Document title	**ABBREVIATED CLINICAL STUDY REPORT SYNOPSIS**
Study title	**Effects of acute and chronic oral administration of S 44121 *versus* placebo on cardiac arrhythmia during exercise testing in patients with catecholaminergic polymorphic ventricular tachycardia type 1 - A randomized, parallel-group, international multicentre study including a 8-week double-blind placebo controlled period followed by a 8-week single-blind period – Phase II exploratory study**
Test drug code	**S 44121**
Indication	**Catecholaminergic polymorphic ventricular tachycardia type 1**
Development phase	**Phase II**
Protocol code	**CL2-44121-008**
Study initiation date	**30 August 2012**
Study completion date	**30 May 2013**
Main coordinator	[redacted] **ITALY**
Sponsor(s)	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex – France** **SERVIER Research and Development ICTR** **Rowley, Wexham Springs; Framewood Road** **Wexham, Slough SL3 6RJ - United Kingdom**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**12 December 2014**
Version of the report	**Final version**
	~~CONFIDENTIAL~~

SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot - 92284 Suresnes Cedex - France		*(For National Authority Use only)*
Test drug: S 44121 **Name of Finished Product:** NA **Name of Active Ingredient:** ***S 44121***		
Individual Study Table Referring to Part of the Dossier	**Volume:**	**Page:**

Title of study: Effects of acute and chronic oral administration of S 44121 *versus* placebo on cardiac arrhythmia during exercise testing in patients with catecholaminergic polymorphic ventricular tachycardia type 1 - A randomized, parallel-group, international multicentre study including a 8-week double-blind placebo controlled period followed by a 8-week single-blind period – Phase II exploratory study.
Protocol No.: CL2-44121-008
EudraCT No.: 2011-000579-15
The description of the study protocol given hereafter includes the modifications of the 7 amendments to the protocol.

International coordinator:
[redacted] Italy.

National coordinators:
[redacted]
Finland.
[redacted] Germany.
[redacted]
United-Kingdom.

Study centres:
The study was initially planned as a multicenter study (9 – 12 centres, 7 countries) but only one centre in Finland had included patients.

Publication (reference): NA.

Studied period:	**Phase of development of the study:**
Initiation date: ***30 August 2012*** (***date of first visit first patient)*** Completion date: ***30 May 2013*** (***date of last visit last patient)***	**II**

Objectives:
The objective of this study was to assess the effects of a single and chronic oral administration of S 44121 *versus* placebo on the occurrence of cardiac arrhythmia during standardized exercise tests (ETs) in patients with catecholaminergic polymorphic ventricular tachycardia type 1 *(*CPVT type 1). The safety profile of S 44121 was also evaluated.
Secondary objectives were to evaluate the effects of S 44121 compared to placebo on the quality of life, to assess the pharmacokinetics of S 44121 and to identify genetic determinants of absorption, distribution, metabolism, and excretion of S 44121 (not analysed due to small sample size).
In addition, the characteristics and functional properties of some ryanodine type 2 channel (RyR2) mutations were to be investigated in induced pluripotent stem cells (iPSCs) derived cardiomyocytes from skin fibroblast (no skin biopsy performed in any patient).

Methodology:
The CL2-44121-008 study was a phase II, parallel-arm, randomised, multicenter, international, exploratory study including a double-blind placebo controlled period followed by a single-blind period.
The randomisation was unbalanced (2 S 44121: 1 placebo), stratified by centre.
This study was performed in strict accordance with Good Clinical Practice including the archiving of essential documents.
The present study was prematurely stopped due to difficulties in patients' recruitment, attributed to the very small number of patients with CPVT type 1 and implantable cardioverter-defibrillator (ICD).

Number of patients:
Planned: 36 included patients (24 in S 44121 arm and 12 in placebo arm).
Included: 7 patients (5 in S 44121 arm and 2 in placebo arm).

Diagnosis and main criteria for inclusion:
Male or female patients aged 18 years or more; -with established diagnosis of CPVT type 1 that included ECG-documented exercise-induced cardiac arrhythmia as well as genetic screening showing at least one RyR2 mutation; -treated with a beta-blocker at optimal dosage (*i.e.* a dosage associated with an individually optimised suppression of CPVT signs and symptoms and, that was tolerated by the patient) and, following Amendment No.7, having an implantable cardioverter-defibrillator for primary or secondary prevention of ventricular arrhythmia for at least 3 months prior to pre-selection.
Patients had to meet positivity and stability criteria regarding the occurrence of cardiac arrhythmia during the ET. For this purpose, two options were applied: presence of bidirectional or polymorphic ventricular tachycardia and persistence of the arrhythmia on two consecutive ETs (option 1) *or,* presence of at least 40 premature ventricular complexes (PVCs) during the complete ET and less than 50% difference in the total number of PVCs between two consecutive ETs (option 2).

