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 a calcium antagonist (amlodipine or nifedipine) in patients with stable angina pectoris.** **A 6-week randomised double-blind parallel-group international multicentre study.**
Study drug	**Ivabradine (S 16257)**
Studied indication	**Stable angina pectoris**
Development phase	**Phase III**
Protocol code	**CL3-16257-068**
Study initiation date	**9 May 2008**
Study completion date	**29 October 2012**
Main coordinator	[redacted] **-Slovakia**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
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 28 August 2013**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

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 a calcium antagonist (amlodipine or nifedipine) in patients with stable angina pectoris.
A 6-week randomised double-blind parallel-group international multicentre study.
Protocol No.: CL3-16257-068. EudraCT No.: 2006-006246-34.

International Coordinator: [redacted] Slovakia.

Study centres:
In all, 136 centres located in 21 countries included at least one patient: Argentina (2 centres – 3 patients), Armenia (7 centres – 315 patients, added by Amendment No.3), Brazil (2 centres – 3 patients), Bulgaria (9 centres – 41 patients), Chile (3 centres – 7 patients), Estonia (1 centre – 1 patient), Hungary (8 centres – 62 patients), India (16 centres – 161 patients), Latvia (3 centres – 35 patients), Lithuania (2 centres – 7 patients), Mexico (1 centre – 3 patients), Moldavia (1 centre – 11 patients, added by Amendment No.6), Peru (5 centres – 30 patients), Philippines (4 centres – 43 patients), Poland (4 centres – 22 patients), Romania (2 centres – 3 patients), Russia (30 centres – 317 patients), Serbia (7 centres – 43 patients, added by Amendment No.3), Slovakia (8 centres – 49 patients),Tunisia (1 centre – 1 patient), Ukraine (20 centres – 120 patients).

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 9 May 2008 (***date of first selection)*** Completion date: 29 October 2012 (***date of last completed visit for selected patients*****)** 04 September 2012 (***date of last completed visit for randomised patients*****).**	III

Objectives:
The purpose of this study was to establish the additional benefit and the safety of ivabradine as an anti-anginal and anti-ischaemic drug when combined with a calcium antagonist (amlodipine or nifedipine) in coronary artery disease (CAD) patients with stable angina pectoris. The study was performed in patients who might benefit from a significant heart rate (HR) reduction but were not suitable for an anti-anginal therapy with beta-blockers and who still presented a positive exercise tolerance test (ETT) and symptomatic angina in everyday life (at least 3 angina attacks/week).

Methodology: Phase III, superiority, international, multi-centre, randomised, double-blind placebo-controlled trial with two parallel groups (ivabradine and placebo), on top of a background therapy with amlodipine or nifedipine.
Balanced and non-adaptative randomisation was centralised with stratification by country and the use of long acting nitrates (LANs) as concomitant treatment at inclusion (presence or absence).
A 2-3 week selection period (with ETT at start (ETT1) and end (ETT2/2bis)) was followed by a 6 week double-blind period with 2 ETTs at the final visit (one at trough of drug activity (ETT3) and one at peak (ETT4)).

Number of patients:
Planned: 1240 (620 in each treatment group).
Included: 1277 (637 in the ivabradine group and 640 in the placebo group).

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

Diagnosis and main criteria for inclusion:

Male or female CAD outpatients aged ≥ 18 years (or the legal age) with a history of stable angina pectoris (duration ≥ 3 months and stable within 1 month preceding selection), with no angina at rest, no angina of class IV according to Canadian Cardiovascular Society classification (in Hungary, no angina of class III patients were permitted following Amendment No.2), treated by amlodipine 5 mg or nifedipine gastrointestinal therapeutic system (GITS) 30 mg (or slow release (SR) at equivalent dosage) for at least 4 weeks before selection and who still presented at least 3 angina attacks per week in everyday life. Amlodipine or nifedipine were not to be associated with any other anti-angina treatment 2 weeks before selection visit, and within 2 months in the specific case of beta-blockers. Patients could receive long-acting nitrates (LANs) but only if initiated at least 2 weeks before the selection and the dose was to remain stable all along the study. Short acting nitrates were authorized during the study.

