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 ivabradine used in combination with an anti-anginal monotherapy in patients with stable effort angina pectoris.
A 6-week, randomised, double-blind controlled, parallel-group, international, multicentre study.
Protocol No.: CL3-16257-064

International Coordinator: [redacted]

Study centres:
A total number of 52 centres in 4 countries were opened, of which 46 centres selected at least one patient: China mainland (33 centres), Indonesia (2 centres), Thailand (4 centres), Vietnam (7 centres).

Publication: not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 10 January 2008. Completion date: 31 May 2010.	Phase III

Objectives:
The primary objective of this study was to demonstrate that over a 6-week treatment period, ivabradine (5 mg b.i.d. then 7.5 mg b.i.d. given orally) used in combination with usual anti-anginal monotherapy was more efficient on angina symptomatology than the use of these anti-anginal monotherapies given alone.
The secondary objectives were to compare, over a 6-week treatment period, the effect of ivabradine in combination with anti-anginal monotherapies on the heart rate *versus* these anti-anginal treatments given alone and to demonstrate that the combination of ivabradine with anti-anginal monotherapies was safe and well tolerated.
A sub-study employing an Exercise Tolerance Test (ETT) was conducted in parallel to evaluate the effect of treatment on ergometric criteria.

Methodology:
This was an international, multicentre, randomised, double-blind, placebo-controlled study with two parallel groups. Study treatment (ivabradine or placebo) was allocated, via an interactive voice response (IVRS) system, by a balanced centralised (non-adaptative) randomisation, stratified on country and ETT sub-study eligibility, and was administered during the study in combination with a background anti-anginal therapy.
The option of participating in the ETT sub-study was open to all patients in selected centres. It consisted of one baseline evaluation and one post-randomisation evaluation.

Number of patients:
Planned in the main study: 370 patients (185 per group).
Planned in the ETT sub-study: 100 patients (participating in the main study) (*i.e.* 50 per group).
Included in the main study: 427 patients (216 in the ivabradine group and 211 in the placebo group), including 334 patients in China (168 in the ivabradine group and 166 in the placebo group).
Included in the ETT sub-study: 100 patients (49 in the ivabradine group and 51 in the placebo group), including 93 patients in China (46 in the ivabradine group and 47 in the placebo group).

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Diagnosis and main criteria for inclusion:
Patients to be selected were male, sterile or post-menopausal female patients, aged ≥ 18 years old, with a history of typical effort angina pectoris, with clinical stability, no angina at rest and no angina of class IV (according to the CCS Classification). Patients could be either untreated for their angina or treated with an authorised anti-anginal monotherapy (but not a beta-blocker, diltiazem, verapamil, or bepridil) and this treatment was to be stable for at least 1 month prior selection. All patients were to be symptomatic with at least 4 angina attacks/week before the inclusion visit. Patients enrolled in the ETT sub-study were required to have a positive ETT for inclusion in the sub-study (where positivity was confirmed by the central reading centre).

Study drug:
Oral ivabradine tablets (S16257) twice daily (target dose: 7.5mg following dose titration based on HR and clinical criteria).
At the inclusion visit, all patients received the 5 mg twice daily starting dose (either ivabradine or matching placebo). After 2 weeks (at the W2 visit) and again at the W4 visit the dose could be adjusted according to the following criteria:

- If HR ≥ 60 bpm, patients received 7.5mg b.i.d. dose of ivabradine or matching placebo.
- If 50 ≤ HR < 60 bpm, patients continued with the same dose of ivabradine (5 or 7.5 mg twice a day) or matching placebo.
- If HR < 50 bpm or in case of symptomatic bradycardia, patients receiving the 7.5 mg twice a day dose were down-titrated to the 5 mg b.i.d. dose whereas patients receiving the 5 mg twice a day dose discontinued their study medication.

Batch numbers: 5 mg: L0005445, L0010982, L0017356, L0025673, L0031123
7.5 mg: L0005446, L0014999, L0020187, L0027764

Comparator: Placebo tablets (matching those of ivabradine).

