A Randomized, international, multi-center, open-label study to document optimal timing of initiation of dronedarone TreatmEnt after conversion with loading dose of aMIodarone in patients with perSistent Atrial Fibrillation requiring conversion of AF

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PrimaryThe primary objective of the study is to evaluate the rate of AF recurrences one month after randomization according to different timings of initiation of dronedaroSecondaryThe secondary efficacy objective is to evaluate the rate of AF…

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

Summary

ID

NL-OMON36400

Source
ToetsingOnline

Brief title
ARTEMIS AF Loading

Condition

- Cardiac arrhythmias

Synonym
atrial fibrillation, cardiac arrythmia

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: sanofi-aventis

Intervention

Keyword: amiodarone, atrial fibrillation, dronedarone, recurrence

Outcome measures

Primary outcome

Evaluate the rate of AF recurrences one month after randomization according to

different timings of initiation of dronedarone.

Secondary outcome

Evaluate the rate of AF recurrences two months after randomization,

Assess the safety of the change from amiodarone to dronedarone and dronedarone

safety.

Explore dronedarone and SR35021 (active metabolite) plasma levels according to

different timings of initiation,

Explore potential PK interaction between dronedarone and amiodarone.

Study description

Background summary

The ARTEMIS AF loading study will specifically and prospectively evaluate the efficacy and safety of immediate change from a loading dose of amiodarone for conversion to long-term dronedarone treatment in comparison to the initiation after a 2-week or a 4-week amiodarone wash-out. As all patients have to reach the same level of impregnation, amiodarone loading regimen will be prescribed for 1 month in all patients groups.

The ARTEMIS AF loading study will aim at providing reliable and comprehensive data to provide guidance for optimal antiarrhythmic drug change modalities after amiodarone treatment aimed at optimizing cardioversion, including different subcategories of AF patients

Study objective

Primary
The primary objective of the study is to evaluate the rate of AF recurrences one month after randomization according to different timings of initiation of dronedaroSecondary
The secondary efficacy objective is to evaluate the rate of AF recurrences two months after randomization.

The secondary safety objective is to assess the safety of the change from amiodarone to dronedarone and dronedarone safety by monitoring:
o Symptomatic bradycardia and tachycardia,
o Laboratory safety tests (RBC, Hb, platelet count, WBC with differential count, creatinine, INR, and thyroid function tests [FT3, FT4 and TSH]),
o ECG parameters,
o Adverse Events (AEs) and Serious Adverse Events (SAEs),
o Adverse events of special interest (AESIs).

Study design

This is a phase IV, international, prospective, multicenter, open-label study randomized in 3 parallel groups according to dronedarone treatment initiation patterns following a loading dose of amiodarone in patients with persistent atrial fibrillation requiring AF conversion

Intervention

Randomisation in 1 out of 3 treatment groups

Study burden and risks

If a patient takes part in this study, before starting amiodarone, the physician should first ensure that the patient is properly anticoagulated. If the patient is not yet receiving an anticoagulant, the physician should initiate this anticoagulation treatment. To be effectively anticoagulated, the patient will have to check his/her coagulation status with INR (= international normalized ratio) test according to the prescription of the physician. Once the patient is effectively anticoagulated, the physician will prescribe decreasing regimen of amiodarone for a period of 4 weeks: 600 mg per day (3 tablets of 200 mg) during one week, then 400 mg per day (2 tablets of 200 mg) and finally 200 mg (1 tablet of 200 mg) during the last two weeks. This decreasing dose of