Resting heart rate (HR) on 12-lead ECG had to be ≥ 60 bpm at selection and inclusion visits. Patients were included if at the end of the selection (run-in) period, they had:

- At least 3 angina attacks (AA) per week and,
- 2 ETTs that meet the following criteria for positivity and stability:
  - Positivity: occurrence of limiting angina pain and significant ST segment depression (≥ 1 mm) within 3 min and 12 min (the criterion for positivity, within 3 min and 9 min initially, was modified by Amendment No.3).
  - Stability: "time to 1 mm ST segment depression" (TST 1 mm) at ETT1 and ETT2, or at ETT1 and ETT2bis (added by Amendment No.3), or at ETT2 and ETT2bis within ± 20% or ± 1 min of each other, as assessed by the core reading centre.

Study drug:

Ivabradine: oral tablet, twice daily (morning and evening) – tablets of 5 mg first until W2 and then tablets of 7.5 mg from W2 to W6 except in patients with HR at W2 < 60 bpm and/or with symptoms of bradycardia (those patients remained at dose of 5 mg twice daily during the entire study).

Ivabradine was given in combination with a CCB once a day in the morning (tablets of amlodipine 5 mg or nifedipine GITS 30 mg).

Batch Nos. (5 mg) L0017356, L0025673, L0031123, L0039046 – (7.5 mg) L0014999, L0020187, L0027764, L0035707.

Reference product:

Placebo: matching placebo oral tablet, twice daily (morning and evening).

Placebo was given in combination with a calcium channel blocker (CCB) once a day in the morning (tablets of amlodipine 5 mg or nifedipine GITS 30 mg).

Duration of treatment:

Run-in period: 2 to 3 weeks single-blind placebo period, on top of amlodipine or nifedipine therapy.

Double-blind period: a 6-week period during which patients received the randomised treatment (ivabradine or placebo) on top of amlodipine or nifedipine therapy. The randomised treatment was up-titrated at the W2 visit according to HR and tolerance.

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

Criteria for evaluation:

Efficacy measurements:

ETTs were performed on a treadmill according to a modified Bruce protocol (McInnis, 1992) at the following timescale:

- *At W0 (ETT2 or 2bis)*: at trough of CCB activity (*i.e.*, 24 ± 2 hours after intake).
- *At W6 (ETT3)*: at trough of ivabradine and CCB activity (*i.e.*, 12 ± 1 hour after ivabradine intake and 24 ± 2 hours after CCB intake).
- *At W6 (ETT4)*: at peak of ivabradine and CCB activity (*i.e.*, 3 ± 1 hour after morning intakes of ivabradine and CCB).

The following parameters were evaluated:

- Total exercise duration (TED, sec)*.
- Time to onset of 1 mm ST segment depression (TST 1 mm, sec)*.
- Time to onset of angina pain (TAO, sec)**.
- Time to limiting angina (TLA, sec)**.
- Heart rate at rest and at peak of exercise (HR, bpm)*.
- Rate pressure product at rest and at peak exercise (RPP, bpm x mmHg)*.

* Evaluated by a Core Reading Centre.
** Evaluated by the investigator.
In addition, reasons for stopping exercise were provided by the investigator.

Symptomatology of angina and short acting nitrates consumption were collected from the patient e-diary between 2 consecutive visits:

- Number of angina attacks/week (AA/week).
- Consumption of short acting nitrates (SAN)/week.

***Primary efficacy criterion*:** Response to treatment (composite endpoint).
The response to treatment was defined as:

- A decrease from the run-in period over a 6-week treatment period of at least 3 AA/week,

and/or,

- An increase from baseline over a 6-week treatment period in TST 1 mm of at least 60 sec during ETTs performed at trough of drug activity.

Safety measurements:

- Adverse events were reported at each visit from baseline, or in case of withdrawal.
- Physical examination: body weight and vital signs, *i.e.*, supine blood pressures (diastolic (DBP) and systolic (SBP)) and HR were measured at each visit, and in case of withdrawal. Height was only measured at selection.
- 12-lead ECG parameters (centrally read values) were measured at rest at each visit, or in case of withdrawal.
- ETT blood pressures were measured at rest and peak of exercise, at W0 and W6 (end visit) at trough and at peak of study drugs activities, or in case of withdrawal.
- Laboratory tests (biochemistry, haematology): blood samplings were performed within 5 days before both W0 and W6 (end visit) in order to have the results at respective visits. In case of premature withdrawal, a final blood sample was taken.

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

Statistical methods:

Efficacy analyses:

Efficacy analyses were carried out on patients of the Full Analysis Set (FAS, based on Intention To Treat principle), on patients of the Per Protocol Set (PPS) as sensitivity analyses and, on pre-defined patient subgroups.

