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Sponsor / Company: Sanofi **Drug substance(s):** DRONEDARONE	**Study Identifiers:** NCT01047566, 2009-018215-53 **Study code:** DRONE_L_05066

Title of the study: The effect of the addition of dronedarone to, versus increase of, existing conventional rate control medication on ventricular rate during persistent atrial fibrillation (AFRODITE)

Study center(s): 26 sites in the Netherlands

Study period:

Date first subject enrolled: 13 April 2010

Date last subject completed: 26 September 2011

Phase of development: Phase 4

Objectives:

Primary objective: to assess whether the addition of dronedarone (Multaq®) to existing conventional rate control therapy leads to a reduced ventricular rate after 1 week in subjects with a high heart rate [HR] at rest during atrial fibrillation [AF] in comparison to an increase of conventional rate control therapy.

Secondary objectives: to compare both study arms with regard to:

- Ventricular rate after 12 weeks.
- Number of registered AF episodes at baseline and after 1 and 12 weeks.
- Number of symptomatic AF episodes at baseline and after 1 and 12 weeks.
- Severity of AF and AF-like symptoms during 12 weeks of treatment (weekly questionnaire).
- Adverse events [AE] throughout the study period.
- Rate of premature study discontinuation ("going off study prematurely").
- Number of symptomatic episodes of bradycardia after 1 and 12 weeks.
- Incidence of low HR (<60 beats per minute [bpm]) after 1 and 12 weeks.

Exploratory objective: to assess the healthcare resource utilization due to AF related events in subjects with premature study discontinuations because of AF related treatment.

Methodology:

This study was a randomized, multicenter, parallel group open label study, in which subjects with a high HR at rest received either additional dronedarone to existing conventional rate control during AF (Arm A) or an increase of conventional therapy (Arm B).

Number of subjects**:**

Planned: 596 (298 in each study arm)

Randomized: 182* (90 to Arm A and 92 to Arm B)
* the study was terminated prematurely because of low recruitment rate

Treated: (90 in Arm A, 92* in Arm B)
* of 1 subject in Arm B no treatment details were available

Evaluated:	**Intention to treat [ITT] population**: 182 (90 in Arm A, 92 in Arm B) (all subjects that provided consent and were randomized) **Per protocol [PP] population**: 173 (83 in Arm A, 90 in Arm B) (subjects from the ITT population excluding those who did not fulfill all in- and exclusion criteria, and who were not treated with assigned medication)

Diagnosis and criteria for inclusion: Persistent AF with HR >80 bpm at rest despite treatment with ≤2 rate control agents (i.e. beta blocker and/or calcium antagonist - subjects using digoxin were eligible), documented AF in the past 24 hours, age >45 years, predefined accepted conventional rate control treatment, and anticoagulant treatment in line with local guidelines.

Main criteria for exclusion were paroxysmal or permanent AF, use of class I or III anti-arrhythmic drugs [AAD], scheduled for cardioversion or pulmonary vein ablation, unstable New York Heart Association [NYHA] class III or all class IV heart failure, atrio-ventricular block grade 2 or 3, known severe renal or hepatic impairment, participation in a clinical drug study in the 3 months prior to inclusion, lactating women and those of childbearing potential who do not use adequate contraception.

Study treatments

Investigational medicinal product(s): dronedarone (Multaq®)

Formulation: Tablet

Route(s) of administration: Oral

Dose regimen: 400 mg twice daily [BID] added to the unchanged existing dose of conventional rate control medication

Non-investigational medicinal product(s): Accepted conventional rate control medication: beta blocker or calcium antagonist or beta blocker plus calcium antagonist or beta blocker plus digoxin or calcium antagonist plus digoxin (all commercially available)

Formulation: Tablet

Route(s) of administration: Oral

Dose regimen: dose increase of existing conventional rate control medication at the discretion of the investigator

Duration of treatment: 12 weeks

Duration of observation: The observation period was 12 weeks (± 5 days)

Criteria for evaluation:

Efficacy:

The primary efficacy parameter was:

- Mean ventricular rate [VR] after 1 week

Secondary endpoints were:

- Mean VR after 12 weeks
- Absolute change from baseline in VR at week 12
- Incidence and duration of a registered AF episode at baseline, after 1 and 12 weeks
- Incidence of a symptomatic AF episode at baseline, after 1 and 12 weeks.
- Severity of registered AF episodes categorized by duration.
- Severity of AF symptoms measured as frequency and severity of symptoms
- Proportion of subjects with symptomatic bradycardia episodes during 12 weeks
- Proportion of subjects with low HR (<60 bpm) during 12 weeks.
- Proportion of subjects with performed cardioversions during 12 weeks
- Number of performed cardioversions during 12 weeks.

Safety: Proportion of subjects with AE during the study period

Statistical methods:

Quantitative data were summarized by number of subjects, mean, standard deviation (SD), median and range;

Categorical variables were presented with frequency and percentage.

Because of the small sample size, statistical comparative analyses were performed for the primary endpoint only.

