Document title	**CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Evaluation of the pharmacodynamics, pharmacokinetics and safety of repeated escalating oral doses of S 38844 *versus* placebo in patients with chronic heart failure and left ventricular systolic dysfunction** **A phase II, randomised, double-blind, parallel-group, placebo controlled, international multicentre study**
Test drug code	**S 38844**
Indication	**Heart Failure**
Development phase	**Phase II**
Protocol code	**CL2-38844-010**
Study initiation date	**01 August 2014**
Study completion date	**08 June 2015**
Main coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France** **Les Laboratoires Servier Representative Office** **Paveletskaya sq 2, bld 3, floor 3** **115054 Moscow - Russia**
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	**4 February 2016**
Version of the report	**Final version**

~~**CONFIDENTIAL**~~

2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Not applicable **Name of Active Ingredient:** S 38844		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**
Title of study: Evaluation of the pharmacodynamics, pharmacokinetics and safety of repeated escalating oral doses of S 38844 *versus* placebo in patients with chronic heart failure and left ventricular systolic dysfunction. A phase II, randomised, double-blind, parallel-group, placebo controlled, international multicentre study. Protocol No.: CL2-38844-010 EudraCT No.: 2013-003000-39 The description of the study protocol given hereafter includes the modifications of the five substantial amendments to the protocol (Amendments No. 1, 2, 3, 4 and 5).		
International coordinator : [redacted]		
Study centres: 130 patients were included in 35 centres located in 10 countries: Belgium (1 centre, 2 patients), Bulgaria (6 centres, 19 patients), Estonia (2 centres, 8 patients), Hungary (5 centres, 13 patients), Latvia (4 centres, 10 patients), Lithuania (4 centres, 11 patients), Russia (5 centres, 13 patients), Singapore (2 centres, 4 patients), Slovakia (1 centre, 15 patients), Ukraine (5 centres, 35 patients).		
Publication (reference): Not applicable		
Studied period: Initiation date: 01 August 2014 (date of first visit first patient) Completion date: 08 June 2015 (date of last visit last patient)	**Phase of development of the study:** Phase II	
Objectives: The **primary objective** was to evaluate the pharmacodynamics in relation to resting heart rate (HR) of two different schemes of starting doses and two step titration doses of S 38844 *versus* placebo in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction (LVEF ≤ 35%), HR ≥ 75 bpm and treated with optimal background therapy. The **secondary objectives** were: - To assess the pharmacokinetics of S 38844 and its main metabolites and the pharmacokinetic/pharmacodynamic (PK/PD) relationship with respect to resting HR for each tested dose of S 38844. - To evaluate the global and cardiac safety of two different schemes of starting doses and two steps titration doses of S 38844 *versus* placebo. **Other objective** was to evaluate the effect of S 38844 compared to placebo on cardiovascular biomarkers: hs-troponin, cystatin-C and NT-proBNP.		
Methodology: This study was an exploratory phase II, international, multicentre, randomised, double-blind, placebo-controlled trial with 3 parallel arms: 2 active with titration conditional steps at W3 and W6 and one placebo group. The randomisation was stratified by country. This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.		
Number of patients: Planned: 200 patients with non-balanced ratio between groups *i.e.* 80 patients in each of the two S 38844 groups and 40 patients in the placebo group, amended (Amendment No. 5) to 125 patients *i.e.* 50 patients in each of the two S 38844 arms and 25 patients in the placebo group. Included: 130 patients: 52 patients in each group S 38844 25 mg and S 38844 50 mg, 26 in the placebo group.		

Diagnosis and main criteria for inclusion:
Main criteria for selection/inclusion:

- Male or female ≥ 18 years
- Symptomatic Chronic Heart Failure (CHF) of New York Heart Association (NYHA) class II, III or IV for at least 3 months prior to selection.
- CHF from all aetiologies except from congenital heart disease or from severe aortic or mitral valve disease.
- In stable clinical condition with regards to CHF symptoms and with optimal and unchanged CHF medications or dosages for at least 4 weeks prior to selection.
- Documented sinus rhythm and HR ≥ 75 bpm on two consecutive resting standard 12-lead ECG at least 5 min apart recording in supine position after a 10-minute rest. If one of the two HR measurements was 73 or 74 bpm at the selection/inclusion visits, the patient could be included provided that the mean of both HR measurements at the visit was ≥ 75 bpm.
- LVEF ≤ 35% as measured and documented within the previous 6 months (in stable clinical condition).