Primary criterion (Response to treatment):
The superiority of ivabradine *versus* placebo was tested on the response to treatment (composite endpoint) over the 6-week treatment period (and at trough of the study drug activity for ETT), using a parametric logistic regression adjusted for the stratification factors LAN intake at randomisation, baseline TST 1 mm value and the mean number of AA/week during the run-in period (main analysis).
A sensitivity analysis was performed using a non-parametric chi-2 test without adjustment.
As secondary analyses, the percentage of responders within each treatment group was estimated using 95% confidence intervals based on a normal approximation. In addition, responders to treatment on the components of the primary criterion (on TST 1 mm (ischaemic response) and on AAs (symptomatic response)) were separately evaluated using the same analyses than those applied to the primary criterion. The TST 1 mm criterion was also evaluated at peak of study drug activity.

Secondary criteria:

- The ETT criteria at trough and at peak of study drug activity:
  The superiority of ivabradine *versus* placebo was tested on the change in mean TED, TST 1 mm, TAO, TLA, HR and RPP at rest and at peak of exercise over the 6-week treatment period.
- Symptomatology of angina (angina attacks/week and weekly short acting nitrates consumption):
  The superiority of ivabradine *versus* placebo was tested on the change in mean number of AA/week over the 6-week treatment period.

The superiority of ivabradine *versus* placebo on change over the 6-week treatment period for ETT criteria and for symptomatology of angina criteria was tested using -a parametric approach (analysis of covariance) with adjustment for LAN intake at randomisation as fixed factor and baseline value (ETT criteria) or run-in value (symptomatology of angina) as covariate (main analysis) and, -a non-parametric approach without adjustment based on the Hodges & Lehmann estimate (Mann-Whitney test).
For all secondary criteria, changes over the 6-week treatment period were calculated in each treatment group and treatment effects were estimated using a two-sided 95% confidence interval calculated with parametric and non-parametric approaches without adjustment (based on the Hodges & Lehmann estimate).

Other criteria (HR on 12-lead resting ECG):
The superiority of ivabradine *versus* placebo was tested on the change in HR over the 6-week treatment period using a parametric approach (analysis of covariance) with adjustment for baseline value as covariate.

Safety analyses:

Descriptive statistics were provided on the Safety Set (SS) for adverse events, vital signs at rest, ECG parameters at rest, ETT blood pressure and laboratory tests.

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients

		Ivabradine	Placebo	Total
Included (randomised)	**n (%)**	**637 (100)**	**640 (100)**	**1277 (100)**
Lost to Follow-up	**n (%)**	-	-	-
Withdrawn due to	**n (%)**	**23 (3.6)**	**15 (2.3)**	**38 (3.0)**
lack of efficacy	n	-	-	-
adverse event	n	7	5	12
non-medical reason	n	12	7	19
protocol deviation	n	4	3	7
Completed	**n (%)**	**614 (96.4)**	**625 (97.7)**	**1239 (97.0)**
Full Analysis Set (FAS)	**n (%)**	**625 (98.1)**	**633 (98.9)**	**1258 (98.5)**
Per Protocol Set (PPS)	**n (%)**	**541 (84.9)**	**565 (88.3)**	**1106 (86.6)**
Safety Set	**n (%)**	**637 (100)**	**640 (100)**	**1277 (100)**

n: number of patients; %: calculated as percentage of randomised patients (Randomised Set).

A total of 3311 patients were selected and 1277 were included with a well-balanced distribution between groups (see Table above). The main reason for non-selection and non-inclusion was the ETT criterion (no positivity and/or no stability).
Twenty three patients (3.6%) in the ivabradine group and 15 patients (2.3%) in the placebo group were withdrawn from the study, mainly due to non-medical reason (12 patients, 1.9% and 7 patients, 1.1%, respectively). No patient was lost to follow-up.

