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 Objective- To evaluate the safety and tolerability of AP30663 in healthy malesSecondary Objectives- To evaluate the pharmacokinetic profile of AP30663.Exploratory Objectives- To evaluate the effect of AP30663 on electrocardiographical...

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

Summary

ID

NL-OMON46496

Source
ToetsingOnline

Brief title
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: Acesion Pharma ApS

Intervention

Keyword: AP30663, Atrial fibrillation

Outcome measures

Primary outcome

Tolerability / safety endpoints

* 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.

Pharmacokinetic endpoints

* Maximum observed plasma concentration (Cmax) for each cohort.

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

* Area under the plasma concentration-time curve (AUC) for each dosing group (area under the plasma concentration-time curve from time zero to infinity [AUCinf],area under the plasma concentration-time curve from time zero to time of last measurable concentration [AUCtlast], area under the plasma concentration-time curve extrapolated from time t to infinity as a percentage of total AUC [AUC%extrapolated]) for each cohort.

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

Pharmacodynamic endpoints

* Based on ECG data, the following pharmacodynamic endpoints are deployed:

- RR interval

- PQ, QRS, QT/QTcF interval duration

- P, P*, QRS, QRS*, T, T* wave duration, amplitude, area and morphology

- R axis

- Atrial and ventricular ectopic beats on Holter recording

Secondary outcome

Not applicable

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.

The current study is a first-in-man study in healthy volunteers, in which AP30663 is administered to assess the safety and tolerability.

Study objective

Primary Objective
- To evaluate the safety and tolerability of AP30663 in healthy males
Secondary Objectives
- To evaluate the pharmacokinetic profile of AP30663.

Exploratory Objectives
- To evaluate the effect of AP30663 on electrocardiographical parameters.

Study design

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

Intervention

Investigational drug substance
AP30663 will be administered as a linear, continuous, intravenous, 30-minute infusion in this study.
Based on a NOAEL of 23.9 mg/kg HED, planned doses in the healthy volunteers (cohorts 1-6) are:
- 1 mg/kg
- 2 mg/kg
- 4 mg/kg
- 8 mg/kg
- 12 mg/kg

Comparative drug
Visually indistinguishable placebo will be administered. Placebo will consist of sodiumchloride 0.9% (B Braun, Melsungen, Germany).

Study burden and risks

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

The risks associated with the administration of AP30663 to humans have not yet been identified, because this compound has not yet been studied in humans. On the basis of data collected from preclinical investigations, myoclonus can occur in subjects in the present study. Tremorography has been implemented in the study to detect tremor. Furthermore, since preclinical data revealed an effect of AP30663 on several electrocardiographical parameters other than the atrial ERP, frequent ECGs are recorded in addition to a 24 hour continuous Holter ECG to detect an effect of AP30663 on other myocardial conduction intervals.

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. Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening, and with a minimum weight of 50 kg.
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 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 (following a detailed

medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature), 12-lead electrocardiogram (ECG), and clinical laboratory parameters (haematology, blood chemistry, 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.
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). 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 msUse 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 productadministration, 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 current use of more than 21 units alcohol per week, 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. Current 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:	Recruitment stopped
Start date (anticipated):	29-01-2018
Enrollment:	48
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AP30663
Generic name:	Not Applicable

Ethics review

Approved WMO Date:	09-01-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-01-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	03-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-06-2018
Application type:	Amendment
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-004597-34-NL
CCMO	NL64017.056.17