Document title	**Clinical Study Report Synopsis**
Study title	**Evaluation *versus* placebo of the effects on heart rate, haemodynamic parameters, safety and tolerability of 5 mg bolus of ivabradine followed by 8-hour infusion of 5 mg of ivabradine, given to patients undergoing a percutaneous coronary intervention following a myocardial infarction with ST segment elevation (STEMI). A pilot, blind, randomised, placebo-controlled, international, multi-centre study. Including the ancillary MRI sub-study.**
Study drug	**S 16257 Ivabradine**
Studied indication	**Acute Myocardial Infarction**
Development phase	**Phase II**
Protocol code	**CL2-16257-060**
Study initiation date	**19 May 2006**
Study completion date	**20 April 2009**
Coordinators	[redacted] **Spain** [redacted] **France**
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 26 May 2010**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study:
Evaluation *versus* placebo of the effects on heart rate, haemodynamic parameters, safety and tolerability of 5 mg bolus of ivabradine followed by 8-hour infusion of 5 mg of ivabradine, given to patients undergoing a percutaneous coronary intervention following a myocardial infarction with ST segment elevation (STEMI).
A pilot, blind, randomised, placebo-controlled, international, multi-centre study. Including the ancillary MRI sub-study.
Protocol No.: CL2-16257-060-INT

International coordinators:
[redacted] - FRANCE
[redacted] - SPAIN

Study centres:
A total of 24 centres in 5 countries included at least 1 patient: France (9 centres), Germany (7 centres), Spain (4 centres), Belgium (2 centres), Australia (2 centres).

Publication (reference): Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 19 May 2006 Completion date: 20 April 2009	Phase II

Objectives:
The primary objective of this pilot study was to evaluate the effect of ivabradine *versus* placebo (as modified by Amendment No. 1) on heart rate (HR) and haemodynamic parameters given, to patients having undergone (or undergoing; following Amendment No. 5), a percutaneous coronary intervention (PCI) following an acute myocardial infarction with ST segment elevation (STEMI).
The secondary objectives were to assess in these patients, the safety and tolerability of ivabradine *versus* placebo (as modified by Amendment No. 1), the pharmacokinetics of ivabradine and its active metabolite (S 18982) as well as the relationship between the pharmacokinetics and the pharmacodynamics (HR at rest obtained during ECG and continuous ECG monitoring).
The main objective of the Magnetic Resonance Imaging (MRI) sub-study (Amendment No. 7) was to evaluate the effects of ivabradine *versus* placebo on myocardial infarcted tissue size at 4 months post-STEMI.
Additional objectives of the sub-study included the evaluation of the effect of ivabradine on infarcted tissue size (area of delayed hyperenhancement) prior to discharge, microvascular obstruction (no-reflow) prior to discharge, LVESV, LVEDV and LVEF (MRI) prior to discharge and at 4 months post-STEMI and regional myocardial contractility (MRI) prior to discharge and at 4 months post-STEMI.

Methodology:
International, multi-centre, randomised, blind, placebo-controlled, unbalanced parallel groups and phase II study (this methodology was introduced by Amendment No. 1), performed in hospitalised patients. Study duration was at least 3 days: Day 1: Selection / Inclusion (P000) and study drug administration (P001); Day 2 (P002); Day 3 (P003); and Day of discharge (PEND). Clinical investigations were mostly concentrated in the 12-hour period following drug administration, with follow-up examinations on P002, P003 and PEND.
In patients enrolled in the sub-study (performed in selected centres) an MRI (Magnetic Resonance Imaging) was performed prior to hospital discharge, followed by a second MRI 4 months later.

Number of patients:
Planned: 75 patients (50 patients on ivabradine, 25 patients on placebo). Following Amendment No. 7 and the addition of the sub-study the planned totals were 120 patients overall, 80 patients on ivabradine and 40 patients on placebo.
Included: 124 patients (82 on ivabradine, 42 on placebo).
The MRI sub-study: Planned: 45 patients (30 *versus* 15); Included: 48 (32 *versus* 16).

