases increased	7	7	0.2	0.1	4	4	0.1	0.1
Hepatic enzyme increased	2	2	0.1	< 0.1	5	5	0.2	0.1
Eye disorders	**132**	**120**	**3.7**	**2.2**	**29**	**25**	**0.8**	**0.5**
Phosphenes	92	87	2.7	1.6	18	16	0.5	0.3
Vision blurred	17	15	0.5	0.3	5	5	0.2	0.1
Nervous system disorders	**44**	**42**	**1.3**	**0.8**	**40**	**37**	**1.1**	**0.7**
Dizziness	27	25	0.8	0.5	16	16	0.5	0.3
Headache	9	9	0.3	0.2	10	9	0.3	0.2
Syncope	2	2	0.1	< 0.1	8	8	0.3	0.2
Gastrointestinal disorders	**39**	**38**	**1.2**	**0.7**	**29**	**26**	**0.8**	**0.5**
Dyspepsia	6	6	0.2	0.1	5	5	0.2	0.1
Gastritis	6	6	0.2	0.1	4	4	0.1	0.1
Diarrhoea	6	6	0.2	0.1	4	3	0.1	0.1
Nausea	5	5	0.2	0.1	4	4	0.1	0.1
General disorders and administration site conditions	**34**	**31**	**1.0**	**0.6**	**15**	**15**	**0.5**	**0.3**
Fatigue	13	13	0.4	0.2	4	4	0.1	0.1
Asthenia	12	10	0.3	0.2	5	5	0.2	0.1
Skin and subcutaneous tissue disorders	**10**	**10**	**0.3**	**0.2**	**19**	**18**	**0.6**	**0.3**
Vascular disorders	**16**	**15**	**0.5**	**0.3**	**8**	**8**	**0.3**	**0.2**
Hypotension	5	5	0.2	0.1	6	6	0.2	0.1
Orthostatic hypotension	8	7	0.2	0.1	1	1	< 0.1	< 0.1
Ear and labyrinth disorders	**10**	**10**	**0.3**	**0.2**	**6**	**6**	**0.2**	**0.1**
Vertigo	5	5	0.2	0.1	6	6	0.2	0.1
Metabolism and nutrition disorders	**3**	**3**	**0.1**	**0.1**	**12**	**12**	**0.4**	**0.2**
Respiratory, thoracic and mediastinal disorders	**10**	**10**	**0.3**	**0.2**	**7**	**7**	**0.2**	**0.1**
Renal and urinary disorders	**7**	**7**	**0.2**	**0.1**	**5**	**5**	**0.2**	**0.1**

NEAE = number of emergent adverse events
* Coding for asymptomatic bradycardia

Bradycardia

Bradycardia, known to be associated with ivabradine, occurred more frequently with ivabradine than with placebo:

– Asymptomatic bradycardia, coded as heart rate decreased, was reported in 181 patients (5.6%) in the ivabradine group, compared with 45 patients (1.4%) with placebo;

– Symptomatic bradycardia, coded as bradycardia, was reported in 148 patients (4.6%) in the ivabradine group, compared with 28 patients (0.9%) with placebo.

Serious symptomatic or asymptomatic bradycardia was reported in 18 patients (0.6%) and treatment withdrawal occurred in 48 patients (1.5%) in ivabradine group.

Visual symptoms

Patients were not systematically asked for about visual symptoms during this trial. Phosphenes were reported in 89 patients (2.8%) in the ivabradine group versus 16 patients (0.5%) with placebo, and blurred vision in 17 patients (0.5%) versus 7 patients (0.2%) with placebo. They were never serious and unlikely to lead to treatment withdrawal (8 patients, 0.3%) in ivabradine group.

Supraventricular arrhythmias

The rate of supraventricular arrhythmias was similar in ivabradine (390 patients, 12.1%) and placebo (408 patients, 12.5%) groups. The most common supraventricular arrhythmia was atrial fibrillation which was reported more frequently with ivabradine (8.3%, 4.9%PY) than with placebo (6.7%, 4.0%PY). These patients tended to be older (mean age 64.3 years), more likely to be in NYHA class III or IV and to have a previous history of atrial fibrillation (in approximately one quarter of these patients) than the overall population.

Table 14: Adverse events related to supraventricular arrhythmias recorded on treatment, ≥ 0.1% of patients

	Ivabradine (N = 3232) (NPY = 5401)			**Placebo (N = 3260) (NPY = 5495)**		
	n	**%**	**%PY**	**n**	**%**	**%PY**
Supraventricular arrhythmias	**390**	**12.1**	**7.2**	**408**	**12.5**	**7.4**
Atrial fibrillation	267	8.3	4.9	217	6.7	4.0
Supraventricular extrasystoles	41	1.3	0.8	50	1.5	0.9
Sinus tachycardia	40	1.2	0.7	102	3.1	1.9
Atrial flutter	37	1.1	0.7	35	1.1	0.6
Supraventricular tachycardia	15	0.5	0.3	24	0.7	0.4
Sick sinus syndrome	6	0.2	0.1	0	0.0	0.0
Atrial tachycardia	4	0.1	0.1	4	0.1	0.1

N: Number of patients; NPY: Number of patient-years; n: Number of patients with at least one EAE in a given level; %: n/N x 100; %PY: Number of patients with at least one EAE per 100 patient-years (n/NPY x 100)

Ventricular arrhythmias

Overall, the rate of ventricular arrhythmias/cardiac arrest was similar in both groups. Ventricular fibrillation occurred more frequently in the ivabradine group (0.7%, 0.4%PY) than in the placebo group (0.4%, 0.2%PY). On the other hand, the level of ventricular tachycardia was lower in the ivabradine group (1.9%, 1.1%PY) than in the placebo group (2.2%, 1.3%PY). There was no difference between group in the numbers of sudden deaths or sudden cardiac deaths.

Table 15: Adverse events related to ventricular arrhythmias recorded on treatment, ≥ 0.1% of patients

	Ivabradine (N = 3232) (NPY = 5401)			Placebo (N = 3260) (NPY = 5495)		
	n	%	%PY	n	%	%PY
Ventricular arrhythmias and cardiac arrest	**227**	**7.0**	**4.2**	**218**	**6.7**	**4.0**
Ventricular extrasystoles	144	4.5	2.7	138	4.2	2.5
Ventricular tachycardia	60	1.9	1.1	70	2.2	1.3
Ventricular fibrillation	24	0.7	0.4	12	0.4	0.2
Ventricular arrhythmia	5	0.2	0.1	9	0.3	0.2

N: Number of patients; NPY: Number of patient-years; n: Number of patients with at least one EAE in a given level; %: n/N x 100; %PY: Number of patients with at least one EAE per 100 patient-years (n/NPY x 100)

Other important adverse events

Third degree atrioventricular block or complete atrioventricular block occurred in 18 patients (0.6%, 0.3%PY) in the ivabradine group and in 6 patients (0.2%, 0.1%PY) in the placebo group. Blood pressure inadequately controlled was slightly more frequent in the ivabradine group (228 patients, 7.1%, 4.2%PY) than with placebo (198 patients, 6.1%, 3.6%PY).

