Document title	**Clinical Study Synopsis Report**
Study title	**Evaluation of the anti-arrhythmic effects of 3 oral dosages of S 44121 versus placebo in patients with chronic heart failure and left ventricular systolic dysfunction at risk for ventricular arrhythmia.** **A 12-week, randomised, double-blind, parallel-group, placebo controlled, international multicentre study.**
Study drug	**S 44121**
Studied indication	**Cardiac arrhythmia in chronic heart failure**
Development phase	**Phase II**
Protocol code	**CL2-44121-006**
Study initiation date	**7 June 2010**
Study completion date	**14 January 2013**
Main coordinator	[redacted]
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot 92284 Suresnes Cedex - France** **Servier Canada Inc., International Centre for Therapeutic Research (ICTR) Canada** **Laboratorios Servier, S.L. Spain** **Servier Research and Development Limited United Kingdom** **Servier Argentina S.A., ICTR Argentina** **Servier Research and Development Benelux S.A., ICTR Benelux** **Servier Korea Limited, Republic of Korea**
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 January 2014**

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2. SYNOPSIS

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study:

Evaluation of the anti-arrhythmic effects of 3 oral dosages of S 44121 *versus* placebo in patients with chronic heart failure and left ventricular systolic dysfunction at risk for ventricular arrhythmia.
A 12-week, randomised, double-blind, parallel-group, placebo controlled, international multicentre study.
Protocol No.: CL2-44121-006 – EudraCT No.: 2009-014940-12

International Coordinator:

[redacted] United Kingdom.

Study centres: 47 centres in 17 countries included at least one patient: 3 centres in Argentina (3 patients), 5 centres in Australia (9 patients), 2 centres in Belgium (2 patients), 2 centres in Canada (9 patients), 3 centres in Czech Republic (11 patients), 2 centres in France (7 patients), 5 centres in Germany (13 patients), 4 centres in Hungary (17 patients), 1 centre in Republic of Korea (2 patients), 1 centre in Netherlands (2 patients), 7 centres in Poland (56 patients), 2 centres in Portugal (2 patients), 1 centre in Singapore (2 patients), 3 centres in Slovakia (5 patients), 2 centres in Spain (8 patients), 2 centres in Taiwan (2 patients), 2 centres in United Kingdom (4 patients).

Publication (reference): Not applicable.

Studied period: Initiation date: 7 June 2010 Completion date: 14 January 2013	**Phase of development of the study:** II

Objective(s):

The aim of this study was to evaluate the anti-arrhythmic efficacy of S 44121 *versus* placebo administered orally for a total of 12 weeks in patients with chronic heart failure (CHF) and left ventricular systolic dysfunction who received an implanted cardioverter-defibrillator (ICD) for primary or secondary prevention of ventricular arrhythmia.
The safety profile of S 44121 was also evaluated.

Methodology:

This study was a phase II, randomised, double-blind, parallel-group, placebo-controlled, international, multicentre, exploratory study conducted in patients with CHF (New York Heart Association [NYHA] functional class I, II or III) and left ventricular (LV) systolic dysfunction (LV Ejection Fraction [LVEF] $\leq$ 40%). The total study duration for patients was to be 16 weeks, of which 12 weeks double-blind treatment period after inclusion.

Number of patients:
Planned: 160 patients: 40 patients for placebo and for each dosage of S 44121 (250, 500 and 1000 mg *b.i.d.*)
Included: 154 patients.

Diagnosis and main criteria for inclusion:

Male or female patients between 18 years and 80 years, except for Czech Republic where the upper limit was 65 years (following Amendment No. 2); fitted with an ICD for primary or secondary prevention of ventricular arrhythmia at least 3 months before selection; symptomatic CHF for at least 6 months before selection; NYHA functional class I, II or III (modified by Amendment No. 11); stable condition with regards to CHF symptoms for at least 4 weeks before selection; documented left ventricular systolic dysfunction by echocardiography (LVEF $\leq$ 40 %); ischemic disease or idiopathic dilated cardiomyopathy as main cause for CHF; documentation of an average number of at least 100 premature ventricular complexes (PVCs) per hour on a 48-hour Holter-based ECG recording; treated for at least 3 months before selection with a maximal tolerated dose of a beta-blocker recommended by the European Society of Cardiology; regular sinus or atrial rhythm (paced or spontaneous) and provided that atrial contraction preceded ventricular contraction (modified by Amendment No. 11).