amiodarone is prescribed in order to restore sinus rhythm (a normal heart rhythm).
If a normal rhythm is not restored using amiodarone per os, the physician may decide to perform an electrical cardioversion from 7 days to 28 days after the start of amiodarone.
Once sinus rhythm is established, the patient will be randomized, that is to say he/she will be allowed to take part into the study.
The patient will be allocated to one of 3 possible dronedarone treatment groups (a bit like flipping a coin). You will not be able to choose which group he/she is allocated to.
• If the patient is allocated to group A: he/she will start receiving dronedarone 24 hours after he/she has received thelast dose of amiodarone and will be treated for a period of 8 weeks.
• If the patient is allocated to group B: he/she will start dronedarone, 2 weeks after he/she has received the last dose of amiodarone (i.e. a period during which the patient will receive neither amiodarone nor dronedarone) and will be treated for a period of 6 weeks.
• If the patient is allocated to group C: he/she will start dronedarone 4 weeks after he/she has received the last dose of amiodarone (i.e. a period during which the patient will receive neither amiodarone nor dronedarone) and will be treated for a period of 4 weeks.
For patients who will not start dronedarone immediately, it is important to note that amiodarone has a long half-life (it takes several weeks for half of the amiodarone in your body to be eliminated) and thus the patient will have protection for several weeks by the amiodarone remaining in your blood system.

The study will be divided in two different periods:
• The screening period will start as soon as the patient has signed the informed consent form and includes the screening visit, the 4-week treatment with amiodarone, the electrical cardioversion if needed and will end on the day of the last dose of amiodarone (i.e. the day immediately prior to randomization day).
o Minimum duration of the screening period = 5 weeks for patients already effectively anticoagulated at screening.
o Maximum duration of the screening period = 10-12 weeks for patients not under anticoagulation treatment at screening.
o The physician is free to prescribe and monitor the anticoagulant (oral route) of his choice.
• The randomization phase will start as soon as the patient israndomized, i.e. if the patient fills in all inclusion and exclusion criteria on Day 1, and will last for 8 weeks. It may include either:
o 24 h after last dose of amiodarone, immediate start of dronedarone with a 8 weeks period of treatment in group A
o start of dronedarone, 2 weeks after last dose of amiodarone, with a 6 weeks dronedarone duration in group B
o start of dronedarone, 4 weeks after last dose of amiodarone, with a 4 weeks dronedarone duration of treatment in group C.

• The total mean study duration will vary between 13 and 18 weeks per patient.

The patient will have between 9 to 10 regular visits during the entire duration of the study, depending in which group he/she will be allocated to. During some of these visits, the patient will be asked to perform blood samples. A total average of 70-85 ml of blood will be needed for the total duration of the study.

Standard procedures performed at each visit (starting after the screening), the physician will perform the following assessments:
• Weight (except V3 and V6) and vital signs (blood pressure at rest)
• Cardiovascular clinical examination, including recent echo (< 1 month) at screening
• Electrocardiogram with status of heart rhythm (atrial fibrillation or normal sinus rhythm)
• Any atrial fibrillation recurrence with or without symptoms (starting at V5)
• Review the latest anticoagulation test (INR)
• Occurrence of adverse events
• New or changes in concomitant medications since the previous visit
• The patient will receive a blood sample prescription to be done in the local laboratory and the results will be needed for the next visit.
• At each visit after randomization, the patient will be given enough study medication until the next planned visit. The patient will have to write down the date at which he/she started each medication wallet, keep all medication wallets even the empty ones, and bring them back at the next visit.

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

•Inclusion criteria at screening:;- Male or female adult aged 18 years or more, ;- Patient with persistent AF for more than 72 hours (documented by an ECG taken within the last 72 hours) for whom cardioversion, anti-arrhythmic treatment and anticoagulation treatment are indicated in the opinion of the Investigator (Note: patient may already be on anticoagulation treatment),;- Naive of amiodarone treatment in the last three months prior to screening, ;- QTcB < 500 ms on 12-lead ECG,;- Patient with at least one cardiovascular risk factor (i.e. age > 70, hypertension, diabetes, prior cerebrovascular disease, left atrial diameter >= 50 mm ;- Signed written informed consent.;•Inclusion Criteria: to be checked at randomization;- Outpatient and Inpatient. (except patients hospitalized during screening period for SAE).;- Patient in sinus rhythm (Note: if cardioversion is performed on Day 1 prior to randomization, then the patient must be in sinus rhythm for at least one hour before randomization),;- Patient under effective anticoagulation according to ACC/AHA/ESC AF treatment;guidelines [18] verified by INR (target > 2).;INR should be closely monitored after initiating dronedarone in patients taking vitamin K antagonist as per their label;- QTcB < 500 ms and PR < 280 ms on 12-lead ECG,;- Patient having received 28 days ± 2 days of amiodarone.

