Document title	**ABBREVIATED CLINICAL STUDY REPORT SYNOPSIS**
Study title	**A randomized, double-blind, placebo-controlled, parallel, international multicentre study assessing the efficacy of S 066913 in patients with paroxysmal atrial fibrillation**. **Double-blind, International study AssessinG efficacy of S066913 in paRoxysmal Atrial Fibrillation - IKur inhibitor (DIAGRAF - IKUR)**
Test drug code	**S 066913**
Indication	**Atrial Fibrillation**
Development phase	**Phase II**
Protocol code	**CL2-066913-002**
Study initiation date	**08 December 2014**
Study completion date	**06 September 2016**
Main coordinator	[redacted]
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France** **Technologie Servier** **25/27, Rue Eugene Vignat** **45000 Orleans - France** **Servier Canada Inc.** **235, Armand Frappier Blvd.** **Laval, Quebec, H7V 4A7 - Canada** **Les Laboratoires Servier (L.L.S.)** **Paveletskaya Square 2, building 3, floor 3, 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	**27 April 2017**
Version of the report	**Final version**
	~~CONFIDENTIAL~~

2 SYNOPSIS

Name of Sponsor: **I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex – France** **Technologie Servier - 25/27, Rue Eugene Vignat - 45000 Orleans - France** **Servier Canada Inc. Laval, Quebec, H7V 4A7 - Canada** **L.L.S. Paveletskaya Square 2, building 3, floor 3, Moscow - Russia**		*(For National Authority Use only)*
Test drug **Name of Finished Product:** Not applicable **Name of Active Ingredient:** S 066913		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: A randomised, double-blind, placebo-controlled, parallel, international multicentre 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)
Protocol No.: CL2-066913-002
EudraCT No.: 2014-002333-63
The description of the study protocol given hereafter includes the modifications of the 5 substantial amendments to the protocol.

International coordinator:
[redacted]

Study centres:
14 centres located in 8 countries included 58 patients: [redacted] Australia (14 patients included). [redacted] Canada (6 patients included), [redacted] Czech Republic (13 patients included), [redacted] Germany (1 patient included), [redacted] Netherlands (1 patient included), [redacted] Poland (19 patients included), [redacted] Russian Federation (3 patients included), and [redacted] Slovakia (1 patient included).

Publication (reference): Not applicable

Studied period: Initiation date: 08 December 2014 Treatment completion date (*i.e*. Last visit of last patient in the double-blind treatment period): 29 October 2015 Study completion (*i.e*. Last visit of last patient in the follow-up period): 06 September 2016 The study treatment was prematurely discontinued as precautionary safety measure (as explained below in the Methodology and Conclusion sections) with the implementation of a longterm clinical follow-up period.	**Phase of development of the study:** Phase II

Objectives:
The aim of this study was to evaluate the efficacy of three doses of S 066913 (5 mg, 25 mg and 100 mg *o.d.*) (referred to hereafter as S 66913) *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 AF ablation and were implanted with insertable cardiac monitoring (ICM) device.

The other efficacy objectives were to investigate the effect of S S 6691366913 in comparison to placebo on other ICM parameters and on patients' quality of life (QoL) using Canadian Cardiovascular Society – Severity of Atrial Fibrillation (CCS -SAF) scale.

The safety and pharmacokinetic profiles of S 66913 were also evaluated.

Methodology:
This was a phase II, randomised, double-blind, placebo-controlled, parallel group (4 arms), international, multicentre, exploratory study. A balanced, adaptive centralised randomisation was used with country and AF/AT burden as stratification factors.

This was the first drug efficacy assessment study using ICM to record the arrhythmias with centralised adjudication of all tracings.

This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.

The findings from on-going toxicology studies in the rat and monkey at the time of the study led to a reduction in the safety margin in humans. 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.

Number of patients:
Planned: 160 included patients in total (40 patients per group), with a maximum of 30 patients with AF/AT burden [1% - 3%[.

