Document title	**Clinical Study Report Synopsis**
Study title	**Effects of a 10 or 15 mg single intravenous bolus of ivabradine *versus* placebo on heart rate control during a multislice computed tomography coronary angiography for the evaluation of coronary artery disease**
Study drug	**S 16257**
Studied indication	**Heart rate control in multislice computed tomography coronary angiography**
Development phase	**Phase III**
Protocol code	**CL3-16257-078**
Study initiation date	**28 October 2008**
Study completion date	**25 September 2009**
Main coordinator	[redacted] **SPAIN**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 Rue Carnot** **92284 Suresnes Cedex - FRANCE**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 20 April 2011**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

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Title of study: Effects of a 10 or 15 mg single intravenous bolus of ivabradine *versus* placebo on heart rate control during a multislice computed tomography coronary angiography for the evaluation of coronary artery disease.
Protocol No.: **CL3-16257-078**

National coordinators: [redacted] (The Netherlands) - [redacted] (Italy) - [redacted] (Republic of Korea) - [redacted] (Romania) - [redacted] (Hungary) - [redacted] (France) - [redacted] (Belgium) - [redacted] (Portugal) - [redacted] (Bulgaria) - [redacted] (Denmark) - [redacted] (Spain) - [redacted] (United Kingdom) - [redacted] (Brazil) - [redacted] (Germany) - [redacted] (Russia) - [redacted] (Poland) - [redacted] (Australia) – [redacted] (Taiwan).

Study centres:
58 centres located in 19 countries included at least one patient:
Taiwan – 3 centres (47 included patients), Italy – 3 centres (46 included patients), Brazil – 7 centres (43 included patients), France – 6 centres (28 included patients), Germany – 7 centres (25 included patients), Hungary – 2 centres (23 included patients), Bulgaria – 1 centre (21 included patients), Australia – 3 centres (19 included patients), Republic of Korea – 2 centres (19 included patients), Russian Federation – 3 centres (16 included patients), Romania – 3 centres (16 included patients), Spain – 4 centres (15 included patients), Portugal – 4 centres (15 included patients), Denmark – 2 centres (12 included patients), Poland – 1 centre (10 included patients), The Netherlands – 2 centres (7 included patients), Belgium – 2 centres (4 included patients), Singapore – 1 centre (2 included patients) and United Kingdom – 2 centres (2 included patients).

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 28 October 2008 Completion date: 25 September 2009	Phase III

Objectives:
The primary objective was:

- To demonstrate that during a planned MSCT CA for the evaluation of CAD, ivabradine administered intravenously was superior to placebo in achieving HR control (HR ≤ 65 bpm) in patients not eligible for intravenous beta-blockers.

The secondary objectives were:

- To assess *versus* placebo during the MSCT CA:
  - The tolerability of intravenous ivabradine.
  - The procedural convenience of the use of intravenous ivabradine.

The objective of the pharmacokinetics (PK) sub-study (added by Amendment No. 1) was to evaluate the pharmacokinetic parameters of S 16257 and its main metabolite S 18982 in a subset of patients.

Methodology:
This was a randomised, double-blind, placebo-controlled, multicentre, international study with a non-centralised unbalanced randomisation (2 ivabradine / 1 placebo) providing 2 parallel treatment arms.
Randomisation was stratified on centre and HR < or ≥ 80 bpm at baseline.

Number of patients:
Planned: 330 patients, *i.e.* 220 in the ivabradine group and 110 in the placebo group.
Included: 370 patients *i.e.* 252 in the ivabradine group and 118 in the placebo group.
44 patients were included in the PK sub-study: 29 patients were in the ivabradine group and 19 in the placebo group.

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Diagnosis and main criteria for inclusion:

Male or female patients ≥ 18 years (or having reached majority if legal majority was over 18 years), planned to undergo a scheduled MSCT CA for the evaluation of suspected or known coronary artery disease (CAD), not eligible for intravenous beta-blockers, with sinus rhythm and an HR ≥ 70 bpm as documented by a resting 12-lead ECG and able to perform a 20 seconds breath-hold.

Study drug:

Ivabradine solution 2 mg/mL in ampoules of 5 mL (10 mg) and 7.5 mL (15 mg), administered as a single intravenous bolus depending on HR: 10 mg if the last baseline HR was between 70 (inclusive) and < 80 bpm or 15 mg if the last baseline HR was ≥ 80 bpm.
Batch Numbers: L0025981 and L0025983.

