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Sponsor / Company: Sanofi	**Study Identifiers:** NCT01199081, 2010-019247-19
Drug substance(s): Dronedarone	**Study code:** DRONE_C_04629

Title of the study: A Randomized, International, Multi-center, Open-label Study to Document Pharmacokinetics and Optimal Timing of Initiation of Dronedarone Treatment Following Long-term Amiodarone in Patients with Paroxysmal or Persistent Atrial Fibrillation Whatever the Reason for the Change of Treatment (ARTEMIS Long Term)

Study center(s): 29 active study centers in 7 countries: Colombia, Czech Republic, Denmark, France, Germany, Mexico, and Spain

Study period:

Date first patient enrolled: 01 October 2010

Date last patient completed: 18 April 2012

Phase of development: Phase 4

Objectives:

The primary objective was to explore dronedarone and SR35021 (active metabolite) pharmacokinetic (PK) profiles according to different timings of dronedarone initiation.

Secondary objectives were:

- To explore potential PK interaction between dronedarone and amiodarone
- To evaluate the atrial fibrillation (AF) recurrence during the study period (from randomization up to 60 days after)
- To assess the safety of the change from amiodarone to dronedarone and dronedarone safety by monitoring symptomatic bradycardia and tachycardia, laboratory safety tests (creatinine, INR, hepatic function tests [AST, ALT, Total Bilirubin] and thyroid function tests [FT3, FT4 and TSH]), ECG parameters, Adverse Events (AEs), Serious Adverse Events (SAEs) and Adverse events of special interest (AESIs).

A genotyping sub-study was also conducted to investigate allelic variants of drug metabolism enzymes or drug transporters as intrinsic factors associated with PK or pharmacodynamic variability of the development compound.

Methodology:

This was an international, prospective, randomized, parallel group, multi-center, open-label study. Patients were randomly assigned to 3 parallel groups according to 3 dronedarone treatment initiation patterns following a long-term regimen of amiodarone in patients with paroxysmal or persistent AF. The timing of initiation of dronedarone after discontinuation of amiodarone treatment differed among the 3 groups as follows:

- Group A: start immediately after discontinuation of amiodarone
- Group B: start after 2-week washout period
- Group C: start after 4-week washout period

Number of patients: Planned: 105 randomized (35 in each group) (lowered from 147 to 105 per protocol amendment)

Randomized: 108

Treated: 98

Evaluated:	Efficacy: 108 Safety: 108 randomized; 98 randomized and treated Pharmacokinetics: 106 Pharmacogenetics: Not performed (genotyping analysis abandoned due to reduced sample size)

Diagnosis and criteria for inclusion:

Male or female patients ≥ 18 years of age were eligible at screening if he/she had paroxysmal or persistent AF, had been receiving at least 6 months of amiodarone before screening with at least the last 2 months at a regimen of 200 mg/day (during at least 5 days per week) prior to screening, required a change from amiodarone treatment whatever the reason but without liver, lung, or thyroid toxicity related to previous use of amiodarone, had at least 1 cardiovascular risk factor, were receiving effective anticoagulation therapy at screening and continued during the study, and had a Bazett corrected QT interval (QTcB) < 500 milliseconds (ms) on a 12-lead electrocardiogram (ECG). Patients were eligible for randomization if they were in sinus rhythm, under effective oral anticoagulation at randomization and continued during the study, and had QTcB < 500 ms and PR < 280 ms on a 12-lead ECG. Patients could be inpatients or outpatients, with the exception of patients hospitalized during screening for a serious adverse event (SAE).

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: 200 mg once daily

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: Each patient was expected to participate in the study for a maximum of 10 weeks

- Screening period of 3 to 10 days before randomization:
- Randomized period of 8 weeks

Criteria for evaluation:

Pharmacokinetic:

Primary Endpoints: Plasma levels of dronedarone and its metabolite SR35021

Using population pharmacokinetic (POP PK) techniques, individual parameters, area under the curve from 0 to 12 hours (AUC0-12 hours) and maximal plasma concentration (Cmax) for dronedarone and its metabolite SR35021 were estimated.

Secondary Endpoints: Plasma levels of amiodarone and its metabolite desethylamiodarone (DEA)

Using pop PK techniques, individual parameters, AUC0-12 hours and Cmax for amiodarone and DEA were estimated.

Efficacy:

The efficacy secondary endpoint was the rate of AF recurrence during the study period (from randomization up to 60 days after) based on ECGs adjudicated by the central blinded adjudication committee.

