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Sponsor / Company: Sanofi **Drug substance(s):** Dronedarone (SR33589)	**Study Identifiers:** NCT01026090 **Study code**: DRONE_L_04742

Title of the study:

A Phase IV, double-blind, placebo-controlled, Canadian multicentre study comparing two treatment strategies of dronedarone administration following elective cardioversion for prevention of symptomatic atrial fibrillation recurrence (ELECTRA)

Study center(s): 43 centers in Canada

Study period:

Date first patient enrolled: 12 November 2009

Date last patient completed: 15 December 2011

Phase of development: Phase 4

Objectives:

Primary: To determine whether daily administration of dronedarone started 5 to 7 days before cardioversion was superior to dronedarone started only after cardioversion with respect to the absence of symptomatic, electrocardiogram (ECG) confirmed, atrial fibrillation (AF) recurrence over 6 months in adult patients with persistent AF, for whom cardioversion is clinically indicated and planned to reduce symptoms and antiarrhythmic treatment is clinically indicated to reduce the risk of cardiovascular hospitalization due to AF.

Main Secondary:

- To assess the number of symptomatic AF recurrences/patient/6 months with and without ECG confirmation
- To assess characteristics of symptomatic AF recurrence in the two treatment arms (frequency, duration of episodes, type, number, and severity of AF symptoms per patient)
- To compare the rates of early recurrences of AF between the two treatment strategies

Other secondary:

- To assess whether there is a difference in proportion of patients with symptomatic AF recurrences (with and without ECG confirmation) between the two treatment strategies
- To assess whether there is a difference in number of electrical cardioversions per patient between the two treatment strategies
- To assess the impact of the two strategies on number of shocks, cumulative amount of energy delivered, shock failure, and immediate success of cardioversion
- To assess whether there is a difference in rate of cardiovascular hospitalizations and length of hospital stay between the two treatment strategies
- To assess whether there is a difference in quality of life between the two treatment strategies

Methodology:

Multicentre, randomized (randomization 1:1), double-blind, placebo-controlled, parallel arms, superiority study.

Double-blind placebo or dronedarone for 5-7 days prior to cardioversion.

After cardioversion open-label dronedarone.

Number of patients:	Planned: 500 Randomized: 277 Treated: 262
Evaluated:	Efficacy: 277 (Intent-to-treat analysis), 262 (modified Intent-to-treat analysis of primary efficacy variable only) Safety: 262

The study was terminated before 500 patients were enrolled. Sites were notified on 25 March 2011 to stop enrollment due to the unlikelihood of reaching the target enrollment of 500 patients by 30 June 2011 after providing the sites an extended enrollment period.

Diagnosis and criteria for inclusion:

Adult patients with persistent AF (current episode at the screening visit >72 hours and <12 months duration), for whom cardioversion was clinically indicated and planned to reduce symptoms and antiarrhythmic treatment was clinically indicated to reduce the risk of cardiovascular hospitalization due to AF.

Study treatments

Investigational medicinal product(s): Placebo or dronedarone 400 mg

Formulation: Tablets

Route of administration: Oral

Dose regimen:

Arm A: Dronedarone 400 mg twice-daily (BID) for 5 to 7 days, followed by electrical cardioversion and continuation of dronedarone 400 mg BID treatment for 6 months

Arm B: Placebo twice-daily (BID) for 5 to 7 days, followed by electrical cardioversion, and followed by dronedarone 400 mg BID treatment for 6 months

Duration of treatment: 6 months

Duration of observation: 6 months

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint was the proportion of patients with at least one symptomatic, ECG confirmed, AF recurrence within 6 months taking into account when the first event occurred.

The main secondary endpoints were: number of symptomatic AF recurrences/ patient/ 6 months with and without ECG confirmation; mean duration of an AF episode per patient; type, number, and severity of AF symptoms per patient; rate of early recurrences of AF.

Other secondary endpoints: proportion of patients with at least one symptomatic AF recurrence with and without ECG confirmation within 6 months taking into account when the first event occurred; number of electrical cardioversions/ patient/ 6 months; number of shocks; cumulative amount of energy delivered; shock failure; immediate recurrence of AF; number of cardiovascular hospitalizations, time when the hospitalization occurred and duration of hospital stay; quality of life (Atrial Fibrillation Severity Scale [AFSS] and Atrial Fibrillation Effect on Quality of Life ([AFEQT]; the AFEQT questionnaire was added as secondary endpoint as per Protocol Amendment No. 1, dated 07-Jun-2010).

Safety: Adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs) (these safety criteria were added as per Protocol Amendment No. 1, dated 07-Jun-2010); vital signs (blood pressure and heart rate); liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin were collected (the monitoring of liver enzymes was added as per Protocol Amendment No. 2, dated 14-Dec-2010).

Statistical methods:

The primary efficacy endpoint was analyzed in the intent-to-treat population defined as all randomized patients. The primary analysis was to compare the Kaplan-Meier curves for symptomatic, ECG confirmed, AF recurrence-free survival with respect to the treatment prior to cardioversion (dronedarone versus placebo) using the log-rank statistic. With 500 patients there was an 80% chance of detecting an absolute difference of 12.5% in the AF recurrence-free survival rates between the two arms of the study. The percentage of patients with recurrence and the two-sided p-value for the log rank statistic were calculated.

