Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Long-term (3 years) ophthalmic safety and cardiac efficacy and safety of ivabradine administered orally at the therapeutic doses (2.5/5/7.5 mg b.i.d.) on top of anti-anginal background therapy, to patients with chronic stable angina pectoris.** **An international, double-blind placebo controlled study.**
Test drug code	**Ivabradine (S 16257-2)**
Indication	**Stable angina pectoris**
Development phase	**Phase III**
Protocol code	**CL3-16257-067**
Study initiation date	**29 April 2008**
Study completion date	**12 February 2015**
International coordinators	[redacted]
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	**07 October 2015**
Version of the report	**Final Version**
	~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Procoralan®, Corlentor® , Coraxan®, Coralan® **Name of Active Ingredient:** Ivabradine (S 16257)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: Long-term (3 years) ophthalmic safety and cardiac efficacy and safety of ivabradine administered orally at the therapeutic doses (2.5/5/7.5 mg b.i.d.) on top of anti-anginal background therapy, to patients with chronic stable angina pectoris.An international, double-blind placebo controlled study. Protocol No.: CL3-16257-067 EudraCT No.: 2006-005475-17 The description of the study protocol given hereafter includes the modifications of the ten substantial amendments to the protocol (Amendments No. 2-6 and 7-12).		
International coordinators: **Ophthalmology:** [redacted] **Cardiology**: [redacted]		
Study centres: 19 cardiologist centres (main investigator, cardiologist) located in 9 countries included 97 patients: Argentina (5 centres, 28 patients), Australia (2 centres, 15 patients), Belgium (2 centres, 4 patients), Finland (1 centre, 7 patients), Hungary (4 centres, 18 patients), Ireland (1 centre, 1 patient), Portugal (2 centres, 16 patients), Singapore (1 centre, 3 patients), Sweden (1 centre, 5 patients). In all countries, ophthalmic (OPH) examinations were carried out by ophthalmologists (OPH investigator) specialised in electrophysiology and perimetry.		
Publication (reference): Not applicable.		
Studied period: Initiation date: 29 April 2008 (date of first visit first patient) Completion date: 12 February 2015 (date of last visit last patient)	**Phase of development of the study:** Phase III	
Objectives: The purpose of this study was to document the absence of retinal toxicity of ivabradine when administered at the therapeutic doses on the long-term (*i.e.* 36 months). **The main objective** was to document the absence of retinal toxicity of ivabradine *versus* placebo in chronic stable angina patients two months after treatment cessation (*i.e.* M38) in the subset of patients with emergent bilateral relevant ERG abnormalities (see primary endpoint hereafter) observed under treatment (*i.e.* M36). **The secondary objectives** were to document on all patients : - The change of each ophthalmic parameter of the four criteria of the primary endpoint (bilateral/unilateral ERG abnormalities) from baseline to M36 and baseline to M38 between groups (ivabradine *versus* placebo), and from M36 to M38 within treatment group. - The evolution over time of all ophthalmic tests results. - The long-term ophthalmic safety on ocular events including visual symptoms. - The cardiac long-term efficacy (at M36) based on the HR reduction and on the reduction of the number of angina attacks and short acting nitrates consumption per month. - The potential rebound phenomenon. - The long-term general safety on adverse events (except ocular adverse events included into the ophthalmic safety), vital signs, blood pressure, ECG abnormalities and on haematology/biochemistry analyses.		

Methodology:
This was a randomised, international multicentre, double-blind, placebo-controlled study on top of standard anti-anginal therapies. The non-adaptative randomisation was stratified on age (> or ≤ 60 years) and on non-severe non-proliferative diabetic retinopathy (presence yes/no).

This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

Number of patients:
Planned: 300 patients (150 per group) in order to obtain 100 patients by treatment group assessable at M36 and M38, amended (Amendment No. 11, 27 April 2012 upon CHMP approval) to 100 patients (50 per group) in order to obtain 40 patients by treatment group assessable at M36 and M38.
Included: 97 patients (50 in the ivabradine group and 47 in the placebo group).