Main criteria for non-selection/ non-inclusion:

- Unstable condition within the previous 4 weeks (*e.g.* documented hospital admission for worsening heart failure, myocardial infarction, cardiogenic shock).
- Documented permanent atrial fibrillation or sick sinus syndrome or sinoatrial block or other cardiac arrhythmia that interfere with the sinus node function, or recent hospitalization for atrial fibrillation within the last 3 months.
- Cardiac Resynchronization Therapy (CRT).
- Implantable pacemaker.
- Congenital long QT syndrome or substance-induced long QT syndrome or treatment with QT prolonging medicinal products.
- Known anaemia (serum haemoglobin < 110 g/L).
- Known liver function test abnormalities (ALT and/or AST > 3 times the upper normal values).

Investigational Medicinal Products (IMP):
S 38844: 25 mg, 50 mg or 100 mg tablets, orally administered once daily (*o.d.*), two tablets in the morning with water during breakfast (one 25 mg tablet and one placebo tablet OR one 50 mg tablet and one placebo tablet OR one 100 mg tablet and one placebo tablet).
In the group S 38844 25 mg: a starting dose of 25 mg *o.d.* was dispensed at W0, then optionally up-titrated to 50 mg *o.d.* at W03 then to 100 mg *o.d.* at W6.
In the group S 38844 50 mg: a starting dose of 50 mg *o.d.* was dispensed at W0, then optionally up-titrated to 100 mg *o.d.* at W3 or at W6. When receiving 100 mg at W3, these patients continued to receive the dose of 100 mg until W9 (a 150 mg dose was planned but this was cancelled by Amendment No. 2).
In the group placebo: 3 successive periods of 3 weeks with dose escalation matching placebo.
Batch No.: S 38844 25 mg (L0051712); S 38844 50 mg (L0051766, L0056666); S 38844 100 mg (L0051716, L0055184).
Dose titration: dose was increased if HR was > 60 bpm, maintained if 50 ≤ HR ≤ 60 bpm or discontinued if HR < 50 bpm or in the presence of signs and/or symptoms likely to be due to bradycardia. No dose reduction was possible.
Placebo tablets matching the active products for double blind masking
Batch No.: L0051605 and L0056664

Duration of treatment:
The run-in period was with placebo tablets (7 to 14 days).
The active treatment period was 9 weeks (3 successive treatments periods of 3 weeks each +/- 5 days).
After the 9 weeks active treatment period, patients were followed during 7 to 14 days without treatment (W9 to WEND).

Criteria for evaluation:

E*fficacy measurements*
Primary pharmacodynamic criterion:
HR was measured in supine position on two consecutive resting (after at least 10 minutes rest) standard 12-lead ECGs at least 5 min apart at IMP trough. HR change from baseline was the main expression of primary endpoint to assess the pharmacodynamic (PD) effects *i.e.* HR reduction of two different schemes of starting doses and two step titration doses of S 38844.

Secondary pharmacodynamic criteria
Sinus rhythm yes/no
Number of patients having reached for the first time a HR in [55;60] bpm

Safety measurements (at each visit):

- Occurrence of emergent adverse events (EAE) including EAE of special interest.
- Other safety criteria:
  - Laboratory blood test (haematology and biochemistry parameters)
  - Physical examination including weight, systolic and diastolic blood pressure change
  - NYHA class change
  - 12-lead ECG parameters
  - 24-hour Holter ECG parameters

Pharmacokinetic measurements:
Plasma pharmacokinetics (PK) parameters of the parent drug S 38844 and of its main metabolites.
PK/PD relationship between HR and the plasma concentrations of active compounds of S 38844.

Cardiovascular biomarkers
3 biomarkers were assessed: hs-troponin, cystatin-C and NT-proBNP.

Statistical methods:
Analysis sets
The analyses were carried-out on patients in Per Protocol Set (PPS) and Full Analysis Set (FAS). The PPS was defined as: all patients of RS having taken at least 1 dose of IMP and having completed the titration treatment period in accordance with the protocol, *i.e.* having an analysable HR value (*i.e.* primary criterion) at baseline and at W9 under treatment without relevant deviation which could affect the HR evaluation. The FAS was defined as: all patients of the RS having taken at least 1 dose of IMP and having an analysable HR value at baseline and at least one post-baseline analysable HR value during the treatment period.

