European Medicines Agency

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SCIENTIFIC DISCUSSION
FOR
Corlentor

International non-proprietary name/Common name:
ivabradine

Procedure No. EMEA/H/C/598/II/0010

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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I. SCIENTIFIC DISCUSSION

I.I Introduction

Procoralan and Corlentor have been registered through a Centralised Procedure in 2005 with the Netherlands being the Rapporteur 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 heart rate lowering agent, acting by reducing the rate of pacemaker activity in the sinoatrial node. 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 is sought.

Anti-anginal therapy is intended in patients with stable angina for 1) symptom relief, 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 new therapeutic class of anti-ischaemic agents with a new mode of action; with specific negative chronotropic action. This new 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.

In this procedure, the MAH is submitting a type II variation to amend the indication to:

"Symptomatic treatment of chronic stable angina pectoris in ***coronary artery disease*** *patients with normal sinus rhythm.* ***Ivabradine is indicated in patients already treated with a beta-blocker,*** *or unable to tolerate or with a contraindication to the use of beta-blockers****."***

The requested variation is based on study **CL3-057** that was already ongoing during the Centralised Procedure in 2005. The study is a 4-month randomised double blind parallel-group international multicentre study, evaluating the anti-anginal efficacy and safety of oral administration of ivabradine compared to placebo on top of background therapy with atenolol in patients with stable angina pectoris. The results of that study were presented and assessed earlier when it was submitted as a follow-up measure (FUM) [EMEA/H/C/597-598/FUM/009] in the Summer of 2008.
At that time, no SPC claim was made by the MAH, as it was a Follow-Up Measure.

In the following part of this report, the study CL3-057 is discussed and the MAH argumented that a suitable patient population and dose of atenolol were used in study CL3-057.

I.2 Clinical aspects

I.2.1 Clinical study CL3-057

I.2.1.1 Study design and objectives

Study objectives:
The primary objective of this study was to demonstrate the superior efficacy of ivabradine (5 mg *b.i.d.* then 7.5 mg *b.i.d.* given orally for 2 months each) *versus* placebo, when given in combination with atenolol (50 mg daily), in patients with stable chronic effort angina pectoris who still present a positive exercise tolerance test (ETT), with or without symptomatic angina in everyday life. The primary efficacy criterion was the improvement between baseline and end of 4 months of treatment (M4) in the total exercise duration (TED) on a treadmill ETT according to the standard Bruce protocol at the

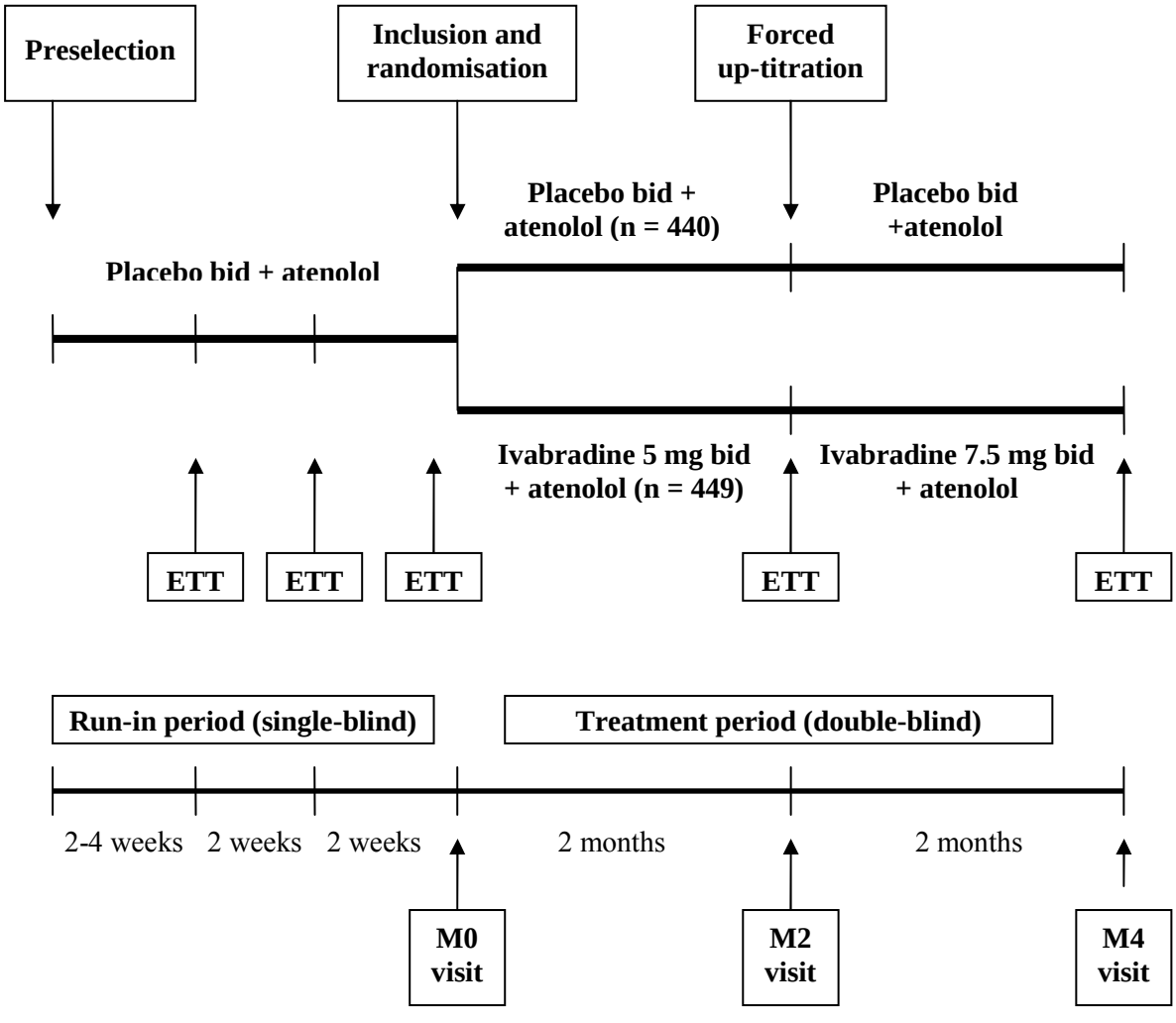
trough of ivabradine and atenolol activity (*i.e.* 12 ± 1 hours and 24 ± 2 hours post-dosing, respectively) on centralised reading values.

The secondary objectives were:
To demonstrate the superior efficacy of ivabradine on:

- The improvement between baseline and end of treatment (M4) of the other ETT criteria at the trough of drug administration.
- The improvement between baseline and end of the first 2 month treatment period (M2) of all ETT criteria at the trough of drug administration.
- To compare the safety and tolerance profile of ivabradine (5 mg *b.i.d.* then 7.5 mg *b.i.d.*) to placebo when given in combination with atenolol (50 mg *o.d.*)

Measuring efficacy
ETTs were performed 3 times during the run-in and twice under treatment, at M2 and M4. The following parameters were measured: Total exercise duration (TED, s) (primary criterion), time to 1 mm ST segment depression (TST, s), time to angina onset (TAO, s), time to limiting angina (TLA, s), heart rate (HR) at rest and at peak of exercise (bpm), rate pressure product (RPP) at rest and at peak of exercise (bpm x mmHg), and reason for stopping exercise.

Study Design:
A randomised double-blind placebo-control parallel-group international multicentre study. After a run-in period lasting 6 to 8 weeks on atenolol (50 mg *o.d.*) and placebo (*b.i.d.*), patients complying with inclusion criteria were randomised to receive either ivabradine (5 mg *b.i.d.* then 7.5 mg *b.i.d.* given orally for 2 months each) or placebo, in combination with atenolol (50 mg *o.d.*). ETT were performed 3 times during the run-in period (the first two at selection visits and the third one 5 days before inclusion visit) and once at the end of each treatment period (*i.e.* at M2 and M4).



Choice of background and comparator therapy

All patients were treated with atenolol (50 mg o.d.) throughout the study. During the run-in period, 6 weeks for patients previously treated with atenolol 50 mg daily and 8 weeks for patients previously treated with another beta-blocker at equivalent dose, patients received a placebo. Then, patients who fulfilled the inclusion criteria were randomised to either placebo or ivabradine at 5 mg b.i.d. dose for the first 2 months and then a 7.5 mg b.i.d. dose for the following 2 months

For patients having received other beta-blocker treatment the following doses were considered equivalent to atenolol 50 mg o.d:
- Atenolol 25 mg b.i.d.
- Betaxolol 20 mg o.d.
- Bisoprolol 5-10 mg o.d.
- Metoprolol 50 mg b.i.d.
- LA metoprolol 50-100 mg o.d.
- Propranolol 80-160 mg o.d.
- Carvedilol 12.5 mg b.i.d

The table below shows pre-study beta blocker therapy in the randomised set

n (%)	**Ivabradine (N = 449)**	**Placebo (N = 440)**	**All (N = 889)**
		n (%)	**n (%)**
Beta blocking agents	**449 (100)**	**439 (99.8)**	**888 (99.9)**
Atenolol	263 (58.6)	253 (57.5)	516 (58.0)
Metoprolol	43 (9.6)	50 (11.4)	93 (10.5)
Metoprolol succinate	47 (10.5)	41 (9.3)	88 (9.9)
Bisoprolol fumarate	45 (10.0)	39 (8.9)	84 (9.4)
Bisoprolol	20 (4.5)	24 (5.5)	44 (4.9)
Metoprolol tartarate	14 (3.1)	16 (3.6)	30 (3.4)
Betataxolol hydrochloride	9 (2.0)	1 (0.2)	10 (1.1)
Carvedilol	21 (4.7)	14 (3.2)	35 (3.9)
Propranolol	2 (0.4)	10 (2.3)	12 (1.3)

Patients were men or women, aged 18-75 years, with a history of stable chronic effort angina pectoris for at least 3 months prior to pre-selection, with no angina at rest and no angina of class IV (classified by the Canadian Cardiovascular Society), with documented CAD, and treated for at least 3 months preceding pre-selection by atenolol 50 mg daily or by a beta-blocker at an equivalent dose and a heart rate at pre-selection ≥ 60 bpm on atenolol (50 mg *o.d.*) or equivalent betablocker treatment. Patients were to have three positive exercise tolerance tests during the run-in, with the second and third being stable.

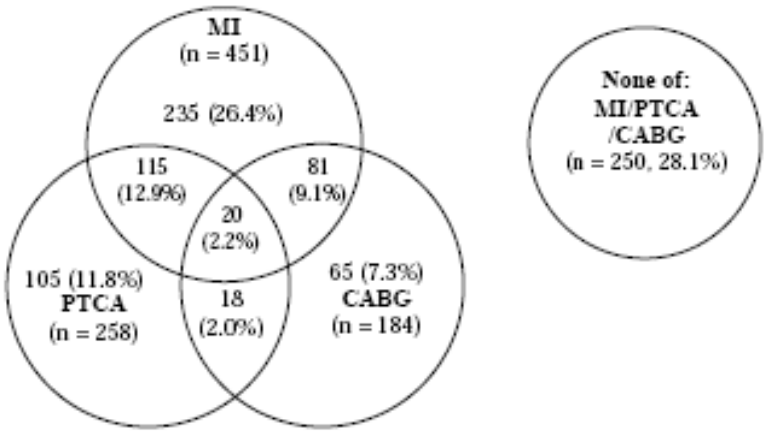
I.2.1.2 Study results

- **Efficacy results :**

Baseline

Randomisation was successful as both treatment arms show similar baseline characteristics. The study population existed indeed of patients with documented CAD of which >70% having had an MI, PTCA or CABG.

Figure (10.4.1) 1 - History of coronary artery disease in the Randomised Set at baseline



Primary Efficacy

(Time in seconds)	Ivabradine (N = 441)	Placebo (N = 434)	Difference * E [95% CI]	p-value**
Changes: over 4-month treatment period				
Total exercise duration	24.3 ± 65.3	7.7 ± 63.8	16.3 [7.9 ; 24.7]	< 0.001
Time to 1 mm ST depression	45.7 ± 93.0	15.4 ± 86.6	28.5 [16.8 ; 40.3]	< 0.001
Time to onset of angina pain	49.1 ± 83.3	22.7 ± 79.1	25.5 [15.0 ; 36.0]	< 0.001
Time to limiting angina	26.0 ± 65.7	9.4 ± 63.8	16.3 [7.9 ; 24.7]	< 0.001
Changes: over 2-month treatment period				
Total exercise duration	15.5 ± 60.0	6.8 ± 56.5	8.2 [0.6 ; 15.7]	0.017
Time to 1 mm ST depression	35.0 ± 84.1	7.8 ± 82.6	25.3 [14.4 ; 36.3]	< 0.001
Time to onset of angina pain	30.2 ± 72.2	17.2 ± 72.3	12.3 [2.9 ; 21.7]	0.005
Time to limiting angina	17.0 ± 60.7	8.2 ± 56.8	8.2 [0.6 ; 15.8]	0.018

**Parametric estimate of the difference ivabradine minus placebo, adjusted for baseline and country factors [95% confidence interval]*
***Student t test (least-square norms) with baseline as a covariate and country as a random factor*

The between group difference in total exercise duration over the 4-month period was significant in favour of a greater increase in the ivabradine group (16.3 s (95% CI [7.9; 24.7]). This improvement was numerically smaller than in the previous study of ivabradine monotherapy using treadmill ETT (study CL3-017), but this is to be expected since the modified Bruce protocol with a more gradual increase in workload was used in CL3-017. The improvements in exercise time in study CL3-057 were obtained at a substantial workload. An improvement was also observed over the 2-month period (8.2 s (95% CI [0.6 ; 15.7]). This was also observed for resting HR after 4 months (before ETT standing at trough of drug activity). Mean change HR was -10.8 ± 10.8 bpm *versus* -2.2 ± 10.1 bpm (diff -8.8 bpm (95% CI: [-10.0 ; -7.6])). At the peak of exercise this was -11.3 ± 13.2 bpm *versus* -0.9 ± 12.3 bpm, respectively, (diff of -10.8 bpm (95%CI: [-12.4 ; -9.1])). The overall change in heart rate at rest in supine position observed in the ivabradine group was 67.0 ± 6.9 bpm at baseline to 58.4 ± 8.7 bpm at month 4. Also, rate pressure product decreased to a greater extent in the ivabradine group than in the placebo group, both at rest and at peak of exercise.
No changes were observed in the number of anginal attacks or short acting nitrates (SAN), see table below.