Reference product:

Placebo solution in ampoules of 5 mL (10 mg) and 7.5 mL (15 mg), administered as for ivabradine, as a single intravenous bolus of 10 mg or 15 mg depending on the last baseline HR.

Duration of study:

- A selection visit (ASSE).
- A procedural visit (D000) within 30 days after selection with 3 periods:
  - D0P0: study inclusion.
  - D0P1: study treatment initiation, which started with the initiation of study treatment (T0) during continuous ECG monitoring in the MSCT CA scanner, followed by the MSCT CA image acquisition (Ta) if possible (typically including a native scan, infusion of contrast agent, and a contrast-enhanced scan).
  - D0P2: patient follow-up in the centre, until 4 hours after the start of study treatment (*i.e.* H1, H2 and H4).
- A study termination visit (DEND) at 3 to 7 days after the procedural visit.

The total study duration from the procedural visit to the termination visit was 3 to 7 days.

Criteria for evaluation:

Efficacy measurements:

- Primary efficacy criterion: HR control achieved at Ta (time of initiation of image acquisition), assessed by continuous ECG monitoring.

A patient was considered as responder if the HR at Ta was not missing and ≤ 65 bpm and non-responder if otherwise. Patients having not completed MSCT CA for reason of "non-sustained HR control" were considered as non-responders.

- Secondary efficacy criteria:
  - Heart rate control after T0 (yes/no).
  - Rate of patients having a scan (MSCT and/or CE) performed (yes/no).
  - Heart rate (bpm) during continuous ECG monitoring.
  - Mean heart rate (bpm) during acquisition of contrast enhanced (CE) scan.
  - Time (min) to initiation of MSCT image acquisition (Ta).
  - Time (min) to end of MSCT procedure (Tx).
  - Heart rate (bpm) at H1.
- Other criteria:
  - Investigator procedural convenience assessment (very bad/bad/neutral/good/very good).
  - Radiation exposure: dose-length product (DLP) (mGy.cm) and effective dose (mSv).
  - Use of ECG controlled tube current modulation (ECTCM) (yes/no).
  - Use of Automatic Exposure Control (yes/no).

HR, assessed by continuous ECG-monitoring, was measured at D0P0 (2 baseline measurements after an interval of 3 minutes) and D0P1 (measurements every 3 minutes from T0 until Tx).

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Criteria for evaluation (cont'd):

Safety measurements:

- Adverse events (AEs), assessed during the whole study period (from ASSE to follow-up).
- Serum creatinine, assessed at D0P0 and DEND.
- Systolic and diastolic blood pressures, measured at selection, D0P0, 3 times during D0P2 (at H1, H2 and H4) and at the termination visit.
- 12-lead ECG (sinus rhythm, HR, QT interval, corrected QT [Bazett and Fridericia formulae], PR interval and duration of QRS), performed at selection, D0P0, 3 times during D0P2 (at H1, H2 and H4) and at the termination visit (DEND).

Pharmacokinetic measurements:

For patients enrolled in the PK sub-study (Amendment No. 1; in selected centres), blood samples (5 mL per sample) were collected for the measurement in plasma of S 16257 and its main active metabolite, S 18982. The samples were drawn at Tx (an optional timepoint) and at 1, 2 and 4 hours post-bolus.

Statistical methods:

Status and characteristics of patients were described on patients of the Randomised Set (RS) and Per Protocol Set (PPS). In patients presenting with suspected CAD, the pre-test probability of CAD was calculated by the score defined by Morise *et al* (1997). This score includes the parameters of age, gender, angina symptoms, oestrogen status, family history of CAD, and the presence or absence of diabetes mellitus, hypertension, smoking, hyperlipidaemia and obesity.

Efficacy analyses were carried out in the Full Analysis Set (FAS) and PPS.

The superiority of ivabradine compared to placebo was tested using a logistic regression adjusted for baseline HR </≥ 80 bpm (Wald test). Odds ratios and 95% confidence intervals were provided. As a sensitivity analysis, the proportion of responders between the 2 treatment groups was compared using a chi-square test.

