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Sponsor / Company: Sanofi	**Study Identifiers:** NCT01140581, 2009-016818-24
Drug substance(s): Dronedarone	**Study code:** DRONE_C_03668

Title of the study: 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

Study center(s): 49 active study centers in 14 countries: Australia, Austria, Estonia, Finland, France, Germany, Italy, Republic of Korea, Mexico, The Netherlands, Portugal, Spain, Taiwan, United Kingdom

Study period:

Date first patient enrolled: 13 September 2010

Date last patient completed: 14 December 2011

Phase of development: Phase 4 loading study

Objectives:

The primary objective of this study was to evaluate the rate of atrial fibrillation (AF) recurrence at Day 30 after randomization, according to different timings of initiation of dronedarone based upon adjudicated electrocardiogram (ECG) data.

The secondary efficacy objective was to evaluate the rate of AF recurrence during the entire study period (i.e. up to 60 days after randomization).

The secondary safety objective was to assess the safety of the change from amiodarone to dronedarone, as well as dronedarone safety, by monitoring:

- Symptomatic bradycardia and tachycardia
- Laboratory safety tests: clinical chemistry tests including creatinine; international normalized ratio; hepatic function tests including aspartate aminotransferase, alanine aminotransferase, and total bilirubin; and thyroid function tests including triiodothyronine, tetraiodothyronine, and thyroid-stimulating hormone
- ECG parameters
- Adverse events (AE), treatment-emergent adverse events, serious adverse events (SAE), and adverse events of special interest (AESI)

A substudy was conducted in a subset of countries too. The objective was to explore dronedarone and its active metabolite (SR35021) plasma levels according to different timings of initiation, to explore potential PK interaction between dronedarone and amiodarone and genotyping.

Methodology:

This was a prospective, multicenter, multinational, randomized, parallel group, open-label study in which dronedarone was administered to patients who had persistent AF requiring conversion at 3 different intervals after a loading dose of amiodarone was administered: immediately after the amiodarone loading dose (Group A), after a 2-week wash-out period (Group B), or after a 4-week wash-out period (Group C). Patients were treated in these assigned groups with dronedarone for 8, 6, or 4 weeks, respectively.

Patients initially entered in a screening period lasting a minimum of 4 weeks (28 days) if patient already under effective anticoagulation therapy and a maximum of 10-12 weeks (70-84 days) if no previous anticoagulation therapy. During this time:

- Patients started anticoagulation therapy at Week -12/-10, if they were not receiving effective anticoagulation therapy.
- Patients received loading regimen of amiodarone for 4 weeks starting at Week-4.
- Patients had an electrical cardioversion at least 7 days after the start of amiodarone but prior to randomization, If they were still in AF.

At Day 1, patients were randomized to Group A, B, or C. Administration of dronedarone was started in Group A and the wash-out periods for Groups B and C were begun. During the next visits for Groups B and C, dronedarone was administered and all postdose visits were conducted to evaluate AF recurrences and to monitor safety parameters.

Number of patients:	Planned: 860 screened, 768 randomized (256 per treatment group)
	Randomized: 176*
	Treated: 163

* The study was discontinued prematurely on 20 Oct 2011 due to lack of sufficient enrollment

Evaluated:	Efficacy: 176
	Safety, Amiodarone period: 176
	Safety, Dronedarone period: 163
	Pharmacokinetics/Pharmacogenomics: Analyses not performed

Diagnosis and criteria for inclusion:

Patients eligible for the study were males and females at least 18 years of age who had persistent AF (more than 72 hours) for whom, in the opinion of the investigator, cardioversion, antiarrhythmic treatment, and anticoagulation treatment were indicated; had 12-lead ECG results showing QT interval corrected by Bazett's formula (QTcB) <500 milliseconds (msec); were naïve to amiodarone treatment within the prior 3 months; and had at least 1 cardiovascular risk factor (ie, age >70, hypertension, diabetes, prior cerebrovascular disease, or left atrial diameter ≥50 mm). At randomization, patients had to be in sinus rhythm, under effective anticoagulation therapy according to protocol-stated guidelines and verified by international normalized ratio (target >2), had a 12-lead ECG result with QTcB interval <500 msec and PR <280 msec, and had to have been receiving amiodarone for at least 28 (±2) days.

