

**Clinical trial results:**

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.

Summary

EudraCT number	2013-003000-39
Trial protocol	HU BE SK EE LT LV
Global end of trial date	08 June 2015

Results information

Result version number	v1 (current)
This version publication date	25 March 2016
First version publication date	25 March 2016

Trial information**Trial identification**

Sponsor protocol code	CL2-38844-010
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France,
Public contact	ITP (Innovative Therapeutic Pole), Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com
Scientific contact	ITP (Innovative Therapeutic Pole), Institut de Recherches Internationales Servier, +33 155 72 43 66, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2015
Global end of trial reached?	Yes
Global end of trial date	08 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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 (CHF) and left ventricular systolic dysfunction treated with optimal background therapy.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy:

Optimal cardiovascular background therapy of the chronic heart failure according to the investigator's judgement based on based on the last recommendations (ESC guidelines 2012).

Evidence for comparator: -

Actual start date of recruitment	01 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Ukraine: 35
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 19
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Latvia: 10
Country: Number of subjects enrolled	Lithuania: 11
Worldwide total number of subjects	130
EEA total number of subjects	78

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	90
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Study population were men or women aged 18 years or more with moderate to severe CHF and left ventricular ejection fraction $\leq 35\%$, with HR ≥ 75 bpm and treated with optimal background therapy.

Period 1

Period 1 title	Double blind treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Treatment randomisation and allocation centralized (interactive response system).
Study products of identical appearance, taste and packaging.

Arms

Are arms mutually exclusive?	Yes
Arm title	S38844 25mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S38844 25mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 successive periods of 3 weeks with dose escalation: a starting dose of 25 mg once daily was dispensed at W0 (baseline) , then optionally up-titrated to 50 mg once daily at W3 then to 100 mg once daily (highest possible dose) at W6.

Arm title	S38844 50mg
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	S38844 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 successive periods of 3 weeks with dose escalation: a starting dose of 50 mg once daily was dispensed at W0 (baseline), then optionally up-titrated to 100 mg once daily (highest possible dose) at W3 or at W6.

Arm title	Placebo
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Arm description: -

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 successive periods of 3 weeks with dose escalation matching placebo tablet once daily.

Number of subjects in period 1	S38844 25mg	S38844 50mg	Placebo
Started	52	52	26
Completed	47	44	23
Not completed	5	8	3
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	2	2	2
Adverse event, non-fatal	1	5	-
Protocol deviation	2	1	-

Baseline characteristics

Reporting groups

Reporting group title	S38844 25mg
Reporting group description: -	
Reporting group title	S38844 50mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	S38844 25mg	S38844 50mg	Placebo
Number of subjects	52	52	26
Age categorical Units: Subjects			
Adults (18-64 years)	40	33	17
From 65-84 years	12	19	9
Age continuous Units: years			
arithmetic mean	57.3	59.8	61.1
standard deviation	± 9.4	± 10.7	± 9.5
Gender categorical Units: Subjects			
Female	13	8	4
Male	39	44	22

Reporting group values	Total		
Number of subjects	130		
Age categorical Units: Subjects			
Adults (18-64 years)	90		
From 65-84 years	40		
Age continuous Units: years			
arithmetic mean	-		
standard deviation	-		
Gender categorical Units: Subjects			
Female	25		
Male	105		

End points

End points reporting groups

Reporting group title	S38844 25mg
Reporting group description:	-
Reporting group title	S38844 50mg
Reporting group description:	-
Reporting group title	Placebo
Reporting group description:	-
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	All patients of Randomised Set having taken at least 1 dose of IMP and having completed the 9-week double blind treatment period (titration period) in accordance with the protocol, i.e. having an analysable HR value (i.e. primary endpoint) at baseline and at W9 under treatment without relevant deviation which could affect the HR evaluation.

Primary: Change in resting heart rate

End point title	Change in resting heart rate
End point description:	
End point type	Primary
End point timeframe:	9-week treatment period

End point values	S38844 25mg	S38844 50mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	40	20	
Units: beats per minute				
arithmetic mean (standard error)	-16.58 (\pm 10.31)	-19.05 (\pm 11.86)	-9.5 (\pm 6.27)	

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	Between-group difference was estimated using an ANCOVA adjusted on heart rate at baseline and treatment group.
Comparison groups	S38844 25mg v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (net)
Point estimate	-5.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.67
upper limit	-0.86
Variability estimate	Standard error of the mean
Dispersion value	2.47

Statistical analysis title	Primary analysis
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Statistical analysis description:

Between-group difference was estimated using an ANCOVA adjusted on heart rate at baseline and treatment group.

Comparison groups	S38844 50mg v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Median difference (net)
Point estimate	-8.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.02
upper limit	-3.05
Variability estimate	Standard error of the mean
Dispersion value	2.51

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported all over the study. Adverse events reported over the 9-week double-blind treatment period are presented here as it was the only period of the study when patients received active treatment (S38844).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	S38844 25mg
Reporting group description:	-
Reporting group title	S38844 50mg
Reporting group description:	-
Reporting group title	Placebo
Reporting group description:	-

Serious adverse events	S38844 25mg	S38844 50mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 52 (7.69%)	4 / 52 (7.69%)	1 / 26 (3.85%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial ischaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Photopsia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
renal failure chronic			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	S38844 25mg	S38844 50mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 52 (42.31%)	22 / 52 (42.31%)	5 / 26 (19.23%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 52 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 52 (3.85%)	6 / 52 (11.54%)	0 / 26 (0.00%)
occurrences (all)	2	7	0
Ventricular extrasystoles			
subjects affected / exposed	1 / 52 (1.92%)	1 / 52 (1.92%)	1 / 26 (3.85%)
occurrences (all)	1	1	1
Atrial fibrillation			
subjects affected / exposed	0 / 52 (0.00%)	2 / 52 (3.85%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Coronary artery stenosis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 52 (0.00%)	0 / 52 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			

subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	2 / 52 (3.85%) 2	0 / 26 (0.00%) 0
Eye disorders Photopsia subjects affected / exposed occurrences (all)	9 / 52 (17.31%) 9	7 / 52 (13.46%) 7	0 / 26 (0.00%) 0
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	1 / 26 (3.85%) 1
Musculoskeletal and connective tissue disorders Musculoskeletal stiffness subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	1 / 26 (3.85%) 1
Infections and infestations Influenza subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 52 (1.92%) 1	1 / 26 (3.85%) 1
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	0 / 52 (0.00%) 0	1 / 26 (3.85%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2014	Pregnancy testing was added at entry and during the study. The list of adverse events to be documented with specific information was updated.
22 July 2014	To implement the recommendations of Data Monitoring Committee, mainly to cancel the IMP dose of 150 mg which was planned in the study protocol. Consequently, highest possible S38844 dose administered to patients during the study was 100 mg once daily.
21 January 2015	Main change: the sample size was reconsidered as a total of 125 patients to be included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported