CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-425

MEDICAL/STATISTICAL REVIEW(S)

CLINICAL and STATISTICAL REVIEW

Application Type	NDA
Submission Number	22-425
Submission Code	N 000
Letter Date	June 27, 2008
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Reviewers Names	Gail Moreschi, MD, MPH, FACP Valeria Freidlin, Ph.D.
Review Completion Date	February 18, 2009
Established Name	Dronedarone hydrochloride
(Proposed) Trade Name	Multaq
Therapeutic Class	Antiarrhythmic drug
Applicant	Sanofi-Aventis, U.S.
Priority Designation	P
Formulation	Tablets
Dosing Regimen	400 mg twice a day
Indication	Prevention of CV Hospitalization & Death
Intended Population	Patients with AF/AFL

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1 EXECUTIVE SUMMARY

The ATHENA Study in this NDA 22-425 is a large multinational study in patients with atrial fibrillation/atrial flutter (AF/AFL) intended to provide a reassurance of dronedarone safety in contrast to the prior ANDROMEDA study (NDA 21-913) which showed statistically significantly (25 vs. 12, p=0.027) increased death rate in patients on dronedarone. In ATHENA, the primary composite endpoint of death from any cause or CV hospitalization was highly statistically significant. However, the dronedarone efficacy in the prevention of death from any cause was not established (p=0.176). The composite endpoint was driven mostly by the other component, CV hospitalizations. Note that the need to hospitalize these patients varies from physician to physician and country to country. Most importantly, the study investigates a population which is different from the ANDROMEDA Study, the patients in this ATHENA trial were not as sick as those in the ANDROMEDA Study.

Relative to a claim for preventing CV death in ATHENA study, there are some important issues.

1. According to the pre-specified hierarchical procedure to control global type 1 error at the 5% level, the secondary efficacy endpoint of CV death can be tested only if the first secondary endpoint, death from any cause, is statistically significant at the 5% level. As death from any cause was not statistically significant (p=0.176), the secondary endpoint of CV death should not be tested at all. The analysis for CV death is shown in this review only as exploratory for the completeness of clinical evaluation.

2. There are some issues with the reliability of classifications of CV deaths and the robustness of p=0.03 for the CV death.

For example, in ATHENA, 12 patients with unknown cause of death were classified as having CV death. If 6 placebo patients with unknown cause of death are reclassified as having non-CV death, then the analysis of CV death in ATHENA becomes non-significant: p=0.07 (log-rank test) or p=0.09 (Wilcoxon test). Even if only 4 placebo patients with unknown cause of death are reclassified as non-CV death, then the analysis for CV death in ATHENA already becomes non-significant: p=0.05 (log-rank test) or p=0.065 (Wilcoxon test).

In the ATHENA Study, with a nominal p-value of only p=0.03 for CV mortality and many other issues mentioned above, the statistical significance based on this p-value is inconclusive and may be due to data dredging. Therefore, an additional study is needed to determine whether this finding is real.

Given the risk of death discrepancy between ANDROMEDA and ATHENA studies, these reviewers are concerned regarding the safety of dronedarone. There is a continuum in patients with AF/AFL, they go in and out of congestive heart failure. We feel that the safety of dronedarone presents a problem that the label alone may not be able to cover. The prior studies in NDA 21-913 for rhythm and rate control did establish that patients stay in normal sinus rhythm a little longer than placebo, but their heart rate on dronedarone when exercising is not within the ACC Guidelines.

1.1 Recommendation on Regulatory Action

To be decided after Advisory Committee Meeting March 18, 2009.

1.2 Recommendation on Postmarketing Actions

To be decided after Advisory Committee Meeting March 18, 2009.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This was a prospective, multinational, multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 3 study to evaluate the effects of dronedarone 400 mg BID versus placebo (ratio 1:1) over a minimum treatment and follow-up duration of 12 months in AF/AFL patients. A total of 4300 patients were to be randomized; ultimately, however, 4628 patients were randomized. All patients were to have documentation of at least 1 risk factor together with documentation of having been in both AF/AFL and sinus rhythm within the last 6 months preceding inclusion.

1.3.2 Efficacy

The primary endpoint in NDA 22-425, the composite of death from any cause or CV hospitalization, was highly statistically significant. However, the efficacy of the prevention of death from any cause was not established (p=0.176). The composite endpoint was driven mostly by the other component, CV hospitalizations. Note that the need to hospitalize these patients varies from physician to physician and country to country. Most importantly, the study investigates a population which is different from the prior ANDROMEDA Study, NDA 21-913, which had a statistically significantly (25 vs. 12, p=0.027) higher rate of death from any cause in the patients on dronedarone. Also, the patients in this ATHENA trial were not as sick as those in the prior ANDROMEDA Study.

1.3.3 Safety

Hospitalizations and death were evaluated as part of efficacy. The same side effects were seen as in NDA 21-913: gastrointestinal disorders, EKG QT prolongation, and increased blood serum creatinine. The population evaluated in this NDA was very different from the earlier, sicker population in the ANDROMEDA Study. Of great concern, is that patients in AF/AFL will go into heart failure; they may not do well if on dronedarone as shown in the ANDROMEDA Study.

This drug, if approved, will be utilized chronically. We do not know if ultimately patients will develop the side effects as seen with amiodarone or if they will develop the endocrine, teratogenicity, and carcinogenicity problems as seen in the animal models described in Dr. Hausner's review.

1.3.4 Dosing Regimen and Administration

The sponsor has proposed that the dronedarone dosage is 400 mg twice daily and is to be given with the morning and evening meal. The Agency recommended to the Sponsor early in the development program that various doses be available.

According to Dr. Kumi's original review for NDA 21-913, healthy elderly males have exposures that are about 40 % higher relative to healthy young males; elderly females have exposures that are approximately 30 % higher relative to elderly males; and healthy Asian (Japanese) males have exposures that are about 100 % higher relative to healthy male Caucasians. Also, Dr. Kumi stated in his earlier review that a clear dose-response relationship was shown for QT prolongation in healthy subjects.

1.3.5 Drug-Drug Interactions

The following table is from Dr. Kumi's original review for NDA 21-913.

Table 1: PK/PD drug-drug interaction information

Drug	Classification	Effect of co-administration		
		PD (either or both drugs)	Dronedarone	Other Drug
	Miscellaneous			
digoxin	PGP substrate	NA	NA	↑ 2.5 fold
pantoprazole	decrease gastric pH	NA	↔	NA
theophylline	CYP1A2 substrate	NA	↔	↓ 20 %
	CYP3A function			
rifampicin	inducer	None	↓ 80 %	NA
dilitiazem	weak inhibitor	↑ repolarization time	↑ 60 %	NA
nifedipine	weak inhibitor	Lowered blood pressure	↑ 20 %	NA
grapefruit juice	moderate inhibitor	NA	↑ 3-fold	NA
ketoconazole	strong inhibitor	↑ PR, no effect on QT	↑ ≥ 9-fold	NA
verapamil	Substrate, inhibitor	↑ repolarization time	↑ 40 %	↑ 40 %
nisoldipine	substrate	↔	↔	↑ 100 %
simvastatin	substrate	↔	↔	↑ 4-fold
ethinylestradiol	substrate	NA	NA	↑ 25 %
levonorgestrel	substrate	NA	NA	↑ 18 %
	CYP2C9 function			
losartan	substrate	↑ heart rate	↔	↔
S-warfarin/R-warfarin	substrate	↑ INR by 7 %	↔	↑ AUC 11 %
	CYP2D6 function			
metoprolol	Substrate	↓ cardiac contractility	NA	↑ 60 -150 %
propranolol	substrate	↓ HR, DBP, SBP	↔	↑ 16 to 33 %

1.3.6 Special Populations

Dronedarone has not been studied in the pediatric population. It is contraindicated with Class 4 and probably Class 3 patients in congestive heart failure (CHF). Also, patients with severe liver failure probably should not take dronedarone.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Dronedarone hydrochloride was previously submitted to the FDA as NDA 21-913 in June 2005 for rhythm and/or rate control in patients with atrial fibrillation/flutter. In this earlier submission the Sponsor included five studies for efficacy: DAFNE, ERATO, ADONIS, ERUIDIS and ANDROMEDA. The DAFNE study was dose ranging in which doses greater than 400 mg twice a day did not provide additional efficacy. However, the Agency as early as 1999 advised the Sponsor to provide a dose range rather than a fixed dose; the Sponsor has chosen not to. In the ERATO study, for rate control, the patients with symptomatic permanent atrial fibrillation on dronedarone showed no improvement over placebo in an exercise test.

In the two pivotal studies of NDA 21-913, ADONIS and ERUIDIS, the primary endpoint was rhythm control with the symptoms documented with ECGs relayed via a transtelephonic device. These studies demonstrated that patients taking dronedarone remain longer in normal sinus rhythm compared to placebo; however, their ventricular rate was not lowered to a clinically acceptable range when they reverted to AF/AFL. The studied population was young and in relatively good health. (A substudy, which has not been reviewed, in the current ATHENA trial, revealed no difference in symptoms in patients on dronedarone or placebo).

The ANDROMEDA study in NDA 21-913 investigated patients with a previous episode of "severe" congestive heart failure (CHF). Death and hospitalizations were the clinical endpoints and dronedarone statistically significantly ($p = 0.027$) increased the risk of death from any cause (more than doubled this risk by 113%) and also dronedarone increased ($p = 0.024$) the risk of hospitalizations for acute cardiovascular reasons as compared to placebo. The ANDROMEDA study was terminated early because of this increase in mortality. The Sponsor received a Not Approvable letter on August 26, 2006, which stated "Conceivably, a study of substantial size in the target population could provide reassurance."

This current NDA 22-425 presents the ATHENA Study that was conducted as an outcome study to answer the high mortality rate seen in the ANDROMEDA study. However, the population studied is quite different which will be discussed in our review.

2.2 Currently Available Treatment for Indications

Currently there are no available pharmacological treatments approved for the prevention of hospitalizations and death in patients with atrial fibrillation and atrial flutter. However, there are medications and procedures for AF/AFL that have not been compared to dronedarone in large prospective trials for the prevention of hospitalizations and death in this population.

2.3 Availability of Proposed Active Ingredient in the United States

Dronedarone is a new molecular entity and is not currently available in the United States and is not marketed in any other country.

2.4 Important Issues With Pharmacologically Related Products

The parent compound, amiodarone, originally marketed as an antianginal agent because of its coronary vasodilator properties, was observed to have potent antiarrhythmic effects. It was approved in 1985 for ventricular arrhythmias. Although amiodarone is not FDA approved for AF/AFL, it is clinically utilized for this indication and appears safe for patients with congestive heart failure (CHF). However, the use of amiodarone may have significant adverse reactions which include pulmonary toxicity, thyroid dysfunction, corneal deposits, and phototoxicity.

2.5 Presubmission Regulatory Activity

Please refer to the original NDA 21-913.

2.6 Other Relevant Background Information

NA

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

This review is not available at this time.

3.2 Animal Pharmacology/Toxicology

Dr. Elizabeth Hausner in her review cites the possible endocrine and carcinogen effects of dronedarone. Regarding the endocrine effects: "There were changes in circulating hormone levels, sometimes statistically significant, in both rats and dogs." Also, Dr. Hausner states that the Sponsor agrees with her that the dronedarone is teratogenic and that it has an effect on female cyclicity. These issues the Sponsor states are addressed in the clinical section of this NDA. However, as the Medical Reviewer, I am unable to locate the information the Sponsor refers to. Additionally, there are

histiocytic sarcoma in male mice, mammary adenocarcinomas in female mice and hemangiomas in male rats which are drug related.

The above findings present a clinical concern as this drug, if approved, will be utilized on a chronic basis.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The only clinical trial, the ATHENA Study, was submitted electronically, reviewed and presented here.

4.2 Tables of Clinical Studies

There was only one new clinical trial, the ATHENA study, submitted for review in this NDA

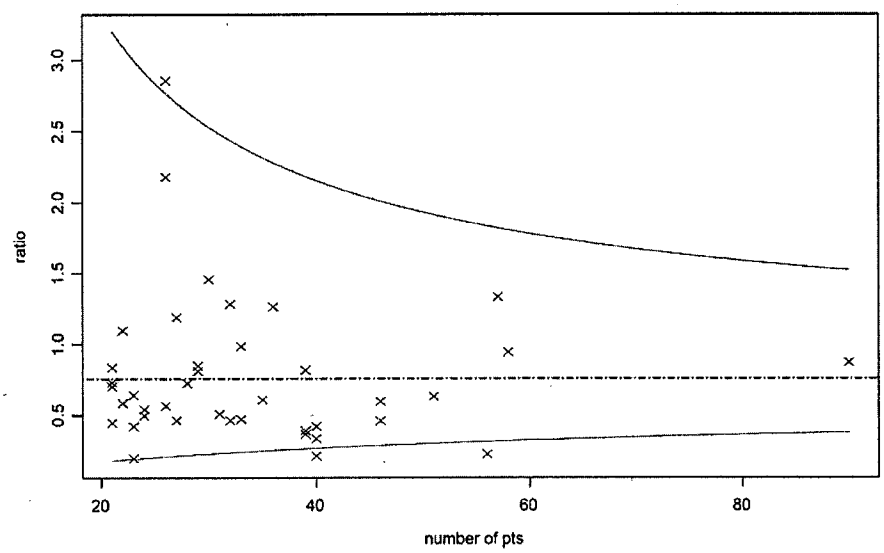
4.3 Review Strategy

This was a joint review done by Dr. Freidlin and Dr. Moreschi together.

4.4 Data Quality and Integrity

Dr. Freidlin did a funnel plot for relative risk for the primary endpoint by center which is shown below.

Figure 1: FDA Analysis of ATHENA Primary Efficacy Results by Large Centers with 95% CI



A large majority of the centers in the trial were outside the United States. The three centers that were recommended for Division of Scientific Investigations' inspection were outliers having outstanding results. The three sites which were inspected were:
1. Site # 203002; Dr. Vratislav Dedek, Czech Republic (N=56, RR=0.22, P=0.03)
2. Site # 643010; Dr. Yuri Shubik, St-Petersburg, Russia (N=23, RR=0.20, p=0.1)
3. Site # 643036; Dr. Vladimir Barbarich, Novosibirsk, Russia (N=40, RR=0.21, p=0.004)

In general, all three sites adhered to the applicable FDA regulations and Good Clinical Practice Guidelines. The study at these sites appears to have been conducted adequately, and the data generated by these sites could be used in support of the indication.

4.5 Compliance with Good Clinical Practices

There is no reason known to these reviewers to doubt that the ATHENA trial was performed under acceptable ethical standards and with Good Clinical Practice.

4.6 Financial Disclosures

The following Clinical Investigators had disclosable financial interests:
1. Dr. Kurt Huber, a Principal Investigator participating in the ATHENA Study, has received payments for speaking fees totaling(b) (6)

2. Dr. Hans-Jürgen Rupprecht, a Principal Investigator participating in the ATHENA Study, has received payments for training fees, consulting fees, and speaking fees totaling(b) (6) .

3. Dr. George Massing, a Subinvestigator participating in the ATHENA Study, has stock holdings totaling more than(b) (6)

4. Dr. George Eyrich, a Subinvestigator participating in the ATHENA Study, has stock holdings totaling more than(b) (6)

5. Dr. Gerald Naccarelli, a Principal Investigator participating in the ATHENA Study, has received payments for Honoraria and consulting engagements totaling(b) (6)

6. Dr. Albert Waldo, a Subinvestigator participating in the ATHENA Study, has received payments for Honoraria and consulting engagements totaling(b) (6)

7. Dr. Eric Prystowsky, a Principal Investigator participating in the ATHENA Study, has received payments for Honoraria and consulting engagements totaling(b) (6) .

8. Dr. Marc Cohen, a Subinvestigator participating in the ATHENA Study, has received payments for Honoraria and consulting engagements totaling (b) (6)

There are five Investigators whose financial disclosure information is missing or incomplete.

5 CLINICAL PHARMACOLOGY

According to Dr. Kumi's review, the new information in this NDA included studies in liver and renal impaired patients. Dr. Kumi recommended that patients with moderately impaired hepatic function should be monitored closely for adverse events and that dronedarone should be contraindicated in patients with severe hepatic impairment unless there is clinical experience. In the study in renal impaired patients, dronedarone plasma concentrations were similar in all patients. Also, creatinine plasma concentrations increased over the first three days, peaking on Day 5. Creatinine plasma concentrations decreased to baseline level three days after treatment was discontinued. The magnitude of creatinine changes was independent of the renal function.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

In the original NDA 21-913, the primary indication was the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL. The secondary objectives included the efficacy on AF/AFL related symptoms and ventricular rate control in case of AF/ AFL recurrence. In this NDA 22-425, the indication is preventing cardiovascular hospitalizations or death from any cause in a population of high risk patients with AF/AFL.

6.1.1 Methods

One study, the ATHENA trial, was submitted in this NDA.

6.1.2 General Discussion of Endpoints

In the prior ANDROMEDA Study, the reduction of death from any cause or hospitalizations for worsening heart failure was investigated, but in patients with recent severe congestive heart failure (CHF). The ANDROMEDA study was terminated early because of an increase in mortality. This present study, the ATHENA Study, was the prevention of cardiovascular hospitalization or death from any cause in patients with AF/AFL. Therefore, the endpoints in these two important trials are different.

6.1.3 Study Design

Study Title: 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 (AF/AFL) (ATHENA Study). (Study EFC5555)

Study centers: 551 active centers in 37 countries: Argentina, Australia, Austria, Belgium, Canada, Chile, China, Czech Republic, Finland, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Malaysia, Mexico, Morocco, Netherlands, New Zealand, Norway, Philippines, Poland, Portugal, Republic of Korea, Russia, Singapore, South Africa, Spain, Sweden, Taiwan, Thailand, Tunisia, Turkey, United Kingdom, United States of America

Principal Investigator: Stefan Hohnloser, MD, J. W. Goethe University, Department of Cardiology, Frankfurt, Germany

Study dates: June 29, 2005 to March 5, 2008

Objectives:
Primary: To assess the efficacy of dronedarone in preventing cardiovascular hospitalizations or death from any cause in a population of high risk patients with AF/AFL.
Secondary: To assess that dronedarone is well-tolerated in this population.

Committees:
1. **The Steering Committee** consisted of 5 cardiologists who:
• provided advice on the scientific and clinical aspects of the study protocol
• had responsibility for the execution and scientific reporting of the study
• had responsibility for the conduct of the study according to good clinical practice
• reassessed the benefit/risk ratio of the Data Monitoring Committee recommendations
• resolved policy issues
• classified all deaths to 4 groups: cardiac/arrhythmic, cardiac/nonarrhythmic, vascular/noncardiac, nonvascular (Protocol Amendment 3)

The **Protocol Amendment 3** dated January 5, 2007 included:
a. Assessment of symptoms using the Bubien and Kay symptom checklist as a substudy.
b. The Steering Committee was recommended to classify all deaths for descriptive purpose as:
• Cardiac, arrhythmic
• Cardiac, nonarrhythmic
• Vascular, noncardiac
• Nonvascular

Reviewer's comment:
It is not clear from this amendment which was dated late into the commencement of the study whether the deaths which had proceeded were described or not. To describe deaths into 1 of 4 categories is different from the adjudication of deaths by a committee as was done in the ANDROMEDA Study.

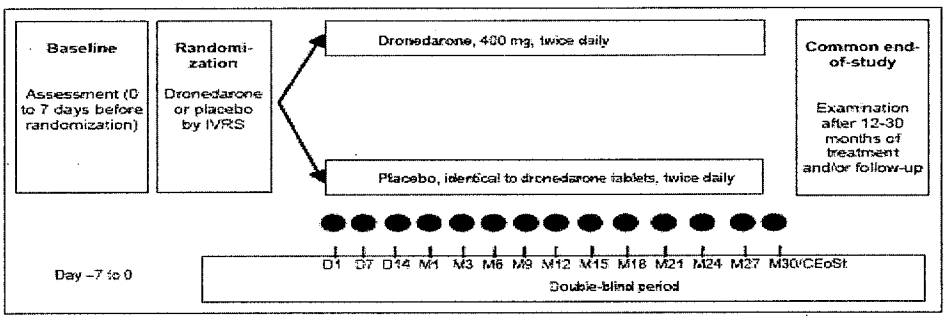
2. **Data Monitoring Committee** consisted of 2 cardiologists and a biostatistician. They performed the ongoing monitoring to provide:
• The safety of patients in the clinical trial
• The ethical conduct of the trial
• Ensure the highest integrity of the trial
• Oversee the interim analysis
• Carry out a review of efficacy and safety data at regular intervals
• Request additional data and/or review meetings as necessary
• Make recommendations to the Steering Committee concerning the conduct of the study

The S-Clinica Randomization Center, Brussels, Belgium, provided randomization of the patients and management of the study drugs.

Study Description: This was a prospective, multinational, multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase 3 study to evaluate the effects of dronedarone 400 mg BID versus placebo (ratio 1:1) over a minimum treatment and follow-up duration of 12 months in AF/AFL patients. A total of 4300 patients were to be randomized. All patients were to have documentation of at least 1 risk factor together with documentation of having been in both AF/AFL and sinus rhythm within the last 6 months preceding inclusion.

Patients could be randomized in the study while in sinus rhythm if conversion had occurred either spontaneously or following a procedure. Patients could also be randomized while in AF/AFL, and then they could undergo cardioversion after appropriate anticoagulation. Patients first entered a screening period for a maximum of 7 days. After randomization they were to be followed until the common study end date, which was to be 1 year after the last patient was randomized and therefore the minimum follow-up time was to be 12 months.

Fig. 2: Study design



Patients were allocated to dronedarone 400 mg BID or placebo according to a central randomization. A placebo was selected by the Sponsor because of the absence of a recognized first-line therapy for the prevention of cardiovascular hospitalization or death in AF/AFL patients.

Medical Reviewer's comment:
Although there are no "first-line therapies" approved explicitly for the prevention of hospitalization or death in AF/AFL patients, there are approved medications and procedures which may prevent hospitalizations and death in these patients. This relatively large study may have been a missed opportunity for a comparative-research study which is in demand today.

Inclusion criteria:
Patients could be either in sinus rhythm, or in AF/AFL to be eligible. Originally, the following criteria had to be fulfilled:
1. One or more of the following risk factors must be present at baseline:
Age equal to or greater than 70 years

Hypertension (taking 2 different classes of drugs)
Diabetes
Prior cerebrovascular accident or systemic embolism
Left atrium diameter greater than or equal to 50 mm by M-mode echocardiography
Left ventricular ejection fraction less than 0.40 by 2D-echocardiography
2. Availability of 1 ECG within the last 6 months showing that the patient was or is in AF/AFL
3. Availability of 1 ECG within the last 6 months showing that the patient was or is in sinus rhythm

Reviewer's comment:
The patients' EKGs were not provided with the case report forms in this NDA.

The Steering Committee recommended an increase in the minimum age for recruitment, and an increase in the threshold for age as an additional risk factor, in order to prevent a lowering of the event rate and to better match the baseline characteristics of the ATHENA patients with those of studies of the AFFIRM study. Accordingly, in Amendment 1 approved on March 8, 2006 (when 1993 patients had been randomized) and was to be implemented on March 25, 2006, the inclusion criteria were changed to:
1. Patients aged 75 years or older are eligible with or without additional risk factors
Or
A minimum age of 70 years with one or more of the following risk factors must be present at baseline:
Hypertension (taking antihypertensive drugs of at least 2 different classes)
Diabetes
Prior cerebrovascular accident (stroke or transient ischemic attack) or systemic embolism
Left atrium diameter greater than or equal to 50 mm by M-mode echocardiography
Left ventricular ejection fraction less than 0.40 by 2D-echocardiography
2. Availability of one 12-lead ECG within the last 6 months, showing that the patient was or is in AF/AFL
3. Availability of one 12-lead ECG within the last 6 months showing that the patient was or is in sinus rhythm

Reviewer's comment:
The Sponsor states that with the change in age they were trying to "better match the baseline characteristics of the ATHENA patients with those of studies of the AFFIRM study". However, there are significant differences in the design of ATHENA study and the AFFIRM trial which include the AFFIRM trial was exclusively in North America, the primary end point was all cause mortality, an inclusion criteria was the ability to be anticoagulated, there were fewer women than men, and 23% had a history of CHF.

Exclusion criteria:
1. Unable to provide informed consent.
2. Any serious non-cardiovascular illness which would limit survival including cancer with metastasis and organ transplantation requiring immune suppression.
3. Pregnant and breastfeeding women.
4. Previous (2 preceding months) or current participation in another clinical trial.

6. Previous participation in this trial

Exclusion Criteria related to a cardiac condition:
"7. Patients in permanent atrial fibrillation
8. Patients in unstable hemodynamic condition such as acute pulmonary edema within 12 hours prior to start of study medication; cardiogenic shock; treatment with intravenous pressor agents; patients on respirator; congestive heart failure of stage New York Heart Association (NYHA) IV within the last 4 weeks; uncorrected, hemodynamically significant primary obstructive valvular disease; hemodynamically significant obstructive cardiomyopathy; a cardiac operation or revascularization procedure within 4 weeks preceding randomization
9. Planned major noncardiac or cardiac surgery or procedures including surgery for valvular heart disease, coronary artery bypass graft, percutaneous coronary intervention, or on urgent cardiac transplantation list
10. Acute myocarditis or constrictive pericarditis
11. Bradycardia <50 beats per minute (bpm) and/or PR-interval ≥0.28 sec on the last 12-lead ECG
12. Significant sinus node disease (documented pause of 3 seconds or more) or second or third degree atrioventricular (AV) block unless treated with a pacemaker"

Reviewer's comment:
These above cardiac exclusions make this study population quite different from the prior Andromeda patients. This study excluded very sick patients.

Exclusion Criteria related to concomitant medications:
"13. Need of a concomitant medication that is prohibited in this trial, including the requirement for Vaughan-Williams Class I and III antiarrhythmic drugs, that would preclude the use of study drug during the planned study period"

Exclusion Criteria related to laboratory abnormalities:
"14. Plasma potassium <3.5 mmol/L (as antiarrhythmic drugs can be arrhythmogenic in patients with hypokalemia, this must be corrected prior to randomization).
15. A calculated glomerular filtration rate (GFR) at baseline <10 mL/min using the Cockroft Gault formula (Protocol Amendment 1)"

Reviewer's comments:
Within the Exclusion Criteria several items are noteworthy. They have excluded patients with cancer however, many died from cancer. Therefore, of clinical concern is what general work-up was carried out by each of the study practitioners prior to enrolling their patients. Also, because they excluded the patients in permanent atrial fibrillation, they have excluded a large percent of AF patients from this study.

Study drug administration: The first study drug intake was to take place as soon as possible after randomization. Both dronedarone and placebo were to be administered as 1 tablet in the morning during or shortly after breakfast and 1 tablet in the evening during or shortly after dinner.

Reviewer's comment:
It is very interesting to note that no comment is made regarding the fact that the level of the drug is higher in women than men and is also higher after a fatty meal. The outcome based on the differences of the sexes and diets in various countries could be affected. Also, no attention is paid to a history of liver disease which also may affect drug blood levels. This study did not provide any pharmacokinetic data.

Instructions related to dronedarone and creatinine: The following information was provided to Investigators in their brochure: "It has been documented that within 1 to 2 weeks following the start of treatment with dronedarone a moderate (10% to 15%) increase in creatininemia may be seen. This increase is rapidly reversible during the week following dronedarone discontinuation. This increase is not due to a decrease in glomerular filtration rate, but to inhibition of creatinine secretion at the tubular level."

Therefore, if a moderate asymptomatic increase in creatininemia was observed after beginning of treatment the Investigator was advised to use clinical judgment, taking into account that this may be expected with dronedarone. Furthermore, it was recommended, depending on patient condition and symptoms, that an increase in creatininemia concentration should not necessarily lead to specific actions such as discontinuation of treatment with ACE inhibitors or AII receptor antagonists. In case of doubt it was recommended that the Investigator consider temporary interruption of study medication administration, with reintroduction of study medication as soon as possible once any concern was resolved."

Prior and concomitant therapy: Patients included in the study could receive the usual standard therapy for their cardiac condition according to published guidelines.