	Run-in period	2 months	4 months
Angina attacks/week			
Ivabradine (n = 447)	1.8 ± 3.3	1.1 ± 2.8	0.9 ± 2.4
Placebo (n = 438)	1.6 ± 2.4	1.0 ± 2.0	0.9 ± 2.1
Consumption of SAN/week			
Ivabradine (n = 447)	1.0 ± 2.1	0.8 ± 2.8	0.7 ± 2.0
Placebo (n = 438)	1.2 ± 2.9	0.8 ± 2.8	0.7 ± 2.1

Post hoc analyses in view of concerns over suboptimally dosed atenolol

Post-hoc complementary analyses of ETT results were performed in the subgroups of patients (1) whose heart rate was ≤ 65 bpm at baseline, and (2) whose background beta-blocker dose was judged to be maximal, due to a resting heart rate ≤ 60 bpm and/or supine systolic blood pressure ≤ 100 mmHg and/or mean PR interval ≥ 200 ms at baseline.

Table (2.7.3) 6 - Changes from baseline in ETT criteria in patients with HR ≤ 65 bpm at baseline

Change (s)	Ivabradine	Placebo	Difference[a] [95% CI]	p-value
Total exercise duration	23.8 ± 65.0 *(N = 224)*	12.2 ± 63.7 *(N = 212)*	12.3 [0.54; 24.1]	0.020
Time to 1-mm ST segment depression	41.7± 93.0 *(N = 223)*	15.2 ± 83.8 *(N = 210)*	26.1 [9.7; 42.6]	<0.001

Mean ± SD unless otherwise stated
[a] Ivabradine minus placebo, adjusted

Table (2.7.3) 7 - Changes from baseline in ETT criteria in patients maximal treated for atenolol

Change (s)	Ivabradine (N = 80)	Placebo (N = 64)	Difference[a] [95% CI]	p-value
Total exercise duration	26.6 ± 63.2	8.8 ± 71.2	16.3 [-5.0; 37.7]	0.066
Time to 1-mm ST segment depression	46.6 ± 84.9	14.8 ± 86.7	28.9 [1.8; 56.0]	0.018

Mean ± SD unless otherwise stated
[a] *Ivabradine minus placebo, adjusted*

Improvements in ETT criteria (at 4-months) with ivabradine in both subgroups were similar to those observed in the FAS, showing that ivabradine improved exercise capacity in patients whose baseline heart rate was relatively low, and in patients for whom an increase in beta-blocker dose would have been impossible.

- **Safety results :**

Seven patients in ivabradine group (1.6%) were withdrawn due to non-serious adverse events, 5 amongst them were withdrawn for adverse events indicated as common in the SPC of ivabradine *i.e.* bradycardia/HR decreased or dizziness and related to study drug.

		Ivabradine (N = 449)	Placebo (N = 440)
Patients having reported			
at least one emergent adverse event	n (%)	130 (29.0)	92 (20.9)
at least one treatment-related emergent adverse event	n (%)	41 (9.1)	12 (2.7)
heart rate decrease / sinus bradycardia / bradycardia	n (%)	19 (4.2)	2 (0.5)
visual adverse event	n (%)	9 (2.0)	4 (0.9)
Patients who died	n (%)	1 (0.2)*	2 (0.5)**
Patients having experienced at least one emergent non-fatal SAE	n (%)	13 (2.9)	8 (1.8)
Patients withdrawn			
due to an adverse event (excluding suicide)	n (%)	12 (2.7)	3 (0.7)
due to heart rate decreased / sinus bradycardia / bradycardia	n (%)	5 (1.1)	-
due to a serious adverse event	n (%)	5 (1.1)	3 (0.7)
due to a treatment-related adverse event	n (%)	5 (1.1)	-
due to a treatment-related serious adverse event (bradycardia)	n (%)	1 (0.2)	-

* *Suicide;* ** *After last study drug intake*

The incidence of treatment-related adverse events was 9.1% in the ivabradine group *versus* 2.7 % in the placebo group, mainly bradycardia (asymptomatic or symptomatic, 4.2% *versus* 0.5%) and visual adverse events (2.0% *versus* 0.9%). No severe case was reported. No patients were withdrawn for a visual adverse event. Phosphenes, which are commonly reported with ivabradine, were observed in 5 patients (1.1%) in the ivabradine group *versus* 3 (0.7%) in the placebo group. Emergent events of ventricular extrasystoles were more frequent in the ivabradine group (6 patients; 1.3%) than in the placebo group (1 patient; 0.2%). Relatively unexpected was difference amongst the 2 treatment groups in the incidence of emergent angina pectoris (6 patients (1.3%) *versus* 0), which appears to be due to the natural progression of the disease in a small number of patients in the ivabradine group, and the incidence of "blood pressure inadequately controlled" (11 patients (2.4%) *versus* 2 on placebo), where it was noted that all concerned patients had a medical history of hypertension and that none of the occurrences were considered as being related to the study drug by investigators. No clinically relevant changes were observed in the Safety Set in biochemical parameters or in vital signs. One suicide in the procoralan group was reported and two patients in the placebo group died after last study drug intake, one from myocardial infarction, and the other from sudden death. No death was related to the study treatment.
While the proportion of patients with ECG abnormalities was slightly higher at baseline in the ivabradine group (85.6%) than in the placebo group (80.9%), these percentages remained stable during the treatment period. Of note were 21 emergent cases of first degree AV block at last assessment under treatment, observed in the ivabradine group (a known abnormality with ivabradine treatment), *versus* 11 in the placebo group.

Adverse event (Preferred term)	Ivabradine (N = 449)			Placebo (N = 440)		
	NEAE	n	%	NEAE	n	%
Heart rate decreased*	15	14	3.1	2	2	0.5
Blood pressure inadequately controlled	14	11	2.4	2	2	0.5
Angina pectoris	8	6	1.3	-	-	-
Ventricular extrasystoles	7	6	1.3	1	1	0.2
Dizziness	6	5	1.1	2	2	0.5
Phosphenes	5	5	1.1	3	3	0.7
Headache	5	5	1.1	2	2	0.5
Sinus bradycardia / Bradycardia**	5	5	1.1	-	-	-
Back pain	7	4	0.9	6	5	1.1
Nasopharyngitis	4	4	0.9	6	6	1.4
Influenza	4	4	0.9	2	2	0.5
Hypotension	3	3	0.7	3	3	0.7
Anaemia	3	3	0.7	-	-	-
Gastritis	2	2	0.4	5	5	1.1
Diarrhoea	2	2	0.4	5	3	0.7
Arteriogram coronary	2	2	0.4	2	2	0.5
Asthenia	2	2	0.4	4	2	0.5
Transaminases increased	2	2	0.4	2	2	0.5
ALL	**215**	**130**	**29.0**	**138**	**92**	**20.9**

** The preferred term "heart rate decreased" was used to code asymptomatic bradycardia*
*** The preferred terms "sinus bradycardia" and "bradycardia" were used to code symptomatic bradycardia and are grouped together in this table*
NEAE: number of emergent adverse events
N: total number of exposed patients in the considered treatment group
n: number of affected patients
% = (n/N) x 100

	Ivabradine (N = 449)			Placebo (N = 440)		
	NEAE	n	%	NEAE	n	%
Phosphenes	5	5	1.1	3	3	0.7
Visual disturbance	1	1	0.2	1	1	0.2
Blurred vision	1	1	0.2	-	-	-
Diplopia	1	1	0.2	-	-	-
Photopsia	1	1	0.2	-	-	-

N: total number of exposed patients in the considered treatment group
NEAE: number of emergent adverse events; n: number of patients affected
%: n/N x 100

I.2.2 Supportive clinical data

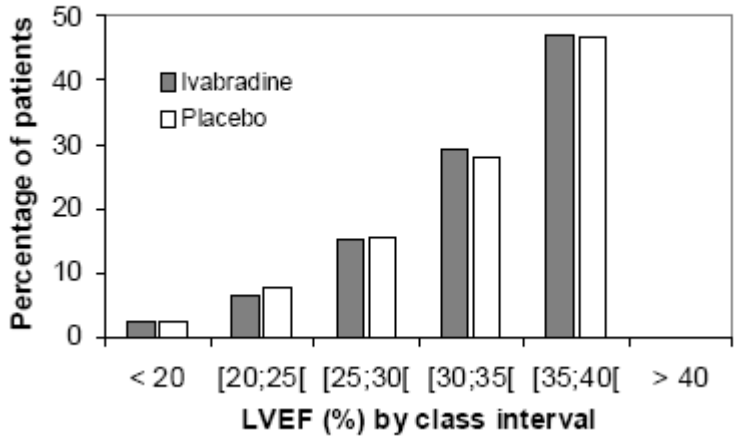
Study CL3-056 (BEAUTIFUL)

Study CL3-056 (BEAUTIFUL) is a three-year, randomised, double-blind, placebo-controlled, international multicentre study assessing the effects of ivabradine on mortality and CV events in patients with stable CAD and LV systolic dysfunction. The study protocol had been developed with the purpose of demonstrating that ivabradine may prevent the aggravation of CAD and therefore the incidence of CV events such as acute MI, hospitalisation for heart failure and CV deaths in a population with documented CAD which is at particularly high risk in the presence of LV systolic dysfunction. Since no specific guidelines are available in this area, the company requested a scientific advice on the study protocol with the objective to review whether the study design and the combined primary endpoint (MI, hospitalisation for heart failure, CV death) were consistent with the above-mentioned objective.

Study CL3-056 was markedly different in design and patient population to phase III studies performed in the course of the pre-Marketing Authorisation clinical programme. It involved a wide spectrum of patients (N=10907), including those with mild, asymptomatic LV dysfunction through to those with moderate heart failure symptoms and markedly impaired LV systolic function. In addition, included patients were at markedly higher risk of major cardiac events and death than patients in other phase III studies. Overall, a majority of patients differed from the scope of the current registered indication. However, some results particularly from subgroup analyses are directly relevant to the approved indication in patients with chronic stable angina pectoris. For example a substantial number of patients had their physical activity limited by anginal pain at baseline (N=1507), and the efficacy and safety of ivabradine in this subgroup is of obvious relevance for the claimed indication.

All patients in study CL3-056 (BEAUTIFUL) had CAD and left ventricular (LV) systolic dysfunction (ejection fraction < 40%) (figure 2).

Figure 2 - Baseline LV ejection fraction by class interval in the Randomised Set



Angina was the main limiting factor in 1507 patients. The subgroup of patients with anginal symptoms at baseline, and particularly those receiving concomitant beta-blockers is of particular interest as this is the subgroup of the greatest relevance to the present indication of ivabradine in stable angina and to the requested variation of indication to use ivabradine in combination with betablockers. The following aspects are discussed:

- Adjudicated efficacy endpoints and adjudicated endpoints with an outcome of death
- Investigator assigned adverse events with an outcome of death
- Adverse events related to cardiac arrhythmias
- Bradycardia
- Angina pectoris as an adverse event

Adjudicated efficacy endpoints and adjudicated endpoints with an outcome of death

Patients with stable angina

In patients with stable angina (N = 1507), there was a significant 24% reduction in the primary composite endpoint (hazard ratio 0.76, p = 0.05), and a 42% reduction in hospitalisation for myocardial infarction (hazard ratio 0.58, p = 0.022). Overall, in patients with stable angina, ivabradine produced significant benefits in terms of the primary composite outcome and myocardial infarction, and numerical but nonsignificant benefits in all-cause and cardiovascular mortality (8.7% vs 10.0% and 7.4% vs 8.3%, respectively).

Patients with stable angina and taking beta-blockers

Results for patients taking beta-blockers (N = 1351) were comparable to those in the full stable angina subgroup, with consistent reductions in incidences of the primary composite endpoint and in secondary endpoints (table 8).

Table 8 - Primary and selected secondary endpoints in patients with angina taking beta-blockers (N = 1351)

	Ivabradine (% PY)	Placebo (%PY)	Hazard ratio [95% CI]	p-value
Taking beta-blockers	**n = 654**	**n = 697**		
Primary composite outcome	80 (7.94)	110 (10.47)	0.76 [0.57;1.01]	0.062
Mortality endpoints:				
All-cause mortality	58 (5.59)	70 (6.38)	0.88 [0.62; 1.24]	0.457
Cardiovascular death	50 (4.82)	60 (5.46)	0.88 [0.61; 1.28]	0.509
CAD death	9 (0.87)	15 (1.37)	0.63 [0.28; 1.45]	0.277
Heart failure endpoint				
Hospitalisation for HF	29 (2.84)	39 (3.65)	0.78 [0.48; 1.26]	0.314
Coronary endpoints				
Hospitalisation for MI	25 (2.46)	44 (4.11)	0.60 [0.37; 0.98]	0.039
Coronary revascularisation	18 (1.76)	33 (3.09)	0.57 [0.32; 1.02]	0.053

CAD: coronary artery disease; HF: heart failure; MI: myocardial infarction; %PY: number per 100 patient-years

Analyses of adjudicated causes of death did not evidence any signal of increased risk of arrhythmic or sudden death with ivabradine; both death from presumed arrhythmia and sudden death of unknown cause were also lower with ivabradine than with placebo (table 9). Thus, cause-specific mortality results in this subgroup did not evidence any pro-arrhythmic effect of ivabradine in stable angina patients.

