I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report Synopsis**
Study title	**Effects of ivabradine IV versus placebo on haemodynamic parameters in patients with a low cardiac output syndrome following planned coronary artery bypass surgery and requiring positive inotropic treatment. A phase II, single blind, exploratory, multicentre study.**
Study drug	**S 16257-2 Ivabradine hydrochloride**
Studied indication	**Low Cardiac Output Syndrome after Coronary Artery Bypass Graft surgery**
Development phase	**Phase II**
Protocol code	**CL2-16257-088**
Study initiation date	**15 July 2010**
Study completion date	**6 June 2012**
Main coordinator	[redacted] **France**
Company / 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	**Final version 27 May 2014**

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2. SYNOPSIS

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Title of study:
Effects of ivabradine IV versus placebo on haemodynamic parameters in patients with a low cardiac output syndrome following planned coronary artery bypass graft surgery and requiring positive inotropic treatment. A phase II, single blind, exploratory, multicentre study.
Protocol No.: CL2-16257-088 – EudraCT number: **2009-018175-14**

National Coordinator:
[redacted]

Study centre*(s)*:
Total number of centres: 5
Total number of countries: 1 (France)

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 15 July 2010 Completion date: 6 June 2012	Phase II

Objective(s):
The primary objective of this study was to evaluate the effect of ivabradine administered by intravenous route *versus* placebo in Coronary Artery Disease (CAD) patients presenting a Low Cardiac Output Syndrome (LCOS) following a planned Coronary Artery Bypass Graft (CABG) and requiring first-line positive inotropic treatment with dobutamine. The effect was assessed on the difference between ivabradine and placebo groups on the number and percentage of patient responders, *i.e.* patients whose heart rate (HR) was within the range of 80 to 90 bpm for at least 30 minutes during the ivabradine/placebo infusion and/or allowing the dobutamine inotropic treatment to be increased.

The secondary objectives were:
- To confirm that the efficacy of the inotropic treatment on haemodynamics is not altered when associated with ivabradine;
- To optimize the inotropic treatment by reducing its related induced excessive tachycardia;
- To evaluate the effect of ivabradine *versus* placebo on the reduction of early cardiovascular events;
- To compare the safety profile of ivabradine to placebo during the immediate post-operative period up to hospital discharge.

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Methodology:

This was a phase II, exploratory, multicentre, randomised, unbalanced, single-blind, placebo-controlled, 2-parallel-group trial. The study was designed to evaluate the effect of ivabradine *versus* placebo in patients presenting a LCOS following a planned CABG surgery and requiring first-line positive inotropic treatment with dobutamine. The treatments were allocated using an unbalanced randomisation method (ratio: 3 ivabradine/1 placebo).

The study was divided into two periods:

(1) An early phase. The post-operative period during which patients with a LCOS and receiving a dobutamine infusion, and for whom HR was ≥ 100 bpm received ivabradine i.v. or matched placebo. It was administered as a bolus of 10 mg followed by continuous infusion of 10 mg over a period of 24 hours. After Amendment No. 3, treatment was amended to continuous infusion of ivabradine 10 mg or matched placebo over a period of 1 hour (fast infusion) and followed by a continuous infusion of ivabradine 10 mg or matched placebo per 24-hours (slow infusion), renewable for a total duration of treatment of 48 hours.

(2) A follow-up period, from the end of the infusion up to hospital discharge, during which the patients received their usual cardiac treatment.

The last evaluation under treatment was performed and the study drug treatment was stopped when the decrease in dobutamine treatment started. If the decrease in dobutamine treatment was not initiated after 48 hours, the study treatment was stopped and the last visit under treatment was completed.

Titration and follow-up period:

All the patients randomised into the study received ivabradine 10 mg or matched placebo either by bolus dose over 5 minutes or, following Amendment No. 3, by continuous infusion over 1 hour (fast infusion). This was followed by a continuous infusion of ivabradine 10 mg or matched placebo over 24 hours (slow infusion), which was renewable for a total treatment duration of 48 hours.

