Extension of the randomized, double-blind, placebo-controlled single ascending dose study to assess the safety and tolerability of AP30663 in healthy subjects.

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Primary ObjectivesTo evaluate the safety and tolerability of AP30663 in healthy males at doses up to 12mg/kgExploratory ObjectiveTo evaluate the effect of AP30663 on electrocardiographical parameters.

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

Summary

ID

NL-OMON49415

Source
ToetsingOnline

Brief title
Extension of the single ascending dose study of AP30663.

Condition

- Cardiac arrhythmias

Synonym
Atrial fibrillation, supraventricular tachycardia

Research involving
Human

Sponsors and support

Primary sponsor: Acesion Pharma ApS
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: AP30663, Atrial fibrillation

Outcome measures

Primary outcome

• Occurrence of all treatment-related AEs.

• Changes in vital signs, temperature, laboratory safety data and ECGs between pre-first infusion and each post-infusion time point.

• Changes in tremorography data.

• Changes in physical examination findings.

• Administration site reactions.

Secondary outcome

• Maximum Cmax for each cohort.

• Maximum free Cmax for each cohort.

• Time to maximum observed plasma concentration (tmax) for each cohort.

• AUC for each dosing group (AUC from time zero to infinity [AUCinf], AUC from time zero to time of last measurable concentration [AUClast], AUC from time t to infinity as a percentage of total AUC [AUC%extrapolated]) for each cohort.

• Clearance (CL), volume of distribution during terminal phase (Vz) and volume of distribution at steady state (Vss) and half-life (t*) for each cohort.

Study description

Background summary

Atrial fibrillation (AF) can be an invalidating arrhythmia, with frequent recurrences requiring pharmacological or electrical cardioversion. Current medical maintenance or ablative procedures are hampered by not infrequent therapy failures. Additionally, pharmacological cardioversion with currently available treatment options is unsuccessful in many patients, predominantly patients with persistent AF.

AP30663 is a first in class compound targeted at cardioversion of both paroxysmal and persistent AF. The compound inhibits the small conductance Ca2+ activated K+ channels (SK channels). These channels are associated with a prolongation of the effective refractory period (ERP) of atrial myocardial cells both in vitro and in vivo. In 2018, the first-in-man study (CHDR1706) was completed in healthy volunteers, in which AP30663 was safe and tolerable at doses up to 6 mg/kg. There is reason to assume that increasing the exposure can increase the intended cardiac pharmacodynamic effects and that a higher dose is needed to reach optimal clinical efficacy. The present study is aimed at evaluating the safety and tolerability of AP30663 at doses up to 12 mg/kg.

Study objective

Primary Objectives
To evaluate the safety and tolerability of AP30663 in healthy males at doses up to 12mg/kg

Exploratory Objective
To evaluate the effect of AP30663 on electrocardiographical parameters.

Study design

Randomized, double-blind, placebo-controlled single dose study. An interim report will be generated after each cohort and reviewed during the dose escalation meeting.

Intervention

AP30663

Study burden and risks

Healthy volunteers in this study are not expected to benefit from treatment with AP30663.

The clinical experience with AP30663 is currently limited after completion of the First into man study and 31 patients in the proof of concept study. In terms of risks, systemic adverse events were not observed except for one case of myalgia. Therefore, the risk is considered appropriate for participating subjects.

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

1. Signed informed consent prior to any study-mandated procedure
2. Healthy male subjects, 18 to 45 years of age, inclusive.
3. Healthy volunteer part only: Body mass index (BMI) between 18 and 30 kg/m2, inclusive and a body weight between 50 and 100 kg, inclusive at screening.
4. All male volunteers must practice effective contraception during the study

and be willing and able to continue contraception for at least 90 days after their last dose of study treatment.
5. Has the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions.

Exclusion criteria

1. Evidence (following a detailed medical history, physical examination, vital signs, 12-lead ECG and clinical laboratory parameters) of any active or chronic disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator.
2. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). Minor deviations of laboratory values from the normal range may be accepted, if judged by the Investigator or medically qualified designee as not clinically significant. In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
3. Positive Hepatitis B surface antigen (HBsAg), Hepatitis B antibodies, Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
4. Systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg at screening.
5. Abnormal findings in the resting ECG at screening defined as:
- QTcF> 450 or < 300 msec
- Notable resting bradycardia (HR < 45 bpm)
- Notable resting tachycardia (HR > 100 bpm)
- Personal or family history of congenital long QT syndrome or sudden death;
- ECG with QRS and/or T wave judged to be unfavorable for a consistently accurate QT measurement (e.g., neuromuscular artefact that cannot be readily eliminated, arrhythmias, indistinct QRS onset, low amplitude T wave, merged T- and U-waves, prominent U waves);
- Evidence of a sustained atrial or ventricular arrhythmia, either by anamnesis or by Holter or telemetric observation.
- Pre-excitation (Wolff-Parkinson-White syndrome)
- PR interval >220 ms
6. Use of any medications (prescription or over-the-counter (OTC)), within 14 days of investigational product administration, or less than 5 half-lives (whichever is longer). Exceptions are paracetamol (up to 4 g/day) and ibuprofen (up to 1g/day). Other exceptions will only be made if the rationale is clearly documented by the investigator.
7. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days

of investigational product administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the investigator.
8. Participation in an investigational product or device study within 3 months prior to first dosing, or >4 studies in the year prior to study participation.
9. History of abuse of addictive substances (alcohol, illegal substances) or use of more than 21 units alcohol per week within 3 months prior to screening, drug abuse, or regular user of sedatives, hypnotics, tranquillizers, or any other addictive agent.
10. Positive test for drugs of abuse at screening or pre-dose.
11. Alcohol will not be allowed from at least 24 hours before screening or pre-dose.
12. Routine smoker or history of nicotine abuse (average of >5 cigarettes per day for >3 months).
13. Excess in xanthine consumption (more than eight cups of coffee or equivalent per day) or unwilling or unable to abstain from xanthine consumption during the stay at CHDR.
14. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
15. Loss or donation of blood over 500 mL within three months (males) prior to screening or intention to donate blood or blood products during the study.
16. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	04-11-2020
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AP30663
Generic name:	N.A.

Ethics review

Approved WMO Date:	08-10-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-11-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 20057
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-003116-27-NL
CCMO	NL74429.056.20

Study results

Date completed: 26-01-2021

Results posted: 30-09-2021

Summary results
Trial ended prematurely

First publication
16-06-2021

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File