MULTAQ® (DRONEDARONE)

Briefing Document

Advisory Committee Meeting of the Cardiovascular and Renal Drugs Division of the US Food and Drug Administration

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EXECUTIVE SUMMARY

Medical need

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the United States (US) population. For most of the last century the primary therapeutic goal in the management of AF was the restoration and maintenance of sinus rhythm. Antiarrhythmic drugs used to prevent recurrences of AF, exhibited proarrhythmic potential, increased risk of cardiovascular death and/or serious noncardiac end-organ toxicity. These liabilities called the rhythm control strategy into question, and studies emerged supporting rate control (achieved with digitalis, beta-blockers and/or verapamil/diltiazem) as a prudent alternative therapeutic strategy. However, rate control strategies allow the atrial arrhythmia to persist, and the long term course of patients remaining in persistent arrhythmia is unknown. Adequate rate control of atrial fibrillation/atrial flutter (AF/AFL) did not obviate the increased risk of cardiovascular hospitalizations and death. It is not known whether this increased risk of death or hospitalization is related to the arrhythmia or to cardiovascular conditions that are commonly present in patients with AF. There remains an unmet medical need for drugs that prevent recurrences of AF and/or control rate while also improving morbidity-mortality.

Dronedarone

Sanofi-aventis US LLC (hereafter referred to as sanofi-aventis) initially developed dronedarone with the intent of replicating the effects of the antiarrhythmic drug, amiodarone, while minimizing its significant toxicity. Like amiodarone, dronedarone is a benzofuran derivative, but with different relative electrophysiological activities on individual ion channels. Specific structural modifications were introduced to minimize the non-cardiovascular adverse effects of amiodarone. A methane-sulfonamyl group was introduced to shorten half-life and decrease lipophilicity, and iodine substituents were eliminated to avoid the risk of thyroid side effects.

Sanofi-aventis submitted a New Drug Application (NDA) for dronedarone (MULTAQ®) to the FDA in June 2005 for an indication of rhythm and rate control in patients with AF/AFL, to maintain normal sinus rhythm or to decrease ventricular rate. The NDA included 3 pivotal studies supporting this proposed indication (EURIDIS, ADONIS and ERATO). The excess mortality observed in ANDROMEDA a trial in high-risk patients with decompensated heart failure, was central to the decision by the FDA to issue a Not Approvable letter for dronedarone in August 2006. A new file, including ATHENA, a morbidity-mortality trial in patients with AF/AFL, was submitted in July 2008 and was granted priority review by the FDA.

Clinical Pharmacology

After oral administration in fed conditions in healthy subjects, dronedarone is well-absorbed; its absolute bioavailability is 15% due to significant first pass metabolism. Peak plasma concentrations of dronedarone are achieved within 3 to 6 hours. When given at 400 mg two times daily (BID), steady state levels of the drugs are reached within 4 to 8 days of treatment. Dronedarone is extensively metabolized primarily by cytochrome P-450 (CYP) 3A4. The

metabolites of dronedarone are excreted primarily in feces, and renal excretion is a very minor route of elimination (6% of the dose). The steady state terminal elimination half-life of dronedarone is approximately 30 hours.

Inhibitors of CYP3A4 can increase exposure to the drug. In addition, dronedarone is a moderate inhibitor of CYP3A4, a weak inhibitor of CYP2D6 and has the potential to inhibit P-glycoprotein (Pgp) transport, potentially increasing exposure to concomitantly administered calcium channel blockers, some statins, beta-blockers and digoxin.

The primary intrinsic sources of variability are gender, weight and age, accounting for less than a 2-fold increase in exposure. Congestive heart failure (CHF), renal function, and in particular, severe renal impairment do not significantly influence the pharmacokinetics of dronedarone in patients. Moderate hepatic impairment modifies moderately (less than 2-fold) the pharmacokinetics of dronedarone.

Rate and Rhythm control trials

The initial development of dronedarone focused on its efficacy for the control of rhythm and rate in patients with AF/AFL.

DAFNE Trial

The DAFNE trial was a double-blind, randomized placebo-controlled, comparing three different doses of dronedarone (400 mg BID, 600 mg BID and 800 mg BID) with placebo for the maintenance of sinus rhythm following electrical cardioversion in 270 patients with atrial fibrillation, treated for 6 months. The 400 mg BID dose of dronedarone was associated with the greatest efficacy and best safety (lower rate of gastrointestinal [GI] adverse events [AEs]). Administration of this dose for 6 months reduced the risk of arrhythmia recurrence by 55% ($p=0.001$). The 400 mg BID dose was also the lowest dose of dronedarone producing 12-lead electrocardiogram (ECG) changes in clinical pharmacology studies. The 400 mg BID dose was selected as the therapeutic dose for future studies.