Included: 58 patients included, with 16 in the S 66913 5 mg group, 13 in the S 66913 25 mg group, 15 in the S 66913 100 mg group, and 14 in the placebo group. Note: only 57 patients received at least one dose of IMP; a patient in the S 66913 100 mg group was withdrawn 2 weeks after his inclusion visit for non-medical reason, without taking any IMP.

The lower than planned number of patients was due to difficulties in patient recruitment and the subsequent premature discontinuation of the study recruitment.

Diagnosis and main criteria for inclusion:
The main selection criteria 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 (as modified by Amendment No. 4 [3 July 2015] which prolonged the window in which a previous AF was admissible by 6 months) and at least two other AF episodes within 30 days, prior to selection visit, indicated for AF ablation and eligible for ICM implantation (or with an already implanted ICM device of the same type as used in the study). For inclusion, the patients had to fulfil AF/AT burden (modified by Amendment No. 1 from AF burden) of $\geq$ 1% and $\leq$ 70% (the upper limit modified by Amendment No. 4 from 50%) and at least 3 episodes of AF, according to ICM recording, in the 4 weeks before inclusion.

Test drug:
S 66913: 5 mg, 25 mg, or 100 mg, to be taken orally once daily during breakfast.
Batch No.: L0056105, L0057506, L0056107, L0057508, L0056108, L0057507

Comparator (Reference product and/or placebo):
Placebo tablets (matching those of S 66913): to be taken orally once daily during breakfast.
Batch No.: L0054760, L0056106, L0056104, L0057505, L0057504

Duration of treatment:
A pre-randomisation baseline period of at least 4 weeks from selection (ASSE) to inclusion (W0) was dedicated to assess the eligibility of patients according to ICM recording and their blood test results. No IMP was dispensed during this period.

A double-blind treatment period lasted 4 weeks (at most 5 weeks). At W0, patients were randomly allocated to one of four arms (S 66913 [5 mg, 25 mg, or 100 mg] or placebo).

A post-treatment follow-up period lasted 1-2 weeks, until WEND visit, during which no IMP was dispensed to patients.

An extended precautionary follow-up period of 6-months with 2 follow-up visits, FU1 and FU2 (added as a precautionary measure by Amendment No. 5).

Criteria for evaluation (Cont'd):

Efficacy measurements:

Note: In view of the low number of included patients, some secondary or tertiary endpoints were not analysed.

Efficacy measurements:

The **primary efficacy endpoint** was the AF/AT burden, expressed mainly in terms of absolute change from baseline period over the 4-week treatment period.

The **secondary endpoints** were other parameters recorded by ICM device:

- The absolute change from baseline in AF burden.
- Mean duration of longest AF/AT episodes.
- Mean number of AF/AT episodes.
- Incidence of persistent AF.
- Percentage of asymptomatic patients (whatever rhythm) and asymptomatic patients (symptoms in sinus rhythm excluded).
- Percentage of patients who have ≥ 30% (≥ 50%) reduction from baseline in AF/AT burden.
- Median ventricular rate in AF.

A **tertiary efficacy endpoint** was to evaluate the QoL using the CCS-SAF scale class.

Safety measurements:

- Adverse events (AEs) throughout the study, especially death, syncope, ventricular tachycardia, Torsade de pointes, hypotension, heart failure, and gastrointestinal AEs (added by Amendment No. 4).
- ICM recorded arrhythmias outside of AF/AT (ventricular tachycardia, bradycardia, pauses [asystole]).
- Physical examination including weight, systolic and diastolic blood pressure (mmHg), and recording of abnormal findings obtained during physical examinations.
- 12-lead ECG: heart rate (bpm), PR interval (ms), QRS duration (ms), QTcF interval (ms), and ECG abnormalities.
- Blood clinical laboratory parameters (biochemistry, including liver function tests, and haematology).

