I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report Synopsis**
Study title	**Evaluation of the anti-anginal efficacy and safety of oral administration of ivabradine compared to placebo on top of a background therapy with atenolol in patients with stable angina pectoris. A 4-month randomised double-blind parallel-group international multicentre study.**
Study drug	**S 16257**
Indication	**Stable angina pectoris**
Development phase	**Phase III**
Protocol code	**CL3-16257-057**
Study initiation date	**08 June 2005**
Study completion date	**17 October 2007**
Main coordinator	[redacted] **Canada H1T 1C8**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 Rue Carnot,** **92284 Suresnes Cedex - France** **Servier Canada Inc., ICTR Canada** **235, Armand-Frappier Blvd.** **Laval, Quebec - Canada H7V 4A7** **Laboratorios Servier, S.L.** **Departamento de Investigacion Desarrollo** **Avenida de los Madronos, 33, 28043 Madrid - Spain** **SERVIER Research and Development** **International Centre for Therapeutic Research** **Gallions,Wexham Springs, Framewood Road - Wexham** **Slough SL3 6RJ - U.K.**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 20 June 2008**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study: Evaluation of the anti-anginal efficacy and safety of oral administration of ivabradine compared to placebo on top of a background therapy with atenolol in patients with stable angina pectoris.
A 4-month randomised double-blind parallel-group international multicentre study.
Protocol number: CL3-16257-057

International Coordinator:
[redacted] CANADA

Study centre:
Total number of 219 centres were opened in 20 countries:
Country (number of centres): Argentina (23), Brazil (17), Bulgaria (9), Canada (12), Chile (8), Czech Republic (8), Germany (6), Hungary (20), Italy (7), Norway (6), Poland (20), Romania (8), Russia (31), Slovakia (5), South Africa (7), Spain (7), Sweden (3), Thailand (5), Ukraine (11), United Kingdom (6).

Publication: Not applicable

Studied period:	**Phase of development of the study:**
- Initiation date: 08 June 2005. - Completion date: 17 October 2007.	Phase III

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 two treatments on their effect on the symptomatology of anginal disease (mean number of angina attacks per week, mean global consumption of short-acting nitrates/week and mean consumption of short-acting nitrates/week for angina attacks).
- 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.*), *i.e.* spontaneously reported adverse events, physical examination including vital signs, 12-lead ECG, ETT safety parameters, 24-hour Holter ECG, biological parameters. In the Holter sub-study the objective was to assess the cardiac parameters and abnormalities on 24-hour Holter ECGs.

Methodology: This was a randomised double-blind placebo-control parallel-group international multicentre study, with a centralised, balanced and non-adaptive randomisation with stratification by centre.
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.*). 3 ETTs were performed during the run-in period (the first two at selection visits and the third one 5 days before inclusion visit) and one ETT at the end of each treatment period (*i.e.* at M2 and M4).

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Number of patients:

- Planned: 750 patients (375 per group).
- Included: 889 patients (449 in the ivabradine group and 440 in the placebo group).

Diagnosis and main criteria for inclusion:

Patients were men or women, outpatients, aged between 18 (or the legal age) and 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 clinical stability (no significant change in frequency, severity or triggering activity within one month preceding pre-selection and no changes in nitrate consumption), with documented coronary artery disease, and who were treated for at least 3 months preceding pre-selection by atenolol 50 mg daily or by a beta-blocker at an equivalent dose. The heart rate (on supine ECG) at pre-selection and inclusion was to be ≥ 60 bpm on atenolol (50 mg *o.d.*) or equivalent beta-blocker treatment. Patients were to have three positive exercise tolerance tests during the run-in, with the second and third being stable.

Study drug:

Ivabradine (S 16257) 5 mg *b.i.d.* then 7.5 mg *b.i.d.* given orally in combination with atenolol (50 mg *o.d.*).
Batch numbers: L0002842, L0005445, L0002924, L0005446.