Test drug:
Sachet sets of S 44121 as a single dose given orally at W0 first (1000 mg) and then as a chronic administration in a forced up-titration of 250, 500 and then 1000 mg doses given orally twice a day in the morning and in the evening.
The content of 3 sachets diluted in 200 mL of water had to be taken by a single intake with a meal.
Batch Nos. L0039806 - L0039808 - L0039810.

Comparator:
Placebo as a single dose given orally at W0 first then twice a day in the morning and in the evening.
The content of 3 sachets diluted in 200 mL of water had to be taken by a single intake with a meal.

Duration of treatment:
A placebo run-in period (from selection to inclusion visit): 1 to 14 days.
A treatment period (from inclusion to W12 visit): 12 weeks (including an 8-week double-blind period (S 44121 or placebo) followed by a 4-week single-blind period on S 44121).
A placebo follow-up period (from W12 to W16 visit): 1 to 4 weeks.

Criteria for evaluation:

The efficacy measurements were ECG parameters during standardized exercise tests at SEL, W0, W4, W8, W12 and W16 visits. The main surrogate endpoint was the mean number of PVCs per minute during the ET. Also of interest was:

- The number of PVCs during the worst minute of the ET (*i.e.*, one minute period with highest frequency of PVCs).
- The ventricular salvos (at least 3 consecutive PVCs) during the ET.
- The occurrence of individual cardiac arrhythmias during the ET.
- The sinus rate threshold of individual cardiac arrhythmias during the ET.
- The test duration.

Safety measurements were:

- Adverse events throughout the study.
- Systolic and diastolic blood pressure at each visit.
- Resting ECG at each visit.
- Blood laboratory parameters at the W0, W8, W12 and W16 visits.
- 24-hour Holter recording at the W0 and W8 visits (optional 24-hour Holter monitoring could be performed at W4 and W12 visits).

Statistical methods:
The present study was prematurely stopped. Consequently, statistical analyses as described in the protocol were no more applicable and only descriptive statistics were provided. No inferential analyses were performed. No analyses on ventricular salvos and from quality of life questionnaires, pharmacokinetic and pharmacogenetic samples were performed. No skin biopsy was done for the iPSCs analysis.

SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME

A total of 7 patients were included and randomly assigned to one of the 2 groups: 5 patients in the S 44121 group and 2 in the placebo group.

They received either S 44121 or placebo in a forced up-titration design of 8 weeks (single oral administration of 1000 mg at inclusion, then successive *b.i.d.* administration of 250 and 500 mg during 4 weeks each) followed by a forced single dose period of S 44121 1000 mg *b.i.d.* for 4 weeks in all patients.
In all, 5 patients completed the study and 2 were withdrawn (both in the S 44121 group 3 and 15 days after the first drug intake, one for adverse event and one for non-medical reason (included without ICD, contra-indicated by Amendment No.7). As the sample size of each group was small, data were heterogeneous resulting in some between-group differences at baseline.

Disposition of patients

	S 44121	***Placebo***	**All**
Included	**5**	**2**	**7**
Withdrawn due to	**2**	**-**	**2**
- adverse event*	1	-	1
- non-medical reason**	1	-	1
- protocol deviation	-	-	-
- lost to follow-up	-	-	-
- lack of efficacy	-	-	-
Completed	**3**	**2**	**5**
Full Analysis Set (FAS)	**3**	**2**	**5**
Safety Set	**5**	**2**	**7**

** Ventricular fibrillation, atrial fibrillation and loss of consciousness in one single patient.*
*** By protocol amendment No.7 which recommended the withdrawal from the study of any patient without an ICD*

Overall, patients were aged from 37 to 64 years with a mean of 53.9 ± 8.5 years. There were 4 women and 3 men. The medians for age were similar between treatment groups and the ratio of women to men well-balanced within each group.

