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(54) **Title**: USE OF DRONEDARONE FOR THE PREPARATION OF A MEDICAMENT FOR THE HOSPITALIZATION BURDEN IN PATIENT WITH ATRIAL FIBRILLATION

(57) **Abstract**: The instant invention relates to the use of dronedarone for the clinical benefit of dronedarone on the number and duration of cardiovascular hospitalizations in patients with atrial fibrillation (AF), with a history of paroxysmal or persistent AF and additional risk factors.

USE OF DRONEDARONE FOR THE PREPARATION OF A MEDICAMENT FOR THE HOSPITALIZATION BURDEN IN PATIENT WITH ATRIAL FIBRILLATION

The instant invention relates to the use of dronedarone for the clinical benefit of dronedarone on the number and duration of cardiovascular hospitalizations in patients with atrial fibrillation (AF), with a history of paroxysmal or persistent AF and additional risk factors.

2-n-butyl-3-[4-(3-di-n-butylaminopropoxy)benzoyl]-5-méthylsulfonamido-benzofuranne or dronedarone and its pharmaceutically acceptable salts are described in European patent EP 0 471 609 B1.

Dronedarone is a multi-channel blocker that affects calcium, potassium and sodium channels and has anti-adrenergic properties.

Dronedarone is an anti-arrhythmic agent for the treatment of patients with a history of atrial fibrillation or atrial flutter.

Atrial fibrillation (AF) affects about 2.3 million people in North America and 4.5 million people in the European Union and is emerging as a growing public health concern because of the aging of the population

AF is a condition in which the upper chambers of the heart beat in an uncoordinated and disorganized fashion, resulting in a very irregular and fast rhythm (i.e., an irregularly, irregular heartbeat). When blood is not completely pumped out of the heart's chambers, it can pool and clot. If a blood clot forms in the atria, exits the heart and blocks an artery in the brain, a stroke results. Consequently, about 15 percent of strokes result from AF. But stroke can also complicate other conditions like for example hypertension. Also hemorrhagic strokes can be a complication of treatment with an anticoagulant prescribed to prevent the formation of thrombi in particular in patients with AF.

AF is increasingly frequent with advancing age and is often caused by age-related changes in the heart, physical or psychological stress, agents that stimulate the heart, such as caffeine, or as a result of cardiovascular disease. The number is expected to double in the next 20 years. Without appropriate management, AF can lead to serious complications, such as stroke and congestive heart failure.

As most of the studies did not assess the complications associated with atrial fibrillation such as stroke, so the effect of antiarrhythmic drugs on these endpoints is unknown (Cochrane Collaboration, The Cochrane Library, 2008, 2).

In addition, two large studies including antiarrhythmic drugs in AF patients, AFFIRM (D.G. Wyse and al., The New England Journal of Medecine, 2002, vol. 347, p.1825-1833) and AF-CHF (D. Roy and al., The New England Journal of Medecine, 2008, vol. 358, p.2667-2677), did not show a significant difference in stroke rates between the rate and rhythm groups (the recommended antiarrhythmic drug in the rhythm group was mainly amiodarone).

Thromboembolic events including strokes are major complications in patients with atrial fibrillation. The etiology of these thromboembolic events are not fully understood. According to the main hypothesis atrial fibrillation leads to blood stasis in the atria, which promotes the formation of blood clots and thereby causes thromboembolic events like stroke if the blood clots reach the systemic circulation. Therefore it was thought that prevention of atrial fibrillation or anticoagulation would prevent thromboembolic events and strokes. Numerous clinical studies have confirmed that proper anticoagulation can prevent thromboembolic events including strokes (Fuster et al.). But, all randomized clinical trials using anti-arrhythmic drugs did not show a reduction in the incidence of stroke, despite effectively maintaining sinus rhythm in the rhythm control or treatment group.

For example, in the AFFIRM trial, Wyse et al. compared a rhythm control (63% amiodarone and 41% sotalol being the most commonly used anti-arrhythmic drugs) to a rate control strategy. As shown in Table 3 of the article by Wyse et al the incidence of stroke or TIA was similar in the rhythm control group (80/2033) compared to the rate control group (77/2027), despite a higher number of patients in the rhythm control group (63%) being in sinus rhythm after 5 years compared to the rate control group (35%).

In the STAF trial, Carlsson el al. compared a rhythm control (42% amiodarone) to a rate control strategy. As shown in Table 2 of the article by Carlsson et al the incidence of stroke or TIA was numerically higher in the rhythm control group (5/100) compared to the rate control group (1/100), despite a highly significant 29% absolute increase in patients with sinus rhythm at the end of the study in the rhythm control group compared to the rate control group.

In the HOT CAFÉ, Opolski et al compared a rate and a rhythm control strategy. As shown in table 2 of the article of Opolski et al 3/104 patients suffered from a stroke during the follow-up in the rhythm control group compared to 0/101 in the rate control group.

In the J-RHYTHM trial, Ogawa et al. compared a rhythm control (85% of patients were on class I anti-arrhythmic drugs) to a rate control strategy. As shown in Table 3 of the article by Ogawa et al the incidence of symptomatic stroke was similar in the rhythm control group (9/419) compared to the rate control group (11/404), despite a highly significant 29% absolute increase in patients with sinus rhythm at 3 years in the rhythm control group compared to the rate control group.

In the SAFE-T trial, Singh et al compared amiodarone, sotalol and placebo in the treatment of patients with persistent atrial fibrillation. Amiodarone and sotalol were both significantly more effective than placebo in increasing the time to a recurrence of atrial fibrillation (a widely used measure for rhythm control) ($P<0.001$). Amiodarone was six times as effective as sotalol in the intention-to-treat analysis ($P<0.001$) and four times as effective in the analysis according to the treatment actually received ($P<0.001$). Despite this effective rhythm control the number of strokes per 100 patient-years of follow-up were similar in all groups for amiodarone: 2.06 major, sotalol: 2.71, and placebo: 1.91 with the lowest rate observed in the placebo group, which had the highest rate of recurrence of atrial fibrillation (calculated from bottom of last paragraph on page 1866)).

Therefore, administering a drug for preventing atrial fibrillation cannot be considered as implying a prevention of stroke, according to the current knowledge in the Art. Unexpectedly, dronedarone has demonstrated, in the ATHENA trial (Hohnloser et al.), its ability to reduce the incidence of stroke. The effect now seen with dronedarone is not based upon rhythm control alone but on the unique combination of properties of dronedarone, which include but are not limited to: effective rhythm control, heart rate lowering effects, blood pressure lowering effects, direct effects on the endothelial function and others.

The Inventors have now clinically proven the benefit of dronedarone on the number and duration of cardiovascular hospitalizations in patients with atrial fibrillation (AF). It was not demonstrated with other antiarrhythmic compounds.

The subject of the instant invention is the clinical benefit of dronedarone on the number and duration of cardiovascular hospitalizations in patients with atrial fibrillation (AF).

Patients in “permanent atrial fibrillation or flutter” are patients that have all scheduled ECGs in this rhythm throughout the period the dronedarone or a pharmaceutically acceptable salt thereof is administered.