Reference product:

Placebo given orally twice daily in combination with atenolol (50 mg *o.d.*).

Duration of treatment:

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 a dose equivalent to atenolol 50 mg daily and switched to atenolol at the pre-selection visit.
Randomised treatment period: 2 months at 5 mg *b.i.d.* followed by a forced titration to 7.5 mg *b.i.d* (unless heart rate < 50 bpm) for a further 2 months (*i.e.* 4 months in total).

Criteria for evaluation:

Efficacy measurements:

- ETTs (on treadmill, with Bruce protocol) were performed 3 times during the run-in (at SEL1, SEL2 and prior to the inclusion visit, M0) and twice under treatment, at the trough of drug activity, 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) defined as time to moderate to severe angina pain (*i.e.* as the severity of pain that would ordinarily cause the patient to stop his/her exercise during normal daytime activity)**.
  - 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)*[&]**.
  - Reason for stopping exercise**.

* Evaluated by Core Reading Centre.
** Evaluated by investigator.

The clinical symptomatology of angina was assessed by analysis of the number of angina attacks and consumption of short-acting nitrates (SAN) between two consecutive visits recovered from the patient diaries.

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Safety measurements:
Adverse events, vital signs at rest (blood pressure, HR), ETT safety parameters (blood pressure at rest and at peak of exercise), 12-lead ECG parameters (central reading) and biological parameters.
24-hour Holter ECG parameters (central reading) were measured on a sub-group of 180 patients (90 patients in each treatment group).
Pharmacokinetic measurements were made on blood samples of a sub-group of 206 patients in selected centres. Blood samples were collected at the selection 2 visit (baseline value), M2 and M4 (5 points at each visits including Cmin). The plasma concentrations of ivabradine (S 16257), its main active metabolite, (S 18982) and atenolol were measured. The methodology and results are reported separately (Internal report NP26571).

Statistical methods:
Efficacy analysis:
The main analysis was carried out on the Full Analysis Set-ETT (FAS-E) and confirmed in the Per Protocol Set-ETT 4 months (PPS-E4).
The superiority of ivabradine *versus* placebo was tested on the change in TED *(primary criterion)* over the 4-month treatment period using a parametric analysis of covariance adjusted on country factor with baseline as a covariate. Two robustness analyses were performed: a parametric analysis of variance without adjustment and a non-parametric covariance analysis with adjustment based on the Wilcoxon Rank Norm.
Secondary criteria:
The analysis of the secondary criteria was carried out on the other ETT criteria (TAO, TLA, TST, HR, RPP, reason for stopping exercise), was performed over the 4-month treatment period (FAS-E and PPS-E4) using similar analyses as for the primary criteria and on all ETT criteria over the 2 month treatment period (FAS-E and PPS-E2).

Symptomatology of angina criteria: the mean number of angina attacks, the mean global consumption of SAN and the mean consumption of SAN for angina attacks per week were studied over the 4-month treatment period and over the 2-month treatment period on the FAS-A, PPS-A4 and PPS-A2. Changes over the 4-month treatment period and over the 2-month treatment period were estimated between ivabradine and placebo and within each treatment group using a two-sided 95% confidence interval calculated with parametric and non-parametric approaches without adjustment (based on the Hodges-Lehmann estimator for independent samples). The same analyses were performed in patients with at least one attack at baseline and in patients with at least SAN intake at baseline. Relative changes were also analysed.

Safety analysis:
Descriptive statistics were provided in the Safety Set for adverse events, biological parameters, vital signs, ETT, ECG and in the Safety Set Holter (SSH) for the Holter parameters.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 2681 patients were screened, 2622 were pre-selected and entered the single-blind atenolol run-in phase. Of these, 1792 were not included (mostly due to lack of positive or stable ETT), but analysed for demographics and baseline characteristics (Non Included Set). A total of 889 patients were included in the study and randomised with 449 in the ivabradine group and 440 in the placebo group.