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Study drug:

Sachets sets of S 44121 (250 mg and 500 mg) allowed an administration of all S 44121 doses levels planned for the study (*i.e.* 250 mg, 500 mg or 1000 mg). Patients were randomised to receive a twice daily fixed-dose oral administration of one of the 3 different dosages of S 44121 *i.e.* 250 mg, 500 mg or 1000 mg (or placebo), morning and evening. The content of 3 sachets (diluted in 200mL of water) had to be taken by a single intake with a meal, twice daily. Batch No.: 250mg blue sachet: L0032745, L0033908, L0038785, L0043320; 250 mg yellow sachet: L0032743, L0033906, L0038783, L0043322; 500 mg pink sachet: L0032747, L0032749, L0033910, L0033912, L0038787, L0043318.

Reference product:

Placebo sachets diluted in 200mL of water had to be taken by a single administration with a meal twice daily.

Duration of treatment:

A 2-week run-in period: from selection to the inclusion visit during which placebo was dispensed *b.i.d.* This run-in period was dedicated to confirm the eligibility of patients, their clinical stability and their compliance.

A 12-week double-blind treatment period: from inclusion visit (W0) to visit W12.

A 2-week follow-up period: This follow-up period, from visit W12 to visit W14 was dedicated to evaluate the safety after the study treatment discontinuation performed at visit W12.

It is to note that during the entire study (from selection to W14), the patient was to continue his/her usual cardiovascular treatment, which had to include a beta-blocker (as per selection criteria).

Criteria for evaluation:

Efficacy measurements:

- Holter-based ECG parameters at the W0, W1, W4 and W12 visits: the average rate of PVCs per hour, the occurrence of individual ventricular arrhythmias and non-ventricular arrhythmias.
- ICD-based ECG parameters measured at the W0, W12 and W14 visits: the occurrence of ventricular arrhythmias (VT, VF), and appropriate electrical ICD-based therapies.
- Echocardiographic parameters at the W0 and W12 visits: LVEF (%), LV (end-diastolic and end-systolic) volumes (ml), LV volumes indexed to body area (mL/m^2), LV internal diameters (mm), and ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity (E/E' ratio).
- N-terminal pro Brain Natriuretic Peptide (NT-proBNP) plasma concentration at the W0 and W12 visits.
- NYHA functional class at the W0, W4, W8, W12, and W14 visits.

Holter-based ECG parameters and ICD printouts were centrally reviewed (Amendment No. 11 specified the centralisation of the event adjudication of ICD printouts in order to optimise data homogeneity). NT-proBNP plasma concentration was measured in a central laboratory. Other parameters were assessed locally.

Safety measurements:

- Adverse events throughout the study.
- Physical examination including weight, systolic and diastolic blood pressure at each visit.
- 12-lead resting ECG at each visit.
- Pacing and defibrillation threshold reported on the ICD.
- Blood haematology parameters at the W0 and W12 visits.
- Blood biochemistry parameters at W0, W4 and W12 visits (The additional blood sample at W4 was only applied in Republic of Korea, specified by Amendment No. 13).

Pharmacokinetic measurements:

Plasma measurement of S 44121 (and if possible its metabolite(s), as required by Amendment No. 12) at the W0, W4 (W4 visit was added by Amendment No. 12 only for Asian countries) and W12 visits.

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Statistical methods:

Statistical analyses were carried out using SAS Enterprise Guide 4.3.