Predefined subgroups based on gender, age, baseline HR and reason for performing MSCT CA were investigated in order to confirm the trend observed on the main patients' sets.

The analyses of secondary and other criteria were mainly descriptive. However, treatment effect was estimated on the change/relative change in HR between baseline and Ta/H1 using a parametric approach based on the Student distribution and a non-parametric approach based on a Hodges and Lehmann estimate. The differences between treatment groups (with post hoc statistical tests to provide p-values) was also tested on:

- The mean HR during acquisition of CE scan (and at H1) using a t-test.
- The proportion of patients having performed a CE scan using a Fisher exact test.
- The investigator procedural convenience, using Mantel-Haenszel test when expressed as classes, and using a t-test when expressed as continuous data.
- The radiation exposure using a t-test.

Safety analyses were carried out on patients of the Safety Set, on:

- Adverse events during the study, emergent adverse events post-bolus (defined as AEs which occurred after or at the time of the bolus injection or AEs, which occurred before the bolus injection and which worsened or became serious after or at the time of the bolus injection), emergent AEs (EAEs) under treatment (same definition as "post-bolus", but with a cut-off at 48 hours after the bolus injection), ECG parameters, blood pressures and serum creatinine were studied using descriptive statistics.
- Change in HR and corrected QT intervals from baseline to H1, H2, H4 and DEND were studied within treatment groups using parametric and non-parametric 95% confidence intervals.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

The **Randomised Set** consisted of 370 patients (Table 1). No clinically relevant difference between treatment groups was noted at the selection regarding the demographic data, cardiovascular status and risk factors. The FAS included 99.7% of the Randomised Set and the PPS included 90.8% of the FAS. The baseline characteristics of patients in the PPS were similar to those described in the RS.

Randomised patients had a mean age of 61.5 ± 10.6 years (40.8% ≥ 65 years), 54.1% were men, 76.2% were Caucasian and 19.2% were Asian. Most patients (71.9%) were planned for an MSCT CA for suspected CAD or known CAD (28.1%, mainly for evaluation of stents and grafts post CABG). For the patients with suspected CAD, the probability of possible CAD was estimated as "intermediate" in 63.2% of patients, "high" in 28.2% and "low" in 8.7%. Overall, 68.4% of patients had current angina symptoms and of these, 38.7% had typical angina, 48.2% had atypical angina and 13.0% had non-anginal chest pain. Overall, 25.7% of patients (n = 95) presented with heart failure (HF) and of these, 69.5% were of NYHA class II, 23.2% were of class III and 7.4% were of class I. LVEF was known in 86.3% of HF patients and for them the mean LVEF was 37.5 ± 14.3%.

Table 1 - Disposition of patients

			Ivabradine	**Placebo**	**All**
Included (randomised)		n (%)[a]	252 (100)	118 (100)	370 (100)
Lost to Follow-up			-	-	-
Withdrawn due to non-medical reason		n (%)[a]	3 (1.2)	1 (0.8)	4 (1.1)
Completed		n (%)[a]	249 (98.8)	117 (99.2)	366 (98.9)
Full Analysis Set (FAS)		n (%)[a]	252 (100)	117 (99.2)	369 (99.7)
Per Protocol Set (PPS)		n (%)[b]	229 (90.9)	106 (90.6)	335 (90.8)
Safety Set		n (%)[a]	252 (100)	118 (100)	370 (100)
Subgroups of FAS					
Gender	Female	n (%)[a]	114 (45.2)	56 (47.9)	170 (46.1)
	Male	n (%)[a]	138 (54.8)	61 (52.1)	199 (53.9)
Age	< 65 years	n (%)[a]	150 (59.5)	68 (58.1)	218 (59.1)
	≥ 65 years	n (%)[a]	102 (40.5)	49 (41.9)	151 (40.9)
Heart rate	[70 ; 80[bpm	n (%)[a]	161 (63.9)	68 (58.1)	229 (62.1)
	≥ 80 bpm	n (%)[a]	91 (36.1)	49 (41.9)	140 (37.9)
Reason for scheduling MSCT scan	Known CAD	n (%)[a]	69 (27.4)	35 (29.9)	104 (28.2)
	Suspected CAD	n (%)[a]	183 (72.6)	82 (70.1)	265 (71.8)

n Number of patients by group
[a] % calculated as percentage of the included patients (Randomised Set)
[b] % calculated as percentage of the FAS

Regarding main risk factors, 28.2% of patients were obese (BMI ≥ 30 kg/m^2; mean BMI of RS = 27.8 ± 5.1 kg/m^2), 71.6% presented with hypertension, 59.5% with lipid metabolism disorders, 22.4% with diabetes mellitus and 23.8% were smokers.