Diagnosis and main criteria for inclusion:
Main selection / inclusion criteria:

- Males or females ≥ 18 years.
- Chronic stable angina pectoris for at least 3 months prior to inclusion.
- Severity of angina: no angina at rest and at least one anginal attack per month during the last 3 months.
- Clinical stability : no significant change in frequency, severity of angina or triggering activity within one month prior to inclusion and stable doses, for at least 1 month, of background cardiovascular medications
- Sinus rhythm with resting HR ≥ 60 bpm.
- Distant visual acuity > 0.5 with the best refraction correction in either eye.
- Reliable baseline ERG and visual fields.
- Informed consent obtained.

Main non-selection / non-inclusion criteria:

- Astigmatism > 3.00 diopters in either eye.
- Myopia > - 5.00 diopters in either eye.
- Hyperopia > + 5.00 diopters in either eye.
- Closed angle glaucoma.
- Decrease in visual acuity > 2 lines in either eye between the selection and inclusion visit.
- Change between the selection and inclusion visit in fundoscopy which might indicate a disease progression towards retinal dysfunction during the course of the study.
- Eye disorders that might alter the visual function.
- Currently treated with ivabradine.
- Contra-indication to the administration of ivabradine.

Test drug:
Ivabradine 2.5 mg, 5 mg or 7.5 mg twice daily: oral administration of one tablet in the morning and one tablet in the evening.
Starting dose of either 5 mg bid, or 2.5 mg bid in patients aged > 75 years, and/or a concomitant treatment with a moderate CYP3A4 inhibitor. At the first post-inclusion visit, the initial dose might be up-titrated to 5 or 7.5 mg bid or down-titrated to 2.5 mg bid, according to the clinical judgement of the investigator, based on the HR and depending on the therapeutic response (clinical evolution of the anginal disease assessed on the number of angina attacks per month).The maintenance dose was 7.5 mg bid. During the course of the study, the dose might be up or down-titrated according to the same criteria as described above.
Batch Nos: L0014993, L0021604, L0025308, L0032791, L0037264 & L0044336 (2.5 mg tablets); L0013977, L0017875, L0020219, L0027232, L0029816, L0036727, L0038676, L0043030 & L0045270 (5 mg tablets); L0018137, L0020220, L0027230, L0032018, L0033608, L0041708 & L0047809 (tablets 7.5 mg).

Comparator:
Matching placebo tablets, twice daily, in the same conditions as specified above for ivabradine.

Duration of treatment:
Pre-inclusion period (up to 28 days): no Investigational Medicinal Product (IMP) was dispensed.
Double blind treatment period: patients received either ivabradine or placebo during 36 months (M36).
Run-out period: patients received single-blind placebo treatment during 1 to 3 months (M36 to M38).
Follow-up period (optional, if unresolved OPH abnormalities at M38): up to three optional OPH visits (no IMP was dispensed during this optional follow-up period).

Criteria for evaluation:
Efficacy measurements (secondary objectives):
Secondary efficacy endpoints were for cardiac evaluation:

- Heart rate at rest.
- Symptoms of angina: mean number of angina attacks per month, mean consumption of short acting nitrates per month.

Cardiac and general safety (secondary objectives):
Cardiac and general secondary safety endpoints:

- Adverse events.
- HR at rest.
- Symptomatology of angina pectoris (rebound phenomenon).
- ECG abnormalities.
- Haematology and biochemistry.
- Blood pressure.

Ophthalmic safety measurements (main objectives):
Primary safety endpoint (composite): within the subset of patients with at least one bilateral relevant abnormality named Potential Clinical Concern (PCC) at M36, presence of a bilateral PCC at M38 (Yes/No) on at least one of the four «main» ERG criteria (central reading assessment):

- Standard combined rod/cone response (3RC) a- and b-waves, amplitude.
- Standard combined rod/cone response (3RC) a- and b-waves, implicit time (IT).
- Single flash cone response (SFC) a- and b-waves, amplitude.
- Single flash cone response (SFC) a- and b-waves, IT.

