I.R.I.S.

INSTITUT DE RECHERCHES INTERNATIONALES SERVIER

Document title	**Clinical Study Synopsis Report**
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 not treated with a beta-blocker.** **A 12-week, randomised, double-blind, parallel-group, placebo controlled, international multicentre study.**
Study drug	**S 44121**
Studied indication	**Chronic Heart Failure**
Development phase	**Phase II**
Protocol code	**CL2-44121-004**
Study initiation date	**25 May 2010**
Study completion date	**28 December 2012**
Main coordinator	[redacted] **Germany**
Company / Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot, 92284 Suresnes Cedex - France** **Laboratorios Servier, S.L.** **Departamento de Investigación y Desarrollo** **Avenida de los Madroños, 33, 28043 Madrid - Spain** **Servier Research and Development** **International Centre for Therapeutic Research** **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 19 November 2013**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

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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 not treated with a beta-blocker.
A 12-week, randomised, double-blind, parallel-group, placebo controlled, international multicentre study.
Protocol No.: CL2-44121-004

International coordinator: [redacted] Germany)
National coordinators: [redacted] (Italy), [redacted] (Poland), [redacted] (Portugal), [redacted] (Russia), [redacted] (Spain), [redacted] (Estonia), [redacted] (Latvia), [redacted] (Romania), [redacted] (United Kingdom) and [redacted] (Ukraine).

Study centres:
38 centres located in 11 countries were opened; 37 centres in 11 countries selected at least one patient, and 32 centres in 10 countries included at least one patient.
Russian Federation – 11 centres (45 included patients), Romania – 3 centres (30 included patients), Latvia - 3 centres (10 included patients), Poland – 3 centres (9 included patients), Ukraine – 6 centres (8 included patients), Italy – 2 centres (7 included patients), Estonia – 1 centres (5 included patients), Portugal – 3 centres (4 included patients), United Kingdom – 2 centres (1 included patients), Germany - 1 centre (1 included patients), Spain – 3 centres (no patient included)

Publication (reference): Not applicable.

Studied period:	**Phase of development of the study:**
Initiation date: 25 May 2010 Completion date: 28 December 2012	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 not treated with a beta-blocker. 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 II or III) and left ventricular (LV) systolic dysfunction (LV Ejection Fraction [LVEF] ≤ 40%) and not treated with a beta-blocker.
The total study duration for patients was 13 weeks: a one week run-in period, followed by a 12-week double-blind treatment period.

Number of patients:
Planned: 125 patients, 25 in each treatment group.
Included: 120 patients in total, *i.e.* 28 patients in the S 44121 250 mg group, 23 in the S 44121 500 mg group, 26 in the S 44121 750 mg group, 20 in the S 44121 1000 mg group, and 23 in the placebo group.

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Diagnosis and main criteria for inclusion:

Patients aged between 18 and 80 years:

- With symptomatic (stable for at least 4 weeks) CHF for at least 6 months before selection, main cause being ischaemic heart disease or idiopathic dilated cardiomyopathy.
- NYHA class II or III.
- Treated with Angiotensin Converting Enzyme (ACE) inhibitors and/or Angiotensin Receptor Blocker (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.
- Not treated with a beta-blocker within 2 months before selection.
- LV dysfunction evidenced by LVEF ≤ 40%, and validated by the Echo Core Lab at inclusion.
- N-terminal prohormone Brain Natriuretic Peptide (NT-proBNP) plasma concentration ≥ 400 pg/mL or Brain Natriuretic Peptide (BNP) plasma concentration ≥ 100 pg/mL.
- Sinus rhythm.

Study drug:

S 44121, twice daily (*b.i.d.*), fixed-dose oral administration of one of the four dosages, 250 mg, 500 mg, 750 mg or 1000 mg. The study drug was delivered in sachets sets of 3 colours: the yellow and blue sachets had doses of 250 mg (or placebo) and pink sachets had a dose of 500 mg (or placebo), thus allowing an administration of each S 44121 doses levels planned for the study (*i.e.* 250 mg, 500 mg, 750 mg or 1000 mg). The content of 3 sachets (diluted in 200 ml of water) had to be taken in a single intake with a meal.