The main reasons for non-eligibility to IV beta-blockers were chronic obstructive pulmonary disease (38.7%), asthma (28.1%) and symptomatic heart failure (18.1%).

All patients had an HR ≥ 70 bpm at baseline and 37.8% had an HR ≥ 80 bpm (mean HR of RS = 79.1 ± 8.5 bpm). The baseline HR was stable; the relative change between the 2 last HR measurements was 0.23 ± 2.92% (absolute value).

Patients received either 10 mg of study drug (62.4% of patients) or 15 mg (37.6%) according to their baseline HR (< or ≥ 80 bpm).

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

93.5% of patients in the RS took at least one concomitant treatment the day of bolus (excluding the use of contrast agents and other treatments for which the start date was the day of bolus administration). These were mainly agents acting on the renin-angiotensin system, antithrombotic agents, lipid modifying agents, drugs for obstructive airway diseases and diuretics. Overall, 20.5% of patients were receiving a background therapy of an oral beta-blocker, as permitted by the protocol (without relevant difference between treatment groups).

PHARMACOKINETIC RESULTS

Individual pharmacokinetic parameters were estimated using a combined population PK model for S 16257 and S 18982 constructed using data from cardiac and hepatically-impaired patients who were administered IV ivabradine.

Among the 29 ivabradine-treated patients who were included in the PK sub-study, 20 patients received the 10 mg bolus and 9 patients the 15 mg bolus. Twenty-four patients were Caucasian with 15 having received the 10 mg dose and 9 the 15 mg dose. Five patients were Asian and all received the 10 mg dose.

The average exposures to S 16257 calculated at the doses of 10 and 15 mg ([redacted] especively), were in agreement with a linear PK.

The comparison between Caucasian and Asian patients showed similar PK (at the dose of 10 mg, [redacted]), with an exposure to the parent drug and its metabolite in the range of the exposure observed in the larger population of cardiac Caucasian patients used to build the combined population PK model.

EFFICACY RESULTS

Primary assessment criterion: heart rate control (≤ 65 bpm) at Ta

The percentage of responders (HR ≤ 65 bpm at Ta) was greater in the ivabradine group (55.2%) than in the placebo group (23.1%; Table 2). Ivabradine was superior to placebo with a clinically relevant response rate and a statistical significance (p-value < 0.0001) according to the logistic regression model adjusted for baseline HR </≥ 80 bpm (main analysis). The estimate of the odds ratio between the 2 treatment groups was 4.5.

The results of the sensitivity analysis confirmed those of the main analysis with an estimate of the difference between treatment group responder proportions equal to 32% and p < 0.0001 (chi-square test).

Similar results were observed in the PPS.

Table 2 - Heart rate control (≤ 65 bpm) at Ta - Responders / Non-responders - FAS and PPS

		FAS		PPS	
		Ivabradine (N = 252)	**Placebo (N = 117)**	**Ivabradine (N = 229)**	**Placebo (N = 106)**
Responders	n (%)	139 (55.2)	27 (23.1)	127 (55.5)	21 (19.8)
Non-responders	n (%)	113 (44.8)	90 (76.9)	102 (44.5)	85 (80.2)
Main analysis					
Adjusted logistic regression	E	4.49		5.63	
	95% CI	[2.65 ; 7.61]		[3.14 ; 10.09]	
	p-value (1)	**< 0.0001**		**< 0.0001**	
Sensitivity analysis					
Chi-square test	E'	0.32		0.36	
	95% CI	[0.22 ; 0.42]		[0.26 ; 0.46]	
	p-value (2)	**< 0.0001**		**< 0.0001**	

E Estimate of ivabradine minus placebo effect odds ratio; logistic model adjusted for baseline HR </≥ 80 bpm
E' Estimate of the difference between treatment group proportions
95% CI 95% confidence interval of the estimated treatment effect (two-sided)
(1) logistic regression model adjusted for baseline HR </≥ 80 bpm (Wald test)
(2) chi-square test

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Table 3 shows the percentages of responders on the primary criterion (HR ≤ 65 bpm at Ta) and the estimates of the treatment effect, in the prespecified and complementary subgroups of the FAS. These analyses confirmed the result observed on the overall FAS.