Serious adverse event (deaths/other significant events) recorded on treatment, restricted to system organ classes and preferred terms with ≥ 1% of patients affected.

	Ivabradine (N = 3232) (NPY = 5401)			Placebo (N = 3260) (NPY = 5495)		
	n	%	%PY	n	%	%PY
All serious EAEs	**1369**	**42.4**	**25.4**	**1481**	**45.4**	**27.0**
Cardiac disorders	**853**	**26.4**	**15.8**	**939**	**28.8**	**17.1**
Cardiac failure	506	15.7	9.4	665	20.4	12.1
Atrial fibrillation	126	3.9	2.3	106	3.3	1.9
Angina unstable	113	3.5	2.1	119	3.7	2.2
Acute myocardial infarction	62	1.9	1.2	54	1.7	1.0
Myocardial infarction	57	1.8	1.1	51	1.6	0.9
Angina pectoris	51	1.6	0.9	55	1.7	1.0
Ventricular tachycardia	31	1.0	0.6	46	1.4	0.8
Infections and infestations	**178**	**5.5**	**3.3**	**198**	**6.1**	**3.6**
Pneumonia	70	2.2	1.3	65	2.0	1.2
Nervous system disorders	**110**	**3.4**	**2.0**	**154**	**4.7**	**2.8**
Ischaemic stroke	34	1.1	0.6	46	1.4	0.8
Respiratory, thoracic and mediastinal disorders	**90**	**2.8**	**1.7**	**113**	**3.5**	**2.1**
Chronic obstructive pulmonary disease	35	1.1	0.7	33	1.0	0.6
Surgical and medical procedures	**82**	**2.5**	**1.5**	**95**	**2.9**	**1.7**
Gastrointestinal disorders	**70**	**2.2**	**1.3**	**87**	**2.7**	**1.6**
Vascular disorders	**68**	**2.1**	**1.3**	**75**	**2.3**	**1.4**
Investigations	**65**	**2.0**	**1.2**	**62**	**1.9**	**1.1**
Neoplasms benign, malignant and unspecified	**64**	**2.0**	**1.2**	**56**	**1.7**	**1.0**
Injury, poisoning and procedural complications	**54**	**1.7**	**1.0**	**63**	**1.9**	**1.2**
Metabolism and nutrition disorders	**42**	**1.3**	**0.8**	**52**	**1.6**	**1.0**
Diabetes mellitus inadequate control	23	0.7	0.4	33	1.0	0.6
Renal and urinary disorders	**40**	**1.2**	**0.7**	**32**	**1.0**	**0.6**
Hepatobiliary disorders	**26**	**0.8**	**0.5**	**36**	**1.1**	**0.7**

Deaths

A total of 1074 fatal events occurred during the study, with 510 deaths (15.8%) in the ivabradine group and 564 deaths (17.3%) with placebo. While on treatment, 400 (12.4%) and 428 (13.1%) deaths occurred in the ivabradine and placebo arms respectively. An additional 246 fatal events

occurred after treatment cessation, 110 additional deaths in the ivabradine group and 136 additional deaths with placebo. The difference between the treatment groups in the additional events was largely due to sudden death (ivabradine: 17 additional deaths, placebo: 27) and sudden cardiac death (ivabradine: 13 additional deaths, placebo: 20).

Table 12: Deaths from any causes linked to on-treatment events by SOC for ≥0.4% of patients

	Ivabradine (N = 3232) (NPY = 5401)			Placebo (N = 3260) (NPY = 5495)		
	n	%	%PY	n	%	%PY
All	**400**	**12.4**	**7.4**	**428**	**13.1**	**7.8**
General disorders and administration site conditions	188	5.8	3.5	190	5.8	3.5
Sudden death	111	3.4	2.1	119	3.7	2.2
Sudden cardiac death	73	2.3	1.4	68	2.1	1.2
Cardiac disorders	147	4.6	2.7	148	4.5	2.7
Cardiac failure	69	2.1	1.3	91	2.8	1.7
Myocardial infarction	26	0.8	0.5	14	0.4	0.3
Acute myocardial infarction	20	0.6	0.4	12	0.4	0.2
Cardiogenic shock	8	0.3	0.2	12	0.4	0.2
Nervous system disorders	21	0.7	0.4	27	0.8	0.5
Infections and infestations	9	0.3	0.2	14	0.4	0.3
Neoplasms benign, malignant and unspecified	14	0.4	0.3	16	0.5	0.3
Respiratory, thoracic and mediastinal disorders	7	0.2	0.1	13	0.4	0.2

Safety in special populations

Patients >75 years of age

The overall incidence of EAEs was similar in the ivabradine group (289 patients, 78.8%) and in the placebo group (274 patients, 77.6%), although there was a slightly higher incidence of AEs related to cardiac disorders (ivabradine 184 patients, 50.1%; placebo 167 patients, 47.3%), including bradycardia, which was more common with ivabradine (27 patients, 7.4%) than with placebo (5 patients, 1.5%). The incidence of AEs related to heart failure was lower with ivabradine (107 patients, 29.1%) than with placebo (120 patients, 34.0%), and the incidence of atrial fibrillation was similar in the two groups (ivabradine: 43 patients, 11.7%; placebo: 41 patients, 11.6%).

Discontinuation due to adverse events

EAEs leading to treatment withdrawal occurred more frequently in the ivabradine group (467 patients, 14.5%) than with placebo (416 patients, 12.8%) The difference was mainly due to events in the system organ classes cardiac disorders (ivabradine: 303 patients, 9.4%; placebo: 270 patients, 8.3%) and investigations (ivabradine: 34 patients, 1.1%; placebo: 11 patients, 0.3%). Among individual preferred terms, the difference was largely due to atrial fibrillation, in line with the protocol-directed withdrawal in case of sustained atrial fibrillation, and to bradycardia and heart rate decreased. On the other hand, withdrawals were slightly less frequent with ivabradine for cardiac failure and ventricular tachycardia.