EURIDIS and ADONIS Trials

The EURIDIS and ADONIS trials were double-blind, randomized (2:1 ratio) and placebo-controlled sister trials, identical in design, which were carried out to demonstrate the efficacy of dronedarone (400 mg BID) in the maintenance of sinus rhythm after electrical, pharmacological, or spontaneous conversion of AF/AFL, in 615 and 629 patients respectively, for one year. Dronedarone reduced the risk of arrhythmia recurrence by 22% in the EURIDIS trial ($p=0.0138$) and by 27.5% in the ADONIS trial ($p=0.0017$). Treatment with the drug also doubled the median time from randomization to the first recurrence of AF/AFL; reduced the risk of first recurrence of symptomatic episodes, and slowed the ventricular response in patients whose atrial arrhythmia recurred.

A post-hoc analysis showed that dronedarone was associated with 27% and 11% lower risk of the combined endpoint of first cardiovascular hospitalization or death, in EURIDIS and ADONIS trials, respectively. Pooled analysis of the data from both trials showed a 20% reduction in the

risk of death or cardiovascular hospitalization (relative risk 0.804 [95% confidence interval {CI}: 0.591, 1.094]. This 20% risk reduction was largely related to a reduction in the risk of cardiovascular hospitalization.

ERATO Trial

The ERATO trial was a double-blind, randomized, placebo-controlled trial to evaluate the efficacy of dronedarone 400 mg BID in controlling the ventricular rate at rest in 174 patients with symptomatic permanent atrial fibrillation, for 6 months. Dronedarone attenuated the ventricular rate, both at rest and during exercise, thus (together with the results of the other placebo-controlled trials) establishing that the drug has the ability to control both rate and rhythm in patients with AF.

DIONYSOS Trial

The DIONYSOS trial was a randomized, double-blind trial to compare the efficacy and safety of dronedarone (400 mg BID) versus amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) for the maintenance of sinus rhythm in 504 patients with AF, followed for at least 6 months. The primary endpoint was defined as recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy. Recurrences of AF were more frequent in the dronedarone group when compared with the amiodarone group, whereas, premature study drug discontinuations due to intolerance were more frequent in the amiodarone group when compared to the dronedarone group.

Outcomes trials

The ANDROMEDA Trial

The US Food and Drug Administration (FDA) was cognizant of the fact that many anti-arrhythmic drugs reduce the risk of an arrhythmia but at the same time increase the risk of death. Consequently, FDA recommended that sanofi-aventis carry out a trial to exclude the possibility that dronedarone increased the risk of death. Patients hospitalized for decompensated heart failure constituted a high risk and vulnerable patient population that could be investigated for this purpose, even though a minority of such patients had AF.

ANDROMEDA was a randomized double-blind, placebo-controlled trial in patients hospitalized for decompensated heart failure, evaluating the effect of dronedarone 400 mg BID on the risk of hospitalizations for worsening heart failure or death. The trial was prematurely terminated upon the recommendation of the trial's Data and Safety Monitoring Board (DSMB) after the enrollment of 627 patients, when it was noted that dronedarone was associated with 25 deaths vs 12 in the placebo group; this imbalance was largely related to an increased risk of death from worsening heart failure. Three other observations were noteworthy:

- The excess mortality seen in ANDROMEDA was not driven by arrhythmic death, and thus, the pattern of increased risk seen in ANDROMEDA differed from that seen in outcome trials with other (pure Class I and III) antiarrhythmic drugs.

- The excess risk of death in dronedarone-treated patients was most apparent in patients with the most advanced heart failure (i.e., those with severe symptoms, very poor ventricular function – wall motion index (WMI) < 1.0 corresponding to an ejection fraction < 30%) and compromised renal function.
- The ANDROMEDA trial raised the possibility that dronedarone-induced changes in serum creatinine might lead physicians to reduce their use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with severe heart failure. Thus, investigators in future studies with dronedarone were advised not to rely on changes in serum creatinine following initiation of treatment with the drug to justify decisions regarding changes in the use of ACE inhibitors or ARBs.

