Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Effects of oral chronic administration of ivabradine (7.5 mg b.i.d.) in comparison to placebo (b.i.d.) on top of beta-blockers, on central aortic blood pressure. Randomised, cross-over, double-blind, multicentre, study over 10 weeks in patients with stable coronary artery disease and a resting heart rate equal or superior to 70 bpm, already treated with beta-blockers.**
Test drug code	**S16257-2** **Ivabradine** **Procoralan®/Corlentor®**
Indication	**Coronary artery disease**
Development phase	**Phase II**
Protocol code	**CL2-16257-096**
Study initiation date	**5 June 2012**
Study completion date	**13 May 2014**
Main coordinator	[redacted]
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
Responsible medical officers	[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	**4 May 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 ® **Name of Active Ingredient:** Ivabradine (S16257-2)		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Effects of oral chronic administration of ivabradine (7.5 mg b.i.d.) in comparison to placebo (b.i.d.) on top of beta-blockers, on central aortic blood pressure. Randomised, cross-over, double-blind, multicentre, study over 10 weeks in patients with stable coronary artery disease and a resting heart rate equal or superior to 70 bpm, already treated with beta-blockers.
The diabetes type II population criterion present in the initial title was deleted by Amendment No. 2.
Protocol No.: CL2-16257-096
EudraCT No.: 2011-004779-35
The description of the study protocol given hereafter includes the modifications of the 3 substantial amendments to the protocol.

International coordinator: [redacted]

Study centres: In all, 3 centres located in 3 countries included 14 patients: France (1 centre, 10 patients), Ireland (1 centre, 3 patients) and Italy (1 centre, 1 patient).

Publication (reference): Not applicable.

Studied period: Initiation date: 5 June 2012 (date of first visit first patient) Completion date: 13 May 2014 (date of last visit last patient)	**Phase of development of the study:** Phase II

Objectives:
The primary objective was to evaluate the effect of ivabradine on central aortic systolic blood pressure (CASBP) in comparison to placebo in patients with stable coronary artery disease (CAD), and a resting heart rate (HR) ≥ 70 bpm, treated by beta-blockers (BBs).

The secondary objectives were to investigate the effect of ivabradine in comparison to placebo on:

- Other central and radial blood pressures and HR parameters obtained by applanation tonometry.
- Carotid-femoral pulse wave velocity (PWV).
- Skin capillary density (Amendment No. 3: only in centres with intravital video capillaroscopy capability).
- Brachial Blood Pressure (BP) parameters.
- Resting HR from 12-lead electrocardiogram (ECG).
- Safety.

Methodology:
Phase II, multicentre, randomised, cross-over, double-blind, placebo-controlled, exploratory study in patients with stable CAD and a resting HR ≥ 70 bpm, already treated with BBs.

Included patients were randomised (non-centralised randomisation with stratification on centre) to the sequence ivabradine-placebo or placebo-ivabradine. The treatment period for each participant was to be 8 weeks, including the following periods:

- A 3-week double-blind active treatment period P1, during which the included patients received either ivabradine (7.5 mg b.i.d.) or placebo twice daily (b.i.d.). At inclusion visit and at the end of the treatment period (Week 3), peripheral and central haemodynamics, pulse wave velocity and capillary density were assessed.
- A 2-week wash-out period, during which patients received no study treatment.
- A 3-week double-blind active treatment period P2, during which patients randomised to ivabradine in period P1 received placebo b.i.d. and patients randomised to placebo in period P1 received ivabradine 7.5 mg b.i.d. At Week 5 visit and at the end of the treatment period (Week 8), peripheral and central haemodynamics, pulse wave velocity and capillary were assessed.

Methodology (Cont'd):

Two weeks after treatment cessation at the end period P2, the study was terminated by an end of study visit at Week 10.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

An abbreviated report was written, since the study was prematurely stopped due to recruitment issue.

Number of patients:

Planned: 60 patients (30 patients / sequence). Due to the exploratory nature of this study, an effective of 60 patients in cross-over design was considered sufficient to assess the effect of ivabradine on CASBP and other central pressure parameters.
Included and randomised: 14 patients (6 patients in the iva/pla sequence and 8 patients in the pla/iva sequence).