Background therapy:
Patients previously untreated for their angina before starting the study (*de novo* patients) were prescribed isosorbide mononitrate (ISMN) 20 mg twice a day (*i.e.* a background anti-anginal therapy) during the whole study. Patients who were already receiving an anti-anginal treatment (as monotherapy and not a betablocker, diltiazem or verapamil), and with treatment stable for at least 1 month before selection, were requested to continue this background treatment during the whole study.

Duration of treatment:
Placebo run-in period: 2 to 3 weeks according to the presence or not of a previous anti-anginal monotherapy.
Treatment period: 6 weeks.

Criteria for evaluation:
Efficacy measurements:
Main efficacy criteria:
Relative change in:

- The mean number of angina attacks per week (AA/week) over a 6-week treatment period.
- The mean consumption of short acting nitrates per week (SAN/week) over a 6-week treatment period.

Secondary efficacy criteria:

- Heart rate (HR, bpm).
- Canadian cardiovascular society (CCS) class.

ETT sub-study efficacy criteria:

- Relative changes of the following ETT parameters over a 6-week treatment period in the ETT sub-group: time of onset of 1 mm ST segment depression (TST, s)*, total exercise duration (TED, s)*, time to limiting angina (TLA, s)**, time to onset of angina pain (TAO, s)**, heart rate (HR, bpm)* and rate pressure product (RPP, bpm x mmHg)* at rest and at peak of exercise, reason for stopping exercise**.

* *evaluated by the Central Reading Centre.* ** *evaluated by the investigator.*

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Safety measurements:

- Spontaneously reported adverse events.
- Vital signs including heart rate (bpm) and blood pressure (mmHg).
- Biochemistry and haematology parameters.
- ETT safety parameters: blood pressure (mmHg) at rest and at peak of exercise.

Statistical methods:

All analysis were performed both in the global population and in the population of China.

Efficacy analysis:

Efficacy analysis was carried out on patients of the Full Analysis Set (FAS-Symptomatology and FAS-ETT, based on the "intention to treat" principle) and on patients of the Per Protocol Set (PPS-Symptomatology and PPS-ETT) as sensitivity analysis.

Main criteria:

Superiority of ivabradine *versus* placebo was tested on the relative change from baseline period over 6-week treatment period of the 2 co-primary endpoints: mean number of angina attacks per week and mean consumption of short acting nitrates per week.The multiplicity of comparisons (angina attacks and short-acting nitrates consumption) was addressed using Hochberg method: for each statistical approach, superiority was reached if the p-values of both criteria were $\leq 2.5\%$ or if at least one p-value was $\leq 1.25\%$.

The main analytical approach was a parametric analysis using two one sided Student t tests for independent samples.

An analysis of robustness was performed: non-parametric analysis based on a Hodges-Lehmann estimate.

The same analysis was performed on the following subgroups of the FAS-S-China (complementary analyses):

- Patients with baseline CCS class II or III: the CCS classification gives an accurate view of the angina severity since it is evaluated by the investigator. In patients with baseline CCS class II or III, *i.e.* patients exhibiting more severe angina symptoms, a greater benefit from the antianginal treatment can be expected. It was thus hypothesised that patients of the FAS with baseline CCS class II or III might obtain a greater benefit from ivabradine treatment. An analysis was therefore made in these patients, who accounted for 92.4% of the FAS-S-China population
- Patients with "coherent" baseline symptomatology: it was observed that some patients of the FAS-S-China reported very high rates of angina attacks at baseline with no, or very low rates of SAN intake. The reason for this clinical inconsistency is not clear, but it was hypothesised that the presence of these "outlier" values could have added imprecision in the statistical analysis; therefore patients with outlying values (defined as AA/week > 20, but with less than 20% of AA treated with SAN) at baseline were removed from the analysis (n = 6).

Secondary criteria:

- Evolution of heart rate observed during 12-lead ECG over 6-week treatment period was described for ivabradine group as compared to placebo group using 95% confidence intervals calculated with a parametric method based on general linear model and a non-parametric method based on Hodges & Lehmann's estimate.
- CCS classes: Descriptive statistics.

ETT sub-study:

The analysis of all the ETT parameters (TST, TED, TLA, TAO, HR, RPP) was performed over 6-week treatment period on the FAS-ETT and PPS-ETT using similar analysis as for the secondary criterion HR above. Descriptive statistics were provided on reason for stopping exercise.