Cardiovascular events may be defined as stroke, acute coronary syndrome or cardiovascular death.

Dronedarone treatment significantly reduced the risk of first cardiovascular hospitalization compared with placebo ($p < 0.0001$), while the risk of first noncardiovascular hospitalizations was similar in both groups ($p = 0.77$). The majority of cardiovascular hospitalizations were AF related, with a median duration of hospital stay of 4 nights. The risk of any hospitalization for AF and the duration of hospital stay were significantly reduced by dronedarone ($p < 0.0001$ vs. placebo). In addition, dronedarone treatment reduced total hospitalizations for acute coronary syndrome ($p = 0.0105$). Hospitalization burden was significantly reduced across all levels of care ($p < 0.05$). Cumulative incidence data indicated that the effects of dronedarone persisted for at least 24 months.

AF = atrial fibrillation
AFL = atrial flutter
ATHENA = A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter
CHF = congestive heart failure
CI = confidence interval
ECG = electrocardiogram
ITT = intention to treat
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
TIA = transient ischemic attack

The lifetime risk of atrial fibrillation (AF) in men and women aged 40 years is 1 in 4 . The incidence and prevalence of AF increases with age, resulting in a substantial public health burden . A community-based cohort study indicated a rise in AF of 13% over the last 2 decades, and if this increase continues, 15.9 million people in the United States will develop AF by the year 2050 . The increasing occurrence of AF is associated with an increase in mortality , as well as debilitating stroke and heart failure . Not unexpectedly, these trends are also associated with increased hospitalizations related to AF.

In the recent ATHENA trial (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter), in 4,628 patients with paroxysmal or persistent AF or atrial flutter (AFL), dronedarone treatment decreased the number of first cardiovascular hospitalizations [675/2301 in the dronedarone group vs 859/2327 in the placebo group (hazard ratio 0.74;95% CI, 0.67 to 0.82; p<0.001)]. This reduction in rate of cardiovascular hospitalizations was mainly driven by a reduction in the number of hospitalizations for atrial fibrillation and for acute coronary syndrome. Furthermore, ATHENA demonstrated that dronedarone treatment increases the time to first hospitalization for cardiovascular reasons. The incidence of adverse events was 72% in the dronedarone group and 69.3% in the placebo group (p = 0.048), with no increase in rates of thyroid or pulmonary disorders with dronedarone.

Here we present the results of a post hoc analysis, using data from the ATHENA study to further evaluate the effect of dronedarone on hospitalizations, by examining all hospitalization events and the length of hospital stay in patients with paroxysmal or persistent AF, or AFL.

Details of the main study protocol have been published previously (10,11). In brief, ATHENA was a randomized, double-blind, placebo-controlled trial conducted in 551 centers in 37 countries. The study was conducted according the principles of good clinical practice. Patients were recruited between June 29, 2005 and December 30, 2006; with a minimum follow up of 1 year. The trial was sponsored by sanofi-aventis.

The aim of this post-hoc data analysis was to evaluate the number of first hospitalizations per treatment group, the number of all hospitalizations, the duration of hospital stay and the hospitalization burden over time.

Patients with paroxysmal or persistent AF, or AFL, were eligible for enrollment if 1 or more of the following risk factors were present: age ≥70 years, arterial hypertension (ongoing therapy with at least 2 antihypertensive drugs of different classes), diabetes mellitus, prior stroke or transient ischemic attack (TIA) or systemic embolism, left atrial diameter ≥50 mm by M-mode echocardiography, or left ventricular ejection fraction (LVEF) ≤40%. For each patient, a 12-lead electrocardiogram (ECG) within 6 months prior to randomization had to be available showing AF or AFL. A second 12-lead ECG within the same period had to show sinus rhythm. During the course of the trial, the inclusion criteria were revised, requiring patients to be aged ≥70 years with 1 or more of the prespecified risk

factors, or aged ≥75 years regardless of whether they had any previously specified risk factors.

Exclusion criteria of note for this analysis included a diagnosis of permanent AF, an unstable hemodynamic condition, NYHA class IV congestive heart failure, any severe noncardiac illness limiting life expectancy, and conditions incompatible with inclusion in a clinical trial.

Patients were randomly assigned to receive dronedarone 400 mg twice daily or placebo (ratio 1:1). Randomization was stratified by center and by the presence or absence of AF or AFL at the time of randomization.

The follow-up visit schedule included clinical evaluations at days 7 and 14, and at months 1, 3, 6, 9, 12, and every 3 months thereafter. The trial was planned to have a minimum follow-up duration of 12 months and all patients, irrespective of the occurrence of a primary end point, were followed at least until the common study end date on December 30, 2007, with the exception of 2 patients in the placebo group who were lost to follow-up.

Any unplanned hospitalization (i.e., admission with an overnight stay in hospital covering at least 2 consecutive dates) was categorized by the investigator as either cardiovascular or noncardiovascular according to prespecified main reasons. The reasons for cardiovascular hospitalizations were defined prior to study start as follows: myocardial infarction or unstable angina; stable angina pectoris or atypical chest pain; atherosclerosis related (if not otherwise specified); transcutaneous coronary, cerebrovascular, or peripheral procedure; cardiovascular surgery except cardiac transplantation; AF and other supraventricular rhythm disorders; ventricular arrhythmia; nonfatal cardiac arrest; worsening congestive heart failure (CHF), including pulmonary edema or dyspnea of cardiac origin; cardiac transplantation; syncope; implantation of a pacemaker, implantable cardioverter defibrillator, or any other cardiac device; TIA or stroke (except intracranial hemorrhage); pulmonary embolism or deep vein thrombosis; blood pressure related (hypotension or hypertension; except syncope); major bleeding (requiring 2 or more units of blood or any intracranial hemorrhage); and cardiovascular infection. For each hospitalization, the number of nights spent in the hospital were recorded according to the following three categories: intensive care unit or coronary care unit, step down or medium care unit, and regular ward.

Data for the primary endpoint and for CV hospitalizations separately were also analyzed for the following regions: North America, South America, Eastern Europe, Western Europe, Asia and "Other."

All analyses were performed according to the intention-to-treat (ITT) principle. Time to first cardiovascular hospitalization was estimated using Kaplan-Meier method and compared by means of the log-rank test. All p values were 2-tailed. The dronedarone-to-placebo hazard ratio with 95% confidence intervals (CIs) were estimated using Cox's proportional hazard model.

Time to all hospitalizations (cardiovascular/noncardiovascular) was analyzed by plotting the mean number of cardiovascular/noncardiovascular hospitalizations over time using Nelson-Aalen nonparametric cumulative incidence functions for each treatment group. The 2 treatment groups were compared using a 2-sided log-rank asymptotic test for repeated event time data. The hazard ratio and associated 95% CIs were estimated within the Andersen-Gill multiplicative intensity regression with treatment group as the only binary variable. The cumulative incidence was described at selected time points (6 months, 12 months, 18 months, 24 months, and 30 months) according to treatment group and cardiovascular hospitalization status, and cumulative incidence for each 6-month period (0 to 6 months, 6 to 12 months, 12 to 18 months, 18 to 24 months, and 24 to 30 months) derived.