Safety:

The safety secondary endpoints were:

- Symptomatic bradycardia (heart rate (HR) at rest <50 beats per minute (bpm)) and symptomatic tachycardia (HR at rest >90 bpm) (Analyses were performed on ECG central reading data and therefore, statistical methods and results were presented in the efficacy section)
- AEs, treatment-emergent AEs (TEAEs), SAEs, and AESIs including CHF, interstitial lung disease (ILD), severe skin disorders, peripheral neuropathy including optic neuropathy, and hepatic events
- Laboratory tests (hematology, creatinine, international normalized ratio [INR], hepatic function tests (aspartate aminotransferase, alanine aminotransferase, bilirubin), thyroid function tests (T3, T4, TSH), ionogram)
- ECG parameters
- Vital signs

Pharmacokinetic sampling times and bioanalytical methods:

Plasma PK samples were drawn at the following time points for the assay of dronedarone, amiodarone, and their respective metabolites:

- at randomization (baseline)
- 3 hours after the first dose of dronedarone
- after 1 week of treatment with dronedarone (before next dronedarone dose)
- after 2 weeks of treatment with dronedarone (before next dronedarone dose)
- after 4 weeks of treatment with dronedarone (before next dronedarone dose)

The bioanalytical method used for the analysis of dronedarone and SR35021 was a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification of 0.5 ng/mL for both compounds (Covance, Indianapolis, Indiana, United States).

The bioanalytical method used for the analysis of amiodarone and DEA was a validated LC-MS/MS method with a lower limit of quantification of 5 ng/mL for both compounds (SGC Cephac, Europe).

Statistical methods:

Sample Size:

To estimate the ratio of dronedarone AUC0-12 hours and Cmax of Group A (Immediate start) versus Group C (4-week washout) or Group B (2-week washout) versus Group C, with a maximum imprecision between 14% and 20%, with an alpha risk of 5% (2-sided), a statistical power of 90%, assuming a standard deviation (SD) of 0.35 and a true ratio equal to 1, at least 72 evaluable patients (24 randomized patients with PK sample per group) were to be included. With an estimated non-evaluability rate of 30%, a randomization of 105 patients (35 in each group) was necessary to achieve a maximal imprecision of 20%.

Analysis populations:

Pharmacokinetic (PK) population: The PK population included randomized patients with dronedarone, SR35021, amiodarone, or DEA evaluable samples. The following deviations were reasons to discard an individual sample from the descriptive statistics and for not including a patient in the PK population:

- Samples with missing date and time of sampling and/or of last drug intake
- For the analysis of maximal concentration (3 hours after the first dose of dronedarone), samples taken outside the [2 hours - 8 hours] window for dronedarone/SR35021 relative to the last dronedarone intake
- For the analysis of trough concentration (after 1, 2, and 4 weeks of treatment with dronedarone), samples taken outside the [8 hours - 16 hours] window for dronedarone/SR35021 relative to the last dronedarone intake
- Sample associated with documented noncompliance in treatment intake
- Samples performed outside theoretical time points, relative to the first intake of dronedarone

Efficacy population: The efficacy population was the intent-to-treat (ITT) population defined as the "all randomized population;" ie, 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.

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

- The randomized population. This population was the basis for analysis of safety during the randomized period.
- 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.

Pharmacokinetic analyses:

Overall POP PK analyses for both dronedarone and its metabolite SR35021 and Amiodarone and its metabolite DEA, were performed with the NONMEM software (version 7.2) using a Bayesian approach.

Methodology (dronedarone and SR35021)

The predictive ability of the PopPK model was evaluated by the careful examination of goodnessof- Fit (GoF) plots and computation of several statistical criteria (such as mean predictor error, root mean squared error or average fold error) on individual and population predicted concentrations and on model parameters.

From individual PK parameter estimates, exposure values were computed. Exposures mainly consisted in Areas Under the concentration versus time Curves (AUCs) computed relatively to the first dronedarone intake. These AUCs were computed during the first 24 hours, the first 2 weeks and the first 4 weeks of dronedarone administration. Cmax of dronedarone and SR35021 concentration estimated at the time of the first dronedarone administration was also reported.

PopPK Model applied on ARTEMIS Amiodarone and DEA data

The PopPK model developed by Pollak et al was the basis of the modeling process. In a first step, Pollak's model was adapted and the zero-order absorption process was replaced by a first-order absorption one.

This model was applied to the ARTEMIS Dataset, using its population parameter estimates as prior estimates for the assessment of individual parameters and concentration predictions for ARTEMIS patients.

From the individual PK parameters, for each patient of ARTEMIS study some exposures were computed for both amiodarone and DEA. Exposures mainly consisted in Areas Under the DEA concentration versus time Curves (AUCs) computed relatively to the first dronedarone intake: AUC24h (computed during the first day of dronedarone administration), AUC336h (computed during the first 2 weeks of dronedarone administration), AUC672h (computed during the first 4 weeks of dronedarone administration) and Cmax (the amiodarone and DEA maximal concentration estimated at the time of the first dronedarone administration).