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Safety analysis:
Descriptive statistics was provided on patients of the Safety Set for adverse events, vital signs, ETT safety parameters (SS-ETT), and biological parameters.

SUMMARY - CONCLUSIONS
STUDY POPULATION AND OUTCOME

Disposition of patients (Global and in China)

	Global			China		
	Ivabradine (N = 216)	**Placebo (N = 211)**	**All (N = 427)**	**Ivabradine (N = 168)**	**Placebo (N = 166)**	**All (N = 334)**
Included	**216**	**211**	**427**	**168**	**166**	**334**
Completed	**203**	**200**	**403**	**157**	**157**	**314**
Withdrawn due to	**13**	**11**	**24**	**11**	**9**	**20**
Adverse event	7	3	10	6	2	8
Non-medical reason	6	8	14	5	7	12
Randomised Set - RS	**216**	**211**	**427**	**168**	**166**	**334**
FAS-Symptomatology (FAS-S)	214	206	420	167	161	328
PPS-Symptomatology (PPS-S)	168	160	328	132	135	267
Safety Set	216	210	426	168	165	333
ETT sub-study						
RS-ETT (RS-E)	**49**	**51**	**100**	**46**	**47**	**93**
FAS-ETT (FAS-E)	46	48	94	43	44	87
PPS-ETT (PPS-E)	39	38	77	36	36	72
Safety Set-ETT (SS-E)	49	51	100	46	47	93

A total of 427 patients with stable effort angina pectoris were included in the study; the global population was recruited in 4 Asian countries (China: 334 patients; Indonesia: 4 patients; Thailand: 7 patients; Vietnam: 82 patients). A balanced distribution was reached with 216 patients in the ivabradine group and 211 in the placebo group (including in China 168 and 166 patients respectively). These patients comprised the RS-Global and the RS-China, which hereafter are described separately.

In the RS-Global, 24 patients (5.6%) were prematurely withdrawn, with similar rates of withdrawals between the ivabradine group (6.0%) and the placebo group (5.2%); 403 patients (94.4%) completed the study. The FAS-S-Global consisted of 98.4% and PPS-S-Global of 76.8% of the RS-Global. 100 patients were included in the ETT sub-study (RS-E-Global): 49 patients in the ivabradine group, and 51 in the placebo group.

In the RS-China, 20 patients (6.0%) were prematurely withdrawn (6.5% in the ivabradine group and 5.4% in the placebo group), and 314 (94.0%) completed the study. The FAS-S-China consisted of 98.2% and PPS-S-China of 79.9% of the RS-China. 93 patients were included in the ETT sub-study (RS-E-China): 46 patients in the ivabradine group, and 47 in the placebo group.

- **Demographic data and history of angina pectoris**

In the RS-Global, patients had a mean age of 59.4 ± 9.7 years. Men represented 69.8% of patients. Symptoms of stable effort angina had been present for 2.0 ± 3.6 years in average, with 60.0% of patients diagnosed for one year or less. Patients had angina pain CCS class I (6.8%), II (79.4%) and III (13.8%). 23.0% of patients had experienced a previous MI, 19.0% a PTCA, and 1.9% a CABG. 56.2% of patients reported a coronary angiography. Slightly more than half of the patients (54.8%) were previously treated for angina pectoris, mainly with organic nitrates (76.9% of them) and calcium channel blockers (23.1% of them). Regarding other medical histories, 63.0% of the patients had hypertension, 19.2% hyperlipidaemia, and 11.9% diabetes mellitus.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

In the RS-China, comparable characteristics were observed as patients had a mean age of 58.8 ± 9.4 years, with 70.7% of men. Symptoms of stable effort angina had been present for 1.9 ± 3.0 years in average, with 61.7% of patients diagnosed for one year or less. Patients had angina pain CCS class I (7.5%), II (79.0%) and III (13.5%). 26.0% of patients had experienced a previous MI, 21.0% a PTCA, and 1.8% a CABG. 53.0% of patients reported a coronary angiography showing a significant stenosis. 60.2% of patients were previously treated for angina pectoris, mainly with organic nitrates (73.1% of them) and calcium channel blockers (26.9% of them). Regarding other medical histories, 62.3% of the patients had hypertension, 22.8% hyperlipidaemia, and 12.9% diabetes mellitus.