Not permitted concomitant therapy: Vaughan-Williams Class I and III antiarrhythmic drugs were not to be administered simultaneously with the investigational product. Amiodarone administration was to be permanently stopped for at least 4 weeks prior to randomization. All concomitant drugs that could cause torsades de pointes were contraindicated; including some phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides.

Given the involvement of the CYP450 3A4 cytochrome in the metabolism of dronedarone, the concomitant use of grapefruit juice and all potent inhibitors of CYP450 3A4, such as ketoconazole, itraconazole, nefazodone, ritonavir, cyclosporin, and troleandomycin, were prohibited. Other drugs, which are CYP450 3A4 substrates and have a narrow therapeutic margin, were to be avoided.

Permitted concomitant therapy:
• Calcium antagonists with depressant effects on the sinus and AV node (e.g., diltiazem and verapamil) could be used with caution.
• Some calcium antagonists such as diltiazem and verapamil are moderate CYP3A4 inhibitors, but their coadministration with dronedarone resulted in a limited interaction on dronedarone only (1.7-fold and 1.4-fold increase in dronedarone exposure, respectively). Nisoldipine, which is a weak

CYP3A4 inhibitor, increased dronedarone exposure only slightly (1.2-fold). If necessary, calcium antagonists could be started concomitantly with the investigational product. In such a case low doses of the calcium antagonist were to be given first and increased after ECG verification of good tolerability.
• Beta-blockers could be used with caution (except sotalol, which was contraindicated). As potentiation of the depressant effects was possible, beta-blockers could be started concomitantly with the investigational product, but with a low dose that would only be increased after ECG verification of tolerability.
• Digoxin could be coadministered, if necessary, with caution and the plasma levels were to be monitored locally. An interaction study had shown that dronedarone increased plasma levels of digoxin. Therefore it was expected that patients would require and tolerate lower than usual doses of digoxin.

Oral anticoagulation was recommended as per current guidelines. The international normalized ratio was to be monitored locally.

Cardioversion: Electrical cardioversion could be performed while on study drug in case of AF/AFL recurrence without prompt spontaneous conversion. Cardioversion was to be considered unsuccessful if sinus rhythm was not restored for at least 10 consecutive minutes after 2 shocks at the highest energy of the device. The standard anticoagulation guidelines were to be followed before cardioversion was performed. If the patient was on digoxin, it was to be withheld and the digoxin plasma level assessed.

Treatment compliance: Compliance was to be assessed based on counts of tablets taken and from packs of the investigational product returned by the patient at routine clinical follow-up visits.

Study Assessments: The following table defines the clinical studies completed at various time frames.

Table 2: Study flow chart – treatment and follow-up

	Treatment / Follow-up phase														
Evaluation Day	Baseline D-7 to D1	D7 ± 2D	D14 ± 5D	M1 ± 7D	M3 ± 14D	M6 ± 14D	M9 ± 14D	M12 ± 14D	M15 ± 14D	M18 ± 14D	M21 ± 14D	M24 ± 14D	M27 ± 14D	M30 ± 14D	Final follow-up visit (common study end date up to +14D)
Design															
Inclusion/exclusion criteria	X*														
Cardiovascular history	X*														
Medical history	X*														
Informed consent/demography	X*														
Prior medication history	X*														
Clinical examination with NYHA for CHF	X*	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**
2D echocardiography***	X*														
IVRS calls	X*					X		X		X		X		X	X
Randomization	X														
Treatment															
IP dispensing	X		X	X	X	X	X	X	X	X	X	X	x	X	
Study drug administration	———														X
Compliance		X	X	X	X	X	X	X	X	X	X	X	X	x	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	x	X
Vital signs															
Weight and height	X*														
Supine blood pressure	X*	X	X	X	X	X	X	X	X	X	X	X	X	x	X
Efficacy															
Endpoints		X	X	X	X	X	X	X	X	X	X	X	X	x	X

	Treatment / Follow-up phase														
Evaluation Day	Baseline D-7 to D1	D7 ± 2D	D14 ± 5D	M1 ± 7D	M3 ± 14D	M6 ± 14D	M9 ± 14D	M12 ± 14D	M15 ± 14D	M18 ± 14D	M21 ± 14D	M24 ± 14D	M27 ± 14D	M30 ± 14D	Final follow-up visit (common study end date up to +14D)
Safety															
12-lead ECG	X*	X	X	X	X	X		X		X		X		x	X
AE/SAE	X*	X	X	X	X	X	X	X	X	X	X	X	X	x	X
Local laboratory tests	Biochem*, β-HCG*	Biochem	Biochem	Biochem	Biochem	Biochem		Biochem		Biochem		Biochem		Biochem	Biochem

* Prior to randomization
** Only in case of hospitalization
*** 2D- and M mode echocardiography in the month preceding randomization (data obtained from echocardiography taken prior to informed consent to the ATHENA study can be used if that investigation was performed for other reasons than baseline evaluation for the study)
****A questionnaire about symptoms of AF/AFL was to be completed either at Month 12 or Month 18 visit (whichever visit was first after implementation of the substudy).
Biochem: Potassium, Creatinine, Urea, Digoxin, INR

Baseline assessments:
Cardiovascular history: Past cardiovascular history was recorded. Prespecified categories for cardiovascular history terms were defined as follows:

- Coronary artery disease: documented history of acute myocardial infarction and/or significant (≥70%) coronary artery stenosis and/or history of a revascularization procedure (percutaneous transluminal coronary angioplasty, stent implantation in a coronary artery, coronary artery bypass graft, etc) and/or a positive exercise test and/or positive nuclear scan of cardiac perfusion
- Ischemic dilated cardiomyopathy: clinically significant left ventricular dilatation secondary to coronary artery disease
- Non-ischemic dilated cardiomyopathy: clinically significant left ventricular dilatation not secondary to coronary artery disease
- Hypertrophic cardiomyopathy: ventricular hypertrophy not secondary to hypertension
- Rheumatic valvular heart disease: typical rheumatic valvular lesions present at baseline echocardiography and/or past surgery for rheumatic valvular heart disease

• Non-rheumatic valvular heart disease: screening echocardiography confirmed clinically relevant non-rheumatic valvular abnormalities including true mitral valve prolapse
• Congenital heart disease
• Tachycardias: ventricular rate above 100 beats per minute
• Supraventricular tachycardia: rapid rhythm of the heart in which the origin of the electrical signal was either the atria or the AV node
• Sustained ventricular tachycardia: ventricular tachycardia that lasted more than 30 seconds
• Ventricular fibrillation
• Hypertension: current treatment with an antihypertensive agent for elevated blood pressure and/or supine diastolic blood pressure >90 mmHg and/or supine systolic blood pressure >140 mmHg

Disease characteristics: the following 3 categories were defined in the statistical analysis plan:
• Structural heart disease: coronary heart disease and/or ischemic dilated cardiomyopathy and/or non-ischemic dilated cardiomyopathy and/or rheumatic valvular heart disease and/or ventricular ejection fraction <45% and/or history of congestive heart failure
• Lone atrial fibrillation: patients without hypertension and without structural heart disease
• Heart failure criteria: considered present if the patient had left ventricular ejection fraction <35% or NYHA class I or above

Cardiovascular examination: Cardiovascular examination performed at screening and then in case of hospitalization, and was to include the NYHA class assessment for congestive heart failure. These data were to be reported in the case report form.

2D-echocardiography: Echocardiography was to be performed at screening, or within the month preceding randomization, and included left atrial diameter (M-mode) and left ventricular ejection fraction (2D-echocardiography) as well as the presence/absence of clinically significant valvular abnormalities.

Efficacy assessments: The efficacy endpoints were to be assessed by the individual Investigators (usually the treating physician) who classified all hospitalizations or deaths as cardiovascular or noncardiovascular on the case report forms. Death from any cause and cardiovascular hospitalization (both primary endpoints) were classified according to prespecified categories. The primary efficacy variable was the time from randomization to the first cardiovascular hospitalization or death from any cause as assessed by the individual Investigator.

Reviewer's comment:
This study differs from the Andromeda Study where both hospitalizations and death were adjudicated by the Critical Events Committee.

Cardiovascular hospitalization: This was defined as any unplanned hospitalization, an admission with an overnight stay in a hospital covering at least 2 consecutive dates. This admission was categorized by the Investigator who was generally also the providing physician and was based on the cause, either cardiovascular or noncardiovascular. The prespecified main causes for cardiovascular hospitalization were:

- Atherosclerosis related (if not otherwise specified)
- Myocardial infarction or unstable angina
- Stable angina pectoris or atypical chest pain
- Syncope
- Transient ischemic attack (TIA) or stroke (except intracranial hemorrhage)
- Atrial fibrillation and other supraventricular rhythm disorders
- Nonfatal cardiac arrest
- Ventricular arrhythmia, subclassified as torsades de pointes, ventricular extrasystole, ventricular fibrillation, ventricular tachycardia (non-sustained and sustained ventricular tachycardia), or other ventricular arrhythmia
- Cardiovascular surgery except cardiac transplantation
- Cardiac transplantation
- Implantation of a pacemaker, implantable cardioverter defibrillator, or any other cardiac device
- Transcutaneous coronary, cerebrovascular, or peripheral procedure
- Blood pressure related (hypotension; hypertension, except syncope)
- Cardiovascular infection
- Major bleeding (requiring 2 or more units of blood or any intracranial hemorrhage)
- Pulmonary embolism or deep vein thrombosis
- Worsening congestive heart failure (CHF), including pulmonary edema or dyspnea of cardiac origin (worsening of CHF was to be understood as including the new onset of CHF as well as reoccurrence of CHF)

Hospitalizations starting prior to randomization, or scheduled prior to randomization (such as an electrical cardioversion) were to be considered planned and were not reported unless the hospitalization was prolonged.

Reviewer's comment:
The definition of what constitutes a hospitalization as defined above certainly would vary from physician to physician, hospital to hospital, and country to country. It is unclear if a patient remained in an ER or a cardiac unit but not on a hospital floor if this is an admission. Many of the above listed hospitalizations, such as syncope or pacemaker implantation, would vary as to whether the patient remained in the hospital for 2 nights from physician to physician and might even be dependent on the patient's insurance.

Death: Death was defined as any death during the study period. For descriptive purpose, deaths were categorized by the Investigator (treating physician) as cardiovascular or noncardiovascular. The prespecified main causes for cardiovascular death were:
- Aortic dissection/aneurysm
- Cardiac tamponade
- Cardiogenic shock
- CHF
- Death during a cardiovascular transcutaneous interventional procedure or cardiovascular surgical intervention
- Hemorrhage (except cardiac tamponade)
- Myocardial infarction or unstable angina (including complications of myocardial infarction,

except arrhythmias)
• Pulmonary or peripheral embolism
• Stroke
• Sudden cardiac death (e.g., unwitnessed death or documented asystole)
• Ventricular arrhythmia, subclassified as torsades de pointes, ventricular extrasystole, ventricular fibrillation, ventricular tachycardia (non-sustained and sustained ventricular tachycardia), or other ventricular arrhythmia
• Unknown cause

Reviewer's comment:
Under the above definition, patients who bled to death from their cancer were classified as vascular and therefore cardiac death.

Additionally, for descriptive purposes only, the Steering Committee classified deaths into 1 of the following 4 categories (This occurred approximately 2 years after the study began, with Protocol Amendment 3):
• Cardiac/arrhythmic
• Cardiac/nonarrhythmic
• Vascular/noncardiac
• Nonvascular

Reviewer's comment:
Again, there appears to be a significant difference between adjudication of hospitalizations and death which was done in the ADROMEDA Study and pre-defined descriptive classification by individual treating Investigators as was done in this ATHENA study.

Secondary efficacy variables:
• Death from any cause
• First cardiovascular hospitalization
• Cardiovascular death

Adverse events: According to the protocol, cardiovascular hospitalizations and death from cardiovascular causes were waived from expedited reporting. For deaths from non-cardiovascular causes, as part of the primary efficacy endpoint, the randomization code was not to be broken by the Sponsor when expedited reporting to Health Authorities was required. Recurrences of AF/AFL and AF/AFL-related symptoms were not to be reported either as adverse events or as serious adverse events.

Reviewer's comment:
It is interesting that symptoms were not reported and yet a substudy on these symptoms was conducted in some of the ATHENA patients and revealed that there was no difference between patients on placebo and those treated with dronedarone.

Vital signs:
Systolic blood pressure and diastolic blood pressure were measured after the patient rested for

3 minutes in the supine position. Height and weight were measured at baseline only.

Reviewer's comment:
Taking the blood pressure after 3 minutes in the supine position is not considered the standard procedure.

Pharmacokinetic assessments were not done in this study.

End of Study and Removal of Patients from Therapy:
The study planned to enroll 4300 patients (4628 patients were randomized). Study common end was to be one year after the last patient was randomized (i.e., on December 30, 2007).

Patients could withdraw from the treatment phase if they decided to do so. Even if treatment with the study drug was stopped, every attempt was to be made to ensure that the patient was following each of the planned study visits until the common study end date.

If a patient was potentially lost to follow-up before he/she had completed the treatment and/or follow-up period, Investigators were asked to make every effort to re-contact the patient; if unsuccessful, Investigators were asked to make every effort to provide the patient's vital status and if he/she had been hospitalized for cardiovascular or non-cardiovascular reasons until the common study end date.

Patients who did not remain in the study until the common study end and who did not die were considered as lost to follow up based on the "End of Study" or "last contact" form; they were summarized by treatment group.

In case of a transient interruption of treatment, treatment could be started again if restarting treatment was considered safe for the patient (interruption was not due to a possibly drug-related adverse event).

Statistical Methods:
All statistical tests were performed at the 5% (2-sided) significance level.
Efficacy analyses were based on all randomized patient population that consisted of those patients who were randomized regardless of the actual study drug intake or the patient's study protocol compliance.

The efficacy analysis considered all assessments from randomization to the end of study date, which was defined as the final follow-up visit/last contact date or the date of death, whatever came first.

The primary analysis was the comparison of the time from randomization to the primary endpoint between the 2 treatment groups using a 2-sided log-rank asymptotic test.

Reviewer's Comment:
As many deaths occurred at the end of the study, this review also looked at the results of the Wilcoxon test which places more weight on the larger survival times.

Cumulative incidence functions in each treatment group were calculated and plotted using nonparametric Kaplan-Meier estimate. The corresponding 95% CI was computed at each scheduled time-point of the protocol using Greenwood's variance estimation.

The hazard ratio with 95% CI was estimated using a Cox model with treatment group as the only factor. Acceptability of proportional hazards assumption was checked graphically, plotting the natural logarithm of the cumulative hazard Kaplan-Meier estimate versus the natural logarithm of time for each treatment group.

Secondary efficacy endpoints:
In order to protect the global type I error of 5%, a hierarchical procedure was to be applied to testing of secondary efficacy endpoints. "All deaths whatever the cause" was to be tested first. If "all deaths" endpoint is not statistically significant at the 5% significance level, then no further testing of the secondary endpoints can be performed. If "all deaths" endpoint is statistically significant at the 5% significance level, then testing of "cardiovascular hospitalization" was to be performed, and then "cardiovascular death" was to be tested lastly. The same analysis approach as for the primary endpoint was used for all secondary endpoints.

Determination of sample size:
Based on the pooled results of EFC4788 (ADONIS) and EFC3153 (EURIDIS) studies, around 1850 patients per group (3700 in total) were originally considered necessary to evaluate the protocol-specified primary objective.

During the course of the study, following blinded review of the overall death event rate, the incidence of death was less than expected. An increase in sample size to 4300 patients (2150 per group) was implemented by Protocol Amendment 2. Based on the historical inclusion rate and the ability to identify the 600 additional patients, the inclusion period was extended to the end of December 2006.

Reviewer's comments:

1. *The ATHENA study did not stop on December 30, 2007, as was to be done according to the Protocol Amendment 2, one year after the last patient was randomized. Instead the study was stopped on March 5, 2008. Five deaths on placebo and one death on dronedarone were recorded after December 30, 2007.*
2. *The ATHENA study randomized 4628 patients instead of randomizing 4300 patients (as was specified in the Protocol Amendment 2).*

Interim analysis:
A formal interim analysis on the primary efficacy endpoint was to be performed when the half (485) of the estimated primary endpoints have occurred. Early termination for favorable results or futility was to be considered. The analysis of efficacy was to be done using a Haybittle-Peto type boundary for alpha spending function to maintain the global alpha at 5% level (alpha=0.0001 for interim analysis and 0.05 for the final analysis).

Amendments to the Study Protocol:
There were 3 amendments to the protocol, which are summarized in the following table.

Table 3: Summary of protocol amendments

Amendment number	Date of sponsor approval	Summary of amendment
1	08 Mar 2006	Inclusion criterion 1 was modified at the recommendation of the Steering Committee to increase the minimum age for recruitment and to increase the threshold for age as an additional risk factor. An interim analysis was planned to prematurely stop the study in case of overwhelming efficacy or futility. The assessment of kidney function was harmonized to the assessment of urea and a conversion for blood urea nitrogen was provided. The Cockcroft-Gault formula for glomerular filtration rate was corrected.
2	25 Aug 2006	The sample size was increased to 4300 patients, and the global inclusion period was consequently increased to 1.5 years and the estimated duration of the study was increased to 2.5 years.
3	05 Jan 2007	A substudy for the assessment of symptoms according to the Bubien and Kay scale was added. Classification of all deaths by the Steering Committee for descriptive purposes was also added.

Amendment 1, which modified the minimum age and risk factor criteria for patient inclusion, was approved on March 8, 2006 when 1993 patients had already been randomized. It was to be implemented on March 25, 2006.

Changes to the analyses, made after the blind was broken:
The median study duration was calculated. In order to further investigate the effect of dronedarone on the number of cardiovascular death during the on-study period, the time from randomization to sudden death as well as the time from randomization to death due to stroke were analyzed with the same analysis used in the primary analysis of the primary endpoint.

In order to further investigate the homogeneity of the effect of pre-defined endpoints (time to cardiovascular hospitalization or death from any cause, all deaths, cardiovascular hospitalization, cardiovascular death) in consideration of baseline characteristics and medications, hazard ratios (labeled in tables as "relative risk") with 95% CI were calculated for each level of the following baseline parameters, and the interaction between the treatment and each baseline covariate was calculated by comparing the model without interaction with the one containing the interaction using the likelihood ratio test:

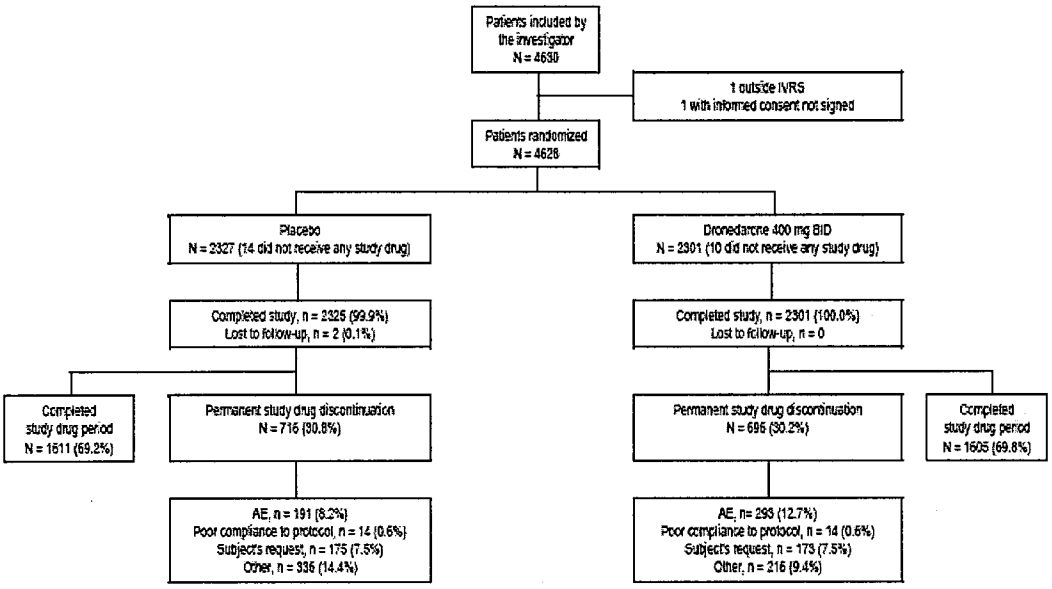
- Age (<65, [65-75[, ≥75)
- Weight (<60, [60; 100[≥100]
- Gender [male (M), female (F)]
- Factor combining age and gender (F+age≥75, F+age<75, M+age≥75, M+age<75)
- Presence of AF/AFL as per stratification factor (Yes, No)
- Hypertension (Yes, No)
- Structural heart disease (Yes, No)
- Left ventricular ejection fraction (LVEF) <35% or Class I or above (Yes, No)
- LVEF (<35%, ≥35%)
- Left atrium diameter (≤40mm, >40mm)
- Diabetes (Yes, No)
- Creatinine clearance (<30 mL/min, [30-50[mL/min, [50-80[mL/min, ≥80 mL/min)

- ACE or AII receptor antagonists (Yes, No)
- Beta blocking agents (Yes, No)
- Digitalis (Yes, No)

Reviewer's comment:
Whether a patient was adequately anticoagulated is an important baseline parameter that was not calculated into interaction using the above likelihood ratio test.

Study Patients: A total of 4630 patients were randomized by the investigators, 2327 patients were randomized to placebo and 2301 to dronedarone. Two patients were excluded; twenty-four never received study drug: 14 patients in the placebo group and 10 in the dronedarone group. The following figure describes the disposition of the patients.

Figure 3: Disposition of patients



N = population size; n = sample size; IVRS = interactive voice response system; BID = twice daily; AE = adverse event

The following table shows the percentage of patients in each category of the inclusion criteria.

Table 4: Number (%) of patients by category of inclusion criteria

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Age >= 75 years with or without any additional risk factors or a minimum age of 70 years with one or more additional risk factors	1610 (69.2%)	1594 (69.3%)	3204 (69.2%)
Hypertension (taking antihypertensive drugs at least two different classes).	1192 (51.2%)	1212 (52.7%)	2404 (51.9%)
Diabetes.	324 (13.9%)	333 (14.5%)	657 (14.2%)
Prior cerebrovascular accident (stroke or transient ischemic attack) or systemic embolism.	236 (10.1%)	233 (10.1%)	469 (10.1%)
Left atrium diameter greater than or equal to 50 mm by M-mode echocardiography.	343 (14.7%)	329 (14.3%)	672 (14.5%)
Left ventricular ejection fraction less than 0.40 by 2D-echocardiography.	139 (6.0%)	102 (4.4%)	241 (5.2%)
Age in [70-75[years without additional risk factor	51 (2.2%)	43 (1.9%)	94 (2.0%)
Age less than 70 years with additional risk factor	660 (28.4%)	662 (28.8%)	1322 (28.6%)
Hypertension (taking antihypertensive drugs at least two different classes).	574 (24.7%)	546 (23.7%)	1120 (24.2%)
Diabetes.	141 (6.1%)	142 (6.2%)	283 (6.1%)
Prior cerebrovascular accident (stroke or transient ischemic attack) or systemic embolism.	64 (2.8%)	83 (3.6%)	147 (3.2%)
Left atrium diameter greater than or equal to 50 mm by M-mode echocardiography.	135 (5.8%)	148 (6.4%)	283 (6.1%)
Left ventricular ejection fraction less than 0.40 by 2D-echocardiography.	47 (2.0%)	53 (2.3%)	100 (2.2%)
No inclusion criteria ticked	6 (0.3%)	2 (<0.1%)	8 (0.2%)

Patients aged 70 to 75 years without additional risk factors and those aged < 70 years with additional risk factors were allowed to be randomized before the implementation of Protocol Amendment 1

Premature permanent treatment discontinuation: The following table shows the proportion of patients who discontinued treatment prematurely, placebo (716 of 2327, 30.8%) and dronedarone (696 of 2301, 30.2%), and was similar for both groups. More patients in the dronedarone group compared with the placebo group discontinued treatment due to adverse events which were mainly gastrointestinal. Patients in the placebo group discontinued for "other reason," which was related to AF/AFL recurrence or the need for an alternative antiarrhythmic medication.

Table 5: Number (%) of patients who prematurely discontinued treatment

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Patients who prematurely discontinued the study drug	716 (30.8%)	696 (30.2%)
Main reason for premature discontinuation		
Adverse event	191 (8.2%)	293 (12.7%)
Poor compliance to protocol	14 (0.6%)	14 (0.6%)
Subject's request	175 (7.5%)	173 (7.5%)
Other reason	336 (14.4%)	216 (9.4%)

Temporary treatment discontinuation: The number of patients who temporarily discontinued their study drug was greater in the placebo group (185 of 2327, 8.0%) than in the dronedarone group (133 of 2301, 5.8%) due to a condition that required other treatment. More patients in the dronedarone group compared to the placebo group temporarily discontinued their study drug due to an adverse event or an increase in creatinine. This is shown in the following table:

Table 6: Number (%) of patients who temporarily discontinued study drug

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Number of patients who temporarily discontinued study drug	921 (39.6%)	928 (40.3%)
Reason for stopping temporarily study drug		
Patient forgot treatment	187 (8.0%)	194 (8.4%)
Condition requiring other treatment	185 (8.0%)	133 (5.8%)
Adverse event	301 (12.9%)	382 (16.6%)
Creatinine increase	11 (0.5%)	39 (1.7%)
Other reason	468 (20.1%)	457 (19.9%)

Note : a patient can be counted more than once in several reasons

The following table shows that only a few patients in either treatment groups stopped their ACE inhibitors or AII receptor antagonists, therefore following the protocol recommendations on the management of creatininemia.

Table 7: Summary of temporary discontinuation of study drug due to creatinine increase

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Number (%) of patients with at least one discontinuation due to creatinine increase	11 (0.5%)	39 (1.7%)
Level of creatinine (umol/L) just before the 1st stop for creatinine increase		
n	11	39
Mean (SD)	195.0 (52.3)	166.1 (65.2)
Median	186	149
Min - Max	134 - 274	74 - 354
Change from baseline of creatinine level(umol/L)		
n	11	37
Mean (SD)	48.5 (41.8)	47.2 (48.3)
Median	44	40
Min - Max	-27 - 122	-29 - 212
Number(%) of patients who stopped ACE inhibitors or AII receptor antagonists after temporary discontinuation due to creatinine increase	1 (<0.1%)	2 (<0.1%)

Reviewer's comment:
More patients on dronedarone temporarily discontinued their study drug due to an increase in creatinine than those on placebo.

Baseline Characteristics:
Demography: In the following table the demographic characteristics are shown. In both treatment groups, more than 40% of the patients were ≥75 years old. In the placebo group there is slightly more men than in the dronedarone group.

Table 8: Summary of demographic characteristics - all randomized patients

Parameter		Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Age (years)	n	2327	2301	4628
	Median	73	73	73
	Mean	71.7	71.6	71.6
	SD	9.0	8.9	9.0
	Min - Max	33 - 95	23 - 97	23 - 97
Age (years) [n(%)]	<65	442 (19.0%)	431 (18.7%)	873 (18.9%)
	[65-75[	907 (39.0%)	923 (40.1%)	1830 (39.5%)
	>=75	978 (42.0%)	947 (41.2%)	1925 (41.6%)
Height (cm)	n	2327	2301	4628
	Median	168	168	168
	Mean	168.1	167.5	167.8
	SD	10.5	10.1	10.3
	Min - Max	126 - 211	139 - 203	126 - 211
Weight (kg)	n	2327	2301	4628
	Median	79.2	79.5	79.4
	Mean	80.54	80.35	80.45
	SD	17.78	17.18	17.48
	Min - Max	31.0 - 208.2	33.0 - 168.2	31.0 - 208.2
BMI (Kg/m²) [n(%)]	<30	1594 (68.5%)	1544 (67.1%)	3138 (67.8%)
	>=30	733 (31.5%)	757 (32.9%)	1490 (32.2%)
Gender [n(%)]	Male	1289 (55.4%)	1170 (50.8%)	2459 (53.1%)
	Female	1038 (44.6%)	1131 (49.2%)	2169 (46.9%)
Race [n(%)]	Caucasian	2072 (89.0%)	2065 (89.7%)	4137 (89.4%)
	Black	31 (1.3%)	19 (0.8%)	50 (1.1%)
	Asian/Oriental	154 (6.6%)	150 (6.5%)	304 (6.6%)
	Other	70 (3.0%)	67 (2.9%)	137 (3.0%)
	- Hispanic	56 (80.0%)	48 (71.6%)	104 (75.9%)
	- Latin	12 (17.1%)	13 (19.4%)	25 (18.2%)
	- Other	2 (2.9%)	6 (9.0%)	8 (5.8%)

Medical History: The medical history is in the following table. Approximately 60% in each group have structural heart disease. In the placebo group there is a higher incidence of coronary heart disease and cardiac valve surgery.