Efficacy analysis:

The following populations were defined for the efficacy analysis:

- Full Analysis Set PVC – FAS_{PVC}: Patients of the Randomised Set, having taken at least one dose of study drug and with at least two evaluations of mean number of overall PVCs per hour: one at baseline and one post baseline.
- Per Protocol Set PVC – PPS_{PVC}: Patients of the FAS_{PVC}, with an evaluation of the mean number of overall PVCs per hour at W12 visit under treatment (date of Holter ≤ date of last intake) and having the studied disease, a protocol-required background therapy before treatment period and a correct and sufficient exposure to study drug during 12-week treatment period.
- Full Analysis Set ECHO – FAS_E: Patients of the Randomised Set, having taken at least one dose of study drug and with one echocardiography at baseline and at least one post baseline considered as assessable, *i.e.* with a LVEF measurable in 4-chamber monoplane views, or if LVEF in 4-chamber view is missing, with a LVEF measurable in biplane view (calculated with biplane Simpson method).
- Per Protocol Set ECHO – PPS_E: Patients of the FAS_E, with an assessable echocardiography on treatment (date of echo ≤ date of last intake +1) at W12 and having the studied disease, a protocol-required background therapy before treatment period and a correct and sufficient exposure to study drug during 12-week treatment period.
- Full Analysis Set NT-proBNP – FAS_N: Patients of the Randomised Set, having taken at least one dose of study drug and with a reliable evaluation of NT-proBNP plasma concentration at baseline and at least one evaluation post baseline based on central analysis.
- Per Protocol Set NT-proBNP – PPS_N: Patients of the FAS_N with an evaluation of NT-proBNP on treatment (sampling date ≤ date of last intake +1) at W12 and having the studied disease, a protocol-required background therapy before treatment period and a correct and sufficient exposure to study drug during 12-week treatment period.

Holter ECG parameters, Echocardiographic parameters and NT-proBNP plasma concentration were analysed on the appropriate Full Analysis Set and Per Protocol Set. The ICD parameters and the NYHA class were analysed on the Randomised Set. NT-proBNP at each visit was logarithmically transformed in order to apply parametric statistical models. The treatment effect of each dose of S 44121 over placebo was estimated on the change of number of PVCs and premature supraventricular complexes (PSVCs) per hour, LVEF, LV volumes and diameters, NT-proBNP from baseline to last post-baseline value (or to W12 value).
The main analysis was a parametric approach without adjustment, based on a variance analysis. Sensitivity analyses were performed: a parametric approach with adjustment based on a covariance analysis adjusted for baseline value and a non-parametric approach without adjustment based on Hodges & Lehmann estimate. Descriptive analyses at each visit and on change from baseline to each visit were performed for all the parameters.

Safety analysis:

Descriptive statistics were carried out on the Safety Set, including descriptive analysis of Emergent adverse events (EAE), Serious EAE (SEAE), Severe EAE, EAE leading to study drug withdrawal, EAE related to study drug, EAE leading to study drug withdrawal and related to study drug, EAE requiring new treatment, fatal EAE and EAE of the adapted list of the standardised MedDRA queries (SMQs) "Gastrointestinal nonspecific inflammation and dysfunctional conditions" and "Gastrointestinal ulceration" and of the adapted list of the SMQs "Cardiac arrhythmias" and "Cardiac arrest", listings of pacing and defibrillation threshold of the ICD, and descriptive analysis of 12-lead ECG parameters, vital signs and blood laboratory parameters.

Pharmacokinetic analysis:

The methodology is described in the appended PK report.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 494 patients were screened for the study and 478 were selected. Among selected patients, 324 patients were not included in the study mainly due to an insufficient number of PVCs per hour on the 48-hour Holter recording at inclusion (< 100 PVCs/h). A total of 154 patients were finally included and randomly assigned to one of the four groups: 44 patients in the 250 mg S 44121 group, 35 in the 500 mg S 44121 group, 37 in the 1000 mg S 44121 group and 38 in the placebo group. The distribution of patient per group differed slightly from the intended 40 per group. No patient was lost to follow-up and 135 (87.7%) completed the study (see the table below).