No relevant difference between treatment groups was detected, in either population.

- **Baseline efficacy parameters**

In the RS-Global, during the run-in baseline period, the mean number of angina attacks per week was 9.0 ± 5.5, with 71.7% of patients having between 4 and 10 attacks per week, and the mean SAN consumption was of 5.6 ± 7.3 intakes per week, with 30.2% of patients who did not take any SAN.

In the RS-China, similar figures were observed: during the run-in baseline period, the mean number of angina attacks per week was 8.5 ± 4.3, with 72.5% of patients having between 4 and 10 attacks per week, and the mean SAN consumption was of 4.9 ± 6.3 intakes per week, with 34.7% of patients who did not take any SAN.

- **Treatment duration and compliance**

The mean treatment duration was 6.0 ± 0.9 weeks in the RS-Global and 6.0 ± 1.0 weeks in the RS-China, which corresponded to the planned duration, and mean compliance was satisfactory (100.5 ± 8.7% in the RS-Global and 100.0 ± 8.9% in the RS-China). The dose titration from 5 mg to 7.5 mg at W2 or W4 was less frequent in the ivabradine group than in the placebo group (80.6% *versus* 94.8% in the RS-Global and 78.6% *versus* 93.9% in the RS-China), reflecting the higher heart rate reduction in the ivabradine group.

EFFICACY RESULTS

- **Primary assessment criteria: angina attacks and short-acting nitrates consumption**

In the FAS-S-Global, the mean number of angina attacks per week decreased over the 6-week treatment period by 56.8 ± 35.5% in the ivabradine group and by 50.3 ± 39.6% in the placebo group. The mean consumption of short-acting nitrates per week decreased by 57.1 ± 83.7% in the ivabradine group and by 55.0 ± 84.2% in the placebo group. For angina attacks, the mean relative decrease was larger in the ivabradine group than in the placebo group, but the statistical significance was not reached using the pre-defined Hochberg method.

In the FAS-S-China, the mean number of angina attacks per week decreased by 57.1 ± 33.9% in the ivabradine group, and by 48.7 ± 36.4% in the placebo group, with a between-group difference estimated at -8.4% using the parametric approach (p-value = 0.015), and at –7.8% using the non parametric approach (p-value = 0.012). The mean consumption of short-acting nitrates per week decreased by 56.8 ± 92.4% in the ivabradine group and by 58.3 ± 56.1% in the placebo group (non significant difference). The superiority of ivabradine on placebo was reached using the non parametric approach since the p-value for angina attacks reduction was lower than 0.0125.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Mean number of angina attacks and short-acting nitrates per week

		FAS-S-Global		FAS-S-China	
		Ivabradine (N = 214)	**Placebo (N = 206)**	**Ivabradine (N = 167)**	**Placebo (N = 161)**
Angina attacks	n	214	206	167	161
Baseline	Mean ± SD	8.4 ± 4.2	9.5 ± 6.5	8.3 ± 4.3	8.7 ± 4.3
	Median	7.4	7.7	7.4	7.5
	Min ; Max	4.0 ; 34.6	2.1 ; 59.4	4.0 ; 34.6	2.1 ; 25.9
Relative change (%)	**Mean ± SD**	**-56.8 ± 35.5**	**-50.3 ± 39.6**	**-57.1 ± 33.9**	**-48.7 ± 36.4**
	Median	-62.8	-57.3	-62.7	-54.0
	Min ; Max	-100.0 ; 66.7	-100.0 ; 183.3	-100.0 ; 66.7	-100.0 ; 113.0
Between-group analysis					
Main: parametric approach	E (SE) (1)	-6.50 (3.66)		-8.42 (3.88)	
	95% CI (2)	[-13.70 , 0.71]		[-16.05 , -0.78]	
	p-value (3)	0.039		0.015	
Sensitivity: non parametric approach	E (4)	-5.56		-7.76	
	95% CI (5)	[-11.81 , 0.21]		[-14.80 , -0.85]	
	p-value (6)	0.037		0.012	
Short-acting nitrates	n*	149*	142*	111*	101*
Baseline	Mean ± SD	8.4 ± 7.7	7.7 ± 7.5	7.8 ± 6.4	7.3 ± 6.4
	Median	6.2	5.1	5.9	4.9
	Min ; Max	0.4 ; 46.9	0.4 ; 40.6	0.4 ; 34.5	0.5 ; 30.4
Relative change (%)	**Mean ± SD**	**-57.1 ± 83.7**	**-55.0 ± 84.2**	**-56.8 ± 92.4**	**-58.3 ± 56.1**
	Median	-76.7	-71.8	-75.4	-71.8
	Min ; Max	-100.0 ; 788.2	-100.0 ; 733.3	-100.0 ; 788.2	-100.0 ; 222.7
Between-group analysis					
Main: parametric approach	E (SE) (1)	-2.11 (9.85)		1.44 (10.63)	
	95% CI (2)	[-21.49 , 17.28]		[-19.51 , 22.38]	
	p-value (3)	0.415		0.446	
Sensitivity: non parametric approach	E (4)	0.00		0.00	
	95% CI (5)	[-1.49 , 5.83]		[-5.50 , 7.04]	
	p-value (6)	0.291		0.387	