Patients in the RS (N = 1277) had a mean age (± SD) of 60.9 ± 8.6 years and 77.5% were men. They had been diagnosed with angina pectoris with a mean duration (± SD) of 5.0 ± 5.4 years and had angina pain of grade I (5.1%), grade II (65.1%), or grade III (29.8%) (Canadian Classification). All had received previous pharmacological treatment for angina, without any clinically relevant difference between treatment groups. All patients were receiving a CCB at selection (amlodipine, 92.2% and nifedipine, 7.8%) and 76.0% were on organic nitrates at inclusion (glyceryl trinitrate in 54.0%, isosorbide dinitrate in 20.8% or mononitrates in 19.1%). LANs were authorized per protocol providing they were taken for at least 2 weeks before selection and maintained at stable dose all along the study. The specific analysis on LAN intake revealed a use rate of 33.8% overall. Only 1.1% of patients had taken previously beta-blockers (stopped at least 2 months before selection).
Among the included patients, 82.1% had ETT stability between ETT1 and ETT2 (unplanned analysis). Distributions of ETT parameters and mean number of AA/week at baseline were similar between the 2 treatment groups: median TED = 596 sec in ivabradine group and 594.5 sec in placebo group; median TST 1 mm = 495 sec in both groups, median HR = 78.0 bpm and 80.0 bpm, respectively; median AA = 5.2 in both groups. A slightly lower weekly consumption of SANs was observed in the ivabradine group than in placebo group (median = 2.5 units *versus* 3.0, respectively).
In all, baseline characteristics were comparable between the ivabradine and placebo groups.

Most patients had concurrent medical conditions (other than cardiac disorders), mainly vascular disorders (83.0%, mostly hypertension/essential hypertension: 75.3%/5.9%, respectively), metabolism and nutrition disorders (51.2%, mostly dyslipidaemia: 33.5% and diabetes mellitus: 23.3%) and gastrointestinal disorders (18.7%).

Concomitant treatments mainly received during the study were anti-thrombotic agents (in 93.3% of patients), serum-lipid reducing agents (71.7%), and agents acting on the renin-angiotensin system (68.1%). No major differences between groups were detected in the prescription of non-specific drug treatments.

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

In the RS, the study treatment duration was comparable in the ivabradine and placebo groups with an overall mean duration (± SD) of 47.4 ± 7.8 days. Calcium antagonist treatment duration over the 6-week double-blind period was also comparable with a mean (± SD) of 47.7 ± 7.7 days. Overall study drug compliance was satisfactory with 99.5% of patients achieving compliance between 70-130% and a mean (± SD) of 99.5 ± 4.3%. At W2, 76.0% of the evaluable patients in the ivabradine group were up-titrated to 7.5 mg *b.i.d.* (*i.e.* HR ≥ 60 bpm and no symptom of bradycardia).

EFFICACY RESULTS

Primary criterion: Response to treatment

The Response to treatment was a composite endpoint of responders on TST 1 mm at trough of study drugs activities and/or responders on mean number of AA/week.

In the FAS (N = 1258), a higher percentage of patients in the ivabradine group had a response to treatment over the 6-week treatment period as compared to placebo (72.1% *versus* 66.2%).

The odds ratio (ivabradine / placebo) was estimated at 1.33 (95% CI [1.04 – 1.70]), using a logistic regression adjusted for LAN intake at randomisation, baseline TST 1 mm and the mean number of AA/week over the run-in period. This main analysis showed the superior efficacy of ivabradine compared to placebo (p = 0.012) (see table below).

This result was confirmed using a sensitivity analysis (p = 0.013) and evidenced trend in favour of ivabradine was observed in the PPS (N = 1106), odds ratio: 1.29 (95% CI [0.99 – 1.68], p = 0.029).

Response to treatment (composite endpoint):
Responders to TST criterion at trough and/or to AA/week criterion over 6-week treatment period in the FAS

		Ivabradine (N = 625)	**Placebo (N = 633)**
Responders	n	609	625
	Yes	439 (72.1)	414 (66.2)
	No	170 (27.9)	211 (33.8)
Main analysis			
Adjusted parametric approach	E (SE) [1]	1.33 (0.17)	
(*Odds ratio,* logistic regression)	95% CI [2]	[1.04 – 1.70]	
	p-value [3]	**0.012**	

Superiority test of ivabradine as compared to placebo, on top of a calcium antagonist– one-sided type I error rate: 0.025.

1: Estimate (E) of the odds ratio (ivabradine/placebo) based on a logistic regression adjusted for LAN intake at randomisation, for baseline value of TST 1 mm and for run-in period value of AA/week, and Standard Error (SE) of the estimate.

2: 95% confidence interval of the estimated treatment effect (two-sided).

3: p-value from the adjusted logistic regression model.

Regarding pre-defined subgroups of patients, responders on TST (1 mm) criterion at trough and/or to AA criterion were also significantly higher on ivabradine in patients who were not receiving LAN intake at randomisation, in patients having a mean number of AA/week ≥ 5 during the run-in period, in patients with combined positive ETT between 3 and 9 minutes at baseline and, a AA/week ≥ 5 during the run-in period (see table below).

