A Phase II, Double-Blind 2-arm study to investigate the effect on ventricular ectopy, safety, tolerability and pharmacokinetics of S48168 (ARM210) compared with Placebo in adults with Type 1 Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT1)

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This is a research study. The purpose of this study is to test if the investigational medicinal product S48168 (ARM210) is safe and effective when given to patients diagnosed with CPVT1. Primairy objective:To assess the effect of S48168 (ARM210) on...

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

Summary

ID

NL-OMON53588

Source
ToetsingOnline

Brief title
The effect of S48168 (ARM210) in adults with CPVT1

Condition

- Cardiac arrhythmias

Synonym
abnormal heart rhythm, arrhythmia

Research involving
Human

Sponsors and support

Primary sponsor: ARMGO Pharma Inc.
Source(s) of monetary or material Support: De Sponsor;ARMGO Pharma;Inc

Intervention

Keyword: CPVT1, S48168 (ARM210), Type 1 Catecholaminergic Polymorphic Ventricular Tachycardia, Ventricular ectopy

Outcome measures

Primary outcome

Change in ectopy scoring scale from baseline to day 28 versus placebo.

Ectopy Scoring Scale (0-4)

No ectopy 0

Isolated PVCs 1

Bigeminy 2

Couplets 3

Non-sustained VT 4

(van der Werf et al. 2011)

Secondary outcome

Incidence of AEs, SAEs and TEAEs.

Change from baseline in safety assessments (vital signs, physical examinations,

laboratory safety tests, ECGs and Columbia-Suicide Severity Rating Scale

(C-SSRS).

Alerts from continuous cardiac rhythm monitoring during 28-day periods.

Study description

Background summary

Patients with CPVT1 have an inherited disorder characterized by an abnormal heart rhythm. CPVT1 is a life-threatening disease that is a major cause of unexplained sudden death, particularly in children and young adults.

The purpose of this trial is to investigate the effect of S48168 (ARM210) on abnormal heart beats, safety, tolerability and blood levels compared with placebo in adults with CPVT1.

Study objective

This is a research study. The purpose of this study is to test if the investigational medicinal product S48168 (ARM210) is safe and effective when given to patients diagnosed with CPVT1.

Primairy objective:

To assess the effect of S48168 (ARM210) on exercise-induced ventricular ectopy in participants with CPVT1.

Secondary Objectives:

To determine safety and tolerability of S48168 (ARM210) in participants with CPVT1.

Exploratory objectives:

To determine the pharmacokinetics (PK) of S48168 (ARM210) in patients with CPVT1.
To evaluate a novel expanded ectopy scale in exercise stress tests which qualifies both the ectopy and the heart rate at which it occurs.
To examine any long-term effect on heart rhythm by treatment with S48168 (ARM210).

Study design

This is a Phase II, randomized two period crossover study of the safety, tolerability, and PK of S48168 (ARM210) in approximately 20 participants with CPVT1 completing the study.

Intervention

Patients will receive 200 mg S48168 (ARM210) daily for a minimum of 28 days during the 1st period and 200mg place daily for a minimum of 28 days during the 2nd period and vice versa.

Study burden and risks

Patients might not benefit from being in this study. However, you might have a short-term improvement in your symptoms. The short nature of this study may limit these benefits.

Taking part in the study can have the following burdens:
- Patients may experience side effects or adverse effects of the study medication.
- There may be some discomfort from the measurements during the study.
- The questionnaires can be confrontational.
- Patients will have to follow strict rules about taking medicines.
- Patients have to comply with the study agreements.

The study medication to be investigated may cause side effects.
So far, the study medication has been tested in four studies of healthy adult male volunteers and is being tested in patients with a genetic muscle disease.
Side effects in these studies included:
• stomach pain,
• diarrhea,
• vomiting,
• constipation,
• nausea,
• dry mouth,
• loss of taste,
• fatigue,
• nose and throat pain,
• muscle stiffness,
• muscle weakness
• joint pain
• lower back pain,
• dizziness,
• headache,
• local numbness,
• excessive sweating.

There is always a chance that an unexpected or serious side effect or allergic reaction may happen. This can happen to people who take this or any other medication. Some symptoms of allergic reactions may include but are not limited to:
• Rash or hives,
• Wheezing and difficulty breathing,
• Dizziness or fainting,

• Swelling around the mouth, throat, or eyes,
• A fast pulse,
• Sweating,
• Anxiety (feeling of worry, nervousness, or unease) and confusion.