The total number of hospitalizations and the number of total hospitalization days were compared using a log-rank test and a Wilcoxon test, respectively.

The ATHENA study enrolled 4,628 patients, of whom 2,301 were assigned to dronedarone and 2,327 to placebo. Baseline characteristics were similar between groups (Table 1). As previously reported, the mean ± standard deviation follow-up duration for all patients was 21 ± 5 months, with a median of 22 months. The minimum follow-up duration was 1 year, and the maximum was 2.5 years.

The number of first hospitalizations by treatment groups is shown in Table 2. The number of first cardiovascular hospitalizations was significantly decreased in the dronedarone group compared with placebo (675 patients in the dronedarone group versus 859 in the placebo group [hazard ratio 0.74; 95% CI, 0.67 to 0.82; $p<0.001$]). First hospitalizations related to AF and acute coronary syndrome were significantly fewer in the dronedarone group compared with the placebo group (335 versus 510; $p<0.0001$ for AF, and 62 versus 89; $p = 0.03$ for acute coronary syndrome, respectively). The number of first hospitalizations for stroke or TIA and for heart failure were non significantly reduced: dronedarone 43 stroke / TIA hospitalizations

vs. placebo 61 (p = 0.08) and dronedarone 112 heart failure hospitalizations vs. placebo 132 (p = 0.22). There was no difference between the number of first noncardiovascular hospitalizations between groups (dronedarone 516, placebo 533; p = 0.77).

Figure 1 shows Kaplan-Meier curves of time to first cardiovascular hospitalization events and noncardiovascular hospitalization events, as well as time to first AF-related hospitalizations and first non-AF–related hospitalizations.

Table 3 shows the number of hospitalizations and their duration when all hospitalizations are included in the analyses, regardless of how many hospitalizations each patient had. Among the patients experiencing at least one AF-related hospitalization during the study, 50% remained in hospital for at least 4 nights and 25% for at least 8 nights. The total number of hospitalizations for AF was reduced from 829 with placebo to 514 (p < 0.001) with dronedarone and the number of days in hospital from 4,637 to 3,132, respectively (p < 0.001). The number of hospitalizations for acute coronary syndrome was reduced from 113 in the placebo group to 71 in the dronedarone group (p = 0.01) and the number of hospitalization days from 1,188 to 816, respectively (p = 0.04). Neither the total number nor the duration of noncardiovascular hospitalizations were reduced significantly by dronedarone.

In table 4, it can be seen that the reduction of the total number of nights spent in hospital is observed at all levels of care. In addition, dronedarone decreased the risk of first cardiovascular hospitalization in intensive care unit or cardiologic care unit by approximately 19% compared with placebo.

Figure 2 shows the time from first AF/AFL recurrence (based on ECGs and cardioversion) to first cardiovascular hospitalization or death from any cause during the on-study period. This analysis includes all randomized patients with a first AF/AFL recurrence (based on ECGs and cardioversion) and without presence of AF/AFL as a stratification factor. The time between recurrence and cardiovascular hospitalization/death was significantly reduced by dronedarone (relative risk [95% CI] = 0.771 [0.643 to 0.925]; p = 0.0048).

The Nelson-Aalen cumulative incidence of all cardiovascular and noncardiovascular hospitalizations is shown in Figure 3A. Repeated cardiovascular hospitalizations were reduced with dronedarone, but noncardiovascular hospitalizations were not. Figure 3B shows the hospitalization burden of cardiovascular and noncardiovascular hospitalization during the first 2 years after randomization. The hospitalization burden

for cardiovascular hospitalization decreased over time and remained lower with dronedarone treatment.

The relative risk estimates and 95% CIs for the primary endpoint and time to first cardiovascular hospitalization events is shown in Figure 4 for the different regions. Results were consistent to the overall population with all risk estimates favoring dronedarone treatment. Only the confidence intervals for South America and for the region "Other" included 1.0 for both the primary endpoint and for cardiovascular hospitalizations, separately.

The main finding of this ATHENA post hoc analysis is that dronedarone reduces the number of cardiovascular hospitalizations and reduces the length of hospital stay for cardiovascular reasons. The reduction in first hospitalizations in intensive care / cardiac care units suggests a reduction in cardiovascular hospitalizations associated with potentially life-threatening conditions. The overall reduction of hospitalization burden, including reduction of cardiovascular events, indicates that dronedarone may reduce the severity of disease in this patient population.

Antiarrhythmic drugs approved for maintainance of sinus rhythm in patients with AF have all been documented to prevent or delay recurrence of AF. ATHENA is the only study powered to demonstrate a clinical benefit beyond maintainance of sinus rhythm specifically in patients with AF.

A post hoc analysis of the AFFIRM study (Atrial Fibrillation Follow-up Investigation of Rhythm Management) also investigated cardiovascular hospitalization as an alternative endpoint for death. In that analysis, patients treated with a rhythm-control strategy (62.8% on amiodarone) were hospitalized for cardiovascular reasons at a higher rate than patients treated with a rate-control strategy (46% vs. 36%, $p < 0.001$). However, when hospitalizations related to treatment (i.e., cardioversion) were excluded, hospitalization rates were similar between the rhythm-control and rate-control cohorts (24% vs 27%, respectively). The AFFIRM researchers further analyzed the data and found significant associations between cardiovascular hospitalization and death in both treatment arms. For patients treated with a rate-control treatment, cardiovascular hospitalization was associated with an HR of 2.15 (95% CI = 1.69 to 2.74; $p < 0.0001$) for death, while rhythm-control treatment was associated with an HR of 1.71 (95% CI = 1.37 to 2.13; $p < 0.0001$).

The AF-CHF (Atrial Fibrillation and Congestive Heart Failure) study was conducted in a patient population with more and worse heart failure than either ATHENA or AFFIRM, but the hospitalization results of AF-CHF were similar to those found in

AFFIRM. Patients in the rhythm-control cohort of that study (82% of whom received amiodarone) were hospitalized at significantly higher rates during the first year than patients in the rate-control cohort (46% vs. 39%, respectively; p = 0.001). Furthermore, hospitalizations for AF were significantly higher in the rhythm-control cohort than the rate-control cohort (14% vs. 9%, respectively; p = 0.001).

Although a reduction in hospitalizations was also demonstrated in patients with AF for dofetilide in the 2 Danish Investigations of Arrhythmias and Mortality ON Dofetilide (DIAMOND), the primary populations of those studies were patients with heart failure or recent myocardial infarction. A pooled post hoc analysis of the 506 patients with AF at baseline in the DIAMOND studies demonstrated a reduction in hospitalizations with dofetilide treatment, accompanied by a more frequent conversion to sinus rhythm.

The reduced number and duration of hospitalizations in the dronedarone group versus placebo seen in the current ATHENA analysis may also be related to maintainance of sinus rhythm. In accordance with this finding, hospitalizations related to AF were markedly reduced in number and duration. This reduction in AF-related hospitalizations was not due simply to fewer cardioversions, but also to a decrease in the severity of recurrent AF episodes.