Secondary safety endpoints
Ophthalmic safety endpoints (measurements recorded for each eye) :

- ERG amplitude (µV) and implicit times (ms) of the following responses: rod response (0.009R) with a weak flash (0.009 cd.s/m^2) [b-wave], high intensity combined rod/cone (12RC) with a very bright flash of 12 cd.s/m^2 [a- and b-waves], (30 Hz) flicker response at peak time with SF and single flash cone (SFC) response [a- and b-waves].
- Visual fields:
  Peripheral visual field (semi-automated kinetic method outside 30° and up to 90° eccentricity) assessed on two isopters III 4e and I 3e) as total isopter area (degrees^2).
  Central visual field (up to 30° eccentricity automated static threshold method (thresholding algorithm) as age matched corrected mean defect (MD) (dB).
- Colour vision test (Lanthony D-15 desaturated test) as Total Error Score (TES, calculated by a computerised analyser).
- Distant Visual Acuity (ETDRS chart): distant vision (log MAR unit).
- Tonometry (applanation according to the Goldmann method): intra ocular pressure (mmHg).
- Clinical examination (anterior segment and fundi oculi): descriptive evaluation.
- Photo of the retina.

Statistical methods:
Efficacy analysis:
The efficacy analyses were carried-out on patients in the Full Analysis Set (FAS). The FAS was defined as all randomised patients having the studied disease, having taken at least one dose of IMP, with at least one evaluation of symptomatology of angina post-inclusion.
Heart rate at rest: an estimate of the difference between groups on the change from baseline to the last post-baseline value under treatment was given using a 95% confidence interval (CI) and standard error based on a parametric analysis of covariance adjusted on age class (≤ or > 60 years) factor and baseline value as a covariate (method 1). Sensitivity analysis using a non-parametric without adjustment based on the Hodges-Lehmann's estimator for independent samples (method 2) were performed.
Symptoms of angina: same analysis as those for heart rate were performed for mean number of angina attacks per month and mean consumption of short acting nitrates per month.

Safety analysis
The cardiac and general safety analyses were carried-out on patients of the Safety Set (SS). The ophthalmic safety analyses were carried-out on patients of the Safety OPH Set (SOS) and Sub Safety OPH Set (SSOS). The SOS was defined as all patients of the SS with at least one evaluation from at least one reliable OPH test for each eye at baseline and at M36 under treatment or at M38. The SSOS was defined as all patients of the SOS with a bilateral relevant ERG abnormality (*i.e.* Potential Clinical Concern *i.e.* PCC) at M36 under treatment on at least one of the four main ERG criteria (composite endpoint) and a reliable ERG test at M36 under treatment for each eye and at M38. A Scientific Safety Ophthalmic Committee provided regular OPH safety advice to the Sponsor and perform the assessment and medical review of the complete file of all patient who presented at least one bilateral emergent PCC at least at one visit.

Primary OPH safety criterion in the SSOS: an estimate of the difference between the two groups using 95% CI based on the Wilson score method was given.

Secondary OPH safety criteria in the SOS:

- For all ERG criteria (amplitude and implicit time), Visual Fields (VFs/VFk), Colour Vision, Tonometry and distant Visual Acuity: change classes were described by shift tables between left and right eye at M36 under treatment and at M38 on patients. Descriptive statistics were also provided by treatment group on the changes baseline/M36 under treatment, baseline/M38 and from M36 under treatment/M38 on each eye. The same analyses were performed on patients of the SS.
- For all ERG criteria and VFs/VFk: evolution classes from baseline to M36 under treatment and to M38 were also described. The same analyses were performed on patients of the SS.
- For the 4 main ERG criteria, VFs/VFk and Colour Vision: an estimate of the difference between groups on the change baseline/M36 under treatment and baseline/M38 was given using 95% CI based on the same models as described above for the efficacy analyses (methods 1 and 2). An estimate of the difference within each group on the change M38/M36 under treatment was also provided using 95% CI and standard error with a parametric analysis of variance without adjustment (method 3) and 95% CI with a non-parametric without adjustment based on the Hodges-Lehmann's estimator using Walsh averages as sensitivity analysis (method 4).
- For Anterior segment and Fundi oculi: descriptive statistics were provided by treatment group on the changes of class (normal/abnormal) from baseline to M36 under treatment and to M38 and from M36 under treatment to M38 on each eye.
- Ocular emergent adverse events (EAEs), including expected visual symptoms, during the double-blind and single-blind treatment periods were analysed using descriptive statistics.