All patients were diagnosed with catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT 1). A RyR2 mutation was present in each patient and all (except one in the S 44121) had a family history of CPVT 1. Initial clinical presentation of CPVT 1 was syncope in all patients. At the time of symptom onset, patients were on average 17.9 ± 11.1 years old and at the time of diagnosis, 41.0 ± 12.9 years. While the median for age at the time of symptoms onset was higher in the S 44121 group than in the placebo (16 years old *versus* 11 years old), medians for age at the time of diagnosis were comparable. Overall, the mean duration of the disease since diagnosis was 12.4 ± 7.2 years.

As required in the protocol, all patients received a beta-blocker: mostly bisoprolol (3 patients in the S 44121 group and both patients of the placebo group, doses from 0.050 mg/kg to 0.160 mg/kg daily *i.e.* from 5 mg to 10 mg daily) and also in the S 44121 group, metoprolol (1 patient, dose of 1.190 mg/kg daily *i.e.* 95 mg daily) and atenolol (1 patient, dose of 0.780 mg/kg daily *i.e.* 75 mg daily).

In addition, all patients had an implanted cardioverter defibrillator at selection (except one in the S 44121 group withdrawn from the study by Amendment No.7 which was requiring ICD in all patients). All received atrial pacing except 2 patients in normal sinus rhythm at baseline (both in the S 44121 group).

All patients presented cardiac arrhythmia induced by exercise and all (but one in each treatment group) suffered from cardiac arrhythmia induced by emotion.

At selection each patient performed exercise tests on a bicycle ergometer under continuous ECG monitoring. All ETs were stopped due to exhaustion, except 2 ETs stopped for occurrence of presyncopal symptoms in the same patient of the S 44121 group. All included patients fulfilled the criteria related to positivity and stability, according to the investigator with at least 40 PVCs during 2 consecutive ETs at selection and with a difference (in number of PVCs) between both ≤ 50%. Ventricular tachycardia was observed in one patient at baseline during the exercise test (non-sustained).

While this patient population corresponded well to the definition in the protocol and Amendment No. 7 (ICD requirement), it was noted that it was a sample that was older and with more comorbidities than is generally seen in cardiology departments.

SUMMARY – CONCLUSIONS (Cont'd)
STUDY POPULATION AND OUTCOME (Cont'd)

During the exercise period at baseline, patients had overall a mean number of PVCs per minute of 15.5 ± 6.4, with a mean time to first event of 320.0 ± 154.2 sec. During the worst minute, patients had a mean number of 74.1 ± 21.8 PVCs. While medians for number of PVCs per minute were comparable between groups, both medians for time to first event and for the number of PVCs during the worst minute were lower in the S 44121 group than in the placebo group (191.0 sec and 57.5 PVCs *versus* 378.8 sec and 94.8 PVCs).

During the recovery period, the mean number of PVCs per minute was 3.9 ± 3.2 overall, with a mean time to disappearance of 140.0 ± 120.1 sec. During the worst minute overall, patients had a mean number of 25.4 ± 17.8 PVCs. Medians for total number of PVCs per minute and during the worst minute were higher in the S 44121 group than in the placebo group (6.1 and 35.5 PVCs *versus* 2.2 and 17.3 PVCs) while median for time to disappearance was lower (81.5 sec *versus* 155.8 sec).

The sinus rate threshold for the occurrence of PVCs during the exercise period was on average 101 ± 10 bpm and for the disappearance during the recovery period, 92 ± 21 bpm. Medians for the sinus threshold of both the occurrence and the disappearance of PVCs were lower in the S 44121 group than in the placebo group (95 and 89 bpm *versus* 110 and 107 bpm).

Overall, the mean resting ECG HR was of 61.0 ± 6.2 bpm. Mean values of PR interval and QRS duration were 178.0 ± 28.1 msec and 89.1 ± 12.9 msec, respectively. Mean values of QTc Bazett and QTc Fridericia intervals were 430.7 ± 15.8 msec and 429.9 ± 13.2 msec, respectively. Sitting SBP / DBP values were on average 118.7 ± 16.9 mmHg / 77.4 ± 13.7 mmHg, respectively. In the S 44121 group, medians for HR and blood pressure (SBP / DBP) were slightly lower than those observed in the placebo (57.0 bpm and 110.0 / 72.0 mmHg *versus* 66.5 bpm and 117.0 / 86 mmHg).

All patients (except one in the placebo group) reported medical history other than CPVT 1. Most of them had treated chronic diseases (5 patients, all in the S 44121 group) including hypertension and/or hypercholesterolemia (each in 2 patients), type 2 diabetes mellitus, asthma, osteoarthritis, back pain, headache and/or, depression (each in one patient).