Similar results were observed in the corresponding prespecified subgroups of the PPS.

Table 3 - Heart rate control at Ta - Responders - Subgroups of the FAS

Responders (HR ≤ 65 bpm)	**Ivabradine** % (n/N')	**Placebo** % (n/N')	**Odds ratio** **E [95% CI]**
Gender			
Men	50.7 (70/138)	27.9 (17/61)	3.0 [1.4 ; 5.8]
Women	60.5 (69/114)	17.9 (10/56)	7.8 [3.4 ; 17.9]
Age			
< 65 years	58.0 (87/150)	27.9 (19/68)	4.0 [2.0 ; 7.9]
≥ 65 years	51.0 (52/102)	16.3 (8/49)	5.7 [2.3 ; 13.7]
< 75 years*	55.8 (119/213)	25.0 (26/104)	4.2 [2.4 ; 7.3]
≥ 75 years*	51.3 (20/39)	7.7 (1/13)	13.4 [1.5 ; 118.4]
HR class			
[70-80[bpm	67.7 (109/161)	36.8 (25/68)	3.6 [2.0 ; 6.5]
≥ 80 bpm	33.0 (30/91)	4.1 (2/49)	11.6 [2.6 ; 50.8]
Reason for scan			
Known CAD	47.8 (33/69)	22.9 (8/35)	3.7 [1.4 ; 9.7]
Suspected CAD	57.9 (106/183)	23.2 (19/82)	4.8 [2.5 ; 9.0]
BMI*			
< 22.5 kg/m²	63.0 (17/27)	12.5 (2/16)	10.0 [1.8 ; 55.7]
≥ 22.5 kg/m²	54.5 (122/224)	24.7 (25/101)	4.2 [2.4 ; 7.4]
Weight*			
< 75 kg	54.9 (62/113)	22.8 (13/57)	3.5 [1.6 ; 7.4]
≥ 75 kg	55.8 (77/138)	23.3 (14/60)	6.4 [3.0 ; 13.9]
COPD/asthma*			
Yes	54.9 (90/164)	26.4 (19/72)	3.6 [1.9 ; 6.9]
No	55.7 (49/88)	17.8 (8/45)	6.7 [2.6 ; 17.1]
Heart Failure*			
Yes	47.0 (31/66)	34.5 (10/29)	2.2 [0.8 ; 5.9]
No	58.1 (108/186)	19.3 (17/88)	5.9 [3.1 ; 11.2]

n number of responder patients in each subgroup
N' total number of patient in each subgroup
E Estimate of ivabradine minus placebo effect odds ratio between the two treatment groups based on a logistic model adjusted for HR </≥ 80 bpm (except for HR class subgroups)
[95% CI] 95% confidence interval of the estimated treatment effect (two-sided)
** complementary subgroups*

Secondary assessment criteria

Patients having HR ≤ 65 bpm during the study

In the patients who underwent a CE scan (n = 296, 80% of FAS), a reading of HR ≤ 65 bpm (as recorded by the scanner; complementary analysis) was observed in 55.0% of patients (121/220) in the ivabradine group *versus* 19.7% (15/76) in the placebo – a difference that was statistically significant (p < 0.0001).

In the FAS at H1 (*i.e.* one hour after study drug administration), a reading of HR ≤ 65 bpm (on 12-lead ECG) was observed in 68.3% of patients (172/252) in the ivabradine group *versus* 16.2% (19/117) in the placebo group (p < 0.0001).

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Heart rate post-bolus and change from baseline

The mean baseline HR in the FAS was similar in the 2 treatment groups at about 79 bpm. A strong and consistent HR reduction was observed in the ivabradine group after the bolus injection as compared to the placebo group.