Disposition of included (randomised) patients by group and main analysis sets

Status		**250 mg (N = 44)**	**500 mg (N = 35)**	**1000 mg (N = 37)**	**Placebo (N = 38)**	**All (N = 154)**
Included (randomised)		**44**	**35**	**37**	**38**	**154**
Lost to follow-up		**-**	**-**	**-**	**-**	**-**
Withdrawn due to		**8**	**4**	**4**	**3**	**19**
adverse event		6	1	3	1	11
non-medical reason		1	-	-	1	2
protocol deviation		1	3	1	1	6
Completed		**36**	**31**	**33**	**35**	**135**
Safety Set	n (%)	44 (100)	35 (100)	38 (102.7)*	38 (100)	155 (100.6)*
Full Analysis Set PVC (FAS_{PVC})	n (%)	42 (95.5)	33 (94.3)	37 (100)	37 (97.4)	149 (96.8)
Per Protocol Set PVC (PPS_{PVC})	n (%)*	33 (78.6)	28 (84.8)	28 (75.7)	32 (86.5)	121 (81.2)
Full Analysis Set ECHO (FAS_{E})	n (%)	39 (88.6)	35 (100)	37 (100)	37 (97.4)	148 (96.1)
Per Protocol Set ECHO (PPS_{E})	n (%)*	30 (76.9)	29 (82.9)	26 (70.3)	33 (89.2)	118 (79.7)
Full Analysis Set NT pro-BNP (FAS_{N})	n (%)	39 (88.6)	32 (91.4)	37 (100)	37 (97.4)	145 (94.2)
Per Protocol Set NT pro-BNP (PPS_{N})	n (%)*	31 (79.5)	27 (84.4)	26 (70.3)	33 (89.2)	117 (80.7)

N Total number of patients by group; n number of patients in a given analysis group.
*% % of the Randomised Set except * calculated as % of the corresponding FAS.*
** 1 patient was not included but took the treatment for at least 1 day.*

Overall, the Randomised Set comprised mainly men (91.6%), mean (± SD) age was 62.9 ± 8.6 years and mean body mass index (BMI) was 28.6 ± 4.4 kg/m², with no relevant differences between treatment groups. The overall mean heart rate (69.0 ± 11.5 bpm) and blood pressure (SBP = 121.1 ± 15.8 mmHg; DBP = 73.2 ± 10.2 mmHg) were similar across treatment groups.

The mean duration of CHF from its diagnosis was 8.5 ± 6.1 years (median, 7.0); for 66.2% of patients the duration was at least 5 years. The main cause of the disease was an ischaemic event (in 62% of patients), with the remainder having an idiopathic dilated cardiomyopathy. When a secondary cause was present (in 13% of patients), it was usually hypertension.
The distribution of patients according to NYHA classification was: class I, 7.1% of patients; class II, 79.9%; and class III, 13.0%.

All patients recruited in the study had received an ICD for primary or secondary prevention of ventricular arrhythmia for at least 3 months before selection. Approximately half of the patients (48.1%) had a single chamber device, 22.7% had a double chamber device and 29.2% had a biventricular ICD.
A beta-blocker treatment was received by 98.7% of patients. In 78.2%, the dose received was at least half the daily ESC recommended dose, with no relevant differences between groups. All patients were receiving at least one concomitant treatment related to CHF apart from beta-blockers and these were mainly agents acting on the renin angiotensin system (97.4%) and diuretics (86.4%).

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SUMMARY – CONCLUSIONS (cont'd)

OUTCOME RESULTS

During the 48h baseline Holter, all patients had an average number of PVCs per hour of at least 100, except 1 patient in the 500 mg group who had 99.5 PVCs per hour (protocol deviation at inclusion). The overall mean number of PVCs per hour on the complete recording was 409.0 ± 402.2 (median = 250.8). The overall mean number of PSVCs per hour on the complete recording was 56.6 ± 137.8 (median = 11.8). It should be noted that there were a high variability between groups in the mean number of PVCs and PSVCs on complete recording.