If the percentage of patients without a recurrence was significantly ($P < 0.05$) greater than the percentage for the placebo group, then it was to be concluded that starting dronedarone 5 to 7 days prior to electrical cardioversion in persistent AF patients resulted in significantly fewer recurrences than starting dronedarone immediately following electrical cardioversion in adult patients with persistent AF, for whom cardioversion is clinically indicated and planned to reduce symptoms and antiarrhythmic treatment is clinically indicated to reduce the risk of cardiovascular hospitalization due to AF. A supportive analysis using Cox Regression was used in order to adjust for age, sex and pooled site. The Cox Regression model included age, sex and treatment. From this analysis, the hazard ratio for treatment and its 95% confidence interval were reported.

Descriptive statistics were calculated for all secondary variables. For the continuous variables, e.g. total number of symptomatic AF recurrences, mean duration of AF recurrences, and maximum Canadian Cardiovascular Society – Severity of Atrial Fibrillation (CCS-SAF) scale score, p-values were obtained from analysis of variance (ANOVA). Rates of events, e.g. symptomatic AF recurrences, cardioversions, and cardiovascular hospitalizations, were analyzed using a generalized non-linear model. For categorical variables, e.g. normal sinus rhythm achieved and immediate recurrence of AF occurred, number and percent of patients for each treatment group were calculated in days with the time horizon being 183 days. Percent of patients, e.g. immediate recurrence of AF for initial cardioversion, was analyzed using a generalized non-linear model. The changes from baseline for the scores from Part A and Part C of the AF Severity Scale and the total and subscale scores from the AF Effect on Quality of Life questionnaire were analyzed using analysis of covariance (ANCOVA).

Summary:

Population characteristics:

A total of 292 patients were screened, 277 were randomized, and 262 received at least one dose of study medication (129 in the placebo BID group, 133 in the dronedarone 400 mg BID group). A total of 164 randomized patients completed the study, and 113 terminated the study primarily due to adverse events. Patients' median age was 66 years (range 35 to 89), most patients were male (68.6%), and most were white (96.4%). There were no relevant differences between the treatment groups with respect to demographics or disease characteristics.

Efficacy results:

No difference (P=0.5528) was found between the two treatment groups with regard to the percentage of patients with symptomatic, ECG-confirmed AF recurrences. At 6 months, 61.3% of the patients treated with placebo BID had experienced an AF relapse, as compared to 57.9% in the dronedarone 400 mg BID group (hazard ratio=0.9235; p=0.6108). The median time to first AF recurrence was 16 days in the placebo BID group, and 29 days in the dronedarone 400 mg BID group. The finding was consistent in all of the subgroups analyzed.

No difference in the number of cardiovascular hospitalizations between the two treatment groups was seen. At the end of the study, 9 patients (7.0%) in the placebo group had been hospitalized due to cardiovascular reasons, as compared with 15 patients (11.3%) in the dronedarone 400 mg BID group. The subgroup analysis revealed no differences between placebo BID and dronedarone 400 mg BID treatment with regard to cardiovascular hospitalizations.

At end of treatment no statistically significant differences were found between placebo BID and dronedarone 400 mg BID in any of the quality of life questionnaires' scores. However, patients in both treatment arms experienced significant improvements in quality of life from baseline to end of treatment.

In conclusion, there is no difference in the AF recurrence rates and other variables between the patients starting dronedarone before cardioversion or after cardioversion.

Safety results:

Thirteen (13) of 129 patients (10.1%) receiving placebo BID experienced AEs and 16 of 133 patients (12.0%) receiving dronedarone 400 mg BID experienced AEs during the double-blind treatment period. The most frequent AEs during this period were nausea and diarrhea. A total of 125 out of 262 patients (47.7%) receiving dronedarone 400 mg BID during the open-label treatment period reported AEs. The main clinical AEs identified were diarrhea, bradycardia and fatigue. No thyroid disorders were reported during the study. Congestive Heart Failure (CHF) was reported in 1 (0.8%) and 2 (1.5%) patients in the placebo BID and dronedarone 400 mg BID group, respectively, during the double-blind treatment period. During open-label, CHF occurred in 6 patients (2.3%).

The incidence of SAEs was low: SAEs were reported for 1 patient (0.8%) receiving placebo BID and for 3 patients (2.3%) receiving dronedarone 400 mg BID during the double-blind treatment period. SAEs were reported for 18 patients (6.9%) during the open-label treatment period. SAEs were mainly involving the SOC of cardiac disorders (11 patients, 4.2%), with CHF being the most frequently reported SAE (6 patients, 2.3%). ALT increased was the second most frequently reported SAE with 2 out of 262 patients (0.8%). Premature discontinuation due to AEs occurred in 0.8% of the placebo-treated and in 3.8% of the dronedarone-treated patients (double-blind treatment period). During open-label, 14.1% of patients discontinued dronedarone treatment due to AEs. The most common reasons for discontinuation were gastrointestinal disorders, mainly due to diarrhea. No deaths occurred during the study period. One patient died from interstitial lung disease and pulmonary embolism 5 weeks after dronedarone discontinuation.

The incidence of shifts in individual liver analytes was low in both treatment groups; changes were random and did not indicate a drug-related effect. Increased ALT levels were reported as AEs in 6 patients (2.3%) taking dronedarone 400 mg BID during the open-label treatment period. AST increased in 1 patient (0.4%). Increase in serum creatinine was reported in 5 dronedarone-treated patients (1.9%).

No clinically significant changes due to study drug administration were seen for blood pressure. Mean heart rate decreased statistically significantly in patients of both treatment groups, in line with the pharmacological action of dronedarone.

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