Primary pharmacodynamic criterion (heart rate)
Primary analysis:
Each group of S 38844 was compared to placebo in the PPS on change from baseline to W9 and in the FAS on change from baseline to last post-baseline value under treatment of HR, using an analysis of covariance (ANCOVA) model. The estimate of the between-group difference as well as its two-sided 95% confidence interval (CI) was provided. Analysis of covariance included the fixed, categorical effect of treatment, as well as the continuous fixed covariate of baseline.

Secondary analyses:

- HR reduction at W3 in the PPS and the FAS with same analysis strategy as the primary analysis.
- HR change from baseline to W6 in the PPS and the FAS and from baseline to W9 in the FAS; as well as change from W9 to WEND in the PPS and change from last post-baseline value under treatment to WEND in the FAS was described in each group.
- HR change from baseline to each post-baseline value under treatment in the PPS and the FAS in subgroups of patients with HR ≤ 85 bpm, and > 85 bpm at baseline was described in each group.

Secondary pharmacodynamic criteria
Descriptive analysis in terms of value in the FAS and in the PPS was provided.

Safety analysis:
The safety analyses were carried-out on patients of the Safety Set. Descriptive statistics of the safety criteria were provided.

Holter ECG: all parameters were described in terms of value at baseline and value at each post-baseline visit under treatment (including last post-baseline value under treatment); as well as in terms of shift tables between baseline and last post-baseline value under treatment (for bradycardia and other Holter abnormalities). Mean lowest and highest HR and mean and longest RR interval were also described in terms of change from baseline to each post-baseline visit under treatment (including last post-baseline value under treatment).

Pharmacokinetic (PK) analysis and pharmacokinetic/pharmacodynamic (PK/PD) relationship
The pharmacokinetics of S 38844 as well as its main metabolites S 41015 and the HR were evaluated by graphical comparison of model-predicted S 38844 and S 41015 concentrations and observed S 38844 and S 41015 concentrations, and HR, using a previously developed population PK/PD (PPK/PD) model which describes the systemic concentrations of S 38844 and its main metabolite S 41015 after repeated oral administration of S 38844 in healthy volunteers (HV) and the resulting heart-rate (HR)-time profile.

Cardiovascular biomarkers
Effect of treatment: value at baseline and W9, change from baseline to W9 in the PPS and in the FAS.
The difference between S 38844 groups and placebo was estimated using the non-parametric approach of Hodges & Lehmann on the change from baseline to W9 as well as its 95% CI in overall patients and by subgroup of HR at baseline.
Relationship between cardiovascular biomarkers and resting HR: the scatter plot of change from baseline to W9 of cardiovascular biomarkers and change from baseline to W9 of resting HR (similarly HR at W9) with the Spearman correlation coefficients and its 95% CI were provided by treatment groups.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 152 patients were screened for the study and 149 patients were selected. Of them, 130 patients were included and randomised: 52 patients in each of the S 38844 25 mg and S 38844 50 mg groups and 26 patients in the placebo group.

The 9-week treatment period was completed by 114 patients (87.7%) while 16 patients (12.3%) were prematurely withdrawn: 5.4% for adverse event, 4.6% for non-medical reason and for 2.3% protocol deviation.

18 patients of the FAS (N = 122) were excluded from the PPS (N = 104) due to no analysable HR value at W9 under treatment (15 patients, 12.3% of the FAS: 8 patients did not attend W9 visit due to prematurely withdrawal, 6 patients had ECG not done at trough and 1 patient was not in sinus rhythm), or due to a concomitant treatment with possible impact on HR (3 patients).

Patient status during the study and number of patients in each analysis sets are presented in Tables 1 and 2.

Table 1 - Disposition of patients

Status		**S 38844 25 mg**	**S 38844 50 mg**	**Placebo**	**All**
Included (randomised)	**N**	**52**	**52**	**26**	**130**
Withdrawn due to	**n (%)**	**5 (9.6)**	**8 (15.4)**	**3 (11.5)**	**16 (12.3)**
adverse event	n (%)	1 (1.9)	5 (9.6)	1 (3.8)	7 (5.4)
protocol deviation	n (%)	2 (3.8)	1 (1.9)	-	3 (2.3)
non-medical reason	n (%)	2 (3.8)	2 (3.8)	2 (7.7)	6 (4.6)
and performed the WEND visit	n	4	6	1	11
Completed	**n (%)**	**47 (90.3)**	**44 (84.6)**	**23 (88.5)**	**114 (87.7)**
and performed the WEND visit	n	47	43	23	113

