Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Effects of ivabradine on plaque burden, morphology and composition in patients with clinically indicated coronary angiography.** **A randomised double-blind placebo-controlled international multicentre study. (MODIFY)**
Test drug code	**Ivabradine (S 16257)**
Indication	**Coronary Artery Disease (CAD)**
Development phase	**Phase III**
Protocol code	**CL3-16257-102**
Study initiation date	**24 April 2013**
Study completion date	**10 September 2014**
International coordinators	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France** **Servier Canada Inc.** **235, Armand Frappier Blvd.** **Laval, Quebec, H7V 4A7 - Canada** **Servier Research and Development Ltd.** **Rowley, Wexham Springs, Framewood Road** **Wexham, Slough SL3 6PJ - United Kingdom** **Laboratorios Servier S.L.** **Avd De los Madronos 33, 28043 Madrid - Spain** **Les Laboratoires Servier (L.L.S.)** **Paveletskaya Square 2, building 3, floor 3, Moscow - Russia**
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	**11 September 2015**
Version of the report	**Final version**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Sponsor: **I.R.I.S., 50 rue Carnot, 92284 Suresnes Cedex - France** **Servier Canada Inc. Laval, Quebec, H7V 4A7 - Canada** **Servier R&D Ltd. Wexham, Slough SL3 6PJ - United Kingdom** **Laboratorios Servier S.L., Avd De los Madronos 33, 28043 Madrid - Spain** **L.L.S. Paveletskaya Square 2, building 3, floor 3, Moscow - Russia**		*(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: Effects of ivabradine on plaque burden, morphology and composition in patients with clinically indicated coronary angiography. **A randomised double-blind placebo-controlled international multicentre study. (MODIFY)** Protocol No.: CL3-16257-102 EudraCT No.: 2012-004779-38 The description of the study protocol given hereafter includes the modifications of the amendments to the protocol (amendments Nos. 1, 2, 3, 4, 5, 6, 7 and 8).		
International coordinators: [redacted].		
Study centres: 80 centres located in 18 countries included 360 patients: 4 centres in Australia (16 patients included), 2 centres in Belgium (5 patients included), 1 centres in Czech Republic (9 patients included), 1 centre in Finland (1 patient included), 1 centre in France (4 patients included), 2 centres in Germany (5 patients included), 5 centres in Hungary (40 patients included), 5 centres in Italy (38 patients included), 14 centres in Republic of Korea (57 patients included), 2 centres in Malaysia (4 patients included), 11 centres in Poland (64 patients included), 2 centres in Portugal (4 patients included), 1 centre in Romania (1 patient included), 14 centres in Russia (60 patients included), 2 centres in Slovakia (14 patients included), 5 centres in Spain (11 patients included), 5 centres in Taiwan (26 patients included), 1 centre in United Kingdom (1 patient included).		
Publication (reference): Not applicable.		
Studied period: Initiation date: 24 April 2013 (date of first visit first patient) Completion date: 10 September 2014 (date of last attended visit of last patient) The study was prematurely discontinued (as explained in the Methodology and Conclusions sections).	**Phase of development of the study:** Phase III	

Objectives:
The purpose of this study was to demonstrate the beneficial effect of ivabradine on plaque burden, morphology and composition, as well as on arterial wall shear stress (WSS) in patients with coronary artery disease (CAD) who had a clinical indication for coronary angiography.
The primary objective was to evaluate the effect of ivabradine treatment for 18 months on atherosclerotic disease progression as assessed using coronary Intravascular Ultrasound (IVUS) in patients with CAD: Percent Atheroma Volume (PAV) for all anatomically comparable slices in a 30-mm segment of the target coronary artery assessed by IVUS.
The secondary objectives were:
- To evaluate the effect of ivabradine on coronary plaque composition and other plaque characteristics using Virtual Histology-Intravascular Ultrasound (VH-IVUS) and Optical Coherence Tomography (OCT) in a subpopulation.
- To assess the relationship between heart rate (HR) and coronary atherosclerosis progression.
- To assess the effect of ivabradine on arterial wall shear stress.
- To evaluate the effect of ivabradine on atherosclerosis progression using Quantitative Coronary Angiography (QCA).
- To assess the effect of ivabradine compared to placebo in the reduction of the following clinical endpoints (time to first occurrence of the event): all-cause mortality, cardiovascular mortality, coronary death, non-fatal myocardial infarction (MI), coronary revascularisation (elective or not), new onset or worsening heart failure leading to hospitalisation or prolongation of hospitalisation.
- To assess the effect of ivabradine on cardiovascular biomarkers including optional genomic biomarkers (added by amendment No. 4).