It is also noteworthy that hospitalizations related to acute coronary syndromes were reduced. While hospitalizations related to acute coronary syndromes could be reduced by less frequent AF, one might speculate that the heart rate–lowering effect of dronedarone may be important. Dronedarone slows the heart rate not only during AF but also during sinus rhythm.

Although the number of hospitalizations due to acute coronary syndrome and AF was significantly reduced by dronedarone, hospitalizations due to other cardiovascular causes were not significantly different from placebo. Interestingly, a previous ATHENA subanalysis demonstrated that the incidence of stroke was significantly reduced with dronedarone treatment, from 1.8% per year with placebo to 1.2% per year (hazard ratio 0.66 [95% CI = 0.46 to 0.96]; p = 0.027). In the current study, there was a noticeable trend toward reduced hospitalization days due to stroke in the dronedarone group (439 vs. 1122 in the placebo group), and although this was not significant (p = 0.079), possibly due to the small number of patients hospitalized due to stroke (43 dronedarone patients vs. 61 placebo patients), it nevertheless provides additional support for the benefits of dronedarone treatment in this patient population.

In this post hoc analysis, the data for the 6 regions for the primary outcome and for cardiovascular hospitalizations, alone, were consistent with the overall study population.

It should be noted that the results of the current study cannot be extrapolated to other antiarrhythmic drugs. In the meta-analysis by Lafuente-Lafuente, although the efficacies of commonly used antiarrhythmic drugs appeared similar, there were some specific differences between them, which could result in important differences in outcomes for patients. Flecainide and propafenone do not lower heart rate and may thereby be less efficacious in reducing hospitalizations. Sotalol has a dual effect of being a beta-blocker and a class III antiarrhythmic drug, but may cause torsades de pointes tachycardia and had an uncertain safety profile in the meta-analysis. Amiodarone appeared to be the most effective of the drugs evaluated by LaFuente-LaFuente in preventing recurrences of AF, while producing fewer adverse events and having less associated mortality than beta-blockers. In comparison with dronedarone, amiodarone may be more efficacious for maintainance of sinus rhythm, but it has a worse side effect profile, particularly during long-term use.

Another object of the invention is a pharmaceutical composition which comprises, as active principle, dronedarone or one of its pharmaceutically acceptable salts. This pharmaceutical composition comprises an effective dose of at least one compound of formula (I) according to the invention, or an addition salt thereof with a pharmaceutically acceptable salt, or a hydrate or solvate thereof, and at least one pharmaceutically acceptable excipient. Said excipients are chosen according to the pharmaceutical form and the administration route desired, among usual excipients known to one of skill in the art.

In the pharmaceutical compositions according to the invention for the oral, sublingual, sub-cutaneous, intramuscular, intra-venous, topical, local, intratracheal, intranasal, transdermal or rectal administration, dronedarone or one of its salt, solvate or hydrate, can be administered as a unitary dosage form, in blend with usual pharmaceutical excipients, to animals and human beings for the prevention or for the treatment of pathological states mentioned above. The appropriate unitary dosage forms comprise the oral forms, such as tablets, hard or soft gelatin capsules, powders, granules and oral solutions or suspensions, the sublingual, buccal, intratracheal, intraocular, intranasal forms, the forms adapted to inhalation, topical, transdermal, sub-cutaneous, intramuscular or intra-venous delivery, the rectal forms and the implants. For the topical application, the compounds of the invention may be used as creams, gels, ointments or lotions.

For its use in therapeutics, dronedarone and its pharmaceutically acceptable salts are incorporated in pharmaceuticals compositions.

These pharmaceutical compositions comprise an effective dose of at least dronedarone or one of its pharmaceutically acceptable salts and at least one pharmaceutically acceptable excipient.

Said excipients are chosen according to the pharmaceutical form and the administration route desired, among usual excipients known of one of skill in the art.

In the pharmaceutical compositions for the oral, sublingual, sub-cutaneous, intramuscular, intra-venous, topical, local, intratracheal, intranasal, transdermal or rectal administration, dronedarone or one of its pharmaceutically acceptable salts, can be administered as a unitary dosage form, in blend with usual pharmaceutical excipients, to animals and human in diseases above mentioned.

The appropriate unitary dosage forms comprise the oral forms, such as tablets, hard or soft gelatin capsules, powders, granules and oral solutions or suspensions, the sublingual, buccal, intratracheal, intraocular, intranasal forms, by inhalation, the topical, transdermal, sub-cutaneous, intramuscular or intra-venous forms, the rectal forms and the implants. For the topical application, the compounds of the invention may be used as creams, gels, ointments or lotions.

As an example, a unitary dosage form for dronedarone or one of its pharmaceutically acceptable salts, in the form of a tablet, can comprise the following ingredients:

Ingredients	mg
dronedarone hydrochloride (corresponding to 400 mg of base)	426
Methylhydroxypropylcellulose	21,1
Lactose monohydrate	46,55
Modified corn starch	45,5
Polyvinylpyrrolidone	65
Poloxamer 407	40
Anhydrous colloidal silica	2,6

magnesium stearate	3,25
	650

Ingredients	mg
dronedarone hydrochloride (corresponding to 400 mg of base)	426
microcristalline cellulose	65
Anhydrous colloidal silica	2,6
anhydrous lactose	42,65
Polyvinylpyrrolidone	13
Poloxamer 407	40
Macrogol 6000	57,5
magnesium stearate	3,25
	650

Ingredients	mg
dronedarone hydrochloride (corresponding to 400 mg of base)	426
microcristalline cellulose	26
corn starch	45,5
Polyvinylpyrrolidone	65
Poloxamer 407	40
Anhydrous colloidal silica	3,25
magnesium stearate	3,25
Lactose monohydrate	41,65
	650

Ingredients	mg
dronedarone hydrochloride (corresponding to 400 mg of base)	213
microcrystalline cellulose	13
corn starch	22,75
Polyvinylpyrrolidone	32,5
Poloxamer 407	20
Anhydrous colloidal silica	1,3
magnesium stearate	1,625
Lactose monohydrate	20,825
	650

Said pharmaceutical composition may be given once or twice a day with food.

The dose of dronedarone administered per day, orally, may reach 800 mg, taken in one or more intakes, for example one or two.

More specifically, the dose of dronedarone administered may be taken with food.

More specifically, the dose of dronedarone administered per day, orally, may reach 800 mg, taken in two intakes with a meal.

The dose of dronedarone administered per day, orally may be taken at a rate of twice a day with a meal for example with the morning and the evening meal.

More specifically, the two intakes may comprise same quantity of dronedarone.

In specific cases, higher or lower dosages may be appropriate; these dosages are comprised within the scope of the present invention. According to usual practice, the dosage suitable to each patient is determined by the physician according to the administration route, the weight, the disease, the body surface, the cardiac output and response of the patient.

Efficacy of dronedarone and its pharmaceutically acceptable salts versus placebo for the prevention of stroke was provided via dronedarone hydrochloride

during a prospective, multinational, double-blind, randomized, multi-center, placebo-controlled, parallel group trial.