Table 9: Number (%) of patients with cardiovascular history - all randomized patients

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Hypertension	1996/ 2327 (85.8%)	1999/ 2301 (86.9%)	3995/ 4628 (86.3%)
Structural heart disease	1402/ 2304 (60.9%)	1330/ 2281 (58.3%)	2732/ 4585 (59.6%)
Tachycardia	797/ 2327 (34.3%)	752/ 2301 (32.7%)	1549/ 4628 (33.5%)
Coronary heart disease	728/ 2327 (31.3%)	661/ 2301 (28.7%)	1389/ 4628 (30.0%)
Non-rheumatic valvular heart disease	354/ 2327 (15.2%)	331/ 2301 (14.4%)	685/ 4628 (14.8%)
Pacemaker	243/ 2327 (10.4%)	214/ 2301 (9.3%)	457/ 4628 (9.9%)
Lone atrial fibrillation	139/ 2318 (6.0%)	140/ 2297 (6.1%)	279/ 4615 (6.0%)
Ischemic dilated cardiomyopathy	118/ 2327 (5.1%)	92/ 2301 (4.0%)	210/ 4628 (4.5%)
Ablation for AF/AFL	106/ 2327 (4.6%)	90/ 2301 (3.9%)	196/ 4628 (4.2%)
Supra-ventricular tachycardia other than AF/AFL	98/ 2327 (4.2%)	97/ 2301 (4.2%)	195/ 4628 (4.2%)
Cardiac valve surgery	95/ 2327 (4.1%)	80/ 2301 (3.5%)	175/ 4628 (3.8%)
Non-ischemic dilated cardiomyopathy	84/ 2327 (3.6%)	82/ 2301 (3.6%)	166/ 4628 (3.6%)
Hypertrophic cardiomyopathy	50/ 2327 (2.1%)	45/ 2301 (2.0%)	95/ 4628 (2.1%)
Implanted cardioverter defibrillator	43/ 2327 (1.8%)	42/ 2301 (1.8%)	85/ 4628 (1.8%)
Rheumatic valvular heart disease	29/ 2327 (1.2%)	51/ 2301 (2.2%)	80/ 4628 (1.7%)
Sustained ventricular tachycardia	19/ 2327 (0.8%)	21/ 2301 (0.9%)	40/ 4628 (0.9%)
Congenital heart disease	16/ 2327 (0.7%)	21/ 2301 (0.9%)	37/ 4628 (0.8%)
Ablation for other reason than AF/AFL	17/ 2327 (0.7%)	12/ 2301 (0.5%)	29/ 4628 (0.6%)
Ventricular fibrillation	12/ 2327 (0.5%)	12/ 2301 (0.5%)	24/ 4628 (0.5%)

Structural heart disease: Coronary heart disease and/or Ischemic dilated cardiomyopathy and/or Non-ischemic dilated cardiomyopathy and/or Rheumatic valvular heart disease and/or Non-rheumatic valvular heart disease and/or Hypertrophic cardiomyopathy and/or LVEF < 45 % and/or History of congestive heart failure (CHF)
Lone atrial fibrillation: patients without hypertension and without structural heart disease

Reviewer's comment:
The fact that structural heart disease, coronary heart disease, and non-rheumatic valvular heart disease are higher in the placebo group may be of some significance.

The medical history at baseline is in the following table. There is slightly more chronic obstructive pulmonary disease, insomnia, cardiac value surgery, and ablation for AF/AFL in the placebo group.

Table 10: Number of patients with medical history

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Hypercholesterolemia	1002/ 2327 (43.1%)	1034/ 2301 (44.9%)	2036/ 4628 (44.0%)
Dyslipidaemia	778/ 2327 (33.4%)	756/ 2301 (32.9%)	1534/ 4628 (33.1%)
Non insuline-dependent diabetes mellitus	398/ 2327 (17.1%)	423/ 2301 (18.4%)	821/ 4628 (17.7%)
Chronic pulmonary disease	314/ 2327 (13.5%)	297/ 2301 (12.9%)	611/ 4628 (13.2%)
Hypothyroidism	227/ 2327 (9.8%)	263/ 2301 (11.4%)	490/ 4628 (10.6%)
Insomnia	190/ 2327 (8.2%)	175/ 2301 (7.6%)	365/ 4628 (7.9%)
Malignant neoplasm	192/ 2327 (8.3%)	165/ 2301 (7.2%)	357/ 4628 (7.7%)
Depression	178/ 2327 (7.6%)	162/ 2301 (7.0%)	340/ 4628 (7.3%)
Embolism and thrombosis (including phlebothrombosis and arterial embolism)	159/ 2327 (6.8%)	172/ 2301 (7.5%)	331/ 4628 (7.2%)
Syncope	140/ 2327 (6.0%)	154/ 2301 (6.7%)	294/ 4628 (6.4%)
Hyperthyroidism	100/ 2327 (4.3%)	77/ 2301 (3.3%)	177/ 4628 (3.8%)
Chronic renal failure	83/ 2327 (3.6%)	85/ 2301 (3.7%)	168/ 4628 (3.6%)
Insuline-dependent diabetes mellitus	68/ 2327 (2.9%)	60/ 2301 (2.6%)	128/ 4628 (2.8%)
Chronic liver disease	25/ 2327 (1.1%)	27/ 2301 (1.2%)	52/ 4628 (1.1%)
Haemorrhagic stroke	23/ 2327 (1.0%)	21/ 2301 (0.9%)	44/ 4628 (1.0%)
Parkinson's disease	24/ 2327 (1.0%)	15/ 2301 (0.7%)	39/ 4628 (0.8%)
Seizures	19/ 2327 (0.8%)	15/ 2301 (0.7%)	34/ 4628 (0.7%)

At baseline three-quarters of the patients were in sinus rhythm and simply had a history of AF/AFL; only one quarter were in AF/AFL at randomization.

Table 11: Number of patients according to the stratification factor atrial fibrillation/atrial flutter

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Number of patients in AF/AFL at randomization stage, as per stratification factor	586 (25.2%)	569 (24.7%)	1155 (25.0%)

Reviewer's comment:
The fact that only 25% were in AF/AFL at randomization in the ATHENA Study is in sharp contrast to the ANDROMEDA study patients where almost 30% were in permanent atrial fibrillation.

The baseline cardiovascular examination is shown in the following table. Approximately 30% of patients in both treatment groups had congestive heart failure, i. e., either a LVEF <35% or NYHA Class I or greater. Only about 4% of patients were NYHA Class III.

Table 12: Baseline cardiovascular examination

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
2D-Echocardiogram - Left atrium diameter (mm)			
n	2279	2265	4544
Median	44.0	44.0	44.0
Mean	44.03	44.08	44.06
SD	7.04	6.79	6.92
Min - Max	20.0 - 75.0	22.3 - 72.0	20.0 - 75.0
LA<=40 mm	698 / 2279 (30.6%)	685 / 2265 (30.2%)	1383 / 4544 (30.4%)
LA>40 mm	1581 / 2279 (69.4%)	1580 / 2265 (69.8%)	3161 / 4544 (69.6%)
2D-Echocardiogram - Left ventricular ejection fraction (%)			
n	2281	2263	4544
Median	60.0	60.0	60.0
Mean	57.31	57.36	57.34
SD	11.25	10.95	11.10
Min - Max	9.4 - 93.0	10.0 - 86.0	9.4 - 93.0
LVEF<35%	87 / 2281 (3.8%)	92 / 2263 (4.1%)	179 / 4544 (3.9%)
LVEF>=35%	2194 / 2281 (96.2%)	2171 / 2263 (95.9%)	4365 / 4544 (96.1%)
Cardiovascular clinical examination			
Patients with left CHF	693 (29.8%)	672 (29.2%)	1365 (29.5%)
NYHA classification [n(%)]			
Class I	178 (7.6%)	208 (9.0%)	386 (8.3%)
Class II	406 (17.4%)	373 (16.2%)	779 (16.8%)
Class III	109 (4.7%)	91 (4.0%)	200 (4.3%)
LVEF < 35% or NYHA class I or above			
Yes	723 (31.1%)	694 (30.2%)	1417 (30.6%)
No	1568 (67.4%)	1578 (68.6%)	3146 (68.0%)

Reviewer's comment:
The small percent of patients who were in heart failure, especially Class II or higher in this ATHENA Study is significantly smaller and is in sharp contrast to the ANDROMEDA study where the percentage in heart failure was 100%.

Table 13: Summary of creatinine clearance at baseline

Parameter		Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Creatinine clearance (mL/min)	n	2306	2282	4588
	Median	65	65	65
	Mean	70.7	70.6	70.6
	SD	29.9	28.8	29.4
	Min - Max	14 - 292	13 - 397	13 - 397
Creatinine clearance (mL/min) [n (%)]	<30	68 (2.9%)	59 (2.6%)	127 (2.8%)
	[30-50[	478 (20.7%)	422 (18.5%)	900 (19.6%)
	[50-80[	1082 (46.9%)	1169 (51.2%)	2251 (49.1%)
	>=80	678 (29.4%)	632 (27.7%)	1310 (28.6%)
	Missing	21	19	40

Reviewer's comment:
The placebo group in the above table had more patients with compromised kidney function at baseline compared to the dronedarone group.

Prior and/or concomitant medication: The baseline medication used reflected the standard of care. The 2 treatment groups appear to be well balanced for baseline medication use. At baseline, approximately 32% of patients in both treatment groups reported use of statins metabolized by CYP3A4.

Table 14: Number baseline selected medications

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Total (N=4628)
Beta blocking agents (except sotalol)	1641 (70.5%)	1628 (70.8%)	3269 (70.6%)
ACE inhibitors or A II receptor antagonists	1602 (68.8%)	1614 (70.1%)	3216 (69.5%)
Oral anticoagulant	1384 (59.5%)	1403 (61.0%)	2787 (60.2%)
Diuretics	1265 (54.4%)	1227 (53.3%)	2492 (53.8%)
Diuretics other than spironolactone	1224 (52.6%)	1187 (51.6%)	2411 (52.1%)
Spironolactone	136 (5.8%)	148 (6.4%)	284 (6.1%)
Low dose of aspirin (<= 365 mg)	1019 (43.8%)	1018 (44.2%)	2037 (44.0%)
Statins	914 (39.3%)	878 (38.2%)	1792 (38.7%)
Statins metabolized by CYP3A4	755 (32.4%)	737 (32.0%)	1492 (32.2%)
Statins not metabolized by CYP3A4	166 (7.1%)	147 (6.4%)	313 (6.8%)
Calcium antagonists with heart rate lowering effects	307 (13.2%)	331 (14.4%)	638 (13.8%)
Digitalis	308 (13.2%)	321 (14.0%)	629 (13.6%)
Drugs interacting with the creatinine tubular secretion	237 (10.2%)	229 (10.0%)	466 (10.1%)
Moderate inhibitors of CYP3A4	226 (9.7%)	214 (9.3%)	440 (9.5%)
Other chronic antiplatelet therapy	166 (7.1%)	126 (5.5%)	292 (6.3%)
NSAID	123 (5.3%)	114 (5.0%)	237 (5.1%)

Reviewer's comment:
It appears from the above table that fewer patients in the placebo group were anticoagulated which may be important.

As expected in AF/AFL patients, the medications most frequently prescribed between the date of first study drug intake and the date of last study drug intake were beta-blocking agents, ACE inhibitors/angiotensin II receptor antagonists, and oral anticoagulants, with rates similar to baseline, reflecting continuation of background therapy as shown in the following table.

Table 15: Number of patients who received concomitant medications

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Beta blocking agents (except Sotalol)	1860 (79.9%)	1785 (77.6%)
ACE inhibitors / A II receptor antagonists	1800 (77.4%)	1771 (77.0%)
Oral anticoagulant	1643 (70.6%)	1601 (69.6%)
Diuretics	1559 (67.0%)	1524 (66.2%)
Diuretics other than Spironolactone	1522 (65.4%)	1492 (64.8%)
Spironolactone	262 (11.3%)	257 (11.2%)
Low dose of aspirin (<= 365 mg)	1231 (52.9%)	1225 (53.2%)
Statins	1131 (48.6%)	1044 (45.4%)
Metabolized by CYP3A4	973 (41.8%)	909 (39.5%)
Not metabolized by CYP3A4	305 (13.1%)	264 (11.5%)
Digitalis	574 (24.7%)	468 (20.3%)
Calcium antagonists with heart rate lowering effects	490 (21.1%)	459 (19.9%)
Drugs interacting with the creatinine tubular secretion	434 (18.7%)	382 (16.6%)
Moderate inhibitors of CYP3A4	369 (15.9%)	323 (14.0%)
NSAID	359 (15.4%)	308 (13.4%)
Other chronic antiplatelet therapy	260 (11.2%)	182 (7.9%)

Reviewer's comment:
It is of interest that more patients in the placebo group were on statins and digitalis.

More patients in the placebo group received drugs that can cause torsades de pointes, Vaughan-Williams Class I or III antiarrhythmic drugs, amiodarone, sotalol, and potent inhibitors of CYP3A4 (10.7%, 8.4%, 8.5%, 2.8%, and 0.7%, respectively) compared with the dronedarone group (8.4%, 5.8%, 5.5%, 1.5%, and 0.4%, respectively) as shown in the following table.

Table 16: Number of patients who received forbidden concomitant medications during study

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Drugs which can cause Torsades de Pointes	250 (10.7%)	194 (8.4%)
Vaughan-Williams class I or III antiarrhythmic drugs (without Amiodarone)	196 (8.4%)	134 (5.8%)
Amiodarone	197 (8.5%)	126 (5.5%)
Sotalol	66 (2.8%)	35 (1.5%)
Substrates of CYP3A4 with a narrow therapeutic margin	15 (0.6%)	17 (0.7%)
Potent inhibitors of CYP3A4	16 (0.7%)	10 (0.4%)

Reviewer's comment:
As may be expected, more patients in the placebo group were on forbidden concomitant medications.

6.1.4 Efficacy Findings

The following table shows that dronedarone decreases by 24.2% the incidence of cardiovascular hospitalization or death from any cause compared with placebo ($p = 2 \times 10^{-8}$).

Table 17: Time from randomization to first cardiovascular hospitalization or death from any cause

	Placebo (N= 2327)	Dronedarone 400mg BID (N= 2301)
Number of events, n	917	734
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at 6 months [95% CI] Cumulative incidence of events at 1 year [95% CI] Cumulative incidence of events at 2 years [95% CI]	0.202 [0.185 ; 0.218] 0.302 [0.283 ; 0.320] 0.422 [0.400 ; 0.444]	0.147 [0.132 ; 0.161] 0.228 [0.211 ; 0.245] 0.354 [0.332 ; 0.377]
Endpoint's composition: Cardiovascular hospitalization Death from any cause - Cardiovascular death - Non cardiovascular death	 859 58 33 25	 675 59 26 33
Log-rank test p-value Relative risk [95% CI]*	2E-8 0.758 [0.688; 0.835]	

* Determined from cause-specific Cox regression model

Death from any cause: The following table shows that fewer deaths from any cause occurred in the dronedarone group (n = 116) compared with the placebo group (n = 139), however, this difference was not statistically significant (p=0.176). Also, there is a reduction in the number of cardiovascular deaths (dronedarone: 65; placebo: 94).

Table 18: Time from randomization to death from any cause

	Placebo (N= 2327)	Dronedarone 400mg BID (N= 2301)
Number of events, n	139	116
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at 6 months [95% CI] Cumulative incidence of events at 1 year [95% CI] Cumulative incidence of events at 2 years [95% CI]	0.016 [0.011 ; 0.021] 0.033 [0.026 ; 0.040] 0.063 [0.052 ; 0.074]	0.012 [0.007 ; 0.016] 0.027 [0.020 ; 0.033] 0.061 [0.049 ; 0.072]
Endpoint's composition: - Cardiovascular death - Non cardiovascular death	 94 45	 65 51
Log-rank test p-value Relative risk [95% CI]*	0.1758 0.844 [0.660; 1.080]	

* Determined from cause-specific Cox regression model

Deaths over time show a reduction in all deaths and cardiovascular deaths in the following table.

Table 19: Deaths over time

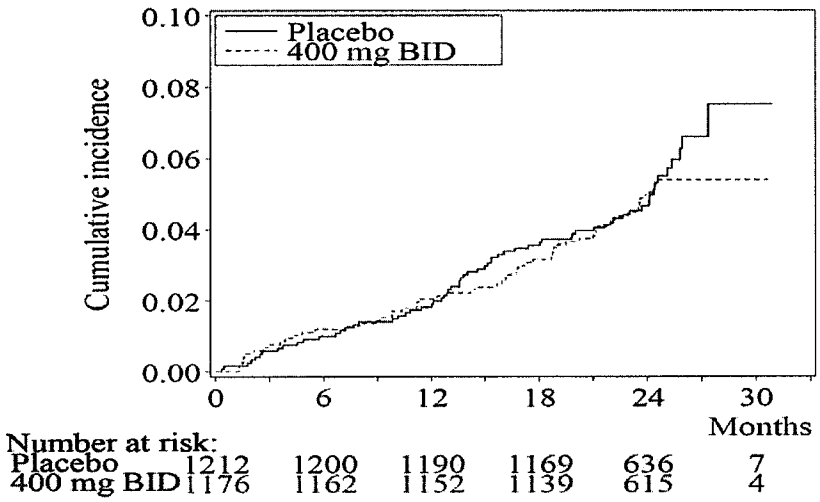
	Placebo (N=2327)		Dronedarone 400 mg BID (N=2301)	
All deaths				
On Study	139	(6.0%)	116	(5.0%)
On Treatment	65	(2.8%)	54	(2.3%)
Beyond study period (a)	1	(<0.1%)	0	(0%)
CV deaths				
On Study	94	(4.0%)	65	(2.8%)
On Treatment	50	(2.1%)	37	(1.6%)
Beyond study period (a)	1	(<0.1%)	0	(0%)
Non CV deaths				
On Study	45	(1.9%)	51	(2.2%)
On Treatment	15	(0.6%)	17	(0.7%)

(a) Data no longer collected systematically

Respiratory events were the most frequent reason for noncardiovascular deaths in both treatment groups. Seven patients in each group had a main reason of death associated with respiratory and mediastinal neoplasm; 4 patients in each group had pneumonia; 1 patient in the placebo group and 6 in the dronedarone died of respiratory disorders (respiratory failure, chronic respiratory disease), while 6 patients in the placebo group and 1 in the dronedarone group died from chronic obstructive pulmonary disease.

In our correspondence with the Sponsor, they provided on November 11, 2008, primary and secondary analyses of those patients who were enrolled prior to the protocol change on March 2006 and those enrolled after the protocol change. The following figure shows the cumulative curves of deaths for any cause for those who were enrolled prior to the protocol change.

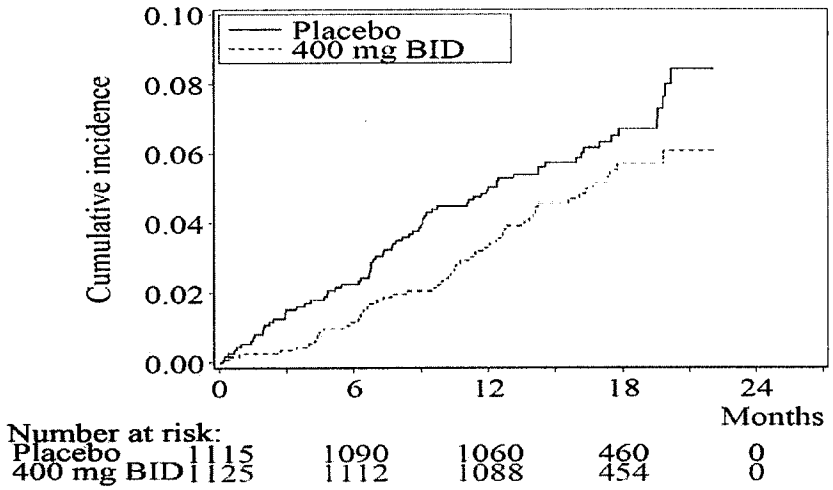
Figure 4: Kaplan-Meier cumulative incidence curves from randomization to death from any cause during the on-study period - All patients randomized before 2006-03-25 (EFC5555/ATHENA)



Reviewers comment:
There was no difference between the treatment groups before month 24.

Below are the respective cumulative curves in Fig. 4 for those enrolled after the protocol change.

Fig. 5: Kaplan-Meier cumulative incidence curves from randomization to death from any cause during the study after Amendment 1



Reviewers comment:
There is a big difference between the cumulative curves before and after the protocol amendment on March 25, 2006.

The Steering Committee classified the reduction of cardiac/arrhythmic deaths in the dronedarone group compared with placebo which is shown in the following table.

Table 20: Summary of death classification as per Steering Committee

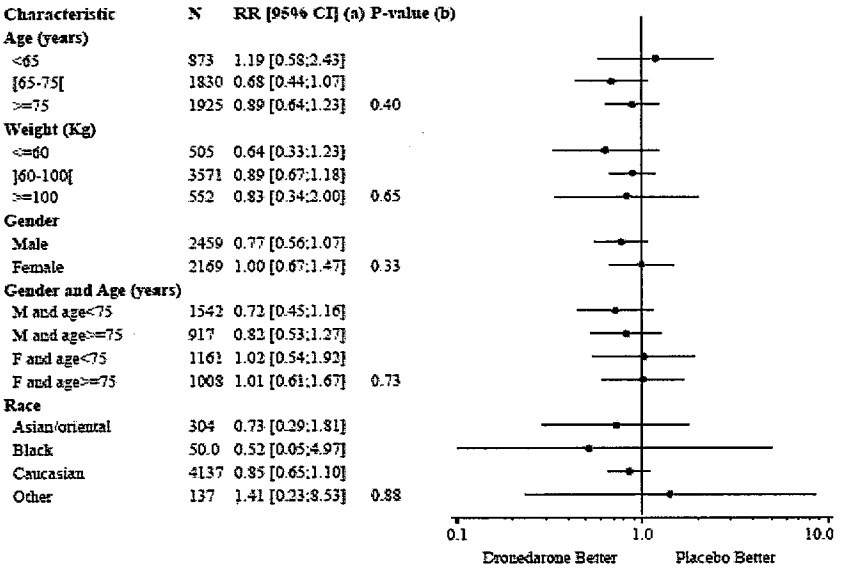
	Placebo (N=2327)		Dronedarone 400 mg BID (N=2301)	
Number of deaths	140	(6.0%)	116	(5.0%)
On study	139	(6.0%)	116	(5.0%)
Cardiac/arrhythmic	48	(2.1%)	26	(1.1%)
Cardiac/non-arrhythmic	18	(0.8%)	17	(0.7%)
Non-vascular	49	(2.1%)	53	(2.3%)
Vascular/non-cardiac	24	(1.0%)	20	(0.9%)
On treatment	65	(2.8%)	54	(2.3%)
Cardiac/arrhythmic	31	(1.3%)	17	(0.7%)
Cardiac/non-arrhythmic	7	(0.3%)	9	(0.4%)
Non-vascular	15	(0.6%)	19	(0.8%)
Vascular/non-cardiac	12	(0.5%)	9	(0.4%)
Beyond study (a)				
Cardiac/non-arrhythmic	1		0	

(a) Data no longer collected systematically

Reviewer's comment:
It is import to remember that the Amendment 3 was not enacted until January 2007 when the Steering Committee classified the deaths. Therefore, many deaths were classified 2 years after they occurred. Essentially the primary cause of death was determined by the treating physician who was the Investigator and only a few autopsies were performed (9.8%).

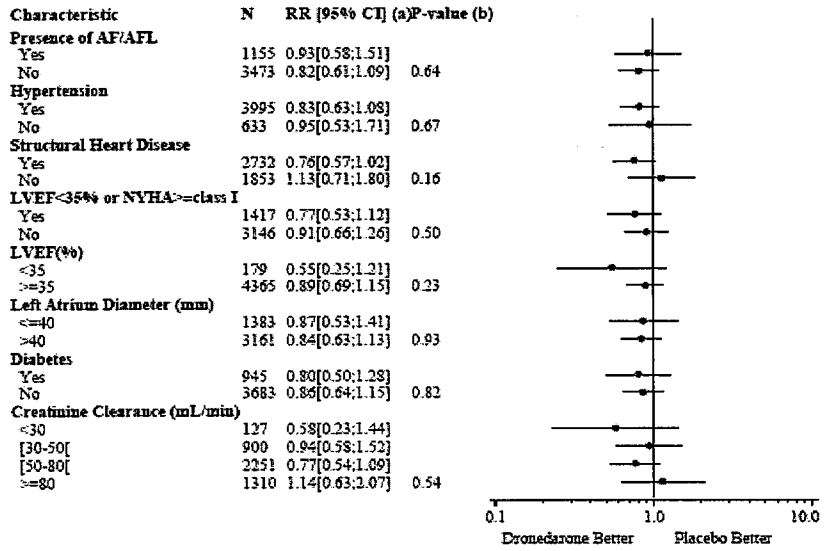
Baseline covariates and selected baseline medications were compared to test their possible influence. This is shown in the following figures.

Figure 6: Relative risk (dronedarone 400 mg BID versus placebo) estimates with 95% confidence intervals according to selected baseline characteristics - death from any cause



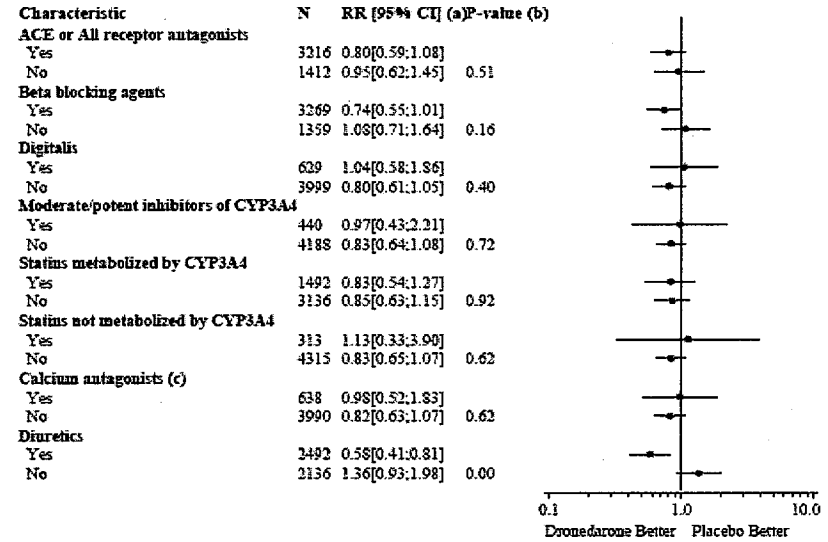
a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model

Figure 7: Relative risk (dronedarone 400 mg BID versus placebo) estimates with 95% confidence intervals according to selected baseline characteristics – death from any cause



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model

Figure 8: Relative risk (dronedarone 400 mg BID versus placebo) estimates with 95% confidence intervals according to selected baseline medications for the time from randomization to death from any cause - All randomized patients



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model
c Calcium antagonists with heart rate lowering effects restricted to diltiazem, verapamil and bepridil

According to the pre-specified hierarchical procedure for testing the secondary endpoints, no further testing of the CV hospitalization or CV deaths should be performed because the first secondary endpoint, all death, was not statistically significant (p=0.176). This review shows the analyses of the CV hospitalization and CV deaths as exploratory, only for the completeness of clinical evaluation.

Cardiovascular hospitalization: The on-study analysis of the time from randomization to the first cardiovascular hospitalization demonstrated that dronedarone significantly decreases by 25.5% the cumulative incidence of cardiovascular hospitalization compared with placebo ($p=9 \times 10^{-9}$). This is shown in the following table.