Table 13: Discontinuation due to adverse events in at least 5 patients in either group

System Organ Class	Ivabradine (N = 3232) (NPY = 5401.1)				Placebo (N = 3260) (NPY = 5495.3)			
	NEAE	n	%	%PY	NEAE	n	%	%PY
All	**467**	**467**	**14.5**	**8.7**	**421***	**416***	**12.8**	**7.6**
Cardiac disorders	**303**	**303**	**9.4**	**5.6**	**272**	**270**	**8.3**	**4.9**
Atrial fibrillation	135	135	4.2	2.5	113	113	3.5	2.1
Cardiac failure	64	64	2.0	1.2	79	79	2.4	1.4
Bradycardia	20	20	0.6	0.4	5	5	0.2	0.1
Atrial flutter	13	13	0.4	0.2	8	8	0.3	0.2
Acute myocardial infarction	9	9	0.3	0.2	6	6	0.2	0.1
Ventricular tachycardia	7	7	0.2	0.1	15	15	0.5	0.3
Ventricular extrasystoles	5	5	0.2	0.1	6	6	0.2	0.1
Ventricular fibrillation	6	6	0.2	0.1	4	4	0.1	0.1
Atrioventricular block complete	6	6	0.2	0.1	2	2	0.1	< 0.1
Sick sinus syndrome	6	6	0.2	0.1	-	-	-	-
Myocardial infarction	5	5	0.2	0.1	5	5	0.2	0.1
Atrioventricular block third degree	5	5	0.2	0.1	2	2	0.1	< 0.1
Investigations	**34**	**34**	**1.1**	**0.6**	**11**	**11**	**0.3**	**0.2**
Heart rate decreased	28	28	0.9	0.5	5	5	0.2	0.1
Nervous system disorders	**26**	**26**	**0.8**	**0.5**	**38**	**38**	**1.2**	**0.7**
Ischaemic stroke	10	10	0.3	0.2	12	12	0.4	0.2
Cerebrovascular accident	2	2	0.1	< 0.1	7	7	0.2	0.1
Gastrointestinal disorders	**21**	**21**	**0.7**	**0.4**	**20**	**20**	**0.6**	**0.4**
Infections and infestations	**10**	**10**	**0.3**	**0.2**	**12**	**11**	**0.3**	**0.2**
Eye disorders	**10**	**10**	**0.3**	**0.2**	**6**	**6**	**0.2**	**0.1**
Phosphenes	7	7	0.2	0.1	3	3	0.1	0.1
Surgical and medical procedures	**11**	**11**	**0.3**	**0.2**	**7**	**7**	**0.2**	**0.1**
Neoplasms benign, malignant and unspecified	**9**	**9**	**0.3**	**0.2**	**11**	**11**	**0.3**	**0.2**
General disorders and administration site conditions	**9**	**9**	**0.3**	**0.2**	**6**	**6**	**0.2**	**0.1**
Vascular disorders	**5**	**5**	**0.2**	**0.1**	**4**	**4**	**0.1**	**0.1**
Renal and urinary disorders	**5**	**5**	**0.2**	**0.1**	**3**	**3**	**0.1**	**0.1**
Injury, poisoning and procedural complications	**5**	**5**	**0.2**	**0.1**	**2**	**2**	**0.1**	**< 0.1**
Skin and subcutaneous tissue disorders	**4**	**4**	**0.1**	**0.1**	**8**	**8**	**0.3**	**0.2**
Respiratory, thoracic and mediastinal disorders	**2**	**2**	**0.1**	**< 0.1**	**8**	**8**	**0.3**	**0.2**

2.4.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

The safety profile shown in this trial was consistent with the safety profile already demonstrated in previous trials. The higher incidence of adverse events is limited to the typical adverse events associated with ivabradine. In addition, the MAH was asked to provide the analysis excluding cardiac failure in their overall presentation of the adverse events, as cardiac failure is part of the efficacy endpoints. The observed reduction in cardiac failure affected the presentation of adverse effects in favour of the active treatment. The MAH provided data on the adverse event rates excluding those attributable to heart failure. This resulted in still slightly higher adverse event rates in patients treated with ivabradine than with placebo. However, now more cardiac events were reported in ivabradine users compared to placebo, which can be attributed to the more frequently reported events of atrial fibrillation and bradycardia. This was also described in section 4.8 of the SmPC. Although, the adverse event rate showed after this analysis a slightly different picture in the opinion of the CHMP it didn't affect the benefit-risk of the product.

Atrial fibrillation (AF) and bradycardia are known adverse effects of ivabradine. AF was reported more frequently with ivabradine (8.3%, 4.9%PY) than with placebo (6.7%, 4.0%PY). The MAH reported that these patients tended to be older (mean age 64.3 years), more likely to be in NYHA class III or IV and to have a previous history of atrial fibrillation (in approximately one quarter of these patients) than the overall population. In provided explanations the MAH has satisfactorily addressed the possible mechanism that may lead to a higher incidence of AF and excluded that this increased numbers of AF led to a higher risk of stroke or sudden death. The CHMP agreed nevertheless on the inclusion of AF as an identified risk in the RMP and mentioning it in sections 4.4 and 4.8 of the SmPC.

The vision related adverse event of phosphenes was not specifically asked for within the trial so incidence was lower as observed in other trials.

Safety in patients with intraventricular conduction defects and desynchronised ventricular action were added as missing information to the RMP.

In the tabulations in the SHIFT study report the reported cases of ventricular fibrillation and myocardial infarction (with fatal outcome but not the total of cases) seemed more common in the ivabradine group. The MAH has demonstrated that there was no increased rate of hospitalisations or deaths for myocardial infarctions based on adjudicated cases. Ventricular fibrillation as (a terminal event) may be difficult to document and may be related to several underlying causes. The approach of the MAH to categorize the verified terminal ventricular fibrillations under category sudden cardiac deaths was considered clinically sound. The MAH has also pointed out that if looking at the number of cases of ventricular tachycardia and ventricular fibrillation together, the incidence is similar in both treatment groups.

These were also known adverse events limiting the use of ivabradine, however, for bradycardia this was at a relative small incidence as patients were on a high HR of more than 70 bpm at baseline. Ventricular arrhythmias were not observed more frequently in the ivabradine group. However, the most serious, ventricular fibrillation, was numerically increased. An increased occurrence of ventricular fibrillation (24 (0.7%) versus 12 (0.4%), for ivabradine versus placebo) did not result in a higher rate of sudden death or sudden cardiac death on or off treatment with ivabradine in the study population and is probably coincidental due to the small number of patients.

In hypertensive patients, blood pressure inadequately controlled was slightly more frequent in the ivabradine group (228 patients, 7.1%, 4.2%PY) than with placebo (198 patients, 6.1%, 3.6%PY).