Figure titles and legends

Figure 1. Kaplan-Meier Cumulative Incidence Curves of Time From Randomization to First Hospitalization for the ITT population. A) Cardiovascular hospitalization; B) Noncardiovascular hospitalization; C) Hospitalization for AF and other supraventricular disorders; D) Non-AF/AFL hospitalization.

Figure 2. Kaplan-Meier Cumulative Incidence Curves of Time From First AF/AFL Recurrence (Based on ECGs and Cardioversion) to First Cardiovascular Hospitalization During the On-Study Period. Data are for all randomized patients with a first AF/AFL recurrence and without presence of AF/AFL as per stratification factor.

Figure 3. Incidence of Cardiovascular and Noncardiovascular Hospitalizations. A) Summary of Nelson-Aalen cumulative incidence curves of all cardiovascular and noncardiovascular hospitalizations during the on-study period (ITT population); B) Curve and summary of cumulative incidence difference between each time point for all cardiovascular and noncardiovascular hospitalizations during the on-study period (ITT Population).

Figure 4. Relative risk (dronedarone 400 mg bid vs placebo) estimates with confidence intervals according to region. A) Primary endpoint (first cardiovascular hospitalization or death from any cause); B) Cardiovascular hospitalization. Data are for all randomized patients. [a]Determined from Cox regression model; [b]P-values are for interaction between regions and treatment based on Cox regression model.

Table 1. Baseline Characteristics of Study Patients

	Placebo (n = 2,327)	Dronedarone (n = 2,301)	All Patients (n = 4,628)
Age, yrs	71.7 ± 9.0	71.6 ± 8.9	71.6 ±9.0
<65	442 (19)	431 (19)	873 (19)
≥65 to <75	907 (39)	923 (40)	1830 (40)
≥75	978 (42)	947 (41)	1925 (42)
Female sex	1038 (45)	1131 (49)	2169 (47)
AF/AFL at baseline	586 (25)	569 (25)	1155 (25)
Structural heart disease*	1402/2304 (61)	1330/2281 (58)	2732/4585 (60)
Hypertension	1996 (86)	1999 (87)	3995 (86)
Coronary heart disease or ischemic dilated cardiomyopathy	737 (32)	668 (29)	1405 (30)
Valvular heart disease	380 (16)	379 (17)	759 (16)
Nonischemic dilated cardiomyopathy or hypertrophic cardiomyopathy	131(6)	123 (5)	254 (6)
History of CHF, NYHA II/III	515 (22)	464 (20)	979 (21)
LVEF†			
<45%	285/2281 (13)	255/2263 (11)	540/4544(12)
<35%	87/2281 (4)	92/2263 (4)	179/4544 (4)
Lone AF‡	139 (6)	140 (6)	279 (6)
Pacemaker	243 (10)	214 (9)	457 (10)
Baseline medications			
Beta-blocking agents (except sotalol)	1641 (71)	1628 (71)	3269 (71)
Ca antagonists with heart rate–lowering effects	307 (13)	331 (14)	638 (14)
Digitalis	308 (13)	321 (14)	629 (14)
ACE inhibitor or ARB	1602 (69)	1614 (70)	3216 (70)
Statins	914 (39)	878 (38)	1792 (39)
Oral anticoagulant	1384 (60)	1403 (61)	2787 (60)
Low dose of aspirin (≤365 mg)	1019 (44)	1018 (44)	2037 (44)

Results are shown as n (%) or mean ± standard deviation. *Structural heart disease: coronary heart disease and/or ischemic dilated cardiomyopathy and/or nonischemic dilated cardiomyopathy and/or rheumatic valvular heart disease and/or nonrheumatic valvular heart disease and/or hypertrophic cardiomyopathy and/or LVEF<45% and/or history of CHF. Complete data on structural heart disease were available for 2,281/2,301 patients receiving dronedarone and for 2,304/2,327 patients receiving placebo, for a total of 4,585 patients. †For LVEF, data were available for 2,263/2,301 patients receiving dronedarone and for 2,281/2,327 patients receiving placebo, for a total of 4,544 patients. The category of LVEF <45% included the patients with LVEF <35%. ‡Lone AF: patients without hypertension and without structural heart disease.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin receptor blocker; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

Table 2. Number of Events and Relative Risk of First Hospitalization According to Prespecified Reasons During the On-Study Period

Reason for Hospitalization	Placebo (n = 2,327)	Dronedarone (n = 2,301)	HR (95%CI)	Log-Rank Test p Value
Cardiovascular hospitalizations				
Acute coronary syndrome Myocardial infarction or unstable angina	89	62	0.699 (0.506 to 0.967)	0.0296
Other ischemia-related events				
Stable angina pectoris or atypical chest pain	63	56	0.898 (0.626 to 1.287)	0.5561
Atherosclerosis related (if not otherwise specified)	14	16	1.151 (0.562 to 2.358)	0.7004
Transcutaneous coronary, cerebrovascular, or peripheral procedure	48	44	0.925 (0.615 to 1.393)	0.7102
Cardiovascular surgery except cardiac transplantation	43	35	0.820 (0.525 to 1.281)	0.3824
Arrhythmias				
AF and other supraventricular rhythm disorders	510	335	0.626 (0.546 to 0.719)	< 0.0001
Ventricular tachycardia (nonsustained and sustained)	8	7	0.882 (0.320 to 2.433)	0.8084
Ventricular fibrillation	2	1	0.503 (0.046 to 5.544)	0.5669
Other ventricular arrhythmia	0	1	NC	NC
Nonfatal cardiac arrest	2	5	2.515 (0.488 to 12.961)	0.2536
Ventricular extrasystoles	1	1	1.007 (0.063 to 16.106)	0.9958
CHF				

Worsening CHF, including pulmonary edema or dyspnea of cardiac origin	132	112	0.855 (0.665 to 1.100)	0.2207
Cardiac transplantation	1	0	NC	NC
Conduction disturbances				
Syncope	32	27	0.853 (0.511 to 1.424)	0.5418
Implantation of a pacemaker, implantable cardioverter defibrillator or other cardiac device	81	64	0.793 (0.572 to 1.101)	0.1655
TIA or stroke (except intracranial hemorrhage)	61	43	0.708 (0.480 to 1.047)	0.0819
Pulmonary embolism or deep vein thrombosis	6	14	2.337 (0.898 to 6.082)	0.0730
Blood pressure				
Hypotension, hypertension; except syncope	38	30	0.797 (0.494 to 1.286)	0.3509
Other				
Major bleeding (requiring 2 or more units of blood or any intracranial hemorrhage)	33	36	1.103 (0.688 to 1.769)	0.6839
Cardiovascular infection	0	4	NC	NC
Noncardiovascular hospitalizations	533	516	0.982 (0.870 to 1.108)	0.7688

AF = atrial fibrillation; CHF = congestive heart failure; NC = not calculable; TIA = transient ischemic attack.