At Ta, the mean HR in the ivabradine group was 67.4 ± 9.7 bpm, corresponding to mean (relative) changes from baseline of -11.4 ± 8.4 bpm (-14.2%). In the placebo group, the mean HR at Ta was 75.2 ± 10.2 bpm, corresponding to mean (relative) changes from baseline of -4.5 ± 7.2 bpm (-5.6%). The estimate of the between-group difference on mean HR change was -6.9 bpm (95% CI [-8.7 ; -5.2]), *i.e.* statistically significant in favour of ivabradine.

In patients who received **10 mg ivabradine,** the mean change from baseline to Ta was -8.6 ± 5.5 bpm and in patients who received **15 mg ivabradine,** the mean change was -16.4 ± 10.2 bpm (unplanned analysis).

The mean HR during the CE scan (in patients who underwent a CE scan: n = 220 in the ivabradine group *versus* 76 in the placebo group) was lower in the ivabradine group with a mean of 65.3 ± 7.7 bpm *versus* 76.2 ± 11.8 bpm in the placebo group ($p < 0.0001$).

At H1, the HR lowering effect of ivabradine (on 12-lead ECG) was marked, with a mean of 62.2 ± 11.2 bpm *versus* 76.6 ± 10.9 bpm in the placebo group ($p < 0.0001$). These values corresponded to mean (relative) changes from baseline of -18.4 ± 11.3 bpm (-22.4%) in the ivabradine group *versus* -3.6 ± 9.6 bpm (-4.1%) in the placebo group. The estimate of the between-group difference on mean HR change was -14.9 bpm (95% CI [-17.2 ; -12.5]), *i.e.* statistically significant in favour of ivabradine.

Rates of scans performed

A CE scan was performed in 87.3% of patients (220 patients) in the ivabradine group *versus* 65.0% of patients (76 patients) in the placebo group, a difference that was statistically significantly in favour of ivabradine ($p < 0.0001$).

The MSCT scan (either native and/or CE scan) was performed in 90.1% of patients (227 patients) in the ivabradine group *versus* 72.7% of patients (85 patients) in the placebo group.

Time from bolus administration to image acquisition initiation

In the FAS, the mean time from T0 to Ta was statistically significantly shorter in the ivabradine group (15.2 ± 8.7 min [median: 15.0 min]) than in the placebo group (16.8 ± 7.3 min [median: 17.0 min]): $p = 0.0045$.

In patients having performed a CE scan, the time from T0 to Ta was 15.0 ± 9.2 min (median: 15.0 min) in the ivabradine group *versus* 15.4 ± 7.0 min (median: 16.0 min) in the placebo group.

Time from bolus administration to end of MSCT procedure

In patients of the FAS having performed a CE scan, the mean time from T0 to Tx was similar between treatment groups: 21.0 ± 9.6 min in the ivabradine group and 21.6 ± 8.1 min in the placebo group.

Procedural convenience

The procedural convenience according to the investigators of using the study drug during the MSCT CA procedure was statistically significantly better in the ivabradine group than in the placebo group: mean score: 4.2 ± 0.9 *versus* 3.8 ± 1.2 ($p = 0.0027$).

The procedural convenience was considered as "very good" or "good" in 79.4% of patients in the ivabradine group *versus* 63.2% of patients in the placebo group, with a distribution of the higher scores in favour of ivabradine ($p = 0.0005$).

This procedural convenience was rated as very bad in 0.8% of patients in the ivabradine group *versus* 6.8% in the placebo group.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Radiation exposure/Use of ECTCM and Automatic Exposure control

The exposure to radiation during the CE scan was statistically significantly lower in patients of the ivabradine group compared to that in the placebo group: the effective doses were 16.3 ± 7.9 mSv *versus* 18.9 ± 8.8 mSv, respectively and the DLPs were 961.2 ± 463.8 mGy.cm *versus* 1110.4 ± 515.1 mGy.cm, respectively ($p = 0.0293$ for both measures). These results were associated with a greater use of HR-dependent low radiation dose protocols during CE scan, *i.e.* scans utilising ECTCM, in the ivabradine group (77.5%) than in the placebo group (68.2%). The use of automatic exposure control was similar: 55.1% versus 57.7%.

SAFETY RESULTS

Between the first and last study visits, 108 patients (29.2%) had 168 adverse events: 32.5% of patients in the ivabradine group *versus* 22.0% in the placebo group. These concerned mainly the SOCs *cardiac disorders* (8.7% *versus* 5.9%), *eye disorders* (8.3% *versus* 0%) and *investigations* (5.6% *versus* 3.4%).

