I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Report Synopsis**
Study title	**Evaluation of the effects of 4 oral dosages of S 44121 *versus* placebo on cardiac function and NT-proBNP in patients with chronic heart failure and left ventricular dysfunction. A 12-week, randomised, double-blind, parallel-group, placebo controlled, international multicentre study.**
Study drug	**S44121**
Indication	**Chronic Heart Failure**
Development phase	**Phase II**
Protocol code	**CL2-44121-003**
Study initiation date	**12 April 2010**
Study completion date	**31 March 2011**
Main coordinator	[redacted] **GERMANY**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE** **Laboratorios Servier, SL** **Avenida de los Madroños, 33** **28043 Madrid - SPAIN** **Servier Research and Development** **Gallions Wexham Springs** **Framewood Road - Wexham** **Slough SL3 6RJ - UNITED KINGDOM**
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 4 July 2012**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

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

Title of study:
Evaluation of the effects of 4 oral dosages of S 44121 *versus* placebo on cardiac function and NT-proBNP in patients with chronic heart failure and left ventricular dysfunction.
A 12-week, randomised, double-blind, parallel-group, placebo controlled, international multicentre study.
Protocol No.: CL2-44121-003

International coordinator: [redacted] (Göttingen – Germany)
National coordinators: [redacted] (Italy), [redacted] (Poland) [redacted] (Portugal), [redacted] (Romania [Amendment No. 1]), [redacted] (Russia), [redacted] (Spain), and [redacted] (United Kingdom [Amendment No. 1]).

Study centres:
34 centres located in 8 countries were opened and included at least one patient.
Spain – 7 centres (12 included patients), Italy – 6 centres (22 included patients), Russian Federation – 6 centres (31 included patients), Poland – 5 centres (43 included patients), Germany – 3 centres (5 included patients), Portugal – 3 centres (4 included patients), Romania – 3 centres (27 included patients), United Kingdom – 1 centre (1 included patient).

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 12 April 2010 Completion date: 31 March 2011	Phase II

Objectives:
To evaluate the effects of chronic oral administration of four oral dosages of S 44121 *versus* placebo on cardiac function and NT-proBNP in patients with chronic heart failure (CHF) and left ventricular dysfunction receiving the recommended therapy for this disease. 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 chronic heart failure (NYHA functional class II or III) and left ventricular systolic dysfunction (LVEF ≤ 35%). The total study duration for patients was to be 13 weeks, of which 12 weeks after inclusion.

Number of patients:
Planned: 150 patients, 30 in each treatment arm (Amendment No. 4, instead of 125 patients, 25 in each treatment arm).
Included: 145 patients in total, *i.e.* 24 patients in the 250 mg group, 28 in the 500 mg group, 30 in the 750 mg group, 30 in the 1000 mg group, and 33 in the placebo group.

Diagnosis and main criteria for inclusion:
Patients aged between 18 and 75 years:

- With symptomatic (stable for at least 4 weeks) chronic heart failure for at least 6 months before selection, main cause being ischaemic heart disease or idiopathic dilated cardiomyopathy.
- NYHA class II or III.
- Treated with ß-blockers (at least half of the target daily dose) and ACE inhibitors/ARB, for at least 3 months before selection, and with optimal and unchanged CHF treatment (drugs and dosages) for at least 4 weeks before selection.
- Left ventricular dysfunction evidenced by LVEF ≤ 35%, and validated by the Echo Core Lab at inclusion.
- NT-proBNP plasma concentration ≥ 400 pg/mL or BNP ≥ 100 pg/mL.
- Sinus rhythm.

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

Study drug:
S 44121, twice daily fixed-dose oral administration (3 sachets) of one of the four dosages, 250 mg, 500 mg, 750 mg or 1000 mg.
Batch No. 250mg blue sachet: L0031469, L0033345; 250 mg yellow sachet: L0031467, L0033343; 500 mg pink sachet: L0031471, L0031473, L0033347, L0033349.

Reference product:
Matching placebo given orally twice daily.

Duration of treatment:
1-week placebo run-in period: from selection (SEL) to inclusion (W000).
12-week treatment period: from visit W000 to visit W012.