Batch No. 250 mg blue sachet: L0031461, L0033367, L0039713; 250 mg yellow sachet: L0031459, L0033365, L0039711; 500 mg pink sachet: L0031463, L0031465, L0033369, L0033371, L0039715.

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 double-blind treatment period: from visit W000 to visit W012.

Criteria for evaluation:

Efficacy measurements:

- Echocardiographic parameters (centrally assessed) at visits: Selection, W000, W004, W008, and W012:
  - Left ventricular ejection fraction (LVEF, %).
  - Left ventricular end-systolic and end-diastolic volumes (LVESV and LVEDV, mL) and volumes indexed to body surface area (LVESVI and LVEDVI, mL/m²).
  - Left ventricular end-systolic and end-diastolic internal diameters (LVESID and LVEDID, mm).
  - Cardiac output (L/min) and cardiac index (L/min/m2).
  - 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 (MPO) plasma concentration (ng/mL) (centrally assessed) at W000, W001, W004, W008, and W012.
- NYHA functional class at visits: Selection, 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 visits: Selection, W000, W004, W008, and W012.

Safety measurements:

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

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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 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 on treatment (date of echo ≤ date of last intake +1) at W012 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 Full Analysis Set NT-proBNP with an evaluation of NT-proBNP on treatment (sampling date ≤ date of last intake +1) at W012 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.

Echocardiographic parameters, NT-proBNP and myeloperoxidase 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 myeloperoxidase 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 myeloperoxidase, 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 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. Descriptive analyses of Emergent adverse events (EAE) were performed, including those that were serious (or fatal), severe, led to study drug withdrawal, related to study drug, led to study drug withdrawal, were related to study drug, and those required new treatment. Descriptive analyses were provided for EAEs of the adapted list of the standard 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”. Descriptive analysis of 12-lead ECG parameters, vital signs and blood laboratory parameters were also provided.

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SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 205 patients were screened and 195 patients were selected for the study. Among them, 120 patients were included and randomly assigned to one of the five groups: 28 patients in the 250 mg group, 23 patients in the 500 mg group, 26 patients in the 750 mg group, 20 patients in the 1000 mg group, and 23 patients in the placebo group (see Table). These patients constituted the Randomised Set (RS). In the RS, 106 patients (88.3%) completed the study and 14 patients (11.7%) were withdrawn from the study: 11 patients due to adverse event, and 3 for non-medical reason. No patient was lost to follow-up.

Status		**S 44121 250 mg**	**S 44121 500 mg**	**S 44121 750 mg**	**S 44121 1000 mg**	**Placebo**	**All**
Included and randomised	n	28	23	26	20	23	120
Lost to follow-up	n	-	-	-	-	-	-
Withdrawn due to	n	3	2	2	1	6	14
adverse event	n	2	1	2	1	5	11
non-medical reason	n	1	1	-	-	1	3
Completed	n	25	21	24	19	17	106
Safety Set	n (%)	28 (100)	23 (100)	26 (100)	20 (100)	23 (100)	120 (100)
Efficacy Sets							
Full Analysis Set ECHO (FAS_E)	n (%)	26 (92.9)	23(100)	26 (100)	20(100)	20 (87.0)	115 (95.8)
Per Protocol Set ECHO (PPS_E)	n (%*)	21 (80.8)	16 (69.6)	22 (84.6)	17 (85.0)	16 (80.0)	92 (80.0)
Full Analysis Set NT-proBNP (FAS_N)	n (%)	27 (96.4)	23 (100)	26 (100)	20 (100)	23 (100)	119 (99.2)
Per Protocol Set NT-proBNP (PPS_N)	n (%*)	23 (85.2)	18 (78.3)	23 (88.5)	17 (85.0)	16 (69.6)	97 (81.5)

% % of the Randomised Set; % % of the corresponding Full Analysis Set.*

In the RS, patients were mainly men (90.8%) and had a mean age of 62.3 ± 9.9 years. The duration since CHF diagnosis was 3.6 ± 3.8 years in average (median = 2.0 years). The main causes of CHF were ischaemic disease (80.8% patients) and idiopathic dilated cardiomyopathy (18.3% patients). The proportion of ischaemic patients was lower in the 1000 mg group (65.0%) than in the other groups. Hypertension was the most commonly reported secondary cause of CHF (12/18, 66.7%).