Emergent adverse events post-bolus were reported by 105 patients overall (21.1%): 25.4% of patients in the ivabradine group *versus* 11.9% in the placebo group. These concerned mainly the SOCs indicated above.

Emergent adverse events during the treatment period were reported by 57 patients overall (15.4%; Table 4): 19.4% of patients (n = 49 with 67 EAEs) in the ivabradine group and 6.8% (n = 8 with 9 EAEs) in the placebo group. The EAEs reported by patients in the ivabradine group during the treatment period, involved mainly the SOCs:

- *Eye disorders*, in 21 patients (8.3%): among the 23 EAEs, 18 cases of phosphenes and 2 cases of vision blurred were considered as related to the study drug by the investigator and recovered.
- *Cardiac disorders*, in 10 patients (4.0%): among the 10 EAEs, 7 were considered as related to the study drug by the investigator: 2 cases of atrioventricular block 1st degree, 2 of supraventricular extrasystoles, and 1 each of atrial tachycardia, palpitations and symptomatic bradycardia (all had an outcome of recovered).
- *Investigations*, in 6 patients (2.4%): including 4 cases of asymptomatic bradycardia, and 1 each of PR prolongation and QT prolongation. All these EAEs except one asymptomatic bradycardia were considered as related to the study drug and all had an outcome of recovered.

The majority of EAEs reported in the ivabradine group were those listed in the European Summary of Product Characteristics of ivabradine. Two EAEs during the treatment period were rated as severe, both in the ivabradine group: angina unstable and acute pulmonary oedema (both were also serious, not related to the study drug and recovered).

Table 4 - Summary of safety results during the treatment period

		Ivabradine N = 252	**Placebo N = 118**
Patients having reported			
at least one emergent adverse event	n (%)	49 (19.4)	8 (6.8)
at least one treatment-related emergent adverse event	n (%)	30 (11.9)	3 (2.5)
at least one eye disorder	n (%)	21 (8.3)	-
at least one asymptomatic bradycardia (HR decrease) or bradycardia (symptomatic)	n (%)	5 (2.0)	-
Patients having experienced			
at least one serious emergent adverse event	n (%)	3 (1.2)	1 (0.8)
at least one treatment-related serious adverse event	n (%)	-	-
Patients who died	n (%)	-	-

Note The treatment period was defined as from the moment of bolus injection until 48 hours later
n number of patients concerned; % = (n/N) x 100

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

No patient died during the study.

Between the first and last study visits, a total of 18 patients (4.9%) reported at least one **serious adverse event** and for 17 of these patients the SAE was emergent (13 (5.2%) in the ivabradine group *versus* 4 (3.4%) in the placebo group). An **SEAE during the treatment period** was declared in 3 patients (1.2%) in the ivabradine group (angina unstable, angioedema and acute pulmonary oedema) *versus* 1 patient (0.8%) in the placebo group (pulmonary granuloma). No serious adverse event was considered as related to the treatment; all events in the ivabradine group were reported as recovered.

The SEAEs that occurred after the treatment period, in the ivabradine group (11 patients; 4.4%) were related to planned coronary procedures or diagnoses for all but 2 events; the exceptions concerned a case of anaemia following bladder catheterisation (not related to the study drug and recovered) and a case of transient ischaemic attack (transient dysarthria, 9 days after bolus, not related to the study drug and recovered).

Serum creatinine

Neither clinically relevant changes over time nor differences between groups were detected for serum creatinine. The mean change between baseline and DEND was 0.3 ± 11.8 µmol/L in the ivabradine group and 1.1 ± 11.1 µmol/L in the placebo group. No patient experienced a potentially clinically significant abnormality, but 5 values at DEND were considered as clinically significant by the investigator: 3 in the ivabradine group, of which one was emergent (141 µmol/L, following a baseline value of 115 µmol/L) *versus* 2 values that were non-emergent in the placebo group.

ECG parameters on 12-lead ECG

The mean HR decrease (on 12-lead ECG) was statistically significant between baseline and each post-bolus measurement time (H1, H2, H4 and DEND) in both treatment groups (see Table 5). The decreases were greater in the ivabradine group (between 17 and 19 bpm) than in the placebo group (between 2 and 4 bpm). At DEND, this decrease was 6 bpm in the ivabradine group *versus* 3 bpm in the placebo group.