Absolute changes in HR from baseline to week 1 were compared between treatment arms using a one-way analysis of covariance (ANCOVA) model, with baseline ventricular rate as covariate and treatment arm as factor. Significance level was set at a two-sided p-value below 0.05. The analysis was performed on the ITT population and the PP population.

Safety data were evaluated descriptively and analyses were performed on the ITT population.

Summary:

Population characteristics:

A total of 70 subjects in Arm A (i.e. dronedarone) [77.8%] and 88 subjects in Arm B [95.7%] completed the study. Among the 20 premature withdrawals for Arm A there were 2 deaths (the third death in this study completed the 12-weeks study protocol), 1 withdrawal of consent, for 1 subject there was no information available, and 16 subjects withdrew prematurely because of other reasons (request sponsor [n=5], AE or abnormal laboratory value [n=8], prohibited co-medication [n=1], refusal further intake of dronedarone [n=1], and request subject [n=1]). Four subjects in Arm B discontinued the study prematurely because of the addition of AAD treatments during the study.

More men were included than women (66.3% versus 33.7%) and the mean age of the subjects was 68 years. Overall, demographic and baseline characteristics and the incidence of cardiovascular risk factors were comparable between the treatment arms. Incidence of symptomatic AF period was reported in 55.6% and 42% of subjects treated in Arm A and B, respectively. Mean estimated number of cardioversions since AF diagnosis was 2.6 (Arm A) and 2.0 (Arm B), and time since last electrocardiogram (ECG) was less than 2 years in both treatment arms.

The most frequently associated cardiovascular risk factors were hypertension (67.8% [Arm A], 70.3% [Arm B]), first grade family history of cardiovascular disease (18.4% [Arm A], 26.1% [Arm B]) and diabetes mellitus (15.6% [Arm A], 17.4% [Arm B]).

Efficacy results:

After 1 week of treatment mean VR decreased from 94 bpm to 79 bpm in Arm A (i.e. dronedarone) and decreased from 93 bpm to 85 bpm in Arm B.

The decrease in mean VR after 1 week of treatment with the addition of dronedarone was significantly more pronounced than the observed decrease in mean VR in the control group (differences between treatment arms 6.9 bpm (95% confidence interval [CI]: 3.3, 10.6), (p<0.001).

A further decrease in mean VR was observed after 12 weeks of treatment, i.e. to 77 bpm in Arm A and 79 bpm in Arm B. The absolute difference in mean VR reduction between treatment arms was 3.0 bpm (95% confidence interval [CI]: -2.1, 8.1), which was no longer significant (p=0.241).

Safety results:

Overall, more AE were observed in Arm A, i.e. dronedarone (400 mg BID) plus unchanged dose of conventional rate control medication compared with Arm B, i.e. increase of conventional rate control medication.

A total of 43 subjects in Arm A (47.8%) and 30 subjects in Arm B (32.6%) experienced one or more AE and 10 subjects in Arm A (11.1%) and 5 subjects in Arm B (5.4%) experienced one or more serious adverse events [SAE]. The majority of adverse reactions were mild to moderate in severity.

The most frequently reported AE were gastrointestinal disorders (16.7% in Arm A [8.9% related to treatment], 5.4% in Arm B), followed by nervous system disorders (12.2% in Arm A [6.7% related to treatment], 2.2% in Arm B) and infections and infestations (4.4% in Arm A, 9.8% in Arm B). Diarrhea, dizziness and nausea were the most commonly reported.

The most frequently reported SAE were cardiac disorders (overall n=4; 3 Arm A, 1 Arm B) and neurologic disorders (overall n=3; 2 Arm A, 1 Arm B), followed by gastrointestinal disorders (overall n=2; 1 Arm A, 1 Arm B), infections and infestations (overall n=2; 1 Arm A, 1 Arm B) and investigations (overall n=2; 1 Arm A, 1 Arm B).

Treatment-related AE and SAE were observed in 22 subjects (24.4%) and 3 subjects (3.3%) in Arm A, respectively. The treatment-related SAE included 1 case of unstable angina and 2 cases of abnormal liver function tests.

A total of 14 subjects (15.6%) who were treated with dronedarone experienced one or more AE leading to permanent discontinuation from the study. There were no treatment-related AE, SAE or AE leading to permanent study withdrawal in the control arm.

There were 3 deaths (kidney failure, sepsis with unknown cause and cerebral bleeding [all in Arm A]). At the time of onset, the treating physician considered none of these fatal cases to be related to the study treatment. However, at that time results of the PALLAS/EFC 11405 study were not released.

Overall, 126 (69.2%) study participants had any co-morbidity (63.3% in Arm A, 75% in Arm B). The most frequent comorbidities were metabolism and nutrition disorders (overall 28.0% [Arm A: 25.6%; Am B: 30.4%), cardiac disorders (overall 21.4% [Arm A: 22.4%; Arm B: 20.7%) and respiratory, thoracic and mediastinal disorders (overall 18.7% [Arm A: 16.7%; Arm B 20.7%). Hypercholesterolemia, chronic obstructive pulmonary disease and cardiac failure were the most commonly reported. In both treatment arms, the majority of comorbidities were of mild to moderate severity.

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