Patients were excluded if they had permanent AF (duration ≥6 months) and attempts to restore sinus rhythm were no longer considered by the investigator, paroxysmal AF (in whom cardioversion was not indicated), bradycardia <50 beats per minute (bpm) on a 12-lead ECG, or clinically overt congestive heart failure (CHF) meeting 1 of the following criteria: 1) New York Heart Association (NYHA) Class III or IV heart failure, 2) left ventricular ejection fraction <35%, 3) NYHA Class II with a recent decompensation requiring hospitalization or a referral to a specialized heart failure clinic, 4) an unstable hemodynamic condition, 5) severe hepatic or renal impairment.

Study treatments

Investigational medicinal product: dronedarone

Formulation: 400-mg tablet

Route(s) of administration: oral (together with meal)

Dose regimen: 400 mg twice daily

Non-investigational medicinal product: amiodarone

Formulation: 200-mg tablet

Route(s) of administration: oral (together with meal)

Dose regimen: 600 mg daily for 1 week, then 400 mg daily for 1 week, then 200 mg daily for 2 weeks

Duration of treatment: Patients were treated with dronedarone for 8, 6, or 4 weeks, depending upon treatment group. The end of treatment was 8 weeks after randomization.

Duration of observation:

- Screening period:

  A minimum of 4 weeks for patients already anticoagulated for the cardioversion according to protocol-specified guidelines;

  A maximum of 10 to 12 weeks for patients with no previous anticoagulation treatment for whom anticoagulation was started at the screening Visit.

  The screening period also included 4 weeks when patients were treated with a loading regimen of amiodarone

- Randomized period: 8 weeks

Criteria for evaluation:

Efficacy:

Primary endpoint was the rate of AF recurrence at Day 30 after randomization.

Secondary endpoint was the rate of AF recurrence at Day 60 after randomization.

Due to premature discontinuation of the study and the associated reduced number of patients, the primary objective was expanded to include the entire study period, which was then defined as a secondary objective.

Only ECGs (12-lead or trans-telephonic ECG monitoring [TTEM]) adjudicated by a central blinded adjudication committee were considered for evaluating AF recurrence. The starting date for evaluation was the day of randomization (Day 1) and the end date was Day 60 after randomization.

The rates of bradycardia (heart rate [HR] <50 bpm) and tachycardia (HR >90 bpm) at Day 60 after randomization were also analyzed. Only ECGs (12-lead or TTEM) from central reading were considered. The starting date for evaluation was the day of randomization (Day 1) and the end date was Day 60 after randomization.

Safety:

The main safety criterion was the incidence in patient-months of treatment-emergent adverse events (TEAEs) during the dronedarone treatment period (including deaths, SAEs, AEs leading to treatment discontinuation, and AESI defined as per the narrow Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query version 14.1). These were defined as AEs that developed or worsened, or became serious during the on-treatment period and included CHF, interstitial lung disease (ILD), severe skin disorders, peripheral neuropathy including optic neuropathy, and hepatic events.

Pharmacokinetics:

Substudy endpoints were the plasma concentration of dronedarone and its metabolite SR35021 as well as the plasma concentration of amiodarone and its metabolite desethylamiodarone.

Due to premature discontinuation of the study and the associated reduced number of patients, a decision was made to not analyze PK or genotyping.

Statistical methods:

Analysis populations:

Efficacy population: The efficacy population was the intent-to-treat (ITT) population defined as all patients who gave their informed consent and for whom there was confirmation of successful allocation of a randomization number through the study treatment allocation system (randomized population).

Safety populations: The safety analysis was conducted in 2 populations:

- The randomized population. This population was the basis for analysis of safety the randomized periods.
- The subset of all randomized patients who received at least one dose of dronedarone (the randomized and treated population). This population was the basis for the analysis of safety during the dronedarone treatment period.

Efficacy analyses:

Due to premature discontinuation of the study, the primary efficacy analysis was not performed. The focus of analysis was on the entire study period rather than the first 30 days.