Table 3. Total Number of Hospitalizations and Hospital Days by Prespecified Classification

	Total No. of Hospitalizations			Total No. of Hospital Days		
Reason for hospitalization	**Placebo (n = 2327)**	**Dronedarone (n = 2301)**	**Log-Rank Test p Value**	**Placebo (n = 2327)**	**Dronedarone (n = 2301)**	**Wilcoxon Test p Value**
Cardiovascular hospitalizations						
Acute coronary syndrome Myocardial infarction or unstable angina	113	71	0.01047	1188	816	0.038
Other ischemia-related events						
Stable angina pectoris or atypical chest pain	72	69	NC	533	402	0.611
Atherosclerosis related (if not otherwise specified)	20	17	NC	269	199	0.693
Transcutaneous coronary, cerebrovascular, or peripheral procedure	55	52	NC	165	168	0.718
Cardiovascular surgery except cardiac transplantation	47	38	NC	436	332	0.519
Arrhythmias						
AF and other supraventricular rhythm disorders	829	514	< 0.0001	4637	3132	< 0.0001
Ventricular tachycardia	10	8	NC	84	32	0.811

(nonsustained and sustained)						
Ventricular fibrillation	2	1	NC	2	3	0.571
Other ventricular arrhythmia	0	1	NC	0	4	0.315
Nonfatal cardiac arrest	2	6	NC	34	52	0.251
Ventricular extrasystoles	1	1	NC	13	3	0.994
CHF						
Worsening CHF, including pulmonary edema or dyspnea of cardiac origin	184	165	0.505	1511	1486	0.202
Cardiac transplantation	1	0	NC	20	0	0.320
Conduction disturbances						
Syncope	33	32	NC	190	102	0.371
Implantation of a pacemaker, implantable cardioverter defibrillator or other cardiac device	83	65	NC	372	334	0.206
TIA or stroke (except intracranial hemorrhage)	64	46	NC	1122	439	0.079
Pulmonary embolism or deep vein thrombosis	6	15	NC	121	137	0.070
Blood pressure						
Hypotension, hypertension; except syncope	40	30	NC	297	238	0.349
Other						
Major bleeding (requiring 2 or more units of blood or any	33	41	NC	349	423	0.687

intracranial hemorrhage)						
Cardiovascular infection	0	5	NC	0	14	0.044
Other cardiovascular hospitalization	285	254	0.2842	1870	1524	0.240
Noncardiovascular hospitalizations	715	676	0.480	6326	5901	0.703

AF = atrial fibrillation; CHF = congenital heart failure; NC = not calculable; TIA = transient ischemic attack.

Table 4. Duration of First Hospitalization During the On-Study Period According to the Level of Care

	Placebo (n = 2327)	Dronedarone (n = 2301)	P values
All cardiovascular hospitalizations			
Patients with at least 1 cardiovascular hospitalization	859 (36.9%)	675 (29.3%)	
Total number of nights	5807	4792	<0.001
Nights in intensive care / coronary care unit	888	482	0.027
Nights in step down unit or medium care	922	724	0.010
Nights on regular ward	3997	3586	0.002
AF hospitalizations			
Patients with at least 1 AF hospitalization	510 (21.9%)	335 (14.6%)	
Total number of nights	2837	2092	<0.001
Nights in intensive care / coronary care unit	358	175	0.007
Nights in step down unit or medium care	518	292	<0.001
Nights on regular ward	1961	1625	<0.001

AF = atrial fibrillation

CLAIMS

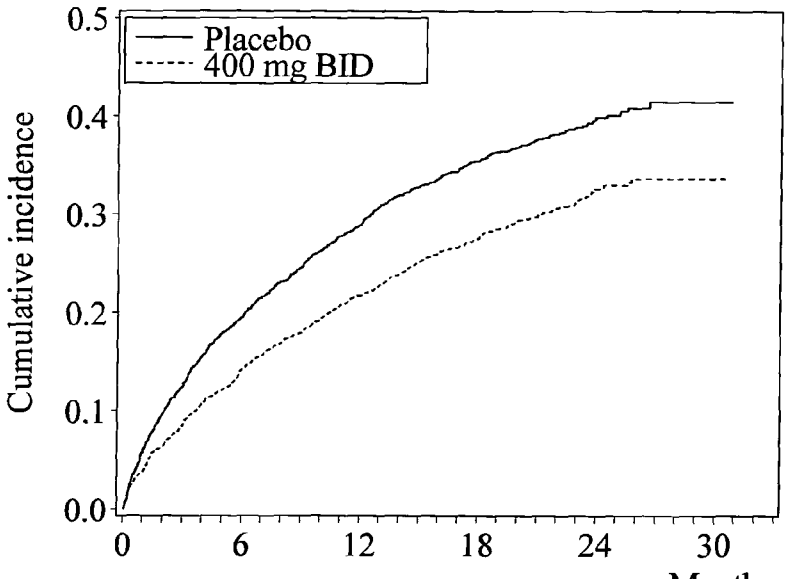
1. Use of dronedarone for the clinical benefit of patients with atrial fibrillation (AF), with a history of paroxysmal or persistent AF and additional risk factors on the number and duration of cardiovascular hospitalizations.

2. Use according to claim 1, characterized in that, for oral administration, dronedarone daily dose may reach 800 mg.

3. Use according to one of the previous claims of an effective dose of at least dronedarone or one of its pharmaceutically acceptable salts.