Exclusion criteria

•Exclusion criteria at screening: ;- Contraindication to oral anticoagulation,;- Any documented AF episode motivating inclusion in the study after an acute condition known to cause AF (e.g. alcohol intake, thyrotoxicosis, acute infection, pericarditis, pulmonary embolism, cardiac surgery),;- Patient with permanent AF defined as patients with an AF duration >= 6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician.;- Patient with paroxysmal AF in whom cardioversion is not indicated,;- Bradycardia < 50 beats per minute (bpm) at rest on the 12-lead ECG,;- Clinically overt congestive heart failure:;o with New York Heart Association (NYHA) class III and IV heart failure, ;o with LVEF < 35%,;o or NYHA class II with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic, ;o as well any patient in unstable hemodynamic conditions.;- Women of childbearing potential without adequate birth control (e.g. oral contraception or intra-uterine device [IUD]) or not menopaused, not sterile or not hysterectomized,;- Pregnant women,;- Breastfeeding women,;- Previous (2 preceding months) or current participation in

another clinical trial with an investigational drug or with an investigational device,;- Clinically relevant hematologic, underlying hepatobiliary disease, gastrointestinal, pulmonary, endocrinologic, psychiatric, neurological or dermatological disease,;- Severe hepatic impairment,;- Severe renal impairment (creatinine clearance < 30 mL/min),;- Serum potassium <3.5 millimol/liter (mmol/L) (in patients with hypokalemia, potassium deficiency must be corrected before randomization) or > 5.5 mmol/l,;- Magnesemia < 0.8 mml/l (in patient with hypo-magnesemia, magnesium deficiency must be corrected before randomization),;- Unstable angina pectoris (ischemic symptoms during the last 7 days) or recent myocardial infarction (MI) (< 6 weeks),;- First degree family history of sudden cardiac death below age 50 years in the absence of coronary heart disease,;- Second- or third-degree Atrio-Ventricular block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker),;- Ongoing potentially severe symptoms when in AF such as angina pectoris, transient ischemic attacks, stroke, syncope, as judged by the investigator,;- Wolff-Parkinson-White Syndrome,;- Previous ablation for atrial fibrillation or any planned ablation in the next following 2 months.;•Exclusion criteria to be checked at randomization;- Bradycardia < 50 bpm on the 12-lead ECG before randomization,;- Clinically overt congestive heart failure:;o with New York Heart Association (NYHA) class III and IV heart failure, ;o with LVEF < 35%,;o or NYHA class II with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic, ;o as well any patients in unstable hemodynamic conditions.;- Serum potassium <3.5 millimol/liter (mmol/L) (in patients with hypokalemia, potassium deficiency must have been corrected before randomization) or > 5.5 mmol/l,;- Magnesemia < 0.8 mml/l (in patient with hypo-magnesemia, magnesium deficiency must have been corrected before randomization);- Women of childbearing potential without adequate birth control (e.g. oral contraception or intra-uterine device [IUD]) or not menopaused, not sterile or not hysterectomized,;- Severe hepatic impairment.;- Patients with permanent AF defined as patients with an AF duration >= 6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-11-2010
Enrollment:	55
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Multaq
Generic name:	dronedarone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-06-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-09-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-10-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-11-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	23-12-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-12-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-12-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-01-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-02-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-03-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-08-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-08-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2009-016818-24-NL
CCMO	NL32635.068.10
Other	Publicatie op clinicaltrials.gov binnen 21 dagen na inclusie eerste patiënt