Baseline Holter parameters on complete recordings – Randomised Set

PVC parameters		250 mg (N = 44)	500 mg (N = 35)	1000 mg (N = 37)	Placebo (N = 38)	All (N = 154)
	n_{obs}	**44**	**35**	**37**	**38**	**154**
PVCs per hour	Mean ± SD	470.8 ± 456.5	372.0 ± 427.2	377.1 ± 336.9	402.8 ± 376.3	409.0 ± 402 2
	Median	330.7	172.9	265.1	232.8	250.8
	Min ; Max	101.2 ; 2625.4	99.5 ; 1762.6	102.6 ; 1595.2	100.8 ; 1762.6	99.5 ; 2625.4
Ventricular runs per hour	Mean ± SD	10.2 ± 37.0	3.3 ± 6.7	8.1 ± 24.5	4.5 ± 9.1	6.7 ± 23.7
	Median	1.3	0 5	0.6	1.1	0.9
	Min ; Max	0.0 ; 244.5	0.0 ; 34.1	0.0 ; 131.2	0.0 ; 41.0	0.0 ; 244.5
PSVCs per hour	n_{obs}	**42**	**32**	**34**	**32**	**140**
	Mean ± SD	36.5 ± 81.2	92.4 ± 164.0	73.3 ± 195.5	29.2 ± 76.5	56.6 ± 137.8
	Median	6.2	13.2	20.4	11.8	11.8
	Min ; Max	0.0 ; 490.4	0.0 ; 572.8	0.2 ; 939.3	0.4 ; 430.5	0.0 ; 939.3

N: number of patients by treatment group.

The baseline echocardiographic assessment showed that 141 patients (91.6%) had a measured LVEF ≤ 40%, with an overall mean LVEF of 29.9 ± 8.0% (median = 30.9).
At baseline, the median NT-proBNP plasma concentration was 739.4 pg/mL, and 73.7% of patients overall had a value ≥ 400 pg/mL.

The mean overall study treatment duration and compliance conformed to the protocol, with means of 80.3 ± 20.5 days (median = 85.0) and 96.5 ± 4.9% (median = 98.4), respectively, without relevant difference between treatment groups.

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EFFICACY RESULTS

- Holter-based ECG assessment

In the FAS_{PVC} (as well as in the PPS_{PVC}), the S 44121 500 mg and 1000 mg treatment groups showed a dose-dependent reduction over the treatment period in the rate of PVCs/h and in the rate of ventricular runs/h on Holter recording (no mean change was evidenced on placebo). The reductions *versus* placebo on the mean rate of PVCs per hour reached 61.2 and 90.3 PVCs/hour for the 500 mg and 1000 mg treatment groups respectively, with a trend towards significance observed in both of these treatment groups (see table below). A similar pattern was observed regarding the rate of ventricular runs per hour. In particular, the 1000 mg treatment group showed a statistically significant reduction in the rate of ventricular runs per hour at the 95% confidence level (see table below), which should however be interpreted with care, in view of the multiple testing in this exploratory study.

PVCs and ventricular runs per hour on complete recording – Change from baseline to last post-baseline visit - FAS_{PVC}

Last post-baseline visit - Baseline		250 mg (N = 42)	500 mg (N = 33)	1000 mg (N = 37)	Placebo (N = 37)
Change of PVCs/h	Mean ± SD	5.1 ± 303.2	-60.0 ± 253.4	-87.8 ± 293.6	-5.2 ± 208.1
S 44121 *versus* placebo	E (SE)	26.1 (57.1)	-61.2 (60.5)	-90 3 (58.8)	-
	95% CI	[-86.8 ; 138 9]	[-180.8 ; 58.5]	[-206.5 ; 25.9]	-
Change of ventricular runs/h	Mean ± SD	-0.5 ± 9.5	-1.1 ± 6.3	-6.3 ± 24.9	0.2 ± 5.4
S 44121 *versus* placebo	E (SE)	1.4 (2.5)	-1.8 (2.7)	-5.3 (2.6)	-
	95% CI	[-3.7 ; 6.4]	[-7.1 ; 3.6]	[-10.4 ; -0.1]	-

E: Estimate (SE) standard error of S 44121 minus placebo effect: difference between group means based on a parametric analysis of covariance adjusted for baseline value.
95% confidence interval of the estimate (two-sided).