The ATHENA Trial

The findings of the ANDROMEDA trial changed the focus of the development program from the symptomatic relief of arrhythmias to the long-term effects of drug therapy on the risk of cardiovascular death and hospitalization. Because a meta-analysis of the EURIDIS and ADONIS trials suggested that patients with AF who were randomized to dronedarone had a lower risk of cardiovascular hospitalization or death than patients who were randomized to placebo, sanofi-aventis shifted its emphasis on the development of dronedarone to the management of cardiovascular risk in patients with AF/AFL. No previous development program for a drug for the treatment of AF/AFL had been focused on morbidity and mortality.

ATHENA was a randomized, double-blind, placebo-controlled trial to evaluate the long-term effect of dronedarone 400 mg BID versus placebo on top of standard care on the combined risk of cardiovascular hospitalization or all-cause mortality in patients with a recent or current history of AF/AFL. The objectives of the ATHENA trial were: (1) to determine if dronedarone's favorable effects in patients with AF/AFL (demonstrated in the DAFNE, EURIDIS, ADONIS and ERATO trials) could result in a long-term reduction in the risk of major adverse cardiovascular events; and (2) to clarify and further elucidate the effect of dronedarone on the risk of death in patients likely to receive the drug in clinical practice. The trial included patients with stable heart failure but excluded patients who were clinically decompensated (who had comprised the patients studied in the ANDROMEDA trial). A total of 4628 patients were randomized (1:1) to either placebo or dronedarone.

By intent-to-treat (ITT), there were 917 cardiovascular hospitalizations or deaths in the placebo group and 734 cardiovascular hospitalizations or deaths in the dronedarone group. Treatment with dronedarone 400 mg BID was associated with a 24% reduction of the combined risk of cardiovascular hospitalization or all cause-death ($p=2 \times 10^{-8}$; hazard ratio [HR] [95%CI] 0.758 [0.688 - 0.835]) when compared with placebo. This reduction was due to both a lower number of both cardiovascular hospitalizations and cardiovascular deaths and was consistent across all subgroups evaluated.

- Treatment with dronedarone reduced time to first cardiovascular hospitalization by 25.5% (HR [95%CI] 0.745 [0.673 – 0.824]) compared with placebo. The decrease in the number of cardiovascular hospitalizations seen with dronedarone was due to a reduction in several contributors, including hospitalizations for AF or other supraventricular rhythm disorders, hospitalizations for myocardial infarction (MI) or unstable angina, hospitalizations for stroke

or transient ischemic attack (TIA), and hospitalizations for worsening heart failure. The reduction in cardiovascular hospitalization was not accompanied by an increase in non-cardiovascular hospitalization and was consistent across all subgroups evaluated.

- Treatment with dronedarone was associated with a 30% lower risk of cardiovascular death (HR [95%CI] 0.698 [0.509; 0.958]) when compared with placebo. The reduction of cardiovascular death with dronedarone 400 mg BID was mainly due to a reduction in the risk of sudden cardiac deaths and stroke. Consistent results were observed across all subgroups evaluated.
- There were numerically fewer deaths for any reasons in the dronedarone group (n=116, 5.0%) when compared with the placebo group (n=139, 6.0%). This difference reflected a trend for 15.6% reduction of risk in dronedarone-treated patients (HR [95%CI] 0.844 [0.660 - 1.080]). Importantly, the upper bound of the 95% CI of 1.08 effectively excluded any clinically meaningful increase in the risk of death on dronedarone in the ATHENA population. The effect of dronedarone on risk of death was consistent whether patients had left ventricular ejection fraction (LVEF) <35% or were NYHA Class III at baseline.

Discussion of ANDROMEDA and ATHENA

Additional analyses indicated that the presence or absence of clinical stability appeared to be the primary feature that distinguished the patients enrolled in the ANDROMEDA trial from those enrolled in the ATHENA trial. Both trials enrolled patients with low ejection fraction and/or with Class II or III heart failure; however, ANDROMEDA patients had been hospitalized recently for worsening heart failure, whereas such unstable patients were excluded from ATHENA. Further analyses of ANDROMEDA and ATHENA subgroups with a low ejection fraction or with Class III heart failure indicated that these subgroups responded differently in the two trials. This suggested that clinical instability was an important determinant of the effect of dronedarone but that ejection fraction or functional class did not influence response to the drug in clinically stable patients. These findings suggest that clinically stable patients with moderate-to-severe left ventricular dysfunction (LVD) or with moderate-to-severe symptoms of heart failure would benefit from treatment with dronedarone, since they showed the greatest absolute benefit from treatment.