Criteria for evaluation:
Efficacy measurements:

- Echocardiographic parameters (centrally assessed) at visit Selection, W000, W004, W008, and W012:
  - Left ventricular (LV) ejection fraction (%).
  - Left ventricular end-systolic and end-diastolic volumes (mL) and index (mL/m^2).
  - Left ventricular end-diastolic and end-systolic internal diameters (mm).
  - Cardiac index (L/min/m^2).
  - Ratio of mitral peak velocity of early filling to mitral peak velocity of late filling (E/A ratio).
  - Ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity (E/e' ratio).
- NT-proBNP plasma concentration (pg/mL) (centrally assessed) at W000, W001, W004, W008, and W012.
- Myeloperoxidase plasma concentration (ng/mL) (centrally assessed) at W000, W001, W004, W008, and W012.
- NYHA functional classification at W000, W004, W008, and W012.
- Patient and physician global assessment at W004, W008, and W012.
- Dutch Exertion Fatigue Scale (DEFS) at W000 and W012.
- 6-Minute Walk Test at W000, W004, W008, and W012.

Safety measurements:

- Physical examination, 12-lead ECG, adverse events at all the visits.
- Blood laboratory parameters (haematology, biochemistry) at W000 and W012.

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

Criteria for evaluation (Cont'd):

Pharmacokinetic measurements:

Blood samples taken at W000 and W004 (see PK separate report).

Statistical methods:

Statistical analyses were carried out using SAS® for Windows version 9.1.

Efficacy analysis:

The following populations were defined for the efficacy analysis:

- 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 an evaluation of LVEF in 4-chamber monoplane views and in sinus rhythm.
- Per Protocol Set ECHO – PPS_E: Patients of the Full Analysis Set Echo, with an assessable echocardiography under treatment (date of echo ≤ date of last intake +1) at W012 and having the studied disease, a correct and sufficient 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 an 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 Full Analysis Set NT-proBNP with an evaluation of NT-proBNP under treatment (sampling date ≤ date of last intake +1) at W012 and having the studied disease, a correct and sufficient background therapy before treatment period and a correct and sufficient exposure to study drug during 12-week treatment period.

Echocardiographic parameters, NT-proBNP and myeloperoxydase plasma concentrations were analysed on the appropriate Full Analysis Set and Per Protocol Set. The NYHA class, Global assessment, DEFS score and total distance walked in 6-minutes were analysed on the Randomised Set. NT-proBNP and myeloperoxydase at each visit were 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 LV ejection fraction, LV volumes and diameters, NT-proBNP and myeloperoxydase, and total distance walked in 6-minutes from baseline to last post-baseline value (or to W012 value).

The main analysis was a parametric approach without adjustment, based on a Student distribution. Sensitivity analyses were performed: a non-parametric approach without adjustment based on Hodges & Lehmann estimate and a parametric approach with adjustment based on a covariance analysis adjusted for baseline value. 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, Severe EAE, EAE leading to drug withdrawal, Related EAE, EAE requiring new treatment and fatal EAE, and descriptive analysis of 12-lead ECG parameters, vital signs and blood laboratory parameters.

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

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 217 patients were selected for the study and 145 patients were included and randomly assigned to one of the five groups: 24 patients in the 250 mg group, 28 in the 500 mg group, 30 in the 750 mg group, 30 in the 1000 mg group, and 33 in the placebo group.

Among the included patients, 129 (89.0%) completed the study.

No patient was lost to follow-up. A total of 16 patients (11.0%) were withdrawn from the study: 11 patients due to adverse event, 4 for non-medical reason, and 1 due to protocol deviation.

Status		**S 44121 250 mg ***	**S 44121 500 mg ***	**S 44121 750 mg ***	**S 44121 1000 mg ***	**Placebo**	**All**
Included and randomised	n	**24**	**28**	**30**	**30**	**33**	**145**
Lost to follow-up	n	**-**	**-**	**-**	**-**	**-**	**-**
Withdrawn due to		**3**	**3**	**2**	**3**	**5**	**16**
adverse event	n	2	3	2	2	2	11
non-medical reason	n	1	-	-	1	2	4
protocol deviation	n	-	-	-	-	1	1
Completed	**n**	**21**	**25**	**28**	**27**	**28**	**129**
Safety Set	n (%)	24 (100)	28 (100)	30 (100)	30 (100)	33 (100)	145 (100)
Efficacy Sets							
Full Analysis Set ECHO (FAS_E)	n (%)[a]	23 (95.8)	25 (89.3)	29 (96.7)	28 (93.3)	31 (93.9)	136 (93.8)
Per Protocol Set ECHO (PPS_E)	n (%)[b]	19 (82.6)	20 (80.0)	25 (86.2)	23 (82.1)	26 (83.9)	113 (83.1)
Full Analysis Set NT-proBNP (FAS_N)	n (%)[a]	24 (100)	26 (92.9)	29 (96.7)	29 (96.7)	33 (100)	141 (97.2)
Per Protocol Set NT-proBNP (PPS_N)	n (%)[c]	18 (75.0)	21 (80.8)	24 (82.8)	25 (86.2)	26 (78.8)	114 (80.9)