Dobutamine treatment was uptitrated according to patient need (noradrenaline and/or adrenaline could be administered in addition to dobutamine in case of systolic blood pressure (SBP) < 90 mmHg).

The decrease in the dobutamine treatment (alone or associated with other inotropic treatments) was initiated according to the investigator's judgment. At the same time, the infusion of ivabradine or matched placebo was stopped. Subsequent cardiac treatments were reinitiated at the discretion of the investigator.

The initial ivabradine regimen (*i.e. bolus followed by a slow infusion)* was evaluated by HR, Holter and PK analyses for the first 14 patients (corresponding to the first 10 patients to be completed on HR, PK and Holter results). Based on these results, the ivabradine regimen was adapted to provide treatment as a fast infusion of the initial dose followed by slow infusion for up to 48 hours. These modifications to the protocol were specified in Amendment No. 3.

Number of patients:

Planned: Between 40 and 60 patients, with a re-evaluation of the ivabradine dosing regimen after a minimum of 10 patients had completed the study (based on HR, PK and Holter results). The planned number of patients was revised to a maximum of 40 patients by Amendment No. 3.

Included (total and by group): 19 patients (14 ivabradine, 5 placebo). The number of patients was lower than expected due to the difficulty to recruit patients for this particular indication.

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Diagnosis and main criteria for inclusion:

Pre-selected patients were men or women of non-childbearing potential, aged ≥ 18 years and < 75 years [changed to ≤ 80 years by Amendment No. 4], who were planned to undergo CABG surgery (single or multiple vessel disease), and who presented a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 40% documented by a transthoracic echocardiography within 1 month before pre-selection.

After CABG, patients were selected if they presented a LCOS requiring first-line positive inotropic treatment with dobutamine. In patients with a body temperature ≥ 36.5°C [changed to a body temperature of 36.5°C ± 0.5 by Amendment No. 3], LCOS is defined as a cardiac index (CI) < 2.2 L/min/m².

Selected patients were included once their HR was ≥ 100 bpm after initiation of dobutamine infusion and if they had a normal sinus rhythm.

Study drug:

Intravenous ivabradine. An initial dose of 10 mg was given either as a bolus or, following Amendment 3, by fast infusion. A further dose of 10 mg was subsequently given by continuous slow infusion over a period of 24 hours, which could be repeated (as specified in Amendment No. 3) for a total treatment duration of 48 hours. No dose adjustment was foreseen during infusion. Ivabradine was administered in combination with inotropic treatment with dobutamine. Ivabradine infusion was stopped when the dobutamine decrease was initiated.
Batch Nos.: U06005, T02011

Reference product:

Matched placebo was administered in same conditions as those of ivabradine and was administered in combination with inotropic treatment with dobutamine.

Duration of treatment:

- Treatment period: The study treatment period with ivabradine or matched placebo was up to 48 hours.
- Open follow-up period: the period between the end of study treatment and the discharge of the patient, in which the patient received the usual cardiac treatment following CABG.

Criteria for evaluation:

During the immediate post-operative period and until the dobutamine initiation of decrease, this included:

Haemodynamic monitoring:

- Heart Rate (HR) and SBP/DBP, as measured by continuous monitoring from the selection visit (ASS2) and throughout the ivabradine infusion; a print-out was performed at selection (ASS2), baseline (H000) and every 30 minutes until the last visit under treatment (*i.e*. up to a maximum of 48 hours). Mean Arterial Pressure (MAP) was calculated,
- Haemodynamic parameters, as measured with the Swan-Ganz catheter and echocardiography.
  - Swan-Ganz catheter was inserted before surgery. Pulmonary Wedge Capillary Mean Pressure (PCWP), Stroke Volume (SV), Mixed Venous Saturation (SvO2) and Right Atrial Pressure (RAP) were measured and cardiac Output (CO), Cardiac Index (CI), and Systemic Vascular Resistance (SVR) were calculated. These measurements and calculations were performed at the selection visit (ASS2), at baseline (H000) and then every hour during the three first hours and then every three hours until the last visit under treatment (*i.e.* up to a maximum of 48 hours),
  - Two-dimensional trans-thoracic echocardiography (or transoesophageal if necessary) was performed at the pre selection visit if not availability of a previous one within the month before the pre-selection, at inclusion visit (H000), at the last visit under treatment, at the post visit and at the follow up visit: end systolic and diastolic volumes were assessed, and the ejection fraction was calculated.
- Diuresis and the creatinin clearance (Crockroft method).
  - Diuresis: assessment at inclusion visit (H000) for the period [ASS2-H0], every hour until H6 and then every 6 hours:]H0, H1[, [H1, H2[, [H2, H3[,[H3, H4[, [H4, H5[, [H5, H6[, [H6, H12[, [H12, H24[, [H24, H30[, [H30, H36[, [H36, H42[, [H42, H48[, or [Hx, Hlast visit under treatment[,

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- Creatinin clearance: assessment at pre selection (ASS1), selection (ASS2), inclusion (H000) and then every 6 hours: H6, H12, H18, H24, H30, H36, H42 and H48 or last visit under treatment and post visit,
- Lactate: assessment at pre-selection (ASS1), selection (ASS2), inclusion (H000) and then every 6 hours: H6, H12, H18, H24, H30, H36, H42 and H48 or last visit under treatment,

Cardiac monitoring:

- A continuous 2-lead Holter recording to assess ventricular arrhythmias was initiated at the selection visit (ASS2) for baseline evaluation and throughout the ivabradine infusion up to the last visit under treatment (*i.e.* up to a maximum of 48 hours).
- Troponin Ic: assessment at pre-selection (ASS1), selection (ASS2), inclusion (H000) and then every 6 hours: H6, H12, H18, H24, H30, H36, H42 and H48 (or last visit under treatment), and post visit.

Other parameters assessed:

- Body temperature: assessment at pre-selection (ASS1), selection (ASS2), inclusion (H000) and every hour during the three first hours and then every three hours until the last visit under treatment (*i.e.* up to a maximum of 48 hours),
- Maximal dose of dobutamine administered,
- Total dose of dobutamine administered,
- Total assisted ventilation (invasive and non-invasive) time duration,
- Pharmacokinetic (three samples) measurements: assessment at 30 minutes and at 4 hours after inclusion and at the end of ivabradine/placebo treatment (*i.e.* the last visit under treatment).

At the hospital discharge, an echography was performed.

Safety measurements:

- 12-lead ECG at rest (supine position for at least 10 minutes) before or at pre-selection visit (ASS1), and at follow-up visit (VEND). The ECG tracings were identified by date, visit name, patient and centre number, and birth date.

Adverse events (AEs): any clinically significant abnormality of all measured biological parameters not previously observed.

Statistical methods:

This study was an exploratory study with only descriptive analyses. Analyses were performed by treatment group on patients of the Included Set (IS). (Some demographic characteristics are provided on patients of the Non-Included Set [NIS]) Complementary descriptive analyses (study outcome and efficacy) were performed in a newly defined Per Protocol Set (PPS): patients having cardiac index $\leq$ 2.2 l/min/m², dobutamine intake < 30 min before selection, ivabradine received prior to 3 days before pre-selection.

Study outcome: descriptive analyses were provided.

Evaluations:

Primary criterion

The percentage of patient responders, *i.e.* patients whose HR was within the range of 80 to 90 bpm for at least 30 minutes during study treatment administration and/or allowing an increase of the inotropic treatment with dobutamine were provided by treatment group.

Secondary criteria

Descriptive statistics were performed by treatment group on haemodynamic parameters, Holter and 12-lead ECG over the treatment period. For some quantitative parameters with repeated measurements, profiles over time were provided.

Safety analyses: descriptive statistics were provided for AEs and electrocardiogram (ECG).