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Response to treatment: composite endpoint
Responders over 6-week treatment period in the subgroups of the FAS

		Ivabradine (N = 625)	**Placebo (N = 6 3)**
No LAN intake at randomisation			
Responders	n	404	412
	Yes	292 (72.3)	267 (64.8)
	No	112 (27.7)	145 (35.2)
Main analysis			
Adjusted parametric approach	E (SE) [1]	1.42 (0.22)	
(*Odds ratio*, logistic regression)	95% CI [2]	[1.05 – 1.92]	
	p-value [3]	**0.011**	
Mean number of AA/week >= 5 during the run-in period			
Responders	n	347	354
	Yes	288 (83.0)	266 (75.1)
	No	59 (17.0)	88 (24.9)
Main analysis			
Adjusted parametric approach	E (SE) [1]	1.64 (0.31)	
(*Odds ratio*, logistic regression)	95% CI [2]	[1.13 – 2.38]	
	p-value [3]	**0.004**	
Positive ETT between 3 and 9 minutes at baseline and mean number of AA/week >= 5 during the run-in period			
Responders	n	142	150
	Yes	123 (86.6)	112 (74.7)
	No	19 (13.4)	38 (25.3)
Main analysis			
Adjusted parametric approach	E (SE) [1]	2.26 (0.71)	
(*Odds ratio*, Logistic regression)	95% CI [2]	[1.23; 4.17]	
	p-value [3]	**0.004**	

Superiority test of ivabradine as compared to placebo, on top of a calcium antagonist– one-sided type I error rate: 0.025.

1: Estimate (E) of the odds ratio (ivabradine/placebo) based on a logistic regression adjusted for LAN intake at randomisation, for baseline value of TST 1 mm and for run-in period value of AA/week, and Standard Error (SE) of the estimate.

2: 95% confidence interval of the estimated treatment effect (two-sided).

3: p-value from the adjusted logistic regression model.

Response to treatment on each of the 2 components of the primary criterion

The trend to benefit of ivabradine (as compared to placebo) when combined with a CCB (amlodipine or nifedipine) was observed on each component of the primary criterion: responders on TST 1 mm at trough or responders on AA/week with adjusted odds ratios = 1.25 (95% CI [0.99 – 1.57]), p = 0.031 and 1.17 (95% CI [0.92 - 1.48], p = 0.100, respectively.

As expected at peak of study drug activity, an even more pronounced beneficial effect in favour of ivabradine *versus* placebo was observed on responders to treatment and on TST 1 mm (adjusted odds ratios = 1.69 (95% CI [1.29 – 2.23]) and 1.71 (95% CI [1.34 – 2.18]), p < 0.001, respectively).

Similar results were observed in the PPS.

ETT criteria (secondary assessment criteria)

The trend to benefit of ivabradine (compared to placebo) when combined with a CCB was also apparent on the ETT criteria (TED, TST 1 mm, TAO and TLA) at trough over the 6-week treatment period in the FAS and, with significant between-group differences observed at peak of ivabradine activity (see table below).

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

In the PPS at trough, the estimate of treatment effect (ivabradine - placebo) was less pronounced in favour of ivabradine (see table below). Sensitivity analyses confirmed these results.

Summary of ETT parameters at trough and at peak: TED, TST 1 mm, TAO and TLA
Change from baseline to last value over the 6-week treatment period in the FAS

Drug activity	Time ((sec)	Ivabradine (N = 625)	Placebo (N = 633)	Difference* E [95% CI]	p-value**
At trough	TED	36.4 ± 93.4	31.2 ± 98.7	5.30 [-5.28 – 15.89]	0.163
	TST	60.5 ± 132.9	53.4 ± 133.7	7.44 [-6.93 – 21.81]	0.155
	TAO	57.4 ± 105.5	54.3 ± 111.2	4.18 [-7.81 – 16.18]	0.247
	TLA	37.6 ± 94.0	31.6 ± 99.7	6.11 [-4.56 – 16.78]	0.131
At peak	TED	80.1 ± 103.6	63.5 ± 105.9	16.55 [5.20 – 27.90]	**0.002**
	TST	112.2 ± 146.3	83.6 ± 139.0	29.26 [14.11 – 44.41]	**< 0.001**
	TAO	108.3 ± 119.2	92.8 ± 122.3	17.17 [3.97 – 30.36]	**0.005**
	TLA	81.5 ± 103.7	64.6 ± 105.4	16.88 [5.56 – 28.21]	**0.002**

* *Difference between group means based on a parametric covariance analysis adjusted for LAN intake at randomisation and baseline value: Estimate (E) of ivabradine minus placebo effect.*

** *p-value from the parametric covariance analysis.*

In the FAS, the *main reason for stopping the ETTs at W6* was limiting angina at trough (> 90% of patients) and at peak of study drug activity (> 85% of patients) in both treatment groups.