Table 5 - HR on 12-lead ECG - Mean changes from baseline to each measurement time - Safety Set

Heart rate (bpm)		**Ivabradine (N = 252)**	**Placebo (N = 118)**
H1 - baseline	n	247	117
	Mean ± SD	-18.8 ± 10.3	-3.6 ± 9.6
	95% CI*	[-20.1 ; -17.5]	[-5.4 ; -1.9]
H2 - baseline	n	248	117
	Mean ± SD	-18.3 ± 11.2	-1.8 ± 9.5
	95% CI*	[-19.7 ; -16.9]	[-3.523 ; -0.0]
H4 - baseline	n	247	117
	Mean ± SD	-17.4 ± 10.0	-3.0 ± 9.8
	95% CI*	[-18.7 ; -16.2]	[-4.8 ; -1.2]
DEND - baseline	n	243	116
	Mean ± SD	-6.0 ± 10.8	-3.2 ± 10.5
	95% CI*	[-7.3 ; -4.6]	[-5.1 ; -1.2]

** 95% confidence interval of the estimate (two-sided) based on t test (parametric approach)*

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

During the D0P2 period (*i.e.* from H1 to H4), between 3.6% and 9.2% of patients in the ivabradine group (depending on measurement time) and 0.8% at DEND had an HR < 50 bpm. Only one patient presented an HR < 40 bpm (39 bpm, asymptomatic, at H1).

As expected, in view or the HR lowering effect of ivabradine, the QT interval lengthened from its baseline value. The corrected QT values (Bazett and Fridericia) however, showed no clinically significant increases in mean values and no clinically relevant change was observed in PR interval.

An emergent QTcB ≥ 500 ms was reported in 12 patients (5.2%) in the ivabradine group *versus* 4 patients (3.5%) in the placebo group; emergent QTcF values ≥ 500 ms were reported by 9 patients (3.8%) *versus* 2 (1.7%), respectively.

Blood pressure

Sitting SBP and DBP decreased during D0P2 in both ivabradine and placebo groups. The reduction was more pronounced in ivabradine-treated patients, with a mean decrease in SBP/DBP at H1 of -5.1/-5.4 mmHg in the ivabradine group *versus* -2.7/0.0 mmHg in the placebo group and at H4, of -6.5/-7.0 mmHg *versus* -5.0/-2.0 mmHg, respectively. By DEND, the changes from baseline were largely attenuated with -4.5/-2.2 mmHg in the ivabradine group *versus* -2.2/-0.9 mmHg in the placebo group. There were no reports of EAE hypotension in the ivabradine group *versus* 1 in the placebo group.

CONCLUSION

This was a phase III, randomised, double-blind, placebo-controlled study in patients awaiting a planned MSCT CA for the evaluation of CAD, who had a resting HR ≥ 70 bpm and were ineligible for intravenous beta-blockers.

The efficacy assessment demonstrated that IV ivabradine (10 or 15 mg) was superior to placebo on the primary endpoint: the achievement of HR control (≤ 65 bpm) at the time of initiation of image acquisition (p < 0.0001) with a response rate of 55% in the ivabradine group *versus* 23% in the placebo group. The procedural convenience according to the investigators was better in the ivabradine group than in the placebo group. A greater proportion of patients in the ivabradine group underwent a Contrast Enhanced scan. There was a higher use of HR-dependant radiation-exposure-lowering techniques in the ivabradine group with a statistically significant lower radiation exposure during Contrast Enhanced scan.

The safety profile of the emergent adverse events reported in the ivabradine group was consistent with the existing European SmPC of this drug. The most frequent events were transient, mild to moderate, visual symptoms. The pharmacokinetic assessment in the PK sub-study showed similar concentration-time profiles between Caucasian and Asian patients, with an exposure to the parent drug and its metabolite in the range of the exposure observed in a larger population of cardiac Caucasian patients.

A single IV bolus of ivabradine achieves a rapid, safe and sustained heart rate lowering effect during a MSCT CA procedure. The HR control response rate was clinically relevant making IV ivabradine a valuable alternative approach to IV beta-blockers for HR control during MSCT CA.

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