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Diagnosis and main criteria for inclusion:

Male or female patients aged from 40 to 80 years, having undergone (or undergoing; Amendment No. 5) a PCI following a STEMI (with an onset in the previous 9 hours before selection). The PCI was to be carried out less than six hours after the onset of chest pain. HR (in sinus rhythm) was to be > 80 bpm and systolic blood pressure > 90 mmHg, as recorded twice (12-lead electrocardiogram (ECG) and sphygmomanometer) within 10 minutes before treatment administration.

Patients enrolled in the MRI sub-study were to have Glomerular Filtration Rate (GFR) ≥ 60 mL/min/1.73 m² (Amendment No. 8).

Study drug:

Intravenous ivabradine 2 mg/mL. For the bolus dose, 2.5 mL (5 mg) was injected and this was immediately followed by an 8-hour infusion of 5 mg ivabradine diluted to a volume not exceeding 50 mL.

Reference product:

Matched placebo.

Duration of treatment:

8-hour continuous perfusion.

Criteria for evaluation:

- *Efficacy measurements:*
  - Heart rate (HR) as measured by 12-lead ECG (4 assessments in P001, then 1 on P003 and 1 at PEND) and continuous ECG monitoring (in P001, from time of study drug administration until 24 hours later).
  - Echocardiography parameters, including left ventricular (LV) end-diastolic volume (LVEDV, mL), LV end-systolic volume (LVESV, mL) and LV ejection fraction (LVEF, %): optional assessment at P000 and at least one assessment between 6 and 48 hour post study drug administration (following Amendment No. 5).
  - Cardiac proteins: CK-MB (µg/L), troponins (TnI and TnT; µg/L) on 1 blood sample at P000, 5 during P001 and one at P002. Also B-type Natriuretic Peptide (BNP; pmol/L) on one blood sample at H5 (5 hours post study drug administration) in P001 (analyses were made in a central laboratory).

  In the MRI sub-study (on centralised reading):
  - At both MRI visits: Infarct size (g; estimated from area of delayed hyperenhancement), and measures of cardiac function (LVEF, cardiac output…) and (at PEND only) area at risk and microvascular obstruction (no-reflow).
- *Safety measurements:*

Adverse events, vital signs at rest (systolic and diastolic blood pressure) and 12-lead ECG parameters including abnormalities.

Pharmacokinetic measurements (central laboratory) were made [redacted]

Statistical methods:

Efficacy analyses:

Efficacy analyses were carried out on patients of the Full Analysis Set (FAS; patients exposed to treatment and having at least 2 reliable HR evaluations, one at baseline and one post-baseline) and on patients of the Per Protocol Set (PPS; all patients of the FAS without deviation affecting the efficacy assessment).

For HR, descriptive statistics by treatment group were performed at each measurement time, with the changes from baseline to each post-baseline measurement time and between baseline and last value over the treatment period (P001). Ivabradine was compared to placebo on the 12-lead ECG assessments using 95% confidence intervals from a parametric method based on the Student distribution and from a non-parametric method based on the Hodges-Lehmann estimator. Graphical presentations of HR over time were produced.

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Statistical methods (Cont'd):

Efficacy analyses (Cont'd):

For echocardiography, descriptive statistics by treatment group were performed at each measurement time. Analyses were made on the baseline value (P000) and the post-baseline value (with 24 hours and over the study). Treatment effect (ivabradine *versus* placebo) was estimated on last value using the same statistical approach as for HR. In fully documented patients the change was calculated between last value and baseline.

For cardiac enzymes, descriptive statistics of troponin I, troponin T and CK-MB were performed by treatment group at each measurement time and according to the total area under the curve (AUC) over the 24 hours following study drug administration. Figures of concentration *versus* time were provided. For BNP, descriptive statistics were performed by treatment group at H5 (including distribution by class interval (≤ 80 pg/mL / > 80 /mL). A figure of concentration *versus* time (FAS) was provided.