%: Expressed as percentage of the included patients

Table 2 - Analysis sets

Analysis sets		S 38844 25 mg	S 38844 50 mg	Placebo	All
Randomised Set (RS)	n	52	52	26	130
Safety Set (SS)	n (%)	52 (100)	52 (100)	26 (100)	130 (100)
Full Analysis Set (FAS)	n (%)	49 (94.2)	49 (94.2)	24 (92.3)	122 (93.8)
Per Protocol Set (PPS)	n (%)*	44 (89.8)	40 (81.6)	20 (83.3)	104 (85.2)

n: number of patient in each group concerned
%: calculated as % of the Randomised Set
** calculated as % of the FAS*

STUDY POPULATION AND OUTCOME

Main baseline characteristics

In the Randomised Set (N = 130), the study population had a mean age (± SD) of 59.0 ± 10.0 years with a range of 26 to 79 years, was 80.8% men and 96.9% Caucasian. BMI was 29.9 ± 5.7 kg/m^2. CHF had been diagnosed for a mean of 49.7 ± 42.2 months. The main origin of the CHF was mostly ischaemic in 70.8% of patients, dilated cardiomyopathy in 20.0% and hypertension in 7.7%. Patients were mostly in NYHA class II (49.2%) or class III (50.0%).

The demographic characteristics and history of CHF were comparable between groups but the proportion of patients in NYHA class III was relatively higher in S 38844 25 mg (61.5%) group than in S 38844 50 mg (38.5%) and placebo (50.0%) groups.

The mean resting ECG HR was 83.2 ± 8.5 bpm overall. Mean values of sitting SBP and DBP were 127.1 ± 13.1 mmHg and 77.8 ± 8.3 mmHg, respectively.

The large majority of patients (94.6%) were receiving at least one specific concomitant treatment for CHF at inclusion which was beta-blockers (93.8%), except one patient in S 38844 25 mg group who received amiodarone and withdrew the study. The most frequently prescribed were bisoprolol (35.2%), carvedilol (23.7%), metoprolol succinate (18.9%) and nebivolol (16.3%). The mean daily dose did not show relevant between-group difference, except for carvedilol with lower dose in S 38844 25 mg (19.4 mg) and in placebo (15.6 mg) groups *versus* S 38844 50 mg (32.7 mg).

The most frequently non-specific concomitant treatments prescribed were antithrombotic agents (91.5%), diuretics (87.7%, mostly spironolactone (54.6%), torasemide (36.9%) and furosemide (32.3%)), agents acting on the renin-angiotensin system (85.4%) and lipid modifying agents (72.3%). No relevant differences between groups were observed.

In the PPS (N = 104), the main baseline characteristics were comparable to those described in the RS. Similarly as in the RS, these characteristics were comparable between groups except for the proportion of patients in NYHA class III which was relatively higher in S 38844 25 mg (61.4%) group than in S 38844 50 mg (42.5%) and placebo (50.0%) groups.

Treatment duration and dose titration

In the RS, the overall mean treatment duration was 61.6 ± 14.0 days, without relevant between-group difference. During both run-in and treatment periods, the mean compliance was good as 95.9% and 97.5% of overall patient, respectively.

More than 50% of patients treated with S 38844 were up-titrated to 100 mg dose. In S 38844 group with 25 mg starting dose, the most frequent dose titration profile was 25/50/100 mg in 53.9% of patients. In S 38844 group with 50 mg starting dose, the most frequent dose profile was 50/100/100 mg in 57.7% of patients. Only 4 patients (7.7%) who started with S 38844 25 mg dose completed the study with 25 mg and 10 patients (19.2%) who started with 50 mg dose completed the study with 50 mg. At W3, the proportion of patients with dose increased was higher in the S 38844 25 mg group (75.0%) than in the S 38844 50 mg group (63.5%). At W6, dose was increased in most of patients (65.4%) in S 38844 25 mg group and unchanged in most of patients (76.9%) in S 38844 50 mg group. At W9, 53.9% of patients in the S 38844 25 mg group and 67.3% in the S 38844 50 mg group reached the 100 mg dose.