As expected, a greater reduction in *mean HR* was observed over the 6-week period in patients treated with ivabradine *versus* placebo. At trough of study drug, the mean resting HR decreased by 10.4 ± 12.3 bpm in the ivabradine group *versus* 0.4 ± 11.8 bpm in the placebo group; at peak of exercise, the mean HR decreased by 9.5 ± 12.6 bpm *versus* 0.2 ± 12.5 bpm, respectively. Similar results were observed at peak of drug activity: the mean resting HR decreased by 13.1 ± 13.1 bpm in the ivabradine group *versus* 1.3 ± 13.3 bpm in the placebo group; *at peak of exercise, the* mean *HR* decreased by 10.6 ± 14.2 bpm *versus* 2.0 ± 14.2 bpm, respectively.

In the ivabradine group, *rate pressure product* (RPP, bpm x mmHg) decreased at trough by 1305 ± 1720 units at rest and by 1520 ± 2680 units at peak of exercise over the 6-week treatment period, whereas in the placebo group RPP decreased by 201 ± 1724 units at rest and 167 ± 2990 units at the peak of exercise. At the ivabradine peak of activity, similar results were obtained.

Similar results were observed in the PPS at trough.

Symptomatology of angina

In the FAS during the run-in period when patients in both groups received only CCB background treatment and placebo, the *mean number of AA/week* in randomised patients was very close, with a median of 5.2 in each group. From the run-in to last period, there was a marked decrease in AA/week in both groups (-2.9 ± 2.6 *versus* -2.7 ± 2.1, respectively), resulting in a mean AA/week of 3.2 ± 3.6 (median 2.5) in the ivabradine group *versus* 3.3 ± 3.1 (median 2.7) in the placebo group (indicating a strong placebo effect). The between-group difference in number was of -0.2, in favour of ivabradine (95% CI [-0.4; 0.1], p = 0.100).

The *weekly SAN consumption* during the run-in period was 3.2 ± 3.3, (median = 2.5) in the ivabradine group *versus* 3.4 ± 3.6 (median = 3.0) in the placebo group. SAN consumption decreased in both groups during the study, resulting in a mean weekly consumption of 1.7 ± 2.6 (median = 0.8) in the ivabradine group *versus* 1.8 ± 2.8 (median = 1.0) in the placebo group over the last post-baseline period (indicating a strong placebo effect). The between-group difference in the mean change was estimated at -0.1 (95% CI [-0.2 - 0.1]).

Similar results were observed in the PPS.

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

Adverse events

Main safety results are summarised in the table below.

Overall summary of adverse events after randomisation – Safety Set

		Ivabradine (N = 637)	Placebo (N = 640)
Patients having reported			
at least one emergent adverse event	n (%)	110 (17.3)	84 (13.1)
at least one treatment-related emergent adverse event	n (%)	43 (6.8)	10 (1.6)
heart rate decrease / bradycardia	n (%)	17 (2.7)	2 (0.3)
visual adverse event	n (%)	12 (1.9)	2 (0.3)
Patients who died*	n (%)	-	1 (0.2)
Patients having experienced at least one emergent non-fatal SAE	n (%)	8 (1.3)	5 (0.8)
Patients withdrawn			
due to an adverse event	n (%)	7 (1.1)	5 (0.8)
due to heart rate decreased / bradycardia	n (%)	1 (0.2)	1 (0.2)
due to a serious adverse event	n (%)	3 (0.5)	2 (0.3)
due to a treatment-related adverse event	n (%)	1(0.2)	1 (0.2)
due to a treatment-related serious adverse event	n (%)	1(0.2)**	-

** 18 months after last study drug intake.*

*** Acute myocardial infarction.*

Overall in the Safety Set (N = 1277), 13 patients (1.0%) experienced at least one emergent non-fatal serious adverse event (SEAE) during the double-blind treatment: 8 in ivabradine group and 5 in placebo group. A SEAE led to treatment discontinuation in 3 patients in ivabradine group (2 acute myocardial infarctions and one angina pectoris) and 2 in placebo group (one unstable angina and one coronary artery disease). Only one was considered to be related to the study drug (an acute myocardial infarction in the ivabradine group). All SEAEs were reported as recovered.