Table 9 - Cardiovascular mortality in patients with stable angina taking beta-blockers (N = 1351)

	Ivabradine (%)	Placebo (%)
Taking beta-blockers	**n = 654**	**n = 697**
All cardiovascular death	50 (7.65)	60 (8.61)
Heart failure	5 (0.76)	5 (0.72)
Acute myocardial infarction	2 (0.31)	8 (1.15)
Presumed arrhythmia	11 (1.68)	13 (1.87)
Sudden death of unknown cause	24 (3.67)	30 (4.30)
Stroke	6 (0.92)	1 (0.14)
Other	0	1 (0.14)
Cardiac procedures	2 (0.31)	2 (0.29)

LV subgroups and NYHA classes subgroups (in patients with AP and beta-blocker)

The efficacy of ivabradine in patients with stable angina taking beta-blockers in study CL3-056 was also evaluated in subgroups with different degrees of LV systolic dysfunction (patients with LV ejection fraction ≥ 35% and < 35%) and with different NYHA classes (class II and class III). There was no evidence of any systematic cause for concern with the use of ivabradine in combination with beta-blockers in patients with more or less severe LV dysfunction or NYHA class II or Class III for all-cause death (table 14), cardiovascular death (table 15), arrhythmia and sudden death (table 16), and myocardial infarction (table 17).

Table 14 - Summary of all-cause mortality in subgroups of patients with stable angina, expressed as n (% PY) except where shown

	Ivabradine	Placebo	Hazard ratio [95% CI]	p-value
All-cause mortality				
Patients with angina (N = 1507)	64 (8.72%)	77 (9.96%)	0.87 [0.62; 1.21]	0.406
Taking beta-blockers (N = 1351)	58 (5.59)	70 (6.38)	0.88 [0.62; 1.24]	0.457
Not taking beta-blockers (N = 156)	6 (4.30)	7 (5.45)	0.80 [0.27; 2.38]	0.688
Patients with angina taking beta-blockers				
LVEF ≥ 35% (N = 714)	21 (3.96)	33 (5.35)	0.75 [0.43; 1.29]	0.293
LVEF < 35% (N = 635)	37 (7.34)	37 (7.69)	0.95 [0.60; 1.50)	0.819
NYHA Class II (N = 1014)	40 (5.06)	44 (5.27)	0.96 [0.63; 1.47]	0.851
NYHA Class III (N = 337)	18 (7.28)	26 (9.88)	0.74 [0.40; 1.34]	0.315

LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; % PY: number per 100 patient-years

Table 15 - Summary of incidence of cardiovascular death in subgroups of patients with stable angina, expressed as n (% PY) except where shown

	Ivabradine	Placebo	Hazard ratio [95% CI]	p-value
Cardiovascular death				
Patients with angina (N = 1507)	54 (7.36%)	64 (8.28%)	0.88 [0.61; 1.26]	0.486
Taking beta-blockers (N = 1351)	50 (4.82)	60 (5.46)	0.88 [0.61; 1.28]	0.509
Not taking beta-blockers (N = 156)	4 (2.87)	4 (3.11)	0.95 [0.24; 3.80]	0.942
Patients with angina taking beta-blockers				
LVEF ≥ 35% (N = 714)	16 (3.02)	28 (4.54)	0.67 [0.36; 1.24]	0.200
LVEF < 35% (N = 635)	34 (6.75)	32 (6.65)	1.01 [0.62; 1.63)	0.973
NYHA Class II (N = 1014)	35 (4.43)	36 (4.31)	1.03 [0.64; 1.63]	0.914
NYHA Class III (N = 337)	15 (6.07)	24 (9.12)	0.67 [0.35; 1.27]	0.214

LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; % PY: number per 100 patient-years

Table 16 - Summary of incidences of presumed arrhythmic death and sudden death of unknown cause in subgroups of patients with stable angina

	Ivabradine (%)	Placebo (%)
Presumed arrhythmic death		
Patients with angina (N = 1507)	12 (1.6)	15 (1.9)
Taking beta-blockers (N = 1351)	11 (1.68)	13 (1.87)
Not taking beta-blockers (N = 156)	1 (1.25)	2 (2.63)
Patients with angina taking beta-blockers		
LVEF ≥ 35% (N = 714)	4 (1.21)	3 (0.78)
LVEF < 35% (N = 635)	7 (2.17)	10 (3.19)
NYHA Class II (N = 1014)	6 (1.22)	7 (1.34)
NYHA Class III (N = 337)	5 (3.11)	6 (3.41)
Sudden death of unknown cause		
Patients with angina (N = 1507)	25 (3.4%)	31 (4.0%)
Taking beta-blockers (N = 1351)	24 (3.67)	30 (4.30)
Not taking beta-blockers (N = 156)	1 (1.25)	1 (1.32)
Patients with angina taking beta-blockers		
LVEF ≥ 35% (N = 714)	8 (2.42)	18 (4.69)
LVEF < 35% (N = 635)	16 (4.97)	12 (3.83)
NYHA Class II (N = 1014)	16 (3.25)	18 (3.45)
NYHA Class III (N = 337)	8 (4.97)	12 (6.82)

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

Table 17 - Summary of incidence of myocardial infarction (fatal and non-fatal) in subgroups of patients with stable angina, expressed as n (% PY) except where shown

	Ivabradine	Placebo	Hazard ratio [95% CI]	p-value
Myocardial infarction				
Patients with angina (N = 1507)	28 (3.81%)	50 (6.47%)	0.58 [0.37; 0.93]	0.022
Taking beta-blockers (N = 1351)	25 (2.46)	44 (4.11)	0.60 [0.37; 0.98]	0.039
Not taking beta-blockers (N = 156)	3 (2.22)	6 (4.83)	0.47 [0.12; 1.88]	0.276
Patients with angina taking beta-blockers				
LVEF ≥ 35% (N = 714)	9 (1.73)	20 (3.31)	0.52 [0.24; 1.15]	0.099
LVEF < 35% (N = 635)	16 (3.25)	24 (5.15)	0.63 [0.34; 1.19]	0.154
NYHA Class II (N = 1014)	12 (1.53)	34 (4.18)	0.37 [0.19; 0.71]	0.002
NYHA Class III (N = 337)	13 (5.52)	10 (3.90)	1.41 [0.62; 3.21]	0.416

LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; % PY: number per 100 patient-years

Safety results of study CL3-056

Investigator assigned adverse events with an outcome of death

All patients

In the full study population of study CL3-056, the overall incidence of all adverse events with an outcome of death was slightly higher in the ivabradine group (575 patients, 10.5%) than with placebo (548 patients, 10.1%), but the between-group difference was not significant (p = 0.515; Table 18). The incidence of death and sudden death was also numerically higher in the ivabradine group (306 patients, 5.6%) than with placebo (264 patients, 4.9%), but the difference was not significant (p = 0.097).

The incidences of deaths related to cardiac disorders, and specifically those due to heart failure, were numerically slightly lower in the ivabradine group (table 18).
The only statistically significant differences were lower rates in the ivabradine group for death due to cardiogenic shock (p = 0.002) and coronary artery disorders NEC (p = 0.030). The clinical significance, if any, of these particular lower rates with ivabradine, is not clear, and it is possible they may be due to chance. When large numbers of statistical comparisons are performed, as here, it is likely that some comparisons will approach or even exceed the significance threshold simply due to random sampling effects. Alternatively, they may reflect the absence of adjudication of the causes of death in this analysis.

Table 18 - Full study population (N = 10 907): adverse events with an outcome of death in system organ classes 'general disorders and administration site conditions' and 'cardiac disorders', restricted to those with > 1 patient in either group

	Ivabradine (N = 5477)		Placebo (N = 5430)		P-value
	n	%	n	%	
All	**575**	**10.5**	**548**	**10.1**	**0.515**
General disorders and administration site conditions	306	5.6	267	4.9	0.127
Fatal outcomes	306	5.6	264	4.9	0.097
Death and sudden death	306	5.6	264	4.9	0.097
Sudden death	253	4.6	227	4.2	0.284
Death	53	1.0	37	0.7	0.121
General system disorders NEC	0	0	3	0.1	0.247
General signs and symptoms NEC	0	0	2	0.0	0.496
Multi-organ failure	0	0	2	0.0	0.496
Cardiac disorders	160	2.9	172	3.2	0.488
Coronary artery disorders	62	1.1	64	1.2	0.890
Ischaemic coronary artery disorders	62	1.1	58	1.1	0.820
Acute myocardial infarction	33	0.6	32	0.6	1.000
Myocardial infarction	24	0.4	21	0.4	0.788
Angina unstable	3	0.1	5	0.1	0.717
Acute coronary syndrome	2	0.0	0	0	0.504
Coronary artery disorders NEC	0	0	6	0.1	0.030
Coronary artery insufficiency	0	0	3	0.1	0.247
Coronary artery disease	0	0	2	0.0	0.496
Heart failures	78	1.4	94	1.7	0.226
Heart failures NEC	72	1.3	88	1.6	0.211
Cardiac failure	70	1.3	76	1.4	0.639
Cardiogenic shock	0	0	10	0.2	0.002
Left ventricular failures	5	0.1	5	0.1	1.000
Acute left ventricular failure	5	0.1	4	0.1	1.000
Cardiac arrhythmias	18	0.3	14	0.3	0.613
Ventricular arrhythmias and cardiac arrest	14	0.3	11	0.2	0.706
Ventricular fibrillation	10	0.2	8	0.1	0.829
Ventricular tachycardia	2	0.0	2	0.0	1.000
Supraventricular arrhythmias	3	0.1	1	0.1	0.631
Atrial fibrillation	2	0.0	1	0.0	1.000

Patients with stable angina
In patients with stable angina, the overall incidence of all adverse events with an outcome of death was slightly lower in the ivabradine group (64 patients, 8.7%) than with placebo (77 patients, 10.0%), but the between-group difference was not significant (p = 0.505). The incidence of death and sudden death was similar in both groups (ivabradine 39 patients, 5.3%; placebo 39 patients, 5.1%; p = 0.910). The incidence of deaths related to cardiac disorders was lower in the ivabradine group (12 patients, 1.6%)

than with placebo (21 patients, 2.7%) although the difference was again not significant (p = 0.206). The incidence of deaths related to cardiac arrhythmias was low and similar in both groups (2 patients in each, p = 1.000).

Patients with stable angina taking beta-blockers

According to the applicant, as with the subgroup of all patients with stable angina, there was no evidence of an increased risk of death or any pro-arrhythmic effect of ivabradine in patients with stable angina taking beta-blockers (table 19). The incidence of death and sudden death was similar in both groups (ivabradine 36 patients, 5.5%; placebo 37 patients, 5.3%; p = 0.973). The incidence of deaths related to cardiac arrhythmias was low and similar in both groups (2 patients in each, p = 1.000).

The rate of deaths related to cardiac disorders were numerically lower with ivabradine than with placebo, but the difference was not significant.

Table 19 - Subgroup of patients with stable angina taking beta-blockers (N = 1350): adverse events with an outcome of death in system organ classes 'general disorders and administration site conditions' and 'cardiac disorders'

	Ivabradine (N = 654)		Placebo (N = 696)		P-value
	n	%	n	%	
All	**58**	**8.9**	**70**	**10.1**	**0.455**
General disorders and administration site conditions	36	5.5	37	5.3	0.973
Fatal outcomes	36	5.5	37	5.3	0.973
Death and sudden death	36	5.5	37	5.3	0.973
Sudden death	28	4.3	33	4.7	0.784
Death	8	1.2	4	0.6	0.328
General system disorders NEC	0	0	0	0	-
Cardiac disorders	11	1.7	19	2.7	0.262
Coronary artery disorders	5	0.8	12	1.7	0.179
Ischaemic coronary artery disorders	5	0.8	9	1.3	0.493
Acute myocardial infarction	2	0.3	5	0.7	0.505
Myocardial infarction	2	0.3	3	0.4	1.000
Angina unstable	1	0.2	1	0.1	1.000
Acute coronary syndrome	0	0	0	0	-
Coronary artery disorders NEC	0	0	3	0.4	0.273
Coronary artery insufficiency	0	0	2	0.3	0.531
Coronary artery disease	0	0	1	0.1	1.000
Heart failures	4	0.6	5	0.7	1.000
Heart failures NEC	4	0.6	4	0.6	1.000
Cardiac failure	4	0.6	3	0.4	0.932
Cardiogenic shock	0	0	1	0.1	1.000
Left ventricular failures	0	0	1	0.1	1.000
Acute left ventricular failure	0	0	1	0.1	1.000
Cardiac arrhythmias	2	0.3	2	0.3	1.000
Ventricular arrhythmias and cardiac arrest	2	0.3	1	0.1	0.962
Ventricular fibrillation	2	0.3	1	0.1	0.962
Cardiac conduction disorders	0	0	1	0.1	1.0000
AV block complete	1	0.1	1	0.1	1.000

AV: atrioventricular

Adverse events related to cardiac arrhythmias

A detailed analysis was performed on adverse events related to cardiac arrhythmias in the full study population, patients with stable angina, patients with stable angina taking beta-blockers, and

subgroups with more or less severe LV dysfunction or NYHA class II or Class III. According to the applicant, no signal of any pro-arrhythmic effect of ivabradine was found for any group or subgroup.

