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

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The objective of this study is 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 CPVT type 1. The safety...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON37671

Source
ToetsingOnline

Brief title
S44121 in CPVT

Condition

- Cardiac arrhythmias

Synonym
catecholaminergic polymorphic ventricular tachycardia; inheritated heartrhythmdisorder

Research involving
Human

Sponsors and support

Primary sponsor: Servier R&D Benelux
Source(s) of monetary or material Support: IRIS (Institut de Recherches Internationales Servier)

Intervention

Keyword: arrhythmia, CPVT, ryanodine receptor modulator

Outcome measures

Primary outcome

The primary efficacy endpoint is:

-The mean number of PVCs per minute during the ET (exercise testing) with S

44121 versus placebo

Study parameters for clinical safety measurements: S 44121 versus placebo:

-ECG at rest: heart rate, sinus rhythm, PR interval, QRS duration, and QT

interval and QRS axis

-24-hour Holter recording,

-Systolic and diastolic blood pressure,

- ICD reading at every visit (ECG events and ICD based therapies)

-Adverse events,

-Blood clinical laboratory parameters (hematology and biochemistry).

Secondary outcome

The secondary efficacy endpoints are: S 44121 versus placebo:

-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

Other study parameters:

- The Quality of Life of the patient will be assessed with the RAND-36 and

AF-Quality of Life (AF-QoL-18) questionnaires

- pharmacokinetic analysis of S44121

- identify genetic determinants of absorption, distribution, metabolism, and

excretion of S 44121 (optional)

- the characteristics and functional properties of some RyR2 mutations of

patients with CPVT type 1 will be investigated in iPSCs-derived (induced

pluripotent stem cells) cardiomyocytes from skin fibroblast (optional)

Study description

Background summary

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a potentially lethal disease characterized by adrenergically mediated ventricular

arrhythmias. CPVT is one of the most severe inherited arrhythmogenic disorders and is the most lethal ion channel-associated cause of sudden cardiac death. The prevalence of the disease is estimated to be 1:10,000 in Europe (Orphanet, 2011).
At present, no treatment is available to cure the condition, but treatments aimed at the prevention or termination of cardiac arrhythmias upon activation of the sympathetic nervous system are available. Beta-blockers are the mainstay of treatment for these patients, and are uptitrated on an individual basis upon tolerability and control of arrhythmias during exercise testing. Periodic re-evaluation of beta-blocker efficacy is performed on the basis of exercise testing performed at the highest tolerated workload. Despite an individually optimised treatment regimen, the protection against cardiac arrhythmias often remains incomplete and many continue to have symptoms and/or documented exercise-induced ventricular arrhythmias. In these cases, an implantable cardioverter-defibrillator (ICD) is the currently recommended treatment option. Given the mortality risk and the incomplete protection with current therapies, a high medical need exists for these patients. The disease-causing gene in CPVT type 1 is the ryanodine receptor 2 (RyR2) gene. The gene codes a ryanodine type 2 channel (RyR2), which has a major role in the intracellular calcium handling in the cardiac muscle. The new investigational compound S 44121, a benzothiazepine derivative, acts as a ryanodine receptor modulator and can improve the rebinding of calstabin-2 to hyperphosphorylised RyR2 channels. Therefore, this compound may be of use in patients with CPVT type 1.
Up to now, S 44121 was administered to a total of 165 healthy volunteers, by the oral or intravenous route. Overall, S 44121 presented a good safety profile. No serious adverse events, biological abnormalities, or electrocardiogram (ECG) abnormalities were reported (Clinical investigator*s brochure, 2011) . A phase II exploratory study has been performed to assess the effects on cardiac arrhythmia of three single oral administrations (500, 1000 and 1500 mg) of S 44121 during exercise testing in patients with CPVT type 1 (n=14 patients). Preliminary results show an efficacy in terms of reduction of PVCs per minute in around 30 % of the patients and a good safety profile. No serious adverse events have been reported and all patients have completed the study. The compound is also currently assessed in chronic heart failure and up today 180 patients have been treated up to 3 months at doses from 250 to 1000 mg b.i.d.. The possible side effects after oral administration are those related to the alimentary tract such as nausea and abdominal pain.
Overall, in view of the preclinical and clinical data showing an anti-arrhythmic efficacy and a good tolerability profile, the benefit-risk balance is considered favourable (Clinical investigator*s brochure, 2011) regarding the proposed study.