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 48 patients were screened and 26 were selected for the study. Among them, 19 patients were included and randomly assigned to one of the two groups: 14 patients in the ivabradine group and 5 patients in the placebo group, with the planned unbalanced distribution (3:1) reached. These patients comprised the IS. In the IS, 14 patients received ivabradine or matching placebo as an initial bolus over 5 minutes (11 patients in the ivabradine group and 3 patients in the placebo group) followed by continuous infusion of ivabradine or matched placebo over 24 hours for a maximum duration of 48 hours. Following Amendment No. 3, 3 patients in the ivabradine group and 2 patients in the placebo group received a fast infusion over 1 hour followed by continuous infusion of ivabradine or matched placebo over 24 hours for a maximum duration of 48 hours.

The PPS consisted of 14 patients (73.7% of the IS). Of the 5 patients excluded, 2 patients were excluded due to a treatment with ivabradine within 3 days before pre-selection (ASS1), 2 patients were excluded due to CI values > 2.2 L/min/m2 (main selection criteria), and one patient was excluded for treatment with dobutamine more than 30 minutes before the selection (ASS2) visit.

Disposition of included (randomised) patients by group

STATUS	**ALL (N = 19)**	**Ivabradine (N = 14)**	**Placebo (N = 5)**
Included (randomised) – Included Set	19	14	5
In conformity with the protocol	6	6	-
With protocol deviation(s) before or at inclusion	13	8	5
Completed	15	10	5
In conformity with the protocol	12	7	5
With protocol deviation(s) after inclusion	3	3	-
Withdrawn due to:	4	4	-
Adverse event	3	3	-
Protocol deviation	1	1	-
Per Protocol Set (PPS)	14	11	3

N number of patients in the treatment group

Overall, a total of 4 patients (21.1%) were withdrawn. A total of 15 patients (78.9%) completed the study (10 in the ivabradine group and 5 in the placebo group), of which 12 (7 in the ivabradine group and 5 in the placebo group) were in compliance with the study protocol.

The mean age (± SD) of the patients in the IS was 60.6 ± 7.1 years (range 49 to 74 years) and most patients (84.2%) were men. Mean body mass index (BMI) (± SD) was 27.3 ± 3.1 kg/m² (range 21.6 to 34.3 kg/m²). All patients had undergone coronary angiography. The coronary lesions concerned 3 vessels for 31.6% of the patients; 4 vessels for 36.8 %; 5 vessels for 15.8 %, and 6 vessels for 10.5 %. Overall, 11 patients (57.9%) had a history of myocardial infarction and 5 (26.3%) had a history of coronary angioplasty. All patients in the IS reported a specific medical history other than CAD. The most frequently reported histories were dyslipidaemia (11 patients, 68.4%), hypertension (12 patients, 63.2%), cardiac heart failure (10 patients, 52.6%), and diabetes mellitus (9 patients, 47.4%). Most patients (68.4%; 13 patients [11 in the ivabradine group and 2 in the placebo group]) had histories of surgical and medical procedures for diseases other than CAD. Previous treatments for CAD were mainly beta-blockers (94.7%), diuretics (89.5%) and ACE inhibitors (84.2%). The mean HR at pre-selection visit was 78.1 ± 18.2 bpm. The overall mean SBP was 123.1 ± 17.4 mmHg and the overall mean DBP was 70.9 ± 11.6 mmHg, with no significant differences between groups. No relevant differences between groups were observed for baseline characteristics except for mean LVESV, which was lower in the ivabradine group (95.6 ± 30.6 mL) than in the placebo group (124.0 ± 5.7 mL).

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Demographic and other baseline characteristics showed same trends in the PPS. To note in the PPS, mean age was 61.9 ± 7.0 years in the ivabradine group and 54.7 ± 3.8 years in the placebo group, and heart rate was 73.4 ± 12.0 bpm and 86.7 ± 35.8 bpm, respectively.