Overall group

According to the applicant, there was no evidence of a pro-arrhythmic effect of ivabradine (see table 25, 26).

The incidence of AEs and serious AEs related to supraventricular arrhythmias was similar in both treatment groups (table 25). There was some evidence of a benefit effect of ivabradine in preventing sinus tachycardia, ventricular tachycardia and left bundle branch block. Sick sinus syndrome was infrequent, but was observed in 9 patients in the ivabradine group compared with 2 patients in the placebo group (difference not significant). No major differences for serious AEs related to supraventricular arrhythmias between groups for individual preferred terms, was observed.

The incidence of AEs relating to ventricular arrhythmias was similar in the ivabradine and placebo (table 26). Incidences of individual preferred terms were generally similar in the two groups, with the exception of ventricular tachycardia which was less frequent with ivabradine. Serious AEs were less frequent with ivabradine than with placebo, largely due to a significantly lower incidence of serious AEs of ventricular tachycardia.

Table 25 - Full study population (N = 10 907): supraventricular arrhythmias

	Ivabradine (N = 5477)		Placebo (N = 5430)		P-value
EAE	**n**	**%**	**n**	**%**	
All supraventricular arrhythmias	393	7.2	388	7.1	0.981
Atrial fibrillation	286	5.2	264	4.9	0.415
Atrial flutter	55	1.0	48	0.9	0.583
Supraventricular extrasystoles	39	0.7	27	0.5	0.185
Sinus tachycardia	14	0.3	44	0.8	<0.001
Supraventricular tachycardia	13	0.2	13	0.2	1.000
Sick sinus syndrome	9	0.2	2	0.0	0.067
Sinus arrest	3	0.1	4	0.1	0.991
Serious EAE					
All supraventricular arrhythmias	169	3.1	172	3.2	0.849
Atrial fibrillation	127	2.3	134	2.5	0.655
Atrial flutter	35	0.6	28	0.5	0.470
Sick sinus syndrome	8	0.1	2	0.0	0.112
Sinus arrest	2	0.0	3	0.1	0.992

EAE: emergent adverse event

Table 26 - Full study population (N = 10 907): Ventricular arrhythmias and cardiac arrest

	Ivabradine (N = 5477)		Placebo (N = 5430)		P-value
EAE	**n**	**%**	**n**	**%**	
All ventricular arrhythmias and cardiac arrest	192	3.5	194	3.6	0.890
Ventricular tachycardia	53	1.0	73	1.3	0.080
Ventricular fibrillation	16	0.3	13	0.2	0.728
Ventricular extrasystoles	107	2.0	102	1.9	0.829
Ventricular arrhythmia	11	0.2	4	0.1	0.122
Cardiac arrest	2	0.0	2	0.0	1.000
Serious EAE					
All ventricular arrhythmias and cardiac arrest	60	1.1	79	1.5	0.112
Ventricular tachycardia	28	0.5	53	1.0	0.006
Ventricular fibrillation	16	0.3	13	0.2	0.728
Ventricular extrasystoles	8	0.1	7	0.1	1.000
Ventricular arrhythmia	4	0.1	2	0.0	0.696
Cardiac arrest	2	0.0	2	0.0	1.000

EAE: emergent adverse event

The incidence of AEs related to cardiac conduction disorders was slightly lower in the ivabradine group (86 patients) than with placebo (98 patients; not significant), largely due to a significantly lower incidence of left bundle branch block (ivabradine 18 patients, placebo 34 patients; p = 0.033). Serious AEs related to cardiac conduction disorders were similar in both treatment groups.

Patients with stable angina

According to the applicant, there was no indication of any pro-arrhythmic effect of ivabradine in stable angina patients (table 20, 21).There was some evidence of less arrhythmic AEs and serious AEs for both supraventricular and ventricular arrhythmias in the ivabradine group as compared to the placebo (table 20).

Table 20 - Patients with stable angina (N = 1506): supraventricular arrhythmias

	Ivabradine (N = 734)		Placebo (N = 772)		P-value
EAE	**n**	**%**	**n**	**%**	
All supraventricular arrhythmias	30	4.1	53	6.9	0.024
Atrial fibrillation	16	2.2	31	4.0	0.056
Atrial flutter	6	0.8	3	0.4	0.458
Supraventricular extrasystoles	5	0.7	6	0.8	1.000
Sinus tachycardia	1	0.1	8	1.0	0.046
Supraventricular tachycardia	1	0.1	5	0.6	0.242
Serious EAE					
All supraventricular arrhythmias	13	1.8	23	3.0	0.171
Atrial fibrillation	8	1.1	19	2.5	0.068
Atrial flutter	5	0.7	2	0.3	0.412
Supraventricular extrasystoles	0	0	0	0	-
Sinus tachycardia	0	0	1	0.1	1.000

EAE: emergent adverse event

There was a significant reduction in the incidence of ventricular extrasystoles with ivabradine compared with placebo, while serious AEs occurred with similar frequency in both treatment groups (table 21).

Table 21 - Patients with stable angina (N = 1506): ventricular arrhythmias

	Ivabradine (N = 734)		Placebo (N = 772)		P-value
EAE	**n**	**%**	**n**	**%**	
All ventricular arrhythmias	22	3.0	32	4.1	0.290
Ventricular tachycardia	6	0.8	5	0.6	0.932
Ventricular fibrillation	2	0.3	1	0.1	0.962
Ventricular extrasystoles	12	1.6	27	3.5	0.033
Ventricular arrhythmia	2	0.3	0	0	0.475
Serious EAE					
All ventricular arrhythmias	6	0.8	5	0.6	0.932
Ventricular tachycardia	3	0.4	2	0.3	0.953
Ventricular fibrillation	2	0.3	1	0.1	0.962
Ventricular extrasystoles	0	0	2	0.3	0.525
Ventricular arrhythmia	1	0.1	0	0	0.975

EAE: emergent adverse event

AEs related to cardiac conduction disorders were also less frequent with ivabradine (7 patients, 1.0%) than with placebo (16 patients, 2.1%), although the difference was not significant.

Patients with stable angina taking betablockers

There was no evidence of any pro-arrhythmic effect of ivabradine in the subgroup of patients with stable angina who were taking beta-blockers.

The incidences of supraventricular arrhythmias, notably atrial fibrillation and sinus tachycardia were numerically lower with ivabradine than with placebo (table 22).

Serious AEs were also less frequent with ivabradine than with placebo.

Table 22 - Patients with stable angina taking beta-blockers (N = 1350): supraventricular arrhythmias

	Ivabradine (N = 654)		Placebo (N = 696)		P-value
EAE	**n**	**%**	**n**	**%**	
All supraventricular arrhythmias	27	4.1	46	6.6	0.057
Atrial fibrillation	15	2.3	28	4.0	0.097
Atrial flutter	5	0.8	2	0.3	0.402
Supraventricular extrasystoles	5	0.8	5	0.7	1.000
Sinus tachycardia	0	0	7	1.0	0.019
Supraventricular tachycardia	1	0.2	4	0.6	0.414
Serious EAE					
All supraventricular arrhythmias	11	1.7	20	2.9	0.200
Atrial fibrillation	7	1.1	18	2.6	0.060
Atrial flutter	4	0.6	2	0.3	0.629

EAE: emergent adverse event

The incidence of AEs related to ventricular arrhythmias was numerically lower with ivabradine (table 23). The incidence of serious AEs was slightly higher in the ivabradine group.

Table 23 - Patients with stable angina taking beta-blockers (N = 1350): Ventricular arrhythmias

	Ivabradine (N = 654)		Placebo (N = 696)		P-value
EAE	**n**	**%**	**n**	**%**	
All ventricular arrhythmias	22	3.4	29	4.2	0.529
Ventricular tachycardia	6	0.9	5	0.7	0.916
Ventricular fibrillation	2	0.3	0	0	0.469
Ventricular extrasystoles	12	1.8	25	3.6	0.068
Ventricular arrhythmia	2	0.3	0	0	0.469
Serious EAE					
All ventricular arrhythmias	6	0.9	4	0.6	0.677
Ventricular tachycardia	3	0.5	2	0.3	0.942
Ventricular fibrillation	2	0.3	0	0	0.469
Ventricular extrasystoles	0	0	2	0.3	0.531
Ventricular arrhythmia	1	0.2	0	0	0.969

EAE: emergent adverse event

The incidence of AEs related to cardiac conduction disorders was similar in both treatment groups (ivabradine 7 patients, 1.1%; placebo 11 patients, 1.6%). There were relatively few serious AEs (ivabradine 2 patients, 0.3%; placebo 4 patients, 0.6%).

LV subgroups and NYHA classes subgroups (in patients with AP and beta-blocker)

Supraventricular arrhythmias

In all patients with stable angina taking beta-blockers, the incidence of atrial fibrillation was lower in the ivabradine group (15 patients, 2.3%) than with placebo (28 patients, 4.0%). Among the different subgroups, the apparent protective effect of ivabradine was most marked in patients with LV ejection fraction < 35% (ivabradine 8 patients, 2.5%; placebo 22 patients, 7.0%) and in patients with NYHA Class II symptoms (ivabradine 9 patients, 1.8%; placebo 18 patients, 3.5%). In patients with LV ejection fraction ≥ 35% the incidence was similar in both treatment groups, and in patients in NYHA Class III the incidence was slightly lower with ivabradine (6 patients, 3.7%) than with placebo (10 patients. 5.7%). Results were similar for serious AEs of atrial fibrillation, with lower incidences with ivabradine in patients with LV ejection fraction < 35% (4 patients, 1.2% versus 17 patients, 5.4%) and patients with NYHA Class II (2 patients, 0.4% versus 13 patients, 2.5%).
The incidence of atrial flutter was relatively low, with no between-group differences in the subgroups.

Ventricular arrhythmias

The incidence of ventricular tachycardia was relatively low, and in all patients with stable angina taking beta-blockers the incidence was similar in both treatment groups (ivabradine 6 patients, 0.9%; placebo 5 patients, 0.7%). There were no marked differences in any of the subgroups for AEs or serious AEs.
The incidence of ventricular extrasystoles was lower in the ivabradine group (12 patients, 1.8%) than with placebo (25 patients, 3.6%), and incidences were similar or lower in the ivabradine groups compared with placebo in all subgroups. The apparent protective effect of ivabradine was most marked in patients with LV ejection fraction < 35% (3 patients, 0.9% versus 13 patients, 4.2%) and those with Class II (6 patients, 1.2% versus 20, 3.8%). There were only 2 patients with serious AEs of ventricular extrasystoles, and both were in the placebo group.

Cardiac conduction disorders

The incidences of atrioventricular block second degree and third degree (complete) were low in both treatment groups, and no differences in subgroups could be determined.

Results of the Holter analysis performed in patients with stable angina and taking betablockers

Holter sub-study in patients with stable angina

A Holter 24-h monitoring sub-study was performed in 840 patients in study CL3-056.

Holter abnormalities

According to the applicant, the incidences of the main abnormalities were similar at 1 month and at the last observation on treatment in the group of patients with stable angina taking betablockers (table 24). However, a slightly higher incidence was observed for supraventricular tachycardia.

Table 24 - Main Holter abnormalities at month 1 and last on treatment in the subgroup of patients with stable angina taking beta-blockers

			Ivabradine (N = 85)		Placebo (N = 91)	
			Month 1	Last on treatment	Month 1	Last on treatment
		N'	82	82	87	90
Supraventricular premature depolarisation		n (%)	5 (6.1)	5 (6.1)	5 (5.7)	5 (5.6)
Supraventricular tachycardia		n (%)	15 (18.3)	16 (19.5)	12 (13.8)	15 (16.7)
Atrial fibrillation		n (%)	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)
Ventricular premature depolarisation		n (%)	5 (6.1)	5 (6.1)	7 (8.0)	7 (7.8)
Accelerated idioventricular rhythm		n (%)	10 (12.2)	5 (6.1)	10 (11.5)	6 (6.7)
Ventricular tachycardia (non-sustained)		n (%)	10 (12.2)	9 (11.0)	11 (12.6)	14 (15.6)
Atrioventricular block 2nd degree		N'	85	85	91	91
Over awake period	**2nd d. AVB Mobitz I**	n (%)	0 (0.0)	0 (0.0)	2 (2.2)	1 (1.1)
	2nd d. AVB Mobitz II	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Over sleep period	**2nd d. AVB Mobitz I**	n (%)	0 (0.0)	0 (0.0)	2 (2.2)	2 (2.2)
	2nd d. AVB Mobitz II	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

n: number of patients with at least one episode of emergent abnormality, i.e. abnormality not present at baseline (or missing information) and present post-baseline. All abnormalities over 24-hour period, except where stated.
% = (n/N') x 100 (with N'= number of assessable patients = N – number of patients with missing post-baseline data)

Bradycardia

As expected, in the full study population, the incidence of the AE bradycardia was significantly higher in the ivabradine group (206 patients, 3.8%) than with placebo (56 patients, 1.0%; $p < 0.001$). Among ivabradine-treated patients, the incidence of bradycardia was lower in stable angina patients (3.1%) and still lower in stable angina patients taking beta-blockers (2.4%), while the incidences for the corresponding placebo groups were approximately unchanged (table 27). Among stable angina patients taking beta-blockers, severity of LV dysfunction and NYHA Classes had no marked influence on the incidence of bradycardia (table 27).
Bradycardia as a serious AE occurred in 22 patients in the ivabradine group and 6 patients with placebo ($p = 0.004$) in the full study population. In patients with stable angina, only one patient (in the ivabradine group) had bradycardia as a serious AE (table 27).