%a % of the Randomised Set
%b % of the Full Analysis Set ECHO
%c % of the Full Analysis Set NT-proBNP
** The names of the treatment groups, i.e. S 44121 250 mg/500 mg/750 mg/1000 mg, refer to doses of 250/500/750/1000 mg taken twice daily.*

In the Randomised Set, patients were mainly men (82.8%) and had a mean age of 61.7 ± 8.4 years, without clinically relevant difference between treatment groups.

The mean duration of CHF from the diagnosis was 4.3 ± 5.1 years, without relevant difference between the groups.

The main cause of CHF was ischaemic in around 75% of patients and idiopathic dilated cardiomyopathy in around 25% of patients. The main additional cause was hypertension in around 20% of patients. At inclusion, the heart rate and blood pressure parameters were similar on average in all treatment groups.

The protocol requested that all patients recruited in the study must be treated with a beta-blocker for at least 3 months before selection. All patients were treated with beta-blocker, of which only two patients were treated for less than 3 months, and the dose being less than half of the target dose only in 9 patients.

It also requested that all patients must be treated with ACE inhibitors and/or ARB for at least 3 months before selection. All patients except 1 fulfilled this requirement. Consistent with the medical history, all patients of the Randomised Set received at least one concomitant treatment related to heart failure during the treatment period, mainly beta-blocking agents (100%), agents acting on the renin angiotensin system (99.3%), and diuretics (89.0%).

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

SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

As requested in the protocol, all patients had CHF classified as NYHA II (71.0%) or III (29.0%).

Symptoms of CHF were present in all patients except 2, mainly fatigue and dyspnoea when walking. Signs of CHF were reported in more than 60% of patients, slightly less frequently reported in the 750 mg group (46.7%) than in the other groups.

The mean DEFS score was 1.1 ± 0.8, without relevant differences between the groups.

The mean total distance walking in 6 minutes was 394.9 ± 90.7 m, without relevant differences between the groups.

Regarding echocardiographic parameters, overall, at baseline, patients suffered from moderate to severe CHF with overall mean LVEF equal to 22.4 ± 6.3 %, mean LVEDVI equal to 120.9 ± 37.7 mL/m², and mean LVESVI equal to 95.0 ± 34.3 mL/m².

At baseline, overall, 87.6% of patients had NT-proBNP plasma concentrations ≥ 400 pg/mL, this percentage being slightly lower in the placebo group (78.8%).

At baseline, the median myeloperoxidase plasma concentration was below the upper limit of normal range in all groups.

In the Randomised Set, the mean overall study treatment duration was 82.1 days, without relevant difference between treatment groups.

During the treatment period, the mean overall compliance in the Randomised Set was satisfactory (97.2% of patients), without relevant difference between treatment groups.

EFFICACY RESULTS

In the FAS ECHO as well as in the PPS ECHO, no statistically significant difference was shown between the active treatment groups and the placebo group for the change from baseline in left ventricular ejection fraction, left ventricular volumes, and left ventricular volume index. A trend towards a reduction of left ventricular end-systolic and end-diastolic volumes was observed from 500 to 1000 mg b.i.d.

Main echocardiographic parameters - Changes from baseline to last post-baseline visit - FAS ECHO

Last post-baseline visit - Baseline		**S 44121 250 mg ** (N = 23)**	**S 44121 500 mg ** (N = 25)**	**S 44121 750 mg ** (N = 29)**	**S 44121 1000 mg ** (N = 28)**	**Placebo (N = 31)**
LVEF (%)	**Mean ± SD**	0.3 ± 6.5	1.8 ± 7.5	1.1 ± 6.8	0.2 ± 6.0	1.9 ± 6.7
***vs* Placebo**	E*	-1.61	-0.10	-0.7	-1.66	-
LVED Volume Index (mL/m²)	**Mean ± SD**	5.0 ± 28.5	-4.6 ± 21.2	-8.2 ± 22.2	-6.2 ± 23.4	-2.2 ± 24.8
***vs* Placebo**	E*	7.21	-2.4	-6.1	-4.0	-
LVES Volume Index (mL/m²)	**Mean ± SD**	5.2 ± 26.9	-5.4 ± 20.5	-7.8 ± 22.3	-5.7 ± 21.4	-3.4 ± 21.4
***vs* Placebo**	E*	8.6	-2.0	-4.4	-2.3	-