There was one death (sudden cardiac death) occurring 18 months after the study completion (patient on placebo during the study). According to the investigator, the event was related to a suspicious myocardial infarction and considered as not related to the study drug.

Four patients (0.6%) in the ivabradine group and 3 (0.5%) in the placebo group were withdrawn due to non-serious adverse event. One event in the placebo group (heart rate decreased) was considered to be related to the study treatment by the investigator.

A total of 194 patients had at least one **emergent adverse event (EAE**) 110 patients (17.3%) in the ivabradine group and 84 (13.1%) in the placebo group.

The incidence of treatment-related EAEs was 6.8% in the ivabradine group *versus* 1.6% in the placebo group, mainly HR decreased (2.5% *versus* 0.3%) or phosphenes (1.9% *versus* 0.3%). None were severe.

No patients were withdrawn for a visual adverse event. Emergent events of ventricular extrasystoles were less frequent in the ivabradine group (11 patients, 1.7%) than in the placebo group (20 patients, 3.1%).

When considering events occurring during the ETT, ventricular extrasystoles were as expected the most frequently reported event (0.2% in the ivabradine group *versus* 2.2% in the placebo group, unplanned analysis).

Few patients reported EAEs of angina pectoris (2, 0.3% *versus* 1, 0.2% in placebo) or unstable angina (none *versus* 2, 0.3% in placebo).

In table below are presented the important identified or potential risks defined in the current Risk Management Plan (RMP) of ivabradine.

As expected, the most frequent risks reported during the study were the identified risks bradycardia (3.3% in ivabradine *versus* 0.3% in placebo, mainly asymptomatic) and phosphenes/blurred vision (2.0% in ivabradine *versus* 0.5% in placebo). None of those events reported as EAEs were severe or serious.

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

One non-sustained ventricular tachycardia (mild and asymptomatic) was reported during the ETT at W6 - the patient recovered the same day.

Emergent adverse events on treatment in the Safety Set corresponding to the important identified and potential risks defined in the ivabradine RMP

	Ivabradine (N = 637)			**placebo (N = 640)**		
	NEAE	n	%	NEAE	n	%
Important identified risks:						
Bradycardia	**21**	**21**	**3.3**	**2**	**2**	**0.3**
Asymptomatic bradycardia	20	20	3.1	2	2	0.3
Symptomatic bradycardia	1	1	0.2	-	-	-
Phosphenes/Blurred vision	**13**	**13**	**2.0**	**3**	**3**	**0.5**
Phosphenes	13	13	2.0	2	2	0.3
Blurred vision	-	-	-	1	1	0.1
Atrioventricular block second and third degree	**-**	**-**	**-**	**-**	**-**	**-**
Increased Blood Pressure*	**2**	**2**	**0.3**	**7**	**6**	**0.9**
Atrial fibrillation (AF)	**1**	**1**	**0.2**	**1**	**1**	**0.2**
ECG prolonged QT interval	**2**	**2**	**0.3**	**-**	**-**	**-**
Important potential risks:						
Supraventricular tachyarrhythmia other than AF	**-**	**-**	**-**	**1**	**1**	**0.2**
Severe ventricular arrhythmia	**1****	**1**	**0.2**	**-**	**-**	**-**
Immune system disorders	**-**	**-**	**-**	**-**	**-**	**-**

RMP: Risk Management Plan.

** Increase in blood pressure was reported in 2 ivabradine patients, both with medical history of hypertension, and 6 placebo patients among which 4 had a medical history of hypertension*

*** The only severe ventricular arrhythmia reported in the ivabradine group was a non-sustained ventricular tachycardia during the ETT.*

MedDRA Terms (version 15) corresponding to the risks:

Bradycardia: *Asymptomatic bradycardia: "heart rate decreased"; Symptomatic bradycardia: "bradycardia", "sinus bradycardia"*