In all, the mean treatment duration was 55.3 ± 40.2 days and 76.4 ± 52.0 days over the W0 – W8 and W0 – W12 periods, respectively. The overall large standard deviation was due to abnormal treatment durations in 3 patients of the S 44121 group (2 low values in early withdrawals and one high value in a patient with treatment interruption). Overall compliance was ≥ 97 % over both W0 – W8 and W0 – W12 periods (except in those 3 patients).

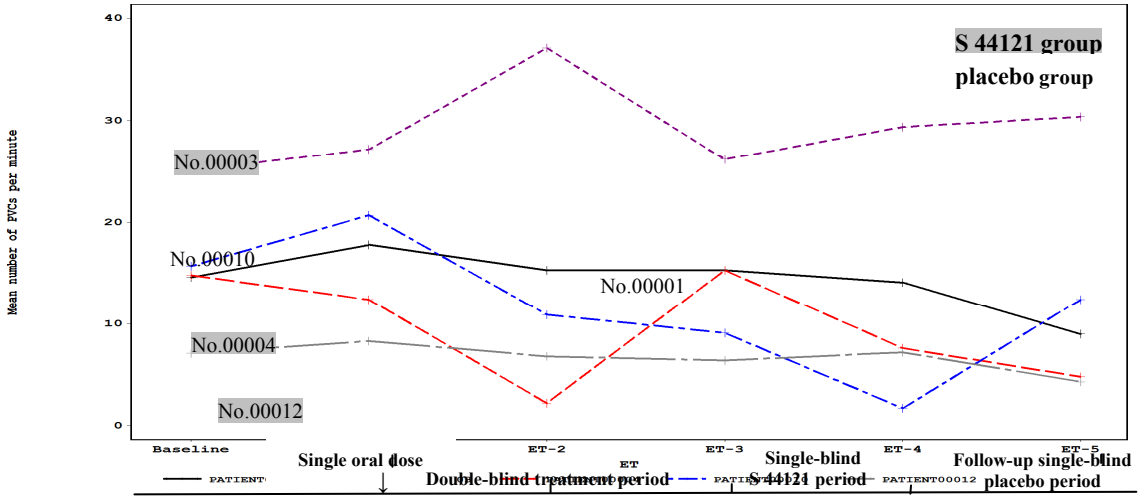
EFFICACY RESULTS

Of the 7 included patients, 3 patients in the S 44121 and 2 patients in the placebo group completed the entire set of exercise tests on treatment during the study (all ETs stopped due to exhaustion), with respective post-baseline efficacy assessments.

The main surrogate endpoint was the mean number of PVCs per minute during the exercise period. Following the single or chronic S 44121 dosing, no clear signal of efficacy on the mean number of PVCs per minute was observed during the exercise period among the limited amount of patients included. The evolution over time by patient and by treatment group of the mean number of PVCs per minute during the exercise period at each test (ET1 to ET5) is presented in the figure hereafter.

SUMMARY – CONCLUSIONS (Cont'd)
EFFICACY RESULTS (Cont'd)

Mean number of PVCs per minute during the exercise period over the study by patient and by treatment group (S 44121 or placebo) in the FAS



↓***ET1*** *1000 mg of S 44121 or placebo;* ***ET2*** *after chronic b.i.d. dose of 250 mg;* ***ET3*** *after chronic b.i.d. dose of 500 mg;* ***ET4*** *after chronic b.i.d. dose of 1000 mg;* ***ET5*** *after chronic b.i.d. dose of placebo.*

Comparable results were observed on other endpoints (mean time to first event, mean number of PVCs during the worst minute, sinus rate threshold for the occurrence of PVCs), including on the rate of ventricular tachycardia during the exercise test that generally occurred only occasionally across study visits. Similarly, no clear signal of efficacy was observed on endpoints during the recovery period.

SAFETY RESULTS

- **Emergent adverse events**

Overall in the Safety Set, 6 /7 patients reported 14 emergent adverse events (EAEs) during the W0 – W12 active treatment period:

- 5 /7 patients reporting 11 EAEs during the double-blind treatment period (W0 – W8).
- 2 /5 patients reporting 3 EAEs during the single-blind S 44121 period (W8 – W12).

From the 7 included patients, only 5 patients entered the W8 – W12 period because 2 in the S 44121 group were withdrawn from the study during the W0 – W8 period.