Safety measurements during extended follow-up, with evaluation by independent local pulmonologists:

- AEs with particular attention to any relevant pulmonary AE.
- Physical examination including respiration and pulmonary auscultation, systolic and diastolic blood pressure
- Chest X-ray (front and lateral view).
- Spirometry (with assessment of at least the following parameters: forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC, forced expiratory flow 25%-75%.
- Body plethysmography (total lung capacity, functional residual capacity, airway resistance).
- Diffusing capacity of the lung for carbon monoxide.
- 12-lead ECG after 5 mins of rest.

Pharmacokinetic measurements:

PK samples were collected at W4 visit in the morning before and after IMP intake. The metabolic profiling of S 66913 planned in the protocol was not performed due to the premature discontinuation of the study treatment.

Statistical methods:

Note: In view of the low number of included patients, the statistical analysis was reduced and modified.

Analysis Sets:

The efficacy analysis was performed on the Full Analysis Set (FAS). The FAS was defined as patients of the Randomised Set (RS) having taken at least one dose of IMP and with at least two evaluations of AF burden on original data from ICM: one over baseline period and one over 4-week treatment period. A Per Protocol Set was not defined. The Safety Set (SS) was defined as all patients having taken at least one dose of IMP.

Efficacy analysis:

AF/AT burden (primary analysis) was described by treatment group in terms of value over baseline period, over 4-week treatment period and on the absolute change from baseline over the 4-week treatment period.

Secondary and tertiary efficacy criteria were mainly analysed using descriptive statistics on the FAS. Other analyses included time to first AF (any AF, first AF of > 5 min duration, first AF of >10 min duration) and time to first symptomatic AF.

Study outcome and safety analysis: Descriptive statistics were provided in the RS or the SS.

All safety analyses were performed in the SS according to randomised treatment, by treatment group over the baseline period and over the 4-week treatment period.

SUMMARY - CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 151 patients were screened and 136 selected for the study. Of them, 58 patients were included and randomly assigned to one of the 4 groups (Table 1). A total of 78 patients were not included; mainly 43 patients (55.1%) for non-compliance of inclusion/non-inclusion criteria in terms of AF/AT burden or AF episodes and 17 patients (21.8%) due to the decision to prematurely discontinue the study treatment.

The study was completed by 43 patients overall (74.1% of those randomised).

For the extended follow-up, contact was established for 51 patients for FU1 (i.e. 87.9% of RS), with 39 (67.2%) attending the visit and 37 (63.4%) attending FU2. Contact was not confirmed at FU1 for 6 patients in one centre in Australia, even after repeated requests from the Sponsor. One further patient in the RS was not contacted since he took no study treatment.

Table 1 - Disposition of patients

	S 66913 5 mg	S 66913 25 mg	S 66913 100 mg	Placebo	All
	n (%)	n (%)	n (%)	n (%)	n (%)
Included	**16**	**13**	**15**	**14**	**58**
Withdrawn due to:	**6 (37.5)**	**2 (15.4)**	**4 (26.7)**	**3 (21.4)**	**15 (25.9)**
Decision to discontinue study treatment	5 (31.3)	1 (7.7)	4 (26.7)[§]	3 (21.4)	13 (22.4)
Protocol violation*	-	1 (7.7)	-	-	1 (1.7)
Other**	1 (6.3)	-	-	-	1 (1.7)
Lost to follow-up	**-**	**-**	**-**	**-**	**-**
Double-blind period completed	**10 (62.5)**	**11 (84.6)**	**11 (73.3)**	**11 (78.6)**	**43 (74.1)**
Follow-up 1 visit attended	9 (56.3)	8 (61.5)	12 (80.0)	10 (71.4)	39 (67.2)
visit declined	5 (31.3)	3 (23.1)	2 (13.3)	2 (14.3)	12 (20.7)
Follow-up 2 visit attended	8 (50.0)	8 (61.5)	11 (73.3)	10 (71.4)	37 (63.4)
visit declined	1 (6.3)	-	1 (6.7)	-	2 (3.4)
Randomised Set	**16**	**13**	**15**	**14**	**58**
Full Analysis Set	**16 (100)**	**13 (100)**	**14 (93.3)**	**14 (100)**	**57 (98.3)**
Safety Set	**16 (100)**	**13 (100)**	**14 (93.3)**	**14 (100)**	**57 (98.3)**

n: Number of patients affected
% : % of the Randomised Set
** A female patient with childbearing potential was enrolled by error and then withdrew 10 days after inclusion visit.*
*** A patient was withdrawn at the W4 visit for having undergone cardioversion the preceding day.*
[§] One of these patients took no IMP before discontinuing the study.