Superiority tests - Hochberg method for multiple comparisons (angina attacks and short-acting nitrates consumption): for each statistical approach, superiority is reached if the p-values of both criteria are ≤ 2.5% or if at least one p-value is ≤ 1.25%.

** A total of 129 patients in the FAS-S-Global and 116 patients in the FAS-S-China had a SAN consumption = 0 during the run-in period and thus were not taken into account in the analysis of relative change of SAN.*

(1) Estimate (standard error) of ivabradine minus placebo: difference between treatment groups means

(2) 95% Confidence Interval of the estimate (two-sided) based on the overall general linear model (least-squares norm)

(3) Student t test

(4) Estimate of the difference between treatment groups based on Hodges-Lehmann estimator for independent samples

(5) 95% Confidence Interval of the estimate (two-sided) based on the difference between groups

(6) Mann & Whitney test

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Post-hoc analyses in subgroups of the FAS-S-China

- **In the subgroup of patients with more severe angina (CCS class II or III, N = 303)**, a statistically significant difference between groups in favour of ivabradine was observed on the reduction of angina attacks with the parametric approach (between-group difference of -9.4%, p-value = 0.011), and confirmed by the non-parametric approach.
- **In the subgroup of patients with "coherent" baseline symptomatology**, *i.e.* when excluding from the FAS-S-China 6 patients with more than 20 angina attacks per week during the baseline period and a discordant consumption of short-acting nitrates **(N = 322)**, a statistically significant difference between groups in favour of ivabradine was observed on the reduction of angina attacks with the parametric approach (between-group difference of –8.9%, p-value = 0.012), and confirmed by the non-parametric approach.

- **Secondary efficacy criteria**
  - *Heart rate from 12-lead ECG*: In both FAS-S-Global and FAS-S-China, mean heart rate was reduced from baseline to last value by around 10 bpm in the ivabradine group, with a statistically significant difference *versus* placebo, estimated at –9.3 bpm in the FAS-S-Global (95% CI = [-11.6 , -7.0]), and -9.2 bpm in the FAS-S-China (95% CI = [-11.8 , -6.7]).
  - *Severity of angina (CCS class)*: in the FAS-S-Global, 31.5% of the patients in CCS class II or III at baseline had an improvement in CCS class in the ivabradine group *versus* 23.2% in the placebo group. In the FAS-S-China, 27.0% had an improvement in the ivabradine group *versus* 19.3% in the placebo group.

- **ETT sub-study**

In patients participating in the ETT sub-study (FAS-E), the mean time to 1-mm ST depression increased in both groups, with between-group differences in favour of ivabradine (+17.8 s in the FAS-E-Global and +9.9 s in the FAS-E-China). Similarly, the total exercise duration was more increased in the ivabradine group than in the placebo group (between-group difference estimated at +31.6 s in the FAS-E-Global, and at +33.6 s in the FAS-E-China). Between-group differences in favour of ivabradine were also seen for other ETT parameters: +10.3 s for TAO and +36.6 s for TLA in the FAS-E-China. Mean heart rate at rest and at peak were markedly reduced under ivabradine as compared to placebo (in the FAS-E-China: -12.6 bpm at rest and –9.7 bpm at peak).