EFFICACY RESULTS

Primary analysis

In the PPS, the mean resting HR decreased over the 9-week treatment period in all groups. Higher HR reduction was observed in S 38844 25 mg group (-16.6 ± 10.3 bpm) and in S 38844 50 mg group (-19.1 ± 11.9 bpm) than in placebo group which nevertheless showed a relatively important reduction (-9.5 ± 6.3 bpm). HR reduction observed in placebo group can be explained by the low sample size and high baseline HR values in overall patients. The estimate of the difference with standard error (E (SE)) in change *versus* placebo group was -5.8 (2.5) bpm in S 38844 25 mg group and -8.0 (2.5) bpm in S 38844 50 mg group. HR change from baseline to W9 with main statistical analysis is presented in the Table 3.

Table 3 - 12-lead ECG HR at rest - Change from baseline to W9 visit in the PPS (N = 104)

HR (bpm)		**S 38844 25 mg**	**S 38844 50 mg**	**Placebo**
	N	44	40	20
Baseline	Mean ± SD	83.44 ± 7.02	83.79 ± 10.32	81.18 ± 7.70
	Min ; Max	75.0 ; 102.5	75.0 ; 130.0	75.0 ; 103.0
W9	Mean ± SD	66.86 ± 10.42	64.74 ± 10.37	71.68 ± 6.32
	Min ; Max	50.0 ; 92.5	48.5 ; 91.5	63.0 ; 85.5
W9 - baseline	**Mean ± SD**	**-16.58 ± 10.31**	**-19.05 ± 11.86**	**-9.50 ± 6.27**
	Min ; Max	-39.5 ; 10.5	-47.5 ; 10.5	-26.0 ; 2.0
Main statistical analysis	E (SE) (1)	-5.76 (2.47)	-8.03 (2.51)	
	95% CI (2)	[-10.67 ; -0.86]	[-13.02 ; -3.05]	

(1) Estimate (Standard Error) of the difference between treatment group means adjusted on baseline: S 38844 25 mg minus placebo and S 38844 50 mg minus placebo (2) 95% Confidence interval of the estimate

In the FAS (N = 122), similar results as those in PPS were obtained on the HR change from baseline to last post-baseline value under treatment.

Secondary analysis

The results presented hereafter were obtained in the PPS.

- HR reduction at W3: after 3-weeks of treatment with starting dose, the mean resting HR markedly decreased. A higher HR reduction was observed in S 38844 25 mg group by -11.5 ± 10.9 bpm and in S 38844 50 mg group by -16.1 ± 9.5 bpm compared to placebo group by -7.4 ± 5.3 bpm. The estimate of the difference in change *versus* placebo group was: E (SE) = -3.1 (2.4) bpm (95% CI [-7.8; 1.6]) in S 38844 25 mg group and -7.6 (2.4) bpm (95% CI [-12.4; -2.7]) in S 38844 50 mg group.
- HR change from baseline to W6 was -13.4 ± 10.0 bpm in the S 38844 25 mg group, -18.1 ± 10.1 bpm in the S 38844 50 mg group and -10.2 ± 10.1 bpm in the placebo group.
- From W9 to WEND, *i.e.* after S 38844 cessation treatment, the mean HR increased in the two S 38844 groups (6.7 ± 10.4 bpm in S 38844 25 mg and 8.2 ± 12.1 bpm in S 38844 50 mg group) while it remained quite stable in the placebo group (change: 1.1 ± 9.0 bpm). At WEND, the mean HR was 72.8 ± 9.3 bpm with no relevant between-groups difference.
- Over the 9-weeks treatment, the subgroup of patients with baseline HR > 85 bpm showed greater HR reduction (-21.9 ± 10.8 bpm in S 38844 25 mg and -28.2 ± 14.1 bpm in the S 38844 50 mg group) than those with baseline HR ≤ 85 bpm (-13.5 ± 8.9 bpm and -15.6 ± 8.9 bpm, respectively). At W3, greater HR reduction was also observed in patients with baseline HR > 85 bpm (-14.3 ± 11.8 bpm in S 38844 25 mg and -23.4 ± 12.0 bpm in the S 38844 50 mg group) than those with baseline HR ≤ 85 bpm (-9.9 ± 10.2 bpm and -13.6 ± 7.1 bpm, respectively).

In the FAS, similar results as those in PPS were observed.

PK and PK/PD results

The observed S 38844 and S 41015 concentrations after repeated administration in CHF patients from CL2-38844-010 were similar to slightly higher than model-predicted values in healthy volunteers. After repeated administration of 25 mg, 50 mg and 100 mg *o.d.* of S 38844, concentrations of S 38844 and S 41015 in CHF patients early after administration (1h after administration) and at trough (24h after administration) were slightly higher than model-predicted concentrations in healthy volunteers, and concentrations of S 38844 and S 41015 in CHF patients from 4h to 8h after dose in patients were similar to model-predicted concentrations in healthy volunteers.