The secondary efficacy analysis was the rate of AF recurrence at Day 60 after randomization (Day 1) in each treatment group analyzed as follows:

- The main analysis for comparisons of group A versus group C and group B versus group C was a non-stratified Log-rank test; significance level for each comparison was 0.025 (2-sided), in order to maintain a global alpha level of 0.05 (2-sided).
- The time to first AF recurrence was defined as the time from Day 1 (randomization) to the date of ECG (12-lead or TTEM) when the first AF recurrence was observed. Patients who did not experience AF recurrence were censored at Day 61; patients who discontinued prematurely were censored at the day of discontinuation.
- Cumulative incidence functions were calculated using non-parametric Kaplan-Meier estimates.
- Cox's proportional hazard model, with the treatment group as the unique factor, was used to calculate hazard ratio, with 2-sided 97.5% confidence intervals.

The same survival analysis performed for AF recurrence was also performed for bradycardia and tachycardia rate (based on central reading data) at Day 60 after randomization.

Safety analyses:

The safety analyses considered all assessments that developed, worsened, or became serious during:

- The randomized period (from randomization to last dronedarone intake date plus 10 days or from randomization to end-of-study date for patients not treated);
- The dronedarone treatment period (from first dronedarone intake to last dronedarone intake plus 10 days).

All AEs/TEAEs were summarized by incidence (in patient-months for analyses done during amiodarone and dronedarone periods), severity, and relationship to study treatment. Frequency tables sorted by system organ class (SOC), high level group term, high level term, and preferred term (PT) from the MedDRA were provided by treatment group. Adverse events of special interest (AESI; CHF, ILD, severe skin disorder, peripheral neuropathy including optic neuropathy, and hepatic events), as well as laboratory values of interest (renal, hepatic, and thyroid function tests) were analyzed separately.

Vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), 12-lead ECG parameters (central reading data only), and laboratory tests (except conjugated bilirubin and all hematology tests) and their changes from baseline were summarized at each protocol-scheduled time point during the dronedarone treatment period. The number and percentage of patients who presented at least 1 post-baseline potentially clinically significant abnormality (PCSA) in laboratory tests, blood pressure, or ECG during the dronedarone treatment period were summarized.

Summary:

Population characteristics:

Baseline demographics were similar among treatment groups, although in the body mass index category "≥30," the percentage of patients was greatest in Group C (4 weeks of wash-out). The mean (±standard deviation) age of patients in the study was 66.2 (±10.6) years (range, 28 to 86 years). Approximately 40% of patients were between 65 and 75 years of age. Most patients were male (76.1%) and most were Caucasian/White (79.5%).

Efficacy results:

In the ITT population, the immediate switch group (Group A) showed a non-statistically significant decrease in risk of AF recurrence by 35.3% compared with the 4-week wash-out period group (Group C; p=0.136). The 2-week wash-out period group (Group B) had a non-statistically significant decrease in risk of AF recurrence by 24.7% compared with the 4-week wash-out period group (Group C; p=0.317).

There were no differences in risks of bradycardia and tachycardia among the 3 treatment groups.

Safety results:

A total of 163 patients were exposed to study treatment, dronedarone, for a mean 41.0 (±14.4) days (range: 3 to 64 days).

During the randomized period, 57 patients (32.4%) had AEs; among these, 13 patients (7.4%) had SAEs, 11 patients (6.3%) had AESIs, and 4 patients (2.3%) had AEs leading to permanent treatment discontinuation. There were no deaths during the study. Considering the low number of patients in the 3 treatment groups, there was no evidence overall of an increase in the frequency of AEs/AEs leading to permanent discontinuation/SAEs/AESIs in the immediate switch compared to the other treatment groups.

During the dronedarone treatment period, 53 patients (23.8% in patient-months) had TEAEs. Among these, 9 patients (4.0% in patient-months) had serious TEAEs, 8 patients (3.6% in patient-months) had treatment-emergent AESI, and 4 patients (1.8% in patient-months) had TEAEs leading to permanent treatment discontinuation. There was no evidence overall of an increase in frequency of TEAEs/TEAEs leading to permanent discontinuation/SAEs/AESIs in the dronedarone immediate switch compared to the other dronedarone treatment groups.

During the randomized period, AEs were most frequently reported in the SOCs Nervous System Disorders (13 patients [7.4%]) and Gastrointestinal Disorders (11 patients [6.3%]), and in PTs of dizziness and dyspnea (5 patients [2.8%] in each) in Nervous System Disorders and Respiratory, Thoracic, and Mediastinal Disorders, respectively.

