



Clinical trial results:

A randomized, double blind, placebo-controlled, parallel, international multicenter study assessing the efficacy of S 066913 in patients with paroxysmal atrial fibrillation

Double-blind, International study AssessinG efficacy of S 066913 in paRoxysmal Atrial Fibrillation – IKur inhibitor (DIAGRAF - IKUR).

Summary

EudraCT number	2014-002333-63
Trial protocol	CZ SK SE DK NL PL
Global end of trial date	06 September 2016

Results information

Result version number	v1 (current)
This version publication date	02 June 2017
First version publication date	02 June 2017

Trial information

Trial identification

Sponsor protocol code	CL2-066913-002
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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 (I.R.I.S.)
Sponsor organisation address	50, rue Carnot, Suresnes, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 0155724366, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 0155724366, 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	06 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2016
Global end of trial reached?	Yes
Global end of trial date	06 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the efficacy of three doses of S 66913 (5 mg, 25 mg and 100 mg o.d.) versus placebo administered for 4 weeks, on atrial fibrillation and/or atrial tachycardia burden (AF/AT burden) in patients with paroxysmal atrial fibrillation (PAF) who were potentially eligible for atrial fibrillation (AF) ablation and were implanted with insertable continuous cardiac rhythm monitoring (ICM) device. The study was divided into 3 periods: A pre-randomisation baseline period (Period 1) of at least 4 weeks during which the ICM was implanted and the eligibility according to ICM data and blood test results was assessed. A double-blind treatment period lasting 4 weeks (Period 2). A post-treatment and extended follow-up period (appears here as part of Period 2 for technical reasons) comprising visits WEND, FU1 and FU2 (6 months after FU1).

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: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Czech Republic: 13
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Slovakia: 1
Worldwide total number of subjects	58
EEA total number of subjects	35

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)	40
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Investigators were cardiologists having expertise in arrhythmology.

Pre-assignment

Screening details:

The patients were adult male or female (non-childbearing potential), in sinus rhythm at selection visit, with at least one AF episode within the last 18 months and at least 2 other AF episodes within 30 days, prior to selection visit, indicated for AF ablation and eligible for ICM implantation (or having an approved ICM device).

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All patients
Arm description: -	
Arm type	ICM
Investigational medicinal product name	No IMP
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant, Transdermal system
Routes of administration	Implantation

Dosage and administration details:

Insertable Continuous Monitoring (ICM) implantation .

Number of subjects in period 1	All patients
Started	58
Completed	58

Period 2

Period 2 title	DB treatment period + extended FU
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

The study was double-blinded with active drugs and matching placebo supplied as identical tablets and

packaging.

Arms

Are arms mutually exclusive?	Yes
Arm title	S 66913 5 mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	S 66913 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The treatment consisted of 3 tablets (2 big and 1 small, either could contain S 66913 5 mg or placebo) administered orally once daily during breakfast i.e. visually identical for each treatment arm.

Arm title	S 66913 25 mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	S 66913 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The treatment consisted of 3 tablets (2 big and 1 small, either could contain S 66913 12.5 mg or placebo) administered orally once daily during breakfast i.e. visually identical for each treatment arm.

Arm title	S 66913 100 mg
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	S 66913 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The treatment consisted of 3 tablets (2 big and 1 small, either could contain S 66913 50 mg or placebo) administered orally once daily during breakfast i.e. visually identical for each treatment arm.

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

Dosage and administration details:

The treatment consisted of 3 tablets (2 big and 1 small) administered orally once daily during breakfast i.e. visually identical for each treatment arm.