Note: Following the decision to prematurely end the study, no post baseline assessments were performed and for several secondary endpoints the baseline assessment was not performed or analysed.

Methodology:
This was a multicentre, double-blind, randomised, placebo-controlled, parallel group study having a non-adaptive centralised randomisation (1:1). It was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.
The study was prematurely terminated, in agreement with the MODIFY Study Executive Committee and the Data Monitoring Committee, following the preliminary results of the SIGNIFY study, which used the same therapeutic schemas as the Modify study (up titration up to 10 mg bid) and which failed to demonstrate the efficacy of ivabradine in preventing cardiovascular events in patients with CAD without clinical heart failure. No post-randomisation efficacy criteria were assessed in the MODIFY study.

Number of patients:
Planned: 500 patients (250 per group).
Included: 360 patients, with 178 patients in ivabradine group and 182 patients in placebo group. The lower than planned number of patients was due to the premature discontinuation of the study.

Diagnosis and main criteria for inclusion:
The main inclusion criteria were male or female (non-childbearing potential) aged 18 years or older, in sinus rhythm with resting heart rate ≥ 70 bpm, suffering from CAD with a sufficient level of atheroma burden (at least one stenosis > 20%) or a prior history of previous coronary revascularisation (PCI), without increasing significantly the risk of IVUS and OCT procedures (no stenosis > 50% in the target artery), who were receiving treatment with optimal dose of lipid lowering therapies as well as recommended treatment for CAD.

Investigational Medicinal Product:
Ivabradine tablets: 5 milligram (mg) tablets, 7.5 mg tablets or 10 mg tablets to be taken orally twice daily during meals.
In patients < 75 years at selection: Starting dose of 7.5 mg twice daily, then at each visit, dose up-titrated to 10 mg or maintained on 7.5 mg or down-titrated to 5 mg or stopped, depending on electrocardiogram (ECG) heart rate and bradycardia symptoms. In elderly patients (aged ≥ 75 years at selection), the starting dose was 5 mg twice daily, with the possibility to up-titrate to 7.5 mg and then to 10 mg, depending on ECG HR and bradycardia symptoms.
Batch Nos.: L0045270 (5 mg); L0047809, L0054050 (7.5 mg); L0044706 (10 mg).

Comparator:
Placebo tablets (matching those of ivabradine) to be taken orally twice daily during meals, with the same titration protocol as described above.

Duration of treatment:
Run-in period: 7 to 45 days without treatment.
Planned treatment period: 18 months.
Follow-up period: 14 ± 7 days.

Criteria for evaluation:

Efficacy measurements:
The **primary efficacy endpoint** (nominal change from baseline to study end) for the assessment of atherosclerotic disease progression (*i.e.* plaque burden) was the coronary Percent Atheroma Volume (PAV) for all anatomically comparable slices in a 30-mm segment of the target coronary artery assessed by IVUS.

Secondary endpoints:
Coronary IVUS endpoints:
- Total atheroma volume for all anatomically comparable slices in the 30-mm target coronary artery segment.
- Atheroma volume for the 5-mm segment centred on the cross-section with largest plaque area at baseline.
- Atheroma volume for the 5-mm segment centred on the cross-section with smallest plaque area at baseline.
- Total vessel volume for all anatomically comparable slices in the 30-mm target coronary artery segment.

Coronary OCT endpoints (sub-population: **availability of the technique).**
- Surface area of fibrous cap thickness < 65 micrometre (µm).
- Surface area of fibrous cap thickness between 65 -150 µm.