Cardiac and general secondary safety criteria in the SS:

- Heart rate and angina symptoms: an estimate of the difference between groups on the change from baseline to M38 was given using 95% CI based on the same models as described above (methods 1 and 2). The change from M36 under treatment to M38 was also estimated within each group using 95% CI based on the same models as described above for the ophthalmic analyses (methods 3 and 4). Furthermore, abnormal HR values and emergent ECG abnormalities were provided.
- Non-ocular EAEs during the double-blind and single-blind treatment periods were analysed using descriptive statistics.
- Other secondary safety analyses: blood laboratory parameters and blood pressure were analysed using descriptive analysis.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 190 patients were screened for the study, 171 were pre-selected. Among these, 102 patients had the 3 ophthalmic tests ERG, VFs and VFk with satisfactory quality (central assessment and quantitative criteria, respectively) and 97 patients were included and randomised: 50 patients to ivabradine and 47 to placebo The completion of the study with 1/3 of the initially planned number of patients was agreed by the CHMP based on the absence of signal from post-marketing reports or clinical studies and on important recruitment difficulties faced.

The 36 months treatment period was completed by a total of 76 patients (78.4%), while 11 patients (11.3%) were prematurely withdrawn for adverse event (OPH AE in 2/11 patients) and 9 patients (9.3%) for non-medical reason. All patients who performed M36 visit entered the run-out period and performed M38 visit (study completed). Additionally, 9 withdrawn patients entered the run-out period: 5 (10.0%) in ivabradine *versus* 4 (8.5%) in placebo group. Consequently, a total of 85 patients performed the M38 visit *i.e.* run-out visit while 1 of them performed only cardiologist visit but not OPH visit at M38. One patient in the placebo group was declared lost to follow-up during the study at the M18C visit.

Patient status during the study and number of patients in each analysis sets are presented in Tables 1 and 2.

Table 1 - Disposition of patients

Status		**Ivabradine**	**Placebo**	**All**
Included (randomised at M00C)	**N**	**50**	**47**	**97**
Withdrawn due to	**n (%)**	**11 (22.0)**	**10 (21.8)**	**21 (21.6)**
adverse event	n (%)	6 (12.0)	5 (10.6)	11 (11.3)
non-medical reason	n (%)	5 (10.0)	4 (8.5)	9 (9.3)
lost to follow-up	n (%)	-	1 (2.1)	1 (1.0)
Performed MRUC (withdrawn patients)	n (%)	5 (10.0)	4 (8.5)	9 (9.3)
Performed M36C	**n (%)**	**39 (78.0)**	**37 (78.7)**	**76 (78.4)**
Study completed (performed M36C and MRUC)	**n (%)**	**39 (78.0)**	**37 (78.7)**	**76 (78.4)**
Performed MRUC (completed and withdrawn)	n (%)	44 (88.0)	41 (87.2)	85 (87.6)

N: Total number of patients included; n: number of patients in each category; % = (n/N) x 100

Table 2 - Analysis sets

Analysis sets		**Ivabradine**	**Placebo**	**All**
Randomised Set (RS)	N	50	47	97
Full Analysis Set (FAS)[(1)]	n (%)	50 (100.0)	47 (100.0)	97 (100.0)
Safety Set (SS)[(1)]	n (%)	50 (100.0)	47 (100.0)	97 (100.0)
Safety OPH Set (SOS)[(2)]	n (%)	42 (84.0)	42 (89.4)	84 (86.6)
Sub Safety OPH Set (SSOS)[(3)]	n (%)	2 (4.8)	3 (7.1)	5 (6.0)

[(1)]% of the Randomised Set; [(2)]% of the SS; [(3)]% of the SOS

STUDY POPULATION AND OUTCOME

Main baseline characteristics

The study population of the Randomised Set had a mean age of 63.5 ± 7.9 years, was 58.8% men and 88.7% Caucasian. The angina history had been diagnosed for a mean of 5.1 ± 5.5 years. Previous myocardial infarction was reported in 46 patients (47.4%) and previous coronary angioplasty in 49 patients (50.5%). The mean number of angina attacks (AA) per month was 5.4 ± 10.3 (median = 1.5) and the mean number of short acting nitrates (SAN) consumption per month was 2.3 ± 5.9 (median = 0.0). These main baseline characteristics were comparable between groups, although the mean duration of angina pectoris was higher in the ivabradine group than in the placebo group (5.9 ± 6.3 years *versus* 4.3 ± 4.5 years). Angina pectoris symptoms were similar in the two groups. To be noted: some patients had no AA (first quartile = 0.0) during the pre-inclusion period; nevertheless, history of chronic stable angina for at least 3 months before the pre-selection visit was confirmed for all included patients.