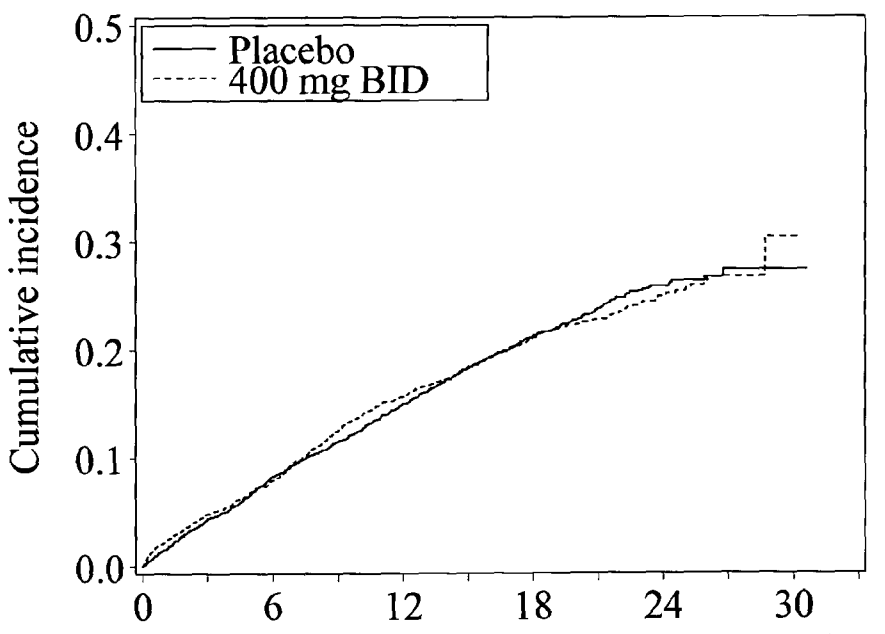
Figure 1

A



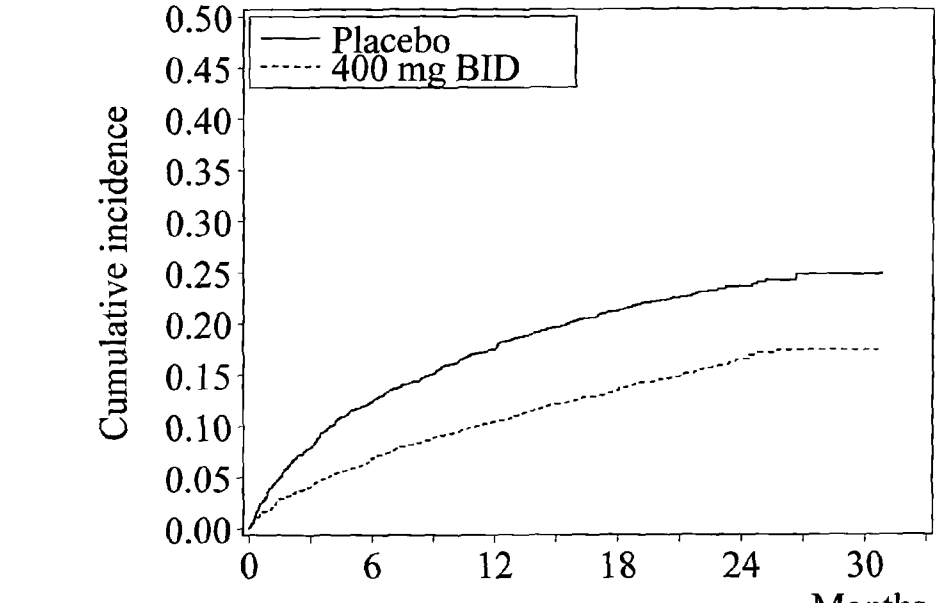
Number at risk:						
Placebo	2327	1858	1625	1072	385	3
400 mg BID	2301	1963	1776	1177	403	2

B



Number at risk:						
Placebo	2327	2114	1936	1311	484	4
400 mg BID	2301	2105	1915	1287	459	2

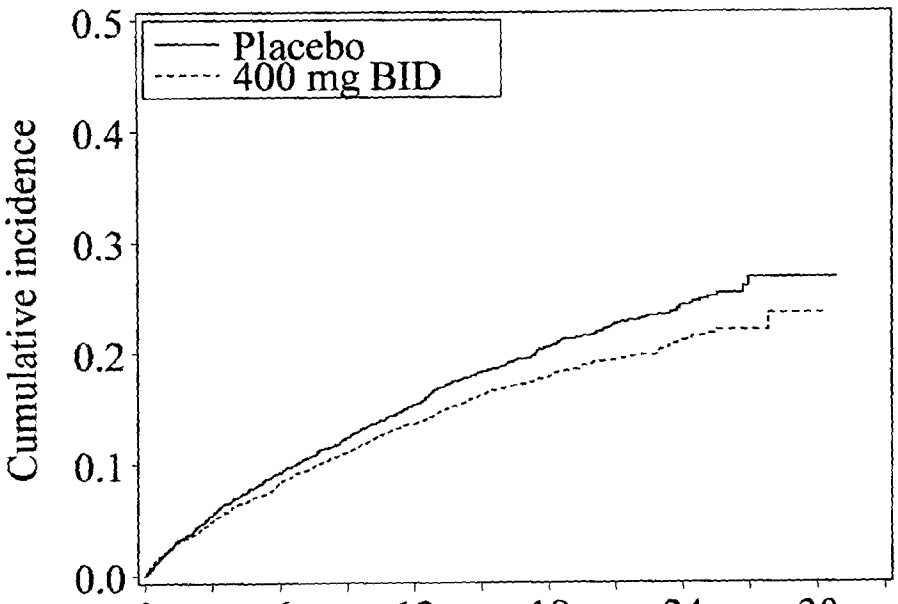
C



Number at risk:

Placebo	2327	2009	1861	1272	474	5
400 mg BID	2301	2121	2011	1374	500	3

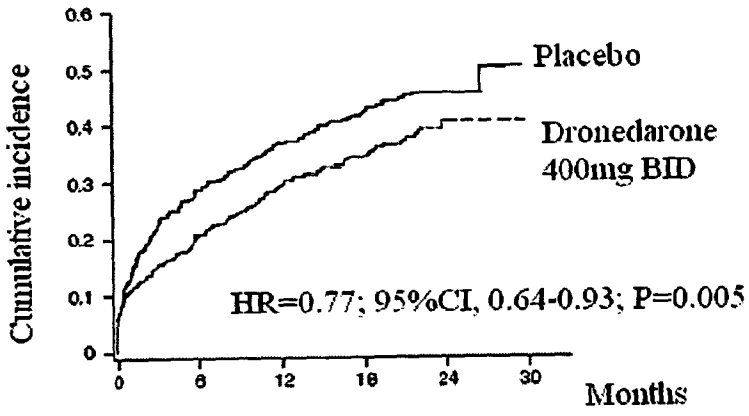
D



Number at risk:

Placebo	2327	2093	1929	1326	497	3
400 mg BID	2301	2096	1957	1338	479	2

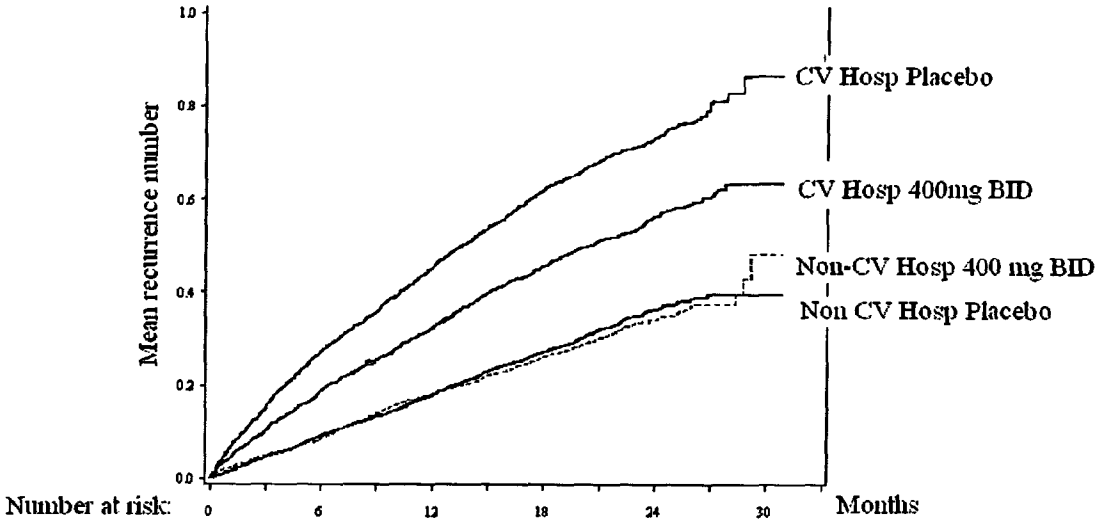
Figure 2.