Table 27 - Incidence of bradycardia as an adverse event and serious adverse event in the full study population, patients with stable angina an subgroups in study CL3-056

	Ivabradine		Placebo		P-value
Bradycardia	**n**	**%**	**n**	**%**	
EAE					
Full study population	206	3.8	56	1.0	<0.001
Stable angina patients	23	3.1	9	1.2	0.013
Stable angina taking beta-blockers	16	2.4	8	1.1	0.109
LVEF ≥ 35%	7	2.1	3	0.8	-
LVEF < 35%	9	2.8	5	1.6	-
NYHA Class II	13	2.6	8	1.5	-
NYHA Class III	3	2.5	0	0	-
Serious EAE					
Full study population	22	0.4	6	0.1	0.004
Stable angina patients	1	0.1	0	0	0.975
Stable angina taking beta-blockers	1	0.2	0	0	0.969
LVEF ≥ 35%	0	0	0	0	-
LVEF < 35%	1	0.3	0	0	-
NYHA Class II	1	0.2	0	0	-
NYHA Class III	0	0	0	0	-

Holter sub-study in patients with angina and taking beta-blockers and in the different subgroups

The lowest heart rates recorded during Holter monitoring at the last assessment under treatment are shown by heart rate class for stable angina patients, stable angina patients taking beta-blockers, and subgroups of patients with different severity of LV dysfunction and NYHA Classes are summarised in Appendix table 19. As expected, the number of patients with lowest heart rate values in each of the heart rate classes was greater with ivabradine than with placebo. However, among ivabradine-treated patients, there were only minor variations in incidence between the different subgroups. Rates were similar among stable angina patients taking beta-blockers and the full stable angina group, and there were no marked differences between the subgroups with different severity of LV dysfunction and NYHA Classes. Thus, none of the subgroups of patients with stable angina taking beta-blockers appeared to be at increased risk of bradycardia.

Appendix Table 19 – Heart rate decrease at last assessment on treatment in stable angina patients, stable angina patients taking beta-blockers and subgroups with different severity of LV dysfunction and NYHA Classes

Assessable patients analysis set (ivabradine *versus* placebo)			During awake period		During sleep period	
			Ivabradine	Placebo	Ivabradine	Placebo
Patients with stable angina						
	Lowest HR < 50 bpm	**n (%)**	28 (31.1)	14 (14.7)	24 (26.7)	10 (10.5)
(N = 90 *vs* 95)	Lowest HR < 40 bpm	**n (%)**	10 (11.1)	2 (2.1)	14 (15.6)	1 (1.1)
	Lowest HR < 30 bpm	**n (%)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stable angina taking beta-blockers						
	Lowest HR < 50 bpm	**n (%)**	25 (29.4)	14 (15.4)	24 (28.2)	9 (9.9)
(N = 85 *vs* 91)	Lowest HR < 40 bpm	**n (%)**	9 (10.6)	2 (2.2)	12 (14.1)	1 (1.1)
	Lowest HR < 30 bpm	**n (%)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Taking beta-blockers and LVEF ≥ 35%						
	Lowest HR < 50 bpm	**n (%)**	15 (33.3)	7 (14.0)	15 (33.3)	4 (8.0)
(N = 45 *vs* 50)	Lowest HR < 40 bpm	**n (%)**	6 (13.3)	1 (2.0)	7 (15.6)	1 (2.0)
	Lowest HR < 30 bpm	**n (%)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Taking beta-blockers and LVEF < 35%						
	Lowest HR < 50 bpm	**n (%)**	10 (25.0)	7 (17.1)	9 (22.5)	5 (12.2)
(N = 40 *vs* 41)	Lowest HR < 40 bpm	**n (%)**	3 (7.5)	1 (2.4)	5 (12.5)	0 (0.0)
	Lowest HR < 30 bpm	**n (%)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Taking beta-blockers and NYHA Class II						
	Lowest HR < 50 bpm	**n (%)**	19 (31.7)	10 (15.2)	17 (28.3)	5 (7.6)
(N = 60 *vs* 66)	Lowest HR < 40 bpm	**n (%)**	5 (8.3)	2 (3.0)	9 (15.0)	1 (1.52)
	Lowest HR < 30 bpm	**n (%)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Taking beta-blockers and NYHA Class III						
	Lowest HR < 50 bpm	**n (%)**	6 (24.0)	4 (16.0)	7 (28.0)	4 (16.0)
(N = 25 *vs* 25)	Lowest HR < 40 bpm	**n (%)**	4 (16.0)	0 (0.00)	3 (12.0)	0 (0.00)
	Lowest HR < 30 bpm	**n (%)**	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

% = (n/N') x 100; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association
For each threshold, emergence was defined as no episode with lowest HR below the same threshold at baseline, but its occurrence post-baseline.

Angina pectoris as an adverse event

The incidence of the AE angina pectoris in the full study population was slightly lower in the ivabradine group (136 patients, 2.5%) than with placebo (175 patients, 3.0%) (table 28). In the subgroup of patients with stable angina and taking beta-blockers, the benefit of ivabradine treatment was more marked, with an incidence of angina pectoris of 20 patients (3.1%) in the ivabradine group compared with 33 patients (4.7%) in the placebo group. This was also noticed within the different subgroups defined by severity of LV dysfunction and NYHA Classes. The same was true for angina pectoris as a serious AE.

Table 28 - Incidence of the emergent adverse event angina pectoris in subgroups of patients with stable angina taking beta-blockers

	Ivabradine			Placebo		
Angina pectoris	**n**	**%**	**%PY**	**n**	**%**	**%PY**
EAE						
Full study population	136	2.5	1.9	162	3.0	2.0
All stable angina patients	23	3.1	2.3	37	4.8	3.2
All stable angina taking beta-blocker	20	3.1	2.3	33	4.7	3.2
LVEF ≥ 35%	10	3.0	2.2	17	4.4	2.9
LVEF < 35%	9	2.8	2.2	16	5.1	3.6
NYHA Class II	16	3.2	2.4	25	4.6	3.2
NYHA Class III	4	2.5	1.9	8	4.5	3.3
Serious EAE						
Full study population	37	0.7	0.5	66	1.2	0.8
All stable angina patients	8	1.1	0.8	17	2.2	1.5
All stable angina taking beta-blocker	8	1.2	0.9	13	1.9	1.3
LVEF ≥ 35%	3	0.9	0.6	5	1.3	0.9
LVEF < 35%	4	1.2	1.0	8	2.6	1.8
NYHA Class II	6	1.2	0.9	9	1.7	1.2
NYHA Class III	2	1.2	0.9	4	2.3	1.6

EAE: emergent adverse event; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

In general , the overall rate of EAE was slightly higher in the ivabradine group (55.7%, 42.1% PY) than in the placebo group (55.5%, 37.0% PY), but the difference between the groups concerned mainly those events already described in the SmPC, in particular symptomatic bradycardia and visual symptoms (mostly phosphenes). Serious EAEs occurred at a similar rate in the ivabradine and placebo groups. EAEs related to CAD and LV dysfunction also occurred at similar rates in the ivabradine (27.0%, 16.6% PY) and placebo (27.4%, 16.8% PY) groups.

The profile of EAE relating to bradycardia was very similar to that in the clinical development programme in stable angina. The concomitant use of ivabradine with several other CV medications did not induce more severe or serious bradycardia. Importantly, no difference was seen in patients taking or not taking beta-blockers for symptomatic or serious bradycardia. The incidence of bradycardia as a serious adverse event was lower in ivabradine treated patients with anginal pain (0.14%) and in patients with asymptomatic LV dysfunction (NYHA Class I) (0.24%) than in the overall Safety Set (0.40%). However, the incidence of serious or symptomatic bradycardia was higher in some subgroups: patients with heart rate <70 bpm at baseline, patients aged ≥75 years, and in female patients.

The profile of visual symptoms and eye disorders (mainly phosphenes) was also similar to what had been observed in previous ivabradine studies of shorter duration; the longer follow-up in Study CL3-056 did not reveal any particular ophthalmic safety concerns. Visual symptoms with ivabradine are typically mild and transient. In fact, the global incidence of EAE in the system organ class 'eye disorders' in the ivabradine group in Study CL3-056 (6.7%) was markedly lower than in the early phase III efficacy studies (15.3% in Study CL3-017, 20.9% in Study CL3-018, and 14.0% in Study CL3-023). These differences may be related to different study procedures. In the early phase III studies, patients were specifically asked about visual symptoms at study visits. In Study CL3-056, patients were informed of the possibility of visual symptoms before starting the study, but were not specifically asked about them during visits. Importantly, in CL3-056, where more than 5000 patients received ivabradine with a longer follow-up (median 19 months) than in previous studies, no adverse event possibly related to retinal degeneration was reported as well as no new unexpected adverse visual events. The incidences of visual symptoms reported as EAE, or reported as a serious EAE or

leading to study drug withdrawal were similar in the overall Safety Set and in the main subgroups of ivabradine-treated patients.

The incidence of atrial fibrillation was 5.2% in the ivabradine group and 4.9% in the placebo group. Most cases were mild or moderate in intensity, with a similar rate of severe cases in the ivabradine (0.46%) and placebo (0.44%) groups. Atrial fibrillation was reported as a serious EAE in 2.3% and 2.5% in the ivabradine and placebo groups respectively. Overall, there is therefore no indication that, in this population particularly at risk for atrial fibrillation, heart rate reduction induced by ivabradine may have increased the incidence or severity of this supraventricular arrhythmia. This was confirmed in the Holter sub-study. Among patients with anginal pain at baseline, the rate of atrial fibrillation was lower in the ivabradine group (2.2%) than with placebo (4.0%). However, in female patients, the rate of atrial fibrillation was higher in the ivabradine group (6.5%) than with placebo (3.9%). As expected, the incidence of atrial fibrillation was higher among patients aged ≥75 years than among those aged <75 years, in both the ivabradine and placebo groups.

I.2.3 Discussion

- ***Efficacy results***

Background therapy prior entry

The number of patients receiving beta blocker therapy other than atenolol prior study entry was considerable. Also, the variety of treatment regimens considered equivalent to atenolol 50mg OD was considerable. In fact, for some patients the extent of beta blockade may have decreased.

The MAH explained that in Study CL3-057, it was required that patients receive the same beta-blocker at the same dosage for at least 3 months before selection to ensure stability of the patients.
To enlarge the potential recruitment, according to the protocol the patients could receive another beta-blocker than atenolol within the 3 months before the study provided that this dosage was equivalent to atenolol 50 mg o.d. (a list of equivalence was proposed to the investigators). Overall 58% of the patients involved in the study received atenolol 50 mg o.d. within the 3 months before the study and 42% another beta-blocker. These percentages were comparable in ivabradine and placebo groups.
Heart rate on ECG at rest is a strong clinical way to assess the extent of beta-blockade. HR on ECG at rest was measured at pre-selection visit when the patients received their pre-selection beta-blocker (atenolol 50 mg o.d. or another beta-blocker) and at inclusion when all patients received atenolol 50 mg o.d. during the run-in period. Overall, HR was stable in patients who received previously atenolol or in patients switched from another beta-blocker to atenolol indicating that there was no modification of the extent of beta-blockade in patients switched.

The list of equivalent beta-blockers is based on clinical experience and judgement and appears justified by the CHMP. In addition, the analysis on heart rates of patients who received previously atenolol and patients switched from another beta-blocker to atenolol indicates that there was no modification of the extent of beta-blockade in patients switched.

Efficacy results / atenolol dose

Overall, a significant additive effect was noted, but the study by its design - a study to evaluate efficacy in atenolol non-responders - used a relatively low dose of atenolol of 50 mg once daily only and patients were not up-titrated to the maximum 100 mg atenolol dose on the basis of heart rate and/or anginal symptoms. The mean heart rate was still 67 bpm, indicating that there was still room for a higher dose of atenolol. Therefore, it is difficult to interpret the value of ivabradine co- treatment that shows a positive effect on the intermediate endpoints that were also used in the phase III studies in the original registration dossier.

The MAH was therefore requested to address this issue of suboptimal dosing by performing post hoc analyses in patients with different baseline HRs to evaluate the efficacy of ivabradine also in patients with (near) target baseline HR.

The first post hoc analysis demonstrated that in patients with a relatively low HR (≤ 65 bpm) at baseline ivabradine retained its efficacy. Similar efficacy was also demonstrated in the second post hoc analysis in a population (n=144) that could be considered optimally treated with beta-blocker, either because of a resting HR < 60 bpm, SBP < 100 mm Hg or PR > 200 ms. Since from a clinicians point of view a patient under these conditions would be maximally dosed as such clear haemodynamic or AV node conduction effects would make him reluctant to increase the dose of the ß-blocker further.

An overview of the literature suggested that stable angina is commonly treated with a combination of two or more drugs. It is important to note that in a study recently performed with ranolazine, it was also given on top of a 50 mg OD atenolol dose. For ranolazine, a post hoc analysis was also required to demonstrate that patients considered on an optimal beta-blocker dose (same criteria as in the second post hoc analysis discussed above for ivabradine) had similar effects as the overall – sub-optimally treated - population. In contrast with ivabradine however ranolazine does not cause bradycardia.