The mean resting ECG HR was 68.4 ± 9.1 bpm overall. Mean values of supine SBP and DBP were 134.0 ± 16.7 mmHg and 76.7 ± 10.0 mmHg, respectively, and the mean weight was 81.5 ± 14.1 kg.

SUMMARY - CONCLUSIONS (Cont'd)
STUDY POPULATION AND OUTCOME (Cont'd)

Background cardiovascular treatments that were considered to be appropriate were allowed before and during the study. Thus, all patients were receiving at least one specific concomitant treatment at randomisation. These treatments were antithrombotic (94.8%), lipid-modifying agent (84.5%), agent acting on the renin-angiotensin system (74.2%), beta-blocker (73.2%) and cardiac therapy (71.1%, mostly organic nitrates (66.0%)). The profile of these specific concomitant treatments was similar between groups. Regarding specific medical history, 83.5% reported hypertension and 25.8% diabetes mellitus.

Ophthalmic (OPH) baseline characteristics were comparable between the two groups. 57.7% of patients drove a motor vehicle. 49.5% of patients reported an OPH disease as medical history, mostly cataract (17 patients, 17.5%). At inclusion, 9 patients (9.3%) had an OPH concomitant treatment on-going: hyaluronate sodium, povidone and cromoglicate sodium (1 patient in each group), anti-inflammatory (1 patient), beta-blocking agent (1 patient), anticholinergic (1 patient), these latter patients in the ivabradine group.

In the SOS (N = 84), main baseline characteristics were similar than those in the RS. No relevant difference between groups was observed.

Treatment duration and dose
In the RS, treatment duration during the double-blind treatment period was comparable in the two groups with a mean duration of 31.9 ± 10.3 months (median =35.9 months). Overall IMP compliance was good with 96.8% of patients achieving compliance between 70-130%.
86 patients (88.7%) received the starting dose 5 mg b.i.d: 38 patients (39.2%) were maintained at the starting dose 5 mg b.i.d. (19 patients in each group), 30 patients (30.9%) were up-titrated once and received 7.5 mg b.i.d (11 patients in the ivabradine group *versus* 19 patients in the placebo group) and 10 patients (10.3%) were down-titrated once and received 2.5 mg b.i.d (8 *versus* 2 patients, respectively).

EFFICACY RESULTS

In the FAS (N = 97) over the double-blind treatment period, as expected, a relevant reduction in resting HR was observed in the ivabradine group (mean change: -8.4 ± 8.6 bpm) while it remained stable in the placebo group (mean change: 1.5 ± 20.3 bpm). This difference between group was statistically significant (E = -7.0 and 95%CI [-12.0;-3.0], non-parametric method).

Over the double-blind treatment period, the mean number of angina attacks per month decreased in both groups (mean change: -3.2 ± 13.8 and -3.5 ± 7.5, respectively) with no between-group difference. Similarly, the mean short acting nitrates consumption per month decreased in both groups (mean change: -2.0 ± 6.0 and -1.9 ± 5.5, respectively) with no between-group difference.

SAFETY RESULTS

During the double-blind treatment period in the SS (N = 97), EAEs were reported in 42 patients (84.0%) in the ivabradine group *versus* 39 patients (83.0%) in the placebo group.

General and cardiac safety
Non-ocular EAEs were reported in 40 patients (80.0%) in the ivabradine group *versus* 38 (80.9%) in the placebo group (Table 3).

The SOCs cardiac disorders (38.0% *versus* 36.2%, respectively) and vascular disorders (22.0% *versus* 27.7%, respectively) were among the most frequently reported SOCs (in at least 20% of patients).