The responder rates (*i.e.* the percentage of patients with a reduction of PVCs/h according to thresholds from baseline) exceeded placebo for the two higher dose levels of 500 mg and 1000 mg *b.i.d.* (see table below).

Responder rate: reduction of PVCs per hour from baseline – FAS_{PVC}

Reduction of PVCs/h on complete recording		250 mg (N = 42)	500 mg (N = 33)	1000 mg (N = 37)	Pooled S 44121 (N = 112)	Placebo (N = 37)
> 50%	n (%)	9 (21.4)	13 (39.4)	11 (29.7)	33 (29.5)	7 (18.9)
> 60%	n (%)	7 (16.7)	11 (33.3)	9 (24 3)	27 (24.1)	5 (13.5)
> 70%	n (%)	2 (4.8)	7 (21.2)	7 (18 9)	16 (14.3)	4 (10.8)
> 80%	n (%)	1 (2.4)	6 (18.2)	7 (18 9)	14 (12.5)	2 (5.4)

*Reduction calculated as: (Last post-baseline value - Baseline)*100/Baseline; n: number of patients; %: (n/N) x 100.*

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SUMMARY – CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

No treatment effect could be discerned on PSVCs. The effect on cardiac arrhythmia was also inconclusive due to the low numbers of the observed events.

In the analysis of **ICD data**, relatively few patients were found to have experienced a ventricular tachycardia during the study. There was a slight decrease (-3.7%) of the rate of patients having at least one VT during the maximal common time windows in the pooled S 44121 group (baseline period 42.1%, treatment period 38.3%) *versus* a slight increase (+2.8%) in the placebo group (baseline period 36.1%, treatment period 38.9%). Among the patients with at least 1 ventricular tachycardia (VT) at baseline, the incidence of patients having no VT during the treatment period was slightly higher in the pooled S 44121 group than in the placebo group (35.6% *versus* 30.8%).

Evolution of the number of patients with at least one ventricular tachycardia at baseline – Randomised Set

		250 mg (N = 44)	500 mg (N = 35)	1000 mg (N = 37)	Pooled S 44121 (N = 116)	Placebo (N = 38)
Patients observed*	n_{obs}	42	32	33	107	36
Patients with ≥ 1 event on baseline period	n	22	7	16	45	13
Evolution of the above patients during the treatment period:						
Patients with ≥ 1 event on treatment period	n (%)	16 (72.7)	4 (57.1)	9 (56.3)	29 (64.4)	9 (69.2)
Patients with no event on treatment period	n (%)	6 (27.3)	3 (42.9)	7 (43.8)	16 (35.6)	4 (30.8)

**Number of patients with an ICD printout on baseline period and on treatment period during the maximal common time window.*
n number of patients.
% (n/N) x 100.

In total only 6 patients at baseline and 7 patients during treatment experienced atrial fibrillation across the four treatment arms.

In the **echocardiographic assessments** in the FAS_E, the estimates of the mean change of LVEDVI between the active treatment groups *versus* placebo consistently showed reductions, but these did not reach statistical significance. The estimates of the mean change of LVESVI were more variable and showed no statistically significant difference between groups (see table below).