BASELINE CHARACTERISTICS

Since the sizes of the treatment groups are small, a certain degree of heterogeneity was observed between the groups in baseline characteristics (Table 2). The mean age at selection was 58.5 ± 10.2 years. Most patients were men (72.4%) and all patients except one was white. A slightly higher proportion of female patients were randomised to the 100 mg group (n = 6; 40.0% of the group) than in other groups; in the 5 mg group there were 3 women (18.8% of group), in the 25 mg group were 2 women (15.4%) and in the placebo group were 5 (35.7%). All patients had a **PAF history** and the median duration of this pathology was 27.4 months. The reported symptoms of AF in the 30 days prior to selection, were mostly palpitations (91.4%), dyspnoea (43.1%) and/or fatigue (39.7%). At inclusion, 70.7% of patients were taking beta blockers and 50.0% were taking anti-thrombotics.

Baseline **AF/AT burden** showed a small number of very high values (according to the centrally adjudicated data) with an overall individual range from 0.0 - 43.2% (although some patients had an AF/AT burden of zero according to the adjudication, the automatic ICM data recording had reported sufficient AF/AT burden for inclusion). The median values were around 9% except for the 5 mg group at 3.7%. **Longest AF duration** was relatively normally distributed in each of the treatment groups with an overall median at 984 mins. The median values of mean **duration of AF** were about 200 mins in each group, except for the 100 mg group where it was 99.6 mins. The median **number of AF episodes** was around 10 overall, but as high as 49 in the 100 mg group. No patient presented **persistent AF** during the baseline period. Regarding the **mean of median ventricular rate during AF** was 104 ± 16.8 bpm (range: 92 – 119) overall and relatively comparable between groups.

According to the **CCS-SAF scale,** all patients except 2 had symptomatic AF. The most frequent class (in 46.6%) was 3 (moderate impact to QoL and activities of daily living) followed by class 2 (minor impact) in 31.0%. The placebo group tended to have more patients with class 3 (71.4%) and less with class 2 (7.1%), in comparison with S 66913 groups.

SUMMARY – CONCLUSIONS (CONT'D)

DISPOSITION OF PATIENTS AND ANALYSIS SETS (CONT'D)