The MAH provided a further discussion on the reasons for the high incidence of uncontrolled BP observed in the SHIFT trial. The most likely reason was that a hemodynamically less stable and an older population was recruited in SHIFT compared to previous trials with ivabradine. Events followed specifically when blood pressure medication had been modified shortly before the event. The CHMP supported therefore to include uncontrolled BP as an identified but not as a potential risk in the RMP. In addition, the SmPC warns that CHF patients treated with ivabradine in need of BP treatment modification should be carefully monitored. Since, BP increases were transient and these patients benefitted equally from the treatment with ivabradine (similar/better effect on the primary endpoint) no further concerns remain. Uncontrolled blood pressure was also added as a common ADR in section 4.8 of the SmPC.

For the subgroup of patients with very low cardiac output / NYHA IV class heart failure safety has not been established conclusively, as these patients were included in the population of NYHA III + NYHA IV. A subgroup analysis was performed and the CHMP agreed to lift the current contraindication for NYHA class IV patients in the SmPC. A higher incidence of adverse events was reported in NYHA IV patients. However, in comparison to placebo, the safety profile was not different. This was also true for adverse events short after treatment initiation. This is reassuring, patients in NYHA IV often have high

heart rates to compensate for poor ventricular function, and it would be this group that would stand to benefit most from a HR lowering therapy. In view of the very small group of patients with NYHA class IV in the SHIFT trial it was decided to include a warning in the SmPC for stable NYHA IV patients. No data have been collected for unstable NYHA IV patients. Unstable heart failure was an exclusion criterion and therefore it is mentioned in the list of contraindications.

When looking more in detail in the safety profile, specific differences can be identified. More cases with ivabradine were identified for bradycardia related events, BP inadequately controlled, AF, and phosphenes. These are all adverse events typically associated with the use of ivabradine except for blood pressure inadequately controlled. This last adverse event was not frequently adverse event associated with treatment. Also discontinuations due to adverse events were higher with ivabradine. This can specifically be related to known safety issues of ivabradine. Symptomatic bradycardia is indeed a side effect limiting the use of ivabradine, however, it occurred relatively infrequently due to the prespecified baseline HR > 70 bpm. AF was the main cardiac associated adverse event leading to treatment discontinuation. In this heart failure population AF appears to be more frequently associated with ivabradine (8.3%) than with placebo (6.7%) treatment. Second and third degree AV block, and sick sinus syndrome were also identified as very rare adverse events.

2.4.2. Conclusions on the clinical safety

The CHMP considers the safety profile of ivabradine demonstrated in the SHIFT trial as consistent with the safety profile already demonstrated in previous trials.

2.5. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure. Based on the safety conclusions, the CHMP requested the submission of an updated Risk Management Plan within this procedure.

Table 1. Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety issues	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Identified risks		
Bradycardia	- Assessment of cardiac rhythm through systematic 12-lead ECG recordings and collection of adverse events at each scheduled and unscheduled visits in all ongoing or planned interventional clinical studies - Registration and *ad hoc* follow-up of spontaneous cases with reinforcement of the routine Pharmacovigilance procedures from prescription sources: all excessive bradycardia (<40 bpm or symptomatic) reported to the Company will be considered as important medical events and will be reported to the local authority and for non-EU cases to the EMA. - Further characterise the risk in a large population of CAD patients with high risk and at dose up to 10 mg bid in study CL3-083 (SIGNIFY, N=11330) - Routine pharmacovigilance	- Information included in the following sections of the SmPC: 4.1; 4.2; 4.3, 4.4, 4.8
Phosphenes/blurred vision	- Routine pharmacovigilance - Documentation of the long-term (3 years) ophthalmic safety of ivabradine (up to 7.5 mg *b.i.d.*) through extensive ophthalmic testings including electroretinogram (ERG), static and kinetic visual fields, colour vision test, distant visual acuity, tonometry and clinical examination (anterior segment and *fundi oculi*) in a double-blind, randomised, placebo-controlled study in patients with chronic stable angina pectoris (n=300) (Study CL3-067) (Follow-Up Measure)	- Information included in the following sections of the SmPC: 4.7, 4.8
2nd and 3rd degree Atrioventricular blocks (AVB II and III)	- Detection of AVB through systematic 12-lead ECG recordings and collection of adverse events at each scheduled and unscheduled visits in all ongoing or planned interventional clinical studies - Registration and *ad hoc* follow-up of spontaneous cases with reinforcement of the routine Pharmacovigilance procedures from prescription sources: all 2nd or 3rd degree AVB reported to the Company will be considered as important medical events and will be reported to the local authority and for non-EU cases to the EMA. - Further characterise the risk in a large population of CAD patients with high risk and at dose up to 10 mg bid in study CL3-083 (SIGNIFY, N=11330) - Routine pharmacovigilance	- Information included in the following sections of the SmPC: 4.3, 4.4, 4.8
Increase in blood pressure in hypertensive patients	- Assessment of systolic and diastolic blood pressure through systematic measurements and collection and precise documentation of adverse events at each scheduled and unscheduled visits in all ongoing or planned interventional clinical studies - Further characterise the risk in a large population of CAD patients at dose up to 10 mg bid in study CL3-083 (SIGNIFY, N=11330) - Routine Pharmacovigilance	- Information included in the following section of the SmPC: 4.4, 4.8
Atrial fibrillation (AF)	- Detection of atrial fibrillation through systematic 12-lead ECG recordings and collection of adverse events at each scheduled and unscheduled visits in all ongoing or planned interventional clinical studies - Registration and *ad hoc* follow-up of spontaneous cases with reinforcement of the routine	- Information included in the following section of the SmPC: 4.4, 4.8