The CHMP questioned whether superiority or non-inferiority would be maintained in comparison to an increased dose of beta-blocker in patients able to tolerate an increase would be maintained. In addition, the clinical relevance of the observed effect size of the primary outcome parameters - in both the total population and post hoc defined groups – e.g. a change in ETT of approximately 16 seconds is unclear. Even though a more strenous exercise treadmill test is used compared to the monotherapy studies no beneficial effects on number of anginal attacks and consumption of short-acting nitrates were observed. In addition, no data are available to assess the benefit/risk on top of a 100mg atenolol dose – this should be reflected in any proposed wording of the SPC.
Therefore, the MAH was asked to provide more evidence and discuss the clinical relevance of the observed effect size of the primary outcome parameters - in both the total population and post hoc defined groups.

The MAH explained that the primary efficacy criterion was total exercise duration (TED) of an exercise tolerance test (ETT) was in accordance with EMEA guideline (CPMP/EWP/234/95 rev 1, 2006). As patients received an efficient background therapy, the standard Bruce exercise protocol was chosen. The improvement in TED in Study CL3-057 of 16 s ($p < 0.001$) (table 1) was achieved, on average, during the third stage of the standard Bruce protocol, which represents a substantial workload (treadmill speed 5.5 km/h, gradient 14%) and will have a great impact on patients' daily life activities (table 2). The improvement in TED was accompanied by improvements in time to angina onset (TAO) of 25 s ($p < 0.001$) and in time to 1 mm ST segment depression (TST) of 28 s ($p < 0.001$). These changes in main ETT criteria with ivabradine are numerically similar to those obtained with the metabolic agent ranolazine when given on top of background therapy with a betablocker or calcium antagonist, and which supported an indication for use of ranolazine as add-on therapy on top of both classes of drug (see also table 1). However, the changes with ranolazine were achieved at a lower workload (treadmill speed 2.7 km/h, gradient 10%) than those with ivabradine. The improvements in ETT criteria with ivabradine as add-on therapy in Study CL3-057 are of substantially greater clinical importance regarding patients' daily life activities than the corresponding changes observed with ranolazine, for which an indication has been obtained.

Table 1: Comparison in TED, TAO and TST between ivabradine and ranozaline

Change from baseline (relative to placebo)	CL3-057	CVT 3033	
	Ivabradine 7.5 mg b.i.d.	Ranolazine 750 mg b.i.d.	Ranolazine 1000 mg b.i.d.
ETT protocol	Standard Bruce*	Modified Bruce**	
Total exercise duration (s)	16.3 (p < 0.001)	23.7 (p = 0.03)	24.0 (p = 0.03)
Time to angina onset (s)	28.5 (p < 0.001)	29.7 (p = 0.01)	26.0 (p = 0.03)
Time to 1 mm ST depression (s)	25.5 (p < 0.001)	19.9 (NS)	21.1 (NS)

NS: not significant
** Change achieved, on average, at speed of 5.5 km/h, gradient 14%*
*** Change achieved, on average, at speed of 2.7 km/h, gradient 10%*

Most published studies of combination anti-anginal therapy have shown only small and non-significant benefits of the combination on ETT criteria at the trough of drug activity. In the meta-analysis performed by Klein (2002), the difference in TED, observed at trough of drug activity,

between the combination of calcium antagonists and beta-blockers and beta-blockers as monotherapy was only 4 s and was not significant. In the meta-analysis used as a reference (Klein et al., 2002,) 23 randomized trials were analyzed. Analyses were performed independently to differentiate peak and trough effects (within or later than 6 h following drug intake). Upon treatment with beta-blocker combined to calcium antagonist, there was an insignificant difference of 29 s at peak and no difference at trough (4 s, 1%, p = 0.14) in TED compared to beta-blocker alone. Time to 1 mm ST-segment depression was 33 s at peak and 10 s (3%, p = 0.21) at trough. Time to onset of pain was 38 s longer at peak and -4 s (0%, p = 0.65) at trough. In the current Study CL3-057, ETT was performed at the trough of ivabradine and atenolol activity, i.e. 12 ± 1 hours and 24 ± 2 hours post-dosing, respectively. Thus, the change in ETT of approximately 16 seconds as well as the results of the secondary endpoints can be considered clinically relevant.

In Study CL3-057, patients were already receiving a background therapy with atenolol 50 mg o.d. and had a low incidence of angina attacks per week (1.7 AA/w). The low frequency of AA/w at baseline could partly explain the lack of a significant treatment effect. The decrease in the mean number of AA/w was greater in the most symptomatic patients. Patients with at least 1, 2 and 3 AA/w during run-in period had a mean number of 3.7, 5.1 and 6.7 AA/w at baseline which decreased to 1.8, 2.5 and 3.3 AA/w respectively (table 3). The mean decrease in AA/w is similar to the decrease observed in a previous Study (CL3-017) when patients had treatment with atenolol in monotherapy increased from 50 mg o.d. to 100 mg o.d. According to the guideline "it has become accepted that measurements of exercise capacity using standardised exercise testing should be, in spite of an intrinsic amount of variability, the major criteria of efficacy and may account for the patient benefit in terms of reduction of symptoms" (CPMP/EWP/234/95 rev 1, 2006). "Assessment of the effect of anti-anginal drugs based on clinical alone is as yet considered too unreliable because of the possible influence of uncontrolled variables" and "the consumption of SAN is highly variable and today is considered of limited clinical value". The differences in angina attack frequency and SAN consumption are considered in the guideline as secondary criteria because they are less sensitive due to the fact that patients can adapt their effort in daily life to their clinical status.

Table 2: Standard Bruce test and Modified Bruce test

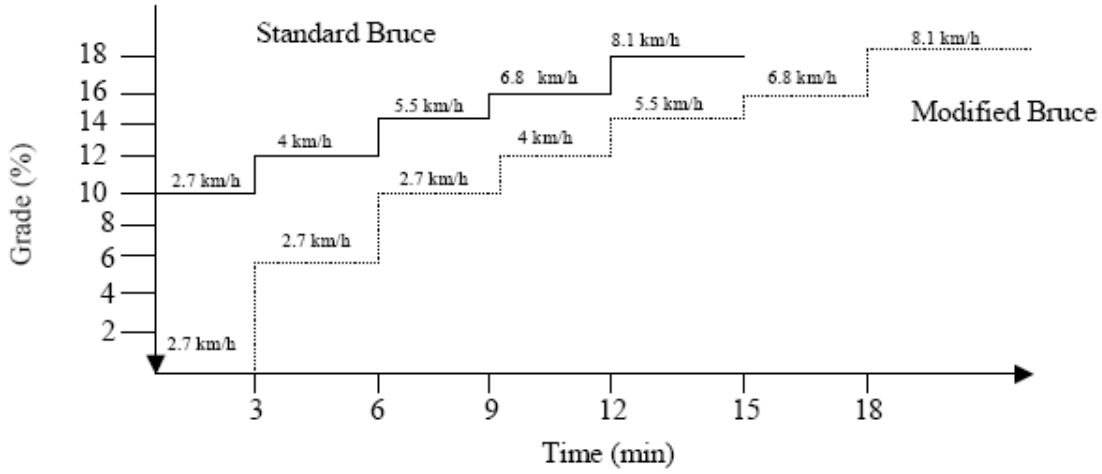


Table 3: Effect on numbers of Angina Pectoris Attacks during run-in and during study phase

		≥ 1 AA/w		≥ 2 AA/w		≥ 3 AA/w	
Descriptive Statistics		**Ivabradine**	**Placebo**	**Ivabradine**	**Placebo**	**Ivabradine**	**Placebo**
	N	198	196	124	117	78	77
Run-in	Mean ± SD	3.7 ± 4.2	3.3 ± 2.7	5.1 ± 4.8	4.6 ± 2.8	6.7 ± 5.5	5.7 ± 2.9
End – Run-in	Mean ± SD	-1.8 ± 3.7	-1.5 ± 2.5	-2.5 ± 4.5	-1.9 ± 3.1	-3.3 ± 5.5	-2.4 ± 3.7

The CHMP considered that an improvement on TED and other exercise test outcomes (time to angina onset and time to 1 mm ST depression) was effectively shown with ivabradine. However, the clinical relevance of the small absolute improvement 16 sec on TED was questioned, especially since no impact was observed on nitrate use and angina attacks. The applicant now shows that the effect size was similar to ranolazine when given on top of beta-blockade but using a more strenous exercise test

in study CL3-057. The standard Bruce test is considerably more intensive than the modified protocol that was used with ranolazine. The smaller absolute change of 16 seconds gain can thus be considered at least comparable to the 24 seconds gain with ranolazine. The other tolerance test endpoints were superior for ivabradine compared to ranolazine. In comparison, combined use of calcium channel blockers and beta-blockers had even less impact on exercise tolerance testing. Thus, improvement in TED by an antianginal agent can be expected to be relatively less when added to a beta-blocker than given as monotherapy. Improvement by ivabradine compares favourably with ranozaline and ca-antagonists added to beta-blockade, that are accepted combinations. Therefore the CHMP considered that the above ivabradine data are in line with the previous conclusion of the CHMP concerning ranolazine.

Choice of atenolol 50mg dose

The MAH considered that it was important to define and to provide the background therapy to demonstrate the efficacy of ivabradine as add-on therapy of beta-blockers. Atenolol was one of the most frequently prescribed products at the initiation of Study CL3-057 and was chosen as a good and usual representative of beta-blockers. The median dose of atenolol in a recent population study of beta-blocker use in 55 000 patients after myocardial infarction was 50 mg/day (Gislason et al., 2006). Similarly, in a recent report from the European Heart Survey, the mean daily dose of atenolol in patients with stable angina after assessment by a cardiologist was 55 mg/day (Daly, 2008). The dose of atenolol of 50 mg/day chosen for background therapy in Study CL3-057, is therefore representative of current general clinical practice.

The MAH explained that for similar reasons, atenolol 50 mg/day was also chosen as background therapy in a study of the metabolic agent ranolazine as add-on therapy. The improvements observed in ETT criteria during a Bruce modified ETT in this ranolazine study were comparable to results observed with ivabradine (although the ranolazine results were obtained at a lower workload they supported the following indication: "*ranolazine is indicated as add-on therapy for the symptomatic treatment of patients with angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies (such as beta-blockers and/or calcium antagonists)"*.

A post-hoc subgroup analysis of the ranolazine study was performed in patients whose dose of background therapy appeared to be maximal at baseline and showed similar results in terms of main ETT criteria to the whole studied population. This result was taken to imply that an effect could be expected also in a population whose background treatment was "state-of-the-art". An equivalent subgroup analysis has been performed in Study CL3-057. A group of patients was identified whose atenolol dose of 50 mg o.d. was judged to be maximal, using the same criteria as in the ranolazine study (resting heart rate ≤ 60 bpm and/or supine systolic blood pressure ≤ 100 mmHg and/or mean PR interval ≥ 200 ms at baseline). Changes in TED and TST over 4 months in this subgroup (N = 144) were similar to those in the whole studied population (FAS). The improvement in TED was 16.3 s, compared with 16.3 s in the FAS, and the improvement in TST was 28.9 s, compared with 28.5 s in the FAS. According to the MAH, these results indicate that the conclusions of Study CL3-057 are unlikely to have been affected by the absence of a formal procedure to maximise the background therapy dose.

Table 4. Study CL3-057 - Changes from baseline in total exercise duration and time to 1-mm ST segment depression in the subgroup of patients whose beta-blocker dose was judged to be maximal. Mean ± SD unless otherwise stated

Change (s)	Ivabradine	Placebo	Difference[b] [95% CI]	p-value
Total exercise duration				
Full Analysis Set	24.3 ± 65.3 (N = 441)	7.7 ± 63.8 (N = 434)	16.3 [7.9; 24.7]	< 0.001
Maximal beta-blocker dose subgroup	26.6 ± 63.2 (N = 80)	8.8 ± 71.2 (N = 64)	16.3 [-5.04; 37.7]	0.066
Time to 1-mm ST segment depression				
Full Analysis Set	45.7 ± 93.0 (N = 441)	15.4 ± 86.6 (N = 434)	28.5 [16.8; 40.3]	< 0.001
Maximal beta-blocker dose subgroup	46.6 ± 84.9 (N = 80)	14.8 ± 86.7 (N = 64)	28.9 [1.82; 56.0]	0.018

[a] *Defined as patients with heart rate ≤60 bpm and/or supine systolic blood pressure ≤100 mmHg and/or mean PR interval ≥ 200 ms at baseline.*
[b] *Ivabradine minus placebo, adjusted*

The CHMP reviewed the MAH justification above summarised and considered that the number of subjects in CL3-057 study with maximal atenolol dosing represent a minority (N=144) of the total study population of 889 subjects. The efficacy data appears similar in both groups, however, statistical significance compared to placebo is not reached for the primary endpoint TED in the maximal beta-blocker dose subgroup (see Table 4).

Up-titration of atenolol, although being a clinically relevant issue, was not requested for the current indication of ranolazine. Ranolazine, via its action to decrease the late sodium current, is considered to reduce these intracellular ionic imbalances during ischaemia. This reduction in cellular calcium overload is expected to improve myocardial relaxation and thereby decrease left ventricular diastolic stiffness. In contrast, ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker. Thus the mechanism of action is different between the two medicinal products and therefore, the combination with beta-blockers can result in different efficacy and safety effects.
The guideline (CPMP/EWP/234/95 rev 1, 2006) requires an optimised and properly defined background therapy.