At inclusion, the heart rate and blood pressure were similar across treatment groups. The mean HR was 71.7 ± 12.5 bpm, and the mean sitting SBP and DBP were 118.8 ± 12.6 mmHg and 73.2 ± 7.9 mmHg, respectively.

As specified in protocol, all patients were treated with an ACE inhibitor and/or an angiotensin receptor blocker (ARB) for at least 3 months before selection and no patient was treated with a beta-blocker within the 2 months before selection. The main reasons for not receiving beta-blocker were concomitant chronic obstructive pulmonary disease and hypotension. During the study, all randomised patients were treated with either an ACE inhibitor (83.3%) or ARB (18.3%). Regarding other medical histories, 65.8% of the patients had hypertension, 53.3% myocardial infarction, 48.3% coronary artery disease, and 36.7% angina pectoris.

The main baseline echocardiographic measurements were: overall mean LVEF ± SD equal to 22.5 ± 7.0%, mean LVESVI ± SD equal to 82.9 ± 28.6 mL/m² and mean LVEDVI ± SD equal to 105.8 ± 31.4 mL/m². Higher mean LV volumes were observed in the 1000 mg group (LVESVI: 98.5 ± 29.4 mL/m², LVEDVI: 124.6 ± 34.6 mL/m²) which may reflect a more severe baseline CHF in the patient of this group. All patients had moderate to severe CHF on clinical evaluation at baseline (NYHA class II [52.5%] or III [47.5%]).

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

The median plasma NT-proBNP concentration at baseline was 1382.5 pg/mL (geometric mean 1432.2 pg/mL); overall, 90.8% patients had NT-proBNP plasma concentrations ≥ 400 pg/mL. The median plasma myeloperoxidase concentration at baseline was 22.1 ng/mL (geometric mean 30.0 pg/mL).

The mean DEFS score was 1.5 ± 0.9 and the mean total distance walked in 6 minutes was 329.2 ± 92.1 m, without relevant difference between the groups.

The overall mean treatment duration was 81.9 ± 19.1 days, which corresponded to the planned duration. During the treatment period, the mean overall compliance in the RS was satisfactory (96.4%), with 99.2% of the patients having compliance between 70% and 130%.

No clinically relevant between-treatment group differences were evidenced for the above parameters, except that higher LV volumes in the 1000mg S 44121 group than in the other groups should be considered when interpreting the results.

EFFICACY RESULTS

In the FAS_E as well as in the PPS_E, S 44121 showed some evidence of efficacy in improving the cardiac function (LVEF and LV volumes). In the 250 mg and 750 mg groups, a clinically significant difference based on effect size estimated from the 95% confidence interval, was observed for the change of LVEF from baseline to post-baseline value *versus* placebo, while there was a consistent trend towards an increase in the 500 mg group. With regards to left ventricular volumes, there was a clinically relevant trend of reduction in LVESVI and LVEDVI in the 750 mg group. There was no dose-effect relationship and no relevant changes were seen in the 1000 mg group, which had greater mean left ventricular volumes at baseline as compared to the other groups.

Main echocardiographic parameters - Changes from baseline to last post-baseline value - FAS_E

Last post-baseline value - Baseline		**S 44121 250 mg (N = 26)**	**S 44121 500 mg (N = 23)**	**S 44121 750 mg (N = 26)**	**S 44121 1000 mg (N = 20)**	**Placebo (N = 20)**
LVEF (%)	**Mean ± SD**	4.4 ± 7.8	1.4 ± 5.5	2.4 ± 7.1	0.7 ± 7.0	-0.6 ± 4.3
Estimate of change vs placebo	E(1)	5.7	2.1	4.0	1.1	-
	95% CI	[2.2 ; 9.3]	[-1.6 ; 5.8]	[0.5 ; 7.6]	[-2.7 ; 4.9]	-
LVESVI (mL/m²)	**Mean ± SD**	-2.9 ± 12.7	0.9 ± 17.1	-7.3 ± 19.1	-1.7 ± 18.7	0.5 ± 18.8
Estimate of change vs placebo	E(1)	-4.2	0.6	-8.9	0.8	-
	95% CI	[-14.1 ; 5.7]	[-9.5 ; 10.7]	[-18.8 ; 0.9]	[-9.8 ; 11.4]	-
LVEDVI (mL/m²)	**Mean ± SD**	1.8 ± 11.5	3.7 ± 18.3	-7.0 ± 20.9	-2.4 ± 20.2	-0.3 ± 20.4
Estimate of change vs placebo	E(1)	1.4	4.3	-7.6	1.8	-
	95% CI	[-9.1 ; 11.9]	[-6.4 ; 15.0]	[-18.0 ; 2.8]	[-9.4 ; 13.1]	-