Due to recruitment issues, the study was prematurely stopped after 14 patients were included.

Diagnosis and main criteria for inclusion:

- Patients with CAD documented by either:
  - A history of previous myocardial infarction (MI) which occurred at least 3 months before the selection visit.
  - A history of Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG) which was carried out at least 3 months before the selection visit.
  - Abnormal findings at coronary angiography (angiographic evidence of ≥ 50% narrowing of ≥ 1 major coronary artery).
  - If there was no history of previous MI or coronary revascularization, nor previous coronary angiography performed as added by Amendment No. 1, CAD could be also documented by at least one of the following:
    - A positive non-invasive stress test, confirmed by either:
      - A positive exercise tolerance test in male patients without a complete left bundle branch block, Wolff- Parkinson-White syndrome, or paced ventricular rhythm, or
      - A positive stress echocardiography showing regional systolic wall motion abnormalities, or
      - A positive scintigraphic test showing stress-induced ischemia, *i.e.* the development of transient perfusion defects during myocardial perfusion imaging.
    - Or patient discharged from hospital with a documented diagnosis of unstable angina within 12 months prior to selection (and at least 3 months previous to selection visit).
- Patients with sinus rhythm, 12-lead ECG HR ≥ 70 bpm after 5 minutes rest, and brachial supine SBP/DBP ≤ 140/90 mmHg at selection (ASSE) and at inclusion (W0) visits.
- Patients with stable and appropriate treatment (according to the investigator) by beta-blockers (except nebivolol and carvedilol) for at least 3 months before the selection visit.
- Patient with tonometry assessment at inclusion performed with operator index ≥ 90% (as added by Amendment No. 2).
- Normal (considering the patient disease) fasting laboratory results for sampling performed between selection and inclusion visits.
- Informed consent obtained.

Note: selection/inclusion criteria related to type II diabetes were deleted, by Amendment Nos. 1 and 2, as it was decided to open the recruitment to both diabetic and non-diabetic patients having CAD.

Test drug:
Ivabradine 7.5 mg tablet, *per os* administration, one tablet twice daily during meals. Batch Nos.: L0038024, L0047809

Comparator (Reference product and/or placebo):
Placebo tablet, *per os* administration, one tablet twice daily during meals. Batch Nos.: L0037877, L0045275

Duration of treatment: active treatment period (3 weeks), placebo treatment period (3 weeks).

- Run-in period (patients did not receive study drug): 2 weeks (ASSE-W0).
- Treatment period P1: 3 weeks period (W0-W3), where patients received either ivabradine or placebo.
- Wash-out period (patients did not receive study drug): 2 weeks (W3-W5).
- Treatment period P2: 3 weeks period (W5-W8), where patients who received ivabradine during P1 were to receive placebo, and the patients who received placebo during P1 were to receive ivabradine.
- Run-out period (patients did not receive study drug): 2 weeks (W8-W10).

Criteria for evaluation:

Primary endpoint (primary efficacy criterion)

Central aortic systolic blood pressure (CASBP) (mmHg) after a 3-week active treatment period.
The statistical analysis plan finalised before database lock specified the main efficacy criterion as the change in CASBP from baseline over the three-week treatment period.

Secondary endpoint

Efficacy measurements:

All the following measurements (derived from applanation tonometry) at baseline (W0 and W5) and after 3-week treatment period (W3 and W8):

- Heart rate (HR).
- Other central blood pressure parameters: central aortic diastolic blood pressure (CADBP), central aortic pulse pressure (CAPP) augmentation index (AIx), augmentation index standardized to a HR of 75 bpm (AI75), augmentation pressure (Ao), subendocardial viability ratio (SEVR), left ventricular ejection time (LVET).
- Radial blood pressure (BP) parameters: Systolic/Diastolic blood pressure (SBP/DBP), pulse pressure (PP).
- Carotid-femoral pulse wave velocity (PWV).

Capillary skin density at baseline (W0 and W5) and after 3-week treatment period (W3 and W8), in patients from centres equipped with intravital video capillaroscopy material.

Safety measurements:

The following safety criteria were assessed at each visit during the study (ASSE, W0, W3, W5, W8 and W10).