The question of whether adding ivabradine in patients receiving a medium beta-blocker dose is superior or non-inferior to increasing the beta-blocker dose could not be addressed directly given the design of Study CL3-057. However, an indirect approach has been used to address this question by combining data from Study CL3-057 (in which ivabradine was added to atenolol 50 mg o.d.) with data from the atenolol group in Study CL3-017 (in which the atenolol dose was increased from 50 to 100 mg o.d.). The improvements resulting from increasing the atenolol dose were approximately 19 s for TED, 32 s for TAO and 29 s for TST during the third or the fourth stage of the modified Bruce protocol (speed 2.7 km/h or 4 km/h, gradient 10% or 12% respectively). In Study CL3-057, the effect of adding ivabradine to atenolol 50 mg o.d. was to increase TED by 24 s, TAO by 49 s and TST by 46 s, and these improvements were obtained during the third stage of the standard Bruce protocol (speed 5.5 km/h, gradient 14%). [These are changes compared to baseline.]

An indirect approach has been used to address the question of superiority or non-inferiority. Results (numerical values not relative to placebo) of the Study CL3-017 (Phase III randomised, double-blind, controlled, parallel group, non-inferiority study of ivabradine versus atenolol) have been compared to those of CL3-057. The indirect method gives some confirmation of the beneficial effect of ivabradine as an add-on therapy to beta-blockers.
In order to get a full answer to this question, the MAH was subsequently asked to perform a direct comparison between patients receiving ivabradine on top of a sub-optimal dose of betablocker versus up-titration of the beta-blocker.

The MAH argued that target doses are rarely used in clinical practice, and are not necessarily optimal for many patients. It was pointed out that the median atenolol dose in a recent population study of beta-blocker use in 55 000 patients after acute myocardial infarction was 50 mg/day (Gislason et al., 2006) and that, in a recent report from the European Heart Survey, the mean daily dose of atenolol in patients with stable angina after assessment by a cardiologist was 55 mg/day (Daly et al., 2008). A

recent report (Setakis et al., 2008) from the UK General Practice Research Database of the UK Medicines and Healthcare Products Regulatory Agency found that only 4.6% of angina patients taking betablockers in clinical practice (N = 12 493) received the target dose (100 mg/day for atenolol), 57.2% received < 50% of the target dose, and the mean dose of atenolol was approximately 40 mg/day. Percentages of target doses were similar for other beta-blockers and for other indications (heart failure and myocardial infarction).

In relatively old and small clinical trials in heart failure, patients vary in their response to beta-blockers and high doses often do not produce greater benefits than moderate doses, and an individualised approach to dosing has been recommended. Similarly, in studies in patients with stable angina, high doses of beta-blockers have produced only modest and inconsistent improvements in exercise tolerance compared with moderate doses.
According to the applicant Ivabradine study CL3-017 is the largest study evaluating the effects of up-titration of atenolol in stable angina published to date. In this study, the additional improvements resulting from the doubling of the atenolol dose were markedly smaller than the improvements seen at 1 month with the 50 mg o.d. dose (table 2).

Table 2 - Effect of up-titration of atenolol dose on ETT variables at trough of drug activity in the atenolol group in study CL3-017, at 1 month (atenolol 50 mg o.d.) and at 4 months (atenolol 100 mg)

ETT Variable	Baseline	1 month (atenolol 50 mg)		4 months (atenolol 100 mg)	
	Value	Value	Change from baseline	Value	Change from 1 month
TED (n = 286)	578.2	638.2	60.0 (10.4%)	657.0	18.8 (2.9%)
TAO (n = 285)	457.6	560.4	102.8 (22.5%)	592.6	32.2 (5.7%)
TST (n = 286)	509.8	577.0	67.2 (13.2%)	606.3	29.3 (4.8%)

TAO: time to angina onset; TED: total exercise duration; TST: time to 1 mm ST segment depression

Like most patients in clinical practice, patients in study CL3-057 were treated with the dose of beta-blocker considered to be optimal for them by the treating physician. In the subgroup of patients in whom the level of beta-blockade at baseline could be judged as maximal in terms of objective heart rate and haemodynamic criteria, improvements in all ETT criteria with ivabradine were the same as in the full patient population, indicating that the efficacy of ivabradine is not reduced in patients maximally treated by a beta-blocker (table 3).

Table 3 - Changes from baseline in ETT variable in the subgroup of patients whose beta-blocker dose was judged to be maximal[a], over the 4-month treatment period. Mean ± SD unless otherwise stated

Change (s)	Ivabradine	Placebo	Difference[b] [95% CI]	p-value
Total exercise duration				
Full Analysis Set	24.3 ± 65.3 (N = 441)	7.7 ± 63.8 (N = 434)	16.3 [7.9; 24.7]	<0.001
Maximal beta-blocker dose subgroup	26.6 ± 63.2 (N = 80)	8.8 ± 71.2 (N = 64)	16.6 [-5.04; 37.7]	0.066
Time to 1-mm ST segment depression				
Full Analysis Set	45.7 ± 93.0 (N = 441)	15.4 ± 86.6 (N = 434)	28.5 [16.8; 40.3]	<0.001
Maximal beta-blocker dose subgroup	46.6 ± 84.9 (N = 80)	14.8 ± 86.7 (N = 64)	28.9 [1.82; 56.0]	0.018
Time to angina onset				
Full Analysis Set	49.1 ± 83.3 (N = 441)	22.7 ± 79.1 (N = 434)	25.5 [15.0; 36.0]	<0.001
Maximal beta-blocker dose subgroup	50.8 ± 93.9 (N = 80)	17.7 ± 82.6 (N = 64)	33.1 [4.2; 61.9]	0.013
Time to limiting angina				
Full Analysis Set	26.0 ± 65.7 (N = 441)	9.4 ± 63.8 (N = 434)	16.3 [7.9; 24.7]	<0.001
Maximal beta-blocker dose subgroup	27.8 ± 63.3 (N = 80)	8.7 ± 70.9 (N = 64)	17.6 [-3.6; 38.9]	0.051

[a] *Defined as patients with heart rate ≤60 bpm and/or supine systolic blood pressure ≤100 mmHg and/or mean PR interval ≥200 ms at baseline.*
[b] *Ivabradine minus placebo, adjusted*

Ivabradine studies CL3-017 and CL3-057 had similar patient populations and represent large and rigorous evaluations of either increasing the dose of a beta-blocker or adding ivabradine to a moderate but optimal dose of a beta-blocker. Taking together the results of the two studies indicate that the addition of ivabradine to atenolol 50 mg/day was at least as efficacious as increasing the atenolol dose from 50 to 100 mg/day (table 5).

Table 5 - Comparison of effect on ETT parameters of increasing atenolol dose from 50 to 100 mg/day (in study CL3-017) and adding ivabradine 5-7.5 mg b.i.d. to atenolol 50 mg/day (in study CL3-057)

ETT variable	Effect of increasing atenolol dose from 50 to 100 mg/day (Study CL3-017, modified Bruce protocol)		Effect of adding ivabradine to atenolol 50 mg/day (Study CL3-057, standard Bruce protocol)	
	Baseline (ETT at 1 month)	Change from baseline	Baseline	Change from baseline
TED (s)	638.2	18.8 (2.9%)	445.6	24.3 (5.5%)
TAO (s)	560.4	32.2 (5.7%)	352.5	49.1 (13.9%)
TST (s)	577.0	29.3 (4.8%)	337.8	45.7 (13.5%)

TAO: time to angina onset; TED: total exercise duration; TST: time to 1 mm ST segment depression

The data presented indicate that in patients receiving a beta-blocker whose symptoms are not controlled, who cannot tolerate a higher dose of the beta-blocker, and whose heart rate is > 60 bpm, the addition of ivabradine represents a real alternative for controlling persistent symptoms.

In order to better describe the population of patients which can benefit from the combination of ivabradine with beta-blockers, the MAH proposed to reword the indication as follows:
Symptomatic treatment of chronic stable angina pectoris in coronary artery disease patients with normal sinus rhythm. Ivabradine is indicated:

- *in patients 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*.

The CHMP reviewed the additional documentation provided by the MAH in its second request for information, providing data from clinical practice which indicate that patients for a number of reasons are frequently not treated with the maximal beta-blocker dose.
These data, as also shown by the analysis of study CL3-017 in which patients were uptitrated from 50 mg atenolol to 100 mg atenolol, do suggest poor clinical practice and that there is still room left for optimizing treatment of these patients.

Study data provided on increasing the atenolol dose from 50 mg to 100 mg daily include seven small clinical studies (with 10-36 subjects) that show a statistically significant increase in exercise capacity compared to placebo. Between-dose significance is not observed or the significance testing is not included, which may be due to the small number of subjects in each dosing group. In the larger CL3-017 study (N=286), a between-dose significance testing is not included in the response, either (see *table 2*). Thus, these data do not provided a solid basis for justifying why a higher dose of 100 mg atenolol was not used in the CL3-057 study. The MAH considered that the betablocker dose of atenolol 50 mg o.d. or equivalent had been judged to be appropriate for each individual patient by the treating physician before inclusion to the study CL3-057. However, without an ongoing study recruitment setting an alternative for add-on therapy with ivabradine could have been an increase of the betablocker dose.
Comparison of the effect of increasing the dose of atenolol from 50 to 100 mg/day with the effect of adding ivabradine 5-7.5 mg b.i.d. to ongoing background therapy of atenolol 50 mg/day on ETT parameters (studies CL3-017 and CL3-057, see *Table 4*) is difficult, as the baseline ETT values of the two studies differ significantly due to the different exercise protocols and as the data is combined from two separate studies. In the CL3-057 study a more strenuous exercise protocol was used and the change from lower baseline status is greater. It can also be asked whether the higher baseline ETT in study CL3-017 leaves less room for improvement.

In conclusion, having reviewed the supplementary information provided by the applicant during the complete procedure, the CHMP considered that the study CL3-057 was able to demonstrate efficacy

of ivabradine when given as add-on therapy on top of a beta-blocker, although the betablocker dose was likely to be suboptimal in some patients. It is considered acceptable that there are some patients on betablocker treatment who would benefit from ivabradine. An additional prospectively trial comparing ivabradine on top of a suboptimal dose of betablocker versus up titration of the beta-blocker is therefore not considered required to demonstrate efficacy for this indication. One restriction should be made, however, and that refers to the heart rate at initiation of the combination. Only patients whose heart rate is > 60 bpm were included as patients with a heart rate below this limit are contraindicated for treatment with ivabradine.
Thus, it is considered that the indication proposed by the MAH is acceptable with slight modification of the current wording:
Symptomatic treatment of chronic stable angina pectoris in coronary artery disease patients with normal sinus rhythm. Ivabradine is indicated:
- in patients 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 betablocker dose***, and whose heart rate is > 60 bpm***.

Safety results

Analysis of the safety data did not reveal new safety concerns, although clearly more adverse events were reported than in the placebo group. The majority of reported adverse events related to the known effects on heart rate and visual disturbances.

The incidence of adverse reactions was higher in the group with combination therapy. The clinical significance of aggravated angina pectoris and ventricular extrasystoles remains unclear. These events appeared to be related to the progression of the disease and all cases were individually discussed by the applicant. On the other hand, when heart rate is decreased the end-diastolic pressure will increase due to increased ventricular filing, this will in turn increase oxygen demands during systolic work that may not be compensated by increased perfusion time.

Especially when ivabradine would be added to higher doses of betablockers such as atenolol 100 mg daily this may lead to further clinical deterioration, e.g. more anginal symptoms due to increased end-diastolic pressure as a result of overly decreased HR and / or ventricular arrhythmias because of re-entry mechanisms.
Therefore, the MAH was asked to discuss further the clinical significance of the above observed findings in particular with the possibility that patients could in daily practice be treated with higher doses of beta-blockers, e.g. atenolol 100 mg.

The applicant explained that the incidence of the adverse event (AE) angina pectoris was higher in the ivabradine group (1.3%, 6 patients) than with placebo (no patients), although the number of patients concerned was small and in 3 cases there was no evidence of any worsening of angina status with treatment. Other lines of evidence indicate that adding ivabradine to a betablocker does not lead to an increased incidence of this AE.
Therefore the results of another study (BEAUTIFUL) with ivabradine were further discussed by the MAH as detailed below:
While BEAUTIFUL study (CL3-056) was markedly different in design and patient population to phase III studies included in the initial submission, some results are directly relevant to the approved indication for ivabradine, particularly from some subgroup analyses (patients who had their physical activity limited by anginal pain at baseline, patients taking and not taking beta-blockers). Data from patients taking ivabradine in combination with a beta-blocker in this much larger and longer study showed that there was no excess of angina pectoris compared with the placebo group, and this was still true in patients taking guidelines-recommended target doses of beta-blockers (Fox et al, 2006). In patients in Study CL3-056 with anginal symptoms and taking betablockers, the incidence of angina pectoris was lower in the ivabradine group (3.1%; n=654) than with placebo (4.7%; n=696). Finally, the incidence of angina pectoris with ivabradine in Study CL3-057 (1.3%) was not higher than in the ivabradine EPAR (2.0% and 1.9% for ivabradine and placebo, respectively). Taken together, these data do not suggest an increase in anginal symptoms when ivabradine is taken in combination with a beta-blocker.

In Study CL3-057, the incidence of the AE ventricular extrasystoles (VES) was higher in the ivabradine group (1.3%, 6 patients) than with placebo (0.2%, 1 patient), although the number of patients concerned was again small and no case was followed by more complex ventricular arrhythmia (table 4). In BEAUTIFUL study, the patients taking ivabradine in combination with a beta-blocker, including those taking target beta-blocker doses, the incidence of VES was similar compared with the placebo group. For the patients with anginal symptoms and taking beta-blockers, the incidence of VES was lower in the ivabradine group (1.8%; n=654) than in the placebo group (3.6%; n=696). Finally, the incidence of VES with ivabradine in Study CL3-057 (1.3%) was not higher than in the ivabradine EPAR (3.0% and 1.3% for ivabradine and placebo, respectively). Overall, no particular risk of excess VES may be expected with the combination of ivabradine and a beta-blocker even in patients receiving high doses of beta-blockers.