PK and PK/PD results (Cont'd)
The accumulation of S 38844 and S 41015 after repeated administration was similar between HV and patients. Observed HR after placebo administration was higher at W0 than at W3, W6 and W9 visits. Under treatment, after the administration of 25 mg, 50 mg and 100 mg *o.d*., HRR after repeated administration of S 38844 25 mg, 50 mg and 100 mg *o.d*. in patients was higher than that simulated in HV, and as the difference between predicted and measured HR under placebo was higher than the difference of HRR between HV and patients, the PKPD relationship was different between CHF patients and HV. After repeated administration of S 38844 25 mg, 50 mg and 100 mg *o.d.* in patients, HR-time profiles were more flattened than in HV, consistently with PK differences between HV and CHF patients.

Biomarkers results:
Regarding effect of treatment and biomarker/resting HR relationship, results were not conclusive.

SAFETY RESULTS
Emergent adverse events
In the SS (N = 130), EAEs were reported in 25 patients (48.1%) in S 38844 25 mg group, 24 patients (46.2%) in S 38844 50 mg group *versus* 5 patients (19.2%) in placebo group.
The most frequently reported SOCs (in at least 10% of patients) were cardiac disorders (15.4% in the S 38844 25 mg and 25.0% in the S 38844 50 mg group *versus* 7.7% in placebo group) and eye disorders (21.2% and 15.4% *versus* none, respectively). The most frequently reported EAEs were, as expected due to the pharmacological profile, visual symptoms which mostly were photopsia *i.e* phosphenes (19.2% in the S 38844 25 mg group and 13.5% in the S 38844 50 mg group) and bradycardia (7.7% and 11.5% of patients, respectively in S 38844 groups). No photopsia or bradycardia was reported in the placebo group. All visual symptoms recovered on treatment, except 2 which recovered after treatment discontinuation. EAE bradycardia were mostly (9/12 events) asymptomatic while 3 of these were symptomatic (reported in 2 patients in the S 38844 50 mg group). All bradycardia events recovered on treatment, except 4 which recovered after treatment discontinuation in the S 38844 50 mg group.
EAE of blood pressure increase in hypertensive patients was observed in 3 patients (2 in S 38844 25 mg and 1 in the S 38844 50 mg). Rhythm and conduction disorders EAEs of interest regarding S 38844 concerned 4 patients (7.7%) in the S 38844 25 mg group, 7 patients (13.5%) in the S 38844 50 mg group and none in placebo group: atrial fibrillation (1 *versus* 3 patients, respectively), atrial flutter (1 patient in S 38844 50 mg), supraventricular tachycardia (1 patient in S 38844 50 mg), sinus tachycardia (1 patient in S 38844 25 mg), sinus arrest (1 patient in S 38844 50 mg) and second degree atrioventricular (1 patient in each S 38844 group) and supraventricular extrasystole (1 patient in each S 38844 group). An isolated and transitory ECG QT prolonged was reported in 1 patient in the S 38844 50 mg group.
Main safety results in the SS are described in the Table 4.

Table 4 - Overall summary of safety results during the treatment period in the Safety Set

		Starting with S 38844 25 mg N = (52)	Starting with S 38844 50 mg N = (52)	Placebo (N = 26)
Patients having reported at least one				
EAE	n (%)	25 (48.1)	24 (46.2)	5 (19.2)
Treatment-related EAE	n (%)	15 (28.8)	16 (30.8)	2 (7.7)
EAE of special interest				
Visual symptoms	n (%)	11 (21.2)	8 (15.4)	-
Bradycardia	n (%)	4 (7.7)	6 (11.5)	-
Atrial fibrillation	n (%)	1 (1.9)	3 (5.8)	-
Blood pressure increase in hypertensive patients	n (%)	2 (3.8)	1 (1.9)	-
ECG QT prolongation	n (%)	-	1 (1.9)	-
Patients with treatment withdrawal due to				
EAE	n (%)	1 (1.9)	5 (9.6)	-
EAE bradycardia	n (%)	-	2 (3.8)	-
EAE atrial fibrillation	n (%)	-	1 (1.9)	-
EAE photopsia (*i.e.* phosphenes)	n (%)	1 (1.9)	-	-
Patients reporting at least one:				
Serious EAE (including death)	n (%)	4 (7.7)	4 (7.7)	1 (3.8)
Serious treatment-related EAE	n (%)	2 (3.8)	1 (1.9)	-
Patient who died	n (%)	-	-	1 (3.8)