Table 21: Analysis of time from randomization to first cardiovascular hospitalization

	Placebo (N= 2327)	Dronedarone 400mg BID (N= 2301)
Number of events, n	859	675
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at 6 months [95% CI]	0.195 [0.178 ; 0.211]	0.141 [0.127 ; 0.155]
Cumulative incidence of events at 1 year [95% CI]	0.289 [0.270 ; 0.307]	0.217 [0.200 ; 0.234]
Cumulative incidence of events at 2 years [95% CI]	0.399 [0.376 ; 0.421]	0.326 [0.304 ; 0.348]
Log-rank test p-value	9E-9	
Relative risk [95% CI]a	0.745 [0.673; 0.824]	

PGM= SR33589/EFC5555/CSR 02/ES/PGM/RPT/t611ATH/Survana.sas OUT= OUTPUT/t611ATH AnaHosp.html (21APR2008 - 15:15)
a Determined from cause-specific Cox regression model

The decrease in the number of cardiovascular hospitalizations with dronedarone group was mainly due to a reduction in AF and other supraventricular rhythm disorders. There was a trend for fewer hospitalizations for worsening congestive heart failure, myocardial infarction or unstable angina, and TIA/stroke in the dronedarone group compared with the placebo group. Hospitalizations for major

bleeding, syncope, or ventricular arrhythmia events (including ventricular extrasystoles, ventricular tachycardia, ventricular fibrillation, and other ventricular arrhythmias) were similar between the treatment groups shown in the following table.

Reviewer's comment:
It is interesting that even though it is a derivative of amiodarone, dronedarone did not seem beneficial for improving hospitalizations for ventricular arrhythmias or syncope.

Table 22: Number of patients with a first cardiovascular hospitalization

	Placebo (N=2327)		Dronedarone 400 mg BID (N=2301)	
Any cardiovascular hospitalization	859	(36.9%)	675	(29.3%)
Atherosclerosis related (if not otherwise specified)	8	(0.3%)	11	(0.5%)
Myocardial infarction or unstable angina	61	(2.6%)	48	(2.1%)
Stable angina pectoris or atypical chest pain	41	(1.8%)	45	(2.0%)
Syncope	24	(1.0%)	21	(0.9%)
TIA or stroke (except intracranial hemorrhage)	35	(1.5%)	28	(1.2%)
Atrial fibrillation and other supraventricular rhythm disorders	457	(19.6%)	296	(12.9%)
Non-fatal cardiac arrest	2	(<0.1%)	3	(0.1%)
Cardiovascular surgery except cardiac transplantation	23	(1.0%)	21	(0.9%)
Implantation of a pacemaker, ICD or any other cardiac device	29	(1.2%)	32	(1.4%)
Transcutaneous coronary, cerebrovascular or peripheral procedure	31	(1.3%)	27	(1.2%)
Blood pressure related (hypotension, hypertension; except syncope)	21	(0.9%)	21	(0.9%)
Cardiovascular infection	0	(0%)	4	(0.2%)
Major bleeding (requiring two or more units of blood or any intracranial hemorrhage)	24	(1.0%)	21	(0.9%)
Pulmonary embolism or deep vein thrombosis	3	(0.1%)	10	(0.4%)
Worsening CHF, including pulmonary edema or dyspnea of cardiac origin	92	(4.0%)	78	(3.4%)
Ventricular extrasystoles	1	(<0.1%)	1	(<0.1%)
Ventricular tachycardia (non-sustained and sustained VT)	6	(0.3%)	6	(0.3%)
Ventricular fibrillation	1	(<0.1%)	1	(<0.1%)
Other ventricular arrhythmia	0	(0%)	1	(<0.1%)

Reviewer's comment:
The above table does show a decrease in hospitalizations for atrial fibrillation and other supraventricular rhythm disorders but frequently in the United States patients are not hospitalized for AF/AFL or simply have an Emergency Room visit.

Reviewer's comment:
According to the pre-specified hierarchical procedure for testing the secondary endpoints, no further testing of the CV hospitalization or CV deaths should be performed because the first secondary endpoint, all death, was not statistically significant (p=0.176). This review shows the analysis of the CV deaths as exploratory, only for the completeness of clinical evaluation.

Cardiovascular death: In the following table it is shown that dronedarone decreased by 30.2% the incidence of cardiovascular death compared with placebo.

Table 23: Unadjusted analysis of time from randomization to cardiovascular deaths

	Placebo (N= 2327)	Dronedarone 400mg BID (N= 2301)
Number of events, n	94	65
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at 6 months [95% CI]	0.012 [0.008 ; 0.017]	0.007 [0.003 ; 0.010]
Cumulative incidence of events at 1 year [95% CI]	0.024 [0.018 ; 0.030]	0.016 [0.011 ; 0.021]
Cumulative incidence of events at 2 years [95% CI]	0.042 [0.033 ; 0.051]	0.033 [0.024 ; 0.041]
Log-rank test p-value	0.0252	
Relative risk [95% CI]a	0.698 [0.509; 0.958]	

a Determined from cause-specific Cox regression model

The significance for CV deaths appeared to be largely driven by Russia. The analysis of time from randomization to CV death by country as shown in the following table was prepared by Dr. Freidlin.

Table 24: Analysis of time from randomization to CV death in ATHENA, by country
(All randomized patients. Countries with large number of patients and events)

Country	Number of patients	Number of CV deaths	RR	P-value
Argentina	94	4	0.99	0.99
Belgium	33	3	1.96	0.58
Canada	148	2	1.08	0.96
Czech Republic	172	7	0.73	0.68
Germany	323	8	1.05	0.95
Hong Kong	38	3	0.42	0.48
Morocco	20	2	1.54	0.76
Poland	198	6	1.01	0.99
Russia	907	49	0.57	0.055
South Africa	54	5	0.80	0.80
Taiwan	35	4	0.93	0.94
United States	1255	47	0.64	0.13

It appears that the reduction of cardiovascular death with dronedarone 400 mg BID was mainly due to a reduction in sudden cardiac deaths and stroke shown in the following table.

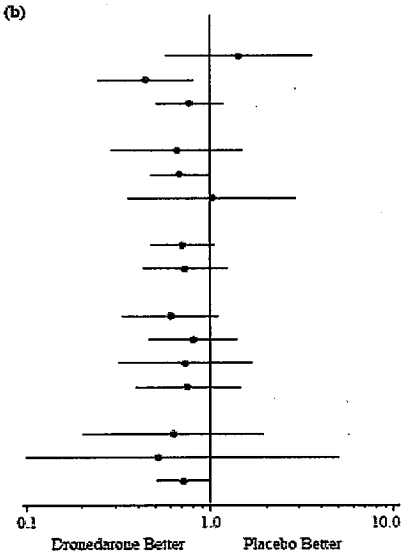
Table 25: Number of patients with cardiovascular death according to pre-specified main reason

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Any cardiovascular death	94 (4.0%)	65 (2.8%)
Aortic dissection/aneurysm	0 (0%)	1 (<0.1%)
CHF	10 (0.4%)	13 (0.6%)
Cardiogenic shock	2 (<0.1%)	5 (0.2%)
Death during a cardiovascular transcutaneous interventional procedure or cardiovascular surgical intervention	2 (<0.1%)	0 (0%)
Hemorrhage (except cardiac tamponade)	5 (0.2%)	6 (0.3%)
Myocardial infarction or unstable angina (including complications of MI, except arrhythmias)	7 (0.3%)	5 (0.2%)
Pulmonary or peripheral embolism	6 (0.3%)	2 (<0.1%)
Stroke	18 (0.8%)	11 (0.5%)
Sudden cardiac death (e.g unwitnessed death or documented asystole)	35 (1.5%)	14 (0.6%)
Unknown cause	6 (0.3%)	6 (0.3%)
Ventricular fibrillation	2 (<0.1%)	2 (<0.1%)
Ventricular tachycardia (non-sustained and sustained vt)	1 (<0.1%)	0 (0%)

A comparison of dronedarone with placebo for cardiovascular death was made with baseline covariates and selected baseline medications to test their possible influence. In the following figure it is shown that there was no interaction for most covariates.

Figure 9: Relative risk of dronedarone 400 mg BID versus placebo according to selected baseline characteristics – cardiovascular death

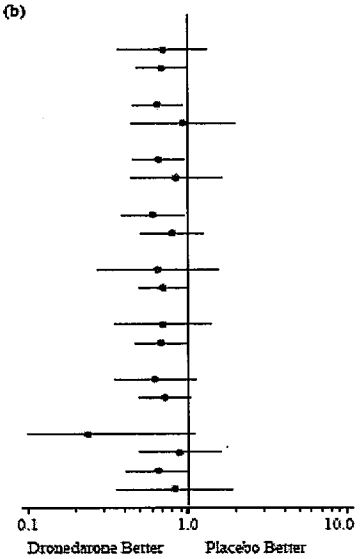
Characteristic	N	RR [95% CI] (a)	P-value (b)
Age (years)			
<65	873	1.42 [0.57;3.54]	
[65-75[	1830	0.44 [0.25;0.80]	
>=75	1925	0.77 [0.50;1.17]	0.08
Weight (Kg)			
<=60	505	0.66 [0.29;1.50]	
]60-100[	3571	0.68 [0.47;0.98]	
>=100	552	1.02 [0.36;2.91]	0.76
Gender			
Male	2459	0.70 [0.47;1.05]	
Female	2169	0.73 [0.43;1.21]	0.93
Gender and Age (years)			
M and age<75	1542	0.61 [0.34;1.10]	
M and age>=75	917	0.81 [0.46;1.40]	
F and age<75	1161	0.73 [0.32;1.69]	
F and age>=75	1008	0.75 [0.39;1.43]	0.92
Race			
Asian/oriental	304	0.63 [0.20;1.91]	
Black	50.0	0.52 [0.05;4.97]	
Caucasian	4137	0.71 [0.51;1.00]	0.99



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model

Figure 10: Relative risk of dronedarone 400 mg BID versus placebo estimates according to selected baseline characteristics – cardiovascular death

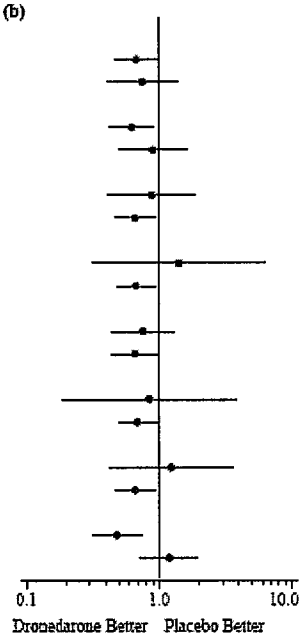
Characteristic	N	RR [95% CI] (a)	P-value (b)
Presence of AF/AFL			
Yes	1155	0.71 [0.38;1.35]	
No	3473	0.70 [0.48;1.00]	0.97
Hypertension			
Yes	3995	0.66 [0.46;0.93]	
No	633	0.94 [0.45;1.98]	0.39
Structural Heart Disease			
Yes	2732	0.67 [0.47;0.96]	
No	1853	0.85 [0.44;1.64]	0.52
LVEF<35% or NYHA>=class I			
Yes	1417	0.61 [0.39;0.95]	
No	3146	0.81 [0.51;1.27]	0.39
LVEF(%)			
<35	179	0.66 [0.28;1.56]	
>=35	4365	0.71 [0.50;1.00]	0.84
Left Atrium Diameter (mm)			
<=40	1383	0.70 [0.36;1.40]	
>40	3161	0.69 [0.48;0.98]	0.94
Diabetes			
Yes	945	0.63 [0.35;1.13]	
No	3683	0.73 [0.50;1.06]	0.68
Creatinine Clearance (mL/min)			
<30	127	0.24 [0.05;1.10]	
[30-50[	900	0.89 [0.50;1.59]	
[50-80[	2251	0.66 [0.42;1.03]	
>=80	1310	0.83 [0.36;1.90]	0.35



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model

Figure 11: Relative risk of dronedarone 400 mg BID versus placebo according to selected baseline characteristics – cardiovascular death

Characteristic	N	RR [95% CI] (a)	P-value (b)
ACE or AII receptor antagonists			
Yes	3216	0.68 [0.47;0.98]	
No	1412	0.75 [0.41;1.38]	0.78
Beta blocking agents			
Yes	3269	0.63 [0.43;0.92]	
No	1359	0.90 [0.50;1.62]	0.31
Digitalis			
Yes	629	0.89 [0.42;1.89]	
No	3999	0.66 [0.47;0.94]	0.48
Moderate/potent inhibitors of CYP3A4			
Yes	440	1.41 [0.32;6.32]	
No	4188	0.67 [0.49;0.93]	0.34
Statins metabolized by CYP3A4			
Yes	1492	0.76 [0.45;1.30]	
No	3136	0.66 [0.45;0.98]	0.67
Statins not metabolized by CYP3A4			
Yes	313	0.85 [0.19;3.79]	
No	4315	0.69 [0.50;0.95]	0.78
Calcium antagonists (c)			
Yes	638	1.24 [0.43;3.57]	
No	3990	0.66 [0.48;0.93]	0.27
Diuretics			
Yes	2492	0.48 [0.31;0.74]	
No	2136	1.19 [0.72;1.95]	0.01



a Determined from Cox regression model
b P-value of interaction between baseline characteristics and treatment based on Cox regression model
c Calcium antagonists with heart rate lowering effects restricted to diltiazem, verapamil and beprodil

6.1.5 Clinical Microbiology

NA

6.1.6 Efficacy Conclusions

In ATHENA study, dronedarone was not statistically superior to placebo in preventing death from any cause (p=0.176). Therefore, a claim for preventing death from any cause cannot be included in the labeling.

Relative to a claim for preventing CV death, there are some important issues.

1. According to the pre-specified hierarchical procedure to control global type 1 error at the 5% level, the secondary efficacy endpoint of CV death can be tested only if the first secondary endpoint, death from any cause, is statistically significant at the 5% level. As death from any cause was not statistically significant (p=0.176), the secondary endpoint of CV death should not be tested at all. The analysis for CV death is shown in this review only as exploratory for the completeness of clinical evaluation.
2. There are some issues with the reliability of classifications of CV deaths and the robustness of p=0.03 for the CV death.

For example, in ATHENA, 12 patients with unknown cause of death were classified as having CV death. If 6 placebo patients with unknown cause of death are reclassified as having non-CV death, then the analysis of CV death in ATHENA becomes non-significant: p=0.07 (log-rank test) or p=0.09 (Wilcoxon test). Even if only 4 placebo patients with unknown cause of death are reclassified as non-CV death, then the analysis for CV death in ATHENA already becomes non-significant: p=0.05 (log-rank test) or p=0.065 (Wilcoxon test).

In the ATHENA Study, with a nominal p-value of only p=0.03 for CV mortality and many other issues mentioned above, the statistical significance based on this p-value is inconclusive and could be due to data dredging. Therefore, an additional study is needed to determine whether this finding is real.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety evaluation was reviewed as presented by the Sponsor. Also, many case reports for death and hospitalizations were reviewed by the Medical Reviewer. The efficacy endpoint was death and hospitalizations so there is an overlap between safety and efficacy.

Reviewer's comment:
Unfortunately this Medical Reviewer (a clinician) did not agree with the Investigator (usually the treating physician) as to the designated cause of death in some of the reviewed cases. For instance, a bleeding esophageal cancer is not a vascular death in a cardiovascular trial. Also, hospital records were not located for those who were hospitalized once or more and then later died.

7.1.1 Deaths

The following table provides the deaths in the randomized and treated population, including cardiovascular and non-cardiovascular deaths. These deaths were not adjudicated by a committee but designated by the Investigator (the treating physician) as to a pre-specified reason. In very few instances was an autopsy performed.

Table 26: Overview of deaths over time

	Placebo (N=2313)		Dronedarone 400 mg BID (N=2291)	
All deaths				
On Study	139	(6.0%)	116	(5.1%)
On Treatment	65	(2.8%)	54	(2.4%)
Beyond study period (a)	1	(<0.1%)	0	(0%)
CV deaths				
On Study	94	(4.1%)	65	(2.8%)
On Treatment	50	(2.2%)	37	(1.6%)
Beyond study period (a)	1	(<0.1%)	0	(0%)
Non CV deaths				
On Study	45	(1.9%)	51	(2.2%)
On Treatment	15	(0.6%)	17	(0.7%)

(a) Data no longer collected systematically

Reviewer's comment:
It is interesting that there is an increase in non CV deaths with dronedarone. As stated above, the designation of what was a CV death was according to a check list by the investigating individual clinician.

In the two treatment groups the incidence of serious adverse events with an outcome of death during the emergent period was similar for the randomized, treated population (placebo: 30 of 2313, 1.3%; dronedarone: 37 of 2291, 1.6%). None of the patients in the placebo group experienced respiratory failure whereas it occurred in 4 patients (0.2%) in the dronedarone group. Pneumonia occurred in 3 patients (0.1%) in the placebo group and in 1 patient (<0.1%) in the dronedarone group. Septic shock occurred in 3 patients (0.1%) in the placebo group and none in the dronedarone group.

Reviewer's comment:
It is interesting that the definition of respiratory failure is not provided. Was this congestive heart failure? Pneumonia is common in this age group and this is the reason both the influenza and pneumococcal vaccine are recommended. We have no information on this aspect of the included patients' health care.

7.1.2 Other Serious Adverse Events

According to the Sponsor the incidence of treatment-emergent serious adverse events was similar in the 2 treatment groups. The most frequently reported events were infections, gastrointestinal disorders, and neoplasms both benign and malignant. Pneumonia was reported in more patients on placebo (45 of 2313, 1.9%) than dronedarone (32 of 2291, 1.4%).

A serious adverse event of torsades de pointes was experienced in one patient on dronedarone. The patient's was in the low normal range. The episode of torsades de pointes was recorded while the patient was in the intensive care unit. The patient suffered anoxic encephalopathy with confusion being the main symptom

Acute renal failure occurred in four patients in the placebo group and 14 in the dronedarone group. Twelve patients recovered in the dronedarone group without permanent drug discontinuation. Two patients on dronedarone did not have the drug permanently discontinued and they died one from congestive heart failure and one from acute renal failure. This patient had a low ejection fraction at baseline and a history of chronic renal failure. Treatment with an ACE inhibitor had been discontinued 6 months before death. Two patients in the placebo group with acute renal failure recovered without permanent study drug discontinuation. One patient recovered after permanent study drug discontinuation. The other patient did not permanently discontinue the study drug and died from chronic obstructive pulmonary disease.

7.1.3 Dropouts and Other Significant Adverse Events

More patients in the dronedarone group (12.7%) withdrew from treatment due to an adverse event compared with placebo (8.1%). In the dronedarone group there was a higher incidence of

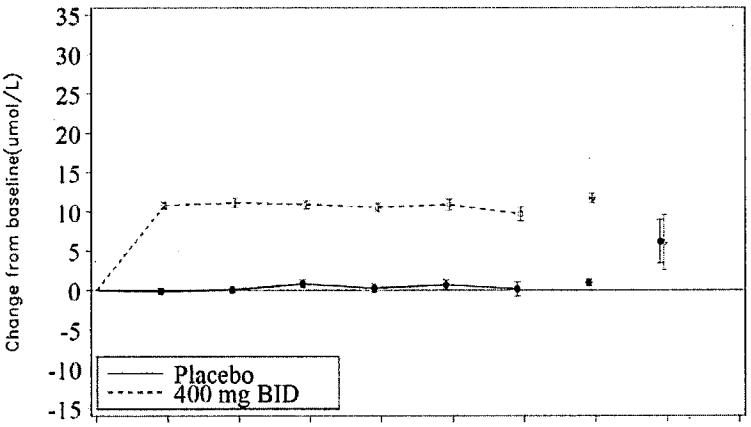
gastrointestinal disorders which included diarrhea, nausea, and vomiting. Also, among the dronedarone patients, there was a higher incidence of withdrawing because of investigation which included ECG QT prolongation and increased blood creatinine.

Patients on dronedarone also withdrew because of fatigue and not feeing well. Dronedarone patients had a higher incidence of withdrawing for a rash, urticaria, and pruritus. Reasons for withdrawal in the dronedarone group included bradycardia, heart failure, ventricular extrasystoles, and palpitations. There was a higher incidence in the dronedarone group of both benign and malignant neoplasms. Reasons for withdrawing in the dronedarone group included anorexia and hyperkalemia.

7.1.4 Laboratory Findings

There was a significant difference between the patients on dronedarone and placebo in serum creatinine as is shown in the following figure.

Figure 12: Mean changes from baseline (+/- SEM) of creatinine over time



Number of patients	B	D14	M3	M6	M12	M18	M24	EOT	F10+
Placebo	2306	2153	1999	1861	1660	1208	614	2267	131
400 mg BID	2282	2083	1952	1826	1655	1207	603	2203	172

A potentially clinically serious adverse event (PCSA) occurred more frequently in the dronedarone group compared to the placebo group regardless of the baseline as shown in the following table.

Table 27: Number (%) of patients with post-baseline PCSA in renal function

Parameter	Baseline status	PCSA criteria	Placebo (N=2313)	Dronedarone 400 mg BID (N=2291)
Creatinine	Missing	>= 150 umol/L	1 / 7 (14.3 %)	2 / 9 (22.2 %)
	>= 150 umol/L	>= 150 umol/L	79 / 98 (80.6 %)	68 / 79 (86.1 %)
	< 150 umol/L	>= 150 umol/L	156 / 2192 (7.1 %)	332 / 2167 (15.3 %)
	Whatever baseline status	>= 150 umol/L	236 / 2297 (10.3 %)	402 / 2255 (17.8 %)
Urea	Whatever baseline status	>= 17 mmol/L	84 / 2293 (3.7 %)	106 / 2255 (4.7 %)

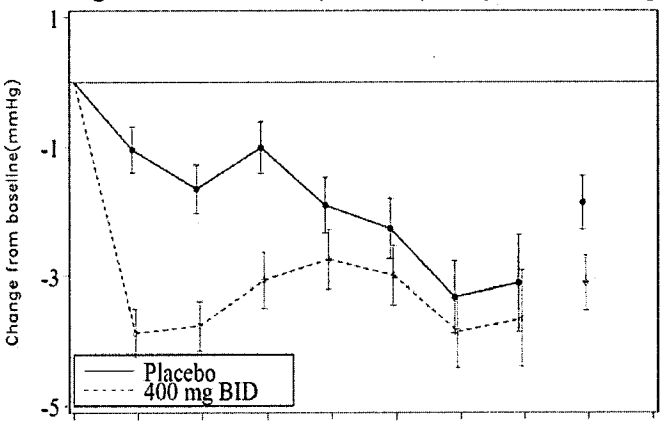
Denominator refers to patients with post baseline value for the parameter

Digoxinemia: Adverse events that led to treatment discontinuation associated with digoxinemia were reported by the Investigators. Two patients in the placebo group had adverse events associated with digoxin; one had anorexia and weight loss, the other digoxin intoxication. Four patients on dronedarone had serious adverse events; 1 an elevated serum digoxin level, and three cases of digoxin intoxication. There was only one patient on dronedarone that had permanent treatment discontinuation because of digoxin intoxication.

7.1.5 Vital Signs

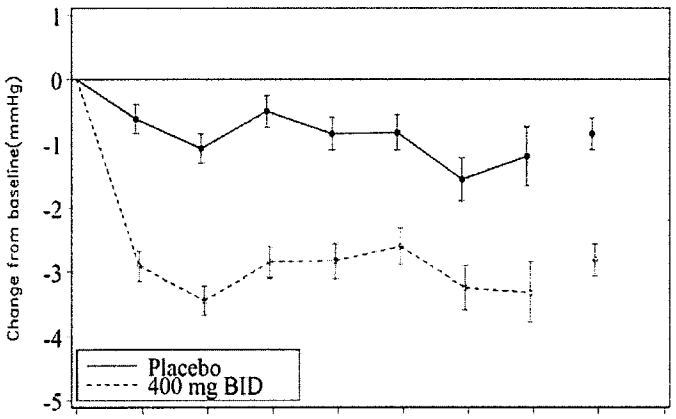
It is interesting that both the systolic and diastolic blood pressures decreased in the patients on dronedarone as shown in the following figures.

Figure 13: Mean changes from baseline (+/-SEM) of systolic blood pressure over time



Number of patients	B	D7	D14	M3	M6	M12	M18	M24	EOT
Placebo	2313	2186	2204	2023	1893	1689	1240	633	2274
400 mg BID	2290	2136	2141	1982	1847	1686	1224	627	2213

Figure 14: Mean changes from baseline (+/-SEM) of diastolic blood pressure over time



Number of patients:	B	D7	D14	M3	M6	M12	M18	M24	EOT
Placebo	2313	2186	2204	2023	1893	1689	1240	633	2274
400 mg BID	2290	2136	2141	1982	1847	1686	1224	627	2213

7.1.6 Electrocardiograms (ECGs)

There was a greater percentage of patients in the dronedarone group with potentially significant clinically adverse events with heart rate decreases, prolonged PR interval, QT ≥500 ms, and QTcB parameters as is shown in the following table.

Table 28: Number (%) of patients with post baseline PCSA for 12-lead ECG parameters

Parameter	PCSA criteria	Placebo (N= 2313)	Dronedarone 400 mg BID (N= 2291)
Heart rate	# <= 50 bpm and decrease >= 15 bpm versus baseline	79 / 1869 (4.2 %)	208 / 1955 (10.6 %)
	# >= 120 bpm and increase >= 15 bpm versus baseline	5 / 1869 (0.3 %)	6 / 1955 (0.3 %)
PR interval	# >= 200 ms and increase >= 20 ms versus baseline	484 / 1869 (25.9 %)	777 / 1953 (39.8 %)
QRS interval	>= 120 ms	392 / 1869 (21.0 %)	369 / 1955 (18.9 %)
QT interval	>= 500 ms	62 / 1869 (3.3 %)	237 / 1955 (12.1 %)
QTc Bazett	431-450 ms (m), 451-470 ms (f) - borderline	443 / 1869 (23.7 %)	481 / 1955 (24.6 %)
	> 450 ms (m), > 470 ms (f) - prolonged	359 / 1869 (19.2 %)	549 / 1955 (28.1 %)
	>=500 ms	79 / 1869 (4.2 %)	130 / 1955 (6.6 %)
	## Increase in [30 - 60] ms versus baseline	427 / 1619 (26.4 %)	561 / 1607 (34.9 %)
	## Increase > 60 ms versus baseline	154 / 1619 (9.5 %)	261 / 1607 (16.2 %)

For patients with missing baseline assessment, only their post baseline assessments are taken
Patients with missing baseline assessment are not taken into account
Denominator refers to patients with post baseline value for the parameter
Only 12-lead ECG in normal sinus rhythm are considered

In the dronedarone group 4 (0.2%) prolonged ECG QT interval was reported as an adverse event compared 1 (<0.1%) of the patients in the placebo group. This QT prolongation lead to treatment discontinuation in 33 (1.4%) of the patients on dronedarone and 12 (0.5%) of the patients on placebo.

7.2 Adequacy of Patient Exposure and Safety Assessments

Dronedarone, if approved, will be utilized on a chronic basis. There is very little information available beyond a year or so of use. Ultimately we do not know if the side effects as seen with amiodarone will develop or the endocrine, teratogenicity, and carcinogenicity concerns as expressed by Dr. Hausner in her review and seen in animal models.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The ATHENA Study confirms the adverse events seen in the earlier NDA 21-913 of gastrointestinal disorders, EKG QT prolongation, and increased blood creatinine.

7.4 General Methodology

The ATHENA Study was in accomplished in a population that was not as sick at the ANDROMEDA Study; therefore, a difference in the death rates is seen in the two studies.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor has proposed that the dronedarone dosage is 400 mg twice daily and is to be given with the morning and evening meal. The Agency recommended to the Sponsor early in the development program that various doses be available.

According to Dr. Kumi's original review for NDA 21-913, healthy elderly males have exposures that are about 40 % higher relative to healthy young males; elderly females have exposures that are approximately 30 % higher relative to elderly males; and healthy Asian (Japanese) males have exposures that are about 100 % higher relative to healthy male Caucasians. Also, Dr. Kumi stated in his earlier review that a clear dose-response relationship was shown for QT prolongation in healthy subjects.

8.2 Drug-Drug Interactions

The following table is from Dr. Kumi's original review for NDA 21-913.