	Pharmacovigilance procedures from prescription sources: all AF reported to the Company will be considered as important medical events and will be reported to the local authority and for non-EU cases to the EMA. - Further characterise the risk in a large population of CAD patients with high risk and at dose up to 10 mg bid in study CL3-083 (SIGNIFY, N=11330) - Routine pharmacovigilance	
Potential risks		
Supra-ventricular tachyarrhythmia (SVT) other than AF	- Detection of SVT through systematic 12-lead ECG recordings and collection of adverse events at each scheduled and unscheduled visits in all ongoing or planned interventional clinical studies - Registration and *ad hoc* follow-up of spontaneous cases with reinforcement of the routine Pharmacovigilance procedures from prescription sources: all SVT reported to the Company will be considered as important medical events and will be reported to the local authority and for non-EU cases to the EMA. - Further characterise the risk in a large population of CAD patients with high risk and at dose up to 10 mg bid in study CL3-083 (SIGNIFY, N=11330) - Routine pharmacovigilance	- Information included in the following section of the SmPC: 4.4
Immune disorders	- Collection of adverse events at each scheduled and unscheduled visits in all ongoing or planned interventional clinical studies - Further characterise the risk in a large population of CAD patients at dose up to 10 mg bid in study CL3-083 (SIGNIFY, N=11330) - Routine pharmacovigilance	- Information included in the following section of the SmPC: 4.3
Missing or limited information		
Children and adolescents (< 18 years old)	- Routine pharmacovigilance	- Information included in the following section of the SmPC: 4.1, 4.2,
Pregnant and lactating women	- Routine pharmacovigilance	- Information included in the following section of the SmPC: 4.3, 4.6
Severe hepatic insufficiency	- Routine pharmacovigilance	- Information included in the following section of the SmPC: 4.2, 4.3
Severe renal impairment	- Routine pharmacovigilance	- Information included in the following section of the SmPC: 4.2
Chronic heart failure patients with intra-ventricular conduction defects	- Routine pharmacovigilance - Further characterise the safety in patients with intraventricular conduction defects in the future studies in CHF.	- Information included in the following section of the SmPC: 4.4

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.6. Changes to the Product Information

The CHMP agreed to the changes to the Product Information (PI), which are described below:

Section 4.1 Therapeutic indications

"Treatment of coronary artery disease

Symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm. Ivabradine is indicated :
- in adults unable to tolerate or with a contra-indication to the use of beta-blockers
- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is > 60 bpm.

Treatment of chronic heart failure
Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy, including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. (see section 5.1)."

4.2 Posology and method of administration

"Treatment of chronic heart failure
The treatment has to be initiated only in patient with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic heart failure.
The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension.
If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.
If during treatment, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. If heart rate increases persistently above 60 beats per minute at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5 mg twice daily or 5 mg twice daily.
Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist (see section 4.4)."

"…Special population

Elderly

~~Since ivabradine has been studied in the limited number of~~ In patients aged 75 years or more, a lower starting dose should be considered for these patients (2.5 mg twice daily i.e. one half 5 mg tablet twice daily) before up-titration if necessary."

4.3 Contraindications

- "…
- Unstable or acute heart failure
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
- ~~Heart failure patients with NYHA functional classification III-IV"~~

4.4 Special warnings and precautions for use

"Special warnings

Cardiac arrhythmias

The risk of developing atrial fibrillation may be higher in chronic heart failure patients treated with ivabradine. Atrial fibrillation has been more common in patients using concomitantly amiodarone or potent class I anti-arrhythmics.
Chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be monitored closely."

"*Chronic heart failure*
~~*Heart failure must be appropriately controlled before considering ivabradine treatment. The use of ivabradine is contra-indicated in heart failure patients with NYHA functional classification III-IV and*~~

~~*in heart failure patients with NYHA functional classification I-II (see section 4.3).*~~ *Chronic heart failure*
Heart failure must be stable before considering ivabradine treatment. Ivabradine should be used with caution in heart failure patients with NYHA functional classification IV due to limited amount of data in this population"

"Hypertensive patients requiring blood pressure treatment modifications.

In the SHIFT trial more patients experienced episodes of increased blood pressure while treated with ivabradine (7.1%) compared to patients treated with placebo (6.1%). These episodes occurred most frequently shortly after blood pressure treatment was modified, were transient, and did not affect the treatment effect of ivabradine. When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval (see section 4.8)."

4.5 Interaction with other medicinal products and other forms of interaction

"Other concomitant use

In pivotal phase III clinical trials the following medicinal products ~~were not restricted and~~ ~~therefore~~ were routinely combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, anti-aldosterone agents, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet medicinal products."

4.7 Effects on ability to drive and use machines

A specific study to assess the possible influence of ivabradine on driving performance has been performed in healthy volunteers where no alteration of the driving performance was evidenced. However, in post-marketing experience, cases of impaired driving ability due to visual symptoms have been reported. Ivabradine may cause transient luminous phenomena consisting mainly of phosphenes (see section 4.8). The possible occurrence of such luminous phenomena should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur, especially when driving at night. Ivabradine has no influence on the ability to use machines.

4.8 Undesirable effects

"~~Approximately 2900 patients have been treated with ivabradine in phase II-III studies.~~ Ivabradine~~Procoralan~~ has been studied in clinical trials involving nearly ~~5~~14,000 participants. ~~Approximately 2,900 patients have been treated with ivabradine in phase II-III studies~~. The most common adverse reactions with ivabradine, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product.
….

System Organ Class	Frequency	Preferred Term
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Metabolism and nutrition disorders	Uncommon	Hyperuricaemia
Nervous system disorders	Common	Headache, generally during the first month of treatment
		Dizziness, possibly related to bradycardia
	Uncommon*	Syncope, possibly related to bradycardia
Eye disorders	Very common	Luminous phenomena (phosphenes)
	Common	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Common	Bradycardia
		AV 1st degree block (ECG prolonged PQ interval)
		Ventricular extrasystoles
	Uncommon	Palpitations, supraventricular extrasystoles
	Very rare	Atrial fibrillation
		AV 2nd degree block, AV 3rd degree block
		Sick sinus syndrome
Vascular disorders	Common	Uncontrolled blood pressure
	Uncommon*	Hypotension, possibly related to bradycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Uncommon	Nausea
		Constipation
		Diarrhoea
Skin and subcutaneous tissue disorders	Uncommon*	Angioedema
		Rash
	Rare*	Erythema

		Pruritus
		Urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps
General disorders and administration site conditions	Uncommon*	Asthenia, possibly related to bradycardia
		Fatigue, possibly related to bradycardia
	Rare*	Malaise, possibly related to bradycardia
Investigations	Uncommon	Elevated creatinine in blood

*Frequency calculated from clinical trials for adverse events detected from spontaneous report"

5.1 Pharmacodynamic properties

"Clinical efficacy and safety

The SHIFT study was a large multicentre, international, randomised double-blind placebo controlled outcome trial conducted in 6505 adult patients with stable chronic CHF (for ≥ 4 weeks), NYHA class II to IV, with a reduced left ventricular ejection fraction (LVEF ≤ 35%) and a resting heart rate ≥ 70 bpm. Patients received standard care including beta-blockers (89 %), ACE inhibitors and/or angiotensin II antagonists (91 %), diuretics (83 %), and anti-aldosterone agents (60 %). In the ivabradine group, 67% of patients were treated with 7.5 mg twice a day. The median follow-up duration was 22.9 months. Treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm from a baseline value of 80 bpm. The difference in heart rate between ivabradine and placebo arms was 10.8 bpm at 28 days, 9.1 bpm at 12 months and 8.3 bpm at 24 months.