During the dronedarone period, TEAEs were most frequently reported in the SOCs Nervous System Disorders (5.8% in patient-months) and Gastrointestinal Disorders (4.5% in patient-months). Among these SOCs, the most frequently reported TEAEs by PT were dizziness and dyspnea (2.2% each in patient-months), and the incidences of these TEAEs were similar among the 3 dronedarone treatment groups.

During the randomized period, among the AESIs, 1.7% of patients each experienced CHF and peripheral neuropathy including optic neuropathy. Of the 2.8% of patients who experienced hepatobiliary AESIs, most (2.3%) were in Investigations. There were no patients who experienced either ILD or severe skin disorder.

During the dronedarone period, among the AESIs, hepatic events were the most common treatment-emergent AESIs (1.8% in patient-months), followed by 0.9% in patient-months for both treatment-emergent CHF and treatment-emergent peripheral neuropathy including optic neuropathy AESIs. There were no patients who experienced either ILD or severe skin disorder AESIs. A few more patients reported these hepatic AESI with dronedarone in the 4-week wash-out group (Group C) compared to Group A and B.

During the randomized period, 7.4% of patients reported SAEs. These were most frequently alanine aminotransferase (ALT) increased in Investigations (1.7% of patients) and cardiac failure congestive in the SOC Cardiac Disorders (1.1% of patients). Considering the low number of patients in the 3 groups, there was no evidence overall of an increase in incidence of SAEs in the immediate switch group compared to the other treatment groups.

During the dronedarone period, 4.0% in patient-months reported serious TEAEs. These were most frequently cardiac failure congestive in the SOC Cardiac Disorders (0.9% in patient-months) and ALT increased in Investigations (0.9% in patient-months). Considering the low number of patients in the 3 groups, the incidences of these serious TEAEs were similar among dronedarone treatment groups.

In the randomized population, 2.3% in patient-months had AEs that led to permanent discontinuation.

In the dronedarone treatment period, 1.8% in patient-months had TEAEs that led to permanent discontinuation. Nervous system disorders were the most common during both randomized and dronedarone periods.

During the dronedarone period, the following laboratory, vital sign, and ECG findings were identified:

- PCSA of renal function showed increases in serum creatinine values after 1 week of dronedarone treatment, consistent with the known safety profile of dronedarone. There were no patients with creatinine clearance values <30 mL/min.
- PCSA of hepatic function tests showed slight increases in mean ALT and aspartate aminotransferase values from baseline. Only 1 patient had ALT >3 × ULN during the dronedarone period (4-week wash-out group). There were no patients who had both ALT >3 × ULN and total bilirubin >2 × ULN during the dronedarone treatment period.
- Small percentages of patients had both triiodothyronine and tetraiodothyronine results both above and below the normal range. Overall, thyroid-stimulating hormone (TSH) values were above normal in approximately 3 times as many patients as those with TSH values below normal. There was no evidence of a greater change in TSH values in the immediate switch group compared to the other groups.
- Overall, a greater number of patients were over-anticoagulated at baseline (38.8%) than at the end of dronedarone treatment (8.4%).
- PCSA in vital signs were mainly reported for increased SBP with similar incidences among treatment groups. Mean changes in SBP and DBP from baseline to protocol-defined time points were stable and changes between time points were small and similar across the treatment groups.
- Electrocardiogram findings with PCSA criteria showed that overall, following dronedarone treatment, 4.3% of patients had an HR ≤50 bpm and a decrease from baseline ≥20 bpm following dronedarone treatment; 8.5% of patients had a PR interval ≥220 msec and an increase from baseline ≥20 msec; 14.7% of patients had a QRS interval ≥120 msec (baseline ≥120 msec in almost all cases); 55.8% and 8.6% of patients had a QTcB prolonged interval (>450 msec male; >470 msec female) or QTcB interval ≥500 msec, respectively (nonetheless, the abnormality was already observed at baseline in most of them); and 4.9% of patients had an increase from baseline in QTcB >60 msec. Overall, these PCSAs were similarly reported between groups except for increased PR, which was more frequently reported in the immediate switch group (15.2%) compared to the 2-week wash-out (4.8%) and 4-week wash-out (3.4%) groups, which may have been possibly related to a combined amiodarone/dronedarone effect.

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