During the **double-blind treatment period** (W0 – W8), patients received either two consecutive doses of S 44121 (250 mg *b.i.d.* and then 500 mg *b.i.d.* for 4 weeks each) or placebo. Were observed:

- 3 /5 patients reporting 7 EAEs in the S 44121 group:
  - 5 events over the 250 mg dose period in 2 patients:
    - One patient had 2 non-serious events: vulvitis and headache.
    - One patient had 3 serious events: Ventricular fibrillation, atrial tachycardia and loss of consciousness (these were considered by the investigator as being unrelated to the study drug; the patient recovered).
  - 2 events over the 500 mg dose period in one patient each:
    - Hypertension in one patient with history of treated hypertension and constipation in the other.
- 2 /2 patients reporting 4 EAEs in the placebo group:
    - Fatigue, abdominal distension and pollakiuria in one patient and nausea in the other.

SUMMARY – CONCLUSIONS (Cont'd)
SAFETY RESULTS (Cont'd)

During the **single-blind S 44121 period** (W8 – W12), all patients received S 44121, 1000 mg *b.i.d.* for 4 weeks. Were observed:

- 2 /5 patients reporting 3 EAEs on S 44121 1000 mg *b.i.d.*:
  - 2 events in one patient of the S 44121 group: Gastrointestinal tract irritation and oesophageal irritation.
  - 1 event in one patient of the placebo group: Uterine leiomyoma.

During the study, all emergent adverse events were of mild or moderate intensity, except 3 events of severe intensity reported the same day in one single patient of the S 44121 group who had an implantable cardioverter defibrillator.
Those 3 **severe EAEs** (ventricular fibrillation, atrial tachycardia, loss of consciousness) occurred during a physical exercise on the 250 mg dose *b.i.d.*, 3 days after the first S 44121 intake, led to treatment discontinuation and were reported as serious. However on the basis of similar episodes of arrhythmia occurring 8 months after the study, the investigator considered these SAEs as not related to the study drug.
No additional EAEs led to treatment discontinuation. No additional serious EAEs were reported.

In all, 4 patients had EAEs considered as **related to the study treatment** by the investigator:

- 2 patients with 3 EAEs in the S 44121 group: constipation in one patient (at the end of the double-blind treatment period) and, gastrointestinal tract irritation and oesophageal irritation in the other (during the single-blind S 44121 period).
- 2 patients with 4 EAEs in the placebo group: fatigue, abdominal distension and pollakiuria in one patient and, nausea in the other (all occurring over the first week of the double-blind treatment period).

All patients with emergent adverse events **recovered** at the study end, except one woman in the S 44121 group with not resolved elbow fracture (of severe intensity, fracture occurring one month before the study participation with possibility of reoperation that did occur during the study), vulvitis and headache (of mild intensity, reported 14 days after first intake).

- **Laboratory tests, other safety evaluation**

Regarding biochemical and haematological parameters, no clinically relevant changes over time were observed during the study. Emergent out-of-reference range values were not clinically relevant. No patient had an emergent potentially clinically significant abnormal value.
Regarding resting ECG parameters, no clinically relevant changes over time were observed. One patient on S 44121 switched from normal sinus rhythm at baseline to atrial pacing at W4 visit and up to the study end. No patients reported any emergent ECG abnormality. During the 24h holter recording performed at the end of the double blind treatment period (placebo or S 44121 500 mg *b.i.d.*), in only one patient in each treatment group ventricular tachycardia was observed (non-sustained).
No clinically relevant changes in mean blood pressure were observed over time.

CONCLUSION

In conclusion, this exploratory phase II double-blind placebo controlled study was prematurely stopped due to difficulties in patient recruitment, attributed to the very small number of patients with CPVT type 1 and ICD. Following the single or chronic S 44121 dosing, no clear signal of efficacy on the mean number of PVCs per minute was observed during the exercise period among the limited amount of patients included. Comparable results were observed on other endpoints. Events of ventricular tachycardia generally occurred only occasionally across study visits. Regarding the safety profile, all emergent adverse events observed in patients on S 44121 were of mild or moderate intensity except 3 events of severe intensity reported the same day in one single patient who had an implantable cardioverter defibrillator. Those 3 EAEs (ventricular fibrillation, atrial tachycardia, loss of consciousness) occurred during a physical exercise on the 250 mg dose *b.i.d.*, 3 days after the first S 44121 intake, led to treatment discontinuation and were reported as serious (the patient was reported as recovered on the same day). On the basis of similar episodes of arrhythmia in this patient, occurring 8 months after the study, the investigator considered these SAEs as not related to the study drug.

Date of the report: 12 December 2014

Version of the report: Final version