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

ETT parameters - Mean change from baseline to last assessment

		FAS-E-Global		FAS-E-China	
		Ivabradine (N = 46)	**Placebo (N = 48)**	**Ivabradine (N = 43)**	**Placebo (N = 44)**
TST (s)	n	41	45	38	41
	Mean ± SD	110.0 ± 164.1	92.2 ± 139.6	110.6 ± 168.9	100.7 ± 136.3
	Median	117	74	119	80
	Min ; Max	-240 ; 476	-145 ; 540	-240 ; 476	-145 ; 540
Between-group analysis					
Parametric approach	E (SE) (1)	17.82 (32.76)		9.87 (34.41)	
	95% CI (2)	[-47.32,82.96]		[-58.65 , 78.39]	
Non-parametric approach	E (3)	26.00		21.50	
	95% CI (4)	[-36.00 , 91.00]		[-46.00 , 85.00]	
TED (s)	n	46	48	43	44
	Mean ± SD	119.1 ± 128.2	87.5 ± 95.6	123.0 ± 131.2	89.5 ± 95.2
	Median	99	82	100	88
	Min ; Max	-189 ; 527	-207 ; 245	-189 ; 527	-207 ; 245
Between-group analysis					
Parametric approach	E (SE) (1)	31.59 (23.26)		33.55 (24.53)	
	95% CI (2)	[-14.61 , 77.78]		[-15.23 , 82.32]	
Non-parametric approach	E (3)	16.00		16.00	
	95% CI (4)	[-27.00 , 59.00]		[-28.00 , 66.00]	
TAO (s)	n	36	43	34	39
	Mean ± SD	157.4 ± 161.0	148.8 ± 162.2	168.2 ± 157.3	157.9 ± 165.0
	Median	164	147	171	158
	Min ; Max	-304 ; 509	-170 ; 478	-304 ; 509	-170 ; 478
Between-group analysis					
Parametric approach	E (SE) (1)	8.57 (36.52)		10.25 (37.89)	
	95% CI (2)	[-64.14 , 81.29]		[-65.30 , 85.79]	
Non-parametric approach	E (3)	13.50		12.00	
	95% CI (4)	[-63.00 , 83.00]		[-67.00 , 86.00]	
TLA (s)	n	46	47	43	43
	Mean ± SD	121.9 ± 128.7	84.9 ± 101.3	125.3 ± 132.5	88.8 ± 95.7
	Median	97	83	110	83
	Min ; Max	-189 ; 527	-207 ; 279	-189 ; 527	-207 ; 264
Between-group analysis					
Parametric approach	E (SE) (1)	36.98 (23.99)		36.56 (24.93)	
	95% CI (2)	[-10.67 , 84.63]		[-13.01 , 86.13]	
Non-parametric approach	E (3)	21.50		20.00	
	95% CI (4)	[-24.00 , 68.00]		[-26.00 , 71.00]	

For ETT at baseline, missing data were not substituted; patients who did not have the corresponding event during their baseline ETT were thus excluded from the analysis.

(1) Estimate (standard error) of ivabradine minus placebo: difference between treatment groups means

(2) 95% Confidence Interval of the estimate (two-sided) based on the overall general linear model (least-squares norm)

(3) Estimate of the difference between treatment groups based on Hodges-Lehmann estimator for independent samples

(4) 95% Confidence Interval of the estimate (two-sided) based on the difference between groups

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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SUMMARY – CONCLUSIONS (Cont'd)
SAFETY RESULTS

Overall summary of emergent adverse events on treatment

Patients having reported		SS-Global		SS-China	
		Ivabradine (N = 216)	Placebo (N = 210)	Ivabradine (N = 168)	Placebo (N = 165)
at least one emergent adverse event	n (%)	79 (36.6)	75 (35.7)	66 (39.3)	63 (38.2)
at least one treatment-related EAE	n (%)	23 (10.6)	6 (2.9)	18 (10.7)	3 (1.8)
Heart rate decreased (asymptomatic bradycardia)	n (%)	14 (6.5)	4 (1.9)	11 (6.5)	3 (1.8)
Bradycardia (symptomatic)	n (%)	3 (1.4)	-	3 (1.8)	-
at least one emergent serious adverse event	n (%)	5 (2.3)	1 (0.5)	3 (1.8)	-
Fatal	n (%)	2 (0.9)	-	2 (1.2)	-
Non-fatal	n (%)	3 (1.4)	1 (0.5)	1 (0.6)	-
Patients withdrawn due to an emergent adverse event	n (%)	7 (3.2)	1 (0.5)	5 (3.0)	-