Two other alternate explanations for the divergent results of the ANDROMEDA and ATHENA trials have been considered.

- One hypothesis is that the reluctance to use ACE inhibitors and ARBs in patients who experience an increase in serum creatinine with dronedarone may have deprived dronedarone-treated patients from a highly effective treatment for heart failure. Further analysis, however, indicates that the differential use of ACE inhibitors and ARBs in a small proportion of ANDROMEDA patients could not account for the increase in risk observed in the ANDROMEDA trial.
- Another hypothesis is that the results of the ANDROMEDA trial may be unreliable because they were based on the analysis of a small number of events observed over a short period of time in a trial that was terminated early. These conditions are known to lead to highly imprecise estimates. However, since the clinically unstable patients enrolled in

ANDROMEDA have not been evaluated in any subsequent trial, this possibility cannot be objectively evaluated.

As a precautionary measure, MULTAQ® is contraindicated in patients with worsening CHF or hospitalized for CHF within the last month.

Safety of Dronedarone

The safety profile of dronedarone 400 mg twice daily in patients with AF or AFL was evaluated on 5 pooled placebo-controlled studies, ATHENA, EURIDIS, ADONIS, ERATO and DAFNE. In these studies, a total of 6285 patients were randomized and treated. Of these, 3282 patients were treated with dronedarone 400 mg twice daily, and 2875 received placebo. The mean exposure across studies was 12 months. In ATHENA, the mean and maximum follow-up was 21 months and 30 months, respectively.

The main AEs identified with dronedarone were diarrhea, nausea or vomiting, serum creatinine increase (shown to be related to inhibition of creatinine secretion at kidney tubular level without decrease in glomerular filtration), rash, and cardiac effects consistent with the pharmacodynamic profile of dronedarone (bradycardia, QT prolongation). There was no evidence of a proarrhythmic effect of dronedarone; one case of torsades de pointes (TdP) was identified during the overall clinical development program. Assessment of intrinsic factors on the incidence of any treatment emergent AEs (TEAEs) did not suggest any excess of AEs in a particular sub-group.

The incidence of serious AEs (SAEs) was similar in the dronedarone 400 mg BID and placebo groups (18.0% and 19.7%, respectively). Those were mainly related to system organ classes (SOCs) of infections and infestations, GI disorders, and cardiac disorders, with similar incidences in the dronedarone 400 mg BID and placebo groups.

Premature discontinuation due to AEs occurred in 11.8% of the dronedarone-treated and in 7.7% in the placebo-treated groups, respectively. The most common reasons for discontinuation of therapy with dronedarone were GI disorders (3.2 % of patients versus 1.8% in the placebo group) mainly due to diarrhea. The incidence of patients who permanently discontinued treatment due to TEAEs of the "Investigations" class was 2.3% on dronedarone 400 mg BID vs. 0.8% on placebo, mostly due to ECG investigations, and in particular, prolonged QT-interval consistently with the pharmacodynamic effects of dronedarone.

Regarding drug-drug interactions, drugs potentially interacting with dronedarone from a pharmacokinetic or pharmacodynamic point of view were allowed in the AF/AFL clinical program. The potential impact of these interactions on patients' safety was evaluated by reviewing specific adverse events that could be induced by these interactions. These safety analyses provided assurance that recommendations given in clinical studies for the use of beta-blockers, calcium channel inhibitors, digitalis, and statins were adequate for the clinical management of the documented interactions.

An evaluation of AEs known to be associated with amiodarone showed that, unlike amiodarone, dronedarone did not reveal endocrinological, neurological, or pulmonary toxicity in the pooled AF/AFL studies. In addition, in the recently completed DIONYSOS trial that compared dronedarone with amiodarone, the following was shown:

- For thyroid disorders, dronedarone decreased the risk of events by 84.2% (HR [95%CI] 0.158 [0.047 – 0.533]) compared to amiodarone. The majority of cases were hypothyrodisms, but 4 amiodarone patients had hyperthyroidism versus none in the dronedarone group.
- For neurological events, dronedarone decreased the risk of events (sleep disorders and tremor) by 87.6% (HR [95%CI] 0.124 [0.037 – 0.413]) compared to amiodarone.
- For bleeding events: dronedarone decreased the risk of hemorrhagic events by 50% (HR [95%CI] 0.504 [0.266 – 0.954]) compared to amiodarone. The higher incidence of hemorrhagic events observed in the amiodarone group was associated with higher incidences of international normalized ratio (INR) increase.