Phosphenes/Blurred vision*: "phosphenes", "photopsia" /" vision blurred";* ***Atrioventricular blocks second and third degree****: "atrioventricular block", "atrioventricular block second degree", "atrioventricular block complete";* ***Increase in blood pressure****: "BP increased, hypertension", "BP systolic increased", "BP inadequately controlled", "systolic hypertension, diastolic hypertension", "BP diastolic increased", "BP ambulatory increased", "BP fluctuation", "essential hypertension";* ***Atrial fibrillation:*** *"atrial fibrillation"*

ECG prolonged QT interval: *"ECG QT prolonged", "long QT syndrome";* ***Supraventricular tachycardia other than AF:*** *"Supraventricular tachycardia", "atrial flutter", "arrhythmia supraventricular", "atrial tachycardia", "tachyarrhythmia";* ***Severe ventricular arrhythmia:*** *"Ventricular tachycardia", "cardiac fibrillation", "cardiac flutter", "torsade de pointes", "ventricular arrhythmia", "ventricular tachyarrhythmia", "ventricular fibrillation", "ventricular flutter";* ***Immune system disorders****: all codes of the SOC.*

Biomedical parameters

From local laboratory reports, few biochemical values reached potentially clinically significant level (less than 5 in either treatment group for any parameters). In all, 6 EAEs (4 on ivabradine and 2 on placebo) were reported; all were of mild or moderate intensity (except one severe in placebo) and considered to be not related to the study drug by the investigator. As regard HbA1c, 15 patients (2.4%) in the ivabradine group and 23 patients (3.6%) in the placebo group had an emergent high PCSA value on treatment (most had history of treated diabetes reported: 7 and 15 patients respectively). In all, 7 EAEs (4 on ivabradine and 3 on placebo) were reported, all were of mild or moderate intensity and one in ivabradine group (HbA1c increased) was considered to be related to the study drug by the investigator.

Name of Company: **I.R.I.S.** **50 rue Carnot, 92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **Procoralan** **Corlentor** **Coraxan** **Coralan**	**Volume:**	
Name of Active Ingredient: **Ivabradine (S 16257*)***	**Page:**	

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Vital signs

The overall SBP mean ± SD were 127.3 ± 10.1 mmHg at baseline and 125.8 ± 10.7 mmHg at last value over the study, with no relevant differences between groups.

No clinically relevant changes in vital signs were observed in the Safety Set.

ETT safety criteria

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

12-lead ECG

As expected, a clinically relevant decrease in HR (on supine 12-lead ECG, assessed by the Core Reading Centre) of -8.6 ± 11.0 bpm was observed only in the ivabradine group at last value over the 6-week treatment period, *versus* -0.4 ± 10.0 bpm in the placebo group. The mean HR decreased on ivabradine from 74.1 ± 10.2 bpm at baseline to 66.8 ± 9.7 bpm at W2 under 5 mg *b.i.d* and then remained quite stable, 65.5 ± 10.7 bpm up to W6 under 7.5 mg *b.i.d. (or* 5 mg *b.i.d.* in about one quarter of patients not eligible to an up-titration at W2).

The centrally read ECGs showed no relevant changes in mean QTc, PR or QRS intervals in either group, nor was any QTc > 500 milliseconds observed.

Among emergent ECG abnormalities observed by the Core Reading Centre, 3 were reported by the investigator as EAEs in the ivabradine group *versus* none in placebo (QT prolongation in 2 patients and ST segment elevation in one). Both cases of QT prolongation were considered to be related to the study drug by the investigator.

CONCLUSION

In conclusion, this 6-week study in patients with stable angina pectoris receiving stable calcium channel blocker therapy (amlodipine or nifedipine), showed that the addition of ivabradine treatment resulted in the superior efficacy when compared to placebo on the rate of response to treatment on a composite endpoint, combining improvements in exercise capacity (TST) and the number of angina attacks per week. This improvement on the composite endpoint was at trough of drug activity and was particularly marked in the pre-defined subgroups of patients who were not receiving long-acting nitrates at baseline, in patients having more frequent angina attacks at baseline (≥ 5) and in patients with combined positive ETT between 3 and 9 min and mean AA/week ≥ 5 at baseline. At peak of ivabradine activity, an even more pronounced effect was observed on the response rate *versu*s placebo.

The safety profile of ivabradine was comparable to that already observed in previous clinical studies and no unexpected safety concern was identified.

The results of the study demonstrate the statistically significant superior efficacy and the safety of ivabradine when combined with a calcium channel blocker as an anti-anginal and anti-ischaemic drug in CAD patients with stable angina pectoris.

Date of the report: 28 August 2013