Table 29: PK/PD drug-drug interaction information

Drug	Classification	Effect of co-administration		
		PD (either or both drugs)	Dronedarone	Other Drug
	Miscellaneous			
digoxin	PGP substrate	NA	NA	↑ 2.5 fold
pantoprazole	decrease gastric pH	NA	↔	NA
theophylline	CYP1A2 substrate	NA	↔	↓ 20 %
	CYP3A function			
rifampicin	inducer	None	↓ 80 %	NA
dilitiazem	weak inhibitor	↑ repolarization time	↑ 60 %	NA
nifedipine	weak inhibitor	Lowered blood pressure	↑ 20 %	NA
grapefruit juice	moderate inhibitor	NA	↑ 3-fold	NA
ketoconazole	strong inhibitor	↑ PR, no effect on QT	↑ ≥ 9-fold	NA
verapamil	Substrate, inhibitor	↑ repolarization time	↑ 40 %	↑ 40 %
nisoldipine	substrate	↔	↔	↑ 100 %
simvastatin	substrate	↔	↔	↑ 4-fold
ethinylestradiol	substrate	NA	NA	↑ 25 %
levonorgestrel	substrate	NA	NA	↑ 18 %
	CYP2C9 function			
losartan	substrate	↑ heart rate	↔	↔
S-warfarin/R-warfarin	substrate	↑ INR by 7 %	↔	↑ AUC 11 %
	CYP2D6 function			
metoprolol	Substrate	↓ cardiac contractility	NA	↑ 60 -150 %
propranolol	substrate	↓ HR, DBP, SBP	↔	↑ 16 to 33 %

8.3 Special Populations

Dronedarone has not been studied in the pediatric population. It is contraindicated with Class 4 and probably Class 3 patients in congestive heart failure (CHF). Also, patients with severe liver failure probably should not take dronedarone.

8.4 Pediatrics

A waiver for pediatric studies at this time has been granted.

8.5 Advisory Committee Meeting

An Advisory Committee Meeting is to be held March 18, 2009.

Please Note: The Sponsor emphasizes in their briefing package to the Advisory Committee the post hoc analysis for stroke although this endpoint was not prespecified and was not submitted in the NDA.

8.6 Literature Review

Articles which were pertinent were reviewed.

8.7 Postmarketing Risk Management Plan

To be decided after the Advisory Committee Meeting March 18, 2009.

8.8 Other Relevant Materials

NA

9 OVERALL ASSESSMENT

9.1 Conclusions

The ATHENA Study which is reviewed in this NDA 22-425 is a large prospective study in patients with AF/AFL accomplished by individual treating physicians throughout the world. The primary endpoint, the composite of death from any cause or CV hospitalization, was highly statistically significant. However, the efficacy of the prevention of death from any cause was not established (p=0.176). The need to hospitalize these patients varies from physician to physician and country to country. Most importantly, the study investigates a population which is different from the prior ANDROMEDA Study which had a statistically significantly (25 vs. 12, p=0.027) higher rate of death from any cause in the patients on dronedarone. The patients in the ATHENA trial were not as sick as those in the ANDROMEDA Study. We have tried to summarize the differences in the two trials in our following table.

Table 30: Differences between ANDROMEDA and ATHENA studies at randomization

	ANDROMEDA		ATHENA	
Regions	Europe		World, Eastern Europe, USA	
	Placebo	**Dronedarone**	**Placebo**	**Dronedarone**
Age	Mean 68	Mean 69	69% were 75+	69% were 75+
AF/AFL	28%	24%	25%	24%
1st episode	48%	43%		
Paroxysmal	11%	19%		
Persistant	12%	11%	0	0
Permanent	29%	28%	0	0
NYHA				
Class I	0	0	8%	9%
Class II	37%	41%	17%	16%
Class III	59%	57%	5%	4%
Class IV	4%	2%	0	0
Ejection fraction	Wall motion index Mean 0.86	Mean 0.90	<35% 4% >35% 96%	4% 96%
Creatinine level				
<50	42%	44%	24%	21%
>50	58%	56%	76%	79%

Inclusion Criteria	**ANDROMEDA**	**ATHENA**
	Older than 18	75+ without risk factors, 70+ with risk factors
	Class II-IV NYHA	Within 6 months EKG with NSA & AF/AFL
	Wall Motion Index ≤1.2, (LVEF ≤ 35%)	
Exclusion Criteria	**ANDROMEDA**	**ATHENA**
	Acute pulmonary edema within 12 hours	Permanent AF
	MI within 7 days preceding randomization	NYHA Class IV within last 4 weeks
	Any illness other than CHF	GFR < 10 mL/min

Other information provided recently by the Sponsor on January 28, 2009, at the Agency's request, provides additional pertinent information regarding the ANDROMEDA study in patients with AF/AFL. The following table shows that dronedarone statistically significantly increased risk of death from any cause in patients with history of AF in ANDROMEDRA study.

Table 31: Analysis of time from randomization to death from any cause up to 16 January 2003; All patients with a history of AF

	Placebo (N= 126)	Dronedarone 400mg BID (N= 114)
Number of events, n	6	14
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at Day 30 [95% CI]	0.009 [0.000 ; 0.025]	0.067 [0.019 ; 0.115]
Cumulative incidence of events at Day 90 [95% CI]	0.099 [0.020 ; 0.178]	0.156 [0.079 ; 0.233]
Cumulative incidence of events at Day 180 [95% CI]	0.099 [0.020 ; 0.178]	0.156 [0.079 ; 0.233]
Log-rank test p-value	0.0444	
Relative risk [95% CI][a]	2.573 [0.988; 6.697]	

[a] Determined from cause-specific Cox regression model

The following table from the ANDROMEDA Study reveals that dronedarone statistically significantly (p=0.0046) increased the risk of cardiovascular death in patients with history of AF. It is important to remember that in ANDROMEDA study deaths and hospitalizations were adjudicated.

Table 32: Analysis of time from randomization to cardiovascular death up to 16 January 2003; All patients with a history of AF

	Placebo (N= 126)	Dronedarone 400mg BID (N= 114)
Number of events, n	3	14
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at Day 30 [95% CI]	0.009 [0.000 ; 0.025]	0.067 [0.019 ; 0.115]
Cumulative incidence of events at Day 90 [95% CI]	0.040 [0.000 ; 0.087]	0.156 [0.079 ; 0.233]
Cumulative incidence of events at Day 180 [95% CI]	0.040 [0.000 ; 0.087]	0.156 [0.079 ; 0.233]
Log-rank test p-value	0.0046	
Relative risk [95% CI][a]	5.053 [1.452; 17.585]	

[a] Determined from cause-specific Cox regression model

In the NDA, in the Investigator's Brochure, and in the Advisory Committee Briefing Package, the Sponsor stated that in the ANDROMEDA Study, the increase of mortality on dronedarone could be because of discontinuations of ACE inhibitors or AII receptor antagonists. However, the following information contradicts this sponsor's conclusion. In response to the FDA request, the Sponsor has submitted the following information regarding ACE or AII receptor Antagonists:

"In the ANDROMEDA study 36 patients in the placebo group and 61 patients in the dronedarone group never took or interrupted ACE inhibitors or AII receptor antagonists. In this subpopulation 2 patients died in the placebo group compared to 15 in the dronedarone group. The hazard ratio of 5.1 appears to be higher in this subpopulation compared to the overall ANDROMEDA population with a hazard ratio of 2.3 (95% confidence interval: 1.1 – 4.2), however the 95% confidence intervals overlap. This observation of an apparent increase in the mortality rate in dronedarone treated patients who never took or interrupted ACE inhibitors or AII receptors antagonists as compared to placebo

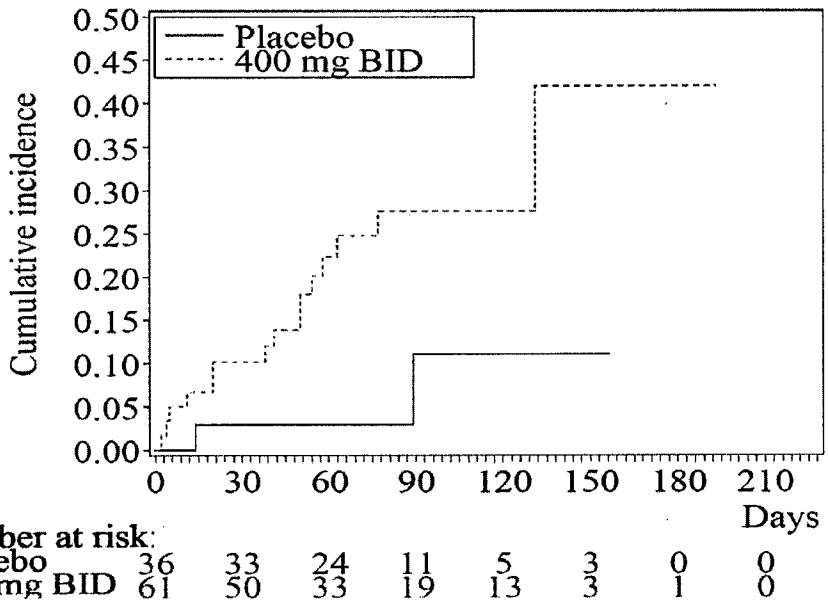
patients challenge the hypothesis that a misinterpretation of the increase in creatinine could have caused the excess of mortality observed in ANDROMEDA."

Table 33: Unadjusted analysis of time from randomization to death from any cause during the on treatment period - All patients who never took or interrupted concomitant ACE inhibitors or AII receptors antagonists (EFC4966/ANDROMEDA)

	Placebo (N= 36)	**Dronedarone 400mg BID (N= 61)**
Number of events, n	2	15
Median survival (95% CI) (days)	NA	NA
Cumulative incidence of events at 30 days [95% CI]	0.029 [0.000 ; 0.086]	0.101 [0.024 ; 0.178]
Cumulative incidence of events at 90 days [95% CI]	0.110 [0.000 ; 0.271]	0.276 [0.149 ; 0.402]
Cumulative incidence of events at 180 days [95% CI]	0.110 [0.000 ; 0.271]	0.421 [0.147 ; 0.694]
Log-rank test p-value	0.0164	
Relative Risk [95% CI] [a]	5.065 [1.157 ; 22.177]	

[a] Determined from Cox regression model, adjusted on studies
Note: protocols : EFC4966/ANDROMEDA

Figure 15: Kaplan-Meier cumulative incidence curves of time to death from any cause up to 16 January 2003 – all patients never took or interrupted ACE or ARB (EFC4966/ANDROMEDA)



9.1.1 Efficacy Conclusions

In ATHENA study, the primary composite endpoint of death from any cause or CV hospitalization was highly statistically significant. However, the efficacy of the prevention of death from any cause was not established (p=0.176). Therefore, a claim for preventing death from any cause cannot be included in the labeling.

The composite endpoint was driven mostly by the other component, CV hospitalizations. Note that the need to hospitalize these patients varies from physician to physician and country to country. Most importantly, the study investigates a population which is different from the prior ANDROMEDA Study, NDA 21-913, which had a statistically significantly (25 vs. 12, p=0.027) higher rate of death from any cause in the patients on dronedarone. Also, the patients in this ATHENA trial were not as sick as those in the prior ANDROMEDA Study.

Relative to a claim for preventing CV death, there are some important issues.

1. According to the pre-specified hierarchical procedure to control global type 1 error at the 5% level, the secondary efficacy endpoint of CV death can be tested only if the first secondary endpoint, death from any cause, is statistically significant at the 5% level. As death from any cause was not statistically significant (p=0.176), the secondary endpoint of CV death should not be tested at all. The analysis for CV death is shown in this review only as exploratory for the completeness of clinical evaluation.

2. There are some issues with the reliability of classifications of CV deaths and the robustness of p=0.03 for the CV death.

For example, in ATHENA, 12 patients with unknown cause of death were classified as having CV death. If 6 placebo patients with unknown cause of death are reclassified as having non-CV death, then the analysis of CV death in ATHENA becomes non-significant: p=0.07 (log-rank test) or p=0.09 (Wilcoxon test). Even if only 4 placebo patients with unknown cause of death are reclassified as non-CV death, then the analysis for CV death in ATHENA already becomes non-significant: p=0.05 (log-rank test) or p=0.065 (Wilcoxon test).

In the ATHENA Study, with a nominal p-value of only p=0.03 for CV mortality and many other issues mentioned above, the statistical significance based on this p-value is inconclusive and may be due to data dredging. Therefore, an additional study is needed to determine whether this finding is real.

These reviewers are concerned regarding the safety of dronedarone. There is a continuum in patients with AF/AFL, they go in and out of congestive heart failure. We feel that the safety of dronedarone presents a problem that the label alone may not be able to cover. The prior studies for rhythm and rate control did establish that patients stay in normal sinus rhythm a little longer than placebo but their heart rate on dronedarone when exercising is not within the ACC Guidelines.

9.2 Recommendation on Regulatory Action

This is to be decided after the Advisory Committee Meeting, March 18, 1009.

9.3 Recommendation on Postmarketing Actions

This is to be decided after the Advisory Committee Meeting, March 18, 1009.

9.4 Labeling Review

This will be accomplished after above Advisory Committee Meeting.

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/s/

Valeria Freidlin
2/18/2009 12:22:53 PM
BIOMETRICS

James Hung
2/18/2009 12:59:00 PM
BIOMETRICS

NDA 22-425
120 Day Safety Update
SR33589B/ MULTAQ

This Safety Update for dronedarone is from March 12, 2008 to September 15, 2008. The DIONYSOS (EFC4968) is the only study not included in the NDA. The DIONYSOS Study is a randomized double blind trial to evaluate the safety and efficacy of dronedarone versus amiodarone.

At the time of this update submission the study was ongoing and therefore the blind was not broken except for 3 Serious Adverse Events (SAEs). These SAEs include for dronedarone one case of acute hepatocellular injury and one case of anaplastic thyroid carcinoma with neck-lymph node metastasis; for amiodarone on patient with 2nd degree AV block/ Wenckebach. The other listed adverse events although they were unblinded were not unexpected.

Gail Moreschi, M.D., M.P.H., F.A.C.P.

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Gail Moreschi
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	N021913
Submission Code	N000
Letter Date	June 10, 2005
Stamp Date	June 10, 2005
PDUFA Goal Date	April 10, 2006
Reviewer Name	Gail Moreschi, M.D., M.P.H. Valeria Freidlin, Ph.D.
Review Completion Date	March 29, 2006
Established Name	Dronedarone hydrochloride
(Proposed) Trade Name	Multac
Therapeutic Class	Antiarrhythmic drug
Applicant	Sanofi-Aventis
Priority Designation	S
Formulation	Tablets
Dosing Regimen	400 mg twice a day
Indication	Rhythm and/or rate control
Intended Population	Atrial fibrillation/flutter

Table of Contents

1 EXECUTIVE SUMMARY

This NDA pertains to an important chronic medical problem, atrial fibrillation and/or flutter (AF/AFL). The incidence has been shown to increase with age and, therefore, as the population ages there will be an increase in the incidence of AF/AFL.

In the clinical submission of this NDA, the Sponsor has included five studies for efficacy. They are seeking two indications at this time: patients will remain longer in normal sinus rhythm on dronedarone compared to patients on placebo and if AF/AFL reoccurs while patients are on dronedarone their ventricular rate will be slower.

The DAFNE study was utilized by the Sponsor to determine the dose. Although the Agency as early as 1999 advised the Sponsor to provide a dosing range rather than a fixed dose, the Sponsor choose not to heed this advice. In the DAFNE study doses greater than 400 mg twice a day (BID) did not appear as efficacious as the 400 mg B.I.D. dose. Although the Sponsor was advised to study lower doses they failed to do this.

The ERATO trial evaluated ventricular rate control. In this study and in the Sponsor's two pivotal studies, the ADONIS and EURIDIS, the rate is not improved to the clinically acceptable range of 60 to 80 bpm at rest and 90 to 115 bpm with exercise. In the ERATO study, the patients on dronedarone showed no improvement over placebo in an exercise test.

In the pivotal ADONIS and ERUIDIS studies, the primary endpoint was surrogate markers for AF/AFL. The patients, when they had symptoms, used a transtelephonic device to transmit their ECG. The Sponsor did demonstrate in these two studies that patients taking dronedarone remain longer in normal sinus rhythm compared to placebo. However, their ventricular rate is not lowered in these studies to a clinically acceptable range should they revert to AF/AFL. The population chosen for these studies was relatively young and in good health.

In the reviewers' opinion, the critical study is the ANDROMEDA study which investigated patients with a previous episode of "severe" congestive heart failure (CHF). This study had clinical endpoints, death and hospitalizations, and not surrogate markers as in the other pivotal studies. The ANDROMEDA study revealed that dronedarone statistically significantly ($p = 0.027$) increased the risk of death from any cause (in fact, it more than doubled this risk, by 113%) and also increased ($p = 0.024$) the risk of hospitalizations for acute cardiovascular reasons as compared to placebo.

Although the Sponsor has another large ongoing trial in patients who are 70 or older with AF/AFL, these reviewers must recommend that this NDA is NOT APPROVABLE because of the increase in mortality. Finally, in evaluating the risk/benefit ratio, there is very little benefit to be gained from this drug which has been shown to statistically significantly increase the risk of death in older, sicker patients.

1.1 Recommendation on Regulatory Action

NOT APPROVABLE

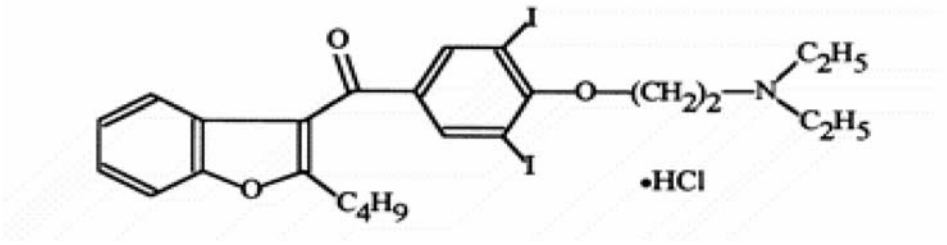
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

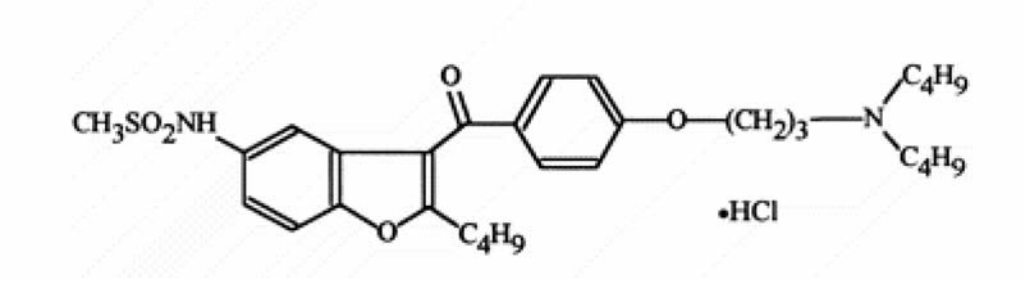
Dronedarone (SR33589B) is a new anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds that also includes amiodarone. Dronedarone has been developed by the Sponsor, Sanofi-Aventis, for the treatment of atrial fibrillation (AF) and atrial flutter (AFL).

There are 2 main physical-chemical differences that distinguish dronedarone from amiodarone: 1. the absence of iodine substituents on the benzofurane ring that was expected to eliminate thyroid side effects, and 2. the adjunction of a methane-sulfonamyl group that was expected to make the drug less lipophilic and therefore less subject to tissue accumulation (a probable mechanism of amiodarone organ toxicity).

The chemical structure of dronedarone in comparison to that of amiodarone is shown below.



Amiodarone (MW = 682)



SR33589B/Dronedarone (MW = 593)

(page 7 Module 2.5)

Figure 1 - Chemical structure of dronedarone compared to that of amiodarone

Like amiodarone, dronedarone demonstrates electrophysiological characteristics belonging to all 4 Vaughan-Williams classes of anti-arrhythmic compounds.

2.2 Currently Available Treatment for Indications

Atrial fibrillation (AF) is the most common tachyarrhythmia. AF maybe related to arterial hypertension, ischemic heart disease, heart failure, or mitral value disease. The incidence increases with age. Since more patients are living longer, the incidence is increasing. Treatment possibilities may include catheter ablation, cardiac surgery, an implantable pacemaker, or pharmacotherapy.

The main pharmacological therapeutic strategies include rate control, termination of the arrhythmia, and the prevention of thromboembolic events. In the choice of an antiarrhythmic drug both safety and efficacy are important considerations. There are two competing clinical strategies for atrial fibrillation: maintenance of sinus rhythm versus rate control. Both methods have advantages and disadvantages. Drugs that are currently used for the management of patients with AF/AFL are shown in the table below.

	Rhythm control	Rate control
Anti-arrhythmic		
Class Ia	Disopyramide Procainamide Quinidine	-- -- --
Class Ic	Flecainide Propafenone	-- --
Class II	--	betablockers (eg metoprolol, carvedilol)
Pure Class III	Dofetilide Ibutilide	-- --
Class IV	-- --	diltiazem verapamil
Multifactorial	Sotalol Amiodarone	sotalol amiodarone
Digitalis	-- --	digoxin digitoxin

(page 12 module 2.5)

Table 1 – Drugs currently used for patients with AF /AFL

2.3 Availability of Proposed Active Ingredient in the United States

Dronedarone is a new molecular entity and is not currently available in the United States. Currently it is not marketed in any country.

2.4 Important Issues With Pharmacologically Related Products

Amiodarone, originally marketed as an antianginal agent because of its coronary vasodilator properties, was observed to have potent antiarrhythmic effects. It was approved in 1985 for ventricular arrhythmias. Although not FDA approved for AF/AFL, it is clinically utilized for this indication and appears safe for patients with CHF. However, in some patients amiodarone has significant adverse reactions which include pulmonary toxicity, thyroid dysfunction and phototoxicity.

2.5 Presubmission Regulatory Activity

Several meetings were held between the original Sponsor, Sanofi Pharmaceuticals, Inc, and the FDA's Division of Cardio-Renal Drug Products.

May 27, 1999, an End of Phase I Meeting was held to discuss the development program. The Sponsor stated that in the initial phase they would focus on an indication for atrial arrhythmias. Later they plan to conduct trials for ventricular arrhythmias. At this meeting the Division recommended that a dosing regimen based on a titration scheme rather than a selection of "the dose" should be considered. Additionally, the Sponsor was to provide any effect on QT prolongation, pulmonary toxicity, thyroid dysfunction, and phototoxicity. Also, the endpoint, pharmacokinetics, drug interactions, and the enrollment of paroxysmal and/or chronic AF patients were discussed.

April 9, 2001, an End-of-Phase 2 Meeting was held with the Division. The Sponsor was seeking feedback on the design of three proposed Phase 3 studies. At this meeting the Agency noted that the risk/benefit ratio of dronedarone was an issue since the desired indication was not an improvement in morbidity or mortality. Since the dose response was not completely characterized, the Agency suggested that the Sponsor study doses below and above 800 mg to find the optimal dose. The Division Director encouraged them to study patients with chronic AF. The Sponsor was informed that for approval the Agency would require either a mortality trial in high-risk patients including AF/AFL patients with no restrictions on concomitant medications, or a DIAMOND-type of study. This meeting was clarified further by phone and mail.

July 13, 2004, a Pre-NDA meeting was held with the Division to discuss the ANDROMEDA results. This was a long term morbidity/mortality trial in CHF patients which was stopped early due to an adverse mortality effect in the dronedarone treated patients. The Sponsor described the positive findings of the ERUIDIS and ADONIS studies. Dr. Temple stated that the overall effectiveness of dronedarone is lower than three other treatments. The Sponsor theorized that in the ANDROMEDA trial more dronedarone patients had their ACE inhibitors discontinued. Dr. Temple noted that an alternative hypothesis is that dronedarone has an adverse effect in CHF patients that is potentially corrected with ACE inhibitors. Dr. Temple advised the Sponsor that the Agency must be assured that dronedarone will not lead to adverse mortality in CHF patients. The Sponsor requested that this trial be done post-marketing. Dr. Temple stated that as there was no obvious survival benefit to rhythm control, the Agency would probably not agree to the

additional trial as a post-marketing commitment. The Sponsor asked if the application could be filed with no additional trials and Dr. Temple said this would be likely.

An additional Pre-NDA meeting was held January 3, 2005, between the Sponsor and the Division to discuss a new protocol evaluating the efficacy of dronedarone for the prevention of cardiovascular hospitalization or death in patients with AF/AFL. Dr. Temple asked the Sponsor if they were sure they have selected the correct dose. The Sponsor stated that the 400 mg BID was the only effective dose in their dose-ranging trial. Dr. Temple stated that the sample size in the new study should be based on the total number of events to be sure that the trial is adequately powered. Also, he stated that because dronedarone is not intended as a life-saving treatment, the Agency must be assured that it does not lead to increased mortality. The Sponsor asked if there was any chance of approval prior to the completion of the trial. Dr Temple said that approval without the final results was very improbable.

2.6 Other Relevant Background Information

The Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) in France and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom are awaiting the results of EFC5555 before granting approval.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

3.2 Animal Pharmacology/Toxicology

The following is from Dr. Elizabeth Hausner's Review.

"A. Brief overview of nonclinical findings: Proposed for atrial arrhythmia, dronedarone is an amiodarone analogue lacking the iodine substituents. In in vitro systems, isolated organ culture and whole animal studies have been used to compare this agent to amiodarone. There are many similarities between the effects of the two agents on the ion channels of the heart and the behavior in various non-clinical models of cardiac function that are intended to show anti-arrhythmic potential.

The drug has relatively low oral bioavailability of in the dog 14 % and rat 22%. The volume of distribution is large, from 12 to 66 l/kg with a moderately high systemic clearance of 2-4 l/h/kg. In all species studied, including human, dronedarone was highly protein bound (>99%). Dronedarone is also highly metabolized with one known active metabolite (SR35021).

In addition to the usual toxicological characterization, dronedarone has also been assessed for immunotoxicologic potential (no significant issues apparent at this time), effect upon thyroid function (incompletely described) and dyslipidosis (occurs to a lesser extent than seen with amiodarone). Mild respiratory effects (decreased respiratory rate and tidal volume) were seen in the single dose respiratory safety pharmacology study. Phototoxicity (mild to moderate at the equivalent of 2X MRHD) has been demonstrated in albino animals. Dronedarone has been demonstrated to bind to melanin. How this will affect phototoxicity is unknown. The sponsor has provided no characterization of the mechanism of the carcinogenic findings or the endocrine effects.

Some aspects of the non-clinical toxicology are puzzling. There are a number of instances where effects do not seem to follow a dose-response. It also appears that there is a lessening or abrogation of effects with extended dosing. That is, effects apparent after 1 month or 3 months of dosing are not evident after 6 months. Yet, plasma levels are no less at 6 months than they were at 3 months.

The sponsor is to be commended on the thoroughness of some aspects of the nonclinical characterization. That is, because of the similarity to amiodarone, immunotoxicity and phototoxicity studies were conducted and comparator compounds (positive controls) appear frequently. An outside review panel was assembled to provide a second opinion on the carcinogenicity studies. Yet the reporting does not do justice to these efforts. For example:
1) There were inconsistencies between the CTD non-clinical summary and the actual study reports.
2) There were inconsistencies within reports where textual numbers were not precisely the same numbers from the summary tables or single animal data
3) There were instances where findings were mentioned within the text of a report for which I could not find tables of numerical summaries.
4) The quality of the Carcinogenicity report by the outside review panel was disappointing at best."

"B. Pharmacologic activity: Dronedarone has been shown to have properties of beta adrenergic blockade, and cardiac Na, K and Ca channel modulation. However, there is inadequate characterization of the receptor binding properties of both dronedarone and the two major metabolites SR35021 and SR90154. In particular, the possibility of interaction with the thyroid receptor, hormonal receptors and steroidal receptors should be investigated.