Number of subjects in period 2	S 66913 5 mg	S 66913 25 mg	S 66913 100 mg
Started	16	13	15
Completed	10	11	11
Not completed	6	2	4
Other	1	-	-
Study discontinuation	5	1	4
Protocol deviation	-	1	-

Number of subjects in period 2	Placebo
Started	14
Completed	11
Not completed	3
Other	-
Study discontinuation	3
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	All patients
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Reporting group description: -

Reporting group values	All patients	Total	
Number of subjects	58	58	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	40	40	
From 65-84 years	18	18	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	58.5		
standard deviation	± 10.2	-	
Gender categorical			
Units: Subjects			
Female	16	16	
Male	42	42	
AF/AT Burden			
Units: percent			
median	9.6		
inter-quartile range (Q1-Q3)	2.7 to 20.4	-	

End points

End points reporting groups

Reporting group title	All patients
Reporting group description: -	
Reporting group title	S 66913 5 mg
Reporting group description: -	
Reporting group title	S 66913 25 mg
Reporting group description: -	
Reporting group title	S 66913 100 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
In accordance with the intention-to-treat principle, all patients of the Randomized Set having taken at least one dose of IMP and with at least two evaluations of AF/AT burden on adjudicated data from ICM: one over baseline period and one over 4-week treatment period.	

Primary: AF/AT Burden

End point title	AF/AT Burden ^[1]
End point description:	
The primary efficacy endpoint was the AF/AT burden derived from ICM device recording, expressed mainly as absolute change from baseline over the 4-week treatment period.	
End point type	Primary
End point timeframe:	
The AF/AT burden is calculated as the percentage time in AF and/or AT (including atrial flutter (AFL)) during the total observation period.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Prematurely discontinued study treatment as a precautionary measure due to a non-clinical safety concern.

End point values	S 66913 5 mg	S 66913 25 mg	S 66913 100 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	13	14	14
Units: percent				
median (inter-quartile range (Q1-Q3))	0.1 (-1.4 to 2.3)	0.5 (-4.4 to 1.8)	-0.3 (-3.1 to 0.5)	0.7 (-2.1 to 6.6)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-blind 4 weeks period (W0-W4) for each group and post-treatment/extended follow-up period for patients who took at least one dose of study drug.

For FU, contact was established for 51 patients: 39 attended FU1; 37 attended FU2.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	S 66913 5 mg
Reporting group description: -	
Reporting group title	S 66913 25 mg
Reporting group description: -	
Reporting group title	S 66913 100 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	FU after starting with S 66913 5 mg
Reporting group description: -	
Reporting group title	FU after starting with S 66913 25 mg
Reporting group description: -	
Reporting group title	FU after starting with S 66913 100 mg
Reporting group description: -	
Reporting group title	FU after starting with Placebo
Reporting group description: -	

Serious adverse events	S 66913 5 mg	S 66913 25 mg	S 66913 100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)	1 / 13 (7.69%)	0 / 14 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (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
Cardiac failure			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	0 / 14 (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
Sinus arrest			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Vitreous adhesions			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			

subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo	FU after starting with S 66913 5 mg	FU after starting with S 66913 25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	3 / 14 (21.43%)	2 / 11 (18.18%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus arrest			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (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
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (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			
Vitreous adhesions			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (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

Pulmonary fibrosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (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
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	0 / 11 (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
Pneumonia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	FU after starting with S 66913 100 mg	FU after starting with Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 14 (7.14%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous adhesions			

subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 14 (7.14%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural cellulitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	S 66913 5 mg	S 66913 25 mg	S 66913 100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 16 (31.25%)	1 / 13 (7.69%)	1 / 14 (7.14%)
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Bronchiectasis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Obstructive airways disorder			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Investigations			
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
International normalised ratio fluctuation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Vital capacity decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Functional residual capacity increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Carbon monoxide diffusing capacity decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Total lung capacity decreased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0

Expiratory reserve volume increased subjects affected / exposed occurrences (all)	Additional description: Residual volume of the lungs increased.		
	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Cardiac disorders			
Bradycardia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Pericarditis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Atrial thrombosis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Phrenic nerve paralysis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Facial paralysis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Gingival recession subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Gastritis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Skin and subcutaneous tissue disorders			
Rash pruritic subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0

Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Infections and infestations Cystitis escherichia subjects affected / exposed occurrences (all) Herpes zoster subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0	0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0	0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0

Non-serious adverse events	Placebo	FU after starting with S 66913 5 mg	FU after starting with S 66913 25 mg
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 14 (21.43%)	3 / 14 (21.43%)	2 / 11 (18.18%)
Vascular disorders Orthostatic hypotension subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Immune system disorders Food allergy subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Reproductive system and breast disorders Prostatitis			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Obstructive airways disorder			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Investigations			
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
International normalised ratio fluctuation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Vital capacity decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Functional residual capacity increased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Carbon monoxide diffusing capacity decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1