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

Participants are eligible to be included in the study only if all the following criteria apply: Age 1. Participant must be at least 18 years of age inclusive, at the time of signing the informed consent Type of Participant and Disease Characteristics 2. Participants who are willing and able to comply with scheduled visits, study drug administration plan, study restrictions, and study procedures. 3. Participants have a confirmed genetic diagnosis of CPVT1 and

supporting clinical phenotype, including residual ventricular ectopy (a complexity score >=2; requiring at minimum the presence of PVCs in bigeminy on exercise stress test) on a stable (at least 1 month) standard-of-care, CPVT1-directed treatment regimen as decided by their CPVT treating physician. Weight 4. Have a body mass index (BMI) <= 38 kg/m2 (inclusive) at screening. Sex and Contraceptive/Barrier Requirements 5. Male participants agree to not donate sperm from the first day of dosing of study drug until 5 half-lives plus 90 days (approximately 94 days) after the last dose of study drug. Female participants: eligible to participate if she is not pregnant or breastfeeding, and uses one of the following highly effective birth control methods (from the first dose until 5 half-lives plus 90 days (approximately 94 days): • Prescribed hormonal oral contraceptives, vaginal ring, or transdermal patch. • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). • Depot/implantable hormone (e.g., Depo-Provera®, Implanon). • Bilateral tubal occlusion/ligation. • Sexual abstinence. • Refraining from heterosexual intercourse during the entire period of risk associated with the study requirements. • If the participant decides to become sexually active during the study, then one of the highly effective birth control methods must be used. OR Is a woman of non-childbearing potential; defined by at least 1 of the following criteria: • Postmenopausal defined as 12 months of spontaneous amenorrhea without a medical cause and follicle stimulating hormone (FSH) serum level > 40mIU/mL without the use of hormonal supplementation. Appropriated documentation of FSH levels is required. • Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure. • Has a congenital condition resulting in no uterus. Informed Consent 6. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply: Medical Conditions 1. History or presence of alcoholism or drug abuse within the past 2 years prior to the first dose of study drug. 2. History or presence of hypersensitivity or idiosyncratic reaction to the study drug, related compounds, or inactive ingredients. 3. ALT or AST levels three times above the upper limits of normal (ULN) at screening (isolated elevations of total bilirubin < 2 X ULN with direct bilirubin below the ULN will be included). A recheck for confirmation is allowed. 4. History of documented, EEG-confirmed epileptic seizures. 5. History of cancer (malignancy). Exceptions: (1) Subjects with adequately treated non-melanomatous carcinoma or carcinoma in situ of the cervix may participate in the trial (2) Subjects with other malignancies who have been successfully treated >10years prior to the screening where in the judgment of the investigator has revealed no evidence of recurrence from the time of treatment through the time of the screening except

those identified at the beginning of the exclusion criterion or (3) Subjects who in the opinion of the investigator are highly unlikely to sustain a recurrence for the duration of the trial. 6. Currently has uncontrolled diabetes defined as HbA1c > 8% at screening visit or diabetic neuropathy. 7. Estimated creatinine clearance < 40mL/minute at screening visit. 8. Clinically significant abnormality on their screening and/or prior to first dosing resting ECG, other than hypertensive related, or heart failure (ejection fraction < 30%) or other clinically significant structural heart disease. 9. History of myocardial infarction in the last five years, or evidence of congestive heart failure. 10. Ongoing medical condition that is deemed by the PI to interfere with the conduct or assessments of the study or safety of the subject. Prior/Concomitant Therapy 11. Unable to refrain from or anticipates the use of: • Any non-approved medicines (prescribed standard-of-care for CPVT is approved) and/or dietary supplements beginning 14 days prior to the first dose of study drug and throughout the study. Thyroid hormone replacement medication may be permitted if subject has been on same stable dose for the last 3 months prior to the first dose of study drug. • Any drugs known to be significant inducers or inhibitors of CYP2C8 enzymes for 28 days prior to the first dose of study drug and throughout the study. Is currently taking any drug which raises gastric pH, including proton pump inhibitors or H2 antagonists. Antacids may be used if taken greater than 6 hours after study drug and/or at night. Prior/Concurrent Clinical Study Experience 12. Participation in clinical trials for other therapeutic investigational drugs simultaneously or within the 4 weeks prior to the first dose of study drug. Diagnostic Assessments 13. Plasma donation within 7 days prior to the first dose of study drug. 14. Donation of blood or significant blood loss within 56 days prior to the first dose of study drug. Other Exclusion Criteria 15. Is mentally or legally incapacitated at the time of screening visit. 16. Is unable to take orally administered tablets. 17. Is an immediate family member of the Sponsor or employee of the clinical site or may consent under duress.

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:	Recruiting
Start date (anticipated):	19-06-2023
Enrollment:	15
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	S48168 (ARM210)
Generic name:	S48168 (ARM210)

Ethics review

Approved WMO Date:	12-01-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2024

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-08-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2024
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	EUCTR2022-002344-44-NL
ClinicalTrials.gov	NCT05122975
CCMO	NL82987.018.22