Coronary QCA endpoints:
- Coronary artery score (defined as the per-patient mean of the minimal lumen diameter for all lesions measured).
- Cumulative coronary stenosis score (calculated by adding all percent diameter stenoses in SI units).

Clinical efficacy endpoints
- All-cause mortality.
- Cardiovascular mortality.
- Coronary death.
- Non-fatal MI.
- Coronary revascularisation (elective or not).
- New onset or worsening heart failure leading to hospitalisation or prolongation of hospitalisation.

Other endpoints:
Cardiac and vascular blood biomarkers
- Exploratory analysis on cardiovascular biomarkers including hs-CRP, BH_2 and BH_4.

Note: Following the decision to prematurely end the study, no post baseline assessments were performed and for several secondary endpoints the baseline assessment was not performed or analysed.

Safety measurements:
- Documenting relevant medical history and inter-visit medical history.
- Recording abnormal findings obtained during physical examinations, including vital signs.
- Recording abnormal findings on electrocardiogram (ECG) recordings.
- Recording abnormal results observed on clinical laboratory tests.

Statistical methods:
Analysis Set:
Randomised set (RS) was defined as all included and randomised patients. The Safety Set (SS) was defined as all patients having received at least one dose of test drug. A Coronary Angiography Set (CAS) comprised all patients having performed selection visit and having coronary angiography done for selection visit.

Coronary Imaging, biomarker and clinical efficacy analysis:
All efficacy endpoints (Coronary endpoints: IVUS, QCA and OCT: hs-CRP and BH_2/BH_4) other than clinical efficacy endpoints, were summarised descriptively by treatment group at baseline in RS.

For the clinical efficacy endpoints, number and percentage of patients with at least one occurrence of the endpoint were provided by treatment group in SS, on treatment and during the study.

Study outcome and safety analysis:
Descriptive statistics were provided in the RS and SS by treatment group or overall in the CAS.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 740 patients were screened for the study, 727 having performed coronary angiography and 562 patients were selected. Of them, 360 patients (64.1% of selected) were included and randomly assigned to one of the 2 groups: 178 patients in the ivabradine group and 182 in the placebo group.

In view of the decision to prematurely terminate the study, none of the included patients completed the full duration of the study. Thus, 95.6% of the included patients withdrew due to premature study termination and a small proportion of patients due to non-medical reason (3.6%) or adverse event (0.8%). Patient status during the study is indicated in Table 1.

Table 1 - Disposition of patients and composition of analysis sets

		Ivabradine	Placebo	All
Included (Randomised)	**N**	**178**	**182**	**360**
Withdrawn due to	**n (%)**	**178 (100)**	**182 (100)**	**360 (100)**
premature study termination	n (%)	167 (93.8)	177 (97.3)	344 (95.6)
non-medical reason	n (%)	8 (4.5)	5 (2.7)	13 (3.6)
adverse event	n (%)	3 (1.7)	-	3 (0.8)
Completed	n (%)	-	-	-
Coronary Angiography Set	**n**	-	-	**727**
Randomised Set	**n**	**178**	**182**	**360**
Safety Set	**n**	**176**	**181**	**357**

N: Total patients of included (randomised) %: n/N x 100

BASELINE CHARACTERISTICS

The main demographic and baseline characteristics in the RS revealed no relevant between-group differences. The mean age (±SD) was 59.6 ± 9.3 years, 70.8% were men and 74.7% were of Caucasian origin. Asian patients made up the second largest ethnic group (24.2%). The mean weight was 82.4 ± 17.0 kg and mean body mass index (BMI) was 28.9 ± 5.0 kg/m². Although a previous coronary revascularisation (PCI) was reported at similar rates in the 2 treatment groups (38.6% overall), slight differences were observed for CAD documentation such as previous MI (32.0% *versus* 27.5% [ivabradine *versus* placebo]), previous history of angina (57.9% *versus* 61.0%) and coronary artery stenosis (44.9% *versus* 42.3%). An emergency coronarography (*i.e.* not scheduled in advance) was reported in 28 patients of the ivabradine group (15.7%) and 21 (11.5%) in the placebo group; mainly due to acute coronary syndrome (71.4% overall) or myocardial Infarction (22.5% overall). A total of 358 patients (99.4%) had at least one coronary artery lesion and 73.5% had at least a 2-vessel disease. Overall, more than half of the patients (53.6% in total, 52.3% in the ivabradine group *versus* 55.0% in the placebo group) performed PCI as the result of coronary angiography.