(1) Estimate of S 44121 minus placebo effect difference between group means based on a parametric analysis of covariance adjusted for baseline value; 95% CI 95% confidence interval.

During the study, the mean LVESID, LVEDID, E/A ratio and E/E' ratio tended to remain stable in all groups between baseline and last post-baseline value. The cardiac output and the cardiac index slightly increased in the 250 mg and 500 mg group while it remained stable in the other groups.

In the FAS_N as well as in the PPS_N, a consistent reduction of NT proBNP plasma concentration from baseline to last post-baseline value was shown in the active treatment groups *versus* the placebo group. More patients had a decrease of more than 30% in NT-proBNP concentration in all S 44121 dosage groups than in the placebo group.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Plasma concentration – NT-proBNP Changes from baseline to last post-baseline value - FAS_N

Last post-baseline value - Baseline	**S 44121 250 mg (N = 27)**	**S 44121 500 mg (N = 23)**	**S 44121 750 mg (N = 26)**	**S 44121 1000 mg (N = 20)**	**Placebo (N = 23)**
NT-proBNP plasma concentration (pg/mL)					
Median	74.0	3.0	-39.0	-4.5	218.0
Estimate of change vs placebo E[(1)]	-232.0	-216.0	-494.5	-315.5	-
95% CI	[-687.0 ; 89.0]	[-931.0 ; 294.0]	[-1687.0 ; -12.0]	[-1077.0 ; 142.0]	

(1) Estimate of S 44121 minus placebo effect difference between group means based on a non-parametric analysis based on Hodges & Lehmann estimate.

Concerning MPO plasma concentrations, no significant difference was observed in the S 44121 groups *versus* the placebo group.

Considering all groups in the RS, the percentages of patients showing improvement in the NYHA class at the last post-baseline value were higher in 250 mg group (25.9%) and 750 mg groups (26.9%), without a clear trend between the groups.

Regarding global assessment by the patient and by the investigator, the rate of improvement at the last post-baseline value did not show a clear trend between the groups.

The mean score of the DEFS at baseline indicated that patients experienced limited degree of fatigue and the mean score remained stable between baseline and the last post-baseline value, in the RS, whatever the treatment group.

Results of the Six-Minute Walk Test distance showed that the mean distance was slightly increased from baseline to the last post-baseline value in all groups (range from 18.6 m to 41.4 m), in the RS, without significant difference between the groups.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS

Overall summary of safety results (EAEs on treatment) – Safety Set

		S 44121 250 mg (N = 28)	S 44121 500 mg (N = 23)	S 44121 750 mg (N = 26)	S 44121 1000 mg (N = 20)	All S 44121 doses pooled (N = 97)	Placebo (N = 23)
Patients having reported							
at least one emergent adverse event	n (%)	9 (32.1)	9 (39.1)	7 (26.9)	7 (35.0)	32 (33.0)	13 (56.5)
at least one treatment-related emergent adverse event	n (%)	1 (3.6)	2 (8.7)	3 (11.5)	1 (5.0)	7 (7.2)	3 (13.0)
Patients having experienced							
at least one serious adverse event (including death)	n (%)	2 (7.1)	4 (17.4)	4 (15.4)	-	10 (10.3)	4 (17.4)
at least one treatment-related serious adverse event	n (%)	-	1 (4.3)	-	-	1 (1.0)	-
Patients withdrawn							
due to adverse event	n (%)	2 (7.1)	1 (4.3)	2 (7.7)	1 (5.0)	6 (6.2)	4 (17.4)
due to serious adverse event	n (%)	1 (3.6)	1 (4.3)	-	-	2 (2.1)	1 (4.3)
due to treatment-related adverse event	n (%)	1 (3.6)	1 (4.3)	2 (7.7)	1 (5.0)	5 (5.2)	3 (13.0)
due to treatment-related serious adverse event	n (%)	-	1 (4.3)	-	-	1 (1.0)	-
Patients who died	n (%)	-	-	-	-	-	1 (4.3)

Overall, a lower frequency of on-treatment EAEs was observed in the pooled S 44121 group than the placebo group; 53 on-treatment EAEs in 32/97 patients (33.0%) in the pooled S 44121 group *versus* 27 EAEs in 13/23 patients (56.5%) in the placebo group. No dose-effect on EAEs was observed in the S 44121 treatment groups.