Table 2 - Main baseline characteristics in the Randomised Set

			S 66913 5 mg (N=16)	S 66913 25 mg (N=13)	S 66913 100 mg (N=15)	Placebo (N=14)	All (N=58)
Age (years)		Mean ± SD	59.6 ± 8.9	59.0 ± 7.7	57.5 ± 12.3	58.1 ± 12.0	58.5 ± 10.2
		Median	57.5	59.0	60.0	60.0	59.5
	[18 ; 64]	n (%)	12 (75.0)	9 (69.2)	11 (73.3)	8 (57.1)	40 (69.0)
Gender	Male	n (%)	13 (81.3)	11 (84.6)	9 (60.0)	9 (64.3)	42 (72.4)
Race	White	n (%)	15 (93.8)	13 (100)	15 (100)	14 (100)	57 (98.3)
Duration of PAF history (months)		Mean ± SD	57.5 ± 118.0	37.2 ± 42.0	57.8 ± 33.2	51.1 ± 74.8	51.5 ± 75.1
		Median	15.6	23.1	51.7	18.2	27.4
Symptoms of AF 30 days before selection		n (%)	16 (100)	13 (100)	15 (100)	14 (100)	58 (100)
Palpitation		n (%)	15 (93.8)	12 (92.3)	13 (86.7)	13 (92.9)	53 (91.4)
Dyspnoea		n (%)	7 (43.8)	4 (30.8)	6 (40.0)	8 (57.1)	25 (43.1)
Fatigue		n (%)	5 (31.3)	6 (46.2)	3 (20.0)	9 (64.3)	23 (39.7)
Specific concomitant treatments at inclusion							
Beta blockers		n (%)	11 (68.8)	7 (53.8)	12 (80.0)	11 (78.6)	41 (70.7)
Anti-thrombotic agents		n (%)	8 (50.0)	6 (46.2)	9 (60.0)	6 (42.9)	29 (50.0)
Main ICM parameters							
AF/AT burden (%)		Median	3.7	8.9	10.0	10.4	9.6
		Geo Mean	3.5	7.7	8.4	4.2	5.5
		Min ; Max	0.0 ; 36.7	0.3 ; 42.9	0.3 ; 29.9	0.0 ; 43.2	0.0 ; 43.2
AF burden (%)		Median	3.7	6.8	10.0	10.3	8.7
		Geo Mean	3.0	5.5	5.9	3.4	4.2
		Min ; Max	0.0 ; 29.4	0.3 ; 42.9	0.0 ; 27.9	0.0 ; 43.2	0.0 ; 43.2
Number of AF episodes		Median	5.0	11.0	49.0	9.0	10.0
		Min ; Max	0 ; 58	1 ; 170	0 ; 159	0 ; 209	0 ; 209
Mean duration of AF episodes (min)		Median	226.6	222.9	99.6	197.2	192.7
		Min ; Max	0.0 ; 2090.7	13.9 ; 1704.7	0.0 ; 1128.0	0.0 ; 912.2	0.0 ; 2090.7
Sitting SBP (mmHg)		Mean ± SD	137.1 ± 19.6	132.8 ± 13.2	128.6 ± 17.3	132.4 ± 13.0	132.8 ± 16.1
		Median	133.0	134.0	137.0	133.0	133.0
Sitting DBP (mmHg)		Mean ± SD	80.3 ± 8.4	82.9 ± 11.0	79.7 ± 11.0	81.6 ± 10.6	81.1 ± 10.0
		Median	79.0	85.0	79.0	81.0	80.0
Heart rate from ECG (bpm)		Mean ± SD	60.8 ± 9.7	57.1 ± 8.9	60.1 ± 11.5	69.1 ± 9.8	61.8 ± 10.7
		Median	59.5	56.0	56.0	70.0	59.5
BMI (kg/m^2)		Mean ± SD	28.3 ± 3.4	28.5 ± 4.3	30.9 ± 5.8	31.6 ± 6.3	29.8 ± 5.2
		Median	27.5	29.1	31.3	29.8	29.6

** Baseline was defined as the last analysable value prior to treatment; Geo Mean: Geometric mean*
n: Number of patients concerned; %: (n/N) x 100

Most patients (87.9%) presented sinus rhythm and 2 patients had clinically significant ECG abnormalities. The mean PR interval and QRS interval were 163.9 ± 21.2 ms and 97.5 ± 14.3 ms, respectively. The mean QTcF interval was 414.4 ± 21.0 ms, with 2 patients (S 66913 100 mg and placebo groups) having values ≥ 450 ms at baseline (451 ms for both). According to centrally adjudicated data, pauses were detected in 9 patients (15.5%) by ICM device during baseline period, but these were within pre-defined limits: 1 patient in both the 5 mg and 25 mg groups, 4 in the 100 mg group and 3 in the placebo group. No other arrhythmias besides AF/AT were detected.

EXTENT OF EXPOSURE

The median of treatment duration was 28 days with a mean value at 25.1 ± 5.8 days. The mean overall compliance was 91.0 ± 18.8% (median of 100.0%) and 86.2% of patients had an overall compliance within the range 70% - 130%.