** Estimate of S 44121 minus placebo effect difference between group means based on a Student distribution*

*** The names of the treatment groups, i.e. S 44121 250 mg/500 mg/750 mg/1000 mg, refer to daily doses of 250/500/750/1000 mg b.i.d.*

The mean left ventricular end-systolic and end-diastolic diameters tended to remain stable in all groups between baseline and last post-baseline visit.

The mean E/A ratio and E/e' ratio tended to remain stable during the study; no relevant difference was observed between groups.

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

SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

In the FAS NT-proBNP as well as in the PPS NT-proBNP, no statistically significant difference was demonstrated between any of the active treatment groups and the placebo group for the change in NT-proBNP (see Table) and myeloperoxidase plasma concentrations, from baseline to the last post-baseline visit. The rate of patients with a decrease of at least 30% in NT-proBNP concentration tended to be similar in all groups.

NT-proBNP plasma concentration - Changes from baseline to last post-baseline visit - FAS_N

Last post-baseline visit - Baseline		**S 44121 250 mg ** (N = 24)**	**S 44121 500 mg ** (N = 26)**	**S 44121 750 mg ** (N = 29)**	**S 44121 1000 mg ** (N = 29)**	**Placebo (N = 33)**
NT-proBNP plasma concentration (pg/mL)	**Median**	-183.0	-13.5	-274.0	-61.0	-70.0
***vs* Placebo**	**E***	1.03	0.95	0.92	1.04	-
Decrease > 30%	**n (%)**	6 (25.0)	7 (26.9)	5 (17.2)	6 (20.7)	8 (24.2)

** Estimate of each dose of S 44121 effect compared to placebo ratio between geometric group means based on Student distribution after logarithmic transformation*

*** The names of the treatment groups, i.e. S 44121 250 mg/500 mg/750 mg/1000 mg, refer to daily doses of 250/500/750/1000 mg b.i.d.*

Considering all groups in the RS, the rate of improvement in the NYHA class at the last post-baseline visit ranged from 11.1% (500 mg group) to 29.2% (250 mg group), without dose effect.

Regarding global assessment by the patient and by the investigator, the rate of improvement at the last post-baseline visit ranged from 51.5% (placebo group) to 82.6% (250 mg group) for the assessment by the patient and from 44.4% (500 mg group) to 76.7% (1000 mg group) for the assessment by the investigator, without dose effect.

The mean score of the DEFS at baseline detected that patients experienced limited degree of fatigue and the mean score remained stable at the last post-baseline visit, in the RS.

Results of the Six-Minute Walk Test distance showed that the mean distance slightly increased from baseline to the last post-baseline visit in all groups, in the RS, without statistically significant difference between groups.

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

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

Emergent adverse events

Overall summary of safety results

		S 44121 250 mg * (N = 24)	S 44121 500 mg * (N = 28)	S 44121 750 mg * (N = 30)	S 44121 1000 mg * (N = 30)	Placebo (N = 33)
Patients having reported						
at least one emergent adverse event	n (%)	13 (54.2)	12 (42.9)	14 (46.7)	16 (53.3)	11 (33.3)
at least one treatment-related emergent adverse event	n (%)	2 (8.3)	4 (14.3)	3 (10.0)	3 (10.0)	-
Patients having experienced						
at least one serious adverse event (including death)	n (%)	5 (20.8)	2 (7.1)	3 (10.0)	3 (10.0)	3 (9.1)
at least one treatment-related serious adverse event	n (%)	-	-	-	-	-
Patients withdrawn						
due to an adverse event	n (%)	2 (8.3)	2 (7.1)	2 (6.7)	2 (6.7)	1 (3.0)
due to a serious adverse event	n (%)	1 (4.2)	-	1 (3.3)	1 (3.3)	1 (3.0)
due to a treatment-related adverse event	n (%)	-	2 (7.1)	-	1 (3.3)	-
due to a treatment-related serious adverse event	n (%)	-	-	-	-	-
Patients who died	n (%)	-	1 (3.6)	1 (3.3)	-	1 (3.0)