Study objective

The objective of this study is 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 CPVT type

1. The safety profile of S 44121 will also be evaluated.

Study design

This study is a phase II, parallel-arm randomised multicentre international exploratory study including a 8-week double-blind placebo controlled period followed by a 8-week single-blind period. The study will be performed in approximately 36 patients with CPVT type 1 .
The total duration of the study per patient is maximum 18 weeks.
Study plan: see protocol pag 19 (fig 8.2.1)

Intervention

S44121 (dosis 250 - 500 - 1000 mg) and placebo, treatment taken twice daily period of 8 weeks double blind, followed by a period of 8 weeks single blind visits:
- preselection visit (Pre-SEL): confirmation of the diagnosis of CPVT
- selection visit (SEL): 2 qualification exercise tests (ETs)- start run-in treatment with single blind placebo, twice a day
- inclusion visit (W000): 1 to 14 days later- start double blind treatment: S44121or placebo, twice a day
duration of 8 weeks double blind period with visits on W004 en W008
- 4 weeks single blind period between W008 en W012: S44121 dosed at 1000mg , twice a day
- single blind periode(1-4 wks) till vist W016: placebo, twice a day

Study burden and risks

The patient will have to perform the following procedures for the study:
- Exercise testings (ETs): 2 (to 3) at the selection visit to determine the qualification of the patient to continue the study. The first ET will have to start 2 hours after the betablocker intake, the second ET again 2 hours later. This is time consuming for the patients. At inclusion, visit week 4 - 8 - 12 - 16 , 1 ET will have to be performed. The patient will have to bicycle around 10 minutes, depending on his physical condition, during which an ECG is taken. The final duration will be decided by the patient or the investigator. All ETs will be performed under strict medical supervision. The results of the standardised ETs are used to evaluate the primary endpoint of the study.
- 24hours Holter monitoring. Minimal burden for the patient. A Holter will have to be performed at inclusion and at visit of week 8. At the visits of week 4 and 12 it is optional.
- Bloodsamplings for analysis of hematology and biochemistry: this will have to be performed fasting, at inclusion, and the visits of week 8 - 1 2 -16. The bloodsamplings need to be taken fasten because food intake can influence certain parameters (blood glucose, cholesterol) and have an impact on the results .

- Blood samplings for pharmacokinetic analysis (at week 4 - 8 - 12). These are more time consuming for the patients. At week 4 the third blood sampling needs to be performed 4 hours after study medication intake, and at week 12, 3hours later. The patient will receive some compensation for the visits with a stay of more than 3 hours in the hospital. When several samplings need to be performed during the same visit, the physician can place a catheter during the duration of the study to facilitate the blood draws and avoid repetitive punctures.
In total a maximum of 100ml blood will be sampled during the whole study duration of 18 weeks.
- Blood sampling for pharmacogenetic anaysis: participation is optional (needs to be approved by the patient): to be done at week 4.
- Skin biopsy (once): participation is optional (needs to be approved by the patient). The skin is anesthesised locally and a small part is excised (not more than the tip of a pen), often at the lower back. Some burden can be experienced by the patient. The major risks are rare.
Up to now, S 44121 was administered to healthy volunteers and patiens with chronic heart failure at similar doses up to 3 months. In patients with CPVT S44121 was adminstered during 2 days and the medication was well tolerated. The possible side effects of S44121 are those related to the alimentary tract such as nausea, indigestion and abdominal pain. Other side effects and burden can appear that are unknown until now and that can not be predicted well at this moment.

The safety of the study patients is verified during the study by the DSMB. On 10/10/2012, 5 patients were included in this study internationally. One of these patients experienced a ventricular fibrillation 2 days after first study drug administration and was withdrawn from the study. After thorough evaulation of this case as well as of the data of other ongoing studies with S44121, the DSMB has decided the trial can continue to safely include patients if patients have an implanted ICD. Following this decision the protocol has been amended accordingly.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Male or female patients aged 18 years or more;- Established diagnosis of CPVT type 1;- Treatment with beta-blocker;- Qualifying ETs meeting a predefined degree of severity and stability of the disease;- Presence of an ICD for primary or secondary prevention of ventricular arrhythmia implanted at least 3 months prior to pre-selection

Exclusion criteria

- Resting ECG with an abnormality that could preclude a proper interpretation of the ECG obtained during the ETs;- Chronic heart failure;- Structural congenital heart disease

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-12-2011
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	S44121
Generic name:	S44121

Ethics review

Approved WMO Date:	16-12-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2012

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-000579-15-NL
CCMO	NL38555.018.11