The type of artery considered as target coronary artery for IVUS were proportioned fairly similarly in the 2 groups, between left anterior descending coronary artery (35.3%), right coronary artery (32.2%) and circumflex artery (31.4%). In the ivabradine group, RCA as target CA was observed in lower proportion, while LAD in higher proportion, compared to placebo.

All of the randomised patients reported at least one other medical history than CAD. The most frequent specific medical history was hypertension (in 80.3% of RS), followed by dyslipidaemia (71.1%) and diabetes mellitus (30.3%). All randomised patients except 3 were receiving at least one concomitant treatment during the study: lipid modifying agents (97.2%), antithrombotic agents (96.7%), agents acting on the renin-angiotensin system (76.1%) and beta blocking agents (69.2%).

The mean supine HR was 78.6 ± 8.2 bpm, and the mean systolic blood pressure (SBP) / diastolic blood pressure (DBP) was 131.4/78.5 mmHg.

SUMMARY - CONCLUSIONS (Cont'd)

Baseline Coronary Imaging Assessments

The baseline measurements are summarised in Table 2.

Table 2 - Baseline imaging assessments in the Randomised Set

			Ivabradine (N = 178)	Placebo (N = 182)
IVUS	**Percent Atheroma Volume**	Mean ± SD	39.4 ± 9.2	40.2 ± 8.8
		Min ; Max	15.9 ; 65.3	15.9 ; 62.2
	Total atheroma volume (mm^3)	Mean ± SD	172.7 ± 67.2	181.3 ± 75.7
		Min ; Max	36.4 ; 422.5	31.0 ; 457.8
	Total vessel volume (mm^3)	Mean ± SD	437.5 ± 138.3	446.8 ± 144.3
		Min ; Max	172.5 ; 899.3	127.0 ; 836.9
	Atheroma volume for 5mm segment (largest) (mm^3)	Mean ± SD	37.2 ± 13.8	38.4 ± 15.1
		Min ; Max	10.7 ; 86.6	8.7 ; 93.1
	Atheroma volume for 5mm segment (smallest) (mm^3)	Mean ± SD	20.4 ± 10.7	22.9 ± 12.4
		Min ; Max	3.0 ; 58.9	2.7 ; 63.8
OCT	**Minimum fibrous cap thickness** (mm)	n	79	86
		Mean ± SD	0.07 ± 0.03	0.07 ± 0.04
		Min ; Max	0.03 ; 0.18	0.02 ; 0.22
		Number (%) patients with cap < 65 µm	39 (49.4)	45 (52.3)
QCA	**Coronary artery score** (mm)	Mean ± SD	1.94 ± 0.47	1.95 ± 0.51
		Min ; Max	0.86 ; 3.68	0.00 ; 3.87
	Cumulative coronary stenosis score (%)	Mean ± SD	212.1 ± 142.6	208.6 ± 141.3
		Min ; Max	14.0 ; 659.0	16.9 ; 610.8

Note: One patient was missing in the ivabradine group for the IVUS assessments and 2 were missing from the QCA assessments

Baseline Cardiovascular Biomarker Assessments

The baseline measurements (in plasma samples) are summarised in Table 3.