Efficacy analyses:

The AF recurrence rate in each treatment group was 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 AF recurrence was defined as the time from Day 1 (Randomization) to the date of ECG where the first AF recurrence was observed. Patients who did not experience AF recurrence were censored at Day 61 or at the end of the study if this date was prior to Day 60 and patients who discontinued prematurely were censored at the day of discontinuation.
- Cumulative incidence functions were calculated using non-parametric Kaplan Meier estimates.
- Cox proportional hazard model, with the treatment group as the unique factor, was used to calculate the hazard ratio, with 2-sided 97.5% CIs.

The same survival analysis performed for AF recurrence was also performed for the bradycardia and tachycardia events (based on central reading data) during the study period (up to Day 60).

Safety analyses:

Safety analyses were provided for the randomized period (from randomization to last dronedarone intake date, plus 10 days or from randomization to EOS date for patients not treated) and for the dronedarone treatment period (from first dronedarone intake to last dronedarone intake plus 10 days). Summary tables were provided for frequency of AEs/TEAEs by number and percentages (percentages in 100 patient-months for TEAEs), by treatment group and by total, and categorized by system organ class and preferred term in decreasing order of frequency. Summary tables included overall frequency of AEs/TEAEs, AESIs/treatment-emergent AESIs, SAEs/TEAEs, and AEs/TEAEs leading to death and discontinuation.

Laboratory values were summarized and change from baseline was determined. Potentially clinically significant abnormalities (PCSA) were flagged and also summarized for the dronedarone treatment period. The same analyses as were done for laboratory values were done for vital signs for the dronedarone treatment period and ECG parameters for the randomized period and the dronedarone treatment period.

Summary:

Population characteristics:

Overall, in the ITT population, 54.6% of patients were men and the mean (SD) age was 67.5 (9.8) years. The majority of patients were Caucasian/White (75.9%), 9.3% were current smokers, and the mean (SD) BMI was 30.3 (5.8) kg/m2. Overall, 97.2% of patients had a history of at least 1 cardiovascular disease, including 90.7% who reported having hypertension. No patients had permanent AF. Only 1 patient in the study required cardioversion to be in sinus rhythm before the randomization visit. There were 74.1% of patients who entered the study with paroxysmal AF, and 25.9% with persistent AF.

Pharmacokinetic results:

The Pop PK model developed and validated in the study POH0224 was used to provide individual estimate of dronedarone and SR35021 exposure values of the patients of the ARTEMIS Long-Term study.

Surprisingly, there was a tendency to higher values for both dronedarone and SR35021 exposures in Group B (2-week washout), while the lowest values were observed in Group C (4-week washout); this was mainly visible on areas under the curve (AUCs) computed after 2 or 4 weeks of dronedarone intake.

This is in accordance with the dronedarone concentrations observed in the ARTEMIS Long-Term study, which were systematically higher in Group B. Similar trends were observed for amiodarone (as stated in BAY0014 study report). Such observations could suggest a possible drug-drug interaction between dronedarone and amiodarone. Nevertheless, as observed amiodarone concentrations collected before any dronedarone intake were also higher in Group B compared to Groups A (immediate start) and C, this assumption must be discarded. These higher amiodarone concentrations obtained before any dronedarone intake may also be due to an unbalanced patients' randomization regarding a specific patients' covariate between the different groups, causing higher amiodarone steady-state exposures in the patients of Group B.

The examination of available covariates (body weight, height, gender, age, race, or creatinine clearance) did not result in any findings of difference between groups. The effect of this possibly existing unknown covariate – which could be a pharmacogenomic polymorphism of metabolizing enzymes such as CYP3A5*1/*3 and/or drug transporters is nevertheless not in accordance with the metabolic ratios which remained roughly constant. Whatever the considered exposure, there was no metabolic interaction that occurred on dronedarone that could have explained these differences. Last, but not least, the observed differences between the 3 treatment-groups might also be due to coincidence. Finally, whatever the assumptions, the significance of these differences could not be assessed due to the low number of patients enrolled in each study group.

Efficacy results:

At 60 days after randomization, 20 patients overall experienced first AF recurrence, with 9 patients in Group B (0.257 [0.112; 0.402] cumulative incidence [95% CI]), 6 patients (0.169 [0.045; 0.292] cumulative incidence [95% CI]) in Group A, and 5 patients (0.167 [0.033; 0.300] cumulative incidence [95% CI]) in Group C. There were no statistically significant differences between treatment groups (HR (97.5% CI) = 1.063 (0.273; 4.131); log-rank p-value = 0.926 for Group A versus Group C and HR (97.5% CI) = 1.885 (0.539; 6.592); log-rank p-value = 0.263 for Group B versus Group C.