Echocardiographic parameters - Change from baseline to last post-baseline visit – FAS_E

		250 mg (N = 39)	500 mg (N = 35)	1000 mg (N = 37)	Placebo (N = 37)
Change LVEF (%)	Mean ± SD	0.1 (8.0)	0.1 (6.3)	2.2 (5.7)	2.6 (7.0)
vs Placebo	E (SE)	-0.9 (1.5)	-1.3 (1.5)	0.3 (1.5)	-
Change LVEDVI (mL/m²)	Mean ± SD	-2.7 (14.4)	2.1 (18.9)	0.8 (15.6)	3.4 (17.2)
vs Placebo	E (SE)	-7.0 (3.9)*	-2.2 (3.9)	-3.7 (3.9)	-
Change LVESVI (mL/m²)	Mean ± SD	-2.5 (11.6)	0.8 (16.6)	-1.4 (13.8)	-1.4 (14.1)
vs Placebo	E (SE)	-2.5 (3.3)	1.1 (3.3)	-1.2 (3.3)	-

E Estimate (SE) standard error of S 44121 minus placebo effect difference between group means based on a parametric analysis of covariance adjusted for baseline value.
** significant.*

The NT-proBNP plasma concentrations showed no evidence of consistent changes over the treatment period in the active treatment groups that could be interpreted as an effect of treatment.

The changes in NYHA classification over the study according to treatment group showed no clear differences between the concentrations of S 44121 or between the active treatment groups and the placebo group.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

An overall summary of safety results (emergent adverse events on treatment) is presented in the following table.

Overall summary of on-treatment emergent adverse events

		S 44121 250 mg (N = 44)	S 44121 500 mg (N = 35)	S 44121 1000 mg (N =38)	All S 44121 doses pooled (N = 117)	Placebo (N = 38)
Patients having reported						
at least one EAE	n (%)	25 (56.8)	19 (54.3)	15 (39.5)	59 (50.4)	21 (55.3)
at least one treatment-related EAE	n (%)	4 (9.1)	1 (2.9)	4 (10.5)	9 (7.7)	2 (5.3)
Patients having experienced						
at least one SEAE (including death)	n (%)	7 (15.9)	4 (11.4)	2 (5.3)	13 (11.1)	6 (15.8)
at least one treatment-related SEAE	n (%)	1 (2.3)	-	1 (2.6)	2 (1.7)	-
Patients withdrawn						
due to an EAE	n (%)	4 (9.1)	1 (2.9)	3 (7.9)	8 (6.8)	1 (2.6)
due to a SEAE	n (%)	3 (6.8)	-	1 (2.6)	4 (3.4)	1 (2.6)
due to a treatment-related EAE	n (%)	1 (2.3)	1 (2.9)	3 (7.9)	5 (4.3)	-
due to a treatment-related SEAE	n (%)	-	-	1 (2.6)	1 (0.9)	-
Patients who died	n (%)	1 (2.3)	-	-	-	-

Emergent adverse events (EAEs) on treatment were reported in 50.4% patients in the pooled S 44121 group *versus* 55.3% patients in the placebo group. When comparing the individual S 44121 dose groups, no dose-effect was observed in the rate of EAEs.

The two most frequently affected system organ classes (SOCs) on treatment were cardiac disorders (23.1% *versus* 21.1%) and gastrointestinal disorders (8.5% *versus* 10.5%) in the pooled S 44121 group *versus* the placebo group, respectively.

In the pooled S 44121 group, the most frequently reported cardiac disorders on treatment were ventricular tachycardia (11 patients, 9.4% *versus* 1 patient 2.6% in the placebo group) and worsening chronic cardiac failure (9 patients, 7.7% *versus* 2 patients, 5.3% in the placebo group). In the placebo group, worsening chronic cardiac failure (2 patients, 5.3%) was the most frequent cardiac event.