In the IS, the mean treatment duration with the study drug from the start of bolus/fast infusion to the end of the continuous slow infusion was higher in the ivabradine group (25.2 ± 14.6 hours) than in the placebo group (15.3 ± 16.7 hours). Treatment duration was between 1.4 and 46.0 hours in the ivabradine group and between 0.8 and 42.8 hours in the placebo group. Seven patients in the ivabradine group and 1 patient in the placebo group were treated for at least 24 hours. The mean total dose of study drug administered was 22.1 ± 7.3 mg (range 10.6 mg and 35.4 mg) in the ivabradine group, with an equivalent of 20.2 ± 8.6 mg in the placebo group. In the PPS, the mean treatment duration was also higher in the ivabradine group than in the placebo group: 27.8 ± 14.7 hours *versus* 20.6 ± 20.2 hours, respectively. The mean total dose of study drug administered was similar to that described for the IS. Due to the low number of patients in each group, especially in the placebo group, the differences between the two groups should be interpreted with caution.

In the IS, the mean duration of dobutamine administration was longer in the ivabradine group (28.9 ± 13.2 hours) than in the placebo group (18.9 ± 16.2 hours) and the mean total dose of dobutamine was higher in the ivabradine group (897.7 ± 396.5 mg) than in the placebo group (619.0 ± 543.2 mg). Similar results were observed in the PPS; the mean duration of dobutamine administration was longer in the ivabradine group (31.5 ± 12.7 hours *versus* 25.1 ± 18.3 hours, respectively), and the mean total dose of dobutamine was higher (908.8 ± 330.2 mg versus 699.0 ± 633.5 mg, respectively).

EFFICACY RESULTS

- **Primary evaluation criterion**

The primary endpoint of the study was the percentage of the patient responders in each treatment group. Responders were patients whose HR fell during the ivabradine/placebo infusion to within 80 to 90 bpm, and which either lasted for at least 30 minutes or allowed the dosage of the dobutamine inotropic treatment to be subsequently increased.

Number and percentage of patient responders by treatment group in the Included Set

			Ivabradine (N = 14)	**Placebo (N = 5)**
Patient responders	ALL	n_{obs}	14	5
	NO	n(%)	1 (7.14)	3 (60.00)
	YES	n(%)	13 (92.86)	2 (40.00)
Heart rate within [80; 90] bpm for at least 30 minutes during study treatment period	ALL	n_{obs}	14	5
	NO	n(%)	1 (7.14)	3 (60.00)
	YES	n(%)	13 (92.86)	2 (40.00)
Heart rate within [80; 90] bpm allowing an increase of the dobutamine dose administration	ALL	n_{obs}	14	5
	N/A	n(%)	8 (57.14)	5 (100)
	NO	n(%)	4 (28.57)	-
	YES	n(%)	2 (14.29)	-

N = number of patients in treatment group, n_{obs} = number of observable patients, n = number of patients, % = (n/n_{obs}) x 100.
[1]N/A refers to patients whose dobutamine dosage was not increased or was increased before the start of study drug treatment.

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Results in the IS

There were a total of 13 responders (92.9%) in the ivabradine group and 2 responders (40.0%) in the placebo group. One patient in the ivabradine group whose HR during treatment was < 80 bpm was not considered as a responder and was withdrawn due to sinus bradycardia. Thirteen patients in the ivabradine group had HRs between 80 and 90 bpm which persisted for at least 30 minutes; 2 of these patients had their dobutamine dosages increased as a result of a reduced HR. In the placebo group, two patients had HRs between 80 and 90 bpm which lasted for at least 30 minutes, however the reduction of HR did not allow an increase of the dobutamine dosage in this group.

Results in the PPS

In the PPS, all 11 patients (100%) treated with ivabradine were considered as responders whereas only 1 of the 3 patients (33.3%) treated with placebo was a responder. Among the responders in the ivabradine group, investigators were able to increase dobutamine dosage in 2 patients because reduced HR allowed this up-titration. No patient in the placebo group had his dobutamine dosage increased.