In addition to the contraindication in patients with worsening CHF or hospitalized for CHF within the last month, MULTAQ® labeling will also include instructions on the management of interacting drugs as well as interpretation of the serum creatinine increase. The proposed REMS aims at preventing the use of dronedarone in the contraindicated unstable CHF population, the concomitant use of potent CYP3A4 inhibitors as well as encouraging early serum creatinine testing as per labeling.

Conclusions

In addition to demonstration of efficacy on rhythm and rate in AF and AFL, dronedarone was shown to provide clinical benefit on cardiovascular hospitalizations or death in a large clinical trial including patients with recent history of or current AF/AFL. This benefit was consistent accross all subgroups evaluated. Since none of the existing antiarrhythmic drugs have ever demonstrated efficacy on morbidity/mortality outcomes, dronedarone represents a new advance in the management of patients with atrial fibrillation/flutter, addressing an important unmet clinical need for patients and physicians. This supports the proposed indication for dronedarone (MULTAQ®):

MULTAQ® is indicated in patients with either a recent history of or current atrial fibrillation or flutter and with associated risk factors. MULTAQ® has been shown to decrease the combined risk of cardiovascular hospitalization or death.

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A-II	angiotensin II
ACE	angiotensin converting enzyme
ACS	acute coronary syndrome
ADONIS	sanofi-aventis Study: *American-Australian-African trial with dronedarone in atrial fibrillation or flutter patients for the maintenance of sinus rhythm*
ADR	adverse drug reaction
AE	adverse event
AF	atrial fibrillation
AFFIRM	Axio Research Study (*Non-sanofi-aventis published study): The atrial fibrillation follow-up investigation of rhythm management.*
AFL	atrial flutter
ALT	alanine aminotransferase (also known as SGPT, or serum glutamate pyruvate transaminase)
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ANDROMEDA	sanofi-aventis Study: *Antiarrhythmic trial with dronedarone in moderate to severe CHF evaluating morbidity decrease*
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase (also known as SGOT, or serum glutamate oxaloacetic transaminase)
ATHENA	sanofi-aventis Study: *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*
AUC	area under the curve
AV	atrioventricular
BID	two times daily
BP	blood pressure
bpm	beats per minute
CAST	Study (*Non-sanofi-aventis published study*): *Cardiac arrhythmia suppression trial*
CHF	congestive heart failure
CI	confidence interval
CYP	cytochrome P-450
DAFNE	sanofi-aventis Study: *Dose-ranging study of the efficacy and safety of dronedarone for the maintenance of sinus rhythm in patients undergoing cardioversion for atrial fibrillation*

DIAMOND	Study (*Non-sanofi-aventis published study)*: *Dofetilide in patients with congestive heart failure and left ventricular dysfunction*
DSMB	data safety monitoring board
DIONYSOS	sanofi-aventis Study: *Randomized double-blind trial to evaluate the efficacy and safety of dronedarone (400 mg BID) versus amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) for at least 6 months for the maintenance of sinus rhythm in patients with atrial fibrillation*
ECG	Electrocardiogram
EMEA	European Medicines Agency
EOT	end of treatment
ERATO	sanofi-aventis Study: *Efficacy and safety of dronedarone for the control of ventricular rate during atrial fibrillation*
ERP	Effective refractory period
EURIDIS	sanofi-aventis Study: *European trial in atrial fibrillation or flutter patients receiving dronedarone for the maintenance of sinus rhythm*
FDA	United States Food and Drug Administration
FT3	free triiodothyronine
FT4	free thyroxine
GFR	glomerular filtration rate
GI	gastrointestinal
HLT	high-level term
HR	hazard ratio
ICD	implantable cardioverter defibrillator
ICU/CCU	intensive care unit or critical care unit
INR	international normalized ratio
ITT	intention-to-treat
ITTM	intent-to-treat-maintenance
IV	Intravenous
IVRS	interactive voice response system
LVEF	left ventricular ejection fraction
LVD	left ventricular dysfunction
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MTD	maximum tolerated dose
MULTAQ®	dronedarone
NDA	New Drug Application
NEC	not elsewhere classified
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association

