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Sponsor/Company : sanofi-aventis	**Study Identifiers** : NCT01213368, U1111-1116-9409
Drug substance : Dronedarone (SR33589)	**Study Code** : DRI10939

Title of the study: Double blind, randomized, placebo controlled dose ranging study of the efficacy and safety of dronedarone (SR33589B) at 300, 400, or 600 mg BID for the control of ventricular rate in Japanese patients with permanent atrial fibrillation.

Study center(s): 25 active centers in Japan

Study period:

Date first patient enrolled: 30-Sep-2010

Date last patient completed: 28-Apr-2011

Phase of development: Dose-ranging study

Objectives:

Primary: to assess the efficacy of dronedarone versus placebo for the control of ventricular rate in patients with permanent Atrial Fibrillation (AF).

Secondary: to assess the safety and the tolerability of dronedarone after repeated oral doses of 300 mg, 400 mg, or 600 mg twice daily (BID) in the selected population and to document SR33589 and its main active metabolite (SR35021) trough plasma levels at steady state.

Methodology: Multicenter, double-blind, randomized, parallel-group, placebo-controlled, assessing 3 doses of dronedarone (300 mg BID, 400 mg BID, and 600 mg BID) administered for 14 days.

An independent Data Monitoring Committee reviewed safety data at regular intervals.

Number of patients: Planned: **180** (45 patients in each group) Randomized: **181** Treated: **180**

Evaluated: Efficacy: **156** (modified Intent-to-Treat Population [mITT])

Safety: **180**

Pharmacokinetics (PK): **114**

Diagnosis and criteria for inclusion: Japanese male or female patients, aged ≥20 years, with permanent Atrial Fibrillation (>6 months) and resting ventricular Heart Rate (HR) ≥80 bpm.

Investigational product: Dronedarone

Formulation : Dronedarone 100 mg, 200 mg, and 400 mg tablets

Dose: 300 mg, 400 mg, or 600 mg BID

Administration: Oral, under fed conditions

Duration of treatment: 14 days

Duration of observation: 31 days maximum

Reference therapy: placebo matching tablets

Dose: 0 mg

Administration: Oral, under fed conditions

Criteria for evaluation:

Efficacy: The primary efficacy variable was the change in mean ventricular rate measured by 24-hour Holter ECG recording on Day 14 (steady state) compared to baseline.

Safety: Adverse events (AEs) reported by the patient or noted by the Investigator, standard hematology and blood chemistry, vital signs, electrocardiogram (ECG) parameters, and chest x-ray.

Pharmacokinetics: Plasma trough concentrations (C_{trough}) for dronedarone and SR35021.

Pharmacokinetic sampling times and bioanalytical methods: Plasma C_{trough} for SR33589 and SR35021 were measured on Day 14. Plasma concentrations of SR33589 and SR35021 were classified as "trough" concentrations if the time interval between the last dose before sampling and sampling was less than 2 hours or between 8 and 18 hours.

Plasma samples were analyzed for dronedarone and SR35021 concentrations using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 0.5 ng/mL for both compounds.

Statistical methods:

Analysis populations:

- The modified Intent To Treat (mITT) population included all randomized patients who had no missing primary endpoint analyzed according to the treatment group allocated by randomization. All efficacy analyses were performed on the mITT population.
- The safety population included all randomized patients who received at least 1 dose or partial of a dose of Investigational Product (IP) according to the treatment actually received.
- The Pharmacokinetic (PK) population included the randomized patients who had available Pharmacokinetic and dosing data.

Efficacy analyses: The primary analysis of the primary endpoint was the comparison of the changes from baseline between treatment groups using an analysis of covariance (ANCOVA). The model included treatment and type of baseline standard rate control drug (beta-blocker, calcium antagonist, and digitalis) as fixed effects and mean ventricular rate at baseline as covariate. Each dose of dronedarone was compared to placebo using appropriate contrast within the framework of the model, and p-values, least square mean difference, and 2-sided 95% confidence interval (CI) were presented. The Hochberg procedure was applied for multiplicity adjustment.

Safety analyses: The frequency of patients with Treatment-Emergent Adverse Events (TEAEs), treatment-emergent Serious Adverse Events (SAEs), TEAEs leading to premature treatment discontinuation, and Adverse Events with Prespecified Monitoring (AEPMs) was summarized. The TEAE observation period was defined as the time from the first dosing up to 10 days after the last dosing. For clinical laboratory parameters, vital signs, and ECG parameters, the incidence of potentially clinically significant abnormalities (PCSAs) during the TEAE observation period was summarized by treatment group, and raw values and changes from baseline were summarized at each protocol timepoint.