	Ivabradine	**Placebo**	**Total**
Included (randomised)	449	440	889
Lost to Follow-up	-	-	-
Withdrawn	18	8	26
due to adverse event	13	4	17
due to non-medical reason	4	3	7
due to protocol deviation	1	1	2
Completed	431	432	863
Full Analysis Set ETT (FAS-E)	**441**	**434**	**875**
Per Protocol Set ETT at 4 months (PPS-E4)	395	401	796
Per Protocol Set ETT at 2 months (PPS-E2)	415	409	824
Full Analysis Set Angina (FAS-A)	**447**	**438**	**885**
Per Protocol Set Angina at 4 months (PPS-A4)	392	385	777
Per Protocol Set Angina at 2 months (PPS-A2)	413	400	813
Safety set	**449**	**440**	**889**
Safety set Holter (SSH)	90	90	180

The FAS-E consisted of 875 patients (98.4% of RS) and the FAS-A consisted of 885 patients (99.6% of RS). The patients in the RS had a mean age (± SD) of 59.8 ± 7.8 years (68.8% were < 65 years old) and 84.4% were men. They had been diagnosed with angina pectoris with a mean duration (± SD) of 70.5 ± 68.8 months (5.9 years) and had angina pain of grade I (19.5%), grade II (68.6%), or grade III (11.9%) (Canadian Classification). All had received previous pharmacological treatment for angina, without any clinically relevant difference between treatment groups. Almost all (99.9%) were receiving selective beta-blocking agents at selection. Baseline characteristics were comparable between treatment groups. The Non Included Set was comparable except for a slightly higher proportion of women (21.8%).

Most patients had concurrent medical conditions, mainly vascular disorders (78.2%), metabolism and nutrition disorders (72.4%), cardiac disorders (27.2%) and gastrointestinal disorders (23.8%). The main non-specific concomitant treatments received during the treatment period were anti-thrombotic agents (94.5%), serum-lipid reducing agents (78.4%), cardiac therapy (70.3%) and agents acting on the renin-angiotensin system (67.3%). No major differences between groups were detected in the prescription of non-specific drug treatments.

In the RS, mean (± SD) study drug treatment duration was 3.8 ± 0.5 months for ivabradine and 3.8 ± 0.4 months for placebo. Overall, 870 patients (97.9%) were treated for at least 3 months. Atenolol mean treatment duration over the 4-month double blind period was 3.8 ± 0.5 months. Overall study drug compliance was good with 886/887 evaluable patients achieving compliance between 70-130%. The overall mean compliance was 99.1 ± 4.2%.

At M2, 93.7% of overall patients were eligible for up-titration and 90.0% in the ivabradine group were actually up-titrated to 7.5 mg *b.i.d.* (*i.e.* patients with HR ≥ 50 bpm at M2).

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EFFICACY RESULTS

The between group difference in TED in the FAS-E over the 4-month treatment period (last – baseline; **primary criterion, main analysis**), was significant in favour of a greater increase in the ivabradine group ($p < 0.001$, t test for superiority). The between-group difference was 16.3 s (95% CI [7.9 ; 24.7]. This result was supported by each statistical model and by the analysis of the between group change in the PPS-E4 ($p < 0.001$).

A significant difference in favour of ivabradine was also observed over the 2-month treatment period in the FAS-E, with a between-group difference of 8.2 s (95% CI [0.6 ; 15.7] ; $p = 0.017$, t test).

The superiority of ivabradine over placebo was also evidenced in the other ETT criteria, after both 2-month and 4-month treatment periods (see table below).

Summary of changes (baseline – last value in period) in ETT parameters – FAS-E

(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*

While at baseline all patients stopped the ETT for the reason of limiting angina, at M4 in the ivabradine group 76.7% of the patients have stopped for this reason *versus* 85.2% in the placebo group.