SAFETY RESULTS (Cont'd)

Treatment-related EAEs were more frequent in the S 38844 groups (28.8% in S 38844 25 mg and 30.8% in S 38844 50 mg) than in placebo (7.7%). The difference was mainly due to photopsia (17.3% and 13.5%, respectively in S 38844 groups) and bradycardia (5.7% and 9.6%, respectively in S 38844 groups).

EAEs leading to study drug withdrawal were observed in 4.6% of patients with lower incidence in S 38844 25 mg group (1.9%, 1 event of photopsia) than in S 38844 50 mg group (9.6%, 5 patients), among which 2 bradycardia and 1 atrial fibrillation.

Serious EAEs on treatment, mostly upgraded as medically important by the Sponsor, were reported in 4 patients (7.7%) in each of the S 38844 groups. These concerned mainly atrial fibrillation (1 patient in each S 38844 group), bradycardia (1 patient in each S 38844 group) and photopsia (1 patient in S 38844 25 mg group). Two of these SEAEs (1 atrial fibrillation, 1 bradycardia) led to IMP withdrawal in S 38844 50 mg group.

One patient died on-treatment in the placebo group. He was found dead in his bed having made no complaint the day before regarding his condition. The investigator reported the death due to an acute cardiac heart failure, with hyperacute ischemic syndrome according to autopsy report information.

EAEs after S 38844 treatment cessation were reported in few patients (2 patients in the S 38844 25 mg, 1 in the S 38844 50 mg).

Blood laboratory evaluation

Emergent Potentially Clinically Significant Abnormal (PCSA) values for the biochemical and haematological parameters were infrequent in all groups, except for high potassium values reported in 3 patients (5.7%) in the S 38844 25 mg group and for high urea values reported in 8 patients (15.4%) in the S 38844 25 mg group and 3 patients (6.0%) in S 38844 50 mg group. The number of patients with emergent high urea PCSA values can be explained by the fact that most upper limit of normal ranges of the local laboratories were very close to the PCSA value. These patients had no associated high emergent creatinine PCSA values.

Blood pressure

Neither clinically relevant changes nor differences between groups in mean sitting SBP and DBP values over time were observed, except a slightly decrease for SBP in placebo group (mean change = -3.4 ± 13.1, median = 0.0 mmHg).

NYHA classification (CHF symptoms)

From baseline to last visit under treatment, NYHA class was unchanged for 92.2% of patients in S 38844 25 mg, 92.0% in S 38844 50 mg and 100% in placebo group or improved for 7.8% of patients in S 38844 25 mg and 8.0% in S 38844 50 mg.

24-hour Holter ECG

In SS, the mean HR change from baseline to last post-baseline visit during the day was: -11.5 ± 13.1 bpm in S 38844 25 mg, -14.2 ± 11.4 bpm in the S 38844 50 mg group and -6.6 ± 11.5 bpm in placebo group. Mean HR change during the night was: -11.1 ± 10.0 bpm in the S 38844 50 mg group, -8.4 ± 12.1 bpm in S 38844 25 mg and -4.6 ± 9.0 bpm in placebo group.

At baseline, the frequency of patients with an episode of HR < 60 bpm during the day was comparable between the three groups while it was higher in S 38844 groups *versus* placebo for patients with HR < 50 bpm during the night. At last post-baseline visit, frequency of patients with HR < 60 bpm during the day as well as those with HR < 50 bpm during the night increased in all groups and were higher in both S 38844 groups *versus* placebo.

Pathological bradycardia (*i.e.* HR < 40 bpm during the day or < 30 bpm during the night) was detected in 2 patients in each S 38844 group at last post-baseline visit during the day; none was detected during the night in any group.

Other Holter abnormalities observed on treatment were as follows:

1 patient in S 38844 50 mg group had one episode of sinus pause on RR interval (duration of 3.1 sec). Few patients (≤ 3 patients in all groups) had episode of atrioventricular block, mostly of degree II Mobitz I. 1 patient in S 38844 50 mg group had an asymptomatic atrial fibrillation (recovered). 2 patients had an atrial flutter (1 in each S 38844 group, both recovered).