C. Nonclinical safety issues relevant to clinical use: Dronedarone has been shown to be teratogenic, genotoxic, carcinogenic and to disrupt female cyclicity. The target organs of toxicity appear to be the kidney, liver, and gastrointestinal tract. Renal changes were usually without histological correlates and manifested primarily as changes in serum creatinine and serum electrolytes, excreted creatinine and electrolytes. Mild to moderate phototoxicity has been shown non-clinically in rats at a dose of 200 mg/kg (1200 mg/m2 or 2.5x MRHD based on a surface area comparison). Dronedarone does affect thyroid metabolism but this is incompletely defined. Hepatic effects range from elevations in ALT and AST to necrotic foci, possibly too small to cause perceptible changes in liver status tests. Safety pharmacology showed that dronedarone

caused decreases in respiratory rate and tidal volume. Dyslipidosis manifested as foamy macrophages occurs but apparently to a lesser extent than seen with amiodarone.

A radiolabel distribution/excretion study showed that the mean concentration of total radioactivity in the heart, liver and lungs was approximately 13, 5 and 20 times higher respectively at 4 hours post-dose on day 14 compared to 24 hours post dose on day 1. This is indicative of tissue accumulation. Comparing 4-hours post-dose at the earliest steady state vs. 4-hour post-dose several weeks later would more clearly address this potential issue.

Cardiac effects are also noted in rats, dogs and macaques. These include such things as decreased heart rate, increased PR interval and increased QT interval. QTc was as decreased heart rate, increased PR interval and increased QT interval. QTc was inconsistently increased, possibly due to the fact that Bazett's formula was uniformly used no matter what the heart rate of the animals. First degree block was reported in rats, dogs and monkeys. Second degree block was also reported in macaques. Increased T wave amplitude was also noted in some studies. Many of the changes can be viewed as extensions of the expected pharmacology. Both dronedarone and the active metabolite SR35021 inhibit the hERG channel with almost the same potency as cisapride, the positive control for the studies."

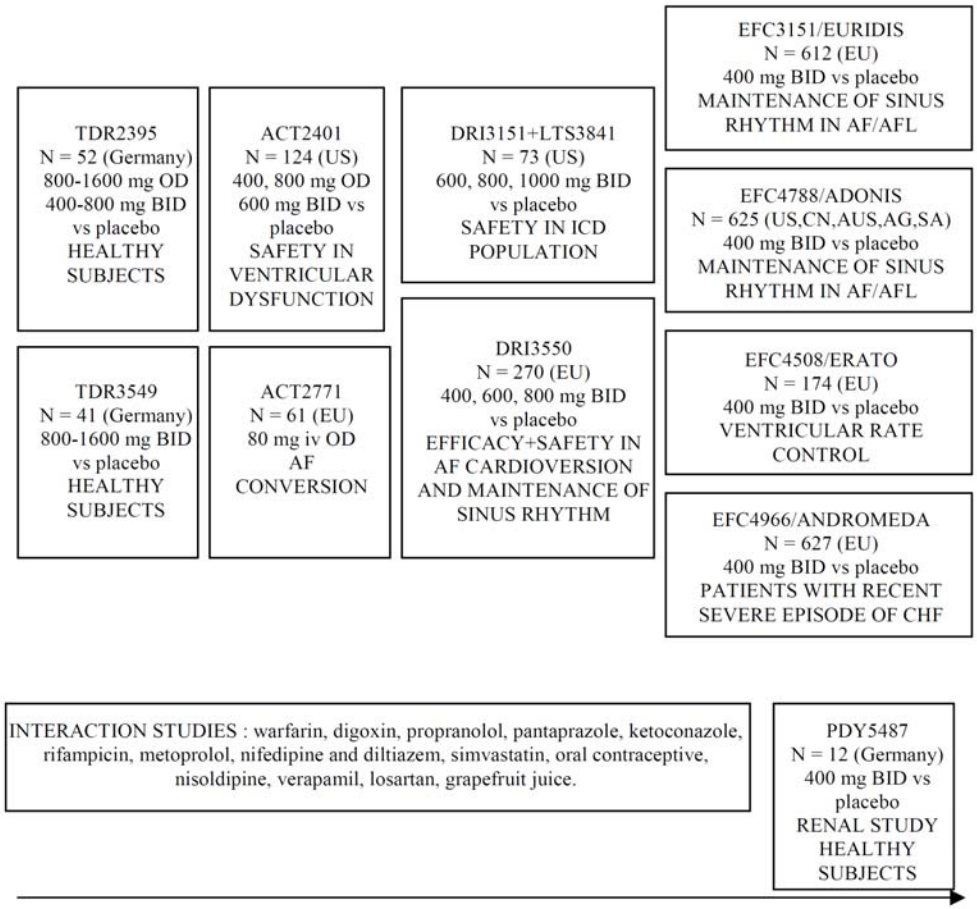
4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical studies were all submitted electronically and reviewed.

4.2 Tables of Clinical Studies

An overview of the clinical program is shown in the following figure.



EU: Europe, US: United States, CN: Canada, AUS: Australia, AG: Argentina, SA: South Africa.
(page 15 module 2.5)

Figure 2 - Clinical development program of dronedarone

4.3 Review Strategy

Drs. Moreschi and Freidlin completed the Efficacy Review together. Dr. Freidlin advised Dr. Moreschi on the Safety Review.

4.4 Data Quality and Integrity

DSI visited Corelab, France. No irregularities were found.

4.5 Compliance with Good Clinical Practices

It appears that all studies were done in compliance with Good Clinical Practices.

4.6 Financial Disclosures

Dr. Jeremy N. Ruskin, a subinvestigator who participated in Study EFC4788, has received honoraria for consultation for another Sanofi-Synthelabo compound. Sanofi-Synthelabo does not believe any bias, intentional or unintentional, was introduced by this significant payment of other sorts.

5 CLINICAL PHARMACOLOGY

This section is from Dr. Robert O. Kumi's Review

5.1 Pharmacokinetics

"1. Dronedarone Pharmacokinetics (ADME)
Absorption/absolute bioavailability and general pharmacokinetics (PK)
• Dronedarone ***absolute oral bioavailability*** (BA) following administration of a capsule formulation (800 mg) is approximately 15 %, but this value may not be reflective of the absolute oral BA of the to be marketed tablet formulation (proposed 400 mg dose) due to differing food effect (formulation dependent) and dose-dependent pharmacokinetics oral administration
• Administration of ***food*** increases mean dronedarone absorption from approximately 2- (low fat meal) to 5-fold (high fat meal)
• Dronedarone exposure increased in a ***greater than dose proportional manner*** following single and multiple dose administration. For a two-fold increase in dose, the exposure increased by 2.5 to 3.5-fold over the 200 to 1600 dose range
• ***Steady state*** is achieved approximately seven days after repeated administration of 400 mg dronedarone twice daily
• The mean accumulation ratio is ~ 2.6 at the proposed dosage
• Dronedarone exhibits dose- and time-dependent PK
• Dronedarone has limited properties associated with PGP substrate status

Distribution
• Dronedarone is approximately 99 % bound to plasma proteins at therapeutic drug concentrations; the main binding component is albumin
• Following single dose administration of IV dronedarone (40 – 80 mg), the volume of distribution associated with the terminal elimination phase was 2500 – 3400 L

Metabolism and P-glycoprotein
In vitro information
• Dronedarone metabolism was mainly mediated by CYP3A, yielding the major metabolite, SR35021
• Dronedarone has a low inhibitory potential towards major CYPs), including on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. The most inhibitory potential was towards CYP3A4 (I/Ki ~ 0.01) and CYP2D6 (I/Ki ~0.06)

• Dronedarone exhibited similar PGP inhibitory potential as cyclosporine A by preventing the efflux of two PGP substrates, digoxin and vincristine

In vivo information
Dronedarone is extensively metabolized following dronedarone administration and negligible amounts of intact dronedarone are present in the feces. N-debutylation appears to be the main metabolic pathway of dronedarone, leading to the formation of SR35021; however additional processes occur including oxidation of SR35021, oxidative deamination, and direct oxidation. Ultimately, several metabolites (> 30) are formed and excreted in the urine and feces. SR35021 is not detected following IV administration, suggesting that it is formed mainly presystemically during first pass.

Properties of metabolites
The activities of all the identified metabolites (n > 30) were not tested; however, the major metabolite, SR35021 is 3 to 10 times less potent than dronedarone. SR35021 plasma levels are approximately half that of dronedarone; other individual metabolites account for < 3 % of the administered dronedarone dose. Based on the low exposure of the metabolites, they are unlikely to impact overall activity associated with dronedarone administration, unless they are individually or collectively more potent than dronedarone.

Overall, SR35021 exhibited PK properties (accumulation, half-life, volume of distribution) that were similar to that of dronedarone.

Excretion (Elimination)
• Mass balance indicates that orally administered dronedarone is ultimately excreted in the urine (6 %) and feces (84 %) primarily as metabolites. No unchanged dronedarone was excreted in the urine. Similar findings were obtained following IV administration. Radioactivity was undetectable after two weeks.
• The systemic plasma clearance (IV administration) ranged from 130 to 150 L/h and the apparent oral clearance (CL/F) was ~ 500 L/h for the 400 mg dose.
• Dronedarone half-life following IV administration was between 13 and 19 hours; following oral administration half-life appeared to be dose- and time- dependent ranging from 27 to 32 hours."

5.2 Pharmacodynamics

"Pharmacodynamic effects of dronedarone
• Alters electrophysiological measures: generally increases QT-, PR- and RR- and QRS-intervals and decreases T-wave amplitude
• Decreases heart rate (bradycardic effect)
• Tends to decrease blood pressure (systolic and diastolic)
• Causes an increase in serum creatinine levels by inhibiting renal tubular secretion of creatinine; which leads to apparent decrease in renal function (CLcr decreased). However, this effect is reversible upon discontinuation of dronedarone therapy."

5.3 Exposure-Response Relationships

"QT/QTc Information
A clear dose-response relationship was shown for QT prolongation in healthy subjects.

Special Populations
• ***Renal Insufficiency:*** The effect of impaired renal function was not evaluated in the dronedarone program
• ***Hepatic insufficiency:*** The effect of impaired hepatic function has not been evaluated, but there is an ongoing study to evaluate this patient population.
• ***Gender:*** Relative to elderly males, elderly females have exposures that are approximately 30 % higher.
• ***Age:*** Relative to healthy young males, healthy elderly males have exposures that are about 40 % higher
• ***Race:*** Relative to healthy male Caucasians, healthy Asian (Japanese) males have exposures that are about 100 % higher."

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The primary indication sought by the Sponsor is the efficacy of dronedarone for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL.

The secondary objectives are:

- assessment of the efficacy of dronedarone versus placebo on AF/AFL- related symptoms;
- assessment of the efficacy of dronedarone versus placebo on ventricular rate control in case of AF/ AFL recurrence;
- assessment of the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/ AFL after the drug plasma level steady state is reached;
- assessment of the tolerability of dronedarone versus placebo in the target population.

The pharmacokinetic (PK) objective was to document dronedarone and SR35021, the main metabolite, trough plasma levels at steady state and to describe the PK of the selected dose in the target population.

6.1.1 Methods

The Sponsor has submitted five trials pertaining to their efficacy claim: DAFNE (DRI3550), ADONIS (EFC4788), EURIDIS (EFC3153), ERATO (EFC4508), and ANDROMEDA (EFC4966). The DAFNE study determined the dose to be utilized and has previously been reviewed by Dr. Williams. His review is attached in the appendix and only a few comments will be included here. Also, this study was reviewed in detail by Dr. Christine Garnett. Her review is included with Dr. Robert Kumi's review.

The two pertinent trials to support the sponsor's claim are the ADONIS and EURIDIS studies which are essentially similar in design and will be discussed here. The ERATO study was a supportive study of their claim for ventricular rate control. These reviewers, however, consider the most important study to be the ANDROMEDA. This study has clinical outcomes as the primary endpoints whereas the other pivotal studies have surrogate primary endpoints. According to the sponsor this study consisted of patients with a recent severe episode of congestive heart failure (CHF). However, it is noted by the reviewers that when the patients were randomized into the study they were in Class II (39 %) or III (58 %) which is only mild to moderate CHF as shown in table 6 on page 26. Only 3% of the randomized patients were in Class IV. These reviewers consider this the most important trial based on the statistically significant ($p = 0.027$) increased number of deaths (more than doubled) in the patients treated with dronedarone.

6.1.2 General Discussion of Endpoints

Clinically atrial fibrillation (AF) is defined as temporary, persistent (intermittent), or chronic. There are two general approaches to the treatment of persistent and chronic AF: rhythm or rate control. Several clinical trials including the AFFIRM, RACE, PIAF, and STAF have attempted to document which approach is superior. However, this decision probably should be individualized for each patient depending on their age, underlying illness, personal choice, and their response to drugs. The Sponsor has attempted to show efficacy for both the rhythm and rate control approaches. Additionally, atrial fibrillation is common in patients with congestive heart failure (CHF). AF increases the risk of cardiovascular morbidity among these patients. Therefore, another efficacy goal of the Sponsor was to show a decrease in the number of deaths and/or hospitalizations in patients with CHF. The endpoints in the pivotal trials, ADONIS and EURIDIS, were surrogate markers whereas the ANDROMEDA study has clinical outcomes, death or hospitalizations, as the primary endpoint.

6.1.3 Study Design

A brief synopsis of the studies submitted for efficacy will follow. Additional information regarding these studies is included in the appendix. Since these reviewers believe the ANDROMEDA to be the most important study, it will be described here first briefly and in more detail in the appendix. The ADONIS and EURIDIS are the two pivotal trials. They have essentially the same design and will be described after the ANDROMEDA. The DAFNE was a phase IIB trial to determine the dose. It was previously reviewed by Dr. Williams and will be

briefly mentioned here. Dr. Williams' review is included in the appendix. The ERATO, designed to be a supportive study for ventricular rate control, will be briefly cited here.

6.1.3.1 The ANDROMEDA Study (EFC4966)

Title: Antiarrhythmic trial with dronedarone in moderate to severe CHF evaluating morbidity decrease

Study dates: June 12, 2002 to August 19, 2003. There was a premature end to both the study drug treatment and randomizations on January 16, 2003, which is discussed later.

Study Population: patients with moderate to severe congestive heart failure with left ventricular dysfunction.

Design: Multicenter, multinational, double-blind, parallel-group, placebo-controlled study of efficacy of dronedarone 800 mg daily, for reducing death or hospitalizations for worsening heart failure.

Study centers: 72 active centers in 6 European countries: Denmark, Hungary, the Netherlands, Norway, Poland, and Sweden

Study objectives:
Primary**:** To evaluate whether dronedarone reduces death from any cause or hospitalizations for worsening heart failure in patients, according to the sponsor, with moderate to severe congestive heart failure (CHF) and left ventricular dysfunction (LVD), when added to usual evidence-based treatments for CHF, over a minimum period of 12 months as compared to placebo.

Secondary objectives were to evaluate whether dronedarone:
• reduces death from any cause;
• reduces hospitalization for worsening heart failure;
• reduces hospitalization for acute cardiovascular reasons;
• reduces arrhythmic/sudden death;
• is effective in maintaining sinus rhythm in the target population.

Safety and tolerability of dronedarone versus placebo were evaluated. Dronedarone and SR35021 plasma levels at steady state were documented.

Methodology**:** Multicenter, multinational, double-blind, parallel-group, placebo-controlled study of dronedarone 800 mg daily (400 mg BID) for reducing death or hospitalizations for worsening heart failure. In addition to the blinded Steering Committee (SC) responsible for the conduct of the trial, a central, independent data safety monitoring board (DSMB) monitored the safety of patients in the study, and an independent, blinded Critical Events Committee (CEC) adjudicated the causes of deaths and hospitalizations.

Number of patients evaluated**:**
Planned: 1,000: Main analysis population: Randomized: 627; Treated: 627;
Evaluated: Efficacy: 627; Safety: 627

On January 16, 2003, 7 months after the randomization of the first patient, the inclusions in the study and ongoing study drug treatment were discontinued following a recommendation of the DSMB, because of a higher number of deaths observed in patients randomized to the active treatment compared to placebo. The DSMB, following a second safety analysis February 17, 2003, recommended follow-up of mortality, major clinical events and renal function for all patients, up to July 17, 2003 (6 months after end of inclusions).

All patients randomized in center 616004 (n = 23) were excluded from the main analysis population by the Sponsor due to a major violation in good clinical practice (GCP) documented in this center, raising doubts about the integrity of the data provided by this center. In Supplement No. 015, the sponsor states there were 23 patients in this center. Eleven patients were randomized to receive dronedarone and 12 were in the placebo group. Among these patients none of them experienced hospitalization for worsening of heart failure or death up to January 16, 2003. Therefore, there was no primary efficacy event at this center.

Inclusion criteria:
Patients $\geq$18 years hospitalized with symptomatic CHF, current New York Heart Association (NYHA) class II-IV, requiring treatment with a diuretic, with at least 1 episode of dyspnea or fatigue at rest or on slight exertion (corresponding to NYHA class III or IV) within the previous month. Wall motion index (WMI) $\leq$1.2 [corresponding to a left ventricular ejection fraction (LVEF) of approximately $\leq$ 0.35], determined by a blinded central evaluation of a recorded standard echocardiography, was required.

Duration of treatment**:** Planned treatment duration for the last randomized patient was 12 months (event driven trial).

Pharmacokinetics: Dronedarone and SR35021 plasma levels were planned to be assessed at Month 1 (M1) and M6 in about 50% of patients. As well, several blood samples (pre-dose, 2h, 4h, 6h, 8h, 10h and 12h post-dose) were to be taken in a subgroup of about 30 patients at M1.

Safety included: Adverse events (AEs), clinical laboratory evaluations [liver function, renal function, electrolytes, metabolism, white blood cells, hemoglobin (Hb) and platelets], vital signs, 12-lead electrocardiogram (ECG).

Statistical methods**:** For all efficacy and safety evaluations, patients were analyzed according to the treatment actually received.

Analysis periods: 3 analysis periods were defined: “Up to January 16, 2003”; “Up to February 17, 2003”; and “Up to July 17, 2003”. These periods were considered for efficacy and safety analyses. In addition, the treatment emergent period (or “on-treatment period”), i.e.,

between first and last study drug administration plus 10 days, was also evaluated for safety, as planned in protocol.

Efficacy: The primary analysis of the primary endpoint, carried out up to January 16, 2003, was the comparison of the 2 treatment groups using a 2-sided Log-rank test (level of significance 0.05). Cumulative incidence functions in each treatment group were calculated using Kaplan-Meier estimate as well as the corresponding 95% confidence interval (CI) at specified time points. Cox's proportional hazard model was used to estimate the hazard ratio (labeled in tables "Relative risk" with 95% CI). The original protocol states the primary and the secondary analyses will not include covariates (Appendix 16.1.1, Sections 10.7.1.2.3 and 10.7.2.2).

Secondary analyses
The primary analysis was also performed up to February 17, 2003.

Sensitivity analysis and per-protocol analysis
A sensitivity analysis including patients randomized in the Polish center 616004 was done on the periods "Up to January 16, 2003" and "Up to February 17, 2003". On treatment analysis was performed on the per protocol population.

The Sponsor's post hoc covariate analyses
The Sponsor submitted post hoc covariant analyses that were not prespecified in the original protocol. The Sponsor's covariate analyses were as follows:
The primary efficacy endpoint was analyzed by the Sponsor using the following covariates: baseline weight, creatinine clearance, WMI, NYHA status, and concomitant intake (up to date of endpoint or censoring) of beta-blocker, digitalis, spironolactone, ACE inhibitors or AII receptor antagonists. First, a Cox proportional hazard model was used with all covariates (intake of concomitant medication was included as time dependent covariates) in order to adjust the treatment effect to variables with possible influence on the endpoint. Then, a Cox proportional hazard model was performed for each subcategory defined by these covariates; in these univariate analyses, intake of co-medication is intake up to the endpoint or censoring date whenever the co-medication started. Kaplan-Meier cumulative incidence curves have been done for each subcategory of the more significant covariates among those defined above. This analysis was performed on the periods "Up to January 16, 2003" and "Up to February 17, 2003".

Analyses of secondary endpoints:

- for death from any cause, the analysis consisted in the comparison of the 2 treatment groups using a 2-sided Log-rank test. Cox's proportional hazard model was used to estimate the hazard ratio with 95% CIs;
- for hospitalization for worsening heart failure and for hospitalization for acute cardiovascular reasons, the cumulative incidence of first hospitalization considering death from any cause as a competing risk was estimated by treatment group and compared by the Log-rank test. The number of days to first hospitalization was summarized as a quantitative variable and compared using a Wilcoxon test;
- for arrhythmic/sudden deaths the same method was used as for death from any cause.

Pharmacokinetics: Descriptive statistics for C_{max}, AUC_{0-12}, C trough, and for $C_{max,av}$ or C_{trough}, were calculated for dronedarone treatment.
There were 2 analyses: 1 compartmental analysis for patients having a full pharmacokinetics (PK) profile at M1, for C_{max}, t_{max}, AUC_{0-12}, and C_{trough}; and 1 descriptive analysis according to time windows.

Safety: The frequency of patients with treatment emergent AEs (TEAEs), deaths, treatment emergent serious AEs (SAEs) and TEAEs leading to discontinuation of study drug were summarized by treatment group, by primary system organ class and preferred term. The TEAEs were also summarized by relationship to study drug and intensity.

Clinical laboratory data, vital signs and ECG parameters (only when in normal sinus rhythm), and their changes from baseline were summarized at each protocol time point. Repeated evaluations of change from baseline were analyzed using a mixed model with the baseline assessment as covariate, for creatinine, potassium and heart rate (HR). The number and percentage of patients presenting at least 1 post baseline potentially clinically significant abnormality (PCSA) in laboratory tests, vital signs and ECG parameters were summarized; comparisons between the 2 treatment groups by Fisher's exact test were restricted to creatinine and potassium.

6.1.3.2 The ADONIS Study (ECF4988)

Title: American-Australian-African trial with Dronedarone in atrial fibrillation or flutter patients for the maintenance of Sinus rhythm (ADONIS)

Study dates: November 29, 2001 to September 25, 2003

Study Population: patients with a recent episode of atrial fibrillation or atrial flutter

Design: Multicenter, multinational, double-blind, parallel-group study, comparing efficacy of dronedarone versus placebo for maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter.

Study centers: 101 active centers in 5 countries: USA, Canada, Australia, South Africa and Argentina.

Objectives:
Primary: To assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter (AF/AFL).

Secondary:

- to assess the efficacy of dronedarone versus placebo on AF/AFL-related symptoms;
- to assess the efficacy of dronedarone versus placebo on ventricular rate control in case of AF/AFL recurrence;
- to assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL after drug plasma level steady state is reached;
- to assess the tolerability of dronedarone versus placebo in the target population;
- to document dronedarone and SR35021, the main metabolite, trough plasma levels at steady state and describe the pharmacokinetics (PK) of the selected dose in the target population.

Methodology:
Multicenter, multinational, double-blind, parallel-group, placebo-controlled study of the efficacy of dronedarone 800 mg daily (400 mg BID) in AF/AFL patients. In addition to the blinded Steering Committee (SC) responsible for the good conduct of the trial, an independent Data Safety Monitoring Board (DSMB) monitored periodically patient safety. The detection of AF/AFL recurrences was based on a centralized review of transtelephonic electrocardiogram monitoring (TTEM) and 12-lead electrocardiogram (ECG) with adjudication of the first AF/AFL recurrence by a group of 4 senior cardiologists of ECG Corelab.

Number of patients planned: 552; Randomized: 629; Treated: 625
Evaluated**:** Efficacy: 625; Safety: 625

Diagnosis and criteria for inclusion: Patients of either sex, aged 21 years or greater, in sinus rhythm for at least 1 hour at the time of randomization and with at least 1 ECG-documented AF/AFL episode in the last 3 months.

Criteria for evaluation:
Efficacy:
Primary endpoint**:** time in days between randomization and the first AF/AFL recurrence, defined as an episode lasting 10 minutes or more, as indicated by 2 consecutive, 12-lead ECGs or TTEM tracings recorded 10 minutes apart, and both showing AF/AFL confirmed by the ECG Corelab.

Secondary endpoints**:**
- symptomatic AF/AFL among the adjudicated first AF/AFL recurrence;
- ventricular rate assessed at the time of the adjudicated first AF/AFL recurrence;
- time elapsed in days between Day 5 midnight (steady state) and the adjudicated first AF/AFL recurrence within 12 months from randomization.

Pharmacokinetics: Plasma concentrations of dronedarone (SR33589) and SR35021 were planned to be assessed at trough, i.e., just before dosing (C_{trough}), in all patients, at visits Day 7, Day 21, Month 4 (M4), M9 and M12.

Safety: Adverse events (AEs), clinical laboratory evaluations (liver function, renal function, electrolytes, metabolism, white and red blood cells and platelets, and endocrinology), vital signs, 12-lead ECG, chest X-ray.

Statistical methods**:** For all efficacy and safety, patients were analyzed according to the allocated treatment by interactive voice response system (IVRS) at time of randomization.

Efficacy:
The primary analysis of the primary endpoint, in the randomized and treated patients population, was the comparison of the 2 treatment groups using a 2-sided Log-rank asymptotic test. Cumulative incidence functions in each treatment group were calculated using the nonparametric Kaplan-Meier estimate. The relative risk with 95% confidence interval (CI) was estimated using a Cox model with treatment group as the only factor.

The primary endpoint was supplemented by:

- a PP approach, considering the time of primary endpoint and the time of last study drug administration plus 10 days as competing risks;
- a baseline covariate analysis (binary prognostic factors: electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization, chronic treatment with amiodarone, structural heart disease) using a Cox model.

The analyses of the secondary endpoints comprised the following:

- the primary endpoint was analyzed according to the presence/absence of symptoms through a survival competing risks analysis;
- ventricular rate assessed at the time of primary endpoint was analyzed using a 2-way analysis of variance (ANOVA), with treatment and ECG recording methods as covariates;
- time between steady state and adjudicated first AF/AFL recurrence was analyzed in the modified randomized and treated patients population, using the same analytical techniques as those used for the primary efficacy endpoint (the PP approach as defined above, was also applied).

Pharmacokinetics: Concentration data were log-transformed for analyses. In the dronedarone group, repeated measures were analyzed using a mixed model including age category, gender, and treatment as between factors in order to determine day of steady state. Average trough plasma concentration ($C_{trough,av}$) and average maximum plasma concentration ($C_{max,av}$) were calculated individually as the average of all values determined to be at steady state for each patient. Comparisons among groups [females / males, <65 years / >65 years, and moderate cytochrome P450 (CYP) 3A4 inhibitor / no CYP3A4 inhibitor] were performed using a 3-way ANOVA (age, gender, moderate CYP3A4 inhibitor categories). Contrasts with 95% CIs were computed and were converted to ratios of means with 95% CIs using the antilog transformation.

Safety: All safety analyses were carried out in the randomized and treated patients population, considering all assessments which occurred from first study drug intake to last study drug intake plus 10 days, i.e., treatment emergent. The frequency of patients with treatment emergent AEs (TEAEs), deaths, treatment emergent serious AEs (SAEs) and TEAEs leading to discontinuation of study drug were summarized by treatment group, by primary system organ class and preferred term. The TEAEs were also summarized by relationship to study drug and intensity.

Clinical laboratory data, vital signs and ECG parameters (only when in normal sinus rhythm), and their changes from baseline were summarized at each protocol time point. Repeated evaluations of change from baseline were analyzed using a mixed model with the baseline assessment as covariate, for creatinine, potassium and heart rate (HR). The number and percentage of patients presenting at least 1 post-baseline potentially clinically significant abnormality (PCSA) in laboratory tests, vital signs and ECG parameters were summarized; comparisons between the 2 treatment groups by Fisher's exact test were restricted to creatinine and potassium.

6.1.3.3. The EURIDIS Study (EFC3153)

Title: European trial in atrial fibrillation or flutter patients receiving dronedarone for the maintenance of Sinus rhythm

Study dates: November 19, 2001 to August 14, 2003

Study Population: patients with a recent episode of atrial fibrillation or atrial flutter

Design: Multicenter, multinational, double-blind, parallel-group study, comparing efficacy of dronedarone versus placebo for maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter

Study centers:
65 active centers in 12 countries: Netherlands, Germany, Poland, Hungary, Italy, France, Czech Republic, Belgium, Spain, Denmark, Finland and United Kingdom.

Objectives:
Primary: To assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of atrial fibrillation/atrial flutter (AF/AFL).