OD	once daily
PCSA	potential clinically significant abnormality
PDUFA	Prescription Drug User Fee Act
Pgp	P-glycoprotein
PIAF	Study (*Non-sanofi-aventis published study)*: *Pharmacological intervention in atrial fibrillation*
PO	per os (by mouth)
PP	per-protocol
PPM	per-protocol-maintenance
PR	PR interval, ie, distance in time on ECG tracing from start of P-wave to start of QRS complex
PT	preferred term
QRS	QRS interval, ie, distance in time on ECG tracing from start of Q-wave to end of S-wave
QT	QT interval, ie, distance in time on ECG tracing from start of QRS complex to end of T-wave
QTc	QT interval corrected for what it would be theoretically at a rate of 60 bpm
QTcB	QT interval corrected by Bazett's formula
RACE	Study (*Non-sanofi-aventis published study)*: *Rate control versus electrical cardioversion for persistent atrial fibrillation*
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAFE-T	Study (*Non-sanofi-aventis published study)*: *Sotalol amiodarone atrial fibrillation efficacy trial*
SD	standard deviation
SEM	standard error of the mean
SMQ	standard MedDRA query
SOC	system organ class
SWORD	Study (*Non-sanofi-aventis published study)*: *Survival with oral D-sotalol*
T3	tri-iodothyronine
T4	thyroxine
TdP	torsades de pointes
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TSH	thyroid stimulating hormone
TTEM	transtelephonic electrocardiogram monitoring
ULN	upper limit of normal
VT	ventricular tachycardia
WMI	wall motion index

1 INTRODUCTION

1.1 CURRENT APPROACH TO THE MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION OR ATRIAL FLUTTER

Atrial fibrillation (AF) is the most common sustained arrhythmia in the United States (US) population (1,2,3) affecting 6% of people over age 65 (1). The overall incidence of AF increases with each decade of age. It is estimated that there are 2.2 million patients with AF in the US (4), and the number of patients with AF is expected to increase 2.5 fold over the next fifty years, due in part to the growing proportion of elderly patients. Atrial flutter (AFL) is similar to AF with respect to risk factors, symptoms, and prognosis (5).

Rhythm control

For most of the last century the primary goal in the management of AF was the restoration and maintenance of sinus rhythm. Many patients became severely symptomatic during episodes of AF, and these symptoms were abated only after sinus rhythm was restored. Even in the absence of symptoms, it was the general view that patients fared better if they spent more time in sinus rhythm than in AF, perhaps because doing so would reduce the risk of stroke. However, although sinus rhythm could generally be restored by electrical conversion, the chance of recurrence of AF during the following year was about 75% in the absence of antiarrhythmic treatment (6).

In the 1980s, Class I antiarrhythmic drugs were widely prescribed to restore and maintain sinus rhythm in patients with AF. However, controlled clinical trials, the Cardiac Arrhythmia Suppression Trial (CAST) study (7) and the CAST II study (8) showed that many Class I agents were associated with an increase in the risk of cardiovascular death, which was presumed to be related (in part) to a proarrhythmic effect. Consequently, the use of Class I agents is limited.

Drug development efforts then shifted toward antiarrhythmic drugs with Class III properties (prolonging repolarization), because amiodarone (a drug with multiple mechanisms of action including a Class III effect), had minimal proarrhythmic effects. However, amiodarone failed to reduce mortality in several trials, and D-sotalol (a pure Class III drug) was shown to increase the risk of death in a large scale survival trial in high risk patients (SWORD) (9). Furthermore, long-term treatment with amiodarone was known to be accompanied by a high risk of serious end-organ toxicity (including thyroid abnormalities, hepatic toxicity, neuropathy, pulmonary fibrosis, and skin discoloration). Pure Class III drugs (eg, dofetilide) are efficacious for rhythm control but are seldom used because of their high torsadogenic potential, complicated titration algorithm, and need for in-hospital initiation (10). Dofetilide is the most recently approved drug with class III antiarrhythmic properties (1999).

Rate control

Because of the toxicity of drugs used for rhythm control, physicians began to question whether rhythm control was needed, and studies began to emerge that anticoagulation together with rate control (achieved with digitalis, beta-blockers and/or verapamil/diltiazem) might be a more prudent therapeutic strategy. The PIAF study that compared rhythm and rate control showed similar efficacy for both approaches on improvement of symptoms (11). The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study demonstrated a trend for a better survival (p=0.08) and decreased rate of ischemic strokes and cardiovascular hospitalizations in patients randomized to rate-control than to rhythm-control after 3.5 year (12). Similar findings were reported in the 522 patients randomized into the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) study (13). Recently, a fourth study in 1376 patients with AF and chronic heart failure did not demonstrate a difference in the primary endpoint of cardiovascular death, which occurred in 182 (26.7%) patients in the rhythm-control group compared with 175 (25.2%) in the rate-control group (HR 1.058, p=0.59) (14).