- **Secondary evaluation criteria**

At inclusion, all patients in the IS had an HR ≥ 100 bpm, with the mean HR equal to 111.9 ± 8.2 bpm in the ivabradine group and 111.8 ± 9.2 bpm in the placebo group. During the study drug treatment period, the time to reach a HR of < 90 bpm (the HR criterion that defined responders) appeared to be shorter in the ivabradine group (2.0 ± 2.5 hours) than in the placebo group (5.7 ± 0.3 hours). Mean HR under treatment was lower in the ivabradine group (88.9 ± 8.6 bpm) than in the placebo group (106.8 ± 14.1 bpm) and the last HR value under treatment was also lower in the ivabradine group (85.6 ± 10.8 bpm) than in the placebo group (103.6 ± 14.7 bpm).

At baseline selection, when patients were experiencing LCOS, mean SBP and mean DBP were similarly low in both groups. At inclusion under inotropic treatment with dobutamine, mean SBP and mean DBP had increased in both groups: in the IS, the mean SBP was similar in both groups (108.8 ± 21.2 mmHg in the ivabradine group and 109.8 ± 21.7 mmHg in the placebo group) whereas mean DBP was higher in the ivabradine group (66.4 ± 20.2 mmHg) than in the placebo group (55.3 ± 9.9 mmHg). At the end of the study treatment, the last SBP and DBP values remained slightly higher in the ivabradine group (127.6 ± 19.7 mmHg and 57.6 ± 8.6 mmHg, respectively) than in the placebo group (107.6 ± 26.5 mmHg and 53.8 ± 14.7 mmHg, respectively).

Echocardiography-based assessments were obtained for only a limited number of patients in each group mainly due to technical and organisational reasons. Due to the very few patients for whom these data were collected, no clear conclusions could be drawn.

Haemodynamic parameters during the study were determined using Swan-Ganz catheters inserted prior to surgery. In the IS, mean values for CO, CI, SV, CPI and LVSWI increased between inclusion and the end of treatment for the ivabradine group and for the placebo group. Mean SVR decreased in both groups between inclusion and the end of treatment. Mean PCWP remained relatively stable over the treatment period in the ivabradine group but decreased in the placebo group; mean RAP tended to decrease in the ivabradine group but increased in the placebo group. Mean SvO2 remained unchanged during the treatment period but tended to be lower in the ivabradine group than in the placebo group both at inclusion and last value under treatment. Similar results were observed in the PPS. These haemodynamic and cardiac function parameters indicate that the positive inotropic effects of dobutamine treatment were not adversely affected by ivabradine, despite the reductions in HR. Regarding the global pharmacodynamic profile, a tendency for a favourable effect was observed in patients treated with ivabradine, as shown by the increases in SV, CO, CI, CPI, LVSWI and the decreases in RAP and SVP. This favourable effect was confirmed in a subset of patients whose dobutamine dose was not increased during the treatment period; these results need to be interpreted with caution due to the low number of patients in each group.

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The most frequently recorded abnormalities detected on Holter 2-lead ECG were VES and SVES. Eighteen patients (14 [100%] in the ivabradine group and 4 [80.0%] in the placebo group) reported at least one VES. In the ivabradine group, 11 patients reported at least one VES during P1; 14 during P2 and 13 during P3. In the placebo group, 3 patients reported at least one VES during P1, 3 during P2 and 4 during P3. Seventeen patients (13 [92.9%] in the ivabradine group and 4 [80.0%] in the placebo group) reported at least one SVES. In the ivabradine group, 11 patients reported at least one SVES during P1; 13 during P2 and 11 during P3. In the placebo group, 2 patients reported at least one SVES during P1, 3 during P2 and 4 during P3. At least one VT, at least one SVT, and at least one atrial fibrillation were reported by 2 patients each in the ivabradine group. VT was reported by both patients during P1, by 1 patient during P2 and by 1 patient during P3. SVT was reported by 1 patient during P2 and by 1 patient during P3. Atrial fibrillation was reported by both patients during P3. At least one accelerated idioventricular rhythm and at least one VF were reported by one patient each in the ivabradine group; both accelerated idioventricular rhythm and VF were reported during P1. No atrial flutter, AV block, pauses, or bradycardia was detected on Holter 2-lead ECG recordings.
The variations in creatinine clearance and serum lactate and troponin Ic concentrations were as expected, and were the result of the LCOS and subsequent cardiac injury due to surgery. Only one patient in the ivabradine group (who later died from septic shock, intestinal ischaemia and bradyarrythmia) had serum troponin Ic concentrations that were clinically abnormal. No clinically relevant changes in body temperature occurred during the study.
Results obtained in the PPS showed same trends.