At 60 days after randomization, 19 patients overall experienced first bradycardia, with 11 patients in Group B (0.392 [0.181; 0.604] cumulative incidence [95% CI]), 6 patients (0.164 [0.044; 0.284] cumulative incidence [95% CI]) in Group A, and 2 patients in Group C (0.067 [0.000; 0.156] cumulative incidence [95% CI]) experiencing bradycardia. The risk of bradycardia was significantly greater in Group B compared to Group C (HR (97.5% CI) = 6.149 (1.095; 34.533); log-rank p-value=0.007). There was no significant difference between Group A and Group C.

At 60 days after randomization, 12 patients overall experienced tachycardia, with 5 patients (0.139 [0.026; 0.253] cumulative incidence [95% CI]) in Group A, 4 patients (0.116 [0.009; 0.223] cumulative incidence [95% CI]) in Group B, and 2 patients (0.067 [0.000; 0.156] cumulative incidence [95% CI]) in Group C. There were no significant differences between treatment groups.

In total, 37.0% of patients experienced a QT/QTc interval > 480 ms 60 days after randomization, with Group A having the highest percentage (43.2%). Overall, 3 patients (2.8%) experienced atrial flutter (2 in Group A, 1 in Group B), with all 3 treatment groups having similar frequencies. No patients experienced supraventricular tachycardia, Torsade de Pointes, or junctional tachycardia 60 days after randomization.

Safety results:

Safety analysis was performed on 2 different periods:

- Randomized period expressed in absolute number of randomized and exposed patients as the denominator for all safety parameters
- Dronedarone treatment period expressed in patient –month exposure due to different dronedarone treatment durations (8, 6 and 4weeks) for clinical safety (TEAEs including SAEs and AESIs)

A total of 98 patients were exposed to the study treatment dronedarone, for a mean 40.8 (±15.2) days (range: 2 to 64 days).

No deaths occurred during the study.

During the dronedarone treatment period:

- Thirty eight patients (28.5% in patient-months) had at least 1 TEAE, with 35.0% in patient-months in Group C, 34.3% in patient-months for Group B, and 22.5% in patient-months for Group A. The most frequently reported TEAEs during the dronedarone treatment period were nasopharyngitis (1.5%, 4.9%, and 7.8% in patient-months in Group A, Group B, and Group C, respectively), diarrhea (4.5%, 2.4%, and 0% in patient-months in Group A, Group B, and Group C, respectively), and dyspnea (1.5%. 2.4%, and 7.8% in patient-months in Group A, Group B, and Group C, respectively).
- Five patients reported 7 serious TEAEs: 3 patients from Group A reported 5 SAEs (rectal prolapse in 1 patient; arrhythmia, cardiac failure, and syncope in 1 patient; and blurred vision in the last patient), 1 patient from Group B reported 1 SAE (congestive cardiac failure), and 1 patient from Group C reported 1 SAE (AF).
- Eight patients (6.0% in patient-months) reported 14 TEAEs that led to discontinuation. The Group B had the highest percentage in patient-months (6 patients, 14.7% patient-months), followed by Group A (2 patients, 3.0% in patient-months). Group C did not have any TEAEs that led to discontinuation.
- Five 5 patients experienced treatment-emergent AESIs; 3 patients (4.5% in patient-months) were in Group A and 2 (4.9% in patient-months) were in Group B. Group C did not experience any AESIs. The reported treatment-emergent AESIs by SOC were: congestive heart failure (n =2, 1 in Group A and 1 in Group B), increased peripheral neuropathies including optic neuropathies (n =1 in Group A), and hepatic event (n =2, 1 in Group A and 1 in Group B).

Few patients reported relevant symptoms that could be linked to bradycardia in all treatment groups. Among them, there was 1 report of dizziness in Group C, 1 report of bradycardia in Group B, and 1 report of syncope in a context of worsening of CHF (from NYHA class I to III) in Group A.

There were no statistically significant changes from baseline to end of freatment (EOT) for mean serum creatinine, alanine aminotransferase, and aspartate aminotransferase values. Few patients had potentially clinically significant abnormalities for triiodothyronine (T3) and tetraiodothyronine (T4) results. There were 19.3% of patients with thyroid-stimulating hormone (TSH) values outside of the normal range, mainly due to increased TSH values during the dronedarone treatment period.

There were no statistically significant changes from baseline to EOT for mean systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, and QTcB. The difference between the mean change for SBP for Group B (7.0 mmHg) and the mean change for SBP for Group C (0.0 mmHg) was statistically significant (p = 0.040).

Potentially clinically significant abnormalities of ECG parameters were observed in all treatment groups during the dronedarone treatment period, including a few bradycardia PCSA (2 in Group B only).

Increase in PR intervals (PCSA) were more frequently reported in Group A (9 patients [25.7%] versus 4 patients [12.5%] in Group B and 2 patients [7.7%] in Group C), which may have been possibly related to a combined amiodarone/dronedarone effect. No relevant TEAEs were observed in patient with PR increased.

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