Table 3 - Baseline biomarker assessments in the Randomised Set

		Ivabradine	Placebo
hs-CRP (mg/L)	n	98	105
	Mean ± SD	0.30 ± 0.34	0.40 ± 0.77
	Median	0.19	0.21
	Min ; Max	0.03 ; 2.31	0.03 ; 6.75
BH_2 (ng/mL)	n	8	6
	Mean ± SD	1.70 ± 0.54	1.34 ± 0.29
	Min ; Max	1.08 ; 2.59	1.02 ; 1.79
BH_4 (ng/mL)	n	6	3
	Mean ± SD	0.19 ± 0.13	0.25 ± 0.26
	Min ; Max	0.03 ; 0.32	0.03 ; 0.53
Ratio BH_2 /BH_4	n	6	3
	Mean ± SD	22.7 ± 31.1	13.6 ± 16.3
	Min ; Max	4.0 ; 84.7	2.3 ; 32.4

SUMMARY - CONCLUSIONS (Cont'd)

EXTENT OF EXPOSURE

The overall mean follow-up duration (± SD) was 4.9 ± 2.8 months (median = 4.6), the mean treatment duration was 4.7 ± 2.8 months (median = 4.5) and the global compliance was satisfactory, with a mean compliance of 94.9 ± 11.2% (median = 98.0%). No relevant difference was observed between the treatment groups.

In patients aged < 75 years and treated with ivabradine, 44.9% were up-titrated to 10 mg twice daily and maintained on this dose during the whole study (*versus* 74.0% in the placebo group). The remainder of patients in this age group were either maintained on the initial dose over the whole treatment duration (32.9%) (*versus* 19.7% in the placebo group), down-titrated to 5 mg twice daily (12.6%) or received a different profile (9.6%). In ivabradine-treated patients aged ≥ 75 years, 6/11 patients (54.6%) were up-titrated twice (to 10 mg) and maintained on this dose, and 1 patient was up-titrated once (to 7.5 mg) and maintained on this dose. In the placebo group 7/9 patients were up-titrated twice.

EFFICACY RESULTS

No post-baseline efficacy coronary imaging measurements or cardiac biomarkers were performed.

The occurrence of clinical efficacy endpoints on treatment was low, was a total of 6 events in the ivabradine group (2 hospitalisations for heart failure, 4 coronary revascularisation procedures) and 5 in the placebo group (2 hospitalisation for heart failure, 3 coronary revascularisation procedures). No difference meaningful difference in event rate was observed between the groups.

SAFETY RESULTS

No fatal events were reported during the study.

Adverse events the CAS

A total of 215 patients of the CAS (29.5%), having performed a selection visit (and subsequently included in the study or not), reported a total of 536 adverse events since selection visit. These events were mostly due to the system organ class (SOC) cardiac disorders, in 7.0% of patients (notably bradycardia: 1.4%). Other SOCs frequently reported were general disorders and administration site conditions 5.1% (including chest pain: 1.0%) and vascular disorders, 5.1% (including hypertension: 2.2%). A total of 128 events in 77 patients having performed a selection visit (and subsequently included in the study or not) were considered as serious events either by the investigator or the Sponsor. These mostly involved cardiac disorders, including atrial fibrillation (7 events in 5 patients), acute myocardial infarction (4 events), coronary artery dissection (4 events), ventricular fibrillation (4 events) and bradycardia (4 events). In addition, there were 7 events of percutaneous coronary intervention (PCI).

A specific review of pre-specified AEs was performed by an independent expert. The purpose of this review was to discriminate events not related to the protocol-requested procedures (related to coronary angiography/angioplasty performed at selection visit) from events related to the protocol-requested procedures (IVUS/OCT performed at selection). Adverse events considered for review were:

- All SAEs considered by investigators/or Sponsor as related to the study protocol-related procedure.
- SAEs considered by investigators and Sponsor as NOT related to the study protocol procedure but for which a potential relationship to the study specific invasive procedure could be suggested.
- 3 non-serious AE were also reviewed by the expert because of their nature and time of onset from CAG date.