The tendency for the heart rate lowering effect of ivabradine to be greatest in patients with the highest initial heart rate, minimising the risk of excessive bradycardia, is preserved when ivabradine is used in combination with beta-blockers. In addition, in the Study BEAUTIFUL the incidence of symptomatic bradycardia was actually lower (3.7%) in patients taking ivabradine in combination with beta-blockers than in those not taking beta-blockers (4.4%).

Results from studies CL2-062 and CL2-053 showed that heart rate reduction with ivabradine, even when given on top of high doses of beta-blockers and in patients with severely damaged ventricles, is not associated with increased left ventricular pressure or diameter, an effect that might be related to the absence of any negative inotropic effect of ivabradine. Analyses submitted in the original application regarding the incidence of coronary events and arrhythmic events (other than bradycardia) in subgroups of ivabradine-treated patients with different levels of lowest heart rate indicated that there is no evidence of a link between bradycardia and coronary or arrhythmic events with ivabradine treatment (table 6).

Overall, the balance of evidence indicates that the combination of ivabradine with betablockers, even in patients receiving high doses of beta-blockers, is not associated with particular safety concerns.

Table 4: Percentage of angina pectoris and ventricular extrasystoles according to betablocker treatment and patient with angina

EAE		All patients with beta-blockers		All patients with beta-blockers at target dose		Patients with angina and with beta-blockers		Patients with angina and with target dose of beta-blockers	
Preferred Term		Ivabradine (N = 4747)	Placebo (N = 4732)	Ivabradine (N = 418)	Placebo (N = 430)	Ivabradine (N = 654)	Placebo (N = 696)	Ivabradine (N = 58)	Placebo (N = 55)
Angina pectoris	%	2.9	3.3	3.1	4.4	3.1	4.7	6.9	12.7

EAE		All patients with beta-blockers		All patients with beta-blockers at target dose		Patients with angina and with beta-blockers		Patients with angina and with target dose of beta-blockers	
Preferred Term		Ivabradine (N = 4747)	Placebo (N = 4732)	Ivabradine (N = 418)	Placebo (N = 430)	Ivabradine (N = 654)	Placebo (N = 696)	Ivabradine (N = 58)	Placebo (N = 55)
Ventricular extrasystoles	%	1.9	1.9	1.2	0.9	1.8	3.6	0.0	3.6

Table 5: Change from baseline for HR during treatment period in patients with or without betablockers

All patients (N = 10917)		With beta-blockers		Without beta-blockers	
		Ivabradine (N = 4749)	Placebo (N = 4738)	Ivabradine (N = 730)	Placebo (N = 700)
Baseline	N	4706	4700	720	695
	Mean ± SD	70.95 ± 9.52	71.20 ± 9.70	75.08 ± 10.78	74.49 ± 10.95
	Median	68	69	74	72
On treatment	N	4706	4700	720	695
	Mean ± SD	63.79 ± 10.73	69.72 ± 11.63	66.44 ± 11.72	71.58 ± 12.20
	Median	62	68	65	70
On treatment - Baseline	N	4706	4700	720	695
	Mean ± SD	-7.15 ± 11.38	-1.48 ± 10.93	-8.63 ± 11.77	-2.91 ± 11.88
	Median	-7	-2	-9	-3
Approach with adjustment	E (SE)	-5.80 (0.21)		-5.44 (0.56)	
Patients with HR < 65 bpm (N = 3045)					
Baseline	N	1107	1275	105	127
	Mean ± SD	61.96 ± 1.64	61.97 ± 1.59	61.99 ± 1.50	62.13 ± 1.57
	Median	62	62	62	62
On treatment	N	1107	1275	105	127
	Mean ± SD	57.78 ± 5.99	63.64 ± 6.47	58.82 ± 5.66	64.47 ± 7.36
	Median	57	63	58	63
On treatment - Baseline	N	1107	1275	105	127
	Mean ± SD	-4.18 ± 6.02	1.66 ± 6.45	-3.17 ± 5.67	2.34 ± 7.54
	Median	-5	1	-3	2
Approach with adjustment	E (SE)	-5.85 (0.26)		-5.58 (0.82)	

Table 6: Rates of coronary artery disorders in patients treated with ivabradine and having one or more resting HR measurements below 50 and below 45 bpm expressed as patients affected per 100 patient-years of exposure

High level group term High level term Preferred term	Ivabradine		
	OSS-047	OSS-047 with one or more HR measurements below a defined threshold	
		Below 50 bpm	Below 45 bpm
	n = 2856	n = 565	n = 164
	PY* = 1061.8	PY*= 242.4	PY* = 70.8
Coronary artery disorders	14.32	9.90	7.06
Coronary artery ischaemic disease	14.03	9.90	7.06
Angina pectoris aggravated	5.18	3.71	1.41
Angina unstable	4.52	3.30	2.82
Myocardial ischaemia	3.39	2.89	1.41
Myocardial infarction	1.70	0.83	1.41
Coronary artery disorders NEC	0.28	-	-
Coronary artery disease aggravated	0.28	-	-

PY: patient-years of exposure

The CHMP reviewed the data above described by the applicant and had the following preliminary conclusions.

The Applicant is referring to safety data of the BEAUTIFUL study (CL3-056) a large three-year study required as a follow-up measure (FUM 008.2) with 10917 subjects with stable coronary artery disease (CAD) and left ventricular systolic dysfunction. It was concluded that ivabradine does not have additional benefit in patients with CAD with LV dysfunction. No new safety concerns were raised, however, small but numerically higher number of sudden deaths and slightly more rhythm abnormalities were observed.

The following text is included in ivabradine EPAR: *"In patients with angina pectoris, mild to moderate bradycardia (40–50 bpm) is generally not a major safety issue. HR can usually be registered by the patients, and causality to dosage and symptoms recognised. However, use of ivabradine is limited to patients with contraindication or intolerance to beta-blockers, and in this group tendency to excessive, symptomatous bradycardia is not uncommon". In SPC Section 4.8 bradycardia is listed as a common undesirable effect: "Bradycardia: 3.3% of patients particularly within the first 2 to 3*

months of treatment initiation. 0.5% of patients experienced a severe bradycardia below or equal to 40 bpm".

In the ivabradine group of Study CL3-057, the incidence of symptomatic bradycardia was 1.1% (5 patients vs. none in the placebo group) and the incidence of asymptomatic bradycardia was 3.1% (14 patients vs. 0.5% or 2 patients in the placebo group). In the larger BEAUTIFUL study (CL3-056), the incidence of bradycardia was 3.7% in patients receiving beta-blockers at baseline and 4.4% in those without beta-blockers. A negative correlation between baseline HR and the change in HR with ivabradine plus beta-blocker was shown in the BEAUTIFUL study as well as in ivabradine-treated patients not receiving betablockers (pooled analysis of patients in the original application). The corresponding data in the current Study CL3-057 has not been shown.

In a subpopulation with anginal symptoms and beta-blocker use in the larger BEAUTIFUL trial (CL3-056) the reported larger number of aggravated angina and ventricular extrasystoles adverse events on treatment in study CL3-057 was not confirmed. Nor were excessive HR reductions observed in patients treated with maximal betablocker doses. However, in the whole population of BEAUTIFUL (and in the Holter substudy provided with the same FUM), there were numerically more deaths in the ivabradine group than in the placebo group, although differences were small: 10.50% versus 10.09%, respectively (table 18). This small difference was also present when death was reported as the event: 5.6% vs. 4.9% and as sudden death: 4.6% versus 4.2%. Cardiac arrhythmias were the cause of death in a minority of patients (0.33 and 0.26%). When cardiac disorders leading to death were analysed separately, incidence was found to be numerically lower and even in a more detailed evaluation of arrhythmic AEs leading to death a specific harmful cause could not be identified. Thus, although this study did not achieve it main goal of showing an overall cardiovascular benefit (only for patients with a heart rate $\geq$ 70 bpm), no detrimental effect on CV outcome was present.

Also, in the subgroup of patients with stable angina taking beta-blockers numerical reductions were seen for the primary and selected secondary endpoints (table 8), at various levels of LV dysfunction or NYHA classes (table 14), and for investigator assigned adverse events with an outcome of death (table 19). These results, although limited by the post-hoc analysis, again suggest no increase in cardiac events when ivabradine is combined with beta-blockers in this high risk group of patients with LV dysfunction and angina.

In contrast to the slightly higher numbers of AF for ivabradine in the total population (table 25), the subgroups of patients with stable angina and in patients with stable angina taking beta-blockers did not reveal a higher incidence of AF with ivabradine (table 20 and 22). Furthermore, the Holter substudy did not show a clear proarrhythmic effect, although minor differences were noted for some of the arrhythmias (table 24).

As expected, more bradycardia events were observed during treatment with ivabradine in the overall population, but this difference in events between ivabradine and placebo was not increased in the anginal betablocker subgroup and this subgroup even demonstrated a lower frequency of events compared to the overall population (table 27). In the LV and NYHA subclasses no marked differences for bradycardia were noticed. In addition, only small numbers of excessive reductions in HR were observed in anginal patients treated with beta-blockers or in any of the LV and NYHA subclasses (appendix table 19). These data are therefore reassuring in terms of risk for severe bradycardia.

In conclusion, the relevance of the slight numerical increase in number of deaths and AF in the overall BEAUTIFUL population with LV dysfunction remains unclear and may be a chance finding. Overall, the data do not indicate a clear proarrhythmic effect, neither do they indicate a pro-anginal effect. The data of the sub analyses in patients with stable angina and concurrent use of beta-blockers are reassuring for the currently claimed indication, although these were part of a post-hoc analysis. These data do not confirm initial concerns raised during the assessment of study CL3-057. It is overall considered that the data on patients with angina taking ivabradine on top of beta-blockers in study CL3-056 is reassuring in terms of cardiac safety profile.

I.3 Changes in the product information

The MAH requested changes in several sections of the SPC and PI which are reflected below :

- 4.1 Therapeutic indications

The wording of the indication was modified following the MAH answer to request for supplementary information and subsequently during the assessment to best reflect the results and targeted population for which the product had shown beneficial effects.

The final indication agreed during CHMP discussions

Symptomatic treatment of chronic stable angina pectoris in coronary artery disease patients with normal sinus rhythm.
Ivabradine is indicated :
- in patients 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.

- 4.3 Contra-indications

Heart failure patients with NYHA functional classification III-IV ~~due to lack of data~~

- 4.4 Warnings and special precautions for use

The SPC is updated with the below changes:

Combination with calcium channel blockers ~~and other anti-anginal therapies~~

Modification of the previous information related to HF patients with NYHA classification II and patients with left ventricular dysfunction :

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 should be used with caution in heart failure patients with NYHA functional classification I-II, (see section 4.3).***

- 5.1 Pharmacodynamics

Addition of the following information:

The antianginal and anti-ischaemic efficacy of Corlentor was studied in ***~~four~~ five*** *double-blind randomised trials (****~~two~~ three*** *versus placebo, and one each versus atenolol and amlodipine). These trials included a total of* ***~~3,222~~ 4,111*** *patients with chronic stable angina pectoris, of whom* ***~~2,168~~ 2,617*** *received ivabradine.*
…..

In a 889-patients randomised placebo-controlled study, ivabradine given on top of atenolol 50 mg o.d. showed additional efficacy on all ETT parameters at the trough of drug activity (12 hours after oral intake).
…..

A large outcome study, BEAUTIFUL, was performed in 10917 patients with coronary artery disease and left ventricular dysfunction (LVEF<40%) on top of optimal background therapy with 86.9% of

patients receiving beta-blockers. The main efficacy criterion was the composite of cardiovascular death, hospitalization for acute MI or hospitalization for new onset or worsening heart failure. The study showed no difference in the rate of the primary composite outcome in the ivabradine group by comparison to the placebo group (relative risk ivabradine:placebo 1.00, p=0.945).
In a post-hoc subgroup of patients with symptomatic angina at randomisation (n=1507), no safety signal was identified regarding cardiovascular death, hospitalization for acute MI or heart failure (ivabradine 12.0% versus placebo 15.5%, p=0.05).

II. OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT

It is accepted that the study CL3-057 was able to demonstrate efficacy of ivabradine when given as add-on therapy on top of a beta-blocker, although the betablocker dose was likely to be suboptimal in some patients. It is considered acceptable that there are some patients on betablocker treatment who would benefit from ivabradine.

Efficacy was not directly demonstrated in a setting where add-on ivabradine is compared to a treatment strategy with an increase to a maximal (tolerated) dose of the given beta-blocker. However, an indirect comparison, with its limitations, showed that ivabradine to atenolol had comparable effects to uptitration of 50 mg to 100 mg of atenolol. In addition, the MAH showed that also those patients with a lower baseline HR (between 60 and 70 bpm) or patients that could be considered to be on a maximal effective atenolol dose had similar benefits, although not significant, of adding ivabradine to their beta-blocker therapy compared with the whole study population. A similar approach was taken during the assessment of ranolazine, another anti-anginal agent approved by the CHMP.

The supportive large safety study results of Beautiful introduced in this procedure are considered relevant and supportive of safety data in this population.

In conclusion, the CHMP considered that the extension of indication is considered acceptable based on the submitted efficacy and safety data showing that the benefit / risk of ivabradine over placebo in combination with beta-blockers in patients inadequately controlled with an optimal betablocker dose and with a heart rate > 60 bpm can be considered positive.

III. CONCLUSION

On 24 September 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, and Package Leaflet.