Secondary:

- to assess the efficacy of dronedarone versus placebo on AF/AFL-related symptoms;
- to assess the efficacy of dronedarone versus placebo on ventricular rate control in case of AF/AFL recurrence;

- to assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL after drug plasma level steady state is reached;
- to assess the tolerability of dronedarone versus placebo in the target population;
- to document dronedarone and SR35021, the main metabolite, trough plasma levels at steady state and describe pharmacokinetics (PK) of the selected dose in the target population.

Methodology: Identical to ADONIS reviewed above.

Number of patients**:** Planned: 552; Randomized: 615; Treated: 612
Evaluated**:** Efficacy: 612; Safety: 612

Diagnosis and criteria for inclusion:
Patients of either sex, aged 21 years or greater, in sinus rhythm for at least 1 hour at the time of randomization and with at least 1 ECG-documented AF/AFL episode in the last 3 months.

Duration of treatment**:** 12 months and observed approximately 13 months

Criteria for evaluation: efficacy, pharmacokinetics, and safety were identical to the ADONIS study cited above.

6.1.3.4. The ERATO Study (EFC4508)

Title: Efficacy and safety of dronedarone for the control of ventricular rate during atrial fibrillation (ERATO)

Study dates: August 8, 2002 to June 9, 2004

Study Population: Patients with symptomatic permanent atrial fibrillation

Design: Multicenter, multinational, double-blind, parallel-group study comparing efficacy of dronedarone versus placebo for control of ventricular rate during atrial fibrillation

Study centers: 35 active centers in 9 countries: Belgium, Czech Republic, France, Italy, Netherlands, Poland, Spain, Sweden and Switzerland.

Objectives:
Primary: To assess the efficacy of dronedarone for the control of ventricular rate in patients with atrial fibrillation (AF) at rest.

Secondary objectives:

- To assess the efficacy of dronedarone in reducing ventricular rate in patients with AF during exercise without decreasing exercise tolerance;
- To assess the tolerability of dronedarone in the selected population;
- To document dronedarone and SR35021 plasma levels.

Methodology: Multicenter, multinational, double-blind, randomized, parallel-group, placebo controlled study of the efficacy of dronedarone 800 mg daily (400 mg BID), in AF patients. An independent Data Safety Monitoring Board (DSMB) monitored periodically patient safety.

Number of patients: Planned: 160; Randomized: 174; Treated: 174
Evaluated: Efficacy: 174; Safety: 174

Diagnosis and criteria for inclusion:
Patients of either sex, aged 21 years or greater, with symptomatic (symptomatic refers to any AF-related symptoms including palpitations) permanent AF (AF > 6 months) for which cardioversion was not considered; and with resting ventricular rate $\geq$ 80 bpm at screening measured on a 6-second rhythm strip.

Duration of treatment**:** 6 months and observed for approximately 7 months

Criteria for evaluation**:**
Efficacy:
Primary endpoint**:** Change in mean ventricular rate (HR) measured by 24-hour Holter recording at rest on Day 14 (steady state) compared to baseline.

Secondary endpoints**:**

- Exercise tolerance on Day 14 compared to baseline (maximal exercise duration defined as time elapsed between the start of the exercise test and its stop).
- evaluation of exercise performance: difference in heart rate (HR) at sub-maximal and maximal exercise between baseline and Day 14;
- difference in HR evaluated by the 24-hour Holter recording between baseline and Month 4.

Pharmacokinetics: Plasma concentrations of dronedarone (SR33589) and its metabolite SR35021 were planned to be assessed at trough, i.e., just before dosing (C_{trough}), on Day 14 (steady state), M2 and M4.

Safety: Adverse events (AEs), clinical laboratory evaluations (liver function, renal function, electrolytes, metabolism, white and red blood cells and platelets), vital signs, and ECG.

Statistical methods:
Efficacy: The primary analysis of the primary endpoint was performed using an analysis of covariance (ANCOVA) taking into account treatment group and baseline intake of medications [beta-blockers, calcium antagonists (diltiazem, verapamil), digitalis considered separately] as factors, as well as age and baseline Holter HR value as covariables. Missing data were imputed

using multiple imputation technique to provide treatment effect assessment based on all randomized patients.

Secondary endpoints:
Maximal exercise duration: Considering a sequential approach, main analysis of maximal exercise duration was performed only if the primary analysis of the primary endpoint was significant, without adjustment, at a significance level of 5%. Missing data were imputed using the same multiple imputation technique as that used for the primary analysis of the primary endpoint.
Other secondary variables: The same ANCOVA, on changes from baseline, was performed without multiple imputation for missing data.

Safety: All safety analyses were carried out, considering all assessments which occurred from first study drug intake to last study drug intake plus 10 days, i.e., treatment emergent. The frequency of patients with treatment emergent AEs (TEAEs), deaths, treatment emergent serious AEs (SAEs) and TEAEs leading to permanent discontinuation of study drug were summarized by treatment group, by primary system organ class and preferred term. The TEAEs were also summarized by relationship to study drug and intensity.

Clinical laboratory data, vital signs and ECG parameters, and their changes from baseline were summarized at each protocol time-point. Repeated evaluations of change from baseline were analyzed using a mixed ANCOVA model for creatinine, potassium, CPK and HR. The number and percentage of patients presenting at least 1 post baseline potentially clinically significant abnormality (PCSA) in laboratory tests, vital signs and ECG parameters were summarized; comparisons between the 2 treatment groups by Fisher's exact test were restricted to creatinine, potassium, creatine phosphokinase and digoxin. The same ANCOVAs on changes from baseline in digoxin and International Normalized Ratio (INR) for patients with concomitant intake of digitalis and oral anticoagulants (OAC), respectively, were performed.

6.1.3.5 The DAFNE Study (DRI3550)

Title: Dose-ranging study of the efficacy and safety of Dronedarone for the maintenance of sinus rhythm in patients undergoing cardioversion for atrial fibrillation

Study dates: February 2, 1999 to July 5, 2000

Indication: Atrial fibrillation

Design: Multinational, multicenter, double-blind, parallel arm, placebo-controlled study of 400, 600, and 800 mg b.i.d. oral dronedarone treatment for six months; Phase IIB

Study centers: There were 50 active centers in 11 countries: 11 in Netherlands, 8 in Spain, 7 in Poland, 6 in France, 5 in Germany, 4 in Belgium, 3 in Sweden, 2 in Switzerland, 2 in Israel 1, in Finland, 1 in Italy.

Objectives:
The primary objective was to determine the most effective dose of dronedarone for the maintenance of sinus rhythm in patients undergoing cardioversion for AF.

Secondary objectives were to assess versus placebo:

- the characteristics of the AF episode in the 3 dronedarone groups in case of AF recurrence;
- the incidences of spontaneous conversion to sinus rhythm occurring in the 3 dronedarone groups during the period of study drug administrations preceding the DC-shock;
- the success rate of cardioversion in the 3 dronedarone groups following the first period of study drug administration;
- SR33589 and SR35021 plasma trough levels during the study;
- the tolerability of 3 dose regimens of dronedarone in the selected population.

Methodology: Multinational, multicenter, double-blind, placebo-controlled, dose-ranging study testing in parallel 3 dronedarone dose levels in comparison with placebo for the maintenance of sinus rhythm. An oral anti-coagulant was started 3 weeks before Day 1 and was continued at least 4 weeks following cardioversion. Two blinded study committees were involved: an independent Safety committee monitored and analyzed study safety through evaluations of data (only the Chairman had access to the unblended treatment list); a Steering committee monitored study conduct and, based on recommendations of the Safety Committee, assessed risk-benefit ratios.

Number of patients:
Planned: a sufficient number of patients randomized in order to have 192 patients in sinus rhythm after cardioversion (cf. Amendment No. 2, October 8,1999).:

Diagnosis and criteria for inclusion:

- patients of either sex aged 21 to 85 years, with persistent AF (>72 hours and <12 months duration of the present episode at the screening visit) for whom cardioversion and anti-arrhythmic treatment was warranted;
- written, informed consent

Duration of treatment**:** 6 months

Criteria for evaluation**:**
Efficacy: The primary efficacy endpoint was the time to first recurrence of AF (duration >10 minutes) in patients converted to sinus rhythm, based on 12-lead Electrocardiogram (ECG) and Trans-telephonic ECG monitoring (TTEM) measurements (Amendment No. 2, October 8, 1999).

Pharmacokinetics: SR33589 and SR35021 plasma concentrations were measured on Days 5-8 (conversion), 14, 30, 90 and 150 and were classified C_{trough}, $C_{max.}$

Safety: Extent of exposure, adverse events (AEs), physical examination, concomitant medications, laboratory measurements, vital signs, ECG, congestive heart failure (CHF, using New York Heart Association [NYHA] functional class), chest x-ray, ophthalmological examination

For complete review please refer to Dr. Williams' review in DFS dated 10/23/02.

6.1.4 Efficacy Findings

6.1.4.1 The ANDROMEDA Study

These reviewers consider the ANDROMEDA study to be the most important study because this study was the only study with clinical outcomes as the primary endpoints. Therefore, the Efficacy Findings from this study will be presented first. Below is a diagram showing the disposition of patients for the primary analysis and vital status.

6.1.4.1.1. Overview

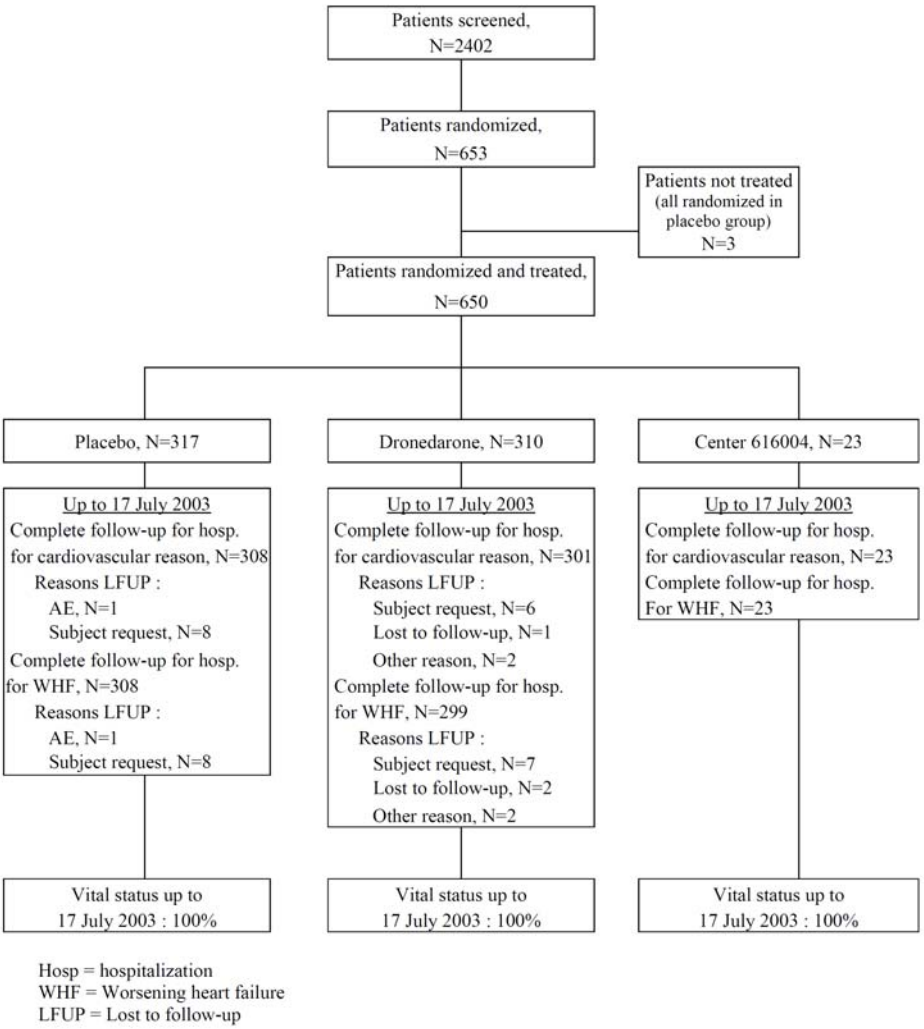


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Figure 3- Disposition of patients for primary analysis and vital status

Center 616004 with 23 patients was excluded by the sponsor from the main analysis population due to major violations in Good Clinical Practice (GCP) which were identified by monitoring and confirmed in another ongoing dronedarone study. Therefore, the Steering Committee (SC) decided to exclude this center from the main analysis population. In Supplement No. 015, the sponsor states there were 23 patients in this center. Eleven patients were randomized to receive dronedarone and 12 were in the placebo group. Among these patients, none of them experienced hospitalization for worsening of heart failure or death up to January 16, 2003. Therefore, there was no primary efficacy event at this center.

Prior to January 16, 2003, in the main analysis population, which is the randomized and treated patients excluding center 616004, 23.0% of patients had permanently discontinued the dronedarone treatment. More patients discontinued dronedarone than the placebo, mainly due to AEs as shown in the table below. The AEs will be addressed in the Safety Section.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Patients who prematurely discontinued the study drug	57 (18.0 %)	87 (28.1 %)	144 (23.0 %)
Main reason for premature discontinuation			
Adverse event	28 (8.8 %)	57 (18.4 %)	85 (13.6 %)
Subject's request	24 (7.6 %)	22 (7.1 %)	46 (7.3 %)
Subject lost to follow-up	0 (0.0 %)	1 (0.3 %)	1 (0.2 %)
Other reason	5 (1.6 %)	7 (2.3 %)	12 (1.9 %)

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Table 2- Number (%) of patients who prematurely withdrew from treatment prior to January 16, 2003, randomized and treated excluding center 616004

Demographic characteristics in the main analysis population between the dronedarone and placebo groups excluding center 616004 were similar as shown in the following table.

Parameter		Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Age (years)	n	317	310	627
	Median	72	71	71
	Mean	68.8	69.5	69.1
	SD	12.1	11.5	11.8
	Min - Max	27 - 96	33 - 90	27 - 96
Age (years) [n (%)]	<65	102 (32.2 %)	101 (32.6 %)	203 (32.4 %)
	[65;75[	93 (29.3 %)	92 (29.7 %)	185 (29.5 %)
	>=75	122 (38.5 %)	117 (37.7 %)	239 (38.1 %)
Height (cm)	n	314	308	622
	Median	172	172	172
	Mean	171.6	171.9	171.8
	SD	8.8	9.3	9.0
	Min - Max	147 - 195	147 - 198	147 - 198
Weight (Kg)	n	314	308	622
	Median	77.5	78.0	77.9
	Mean	79.13	77.72	78.43
	SD	18.70	17.00	17.88
	Min - Max	36.8 - 188.7	37.5 - 147.0	36.8 - 188.7
Gender [n (%)]	Male	242 (76.3 %)	230 (74.2 %)	472 (75.3 %)
	Female	75 (23.7 %)	80 (25.8 %)	155 (24.7 %)
Race [n (%)]	Caucasian	316 (99.7 %)	308 (99.4 %)	624 (99.5 %)
	Black	1 (0.3 %)	0 (0.0 %)	1 (0.2 %)
	Asian / oriental	0 (0.0 %)	1 (0.3 %)	1 (0.2 %)
	Other [a]	0 (0.0 %)	1 (0.3 %)	1 (0.2 %)

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Table 3- Summary of demographic parameters (excluding center 616004)

The above table shows an older population in the ANDROMEDA Study compared to the ADONIS and EURIDIS Studies. There are more males than females who are primarily Caucasian.

6.1.4.1.2. Cardiovascular History

The cardiovascular history of the main analysis population is displayed in the table below. Looking carefully at this table, in the placebo group there is a higher number of patients with an ICD and also with a history of AF/AFL. Among the patients in the placebo group with AF/AFL, there in an increase in the number of patients with their first episode, and there is a higher number of patients with persistent and permanent AF/AFL. At randomization there are a higher number of patients in AF/AFL in the placebo group which gives the study some imbalance in favor of dronedarone.

	Placebo (N=317)	**Dronedarone 800 mg (N=310)**	**Total (N=627)**
Patients with an ICD	6 (1.9 %)	4 (1.3 %)	10 (1.6 %)
Patients with an history of AF/AFL	126 (39.7 %)	114 (36.8 %)	240 (38.3 %)
Type of AF history			
First episode	58 (48.3 %)	45 (42.9 %)	103 (45.8 %)
Paroxysmal	13 (10.8 %)	20 (19.0 %)	33 (14.7 %)
Persistent	14 (11.7 %)	11 (10.5 %)	25 (11.1 %)
Permanent	35 (29.2 %)	29 (27.6 %)	64 (28.4 %)
Patients in AF/AFL at the randomization stage [a, b]	85 (28.0 %)	72 (24.1 %)	157 (26.0 %)

[a] According to the 12-lead ECG done at the randomization stage
[b] Patients with a pacemaker atrial drive have been considered as being in sinus rhythm

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Table 4- Number (%) of patients according to their arrhythmic history (exclude c. 616004)

The cardiovascular history was similar in both treatment groups, although the table below shows some variation between the placebo and dronedarone groups. Most patients suffered from coronary artery disease and/or cardiac valve disease.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Coronary heart disease	201 (63.4 %)	206 (66.5 %)	407 (64.9 %)
Valvular heart disease	175 (55.2 %)	171 (55.2 %)	346 (55.2 %)
Hypertension	107 (33.8 %)	123 (39.7 %)	230 (36.7 %)
Dilated cardiomyopathy	103 (32.5 %)	79 (25.5 %)	182 (29.0 %)
Diabetes mellitus	62 (19.6 %)	73 (23.5 %)	135 (21.5 %)
Coronary artery bypass grafting	42 (13.2 %)	57 (18.4 %)	99 (15.8 %)
Documented severe ventricular arrhythmia	33 (10.4 %)	33 (10.6 %)	66 (10.5 %)
Stroke	31 (9.8 %)	24 (7.7 %)	55 (8.8 %)
Percutaneous coronary revascularisation	26 (8.2 %)	27 (8.7 %)	53 (8.5 %)
Pacemaker	17 (5.4 %)	21 (6.8 %)	38 (6.1 %)
Alcohol induced cardiomyopathy	6 (1.9 %)	13 (4.2 %)	19 (3.0 %)
Hypertrophic cardiomyopathy	7 (2.2 %)	11 (3.5 %)	18 (2.9 %)
Congenital heart disease	0 (0.0 %)	2 (0.6 %)	2 (0.3 %)

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Table 5- Number (%) according to cardiovascular history (excluding c. 616004)

The primary causes for CHF were similar in the 2 treatment groups. The most frequent primary causes were myocardial infarction, coronary heart disease, and dilated cardiomyopathy as shown in the table below.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Myocardial infarction	99 (31.2 %)	106 (34.2 %)	205 (32.7 %)
Coronary heart disease [a]	76 (24.0 %)	73 (23.5 %)	149 (23.8 %)
Dilated cardiomyopathy	77 (24.3 %)	58 (18.7 %)	135 (21.5 %)
Hypertension	30 (9.5 %)	31 (10.0 %)	61 (9.7 %)
Atrial fibrillation	19 (6.0 %)	16 (5.2 %)	35 (5.6 %)
Alcohol induced cardiomyopathy	6 (1.9 %)	6 (1.9 %)	12 (1.9 %)
Hypertrophic cardiomyopathy	2 (0.6 %)	3 (1.0 %)	5 (0.8 %)
Mitral regurgitation	1 (0.3 %)	3 (1.0 %)	4 (0.6 %)
Aortic stenosis	1 (0.3 %)	2 (0.6 %)	3 (0.5 %)
Aortic regurgitation	1 (0.3 %)	1 (0.3 %)	2 (0.3 %)
Diabetes mellitus	0 (0.0 %)	2 (0.6 %)	2 (0.3 %)
Mitral stenosis	0 (0.0 %)	1 (0.3 %)	1 (0.2 %)
Other valvular heart disease	1 (0.3 %)	0 (0.0 %)	1 (0.2 %)

Note: 4 patients under Placebo, 8 patients under Dronedarone have not reported primary cause.
[a] Except Myocardial infarction

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Table 6- Number (%) of patients according to primary cause of CHF (excluding c. 616004)

The range of Wall Motion Index (WMI) determined by echocardiography, always ≤1.2, was in line with the inclusion criteria. The majority of patients in both groups were class II or III of the NYHA classification. Patients in class II were to have had an episode of class III or IV in the month preceding inclusion. This is summarized in the table below showing the WMI and cardiovascular clinical examination (NYHA class) at baseline. The table shows an increase in the number of patients in the placebo group who are in Class III and IV CHF; therefore revealing another slight imbalance in favor of dronedarone.

	Placebo (N=317)	**Dronedarone 800 mg (N=310)**	**Total (N=627)**
Echocardiography - Wall motion index			
n	316	309	625
Median	0.9	1.0	0.9
Mean	0.86	0.90	0.88
SD	0.23	0.23	0.23
Min - Max	0.3 - 1.2	0.3 - 1.2	0.3 - 1.2
Cardiovascular clinical examination - NYHA classification [n (%)]			
CLASS I (Asymptomatic)	0	0	0
CLASS II (Mild)	118 (37.2 %)	126 (40.6 %)	244 (38.9 %)
CLASS III (Moderate)	186 (58.7 %)	178 (57.4 %)	364 (58.1 %)
CLASS IV (Severe)	13 (4.1 %)	6 (1.9 %)	19 (3.0 %)

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Table 7- Summary of echocardiography and cardiovascular clinical examination (NYHA class) at baseline (excluding center 616004)

6.1.4.1.3. Other important baseline characteristics

The following table summarizes the baseline calculated creatinine clearance (mL/minute) using the Cockroft formula. As seen in this table, at baseline, almost half of the patients in both groups had a calculated creatinine clearance levels <50 mL/minute, indicating some degree of renal insufficiency in the study populations. It should be noted that in the placebo group there was a slightly larger percent of patients with limited creatinine clearance compared to dronedarone therefore giving a slight imbalance in favor of dronedarone regarding kidney function at baseline.

	Placebo (N=317)	Dronedarone 800 mg (N=310)
Missing	10	9
<50	128 (41.7%)	133 (44.2%)
<30	31 (10.1%)	41 (13.6%)
[30 ; 50[	97 (31.6%)	92 (30.6%)
>=50	179 (58.3%)	168 (55.8%)
[50 ; 80]	115 (37.5%)	114 (37.9%)
>80	64 (20.8%)	54 (17.9%)

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Table 8- Summary of baseline calculated creatinine clearance (mL/minute) (excluding center 616004)

The baseline vital signs are summarized in the table below which shows that the baseline mean systolic and diastolic blood pressures show a slight imbalance in favor of dronedarone.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Systolic blood pressure (mmHg)			
n	314	308	622
Median	120	120	120
Mean	122.2	119.8	121.0
SD	19.7	18.6	19.2
Min - Max	80 - 200	80 - 190	80 - 200
Diastolic blood pressure (mmHg)			
n	314	308	622
Median	75	70	70
Mean	74.4	72.5	73.4
SD	12.8	11.7	12.3
Min - Max	45 - 118	44 - 115	44 – 118

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Table 9- Summary of the baseline vital signs (excluding c. 616004)

In the following table the baseline ECG parameters (heart rate and QTc-Bazett interval) are summarized. The median and mean heart rates are slightly higher in the placebo group therefore showing a slight imbalance in favor of dronedarone.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Heart rate (bpm)			
n	219	227	446
Median	80	77	78
Mean	80.7	78.0	79.3
S.D.	16.8	15.7	16.3
Min - Max	48 - 126	44 - 128	44 - 128
QTc Bazett interval (ms)			
n	219	227	446
Median	444	451	450
Mean	442.3	445.7	444.0
S.D.	40.8	35.8	38.3
Min - Max	292 - 632	328 - 551	292 - 632

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Table 10- Summary of 12-lead ECG at baseline (excluding c. 616004)

6.1.4.1.4 Concomitant medication

The following table summarizes the number (%) of patients who received not permitted concomitant medications. This table shows that the dronedarone patients had a higher rate of not permitted medications including amiodarone.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Total forbidden concomitant medications	17 (5.4%)	22 (7.1%)	39 (6.2%)
Drugs which can cause Torsades de Pointes	16 (5.0%)	21 (6.8%)	37 (5.9%)
Amiodarone	4 (1.3%)	8 (2.6%)	12 (1.9%)
Potent inhibitors of CYP3A4	3 (0.9%)	7 (2.3%)	10 (1.6%)
Vaughan-Williams class I or III antiarrhythmic drugs [a]	3 (0.9%)	1 (0.3%)	4 (0.6%)

[a] Including Sotalol and excluding Amiodarone
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Table 11- Number (%) of patients who received not permitted concomitant medications (excluding center 616004)

In the table below, the number (%) of patients who received specific permitted medications at baseline is summarized. Although the Sponsor states “The number of patients who received evidence-based medicine treatment, such as ACE inhibitors, AII receptor antagonists, beta blocking agents, or statins, was high and not different between treatment groups at baseline,” these reviewers note that there is a slight increase in the patients on dronedarone who were on ACE inhibitors or Angiotensin II receptor antagonists at baseline.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Total specific medications	317 (100.0%)	309 (99.7%)	626 (99.8%)
Diuretics	309 (97.5%)	297 (95.8%)	606 (96.7%)
Diuretics (other than spironolactone)	302 (95.3%)	288 (92.9%)	590 (94.1%)
Spironolactone	124 (39.1%)	131 (42.3%)	255 (40.7%)
ACE inhibitors or Angiotensin II receptor antagonists	267 (84.2%)	274 (88.4%)	541 (86.3%)
ACE inhibitors	241 (76.0%)	242 (78.1%)	483 (77.0%)
Angiotensin II receptor antagonists	28 (8.8%)	36 (11.6%)	64 (10.2%)
Chronic antiplatelet therapy	196 (61.8%)	203 (65.5%)	399 (63.6%)
Oral anticoagulant	102 (32.2%)	92 (29.7%)	194 (30.9%)
Beta blocking agents	192 (60.6%)	192 (61.9%)	384 (61.2%)
Beta blocking agents (except Sotalol)	191 (60.3%)	192 (61.9%)	383 (61.1%)
Statins	97 (30.6%)	113 (36.5%)	210 (33.5%)
Metabolized by CYP3A4	73 (23.0%)	94 (30.3%)	167 (26.6%)
Not metabolized by CYP3A4	24 (7.6%)	20 (6.5%)	44 (7.0%)
Digitalis	101 (31.9%)	96 (31.0%)	197 (31.4%)
Digoxin	92 (29.0%)	84 (27.1%)	176 (28.1%)
Digitalin	5 (1.6%)	7 (2.3%)	12 (1.9%)
Digitalis other than Digoxin or Digitalin	6 (1.9%)	5 (1.6%)	11 (1.8%)
Moderate inhibitors of CYP3A4	14 (4.4%)	10 (3.2%)	24 (3.8%)
Calcium antagonists with heart rate lowering effects [a]	12 (3.8%)	9 (2.9%)	21 (3.3%)
NSAID	12 (3.8%)	8 (2.6%)	20 (3.2%)

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Table 12- Number (%) of patients who received specific permitted medications at baseline (excluding center 616004)

In the table below is the number (%) of patients (after baseline) who received specific permitted concomitant medications. Tables 12 and 13 show the use of ACE inhibitors or Angiotensin II receptor antagonists increased from the baseline by 10.1% in the placebo group and by 5.1 % in the dronedarone group. Note that there is only a 0.8% difference between the dronedarone group and the placebo group relative to taking ACE inhibitors or Angiotensin II receptor antagonists during this study.