A total of 45 events (included multicoded ones) were considered by sponsor for review by the expert for 29 patients: 42 serious and 3 non-serious:

- 26 events concerned 16 patients who were not subsequently included in the study: 2 of these events were considered by the expert as being related to the protocol-requested procedures (*i.e.*, IVUS and/or OCT) (myocardial infarction and ventricular fibrillation), 12 were considered as related to the invasive procedures not requested by protocol (*i.e.*, CAG/PCI) and 12 were considered as not related to any invasive procedures performed at selection.
- 19 events concerned 12 patients who were subsequently included in the study (with 3 of them [in 2 patients] emergent after the first intake of study drug [placebo] but occurred still within 1 moth following the CAG performed at selection): 3 of these were considered by the expert as being related to the IVUS and/ or OCT procedure (angina pectoris, bradycardia and hypotension), 13 were considered as related to the CAG/PCI procedure and 3 were considered as not related to any invasive procedure performed at selection.

There was good overall correlation between the judgement of the investigators/sponsor and the independent expert. All IVUS and /or OCT-related (*i.e.*, protocol-requested procedures) events, as adjudicated by the Independent Expert, (n = 5) represented 0.9% of reported adverse events (= 5/536) in the CAS and 3.9% of all serious adverse events (= 5/128). They were reported in 4 patients, *i.e.* 1.9% of patients in CAS having an adverse event (= 4/215) and 5.2% of patients in CAS having reported a serious adverse event (= 4/77).

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Emergent adverse events (EAEs) in the Safety Set

Main safety results in the SS are summarised in the Table 4.

At least one EAE during the treatment period was reported by 88 patients (50.0%) in the ivabradine group *versus* 83 patients (45.9%) in the placebo group. The most frequently affected SOCs were: with a higher incidence in the ivabradine group than in the placebo group, eye disorders (13.6% *versus* 3.3%), vascular disorders (10.2% *versus* 7.7%), cardiac disorders (9.1% *versus* 6.1%), general disorders and administration site conditions (9.1% *versus* 6.1%), gastrointestinal disorders (9.1% *versus* 5.5%) and investigations (9.1% *versus* 5.0%). The SOC infections and infestations were reported with a similar frequency (9.1% *versus* 7.7%).

Table 4 - Overall summary for adverse events in the Safety Set

		Ivabradine (N = 176)	Placebo (N = 181)
Patients having reported at least one:			
Emergent adverse event	n (%)	88 (50.0)	83 (45.9)
Treatment-related emergent adverse event	n (%)	38 (21.6)	12 (6.6)
Photopsia	n (%)	14 (8.0)	1 (0.6)
Vision blurred	n (%)	8 (4.5)	3 (1.7)
Heart rate decreased	n (%)	9 (5.1)	1 (0.6)
Bradycardia	n (%)	6 (3.4)	1 (0.6)
Patients having experienced at least one:			
Serious EAE	n (%)	22 (12.5)	25 (13.8)
Treatment-related serious adverse event	n (%)	4 (2.3)	2 (1.1)
Patients with treatment withdrawal			
due to an emergent adverse event	n (%)	6 (3.4)	3 (1.7)
Bradycardia	n (%)	2 (1.1)	-
due to an emergent serious adverse event	n (%)	3 (1.7)	1 (0.6)
due a treatment-related emergent serious adverse event	n (%)	2 (1.1)	1 (0.6)
Patients who died	n (%)	-	-

The most frequently reported preferred terms in the ivabradine group were: photopsia (8.5% *versus* 0.6% in the placebo group), hypertension (5.7% *versus* 3.3%), vision blurred (5.7% *versus* 1.7%), heart rate decreased 5.1% *versus* 0.6%), bradycardia (3.4% *versus* 0.6%), chest discomfort (2.8% *versus* 0.6%) and ventricular extrasystoles (2.8% *versus* 0.6%).

The **severe EAEs** were reported by 7 patients in the ivabradine group (13 events) *versus* 5 patients in the placebo group (5 events). These were mostly cardiac disorders, with 3 events (bradycardia, mitral valve incompetence, acute cardiac failure) versus 1 event (left ventricular dysfunction) , respectively.