- Adverse events.
- HR from 12-lead ECG after 5 minutes rest.
- Brachial supine blood pressure (SBP/DBP).

Statistical methods:

Analysis Set:
The main efficacy analysis was performed on the Per Protocol Set (PPS) with supporting analysis on the Full Analysis Set (FAS). The PPS was defined as patients of the FAS having taken both treatments of the sequence and with evaluation of efficacy on both periods without relevant deviation. The FAS was defined as randomised patients having taken at least one dose of one of the two treatments and with at least one evaluation of primary efficacy criteria.

Study outcome analysis: Descriptive statistics were provided in the Randomised Set (and in the PPS for several parameters).

Efficacy analysis: Descriptive statistics for efficacy analysis were provided primarily on the PPS and confirmed on the FAS.

Safety analysis: Descriptive statistics were provided in the Safety Set (SS).

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

Disposition of randomised patients by sequence of treatment and overall

Status by sequence of treatment	Iva/Pla	Pla/Iva	All
	n (%)	n (%)	n (%)
Included	**6**	**8**	**14**
Withdrawn due to	**-**	**2 (25.0)**	**2 (14.3)**
Adverse event	-	1 (12.5)	1 (7.1)
Protocol deviation	-	1 (12.5)	1 (7.1)
Lost to follow-up	-	-	-
Study completed	**6 (100)**	**6 (75.0)**	**12 (85.7)**
Randomised Set (RS)	**6**	**8**	**14**
Full Analysis Set (FAS) [(1)]	**6 (100)**	**8 (100)**	**14 (100)**
Per Protocol Set (PPS) [(2)]	**4 (66.7)**	**5 (62.5)**	**9 (64.3)**
Safety Set (SS) [(1)]	**6 (100)**	**8 (100)**	**14 (100)**

% calculated according to the number of patients included in each sequence of treatment; n: number of patients affected;
(1) % calculated as % of the Randomised Set; (2) calculated as % of the FAS. In all, 5 patients were excluded from the PPS (2 for intake of unauthorised beta-blocker, 2 for incomplete duration of treatment period and 1 for change in antihypertensive treatment.

BASELINE CHARACTERISTICS

Since the sample size of the RS (and PPS) was small, the data were heterogeneous resulting in some between group differences at baseline. The comparisons between groups or sequences of treatment should therefore be interpreted with caution.

The main baseline characteristics in the Randomised Set are described in the table hereafter.

At inclusion, all randomised patients were receiving at least one **concomitant treatment for their CAD,** and all received beta-blockers (at dose estimated adapted to their clinical status by the investigator), mainly bisoprolol (8/14 patients). Other main concomitant treatments for CAD were agents acting on the renin-angiotensin system (12/14 patients) including ACE inhibitors (7/14 patients), and hypoglycemic agents (9/14 patients).

All but one of the randomised patients reported a **medical history besides CAD**. Most reported medical histories were vascular disorders (12/14 patients) including hypertension (12/14 patients), and metabolism and nutrition disorders (9/14 patients) including 6/14 patients with hypercholesterolemia and 2/14 patients with dyslipidaemia.

At baseline, the median CASBP (**primary efficacy criterion)** was 126.0 mmHg (mean ± SD: 121.5 ± 13.2 mmHg), with a higher value in the iva/pla sequence than in the pla/iva sequence: 131.0 mmHg (124.8 ± 16.9 mmHg) *versus* 123.0 mmHg (119.0 ± 10.2 mmHg) respectively.

The median brachial **SBP** was 133.0 mmHg (128.4 ± 12.9 mmHg), with a higher value in the iva/pla sequence than in the pla/iva sequence: 138.0 mmHg (129.0 ± 17.2 mmHg) *versus* 129.5 mmHg (127.9 ± 9.8 mmHg) respectively. The median brachial **DBP** was 81.0 mmHg (79.9 ± 7.5 mmHg). The median **heart rate** was 72.5 bpm (74.6 ± 4.2 bpm). All patients had a 12-lead ECG HR ≥ 70 bpm and were in sinus rhythm, as required by the protocol.

Regarding demographic data, history of the disease, and medical and surgical history other than CAD at selection, the values observed in the PPS were comparable to those described in the RS, except the median duration since CAD diagnosis in the PPS, which was slightly lower in the iva/pla sequence than in the pla/iva sequence (68.0 months *versus* 78.0 months, respectively).