	Placebo (N=317)	Dronedarone 800 mg (N=310)	Total (N=627)
Total other specific concomitant medications	317 (100.0%)	310 (100.0%)	627 (100.0%)
Diuretics	315 (99.4%)	305 (98.4%)	620 (98.9%)
Diuretics (other than spironolactone)	309 (97.5%)	299 (96.5%)	608 (97.0%)
Spironolactone	168 (53.0%)	172 (55.5%)	340 (54.2%)
ACE inhibitors or Angiotensin II receptor antagonists	299 (94.3%)	290 (93.5%)	589 (93.9%)
ACE inhibitors	271 (85.5%)	260 (83.9%)	531 (84.7%)
Angiotensin II receptor antagonists	41 (12.9%)	47 (15.2%)	88 (14.0%)
Chronic antiplatelet therapy	211 (66.6%)	212 (68.4%)	423 (67.5%)
Oral anticoagulant	118 (37.2%)	109 (35.2%)	227 (36.2%)
Beta blocking agents (except Sotalol)	235 (74.1%)	241 (77.7%)	476 (75.9%)
Statins	116 (36.6%)	127 (41.0%)	243 (38.8%)
Metabolized by CYP3A4	88 (27.8%)	103 (33.2%)	191 (30.5%)
Not metabolized by CYP3A4	32 (10.1%)	28 (9.0%)	60 (9.6%)
Digitalis	112 (35.3%)	109 (35.2%)	221 (35.2%)
Digoxin	101 (31.9%)	97 (31.3%)	198 (31.6%)
Digitalin	6 (1.9%)	7 (2.3%)	13 (2.1%)
Digitalis other than Digoxin or Digitalin	7 (2.2%)	5 (1.6%)	12 (1.9%)
NSAID	26 (8.2%)	18 (5.8%)	44 (7.0%)
Moderate inhibitors of CYP3A4	19 (6.0%)	13 (4.2%)	32 (5.1%)
Calcium antagonists with heart rate lowering effects [a]	17 (5.4%)	11 (3.5%)	28 (4.5%)

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Table 13- After baseline, the number (%) of patients who received specific permitted concomitant medications (excluding center 616004)

6.1.4.1.5 Analysis of primary endpoint: death or hospitalization for worsening of heart failure

The results of the primary analysis which was death or hospitalization for worsening of heart failure up to January 16, 2003 are summarized in the following table. This is a troublesome table showing that dronedarone increased by 38% the risk of death or hospitalization for heart failure as compared to placebo.

	Placebo (N=317)	Dronedarone 800 mg (N=310)
Number of patients who died or who have been hospitalized for worsening heart failure	40	53
Relative risk[a]	1.38	
95% CI[a]	[0.918 ; 2.088]	
Log-rank's test result (p-value)	0.118	

a Determined from unadjusted Cox regression model
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Table 14- Analysis of time from randomization to death or hospitalization for worsening of heart failure up to January 16, 2003 (excluding center 616004)

This analysis of death or hospitalization for worsening of heart failure is also shown in the Kaplan-Meier cumulative incidence curve below.

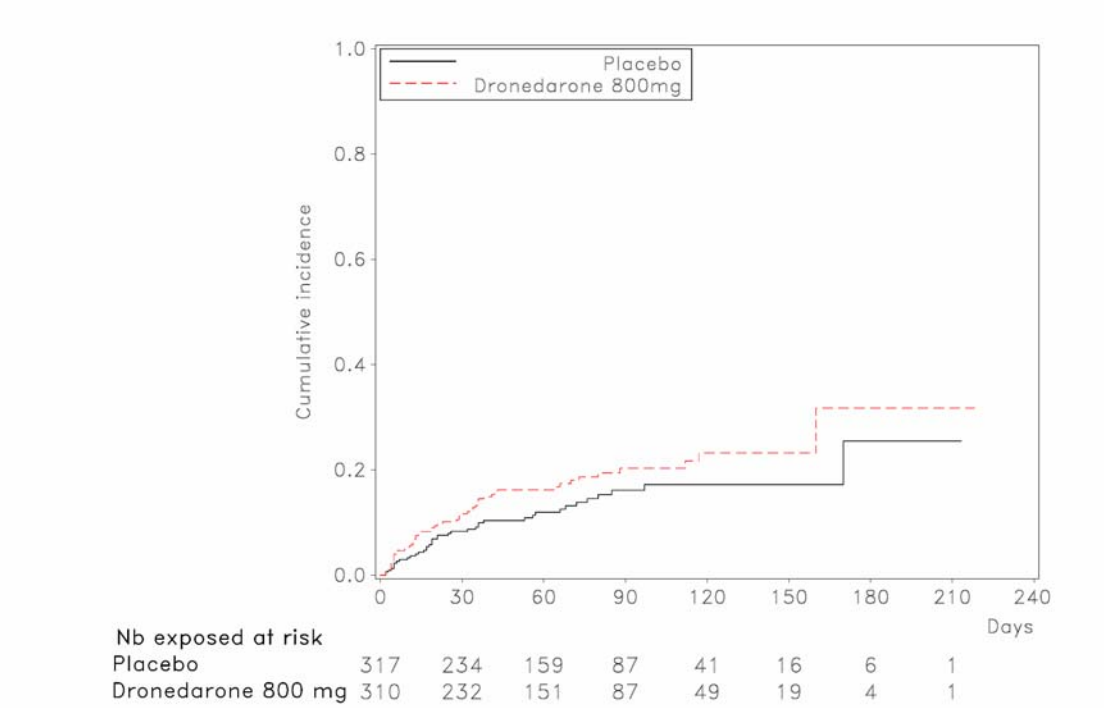

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Figure 4- Kaplan-Meier incidence curves to January 16, 2003 (excluding c. 616004)

6.1.4.1.5.1. The Sponsor's post hoc secondary supportive analyses of primary endpoint

The post hoc adjusted relative risks based on prognostic factors for the primary endpoint are summarized in the following table. This analysis was not pre-specified in the original protocol.

Prognostic factor	Risk	Adjusted relative risk[a]		
		Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake / No intake	0.32	[0.192 ; 0.520]	579E-8
Baseline creatinine clearance[b]	>= 50 ml/min / < 50 ml/min	0.46	[0.271 ; 0.793]	0.00499
Baseline NYHA	> II / II	1.75	[1.061 ; 2.881]	0.02823
Digitalis	Intake / No intake	1.58	[1.024 ; 2.423]	0.03876
Weight (Kg)	Continuous parameter	1.01	[0.996 ; 1.025]	0.150
Treatment	Dronedarone / Placebo	1.29	[0.841 ; 1.989]	0.241
Beta-blocker[c]	Intake / No intake	1.28	[0.799 ; 2.038]	0.308
Baseline WMI[d]	Continuous parameter	1.01	[0.388 ; 2.636]	0.983
Spironolactone	Intake / No intake	1.00	[0.649 ; 1.544]	0.996

Note: intake of medications has been analyzed as time dependent variable
a Determined from Cox regression model
b Creatinine clearance estimate using Cockroft formula
c Excluding Sotalol
d WMI is used to estimate LVEF, with LVEF = WMIx30 (5)
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Table 15- Post hoc adjusted relative risk of death or hospitalization for worsening heart failure by prognostic factors up to January 16, 2003 (excluding center 616004)

The following table shows the unadjusted relative risk of death or hospitalization for worsening of heart failure by prognostic factor subcategories up to January 16, 2003. In this table the patients with a higher baseline creatinine clearance have a greater risk with dronedarone than with placebo.

Prognostic factor	Category	Number of patients: Placebo N	Placebo Nb of events	Dronedarone 800 mg N	Dronedarone 800 mg Nb of events	Unadjusted relative risk[a] Dronedarone/Placebo: Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake	289	31	261	36	1.33	[0.821 ; 2.149]	0.247
	No intake [b]	28	9	49	17	0.99	[0.440 ; 2.226]	0.980
Baseline creatinine clearance	<50 ml/min	128	25	133	29	1.12	[0.658 ; 1.918]	0.671
	>=50 ml/min	179	13	168	21	1.85	[0.924 ; 3.714]	0.08244
Baseline NYHA	II	121	9	131	15	1.58	[0.689 ; 3.600]	0.281
	>II	196	31	179	38	1.34	[0.835 ; 2.156]	0.225
Digitalis	Intake	107	18	90	23	1.43	[0.770 ; 2.646]	0.258
	No intake [b]	210	22	220	30	1.37	[0.789 ; 2.372]	0.265
Weight	<78 kg	162	24	154	25	1.10	[0.629 ; 1.930]	0.735
	>=78 kg	155	16	156	28	1.85	[0.997 ; 3.421]	0.05114
Beta-blocker [c]	Intake	227	29	222	36	1.33	[0.813 ; 2.162]	0.259
	No intake [b]	90	11	88	17	1.52	[0.710 ; 3.256]	0.281
Baseline WMI	<1	181	18	145	29	2.05	[1.137 ; 3.687]	0.01698
	>=1	136	22	165	24	0.92	[0.513 ; 1.638]	0.770
Spironolactone	Intake	154	21	132	18	1.07	[0.570 ; 2.020]	0.827
	No intake [b]	163	19	178	35	1.66	[0.952 ; 2.909]	0.07413

a Determined from Cox regression
b No intake is co-medication either never taken or prematurely stopped (i.e. prior to endpoint or censoring date)
c Excluding Sotalol
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Table 16- Unadjusted relative risk of death or hospitalization for worsening heart failure by prognostic factors up to January 16, 2003 (excluding center 616004)

A sensitivity analysis performed on all randomized and treated patients (including center 616004) is shown in the following table. This analysis supported the primary efficacy analysis which excluded center 616004. No deaths in the dronedarone treatment group were recorded in center 616004.

	Placebo (N=329)	Dronedarone 800 mg (N=321)
Number of patients who died or who have been hospitalized for worsening heart failure	40	53
Relative risk[a]	1.38	
95% CI[a]	[0.918 ; 2.088]	
Log-rank's test result (p-value)	0.119	

a Determined from unadjusted Cox regression model
(page 125 EFC4966)

Table 17- Analysis of time from randomization to death or hospitalization for worsening heart failure up to 16 January 2003, including center 616004

6.1.4.1.6 Secondary efficacy endpoints

6.1.4.1.6.1. Death from any cause

In the following table are the results of the analysis of death from any cause up to January 16, 2003. This is a very troublesome table showing that dronedarone significantly (p = 0.027) increased, by 113%, (more than doubled) the risk of death from any cause as compared to placebo.

	Placebo (N=317)	Dronedarone 800 mg (N=310)
Number of patients who died	12	25
Relative risk[a]	2.13	
95% CI[a]	[1.071 ; 4.247]	
Log-rank's test result (p-value)	0.02717	

(page 71 EFC4966) (This analysis was confirmed by Dr. Valeria Freidlin)

Table 18- Analysis of death up to January 16, 2006, (excluding center 616004)

This analysis was confirmed by the statistical reviewer. In this reviewer's analysis, p=0.025 in Log-rank test and relative risk (hazard ratio) = 2.15 with the 95%CI of (1.081, 4.28) was in favor of placebo.

The primary causes of death up to January 16, 2003, as adjudicated by the Critical Events Committee (CEC) are summarized in the following table. The majority of deaths in both treatment groups were of cardiovascular origin. This table shows among the dronedarone patients there is a worsening of congestive heart failure and an increase in documented arrhythmias.

	Placebo (N=12)	Dronedarone 800 mg (N=25)
Cardiovascular death	9 (75%)	24 (96%)
Myocardial infarction	2 (16.7%)	0 (0.0%)
Worsening CHF	2 (16.7%)	10 (40%)
Documented arrhythmia	2 (16.7%)	6 (24%)
Procedure related	0 (0.0%)	1 (4%)
Other cardiovascular reason	0 (0.0%)	2 (8%)
Presumed cardiovascular reason	3 (25%)	5 (20%)
Non cardiovascular death	2 (16.7%)	1 (4%)
Cancer	1 (8.3%)	1 (4%)
Other non cardiovascular reason [a]	1 (8.3%)	0 (0.0%)
Non adjudicated death [b]	1 (8.3%)	0 (0.0%)

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Table 19- Number (%) of patients according to adjudicated primary cause of death up to January 16, 2003 (excluding center 616004)

In both treatment groups the majority of deaths were of cardiovascular origin. Within the dronedarone group, non-sudden deaths accounted for the majority of deaths as shown in the table below.

	Placebo (N=9)	Dronedarone 800 mg (N=24)
Sudden death unwitnessed	3 (33.3%)	3 (12.5%)
Sudden death witnessed	3 (33.3%)	7 (29.2%)
Non-sudden death	3 (33.3%)	14 (58.3%)

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Table 20- Number (%) of patients according to adjudicated timing of cardiovascular deaths up to January 16, 2003 (excluding center 616004)

The Sponsor submitted the following post hoc covariate analyes which were not prespecified in the protocol. The table below summarizes the post hoc adjusted relative risk of death by prognostic factors up to January 16, 2003. According to the Sponsor, the most important risk factor for death was the absence of treatment with ACE inhibitor or Angiotensin II receptor antagonist in the dronedarone group. However, the reviewers believe these covariate analyses are difficult to interpret because: 1. the analyses were not prespecified and therefore are data driven; 2. ACE inhibitor and A II receptor antagonist intake were not baseline characteristics and therefore, this relationship cannot be determined; and 3.the Table 6 on page 26 shows that there was a very small (0.8 %) difference between the groups relative to treatment with ACE inhibitors or Angiotensin II receptor antagonists.

Prognostic factor	Risk	Adjusted relative risk[a]		
		Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake / No intake	0.21	[0.097 ; 0.432]	0.00003
Treatment	Dronedarone / Placebo	1.83	[0.887 ; 3.782]	0.102
Baseline creatinine clearance[b]	>= 50 ml/min / < 50 ml/min	0.65	[0.267 ; 1.604]	0.353
Beta-blocker[c]	Intake / No intake	0.79	[0.386 ; 1.624]	0.525
Weight (Kg)	Continuous parameter	0.99	[0.967 ; 1.018]	0.557
Baseline NYHA	> II / II	1.18	[0.555 ; 2.501]	0.669
Digitalis	Intake / No intake	1.10	[0.536 ; 2.268]	0.792
Baseline WMI[d]	Continuous parameter	1.18	[0.247 ; 5.666]	0.834
Spironolactone	Intake / No intake	1.05	[0.511 ; 2.170]	0.888

Note: intake of medications has been analyzed as time dependent variable
a Determined from Cox regression model
b Creatinine clearance estimate using Cockroft formula
c Excluding Sotalol
d WMI is used to estimate LVEF, with LVEF = WMIx30 (5)
(page 74 EFC4966)

Table 21- Post hoc adjusted relative risk of death by prognostic factors up to January 16, 2003 (excluding center 616004)

In the following table is the unadjusted relative risk by prognostic factor subcategories from randomization to death up to January 16, 2003. This table shows that in the unadjusted analysis, dronedarone treatment significantly increased the risk of death in patients with moderate to severe renal insufficiency (baseline creatinine clearance <50 mL/minute). Also, in the dronedarone group there was significantly increased death with more severe heart failure (NYHA class >II), in the patients with no intake of ACE inhibitor/AII receptor antagonist, or with spironolactone, and with baseline WMI <1.

In the main analysis population up to February 17, 2003, 34 dronedarone patients and 18 placebo patients died. This analysis was consistent with the analysis up to January 16, 2003; dronedarone significantly (p = 0.019) increased, by 96%, the risk of death.

Prognostic factor	Category	Number of patients: Placebo N	Placebo Nb of events	Dronedarone 800 mg N	Dronedarone 800 mg Nb of events	Unadjusted relative risk[a] Dronedarone/Placebo: Relative risk	95% CI	p-value
ACE inhibitor or A II receptor antagonist	Intake	281	10	249	10	1.14	[0.472 ; 2.737]	0.774
	No intake [b]	36	2	61	15	5.06	[1.157 ; 22.177]	0.03131
Baseline creatinine clearance	<50 ml/min	128	6	133	17	2.70	[1.065 ; 6.867]	0.03644
	>=50 ml/min	179	5	168	6	1.36	[0.412 ; 4.492]	0.614
Beta-blocker [c]	Intake	221	7	209	12	1.85	[0.728 ; 4.699]	0.196
	No intake [b]	96	5	101	13	2.34	[0.834 ; 6.587]	0.106
Weight	<78 kg	162	9	154	14	1.63	[0.705 ; 3.768]	0.253
	>=78 kg	155	3	156	11	3.72	[1.035 ; 13.345]	0.04409
Baseline NYHA	II	121	5	131	7	1.28	[0.405 ; 4.029]	0.676
	>II	196	7	179	18	2.77	[1.156 ; 6.625]	0.02234
Digitalis	Intake	101	2	89	12	6.45	[1.443 ; 28.802]	0.01470
	No intake [b]	216	10	221	13	1.27	[0.555 ; 2.892]	0.574
Baseline WMI	<1	181	4	145	15	4.60	[1.526 ; 13.868]	0.00671
	>=1	136	8	165	10	1.05	[0.415 ; 2.674]	0.912
Spironolactone	Intake	150	6	134	8	1.58	[0.547 ; 4.552]	0.399
	No intake [b]	167	6	176	17	2.55	[1.007 ; 6.480]	0.04840

a Determined from Cox regression
b No intake is co-medication either never taken or prematurely stopped (i.e. prior to endpoint or censoring date)
c Excluding Sotalol
(page 75 EFC4966)

Table 22- Unadjusted relative risk by prognostic factor subcategories for death up to January 16, 2003, (excluding center 616004)

The analysis performed 6 months after discontinuation of inclusions and the ongoing study drug treatment, July 17, 2003, showed a similar number of deaths in both treatment groups: 42 patients in the dronedarone group, and 39 in the placebo group. The number of deaths due to worsening heart failure was similar in both treatment groups: 15 patients in the dronedarone group, and 13 in the placebo group. To these reviewers the significance of this is unknown. Among the arrhythmic/sudden death there were no reported cases of torsades de pointes. The deaths will be reviewed in the safety section.

Analysis of the per protocol population supported the results of the main population analysis. In the table below is the efficacy response data of the secondary efficacy parameters per-protocol population up to January 16, 2003, regarding death from any cause.

Primary cause of death	Placebo (N=294)	Dronedarone 800 mg (N=278)
Total (a)	11	21
Missing cause	1 (9.1 %)	0 (0.0 %)
Cardiac death		
Sudden death - Witnessed	2 (18.2 %)	5 (23.8 %)
Sudden death - Alive within 24 H prior death	1 (9.1 %)	0 (0.0 %)
Sudden death - Arrhythmic death	1 (9.1 %)	0 (0.0 %)
Sudden death - Other	0 (0.0 %)	1 (4.8 %)
Worsening CHF	1 (9.1 %)	8 (38.1 %)
Cardiac procedure	0 (0.0 %)	1 (4.8 %)
Myocardial infarction	2 (18.2 %)	1 (4.8 %)
Other cardiac death	0 (0.0 %)	1 (4.8 %)
Vascular death		
Other vascular death	0 (0.0 %)	1 (4.8 %)
Non-cardiovascular death	2 (18.2 %)	2 (9.5 %)
Unknown cause	1 (9.1 %)	1 (4.8 %)

(page 3202, Appendix 16.2.6.2.2.1.1.7 EFC4966)

Table 23- Summary of local primary cause of death January 16, 2003, per protocol population

The above table shows the dronedarone patients had an increase in sudden death (probably an arrhythmia). This table also shows a worsening of congestive heart failure in the dronedarone treated patients.

The following table shows the efficacy response data of the secondary efficacy parameters of the per-protocol population a month later regarding death from any cause. This table reveals an increase in death from worsening of CHF.

Primary cause of death	Placebo (N=294)	Dronedarone 800 mg (N=278)
Total (a)	16	28
Missing cause	2 (12.5 %)	0 (0.0 %)
Cardiac death		
Sudden death - Witnessed	2 (12.5 %)	5 (17.9 %)
Sudden death - Alive within 24 H prior death	1 (6.3 %)	0 (0.0 %)
Sudden death - Arrhythmic death	2 (12.5 %)	0 (0.0 %)
Sudden death - Other	0 (0.0 %)	2 (7.1 %)
Worsening CHF	4 (25.0 %)	11 (39.3 %)
Cardiac procedure	0 (0.0 %)	1 (3.6 %)
Myocardial infarction	2 (12.5 %)	2 (7.1 %)
Other cardiac death	0 (0.0 %)	1 (3.6 %)
Vascular death		
Hemorrhagic stroke	0 (0.0 %)	1 (3.6 %)
Other vascular death	0 (0.0 %)	1 (3.6 %)
Non-cardiovascular death	2 (12.5 %)	3 (10.7 %)
Unknown cause	1 (6.3 %)	1 (3.6 %)

(page 3224 Appendix 16.2.6.2.2.2.1.7. EFC4966)

Table 24- Summary of local primary cause of death February 16, 2003 in the per protocol population

6.1.4.1.6.2 Hospitalization for worsening of heart failure

An analysis of the time to first hospitalization for worsening heart failure up to January 16, 2003, is summarized in the following table. Although the Sponsor states that "There was no statistically significant difference between groups in first hospitalization for worsening heart failure," it is apparent from this table that more patients on dronedarone were hospitalized (39 = 13%) as compared to placebo (31 = 10%).

	Placebo (N=317)	**Dronedarone 800 mg (N=310)**
Number of patients hospitalized for worsening heart failure	31	39
Log-Rank	0.271	

(page 77 EFC4966)

Table 25- Analysis of time to first hospitalization for worsening of heart failure up to January 16, 2003 (excluding center 616004)

The following table provides an analysis of acute cardiovascular reasons from randomization to the first hospitalization up to January 16, 2003. This table shows that statistically significantly (p = 0.024) more dronedarone patients (71 = 23%) were hospitalized for cardiovascular reasons as compared to placebo (50 = 16%).

	Placebo (N=50)	**Dronedarone 800 mg (N=71)**
Worsening CHF	30 (60%)	35 (49.3%)
Myocardial ischemia	8 (16%)	13 (18.3%)
Ventricular arrhythmia	2 (4%)	3 (4.2%)
Supraventricular arrhythmia	1 (2%)	4 (5.6%)
Stroke	3 (6%)	4 (5.6%)
Other cardiovascular reason	4 (8%)	9 (12.7%)
Presumed cardiovascular reason	2 (4%)	3 (4.2%)

(page 80 EFC 4966)

Table 26- Number (%) of patients according to adjudicated primary cause of the first hospitalization for acute cardiovascular reasons up to January 16, 2003 (excluding c.616004)

6.1.4.1.7 The Andromeda Study Conclusions

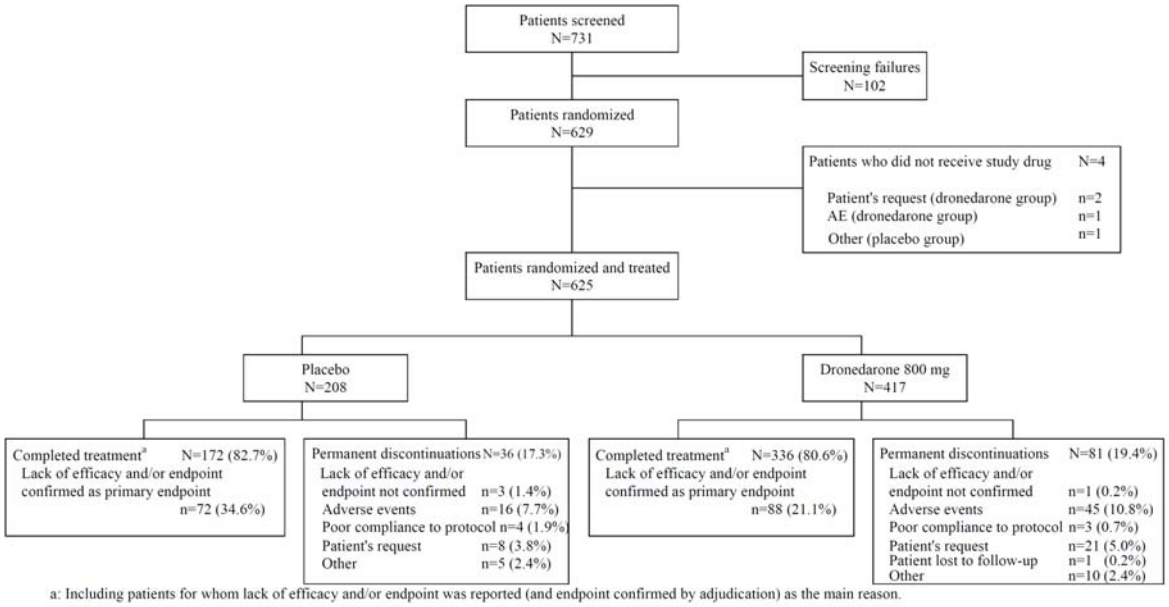
Among the patients on dronedarone there were statistically significantly ($p \leq 0.027$) more deaths from any cause and more hospitalizations for acute cardiovascular reasons as compared to placebo. Although the Sponsor attributes this increase in mortality and morbidity to the lack of ACE inhibitors or Angiotensin II receptor antagonists in the dronedarone patients, these reviewers do not concur with the sponsor's conclusions. The reviewers believe that the covariate analyses including ACE inhibitors or Angiotensin II receptor antagonists intake are difficult to interpret because: 1. the analyses were not prespecified and therefore are data driven; 2. ACE inhibitor and A II receptor antagonist intake were not baseline characteristics and therefore, this relationship cannot be determined; and 3. the Table 6 on page 26 shows that there was a very small ((0.8 %) difference between the groups relative to treatment with ACE inhibitors or Angiotensin II receptor antagonists.

The percentage for both groups receiving ACE inhibitors or Angiotensin II receptor antagonists was similar, dronedarone 93.5% and placebo 94.3%, during the study. This study is the most important study as the clinical outcomes were the primary endpoints whereas the other pivotal studies have surrogate primary endpoints.

6.1.4.2. The ADONIS Study (EFC4788)

6.1.4.2.1 Overview

The following figure summarizes the patients who have completed the drug study treatment and those who prematurely permanently discontinued.



(page 53 ECF4788)

Figure 5- Disposition of patients

The following table lists the deviations leading to exclusion from analysis.

Category/reason[a]	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Deviation related to inclusion criteria	10 (4.8 %)	14 (3.4 %)	24 (3.8 %)
No qualifying AF/AFL episode[b]	9 (4.3 %)	8 (1.9 %)	17 (2.7 %)
No ECG documenting SR before randomization[c]	2 (1.0 %)	6 (1.4 %)	8 (1.3 %)
Deviations related to study drug administration	5 (2.4 %)	11 (2.6 %)	16 (2.6 %)
Treatment received not equal at least once to the randomized treatment	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Compliance to study drug < 75% [d]	5 (2.4 %)	11 (2.6 %)	16 (2.6 %)
Deviations related to previous or concomitant medications	12 (5.8 %)	32 (7.7 %)	44 (7.0 %)
Previous medications not correctly discontinued[e]	2 (1.0 %)	3 (0.7 %)	5 (0.8 %)
Forbidden concomitant medications[f], [g]	12 (5.8 %)	32 (7.7 %)	44 (7.0 %)
Adjudicated first AF/AFL recurrence prior to first study drug intake	2 (1.0 %)	0 (0.0 %)	2 (0.3 %)
Total of patient excluded from the per-protocol population	28 (13.5 %)	52 (12.5 %)	80 (12.8 %)

a A patient could be counted in more than one category/reason
b No 12-lead ECG within 100 days before randomization indicating 'atrial tachycardia' or 'atrial fibrillation' or 'atrial flutter' or 'paroxysmal atrial fibrillation'
c Last ECG within 7 days before randomization not indicating SR; patients with first ECG between randomization and first study drug intake documenting SR were not excluded (SR: 'sinus rhythm' or 'coronary sinus pace-maker' or 'junctional rhythm' or 'junctional tachycardia' or 'atrial drive' or 'atrio-ventricular drive')
d Compliance is assessed by the ratio of the number of tablets actually taken from first study drug intake to last study drug intake over the theoretic number of one tablet BID from day of first study drug intake to day of last study drug intake
e Includes Vaughan-Williams-Singh class I or III antiarrhythmics drugs, amiodarone, Sotalol
f Not permitted (i.e., forbidden) concomitant medications include Vaughan-Williams-Singh class I or III antiarrhythmics drugs, amiodarone, Sotalol, drugs which can cause torsades de pointes, potent inhibitors of CYP3A4, substrates of CYP3A4 with a narrow therapeutic margin
g Between day of first study drug intake (included) and day of last study drug intake or adjudicated first AF/AFL recurrence whichever occurred first (excluded). Patients who stopped amiodarone the day of first study drug intake are not excluded, as per-protocol this treatment might be stopped the day of randomization.
(page 54 EFC4788)

Table 27- Number (%) patients excluded by reason

6.1.4.2.2. Patients' characteristics

The demographic data for randomized and treated patients is summarized in the following table.