Asymptomatic bradycardia [HR decrease] was reported in 5 patients (10.0%) *versus* 2 patients (4.3%), respectively and symptomatic bradycardia in 3 patients (6.0%) in the ivabradine group. The other most frequently reported EAEs were with similar frequency in each group (angina pectoris: 8 patients in each group, 16.0% *versus* 17.0%) or with lower frequency in the ivabradine group: hypertension (6 patients (12.0%) *versus* 9 patients (19.1%), respectively) and unstable angina (2 patients (4.0%) *versus* 6 patients (12.8%), respectively).

SUMMARY - CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

Main safety results in the SS are summarised in the Table 3.

Table 3 - Overall summary of safety results (non-ocular EAE) during the double-blind treatment period in the Safety Set

		Ivabradine (N = 50)	Placebo (N = 47)
Patients reporting at least one:			
EAE	n (%)	40 (80.0)	38 (80.9)
Treatment-related EAE	n (%)	10 (20.0)	8 (17.0)
EAE leading to IMP withdrawal	n (%)	4 (8.0)	4 (8.5)
Patients reporting at least one:			
Serious EAE (including death)	n (%)	21 (42.0)	19 (40.4)
Serious treatment-related EAE	n (%)	2 (4.0)	1 (2.1)
Serious EAE with fatal outcome	n (%)	1 (2.0)	1 (2.1)

N: total number of exposed patients in the treatment group; n: number of affected patients; % = (n/N) x 100

Treatment-related EAEs were reported by 10 patients (20.0%) in the ivabradine group and 8 patients (17.0%) in the placebo group. In the ivabradine group, 3 patients reported symptomatic bradycardia, considered as treatment-related and recovered.
EAEs leading to IMP withdrawal were reported in 4 patients in each group (8.0% and 8.5%, respectively), mainly due to cardiac disorders. Symptomatic bradycardia led to IMP withdrawal in 1 patient in ivabradine group.
At least one ***serious EAE*** was reported at similar rates in the two groups (42.0% of patients in the ivabradine group *versus* 40.4% in the placebo group). These concerned mostly cardiac disorders (22.0% *versus* 21.3%, respectively) with between group differences for angina unstable (2 patient (4.0%) *versus* 6 patients (12.8%), respectively). 2 patients (4.0%) had a serious symptomatic bradycardia, both in the ivabradine group.

2 patients died on-treatment: 1 in the ivabradine group from septic shock and 1 in the placebo group from sudden cardiac death. Neither of these deaths was considered as treatment-related.

During the run-out period in the SS, EAEs were reported in 6 patients (12.0%) *versus* 5 patients (10.6%), respectively. Non-ocular EAE concerned mostly cardiac disorders: 3 patients (6.0%) in ivabradine group *versus* none in placebo group.

Emergent PCSA values during the double-blind treatment period for the biochemical and haematological parameters were infrequent in both groups, except for high triglycerides values reported in 3 patients (6.8%) *versus* 4 patients (8.9%), respectively.

The analysis over the double-blind treatment period of supine blood pressure in the SS showed a trend toward a decrease for both SBP and DBP in the ivabradine group: -1.6 ± 15.9 mmHg (median = 0.0) and -2.0 ± 11.3 mmHg, (median = -1.5), respectively; while minimal changes were observed in the placebo group in both supine SBP and DBP: 0.4 ± 17.7 mmHg and 0.9 ± 12.3 mmHg, respectively.

After cessation of ivabradine treatment at the end of run-out period, the mean HR change from baseline was -2.5 ± 10.1 bpm (median = -2.0) in the ivabradine group while it was 0.1 ± 10.3 bpm (median = -1.0) in the placebo group. On the same time interval, the mean number of angina attacks per month decreased in both groups: -3.3 ± 9.8 *versus* -3.7 ± 7.0, respectively; as well as the mean number of SAN consumption: -1.9 ± 6.5 *versus* -2.4 ± 6.4, respectively. No rebound phenomenon on the angina pectoris symptoms after ivabradine treatment cessation was observed in the study. The analysis of abnormal HR value and ECG abnormalities did not show any safety concern.