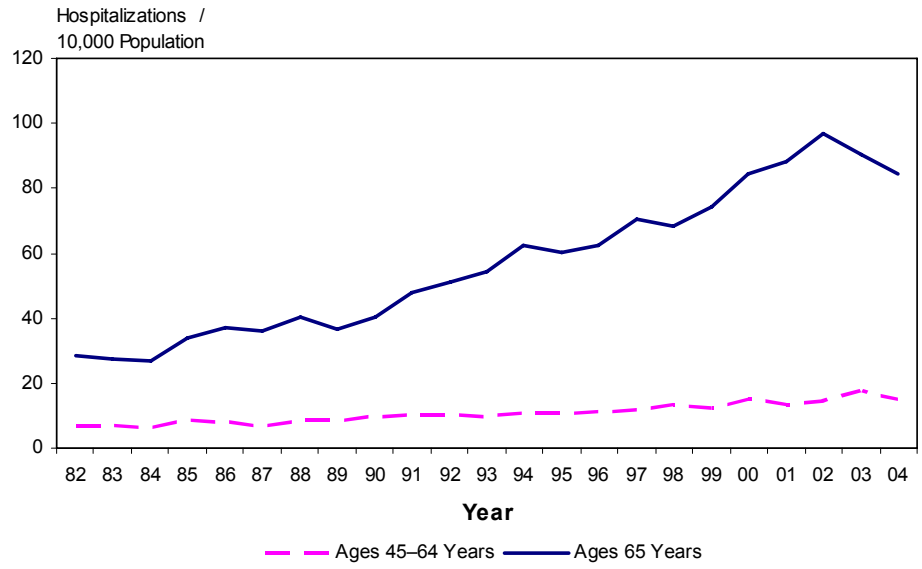
Several types of drugs are used to control the ventricular response in patients with AF.

- **Digoxin** is frequently used for rate control in patients with permanent AF/AFL. However, digoxin is not effective in controlling the ventricular response during physical exercise, and it has not been shown to prevent morbidity/mortality in patients with AF (15).
- **Beta-blockers** and certain calcium channel blockers (verapamil and diltiazem) control the ventricular response, both at rest and during exercise, but they are generally considered ineffective for rhythm control (16).
- **Sotalol**, a beta-blocker (Class II) with Class III properties, is modestly effective for the maintenance of normal sinus rhythm (17), and has a significant torsadogenic potential, thus it requires in-hospital initiation and a complicated titration algorithm (18).
- **Amiodarone** acts to control both rate and rhythm, and is superior to both sotalol and propafenone for the maintenance of sinus rhythm (19). However, long-term use of amiodarone can lead to significant toxicity (e.g., dysthyroidism, pulmonary complications, skin complications, and ocular effects, many of which are severe or require drug discontinuation). Side effects lead to discontinuation of amiodarone in about 8% of patients within 1 year, 18% at 16 months, and up to 23% versus 15.4% on placebo according to a recent meta-analysis (20). In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) study, in which amiodarone and sotalol were compared with placebo in patients with persistent AF and who received anticoagulants, the AF recurrence rates at 1 year were 48% for amiodarone, 68% for sotalol, and 87% for placebo (21). Although the study was statistically underpowered to evaluate mortality differences, there was no apparent difference between the treatment groups.

1.2 UNMET NEED IN THE MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION OR FLUTTER

Although rhythm and rate control may reduce symptoms, it is not clear that either strategy has any meaningful favorable impact on the long-term course of patients. Despite efforts at both rhythm and rate control, patients with AF/AFL are at a markedly increased risk of cardiovascular hospitalizations and cardiovascular death. Atrial fibrillation is the most frequent arrhythmic cause of hospital admission in the US, representing more than one-third of all patient discharges with arrhythmia as a principal diagnosis (22). According to a National Institute of Health (NIH) survey, the increased risk of hospitalization rate is more pronounced in patients older than 65 years of age than in patients 45 to 65 years of age (Figure 1).