The study demonstrated a clinically and statistically significant relative risk reduction of 18% in the rate of the primary composite endpoint of cardiovascular mortality and hospitalisation for worsening heart failure (hazard ratio: 0.82, 95%CI [0.75;0.90] – p<0.0001). apparent within 3 months of initiation of treatment. The absolute risk reduction was 4.2%. The results on the primary endpoint are mainly driven by the heart failure endpoints, hospitalisation for worsening heart failure (absolute risk reduced by 4.7 %) and deaths from heart failure (absolute risk reduced by 1.1 %).

Treatment effect on the primary composite endpoint, its components and secondary endpoints

	Ivabradine (N=3241) n (%)	Placebo (N=3264) n (%)	Hazard ratio [95% CI]	p-value
Primary composite endpoint	793 (24.47)	937 (28.71)	0.82 [0.75; 0.90]	<0.0001
Components of the composite: - CV death - Hospitalisation for worsening HF	449 (13.85) 514 (15.86)	491 (15.04) 672 (20.59)	0.91 [0.80; 1.03] 0.74 [0.66; 0.83]	0.128 <0.0001
Other secondary endpoints: - All cause death - Death from HF - Hospitalisation for any cause - Hospitalisation for CV reason	503 (15.52) 113 (3.49) 1231 (37.98) 977 (30.15)	552 (16.91) 151 (4.63) 1356 (41.54) 1122 (34.38)	0.90 [0.80; 1.02] 0.74 [0.58;0.94] 0.89 [0.82;0.96] 0.85 [0.78; 0.92]	0.092 0.014 0.003 0.0002

The reduction in the primary endpoint was observed consistently irrespective of gender, NYHA class, ischaemic or non-ischaemic heart failure aetiology and of background history of diabetes or hypertension.

In the subgroup of patients with HR ≥ 75 bpm (n=4150), a greater reduction was observed in the primary composite endpoint of 24 % (hazard ratio: 0.76, 95%CI [0.68;0.85] – p<0.0001) and for other secondary endpoints, including all cause death (hazard ratio: 0.83, 95%CI [0.72;0.96] – p=0.0109) and CV death (hazard ratio: 0.83, 95%CI [0.71;0.97] – p=0.0166). In this subgroup of patients, the safety profile of ivabradine is in line with the one of the overall population.

A significant effect was observed on the primary composite endpoint in the overall group of patients receiving beta blocker therapy (hazard ratio: 0.82, 95%CI [0.76;0.94]). In the subgroup of patients with HR ≥ 75 bpm and on the recommended target dose of beta-blocker, no statistically significant benefit was observed on the primary composite endpoint (hazard ratio: 0.97, 95%CI [0.74;1.28]) and other secondary endpoints, including hospitalisation for worsening heart failure (hazard ratio: 0.79, 95% CI [0.56;1.10]) or death from heart failure (hazard ratio: 0.69, 95% CI [0.31;1.56]).

There was a significant improvement in NYHA class at last recorded value, 887 (28%) of patients on ivabradine improved versus 776 (24%) of patients on placebo (p=0.001)."

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Overall conclusion and impact on the benefit/risk balance

Benefits

Beneficial effects

Ivabradine is a heart rate lowering agent, acting by reducing the rate of pacemaker activity in the sinoatrial node. Ivabradine has been registered for treating chronic stable angina pectoris with coronary artery disease. The MAH initially proposed to extend the indication to patients with chronic heart failure and a heart rate above 70 bpm. This was based on the SHIFT trial including patients with stable heart failure NYHA class II to IV and LVEF ≤35%. The CHMP recommended the approval of the extension of indication with modified wording: "*treatment in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy, including beta-blocker therapy, or when beta-blocker therapy is contraindicated or not tolerated.*"

The MAH demonstrated a significant and clinically relevant efficacy of ivabradine versus placebo in addition to current standard treatment on the chosen composite endpoint of cardiovascular death and hospitalization for worsening of the heart failure (HR 0.82 [95% CI 0.75-0.90], p<0.0001) with an absolute risk reduction of 4.2% during a median follow-up duration of 22.9 months. A separation of effect appeared within the first 6 months. The effect is driven by the observed difference between treatment groups in the 'hospitalisation due to worsening of the heart failure' component of the composite endpoint. Cardiovascular death showed a numerical benefit, but this change did not reach statistical significance. All other secondary endpoints showed consistent statistically significant beneficial effects of ivabradine compared to placebo, except for the – most robust - overall death endpoint where only a numerical advantage could be shown. Symptomatic improvements demonstrated similar absolute effects as the composite endpoint, although the relevance of an additional 4% of patients improving one NYHA class, or a similar proportion of physicians and patients reporting improved symptomatology appears small.

The primary endpoint preferred by *EMA Guideline on clinical investigation of medicinal products for the treatment of the heart failure [CPMP/EWP/235/95 Rev. 1]* including all-cause mortality and hospitalisation for worsening heart failure, although not defined as primary endpoint, showed a similar

beneficial effect as the MAH-defined primary endpoint. The reported hazard ratio (HR 0.82 (95% CI 0.75-0.90), p<0.0001) is exactly similar, but based on slightly higher absolute event rates in both treatment arms. All primary and secondary analyses, including all-cause mortality as a single endpoint, were in the same – beneficial – direction.

Uncertainty in the knowledge about the beneficial effects.

Objective measurements to assess the clinical status of the patients (such as 6 min. walking test, spiroergometry, or regular exercise tolerance test) were not used due to practical reasons (difficulties in a large study population). NT-Pro-BNP measurements were carried out in a subpopulation of 611 patients with beneficial trends attributable to ivabradine use but not reaching statistical significance.

Two study centres of the SHIFT study were excluded due to GCP violations. However, taking into account also the results from 46 subjects in these centres had no effect on the study outcome. A GCP inspection was performed and concluded that the SHIFT trial had been performed in accordance with the GCP guidance.

Determining HR after 5 min rest from single ECG was not considered by the CHMP very reliable. The MAH explained that two ECGs (after 5 min rest) were used for HR determinations. They were obtained during selection and inclusion visits performed with 14 days interval in between. A 24-h ambulatory ECG ancillary analysis was conducted in 602 patients participating in the main study. 524 patients had the baseline HR analysable by ambulatory monitoring and from the ECG. Correlation of the results was excellent mean HR 78.8 ± 11.0 bpm from ambulatory recordings and 78.3 ± 8.8 bpm from 12-lead ECGs at the inclusion visit.