SUMMARY – CONCLUSIONS (CONT'D)

EFFICACY RESULTS

The main efficacy results are summarised in Table 3.

AF/AT burden (Primary endpoint) was highly variable both at baseline (as mentioned above) and during the study. The median change in AF/AT burden over the 4-week treatment period, showed small and inconsistent changes in the treatment groups that were not clinically meaningful.

Table 3 – Changes of main ICM parameters from baseline over the 4-week treatment period according to adjudicated data in FAS

		S 66913 5 mg (N=16)	S 66913 25 mg (N=13)	S 66913 100 mg (N=14)	Placebo (N=14)
Change of AF/AT burden	n	15	13	14	14
(%)	Mean ± SD	0.7 ± 3.7	-0.8 ± 4.8	-1.6 ± 3.9	3.3 ± 8.4
	Median	0.1	0.5	-0.3	0.7
	Min ; Max	-6.2 ; 7.9	-8.6 ; 6.4	-9.2 ; 3.5	-4.1 ; 28.0
Change of AF burden (%)					
Over 4-week period	n	15	13	14	14
	Mean ± SD	0.9 ± 5.4	1.2 ± 6.0	-0.5 ± 4.3	3.6 ± 8.5
	Median	-1.0	0.4	0.0	0.5
	Min ; Max	-6.2 ; 15.2	-7.4 ; 11.2	-9.2 ; 5.5	-3.5 ; 27.7
Over last 3-week period	n	15	12	13	14
	Mean ± SD	0.7 ± 4.3	2.4 ± 8.2	-1.6 ± 4.8	-0.2 ± 7.5
	Median	0.2	-0.0	-0.3	0.0
	Min ; Max	-6.4 ; 9.4	-5.3 ; 20.7	-9.1 ; 4.9	-14.5 ; 12.9
Over 4-week period in completed patients	n	9	11	11	11
	Mean ± SD	1.9 ± 6.1	1.8 ± 6.3	-1.0 ± 4.4	3.8 ± 9.0
	Median	0.0	2.0	0.0	1.0
	Min ; Max	-5.5 ; 15.2	-7.4 ; 11.2	-9.2 ; 4.7	-3.5 ; 27.7
Change of duration of the longest AF (min)	n	15	13	14	14
	Mean ± SD	-178.1 ± 577.0	665.4 ± 2095.0	-161.4 ± 386.3	266.0 ± 2356.3
	Median	-268.0	-76.0	-143.0	-1.0
	Min ; Max	-1213 ; 1222	-680 ; 7292	-886 ; 724	-2084 ; 8144
Change of mean duration of AF episodes (min)	n	15	13	14	14
	Mean ± SD	-10.7 ± 501.7	225.9 ± 579.4	38.4 ± 149.7	49.9 ± 438.7
	Median	-3.4	-5.1	1.2	3.4
	Min ; Max	-855.5 ; 1051.3	-126.0 ; 1754.9	-275.0 ; 384.2	-604.4 ; 1460.4
Change of number of AF episodes	n	15	13	14	14
	Mean ± SD	-2.2 ± 6.8	-8.8 ± 16.6	-9.8 ± 24.6	1.9 ± 44.3
	Median	-1.0	-3.0	-1.5	0.5
	Min ; Max	-20 ; 9	-46 ; 5	-82 ; 12	-88 ; 108
Reduction in AF burden	n	15	13	14	14
≥ 30 %	n' (%)	5 (33.3)	3 (23.1)	4 (28.6)	2 (14.3)
≥ 50 %	n' (%)	3 (20.0)	2 (15.4)	2 (14.3)	1 (7.1)

n: Number of patients with available values during baseline and over the 4-week treatment period
n': Number of patients concerned
%: (n'/n) x 100

SUMMARY – CONCLUSIONS (CONT'D)
EFFICACY RESULTS (CONT'D)

Secondary efficacy endpoints: Other ICM derived parameters

AF burden was highly variable both at baseline and during the study. The median change in AF burden over the 4-week treatment period, showed a small decrease in the 5 mg group (-1.0%), whereas it remained stable in 100 mg group (0.0%), and slightly increased in 25 mg (0.4%) and placebo groups (0.5%). In the 42 completed patients (75.4%), the results were inconsistent but there was no clear evidence of a treatment effect.