In the sub-study, the efficacy analysis was performed on the FAS-MRI and PPS-MRI.
For each parameter, descriptive statistics by treatment group were performed at each measurement time and on change between 4-month post-STEMI value and PEND value.
Ivabradine and placebo were compared using parametric and non-parametric 95% confidence intervals on PEND value, and then on 4-month post-STEMI value. The 95% confidence interval was calculated using the same methodology as those described for the main study.

Safety analyses:

Safety analyses were performed on patients of the Safety Set.
Descriptive statistics were provided at each measurement time for haemodynamic parameters and for parameters collected during 12-leads ECG (other than HR). Emergent abnormalities and adverse events were described.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

From a total of 126 patients selected, 124 were included and randomised in the main study, with 82 in the ivabradine group and 42 in the placebo group. In the sub-study, a total of 48 patients were included, with 32 in the ivabradine group and 16 in the placebo group.

Disposition of included (randomised) patients by group and Analysis Sets

		Ivabradine	Placebo	All
Included (randomised)	n	**82**	**42**	**124**
Lost to Follow-up	n	-	-	-
Withdrawn	n (%)	3 (3.7)	2 (4.8)	5 (4.0)
due to adverse event	n	2	-	2
due to non-medical reason	n	1	2	3
Completed	n (%)	**79 (96.3)**	**40 (95.2)**	**119 (96.0)**
Full Analysis Set (FAS)	n (%)	81 (98.8)	40 (95.2)	121 (97.6)
Per Protocol Set (PPS)	n (%)	67 (81.7)	36 (85.7)	103 (83.1)
Safety Set	n (%)	82 (100)	41 (97.6)	123 (99.2)
Included Set-MRI (IS-MRI)	n (%)	32 (39.0)	16 (38.1)	48 (38.7)
FAS-MRI	n (%')	26 (81.3)	14 (87.5)	40 (83.3)
PPS-MRI	n (%')	21 (65.6)	13 (81.3)	34 (70.8)

Note: One patient (placebo) was excluded from the Safety Set because no study drug was administered
%: % of the Randomised Set; %': % of Included Set-MRI
RS: Randomised Set

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SUMMARY - CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

Patients were on average 59.4 ± 11.0 years old. Most were male (78.2%) and BMI was on average 27.2 ± 3.5 kg/m². Most patients did not smoke (61.3%). As required by the protocol, all patients had a STEMI followed by a PCI at the time of study entry. Most (96.0%) had an angioplasty with stent implantation the remainder received balloon angioplasty). For 62.1% of the population the CAD concerned a single vessel; for 22.6% 2 vessels were concerned; and for 15.3% 3 vessels were concerned. The incidence of previous MI was 9.8% in the ivabradine group *versus* 2.4% in the placebo group.

Most patients had concurrent medical conditions, with 54.0% having metabolism and nutrition disorders (mainly lipid metabolism disorders 41.1% or diabetes 18.5%) and 49.2% having vascular disorders (mainly hypertension 47.6%). There were somewhat lower frequencies of patients in the ivabradine group than in the placebo group with lipid metabolism disorders (36.7% vs 50.0%, respectively), hypertension (40.2% *versus* 61.9%, respectively) and diabetes (15.9% *versus* 23.8%, respectively).

The background treatments at inclusion were mainly antithrombotic agents (91.1%), statins (60.5%) and organic nitrates (58.9%). Beta-blocking agents were more frequently used by patients in the placebo group (26.8% *versus* 42.9%).

The mean baseline HR was 87.8 ± 9.3 bpm. Mean LVEDV and LVESV were respectively 105.3 ± 40.4 mL and 55.9 ± 30.4 mL (assessed in 33 patients) and mean LVEF was 49.1 ± 12.5% (assessed in 41 patients) without relevant differences between groups. No relevant between-group differences were seen on cardiac proteins at baseline.

The mean duration between the STEMI (onset of chest pain) and the PCI was about 3½ hours (215.0 ± 105.3 min) and the mean duration between the PCI and the bolus injection just under 2 hours (111.7 ± 68.6 min).

The mean total dose was 10.2 ± 2.3 mg in the ivabradine group *versus* 10.2 ± 1.9 mg in the placebo group. The bolus dose was administered to all patients except one in placebo group (123 patients) and the infusion was started in 122 patients (1 patient in the placebo group withdrawn).