Slight problems in blinding were noticed by the CHMP as the patients and physicians could assess the HR affected by ivabradine (a decrease by 15 bpm in general). Adjudication of the hard endpoints by the Endpoint Committee blindly of the treatment or baseline HR was not affected by any investigator bias. Reduced heart rates (up to 15 bpm) were observed in 16% to 20% of the placebo patients whereas up to 14% to 18% of the ivabradine patients had a reduction less than 5 bpm.

Despite the inclusion criteria aiming to include a broad range of symptomatic HF patients, from NYHA HF class II to IV, only 111 (1 to 2%) were in NYHA class IV. Observed benefits in these patients were, however, essentially similar with those in the overall population. These findings were robust when patients were considered with very low ejection fractions (LVEF<15%, n=124 and LVEF<20%, n=614). Although, adverse event rates were also somewhat higher in this population of *stable* NYHA IV the benefit / risk seems not different from that of the NYHA II-III patient population. In NYHA IV, patients often have high heart rates to compensate for poor ventricular function, and it is this group that would stand to benefit most from ivabradine therapy. Following the results of the SHIFT study the CHMP recommended removing from the SmPC the previous general contraindication for patients in NYHA III and IV classes. An appropriate warning that only few NYHA IV patients were included in the study was mentioned in section 4.4 of the SmPC. Patients in SHIFT study had to be in stable clinical condition with regards to CHF symptoms. In line with beta blockers approved for treatment of heart failure, patients with unstable or in acute heart failure were added to the list of contraindications.

Relatively young patients (60±11 years) were included in the SHIFT trial. Subgroup analyses in patients over 65 and 70 years of age showed some inconsistent effects on the primary endpoint. However, when these analyses were limited to patients with baseline HR≥ 75 bpm consistent positive effects on the primary (and secondary) endpoints were observed that were irrespective of the age cut-off chosen.

Around 10% of the SHIFT-study population took potent anti-arrhythmics. 188 patients received amiodarone (class III) at randomisation and 415 patients started amiodarone during the study (total

n=603). 52 patients received either propafenone (n=13, class Ic), mexiletine (n=5, class Ib), quinidine (n=4, class Ia), or procainamide (n=2, class Ia). Further 32 patients were at least once administered lidocaine (class Ib). In this subpopulation, the incidence of the PCE (primary composite endpoint) was 36.2% in the ivabradine group and 44.0% in the placebo group, RR 0.72, 95% CI 0.56 to 0.93, p=0.017. For hospitalisations from heart failure the figures were 21.6% vs. 30.8%, RR 0.60, 95% CI 0.44 to 0.82, p=0.0014, and for death from heart failure 8.5% vs. 13.2%, RR 0.59, 95% CI 0.36 to 0.97, p=0.038. Atrial fibrillation was more common in this subpopulation and use of ivabradine increased it further. No additional safety concerns could be observed. Thus, the benefit/risk ratio of ivabradine was considered by the CHMP favourable in patients taking amiodarone or potent class I anti-arrhythmics.

In SHIFT a similar dosing scheme as included in the SmPC was used, where patients were up- or down-titrated to 7.5 mg or 2.5 mg BID, respectively based on tolerability (especially HR<50 bpm or bradycardia). Sixty percent of patients reached the maximal dose, while 40% of patients ultimately reached maintenance doses of 2.5 or 5 mg. Patients reaching 7.5 mg doses had higher baseline heart rates compared to the low maintenance dose patients. Both strategies resulted in considerable reductions in heart rate (14.9 and 12.6 bpm) resulting in on therapy mean heart rates (last recorded HR) that remained lower in low dose patients (61.2 bpm) than in high dose patients (68.8 bpm). Finally, no difference was observed in effect size for patients on lower maintenance doses, 2.5 or 5 mg, versus those on a 7.5 mg dose. These results are in line with the McAllister paper [2009 Ann Int Med] that showed that heart rate control may be more relevant than achieving target beta blocker dose. These data support the proposed flexible dosing scheme that was introduced in the SmPC.

Pre specified subgroup analyses showed consistent effects of ivabradine. However, the pre specified subgroup of patients with the higher baseline HR (≥77 bpm) showed the greatest benefit (p for interaction 0.029). This is in line with the proposed MoA, but leads to the question what baseline HR is the most appropriate cut-off. In the published study of Böhm (Lancet 2010) the effect of ivabradine treatment increases with HR, only improves from a null effect above a baseline HR of 75. In its response document the MAH presented the SHIFT data for 4150 patients with heart rate ≥ 75 bpm, i.e. 65% of the overall population. Their demographic data and baseline characteristics did not differ substantially from the randomized set and did not show relevant differences between the treatment groups. In these patients, the effect of ivabradine was larger than in the overall population, with a significant improvement of all outcomes. In comparison to placebo, the PCE was reduced by 24% (hazard ratio 0.76, 95% CI [0.68;0.85] p<0.0001), cardiovascular death by 17% (hazard ratio 0.83, 95% CI [0.71;0.97] p= 0.0166), and hospitalization for worsening heart failure by 30% (hazard ratio 0.70 95% CI [0.61;0.80] p<0.0001). All cause death was also reduced by 17% (hazard ratio 0.83 95% CI [0.72;0.96] p=0.0109). In the above described pre specified subgroup analyses, but now confined to patients with heart rate ≥ 75 bpm, consistent findings were shown. Based on these results, the company is proposing to amend the indication to treatment of patients whose heart rate is ≥ 75 bpm which is acceptable.

It is to be noted that in patients with intraventricular conduction defects (LBBB, n=865, RBBB n=177) the efficacy of ivabradine was reduced regarding the PCE and all secondary endpoints. CHF patients with ventricular dyssynchrony may not benefit from reduction of HR.

Concomitant use of beta-blockers reduces the effect size, albeit that no statistical significant interaction was observed in the pre specified subgroup analysis (yes/no beta-blocker use). Efficacy of ivabradine treatment seems to be inversely related to beta-blocker dose used in the SHIFT trial. A significant effect was observed on the primary composite endpoint in the overall group of patients receiving beta blocker therapy (hazard ratio: 0.82, 95%CI [0.76;0.94]). In the subgroup of patients with HR ≥ 75 bpm and on the recommended target dose of beta-blocker, no statistically significant benefit was observed on the primary composite endpoint (hazard ratio: 0.97, 95%CI [0.74;1.28]) and

other secondary endpoints, including hospitalisation for worsening heart failure (hazard ratio: 0.79, 95% CI [0.56;1.10]) or death from heart failure (hazard ratio: 0.69, 95% CI [0.31;1.56]). In addition, only 26% of patients were on target dose and 56% of patients received 50% or more of target beta blocker dose. This may be in line with clinical practice and despite effort of SHIFT investigators to optimize background therapy. The principal reason for not achieving beta-blocker target dose was hypotension that was reported as reason for half of the patients not reaching target dose.