Number at risk						
Placebo	793	461	328	181	46	0
Dronedarone	673	419	299	163	38	0

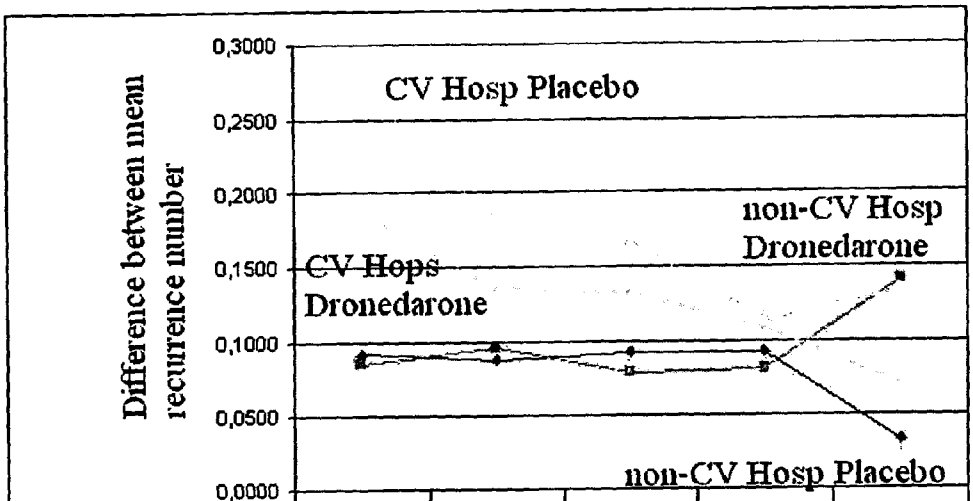
Figure 3.

A



Number at risk:	0	6	12	18	24	30	Months
	2327	2290	2250	1629	636	7	Non CV Hosp Placebo
	2301	2274	2240	1593	615	4	Non CV Hosp 400mg BID
	2327	2290	2250	1629	636	7	CV Hosp placebo
	2301	2274	2240	1593	615	4	CV Hosp 400mg BID

B



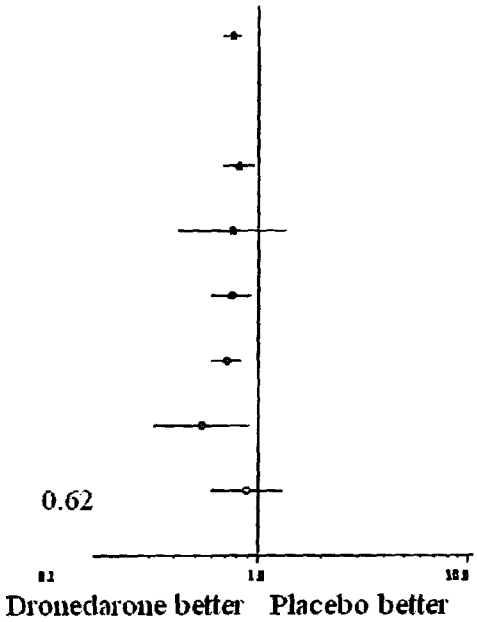
Number at risk in each 6 months period	0-6 months	6-12 months	12-18 months	18-24 months	24-30 months
Non-cardiovascular hospitalization _ Placebo	2290	2250	1629	636	7
Non-cardiovascular hospitalization _ Dronedarone	2274	2240	1593	615	4
Cardiovascular hospitalization _ Placebo	2290	2250	1629	636	7
Cardiovascular hospitalization _ Dronedarone	2290	2240	1593	615	4

Difference of cumulative risk at each time point (%)					
Noncardiovascular hospitalization _ Placebo	+9.11	+8.73	+9.24	+9.22	+3.23
Noncardiovascular hospitalization _ Dronedarone	+8.52	+9.56	+7.91	+8.03	+14.04
Cardiovascular hospitalization _ Placebo	+27.12	+17.91	+16.69	+11.43	+13.31
Cardiovascular hospitalization _ Dronedarone	+18.61	+13.54	+13.31	+10.83	+7.00

Figure 4.

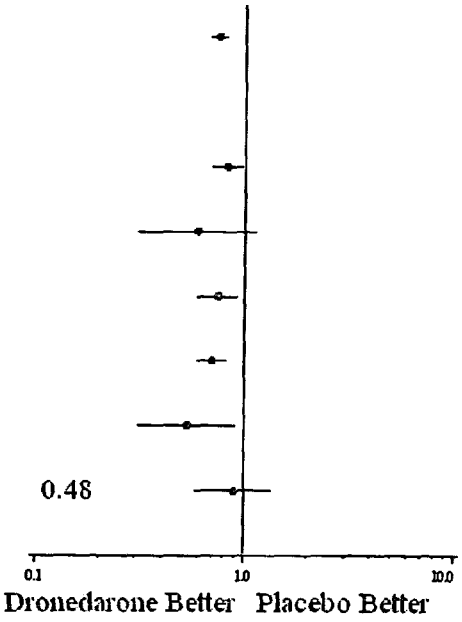
A

Population	N	RR[95%CI](a)	P-value(b)
All ATHENA regions	4628	0.76 [0.69,0.84]	
North America	1403	0.81 [0.69,0.96]	
South America	206	0.75 [0.42,1.37]	
Western Europe	1042	0.75 [0.60,0.94]	
Eastern Europe	1439	0.71 [0.61,0.84]	
Asia	268	0.54 [0.32,0.91]	
Other	270	0.89 [0.60,1.32]	0.62



B

Population	N	RR[95%CI](a)	P-value(b)
All ATHENA	4628	0.74 [0.67,0.82]	
Regions			
North America	1403	0.82 [0.68,0.98]	
South America	206	0.59 [0.31,1.13]	
Western Europe	1042	0.74 [0.59,0.93]	
Eastern Europe	1439	0.70 [0.59,0.82]	
Asia	268	0.53 [0.31,0.91]	
Other	270	0.89 [0.58,1.36]	0.48



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/063000

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/343 A61P43/00 A61P9/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CONNOLLY STUART J ET AL: "Analysis of Stroke in ATHENA: A Placebo-Controlled, Double-Blind, Parallel-Arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter", CIRCULATION, vol. 120, no. 13, September 2009 (2009-09) , pages 1174-1180, XP002664647, ISSN: 0009-7322 abstract page 1179, last paragraph ----- -/--	1-3

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 November 2011	09/12/2011

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/063000

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOHNLOSER STEFAN H ET AL: "Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation", NEW ENGLAND JOURNAL OF MEDICINE, vol. 360, no. 7, February 2009 (2009-02), pages 668-678, XP002664648, ISSN: 0028-4793 abstract page 677, right-hand column, last paragraph --- STEFAN H HOHNLOSER ET AL: "Rationale and Design of ATHENA: A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg Bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in PatiENts with Atrial Fibrillation/Atrial Flutter", JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY, FUTURA PUBLISHING CO., ARMONK, NY, US, vol. 19, no. 1, 1 January 2008 (2008-01-01), pages 69-73, XP007905687, ISSN: 1045-3873, DOI: 10.1111/J.1540-8167.2007.01016.X the whole document ---	1-3
A		1-3