SUMMARY - CONCLUSIONS (Cont'd)

BASELINE CHARACTERISTICS (Cont'd)

Main baseline characteristics in the Randomised Set

			Iva/Pla (N = 6)	Pla/Iva (N = 8)	All (N = 14)
		n_{obs}	6	8	14
Age (years)		Mean ± SD	69.0 ± 7.8	58.4 ± 5.9	62.9 ± 8.5
		Median	70.0	57.0	61.0
	< 65 years	n (%)	2 (33.3)	7 (87.5)	9 (64.3)
Gender	Male	n (%)	5 (83.3)	7 (87.5)	12 (85.7)
Race	Caucasian	n (%)	5 (83.3)	3 (37.5)	8 (57.1)
Body Mass Index (kg/m²)		Mean ± SD	27.2 ± 3.5	30.3 ± 7.6	28.9 ± 6.2
		Median	27.0	28.2	27.3
Duration since CAD diagnosis (months)		Mean ± SD	127.5 ± 142.1	58.0 ± 57.8	87.8 ± 104.1
		Median	68.0	46.5	53.0
Patients with previous:					
MI*		n (%)	5 (83.3)	3 (37.5)	8 (57.1)
PCI or CABG*		n (%)	6 (100)	7 (87.5)	13 (92.9)
Abnormal findings at coronary angiography		n (%)	4 (66.7)	6 (75.0)	10 (71.4)
Type II diabetes		n (%)	4 (66.7)	6 (75.0)	10 (71.4)
Duration since diagnosis (months)		Mean ± SD	134.5 ± 75.1	195.2 ± 80.0	170.9 ± 80.1
		Median	161.5	184.0	162.5
Specific concomitant treatments at inclusion					
Beta blockers		n (%)	6 (100)	8 (100)	14 (100)
Hypoglycemic agents		n (%)	3 (50.0)	6 (75.0)	9 (64.3)
Main tonometric parameters					
CASBP (mmHg)**		Mean ± SD	124.8 ± 16.9	119.0 ± 10.2	121.5 ± 13.2
		Median	131.0	123.0	126.0
HR from tonometry (bpm)		Mean ± SD	67.8 ± 3.8	73.9 ± 4.5	71.3 ± 5.1
		Median	68.5	72.5	71.5

** at least 3 months before ASSE, **: primary efficacy criterion*
N: Total number of patients in each set or sequence of treatment considered, n_{obs}: Number of patients with an assessable value, n: Number of patients in a class or in a category, %: $(n/n_{obs})x100$
MI: Myocardial Infarction, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Graft, CASBP: central aortic systolic blood pressure, AIx: central augmentation index

EXTENT OF EXPOSURE

In the Randomised Set, the median **treatment duration** was 21.0 days in both sequences of treatment (both periods pooled) and the median duration of the wash-out period was 14.0 days (17.4 ± 10.4 days) as expected. The treatment **compliance** was satisfactory, with a median of 98.0% in the ivabradine group *versus* 99.0% in the placebo group (both periods pooled).

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

It should be noted that because of the low number of patients in this study, some heterogeneous median (and mean) values were observed resulting in between-group differences at baseline. Therefore, the evaluation of treatment effect based on the pool of the 2 periods should be interpreted with caution.

- **Primary assessment criterion: Central aortic systolic blood pressure**

In the PPS (N = 9), the median value of CASBP over the 3-week treatment period tended to decrease by 4.0 mmHg (mean change ± SD = -3.3 ± 10.2 mmHg) under ivabradine (both periods pooled) and by 1.0 mmHg under placebo (mean change ± SD = +1.0 ± 9.4 mmHg) (see the table below).