Total lung capacity decreased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Expiratory reserve volume increased subjects affected / exposed occurrences (all)	Additional description: Residual volume of the lungs increased.		
	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Cardiac disorders			
Bradycardia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	1 / 11 (9.09%) 1
Pericarditis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Atrial thrombosis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 14 (7.14%) 1	0 / 11 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Phrenic nerve paralysis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Facial paralysis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Gingival recession subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Gastritis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Skin and subcutaneous tissue disorders			

Rash pruritic subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Infections and infestations Cystitis escherichia subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Herpes zoster subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 14 (7.14%) 1	1 / 11 (9.09%) 1
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 14 (0.00%) 0	0 / 11 (0.00%) 0

Non-serious adverse events	FU after starting with S 66913 100 mg	FU after starting with Placebo	
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 14 (21.43%)	3 / 12 (25.00%)	
Vascular disorders Orthostatic hypotension subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 12 (0.00%) 0	
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 12 (8.33%) 1	
Immune system disorders Food allergy subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	

Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Pleural effusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	0 / 14 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 14 (7.14%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Obstructive airways disorder			
subjects affected / exposed	1 / 14 (7.14%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Investigations			
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
International normalised ratio fluctuation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Vital capacity decreased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Functional residual capacity increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Carbon monoxide diffusing capacity decreased			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Total lung capacity decreased subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 12 (8.33%) 1	
Expiratory reserve volume increased subjects affected / exposed occurrences (all)	Additional description: Residual volume of the lungs increased.		
	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 12 (0.00%) 0	
Pericarditis			
subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Atrial thrombosis			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 12 (0.00%) 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 12 (0.00%) 0	
Phrenic nerve paralysis			
subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Facial paralysis			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 12 (8.33%) 1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 12 (0.00%) 0	
Gingival recession			
subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 12 (0.00%) 0	
Gastritis			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Skin and subcutaneous tissue disorders Rash pruritic subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 12 (0.00%) 0	
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 12 (0.00%) 0	
Infections and infestations Cystitis escherichia subjects affected / exposed occurrences (all) Herpes zoster subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0	0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1	
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	0 / 12 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2014	Amendment n°1 applicable in all countries: modification of selection criterion 1 regarding the inclusion of women of childbearing potential who were to be excluded. A pregnancy test was therefore no longer appropriate and birth control method was updated.
27 January 2015	Amendment n°3 applicable in all countries: interdiction of rosuvastatin (a BCRP substrate) as a precautionary measure.
03 July 2015	Amendment No. 4 applicable in all countries: Clarification or modification of the study selection and inclusion criteria : - Selection criterion 3: Paroxysmal atrial fibrillation: sinus rhythm was to be recorded within maximum 7 days since the onset of this AF episode. - Selection criterion 4: Paroxysmal AF could be documented by an ECG within 18 months to demonstrate the existence of the disease. - Selection criterion 5: Wording for AF ablation slightly modified to allow countries to select patients according to local guideline (HRS/EHRA/ECAS, 2012; AHA/ACC/HRS, 2014). - Non-selection criterion 17: Patients who had been treated for persistent atrial fibrillation were considered as eligible under certain circumstances. A precautionary measure concerning gastrointestinal events was added.
30 October 2015	Amendment No. 5 applicable in all countries: Addition of extended clinical follow-up further to the decision (in agreement with the DIAGRAF-IKUR study Executive Committee, the Data Monitoring Committee) to prematurely discontinue the study treatment in all patients as a precautionary measure for all randomized patients who received at least one dose of study treatment (either placebo or S066913). The follow-up consists of an initial visit and a second follow-up visit 6 months later.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 September 2015	The Sponsor decided, in agreement with the study Data Monitoring Committee and Executive Committee, to prematurely discontinue the study treatment as a precautionary measure and to implement a clinical follow-up period with two visits separated by 6 months in all patients having taken the study treatment at least once.	-

Notes:

Limitations and caveats

None reported