A total of 48 patients were included into the sub-study: 32 in the ivabradine group and 16 in the placebo group. 43 patients (89.6%) completed the sub-study: 5 patients (4 *versus* 1) having withdrawn for non-medical reason before the 4-month follow-up visit.

The main demographic and baseline characteristics of the IS-MRI were similar to the RS, except that diabetes was more frequently reported in the ivabradine group than in the placebo group (23.1% *versus* 14.3%). Patients were on average 58.4 ± 10.7 years old. Most were male (79.2%) and BMI was on average 27.9 ± 3.3 kg/m²; none had a previous myocardial infarction. The mean baseline HR was 86.2 ± 7.1 bpm.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS

- **Primary assessment criterion: HR on 12-lead ECG**

The mean change in HR over the treatment period in ivabradine group was -22.0 ± 11.8 bpm (see Table) *versus* -8.9 ± 11.4 bpm in the placebo group. The estimated between-group difference in favour of ivabradine was -13.1 bpm (95% CI: [-17.5 ; -8.6]), indicating a clinically relevant (and statistically significant) difference in HR reduction.

HR on 12-lead ECG – Baseline and change over treatment period in the FAS

HR (bpm)		**Ivabradine (N = 81)**	**Placebo (N = 40)**
Baseline	n	81	40
	Mean ± SD	88.2 ± 9.8	87.2 ± 8.1
	Min - Max	64 - 137	69 - 113
Change			
last value in	Mean ± SD	-22.0 ± 11.8	-8.9 ± 11.4
P001 - Baseline	Min - Max	-75 - 13	-41 - 14
Statistical Analysis	Estimate (1)	-22.0 (1.3)	-8.9 (1.8)
	95% CI (2)	[-24.6 ; -19.4]	[-12.6 ; -5.2]
	Diff Adj Estimate (3)	-13.1 (2.3)	
	95% CI (4)	[-17.5 ; -8.6]	

(1) Estimate (Standard error) of the change in each group
(2) 95% CI of change in each group
(3) Estimate (Standard error) of the change difference: ivabradine minus placebo
(4) 95% CI of the change difference

These mean changes were confirmed by the non-parametric approach in the FAS as well as by the results in the PPS.

- **Primary assessment criterion: HR on continuous ECG monitoring**

The results were similar to those described on the 12-lead ECG The mean change (baseline to last value in P001) was -19.3 ± 10.9 bpm in the ivabradine group *versus* -8.4 ± 11.6 bpm in the placebo group.

- **Secondary assessment criteria**

Echocardiographic changes:

Mean LVEDV was slightly lower in ivabradine-treated patients than in placebo-treated patients at last value after bolus administration (102.4 ± 36.3 mL *versus* 110.4 ± 29.8 mL, respectively; medians: 99.0 *versus* 107.0). The mean values were similar in the 2 treatment groups for LVESV (54.4 ± 28.2 mL *versus* 55.0 ± 19. 6 mL, respectively) and LVEF (51.4 ± 12.1% *versus* 51.7 ± 11.2%, respectively).

In the fully documented patients in the FAS (*i.e.* patients having both pre- and post-bolus evaluations) these was a trend to clinically relevant reductions in left ventricular volumes in the ivabradine group *versus* the placebo group over the study (see table), suggesting a better preservation of cardiac function in the ivabradine group. Very similar results were observed in the PPS.

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SUMMARY - CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

LVEDV, LVESV and LVEF: Baseline, last post-baseline value and change between assessments - FAS

	Ivabradine (N = 81)			**Placebo (N = 40)**		
	Baseline	**Last value***	**Change**	**Baseline**	**Last value***	**Change**
LVEDV (mL)						
n	18	18	**18**	8	8	**8**
Mean ± SD	106.7 ± 41.0	87.1 ± 28.2	**-19.6 ± 33.4**	114.9 ± 45.3	117.8 ± 21.4	**2.9 ± 33.0**
Median	96.0	78.0	**-8.5**	121.5	113.5	**3.0**
LVESV (mL)						
n	17	17	**17**	8	8	**8**
Mean ± SD	58.1 ± 33.7	42.5 ± 19.0	**-15.5 ± 21.8**	61.3 ± 30.6	59.1 ± 11.3	**-2.2 ± 24.2**
Median	50.0	36.0	**-12.0**	52.9	63.5	**-2.9**
LVEF (%)						
n	23	23	**23**	11	11	**11**
Mean ± SD	48.2 ± 11.9	50.4 ± 10.7	**2.2 ± 8.5**	48.5 ± 13.6	49.0 ± 13.0	**0.6 ± 5.2**
Median	50.0	53.0	**5.0**	45.0	54.0	**0.0**

**Last value after bolus administration; N: Number of patients in treatment group; n: Number of evaluable patients*
SD: standard deviation

Cardiac proteins: The mean 24-hour AUC (following bolus) for CK-MB, TnI, and TnT were lower in the ivabradine group than in the placebo group (µg/L.hour: 2624.1 *versus* 2739.4; 1851.4 *versus* 1918.7 and 102.8 *versus* 133.3, respectively). The mean value for plasma BNP at H5 was 123.6 ± 175.8 pg/mL (median: 72.3 pg/mL) in the ivabradine group *versus* 83.7± 90.4 pg/mL (median: 61.3 pg/mL) in the placebo group. Similar results were observed in the PPS.

- **MRI sub-study: HR on 12-lead ECG, infarct size and global LV function**

In the FAS-MRI, the mean changes in HR on 12-lead ECG over the treatment administration period were similar to those seen in the FAS, *i.e.* –20.2 ± 10.8 bpm in the ivabradine group *versus* –12.9 ± 14.7 bpm in the placebo group. At PEND, the MRI examination revealed that the area of delayed hyperenhancement (indicative of the infarcted volume, % of LV mass) was smaller in the ivabradine group than in the placebo group: 12.7 ± 9.6% *versus* 17.2 ± 10.1%, respectively. The mean relative area at risk, evaluated in 15 patients in the ivabradine group and 10 patients in the placebo group was similar in the 2 treatment groups (30.6 ± 17.4% *versus* 29.6 ± 13.2%). At the 4-month follow-up MRI, the difference between the mean relative infarct sizes in the 2 groups was negligible (9.9 ± 8.2% *versus* 9.7 ± 8.4%).

The left ventricular ejection fraction (51.5 ± 12.2% *versus* 50.7 ± 12.4%) and volumes were similar in both treatment groups at discharge with a slight trend to reduced volumes in the ivabradine group (146.4 ± 36.0 mL *versus* 151.1 ± 32.3 mL and 70.9 ± 23.9 mL *versus* 75.8 ± 29.5 mL for LVEDV and LVESV, respectively. No differences were observed at PM04 with ejection fractions or volumes.

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS

Main safety results are summarised in the table below.

Overall summary of safety results - Safety Set

		Ivabradine (N = 82)	**Placebo (N = 41)**
During the treatment period (bolus + 2 days) - Patients having reported at least one:			
EAE	n (%)	46 (56.1)	17 (41.5)
severe EAE	n (%)	6 (7.3)	-
treatment-related EAE	n (%)	7 (8.5)	1 (2.4)
treatment-related severe EAE	n (%)	1 (1.2)	-
serious EAE	n (%)	5 (6.1)	-
treatment-related serious EAE	n (%)	1 (1.2)	-
Patients withdrawn due to an adverse event	n (%)	2 (2.4)	-
Patients who died	n (%)	2 (2.4)*	-

n: number of patients concerned; % = (n/N) x 100

** More than 48 hours after study drug administration*

During the treatment period (between the start of the bolus injection and 2 days later), a total of 63 patients (51.2%) reported at least one emergent adverse event: 46 patients (56.1%) in the ivabradine group *versus* 17 patients (41.5%) in the placebo group. The most frequently reported SOCs were *cardiac disorders* (25.6% *versus* 19.5%), *nervous system disorders* (9.8% *versus* 4.9%) and *musculoskeletal and connective tissue disorders* (8.5% *versus* 4.9%). The most frequent EAEs were ventricular tachycardia (VT; 11.0% *versus* 9.8%) headache (4.9% *versus* 4.9%) and hypotension (6.1% *versus* none). The incidence of heart failure related events was slightly lower in ivabradine group (6.1% of patients *versus* 7.3% in placebo group). The most frequent drug-related event was asymptomatic bradycardia (HR decreased; 2.4%).