Central aortic systolic blood pressure - Change from baseline over 3-week treatment period - by treatment (both periods pooled) - PPS (N = 9)

CASBP (mmHg)		Ivabradine (N = 9)	Placebo (N = 9)
Baseline	**n_{obs}**	**9**	**9**
	Mean ± SD	115.9 ± 16.7	112.3 ± 9.3
	Median	117.0	107.0
	Min ; Max	91 ; 135	100 ; 126
Final value after 3-week treatment period	**n_{obs}**	**9**	**9**
	Mean ± SD	112.6 ± 11.9	113.3 ± 12.2
	Median	116.0	114.0
	Min ; Max	94 ; 129	96 ; 130
Change from baseline	**n_{obs}**	**9**	**9**
	Mean ± SD	-3.3 ± 10.2	1.0 ± 9.4
	Median	-4.0	-1.0
	Min ; Max	-19 ; 18	-14 ; 20

N: Total number of patients in each treatment group, n_{obs}: Number of patients with observed at baseline and final value

- **Secondary criteria**

In the PPS, the median HR from applanation tonometry was markedly decreased over the 3-week treatment period by 19.0 bpm (-17.3 ± 8.4 bpm) under ivabradine, while no relevant change was observed under placebo: -1.0 bpm (-0.3 ± 6.3 bpm).

The median CADBP decreased over the 3-week treatment period by 10.0 mmHg (-8.8 ± 6.9 mmHg) under ivabradine, while no relevant change was observed under placebo: 0.0 mmHg (0.4 ± 5.5 mmHg). For CAPP, the median value increased under ivabradine by 8.0 mmHg (5.4 ± 7.7 mmHg) and tended to decrease under placebo: -2.0 mmHg (0.6 ± 5.8 mmHg).

The median AIx slightly decreased over the 3-week treatment period under ivabradine by 4.0% (-0.7 ± 11.4%) while it tended to remain stable under placebo: 2.0% (1.2 ± 7.4%).
Median of AI75 decreased under ivabradine by 5.0% (-7.9 ± 8.8%), while it remained stable under placebo: 0.0% (0.8 ± 7.0%).
The median Ao slightly increased by 2.0 mmHg (1.1 ± 5.6 mmHg) under ivabradine, while no relevant change was observed under placebo: 0.0 mmHg (0.7 ± 4.6 mmHg).

The median SEVR showed a clinically relevant increase under ivabradine of 48.0% (43.7 ± 27.2%), while it remained quite stable under placebo: 3.0% (2.4 ± 9.3%). A slight increase of median LVET was observed under ivabradine: 14.0 ms (19.6 ± 18.6 ms) *versus* no relevant change under placebo: 0.0 ms (0.6 ± 20.5 ms).

In a complementary analysis (unplanned analysis) in the population of patients completing the study (N = 12), a great median augmentation in diastolic time of 176 ms was observed under ivabradine *versus* a stability (-1.4 ms) under placebo. This increase in median represented 33.5% of the baseline median value (525 ms).

SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

As regards radial blood pressures, the median change of SBP/DBP over the 3-week treatment period was -4.0/-10.0 mmHg (mean change ± SD = -2.7 ± 9.1/-8.4 ± 6.8 mmHg) under ivabradine, whereas no relevant change was observed under placebo: 0.0/0.0 mmHg (0.1 ± 7.9/0.2 ± 5.4 mmHg). As for central aortic PP, the median radial PP increased under ivabradine by 6.0 mmHg (5.8 ± 7.5 mmHg), and tended to decrease under placebo: -2.0 mmHg (-0.1 ± 4.4 mmHg).

Median change of PWV tended to remain stable under both treatments after 3 weeks of treatment: -1.0 m/s (-1.2 ± 2.1 m/s) under ivabradine *versus* -0.6 m/s (-0.5 ± 2.3 m/s) under placebo.

Concerning skin capillary density in the PPS, the median capillary density under control conditions (CDc) was quite stable, increasing only by 1.2 units (1.8 ± 12.1 units) under ivabradine and by 2.9 units (+3.8 ± 3.6 units) under placebo. Similarly, under venous occlusion conditions, the median remained quite stable, increasing by only 0.4 units (3.3 ± 9.2 units) under ivabradine, and by 1.9 units (2.9 ± 6.5 units) under placebo.

All the results presented in the PPS showed similar trends in the FAS, except for PP (radial and central aortic), and LVET that tended to slightly increase under ivabradine and under placebo.