As expected, a greater reduction in resting HR was observed in patients treated with ivabradine *versus* placebo. The mean HR (before ETT standing at trough of drug activity) changed over the 4-month treatment period by -10.8 ± 10.8 bpm in the ivabradine group *versus* -2.2 ± 10.1 bpm in the placebo group (in the FAS-E). The between-group difference was -8.8 bpm (95% CI: [-10.0 ; -7.6]). At the peak of exercise the mean HR change was -11.3 ± 13.2 bpm *versus* -0.9 ± 12.3 bpm, respectively, with a between-group difference of -10.8 bpm (95%CI: [-12.4 ; -9.1]). Similarly, RPP decreased to a greater extent in the ivabradine group than in the placebo group, both at rest and at peak of exercise.

The mean number of angina attacks/week at baseline, in the FAS-A, was < 2 in both groups, with medians < 1, indicating that the angina was not very severe in this population. Despite these relatively low rates, slight reductions were observed in both treatment groups over the 4-month treatment period: -0.9 ± 2.6 attacks/week in ivabradine group *versus* -0.7 ± 1.8 attacks/week in the placebo group (the median changes were -0.4 *versus* -0.3, respectively). The between-group difference was not significant.

The global SAN consumption at baseline was low, with means of ≤ 1.2 intakes/week and medians of 0 (FAS-A). As observed for angina attacks and despite the low baseline values, slight reductions were observed in both treatment groups over the 4-month treatment period: -0.3 ± 1.3 intakes/week in ivabradine group *versus* -0.5 ± 1.7 intakes/week in the placebo group (the median change was zero in both groups). The between-group difference was not significant.

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SAFETY RESULTS

- Adverse events

Main safety results are summarised in the table below.

Overall summary of safety results after randomisation – Safety Set

		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*

Twenty-one patients (2.4%) experienced at least one emergent non-fatal serious adverse event: 13 in the ivabradine group and 8 in the placebo group. A serious adverse event led to treatment discontinuation in 5 patients in ivabradine group and 3 in placebo group. These concerned mostly cardiac disorders: 5 patients (1.1%) *versus* 2 (0.5%); only one of which was considered to be related to the study treatment (a sinus bradycardia in the ivabradine group). The other SOCs concerned had no particular relationship to the disease or to the study treatment. All SAEs were reported as recovered.

There was one death (suicide; ivabradine) during the randomised study period. 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.

Seven patients in ivabradine group (1.6%) were withdrawn due to non-serious adverse event, 5 amongst them were withdrawn for adverse events indicated as common in the European Summary of Product Characteristics of ivabradine *i.e.* bradycardia/HR decreased or dizziness.

Overall in the Safety Set (N = 889), 222 patients had at least one **emergent adverse event**: 130 patients (29.0%) in the ivabradine group and 92 (20.9%) in the placebo group.

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. 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 incidences 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.

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SAFETY RESULTS (Cont'd)

ETT safety criteria

No relevant changes in blood pressure at rest or at peak of exercise were evidenced, nor were relevant cardiac abnormalities observed during ETT in either group.

12-lead ECG

As expected, a clinically relevant decrease in heart rate was observed in the ivabradine group from 67.0 ± 6.9 bpm at baseline to 58.4 ± 8.7 bpm at last value under treatment: E (SE) = -8.62 (0.48) bpm, with 95% CI [-9.6 ; -7.7]. In the placebo group, only a slight decrease was observed with no clinical relevance: E (SE) = -1.4 (0.5) bpm, with 95% CI [-2.3 ; -0.4]. The decrease in mean heart rate was already apparent at M2 in the ivabradine group, with a mean value of 60.1 ± 9.3 bpm.

The centrally read ECGs showed no relevant changes in mean QTc, PR or QRS intervals in either group, nor was any QTc > 500 ms was observed. 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. At all visits, the most frequently reported abnormality was ischaemia, (logical in this patient indication) with an incidence at baseline of 52.0% in ivabradine group and 45.1% in placebo group. At M4, the incidence remained stable in ivabradine group (51.8%), while it increased to 49.6% in the placebo group.