Pharmacokinetic analyses: Dronedarone and SR35021 C_{trough} on Day 14 were summarized in descriptive statistics. Dose proportionality was assessed using an empirical power model. Relationships between the change from baseline in mean ventricular rate (primary endpoint) and dronedarone and SR35021 plasma C_{trough} were explored using graphical and regression methods.

Summary:

Patient demographic and baseline characteristics were well balanced across treatment groups. A total of 24 patients, 14 in the dronedarone 600 mg BID group, 7 in the 400 mg BID group, 2 in the 300 mg BID group, and 1 in the placebo group, did not complete the study treatment period. The only reason for premature treatment discontinuation was Adverse Event.

Efficacy results:

Dronedarone significantly reduced the mean 24-hour ventricular rate (primary endpoint) compared to placebo at the 3 doses tested. The least square (LS) mean differences from placebo were -11.8 bpm, -13.1 bpm, and -20.1 bpm for dronedarone 300 mg, 400 mg, and 600 mg BID, respectively ($p<0.0001$). The extent of the ventricular rate reduction increased with the dose.

Analyses of secondary endpoints, those measured by the 24-hour Holter ECG (diurnal and nocturnal ventricular rate, minimum and maximum 24-hour ventricular rate, and standard deviation of normal RR-intervals [SDNN]) and those measured by the 12-lead ECG (ventricular rate at rest) all gave consistent results. Dronedarone significantly reduced the mean diurnal (8:00 AM to 9:00 PM) and nocturnal (11:00 PM to 6:00 AM) ventricular rates compared to placebo at the 3 doses tested and with a greater effect observed at the highest 600 mg BID dose. The mean minimum and maximum 24-hour ventricular rates were significantly reduced by dronedarone compared to placebo at the 3 doses tested and with a greater effect observed at the highest 600 mg BID dose.

The heart variability measure, SDNN, was significantly increased in the dronedarone groups compared to placebo.

The percentage of patients with ventricular rate >80 bpm at rest on Day 14 was lower in the dronedarone groups compared to placebo.

Safety results:

The overall incidence of TEAEs was higher in the dronedarone groups compared to placebo and increased with the dose: 31.9%, 40.0%, and 61.7% patients of the dronedarone 300 mg, 400 mg, and 600 mg BID groups, versus 24.4% in the placebo group. The number of serious TEAEs was low overall but slightly higher in the dronedarone 600 mg BID group (6.4%) compared to other groups (2.4%, 4.3%, and 4.4% for the placebo, dronedarone 300 mg and 400 mg BID groups, respectively). There were no deaths reported during the study. The number of patients with TEAE leading to permanent treatment discontinuation was higher in the dronedarone 400 mg BID and 600 mg BID groups (15.6% and 29.8%, respectively) compared to the lowest 300 mg BID dose (4.3%) and placebo (2.4%) groups.

Gastrointestinal disorders (mainly nausea/ vomiting and diarrhea) were the most frequently reported TEAEs and the main cause for permanent treatment discontinuation, and the incidence increased with the dose.

Cardiac failure was reported in 3 patients in the 600 mg BID group and 1 patient in the 400 mg BID group versus 1 patient in the placebo group.

Increase in ALT (>3 Upper Limit of Normal ULN) occurred in 3 patients in the dronedarone 600 mg BID group and 1 patient in the 400 mg BID group versus 1 patient in the placebo group.

There were no cases of interstitial lung disease, severe skin disorders, or peripheral neuropathy reported during the study.

The number of patients presenting with increased creatinine and decreased creatinine clearance was higher in the dronedarone groups compared to placebo. No apparent differences in other biochemistry parameters were observed between treatment groups.

The number of patients presenting with prolonged QTcF (Fridericia corrected QT interval) and/or increase from baseline in QTcF was higher in the dronedarone groups and in particular the 600 mg BID group compared to placebo, which was consistent with the known electrophysiological properties of dronedarone. No cases of torsades de pointes were reported.

Pharmacokinetic results:

The plasma concentrations of dronedarone and its metabolite observed in these patients were in line with the pharmacokinetic characteristics of dronedarone determined in the Japanese population.

A supra-dose proportionality was observed between 300 and 600 mg BID of dronedarone, with a 2-fold increase in dose leading to a 2.63-fold increase in exposure of dronedarone and a 3.14-fold increase in exposure of SR35021, respectively.

A significant relationship was found between the increase in concentration of dronedarone and SR35021 and the negative change from baseline in mean ventricular rate on Day 14 ($p<0.05$).

Date of ~~report~~: 23 APR 2012