Ophthalmic safety (primary objective)

Ocular adverse events (including expected "visual symptoms" i.e. phosphenes-photopsia)

In the SS, ocular EAEs were reported in 20 patients (40.0%) in the ivabradine group *versus* 16 patients (34.0%) in the placebo group. The most frequently reported high group level terms were cataract conditions (8 patients (16.0%) *versus* 6 patients (12.8%), respectively) and "visual disorders NEC" (6 patients (12.0%) *versus* 4 patients (8.5%), respectively). Photopsia was reported in 4 (8.0%) *versus* 2 (4.3%) patients, respectively, and blurred vision in 1 patient in each group.

SUMMARY - CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

An ***ocular EAE leading to IMP withdrawal*** was reported in 2 patients: 1 event of perception disturbances ([hallucination, visual], recovered) in the ivabradine group and 1 event of visual impairment (considered as possibly related to a cerebral transient ischaemic attack by the investigator) in the placebo group. One patient in the ivabradine group experienced a ***serious ocular EAE*** (ophthalmic zona) which recovered.
In the SOS (N = 84), the profile of ocular EAEs were similar to the SS. During the run-out period in the SS, ocular EAEs were reported in 3 patients (6.4%) in the placebo group.

Primary composite safety endpoint (main ERG criteria) in the SSOS
The SSOS (N = 5) was composed of 2 patients in ivabradine group and 3 in placebo group, having an ERG bilateral relevant abnormality (*i.e.* PCC) reported at the end of the 3-year treatment period (M36). These patients were aged from 51 to 77 years. No ophthalmic disease was reported in SSOS as medical history except one case of hypermetropia.
At the end of the two-month run-out period after cessation of ivabradine treatment, PCCs were resolved in both patients of the ivabradine group (2/2) while they remained unresolved in all 3 patients of the placebo group (unilaterally in 2 patients and bilaterally in 1 patient). In ivabradine group, the PCC affected solely the b-wave IT; in the placebo group, the PCC affected several responses and components (a- or b-wave, amplitude or IT).

Ophthalmic examination results (secondary safety endpoints) in the SOS
Electroretinogram
In the ivabradine group, the mean changes between baseline and M36 in any ERG responses (3RC, SFC, 0.009R, 12RC, 30 Hz Flicker) showed amplitude reductions less than -25% and an IT increase less than one SD for these parameters. There were neither statistically significant (3RC and SFC) nor relevant (other parameters) between-group differences. The magnitude of the b-wave IT prolongation (3RC mean change: 1.75 ± 2.78 ms in RE (Right Eye), 1.72 ± 2.59 ms in LE (Left Eye)) is similar to the effect observed after one year of exposure to ivabradine (CL3-019 double blind randomised study). This prolongation is in accordance with the expected pharmacological ivabradine effect as stated in the European Public Assessment Report (2005). Same results were observed for the changes at M38.
Between M36 and M38, the within-group changes were not statistically significant in the two groups, except statistically significant change for the b-wave IT in ivabradine group: 3RC mean change = -1.09 ± 2.96 ms (E = -1.25; 95%CI [-2.00; -0.50]) in RE, -1.33 ± 2.55 ms (E = -1.25; 95%CI [-2.25 ; -0.50]) in LE; the same trend was observed in SFC even if not statistically significant: mean change = -0.40 ± 0.91 ms in RE, -0.35 ± 0.85 ms in LE (E = -0.25; 95%CI [-0.75; 0.00] for both eyes). This is supporting the reversibility of the expected pharmacological effect of ivabradine.
Regarding ERG responses other than those of primary endpoint criteria *i.e.* in patients other than those in SSOS, 3 patients in each group reported a bilateral PCC at M36. In the ivabradine group, 2/3 patients had PCC resolved at M38 and one not documented at M38 (patient's refusal, no ophthalmic AE was reported at the M38 cardiologist visit; however, this PCC affected b-wave IT which was correlated with expected pharmacological effect of ivabradine). Similarly as for ERG primary endpoint components, b-wave IT was affected in the ivabradine group. In the placebo group, the PCC affected several responses components and none of the patients had PCC resolved at M38. Electrophysiological data collected over the three years study did not indicate any sign of a retinal degenerative pathology.