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. There were also 24 emergent cases of prolonged QT interval (QT or QTc > 450 ms in man and > 470 ms in woman) at last assessment under treatment in the ivabradine group *versus* 13 emergent cases in the placebo group (although the descriptive analysis QTc did not raise any concern). Other abnormalities were reported in similar proportions at M0, M2, and M4 in both groups, with no relevant differences between them.

24-hour Holter ECG

A total of 180 patients (90/group) were included in the Holter Safety Set. The mean HR during the awake period at the end of the 4-month period in fully documented patients was 58.9 ± 8.2 bpm on ivabradine *versus* 68.5 ± 7.7 bpm on placebo whereas during the sleep period, mean HR was 52.3 ± 6.6 *versus* 59.5 ± 8.2 bpm, respectively. The mean lowest HR during the sleep period was 43.2 ± 5.3 *versus* 47.7 ± 5.8 bpm, respectively. HR never descended below 34 bpm in either group.

The main differences in emergent abnormalities on the Holter recordings at the last value over the study period were in the incidence of (in % patients, ivabradine *versus* placebo): bradycardia during awake (18.3% *versus* 1.2%, with none reported as symptomatic adverse event by investigators), supraventricular premature depolarisation doublets (24.4% *versus* 16.3%), supraventricular tachycardia (12.2% *versus* 4.7%), ventricular premature depolarisations (12.2% *versus* 5.8%) and accelerated idioventricular rhythms (7.3% *versus* 1.2%).

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CONCLUSION

The patients randomised in this double-blind, phase III, superiority trial of ivabradine *versus* placebo had stable angina pectoris and were receiving atenolol (50 mg *o.d.*), as well as concomitant treatments commonly prescribed for this patient population. They had undergone a selection and inclusion process that verified their positivity and stability on an ETT. After 2 months of randomised treatment, patients were assessed for an up-titration of study drug based on HR criteria (ivabradine 5 mg *b.i.d.* to 7.5 mg *b.i.d.* or placebo to placebo): 90.0% of the ivabradine group were up-titrated.

Ivabradine treatment induced a clinically and statistically significant improvement in exercise capacity at the end of the 4-month study period as evidenced by the between-group difference in total exercise duration (TED) in the FAS-E (n = 875): 16.3 s (95% CI [7.9 ; 24.7] ($p < 0.001$, t test). This significant result was supported by all robustness analyses, by the analysis in the Per Protocol set and in the analyses of the other ETT parameters over the 4-month treatment period. Statistically significant improvements in exercise capacity were also observed in favour of ivabradine over the 2 month treatment period in the FAS-E (n = 875): 8.2 s (95% CI [0.6 ; 15.7]; $p = 0.017$, t test).

These changes in ETT parameters were concurrent with clinically relevant reductions of HR in the ivabradine group, both at rest and peak of exercise. Reductions were also observed in the number of angina attacks per week and in the number of short-acting nitrates consumed per week, however the between-group differences for these last parameters (ivabradine *versus* placebo) were not significant.

Ivabradine was well tolerated. The adverse drug reactions observed were generally those recognised in the European Summary of Product Characteristics of ivabradine as being common, at frequencies and levels of severity that are consistent with this type of population.

In conclusion, the ivabradine treatment given in combination with atenolol in patients with stable angina pectoris, led to clinically relevant improvements in exercise capacity (total exercise duration, time to limiting angina, time to angina onset and time to 1mm ST segment depression), that were statistically greater from the changes observed in the placebo comparator group (superiority analysis). The safety profile of ivabradine was comparable to that observed in previous clinical studies and no unexpected safety concern was identified. The results of the study show that ivabradine given in combination with atenolol is well tolerated by patients and can provide meaningful improvements in exercise capacity.

Date of the report: Final version of 20 June 2008