Severe on-treatment EAEs occurred in the ivabradine group with an incidence of 7.3% (6 patients with 13 events; no severe events were reported in the placebo group). Of these events, 9 were related to cardiac disorders/investigations (non cardiac events included hypotension, renal impairment, overdose and sepsis).

During the study (from selection to PEND, or PM04 for sub-study patients) the EAE incidence was 72.0% in the ivabradine group *versus* 68.3% in the placebo group. The most frequently EAEs were VT (11.0% *versus* 9.8%), PCI (6.1% *versus* 4.9%) and headache (6.1% *versus* 4.9%).

A total of 8 serious emergent adverse events were reported by 5 patients (6.1%) in the ivabradine group during the treatment period. For 3 patients the (first) event(s) was emergent on the day of treatment administration: one patient had an accidental overdose with bradycardia (recovered). In the same patient persisting ST segment elevation and complete AV block was also reported; 1 patient reported a ventricular arrhythmia. Later reported (on-treatment) SEAEs included 2 cases of acute LV failure, a case of renal impairment and a case of cardiogenic shock. All events were reported as recovered at the end of the study, except for cardiogenic shock (the patient died from mesenterial infarction 5 days later). One of the cases of acute LV failure was considered by the investigator as being doubtfully related to the study treatment.

A total of 2 patients were withdrawn from the study for adverse event in the ivabradine group: 1 for overdose and bradycardia and 1 following mesenterial infarction (with fatal outcome).

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SUMMARY - CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Two patients died (both in the ivabradine group) during the follow-up of the study, one from worsening COPD reported 5 days after the bolus and one from mesenterial infarction, 7 days after the bolus. Neither event was considered by the investigator as being related to study treatment.

In both treatment groups, slight and parallel decreases were observed in mean SBP and DBP between baseline and PEND. In the ivabradine group there were 5 cases of hypotension (1 mild, 3 moderate, 1 severe). None of these was considered as serious or related to the study drug; they were related to bleeding from catheter, excessive diuresis or qualifying acute MI. Also, there was 1 case of orthostatic hypotension and 2 cases of hypertension in the ivabradine group. All of these events were reported as recovered.

The ECG assessments revealed no clinically relevant changes in mean values, other than the slowing of the HR and the expected increase in mean QT interval.

CONCLUSION

This randomised pilot study in STEMI patients who underwent PCI, showed that a post-operative intravenous bolus administration of ivabradine 5 mg followed by an 8-hour i.v. infusion of ivabradine 5 mg produced a statistically significant, rapid and sustained decrease in mean heart rate, compared to placebo-treated patients. Echocardiographic data suggested that ivabradine treatment was associated with a preservation of the LV function and reductions in LV volumes over the period from bolus administration to discharge from the medical facility. Analyses of circulating protein markers of myocardial damage (troponins and CK-MB) indicated lower levels in the ivabradine group.

In the MRI sub-study, the mean area of delayed hyperenhancement (indicative of the infarcted volume) at discharge was smaller in ivabradine-treated patients as compared to placebo-treated patients, while the area at risk was comparable in the 2 groups. At the 4-month follow-up visit, the mean infarct size was similar in the 2 groups.

The safety analysis found that intravenous ivabradine was fairly well tolerated. Cardiac events (including rhythm disorders) occurred at a slightly greater frequency in the ivabradine group than in the placebo group, but these were mostly mild and recovered.

The results of the study suggest that intravenous ivabradine could play a role in myocardial protection in patients with STEMI and should be evaluated for its ability in improving outcomes.

Date of the report: 26 May 2010.