N: total number of exposed patients in the considered treatment group n: number of patients affected %: n/N x 100

- Emergent adverse events

The rate of patients with emergent adverse events on treatment was similar between groups: 36.6% of patients in the ivabradine group *versus* 35.7% in the placebo group in the Safety Set-Global, and 39.3% *versus* 38.2% respectively in the Safety Set-China. The most frequently reported emergent adverse events were asymptomatic bradycardia (coded as heart rate decreased) and hyperlipidaemia.

As expected from the mechanism of action of ivabradine, asymptomatic bradycardia (coded as heart rate decreased) was more frequent in the ivabradine group than in the placebo group (in the Safety Set-Global: 6.5% *versus* 1.9%, and in the Safety Set-China: 6.5% *versus* 1.8%). Symptomatic bradycardia (coded as bradycardia) was reported in the ivabradine group in 1.4% of patients in the Safety Set-Global (1.8% in the Safety Set-China) *versus* none in the placebo group.

No relevant difference between groups was observed for hyperlipidaemia (5.1% *versus* 4.3% in the Safety Set-Global and 6.5% *versus* 5.5% in the Safety Set-China).

Treatment-related emergent adverse events were more frequent in the ivabradine group than in the placebo group (in the Safety Set-Global: 10.6% *versus* 2.9%, and in the Safety Set-China: 10.7% *versus* 1.8%). They consisted mainly in expected adverse drug reactions: asymptomatic and symptomatic bradycardia; indeed all cases of these adverse events observed during the treatment period were considered as treatment-related.

- Deaths, non-fatal serious adverse events and other significant adverse events

In the Safety Set-Global, 3 patients from China in the ivabradine group died during the study. Two patients died from an emergent adverse event (bile duct cancer and sudden death), and one patient died from an adverse event occurred 1 week after the end of the treatment period (angina unstable). None of these fatal adverse events was considered as related to the study treatment by the investigator.

In the Safety Set-Global, 5 patients in the ivabradine group and 6 in the placebo group had at least one non-fatal serious adverse event during the study (in the Safety Set-China: 2 and 5 patients, respectively). The serious adverse event was emergent in 3 patients in the ivabradine group (worsening of angina pectoris in China, gastrointestinal infection and planned percutaneous coronary intervention in Vietnam) and 1 in the placebo group (acute myocardial infarction in Indonesia). Adverse events led to study treatment discontinuation in 7 patients in the ivabradine group and 2 patients in the placebo group (in the Safety Set-China: 5 and 1 patients, respectively).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Laboratory exams**

No relevant difference between groups was observed on emergent potentially clinically significant abnormal values.

- **Vital signs**

Mean heart rate markedly decreased from baseline to last value in the ivabradine group (Safety Set-Global: -11 ± 13 bpm and Safety Set-China: -10 ± 13 bpm), while no relevant change was observed in the placebo group. Other vital signs (sitting blood pressures and weight) did not change during the study.

CONCLUSION

In both the global study population and patients enrolled in China, there were meaningful and clinically relevant reductions in the numbers of angina attacks and in the consumption of short-acting nitrates during the treatment period in patients randomised to ivabradine. Statistical significance was not reached using the pre-defined Hochberg method, but a statistically significant effect of ivabradine was demonstrated in the Chinese patients as the majority group of the global study population (non-parametric approach: p = 0.012 for the reduction in angina attacks) and in the analysis of angina attacks as a single primary endpoint using either parametric or non-parametric methods. The primary pharmacodynamic action of ivabradine was also demonstrated as mean heart rate was significantly reduced as compared to placebo. Moreover, the results of the ETT sub-study showed a consistent trend toward a greater improvement for all the ETT parameters in patients in the ivabradine group as compared to the placebo group.

No unexpected safety concern was identified.

Date of the report: 12 April 2011