2 patients had an emergent sustained (≥ 60 sec) supraventricular tachycardia (SVT) (one of these patients also had non-sustained SVT episodes) both in S 38844 50 mg group after 3-week of treatment.

Ventricular tachycardia episodes were all non-sustained (< 30 sec). In S 38844 groups, it affected a comparable proportion of patients at baseline (33.3% in S 38844 25 mg and 25.0% in S 38844 50 mg group and at last post-baseline visit (28.9% and 22.5%, respectively) while, in placebo, the proportion of patients affected decreased from baseline (46.2%) to last post-baseline (28.0%).

CONCLUSION

This was an exploratory phase II, multicentre, international, randomised, double-blind, placebo-controlled study with two dose escalation S 38844 groups and one matching placebo escalation group in patients with CHF, left ventricular systolic dysfunction (LVEF ≤ 35%), HR ≥ 75 bpm and under optimal background therapy. In S 38844 25 mg group, starting dose was 25 mg *o.d.* and patients were optionally up-titrated to 50 mg then 100 mg *o.d.* In S 38844 50 mg group, starting dose was 50 mg *o.d.* and patients were optionally up-titrated once to 100 mg *o.d.* The primary objective of the study was to assess the pharmacodynamics effect of S 38844 *i.e.* resting HR reduction with the two different schemes of escalating doses.

130 patients were randomised (52 to each of the S 38844 groups and 26 to the placebo group). The 3 treatment groups were comparable in terms of demographics, baseline characteristics, concomitant medication and treatment duration, except in proportion of patients with severe CHF symptoms (NYHA class III) which was relatively higher in S 38844 25 mg group. More than half of patients treated with S 38844 were up-titrated to 100 mg *o.d.*

In PPS (N = 104), over the 9-week treatment period, resting HR reduction was observed in the 3 groups. Higher reduction was observed in S 38844 25 mg group (-16.6 ± 10.3 bpm) and in S 38844 50 mg group (-19.1 ± 11.9 bpm) than in placebo group which nevertheless showed a relatively important reduction (-9.5 ± 6.3 bpm). HR reduction observed in placebo group can be explained by the low sample size and high baseline HR values in overall patients. The estimate of the difference with standard error (E (SE)) in change *versus* placebo group was -5.8 (2.5) bpm in S 38844 25 mg group and -8.0 (2.5) bpm in S 38844 50 mg group. After 3-week of treatment, HR reduction was observed in the two S 38844 groups and was higher with 50 mg starting dose (-16.1 ± 9.5 bpm, E (SE) = -7.6 (2.4) bpm) than with 25 mg starting dose (-11.5 ± 10.9 bpm, E (SE) = -3.1 (2.4) bpm). Over the 9-weeks treatment, the subgroup of patients with baseline HR > 85 bpm showed greater HR reduction (-21.9 ± 10.8 bpm in S 38844 25 mg and -28.2 ± 14.1 bpm in the S 38844 50 mg group) than those with baseline HR ≤ 85 bpm. These results were similar in the FAS (N = 122).

The safety assessment showed a higher frequency of emergent adverse events (EAEs) in both S 38844 groups compared to placebo group. The most frequently reported EAEs in patients receiving S 38844 were, as expected due to the pharmacological profile, visual symptoms (mostly photopsia) and bradycardia. All these events recovered, mostly while on treatment. In the S 38844 group with 50 mg starting dose, two patients prematurely stopped the treatment due to bradycardia *versus* none in the S 38844 group with 25 mg starting dose.

The Holter assessment over 24-hour showed a higher reduction of mean HR on treatment in S 38844 groups compared to placebo. At last post-baseline visit, frequency of patients with HR < 60 bpm during the day as well as those with HR < 50 bpm during the night increased in all groups and were higher in both S 38844 groups *versus* placebo. There was a low incidence of bradycardia during the day (HR < 40 bpm) in the two S 38844 groups and none during the night (HR < 30 bpm) in any group. Over the 9-week of treatment, Holter assessment did not show any other significant emergent abnormalities.

Overall, the pharmacodynamics effect of S 38844 *i.e.* HR reduction was confirmed in the targeted study population with the two S 38844 dose escalation schemes. The reduction was higher with S 38844 50 mg *versus* 25 mg starting dose as well as in patients with baseline HR > 85 bpm *versus* ≤ 85 bpm.

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