Visual fields
Between baseline and M36, the mean defect change (central static VF, *i.e.* VFs) and the relative change for the total area of the two isopters (peripheral kinetic VF, *i.e.* VFk) were less than 1 dB (VFs) and -10% (VFk). There were no statistically significant between-group differences. Same results were observed for the changes at M38. Between M36 and M38, the within-group changes were not statistically significant in the two groups for both VFs and VFk.
At M36, 1 patient had a VFs bilateral PCC in the ivabradine group which resolved at M38. Regarding VFk, no patient had bilateral PCC related to III 4e isopter. And regarding isopter I 3e, 1 patient in ivabradine group had bilateral PCC which resolved at M38 *versus* 3 patients in the placebo group which did not resolved at M38 (1 unilaterally, 2 bilaterally). These data showed no functional changes on static or kinetic visual fields.

Colour vision
Between baseline and M36, the total error score change was less than 20. There were no statistically significant between-group differences. Same results were observed for the changes at M38.
Between M36 and M38, the within-group changes were not statistically significant in the two groups. 1 patient in ivabradine group reported a bilateral PCC at M36: the PCC resolved at follow-up visit. 1 patient in placebo group reported a bilateral PCC at M36: the PCC did not resolve unilaterally at follow-up visit. Colour vision remained unchanged in all patients during the study.

SUMMARY - CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

Other ophthalmic examinations
The mean change in distant visual acuity from baseline M36 and M38 was clinically not relevant in either eye with no relevant between-group differences. No patient reported any bilateral relevant change.
The intra-ocular pressure was stable during the study in the two groups and in either eye. Regarding the clinical examination of the anterior segment or of the retina by ophthalmoscopy, no relevant abnormality was observed.

The results of ophthalmic examinations in the SS were similar as those in the SOS.

CONCLUSION:

This was a phase III, randomised, double-blind comparison study of ivabradine *versus* placebo in patients with chronic stable angina pectoris on top of anti-anginal therapies. The main objective was to document the absence of retinal toxicity of ivabradine when administered at the therapeutic doses in the long-term (3 years). The main assessment was done two months after treatment cessation within the subset of patients having reported emergent bilateral relevant electroretinogram (ERG) abnormalities at the end of the 3-years treatment on at least one of the four main criteria of the composite primary criteria (dark adapted rod/cone (3RC) and light adapted single flash cone (SFC), in a- and b-wave amplitudes and implicit times).
The randomised population (N = 97) conformed to the target population (*i.e.* the registered indication of ivabradine at time of study set-up) and the two groups were well balanced in terms of demographics, baseline characteristics, concomitant medication and study duration. A sustained resting HR reduction was observed with ivabradine treatment over the 3-years. Angina pectoris symptoms symptoms (number of angina attacks and short acting nitrates consumption) decreased in both groups. No rebound phenomenon on the angina pectoris symptoms was observed after ivabradine treatment cessation.
The safety assessment showed that ivabradine was very similar compared with placebo in terms of frequency of emergent adverse events as well as AE profile, including ocular events. In line with the known safety profile of ivabradine, drug related events such as symptomatic or asymptomatic bradycardia were observed more frequently in the ivabradine group. The most frequent ocular adverse events were cataract conditions and visual disorders in both groups as expected in a population of a mean age of 63.5 ± 7.9 years.
Regarding the ERG primary endpoint for ophthalmic safety assessment, 2 patients (4.0% in RS) in the ivabradine group showed a bilateral relevant abnormality which affected the b-wave implicit time at the end of treatment period and all resolved 2 months after treatment cessation; in the placebo group, 3 patients (6.4% in RS) reported a bilateral relevant abnormality on several ERG responses and components and only one resolved within the 2 months after treatment cessation. In the ivabradine group, in other than primary endpoint, all bilateral relevant abnormalities observed in ERG responses, visual field and colour vision resolved after treatment cessation, supporting the pharmacological effect of ivabradine and the absence of retinal dysfunction and retinal neurodegenerative processes.
In conclusion, the ophthalmologic data collected during extensive investigations in patients treated with ivabradine for chronic stable angina pectoris over 3 years did not indicate any sign of safety concern for the retina or other ophthalmic structure or function.

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