Treatment-related EAEs were more frequently reported in the ivabradine group (21.6%) than in the placebo group (6.6%), with the similar trend for the most common treatment-related EAEs (with an incidence of > 3% in the ivabradine group): photopsia (8.0% in the ivabradine group *versus* 0.6% in the placebo group), vision blurred (4.5% *versus* 1.7%), bradycardia (3.4% *versus* 0.6%) and heart rate decreased (5.1% *versus* 0.6%).

At least one **serious emergent adverse event** during the treatment period was reported by 22 patients (12.5%) in the ivabradine group, with a total of 36 SEAEs, *versus* 25 (13.8%) in the placebo group, with a total of 42 SEAEs. The most affected SOC was cardiac disorders (4.0% *versus* 1.7%); mostly events of bradycardia (3 patients *versus* none), PCI (2 patients *versus* 3), cardiac rehabilitation therapy (1 *versus* 2), photopsia (2 *versus* 1) vision blurred (2 *versus* 1), activities of daily living impaired (3 *versus* 1) and hypertension (1 *versus* 2).
Of these events, 11 in 4 patients (2.3%) were considered as treatment-related SEAEs in the ivabradine group *versus* 5 events in 2 patients (1.1%) in the placebo group.

A total of 9 patients reported EAEs that led to **treatment withdrawal**: 6 patients (3.4%) in the ivabradine group *versus* 3 patients (1.7%) in the placebo group. In the ivabradine group: (patient) #303, photopsia, vision blurred, activities of daily living impaired, diarrhoea and bradycardia; #314, bradycardia and syncope; #107, ventricular extrasystoles and heart rate decreased; #617, chest discomfort and dyspnoea; #197, chest pain; #152, abdominal pain upper. In the placebo group: #479, atrial fibrillation; #689, pruritus generalized; #59, dizziness and vision blurred.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Laboratory tests
In the SS, emergent potentially clinically significant abnormal (PCSA) biochemical and haematological values were sparse in all groups and for each parameter, except for high triglycerides, reported in 8 patients (6.3%) in the ivabradine group *versus* 9 patients (6.16%) in the placebo group, and high glucose in 3 patients (2.5%) *versus* 5 patients (3.5%).

Heart rate and blood pressure

The heart rate decrease was observed in both groups from baseline to last post baseline value, and as expected the decrease was more profound in the ivabradine group (-17.4 ± 10.5 bpm) than in the placebo group (-8.1 ± 11.8 bpm).

The mean SBP tended to slightly increase from baseline to last post baseline value in the ivabradine group (2.2 ± 15.8 mmHg), while it showed slightly decrease in the placebo group (-1.1 ± 15.9 mmHg).

The mean DBP tended to slightly decrease from baseline to last post baseline value in the ivabradine group (-1.6 ± 8.3 mmHg), while it remained stable in the placebo group (-0.1 ± 9.5 mmHg).

CONCLUSION

This phase III, randomised, double-blind placebo-controlled multicentre study (MODIFY) was designed to demonstrate the beneficial effect of ivabradine *versus* placebo on plaque burden progression. It was conducted in patients with CAD who were receiving an optimal treatment of lipid lowering therapies and recommended treatments CAD and who had a clinical indication for coronary angiography that showed a sufficient level of atheroma burden. Care was taken to ensure that the plaque burden in the target artery was not too high as to significantly increase the risk incurred by the intraluminal imaging procedures (IVUS and OCT).

The study was prematurely terminated, in agreement with the MODIFY Study Executive Committee and the Data Monitoring Committee after a median follow-up of 4.6 months (mean = 4.9 ± 2.8), following the results of the SIGNIFY study in the ivabradine program, which did not provide evidence of any benefit of ivabradine induced heart rate lowering on cardiovascular outcomes. Further to the decision on the MODIFY study premature discontinuation, no post-baseline efficacy assessment of coronary imaging was performed.

There was no difference between the treatment groups for the few major cardiovascular events reported during the treatment period.
The safety profile of ivabradine was as expected and no new safety concern (including those due the protocol-requested invasive procedures performed at selection) was identified.

Date of the report: 11 September 2015

Version of the report: Final version