Other – sometimes overlapping – reasons were recorded for not being on target beta-blockers dose. The main reasons were also in SHIFT: hypotension, older age, lower LVEF, NYHA III/IV and other reasons similar to those reported in previous CHF trials and clinical practice surveys. The relation between a patient's CYP2D6 status and reaching target beta-bloker dose in an individual patient could not be fully established. Genotyping has not been performed, therefore it is unknown whether patients were poor metabolisers. The MAH showed that across all beta blockers the ratio of achieved BB dose over target beta blocker dose was approximately 0.5. This was irrespective of the role of CYP2D6 in their metabolism. Taking these observations together it seems unlikely that inhibition – drug induced or genetic – of the CYP2D6 iso-enzyme played a major role in patients not reaching target BB dose.

In the published study of Böhm (Lancet 2010), HR was divided into quintiles to evaluate the relation of HR to clinical outcome in the SHIFT trial. Beta-blockers were prescribed more in the lowest quintile compared to the highest quintile, ranging from 93% in the lowest quintile (70 to 72 bpm) and 82% in the highest quintile (≥87 bpm) of patients [Böhm 2010 Lancet]. Beta-blocker doses were somewhat lower in the higher heart rate quintile groups, with hypotension in these groups more frequently reported as a reason for not reaching target BB dose.

The need to initiate a beta blocker or increase the beta blocker dose during the study was slightly higher in patients taking placebo. The reasons for such actions were not elucidated individually, but they may have to do with optimal HR control. The assumption that increasing the dose of beta blocker improves HR control and would cause more benefit for the placebo patients than ivabradine patients, only strengthens the observed benefit of ivabradine in the primary and secondary efficacy outcomes.

Also when patients used concomitant digoxin (with or without concomitant beta blocker at any dose) ivabradine lowered HR consistently. In these patients, however, the efficacy results seemed not as favourable for ivabradine as in the entire randomised set. Hospitalisations for heart failure were reduced in a statistically significant fashion. The efficacy of ivabradine on top of beta blocker at target dose and concomitant digoxin was comparable to that of placebo. It is a reassuring finding, that bradycardia was not more common in patients taking both digoxin and ivabradine (or even beta blocker on top of that). Atrial fibrillation was seen more in the ivabradine patients also in these subgroup analyses. Since only very few patients were treated concomitantly with target beta-blockers dose and digoxin, further analyses in the new target population with higher baseline HR are not meaningful. Individual approach to control the HR of CHF patients can be safely accomplished using ivabradine on top of routine digoxin (and beta blocker) therapy with their different modalities of pharmacological action.

Risks

Unfavourable effects

The safety profile shown in this trial does not show many surprises as it is consistent with the safety profile already demonstrated in previous trials. The higher incidence of adverse events is limited to the typical adverse events associated with ivabradine. The observed reduction in cardiac failure affects, however, the presentation of adverse effects in favour of the active treatment. Excluding these adverse events, cardiac adverse events are slightly higher in the ivabradine group mainly resulting from a

higher incidence of atrial fibrillation and bradycardia adverse events. These are known typical pro-arrhythmic events associated with ivabradine. Also, second and third degree AV block, and sick sinus syndrome were reported at a low rate. Atrial fibrillation was reported more frequently with ivabradine (8.3%, 4.9%PY) than with placebo (6.7%, 4.0%PY) and have also been added in section 4.8 of the SmPc. These patients tended to be older (mean age 64.3 years), more likely to be in NYHA class III or IV and to have a previous history of atrial fibrillation than the overall population. The higher incidence of atrial fibrillation was not associated with increased risk of stroke or sudden death, or with a reduction in the efficacy of ivabradine. Nevertheless the higher incidence in CHF versus angina population is mentioned in section 4.4 of the SmPC. In the currently targeted population bradycardia led only in a relatively few instances to treatment discontinuation in view of the high heart rate at baseline, initially 70 and now 75 bpm and possible also due to the flexible dose titration scheme. Ventricular arrhythmias were not observed more frequently in the ivabradine group. However, the most serious, ventricular fibrillation, was numerically increased, but did not result in more sudden cardiac deaths or sudden deaths.

Uncertainty in the knowledge about the unfavourable effects

In SHIFT patients were not specifically queried as whether they experienced the known ivabradine vision related adverse event of phosphenes and the reported incidence was therefore lower than in previous trials.

The only unexpected adverse event was "blood pressure inadequately controlled"; i.e. increased in blood pressure in hypertensive patients. This adverse event was more often reported in the ivabradine group (7.1%, 4.2%PY) than in the placebo group (6.1%, 3.6%PY). These events had also been reported in previous ivabradine trials, albeit at lower rates. The most likely reasons were that a less hemodynamically stable and an older population in SHIFT was recruited compared to previous trials. Events followed specifically when blood pressure medication had been modified shortly before the event. Since, blood pressure increases were transient and these patients benefitted equally from treatment with ivabradine this issue was included in the warning and undesirable effect sections of the SmPC and added as an identified risk in the RMP.

For the subgroup of patients with very low cardiac output / NYHA IV class heart failure safety data do not show an essentially different profile as for the safety of the overall population, although adverse events occurred in general more than in the overall population in both the ivabradine as well as the placebo group. However, this is still based on a limited subgroup and therefore caution is still warranted which is reflected in the SmPC.

Discussion on the benefit-risk balance

A beneficial effect for ivabradine has been demonstrated in patients with heart failure, low LVEF and high heart rate. An appropriate heart rate cut off at baseline has been identified as ≥ 75 bpm, that leads to a positive benefit/risk across all pre specified subgroups. The treatment effect is attenuated in patients on target beta-blocker dose, but clinically relevant changes have been observed on secondary endpoints in patients with heart rates ≥75 bpm.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to add the treatment in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy, including beta-blocker therapy, or when beta-blockers are contraindicated or not tolerated. The MAH proposed the update of sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8 and 5.1 of the SmPC in order to extend the indication and to introduce new information following the results of the SHIFT study. The Package Leaflet was proposed to be updated in accordance.

In addition it was proposed to delete version of the RMP from Annex IIB.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

Risk management system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

The PSUR cycle for the product will follow a half-yearly cycle until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.