** The names of the treatment groups, i.e. S 44121 250 mg/500 mg/750 mg/1000 mg, refer to daily doses of 250/500/750/1000 mg b.i.d.*

Overall, 108 EAEs in 66/145 (45.5%) patients (while on treatment) were reported (91 EAEs in 55/112 patients (49.1%) in the pooled S 44121 group *versus* 17 EAEs in 11/33 patients (33.3%) in the placebo group. No dose-effect was observed in the S 44121 treatment groups (54.2% in the 250 mg group, 42.9% in the 500 mg group, 46.7% in the 750 mg group, 53.3% in the 1000 mg group).

The first two most frequently affected SOCs were infections and infestations (14.3% *versus* 12.1%) and cardiac disorders (13.4% *versus* 6.1%) in the pooled S 44121 group and in the placebo group.

In the pooled S 44121 group, the most frequently reported cardiac disorders were worsening chronic cardiac failure (5 patients, 4.5%), sinus bradycardia and ventricular extrasystoles (3 patients each, 2.7%). Two cardiac EAEs (sinus tachycardia and angina pectoris, each in 1 patient, 3.0%) were reported in the placebo group.

More gastrointestinal (GI) disorders in the pooled S 44121 group were reported (13.4% *versus* 3.0% in the placebo group), including 11 patients with upper GI disorders such as dyspepsia, gastritis and nausea, and 6 patients with lower GI disorders such as diarrhoea, abdominal pain and abdominal distension.

The intensity of EAEs was mostly rated as mild or moderate, whichever the group. The percentages of severe EAE were 6.3% (7/112 patients) in the pooled S 44121 group and 3.0% (1/33 patients) in the placebo group. No dose-effect was observed in the S 44121 treatment groups. All severe EAEs but one (*i.e.* upper abdominal pain in the 500 mg group) were considered by the investigator as not related to the study treatment.

14 EAEs in 12/145 (8.3%) patients were considered by the investigator to be related to the study treatment, all on S 44121 (12/112, 10.7%). Treatment-related EAEs (TEAEs) were mainly gastrointestinal disorders (12/14 TEAEs) such as dyspepsia, upper abdominal pain, gastritis, etc, without a clear dose-effect.

EAEs led to treatment discontinuation in 8/112 (7.1%) patients in the pooled S 44121 group (3 gastrointestinal disorders, 2 cardiac disorders and 3 others) and 1/33 (3.0%) in the placebo group (angina pectoris).

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

SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

The percentages of not recovered EAEs were 22.0% (20/91 EAEs, mainly cardiac disorders and GI disorders) in the pooled S 44121 groups and 11.8% (2/17 EAEs; hyperuricaemia and anaemia) in the placebo group.
None of the non-recovered EAEs in the S 44121 groups was considered by the investigator as related to the study treatment except for one case of ventricular extrasystoles.

Serious EAEs were reported in 13/112 (11.6%) patients in the pooled S 44121 group and 3/33 (9.1%) patients in the placebo group. No serious gastrointestinal disorders were reported.
Two fatal EAEs (sudden death and fatal ischemic stroke) were reported in the S 44121 group and considered by the investigator as not related to the study drug. One fatal EAE (sudden death) was reported in the placebo group.

Regarding blood biochemistry and hematology, there were no evident differences between the active-treatment and placebo groups in mean changes from baseline for any analyte. Emergent potentially clinically significant abnormal values 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, weight, BMI and ECG parameters (heart rate, PR interval, QRS duration, and QTc interval). In particular, no dose-dependent effect was detected regarding ECG parameters.

In conclusion, the safety of S 44121 was satisfactory.

CONCLUSION

In conclusion, in this exploratory study, no significant difference was shown between the active treatment groups and the placebo group for the change from baseline in left ventricular ejection fraction and left ventricular volumes, in patients suffering from NYHA II or III-class chronic heart failure with left ventricular dysfunction. A trend towards a reduction of left ventricular end-systolic and end-diastolic volumes was observed at a dose range of 500 to 1000 mg b i.d. *versus* placebo. Upper gastrointestinal adverse events, predominantly mild, were more common on active drug. Overall, the safety profile was satisfactory.

Date of the report: 4 July 2012