The comparison of the changes in **AF burden over the last 3 weeks** of treatment did not reveal any relevant differences between the treatment groups.

The median duration of **the longest AF episodes** decreased modestly in all S 66913 groups and remained stable in the placebo group. No trend toward greater change with increasing dose could be discerned.

The median change of **mean duration of AF** over the 4-week treatment period from baseline was small in all groups, with no relevant significance between groups. The mean was relatively stable in 5 mg and increased in other groups, notably in the 25 mg group, while with large SDs for these mean changes. The median **number of AF episodes** remained relatively stable in all groups.

The mean of median ventricular rate during AF showed no relevant changes in any treatment group.

About 90% of patients had AF automatically detected by ICM, during the 4-week treatment period. Only 5 patients had no AF occurrence: 2 in the 5 mg group and 1 in each of other 3 groups. One patient in the 25 mg group presented persistent AF over the 4-week period.

The median time to **first event of AF**, was within 3 days for all groups: around 2 - 3 days for 5 mg group, 1 day for 25 mg group and about 2 days for the placebo group. In the 100 mg group, the median time to first AF was earlier than other groups at 14.6 hours. These small differences allow no relevant clinical interpretation.

Symptomatic AF, i.e. feelings including palpitations, chest pain, dyspnea, fatigue, lightheadedness, or syncope which led patients to manually trigger a recording the ICM, occurred in about 40% of patients, without relevant difference between groups. The mean time to first occurrence was higher in the 5 mg group (221 hours) compared to the other groups (165 to 169 hours).

The proportion of patients with a **reduction ≥ 30% of AF burden** ranged between 23.1% and 33.3% in S 66913 groups, whereas it was slightly lower at 14.3% in the placebo group. Few patients reached AF burden reduction ≥ 50% in any group.

The CCS-SAF scale: Most patients (77.2%) had symptoms of class 2 or 3, indicating a minor to moderate impact to patients' QoL at baseline, without relevant difference between groups. No clinical relevant change at the end of the treatment period was observed.

SUMMARY – CONCLUSIONS (CONT'D)
SAFETY RESULTS

The emergent adverse events occurring during the study are summarised in Table 4

Table 4 - Overall summary of emergent adverse events in the Safety Set

		S 66913 5 mg (N=16)	S 66913 25 mg (N=13)	S 66913 100 mg (N=14)	Placebo (N=14)
Emergent adverse events on treatment					
Patients having reported at least one:					
Emergent adverse event	n (%)	6 (37.5)	1 (7.7)	1 (7.1)	3 (21.4)
Treatment-related emergent adverse event	n (%)	-	-	-	2 (14.3)
Serious adverse event	n (%)	2 (12.5)	1 (7.7)	-	-
Emergent adverse events after treatment					
Patients having reported at least one:					
Emergent adverse event	n	4	3	5	3
Serious adverse event	n	3	2	2	-

N: Total number of patient in each treatment group
n: Number of patients concerned; %: (n/N) x100
Note: percentages are not calculable during the follow-up because of dropouts at FU2

No death occurred in the study. No patient experienced an EAE that led to IMP withdrawal and no EAE occurred in patients under S 66913 treatment that was considered treatment-related.

A total of 11 EAEs were reported, during the treatment period, in 8 patients out of 43 (18.6%) randomised to S 66913: 8 EAEs in 6 patients in the S 66913 5 mg group, 2 EAEs in 1 patient in the S 66913 25 mg group, and 1 EAE in 1 patient in the 100 mg group. Four EAEs in 3 patients (21.4%) were reported in the placebo group.

Each EAE, by preferred term, only occurred once in any patient except for sinus arrest, which occurred twice in one patient (5mg group; once on-treatment; once off-treatment). No dose effect on EAE incidence was seen.