SAFETY RESULTS

- **Emergent adverse events**

Summary of emergent adverse events during the treatment period in the Safety Set (N = 14)

		Ivabradine (N = 12)		Placebo (N = 14)	
		P1 (N = 6)	P2 (N = 6)	P1 (N = 8)	P2 (N = 6)
Patients having reported at least one:					
Emergent adverse event	n (%)	1 (16.7)	3 (50.0)	1 (12.5)	1 (16.7)
Treatment-related emergent adverse event	n (%)	1 (16.7)	3 (50.0)	-	-
Patients having experienced at least one:					
Serious emergent event (including death)	n (%)	-	-	1 (12.5)	-
Treatment-related serious adverse event	n (%)	-	-	-	-
Patients with treatment withdrawal*					
due to an EAE	n (%)	-	-	-	-
Patients who died	n (%)	-	-	-	-

N: Total number of patients in each treatment group or in each period of treatment according to sequence of treatment
n: Number of patients concerned
One patient was withdrawn during the run-out period following his placebo treatment period due to a **non-emergent serious AE (suicidal depression).*

No death occurred in this study and no patient experienced an EAE that led to study drug withdrawal.

A total of 4 patients under ivabradine reported 6 EAEs and 2 patients under placebo reported a total of 3 EAEs during the treatment period.

SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Most of these EAEs (6/6 under ivabradine and 1/3 under placebo) were rated mild, and one (coronary artery restenosis, reported under placebo) was rated severe and resolved after new stent implantation.

A total of 5 EAEs considered to be related to the study drug according to investigator's opinion were reported in 4 patients under ivabradine: 4 cases of photopsia and one case of asthenia, non-serious, that resolved.

One EAE was reported as not recovered at the end of the study: retinal disorder (thickening of the retina in patient with history of glaucoma, emergent under ivabradine; mild intensity, non-serious, not related).

- In all, one serious EAE (coronary artery stenosis) was reported, and this was under placebo treatment. This serious event was considered not related to the study drug and resolved after new stent implantation. In addition, one serious adverse event, depression suicidal occurred during the wash-out period in a patient having taken placebo in period P1, and led to his withdrawal from the study at the W5 visit. Since patient did not start a P2 period, the wash-out period became a run-out and the SAE was considered as non-emergent.**HR from 12-lead ECG and supine brachial blood pressures**

In the Safety Set, the median HR decreased over the 3 week treatment period under ivabradine (both periods pooled) while it remained stable under placebo: -14.5 bpm (-16.6 ± 9.3 bpm) *versus* -1.0 bpm (-0.2 ± 5.8 bpm) respectively.

The median supine brachial SBP tended to slightly decrease in both groups: -3.5 mmHg (-2.8 ± 7.4 mmHg) *versus* -2.0 bpm (+1.9 ± 10.3 mmHg) respectively.

With regard to median supine brachial DBP, it decreased under ivabradine by 10 mmHg (-8.7 ± 5.7 mmHg) while it remained stable in the placebo group: -0.5 mmHg (-1.9 ± 10.2 mmHg).

CONCLUSION

This cross-over, double-blind, placebo-controlled, phase II study was conducted in 14 patients with stable CAD on top of beta-blockers, with the objective of evaluating the effect of ivabradine on CASBP. The study was prematurely terminated with 14 patients included, due to difficulties in patient recruitment.

In the per protocol population (N = 9), treatment with ivabradine 7.5 mg b.i.d. over 3 weeks tended to slightly decrease central aortic systolic blood pressure (CASBP; primary criterion) as compared to placebo (median change: -4.0 mmHg *versus* -1.0 mmHg, respectively), The effect of treatment on central aortic diastolic blood pressure was greater under ivabradine than under placebo (-10.0 mmHg *versus* 0.0 mmHg, respectively) and consequently there was an increase in central pulse pressure under ivabradine (+8.0 mmHg) *versus* a quasi-stability under placebo (-2.0 mmHg). The augmentation index (AIx) decreased by (median) 4.0% under ivabradine *versus* an increase of 2.0% under placebo.

Taken together these data do not support the hypothesis of an inverse correlation between heart rate and CASBP or AIx in patients with CAD, however the strength of this conclusion is limited by the small number of patients and the absence of robust statistical analysis.

The safety profile was as expected and no new concerns were reported.

Date of the report: 4 May 2015

Version of the report: Final version