The two most frequently affected System Organ Classes (SOCs) in the pooled S 44121 group were cardiac disorders (14.4% *versus* 21.7% in the placebo group) and infections and infestations (10.3% *versus* 8.7% in the placebo group). Thus, emergent cardiac disorders were reported at a lower incidence rate in the pooled S 44121 group compared to the placebo group. The most frequently reported cardiac disorders in the pooled S 44121 group were worsening of chronic cardiac failure (3.1% *versus* 13.0% in the placebo group) and ventricular extrasystoles (3.1% *versus* 4.3% in the placebo group).

Concerning specific SMQ "Gastrointestinal nonspecific inflammation and dysfunctional conditions" and "Gastrointestinal ulceration", fewer cases were reported in the pooled S 44121 group (4.1% versus 13.0% in the placebo group). Concerning specific SMQs "Cardiac arrhythmias" and "Cardiac arrest", fewer cases were reported in the pooled S 44121 group (12.4% versus 21.7% in the placebo group).

Most EAEs were rated as mild or moderate in all groups. The percentages of severe EAE were 4.1% (4/97 patients) in the pooled S 44121 group and 17.4% (4/23 patients) in the placebo group. No dose-effect was observed in the S 44121 treatment groups. None of the severe EAEs except two were considered by the investigator as related to the study treatment (electrocardiogram QT prolonged in the 500 mg group, food aversion in the placebo group).

Eleven treatment related EAE (TEAE) were reported in 7 patients (7.2%) in the pooled S 44121 group *versus* 4 TEAE in 3 patients (13.0%) patients in the placebo group, mainly gastrointestinal disorders (4 TEAEs in 3 patients (3.1%) in the pooled S 44121 group *versus* 3 TEAEs in 3 patients (13.0%) in the placebo group), without a clear dose-effect.

EAEs leading to study drug withdrawal were reported in 6/97 (6.2%) patients in the pooled S 44121 group (2 cardiac disorders, 1 gastrointestinal disorder, 1 investigation, 1 metabolism and nutrition disorder, and 1 nervous system disorder) and 4/23 (17.4%) patients in the placebo group (1 cardiac disorder, 2 gastrointestinal disorders, and 1 psychiatric disorder).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

The percentages of not recovered EAEs were 15.1% (8/53 EAEs) in the pooled S 44121 groups and 33.3% (9/27 EAEs) in the placebo group. Among the non-recovered EAEs, one event in the 750 mg group was considered by the investigator as related to the study drug (electrocardiogram QT prolonged).

Twelve SEAEs on treatment were reported in 10 patients (10.3%) in the pooled S 44121 group and 7 SEAEs were reported in 4 patients (17.4%) in the placebo group. No serious gastrointestinal EAE on treatment was reported. One fatal EAE (sudden cardiac death) was reported in the placebo group which was considered by the investigator as unlikely related to the study drug, while no death occurred in any of the S 44121 groups. All non-fatal SEAE recovered.

Regarding 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 exploratory study showed that the S 44121 had some efficacy in patients with chronic heart failure and left ventricular dysfunction not treated with beta-blocker on the main efficacy parameters (echocardiography, NT-proBNP) with clinically significant differences, based on effect size estimated from the 95% confidence interval, for the doses of 250 mg and 750 mg b.i.d. *versus* placebo. There was no dose-effect relationship. No beneficial effect was seen in the 1000 mg group, which had higher left ventricular volumes at baseline as compared to the other groups. Regarding safety, the data showed a favourable profile for S 44121 as compared to placebo. Notably, the rates of cardiac and gastrointestinal adverse events were lower in the group treated with the S 44121 *versus* placebo.

Date of the report: 19 November 2013