A total of 2 events (diarrhoea and dizziness) in 2 patients under placebo were considered as related to IMP.

A serious adverse event was reported, during the treatment period, in 3 patients treated with S 66913. Two of these events were in the S 66913 5 mg group: AF and sinus arrest ("asymptomatic 5-second pause after a run of AF"). One further event, cardiac failure, was reported in the S 66913 25 mg group.

Emergent out-of-reference-range biochemical and haematological values during the treatment period were sparse in all treatment groups, without relevant differences. Only one potentially clinically significant abnormal value was observed: a high value of gamma glutamyl transferase in the placebo group, considered not clinical significant.

The median change in **SBP** from baseline to W4 was minor in the 5 mg (-1.5 mmHg), 100 mg (-1.0 mmHg) and placebo groups (-1.0 mmHg), notably greater in the 25 mg group (-7.0 mmHg). The mean change showed similar trends, except that an increase of 3.9 ± 12.8 mmHg was observed in the 100 mg group. The mean and median **DBP** was relatively stable in the 5 mg group from baseline to W4 visit, while they decreased in the other groups. According to 12-lead ECG recordings at each visit, the median and mean **heart rates** were quite stable in any treatment groups during the study, except for a decrease in the placebo group from baseline to W4 visit.

SUMMARY – CONCLUSIONS (CONT'D)
SAFETY RESULTS (CONT'D)

After the treatment period including extended safety follow-up

A total 38 of the 39 patients participating in the follow-up program underwent pulmonary examinations (one patient having refused). Of these, 14 patients had at least one clinically significant respiratory abnormality at WFU1 or WFU2 or a respiratory adverse event during the study period, but they were not, or unlikely, related to the study treatment according to the investigator.

After the treatment period and during the extended clinical follow-up (without study treatment), 27 EAEs (33 with multiple coding) were reported in 15 patients: 12 patients in the S 66913 groups and 3 patients in the placebo group. In addition a non-serious EAE on treatment (bronchiectasis; S 66913 5mg group) became serious five months after end of study treatment (hospitalization). Another non-serious event (bronchitis; S 66913 100 mg group) occurred between W4 and WEND became serious at WEND. Thus, 7 patients in the S 66913 groups reported at least one event as serious (or upgraded to medically important by the Sponsor) during the extended follow-up. These events included sinus arrest (asymptomatic), influenza, dyspnoea, non-cardiac chest pain, hypothyroidism, bronchiectasis (an event emergent during the treatment period, but worsened), haematuria, vitreous adhesions, pulmonary fibrosis, bronchitis, vascular pseudoaneurysm, post-procedural cellulitis and pneumonia. None of them were considered as related to the study treatment.

These results were reviewed and validated by the DMC.

CONCLUSION

This phase II, placebo-controlled, double-blind, 4-arm parallel group, exploratory study (DIAGRAF-IKUR) was conducted in PAF patients potentially eligible for AF ablation, with the objective of evaluating the efficacy of three doses of S 66913 (5 mg, 25 mg and 100 mg) on AF/AT burden. The study treatment was prematurely discontinued as precautionary safety measure with 58 patients included, due to the findings from on-going toxicology studies in the rat and monkey, which led to a reduction in the safety margin in humans. The clinical relevance of these findings to the human condition could not be evaluated at that stage.

This is the first study that has used insertable continuous cardiac rhythm monitoring device (ICM) with central data adjudication to evaluate drug efficacy. Due to the premature treatment discontinuation, the AF profile among the groups was not well balanced. The study did not show any tendency towards drug efficacy on the change of AF/AT burden or AF burden, nor in the mean duration and number of events, or time to 1st AF recurrence. The safety profile was satisfactory with overall rates on adverse events lower in the S 66913 groups as compared to the placebo group. The results from the long-term clinical follow-up did not show any specific safety concern. The reported respiratory adverse events were mild and the study treatment appeared to have no causal role on incidence.

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