Regarding particular adverse events (cardiac specific events and gastrointestinal specific events of the adapted list of the SMQs), 16.2% (19 patients) in the pooled S 44121 group *versus* 13.2% (5 patients) in the placebo group, reported specific EAEs on treatment related to "Cardiac arrhythmia" and "Cardiac arrest", including mostly VT (9.4%, 11 patients, in the pooled S 44121 group *versus* 2.6%, 1 patient, in the placebo group). Specific gastrointestinal EAEs on treatment related to "Gastrointestinal nonspecific inflammation and dysfunctional conditions" and "Gastrointestinal ulceration" during the treatment period were reported in 7.7% (9 patients) in the S 44121 pooled group *versus* 10.5% (4 patients) in the placebo group, including mainly diarrhoea (2.6%, 3 patients, *versus* 2.6%, 1 patient, respectively).

The intensity of EAEs was mostly rated as mild or moderate, whichever the group. Overall, in the pooled S 44121 group, severe EAEs were reported in 6.8% (8 patients, with 17 severe EAEs) *versus* 7.9% (3 patients, with 7 severe EAEs) in the placebo group. No dose-effect was observed in the S 44121 treatment groups. In all, 3/24 severe EAEs were considered by the investigator as related to the study treatment (*i.e.* ventricular fibrillation in the 250 mg group, ventricular tachycardia and angina pectoris, both in one patient in the 1000 mg group).

Name of Company: I.R.I.S. 50 rue Carnot 92284 Suresnes - FRANCE	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: **S 44121**	**Page:**	

SUMMARY – CONCLUSIONS (cont'd)
SAFETY RESULTS (cont'd)

In all, treatment-related EAEs (TEAEs) on treatment period were reported in 7.7% (9 patients) in the pooled S 44121 group (18 TEAEs) *versus* 5.3% (2 patients) in the placebo group (3 TEAEs). Treatment-related EAEs were mainly gastrointestinal disorders (10/21 TEAEs) and cardiac disorders (6/21 TEAEs), without a clear dose-effect.

EAEs led to treatment discontinuation in 6.8% (8/117 patients) in the pooled S 44121 group *versus* 2.6% (1/38 patients) in the placebo group. The events involved mostly cardiac disorders (4.3% [5 patients] in the pooled S 44121 group *versus* 1 in the placebo group).

EAEs on treatment that were reported as not recovered at the end of the study occurred in 12.0% (15/125 EAEs) in the pooled S 44121 group (mainly cardiac disorders, 5 EAEs) *versus* 12.8% (5/39 EAEs) in the placebo group. None of the non-recovered EAEs (whatever the group), was considered by the investigator as related to the study treatment.

Serious EAEs on treatment were reported in 11.1% (13/117 patients) in the pooled S 44121 group and 15.8% (6/38 patients) in the placebo group. No serious gastrointestinal disorders were reported.
Two fatal EAEs (ventricular fibrillation and low cardiac output syndrome) were reported in the S 44121 250 mg group, of which one (ventricular fibrillation) occurred on treatment and was considered by the investigator as related to the study drug.

Concerning blood biochemistry and haematology, emergent potentially clinically significant abnormal values (PCSA) were infrequent in each group.

Neither relevant mean changes between baseline and last post-baseline value under treatment in each group nor relevant differences between treatment groups were observed in blood pressure, BMI or ECG parameters. In particular, no dose-dependent effect was detected regarding QTc or other ECG parameters.

CONCLUSION
In conclusion, this randomised, double-blind, placebo-controlled exploratory study conducted over 12 weeks in patients with CHF and LV dysfunction (fitted with an ICD) and at risk for ventricular arrhythmia, showed that oral treatment with S 44121 *b.i.d.* resulted in a dose-dependent reduction in the rate of premature ventricular complexes per hour as well as in the rate of ventricular runs per hour. The responder rates on PVC reduction exceeded placebo for the higher two dose levels of 500 and 1000 mg *b.i.d.* However, the magnitude of the effect did not attain clinical relevance with the doses and treatment duration assessed in this study. In the analysis of ICD data, relatively few patients experienced a ventricular tachycardia during the study making the evaluation of a treatment effect on VT difficult. There was no strong evidence that S 44121 was associated with any improvements on haemodynamic parameters on echocardiographic assessments. The safety profile of S 44121 was acceptable.

Date of the report: 20 January 2014