SAFETY RESULTS
All patients in the IS received at least one dose of study drug and were included in the safety analysis. Safety assessments consisted of the collection of AEs and 12-lead ECG recordings.

Adverse events. Overall, a total of 34 AEs were reported for a total of 14 patients during the study period. Of these events, 32 were treatment-emergent adverse events (EAEs). In the ivabradine group, 26 EAEs were reported for 9 of the 14 patients, with 16 EAEs reported for 2 patients. In the placebo group, 6 EAEs (17.6%) were reported for 4 (80.0%) of the 5 patients. Overall, the most frequently reported EAEs by preferred term were atrial fibrillation (5 patients in the ivabradine group *versus* none in the placebo group), heart rate decrease (2 patients *versus* none, respectively), and hypotension (2 patients *versus* none, respectively). The outcome of most events was reported as recovered. A total of 3 EAEs were considered related to the study treatment (2 patients with heart rate decreaseand 1 patient with sinus bradycardia), all 3 occurred in the ivabradine group. A total of 8 SAEs were reported for 3 patients in the ivabradine group but none were related to the study treatment. One death (following septic shock, intestinal ischaemia, and hypotension considered as not related to the study treatment) occurred in the ivabradine group.

Overall summary of safety results

		Ivabradine (N = 14)	**Placebo (N = 5)**	**All (N = 19)**
Number of patients reporting:				
Emergent adverse event (EAE)	n (%)	9 (64.3)	4 (80.0)	13 (68.4)
EAE, related to treatment	n (%)	3 (21.4)	-	3 (15.8)
SEAE (including death)	n (%)	2 (14.3)	-	2 (10.5)
SEAE, related to treatment	n (%)	-	-	-
Patients discontinuing treatment due to treatment-related EAE	n (%)	2 (14.3)	-	2 (10.5)
Patients who died	n (%)	1 (7.1)	-	1 (5.3)

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Overall, 3/19 (15.8%) patients experienced at least one EAE rated as severe; all were in the ivabradine group. These events consisted of renal impairment and metabolic acidosis not related to the study treatment in 1 patient; pneumonia and sepsis not related to the study treatment in 1 patient; and decreased HR related to study treatment in 1 patient.

The 3 AEs that led to study withdrawal were atrial fibrillation and bradyarrhythmia not related to study treatment in 1 patient who did not recover, and sinus bradycardia in 2 patients both of whom recovered. The single death in the ivabradine group was subsequent to SAEs that occurred 5 days after treatment. None of the events leading to death were considered as having a relationship with the study treatment, according to the investigator.

12-lead ECG recordings and abnormalities. A total of 41 ECG abnormalities were reported for 13 (92.9%) patients in the ivabradine group. A total of 12 ECG abnormalities were reported for 4 (80.0%) patients in the placebo group. None of the abnormalities in either group were of clinical significance.

CONCLUSIONS

In conclusion, this exploratory Phase II study, conducted in CABG patients experiencing LCOS, showed that the frequency of responders was higher in the ivabradine group than in the placebo group: 92.9% *versus* 40.0%, respectively (*i.e.* patients with HR within the range of 80 to 90 bpm for at least 30 min, and/or allowing an increase of the inotropic treatment with dobutamine). Ivabradine treatment during inotropic dobutamine therapy induced clinically relevant reductions in HR without disrupting the inotropic effects of dobutamine. Safety results were in accordance with the known safety profile of ivabradine.

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