Figure 1 - Hospitalization rates for atrial fibrillation by age - 1982 to 2004



Source: (23)

In addition, AF is associated with a 1.5- to 1.9-fold increase in the risk of death, which cannot be explained by its association with embolic complications (24). Atrial fibrillation has been shown to be associated with increased mortality across all age and sex groups (25), and sudden death is estimated to account for 40% to 50% of these cardiovascular deaths (26,27).

Therefore, when treating patients with AF, there is a need to change the focus of drug development from the short-term relief of symptoms to the long-term reduction of morbidity and mortality. Previous efforts to develop drugs for AF often yielded drugs that reduced the arrhythmia but often increased the risk of death or hospitalization. Unfortunately, even when such drugs are avoided, patients with AF remain at significantly increased cardiovascular risk. It is not known whether this increased risk of cardiovascular death or hospitalization is related to the arrhythmia or to cardiovascular conditions that are commonly present in patients with AF.

1.3 HISTORY OF DRONEDARONE DEVELOPMENT

Sanofi-aventis has developed dronedarone with the intent of replicating the effects of the antiarrhythmic drug, amiodarone, but minimizing the significant toxicity that characterizes the use of amiodarone. Dronedarone was designed with the same basic chemical structure as amiodarone but with a methane-sulfonamyl group (leading to a shorter half-life and decreased lipophilicity, thereby lowering tissue accumulation of the drug and minimizing the risk of end-organ toxicity) and without iodine substituents (thus avoiding the risk of thyroid side effects).

Amiodarone is most commonly prescribed in the US for the treatment of AF and AFL, although the drug is not approved for this indication. Accordingly, dronedarone was initially developed to mimic the current use of amiodarone in the community, and the placebo-controlled clinical trials EURIDIS, ADONIS and ERATO confirmed the ability of dronedarone to maintain normal sinus rhythm by reducing the recurrence of AF and to decrease the rapidity of the ventricular response if AF were to recur.

Despite these benefits, the FDA was cognizant of the fact that many anti-arrhythmic drugs reduce the risk of an arrhythmia but at the same time increase the risk of death. Consequently, the FDA recommended that sanofi-aventis carry out a trial to exclude the possibility that dronedarone increased the risk of death. Patients with decompensated heart failure constituted a high risk and highly vulnerable patient population that could be investigated for this purpose, even though a minority of such patients had AF. This resulting trial (ANDROMEDA) was terminated early by the study's DSMB, when it noted 25 deaths in the dronedarone group vs 12 in the placebo group.

Sanofi-aventis submitted a NDA for dronedarone (MULTAQ®) to the FDA in June 2005 for an indication of rhythm and rate control in patients with AF/AFL, to maintain normal sinus rhythm or to decrease ventricular rate. The NDA included 3 pivotal studies supporting this proposed indication (EURIDIS, ADONIS and ERATO). The adverse effect seen in ANDROMEDA was central to the decision by the FDA to issue a Not Approvable letter for dronedarone in August 2006.

The findings of the ANDROMEDA trial changed the focus from the symptomatic relief of arrhythmias to the long-term effects on cardiovascular hospitalization and/or death, highlighting the fact that little was known about the long-term effects of drugs currently approved in the US for the treatment of AF/AFL, and that this endpoint was never evaluated for amiodarone. However, a meta-analysis of the EURIDIS and ADONIS trials suggested that patients with AF who were randomized to dronedarone had a lower risk of cardiovascular hospitalization than patients who were randomized to placebo. Hence, sanofi-aventis shifted its emphasis on the development of dronedarone from its original focus (i.e. the management of symptoms in patients with AF and AFL) to a new focus (i.e. the management of cardiovascular risk in patients with AF and AFL). No previous development program for a drug for the treatment of AF and AFL had been focused on morbidity and mortality.

In January of 2005, sanofi-aventis gained agreement from FDA on the design of a study (ATHENA) to evaluate the effect of dronedarone on the composite outcome of cardiovascular hospitalization or death from any cause in patients with AF and AFL. Patients with heart failure were allowed in the ATHENA trial but only if they were clinically stable and had a recent or

current history of these atrial arrhythmias. Following the positive outcome of the ATHENA trial, sanofi-aventis submitted a new NDA in July 2008, for which priority review was granted by FDA. The benefits observed in the ATHENA trial had led sanofi-aventis to seek the following indication for dronedarone:

MULTAQ® is indicated in patients with either a recent history or current atrial fibrillation or flutter with associated risk factors. MULTAQ® has been shown to decrease the combined risk of cardiovascular hospitalization or death.

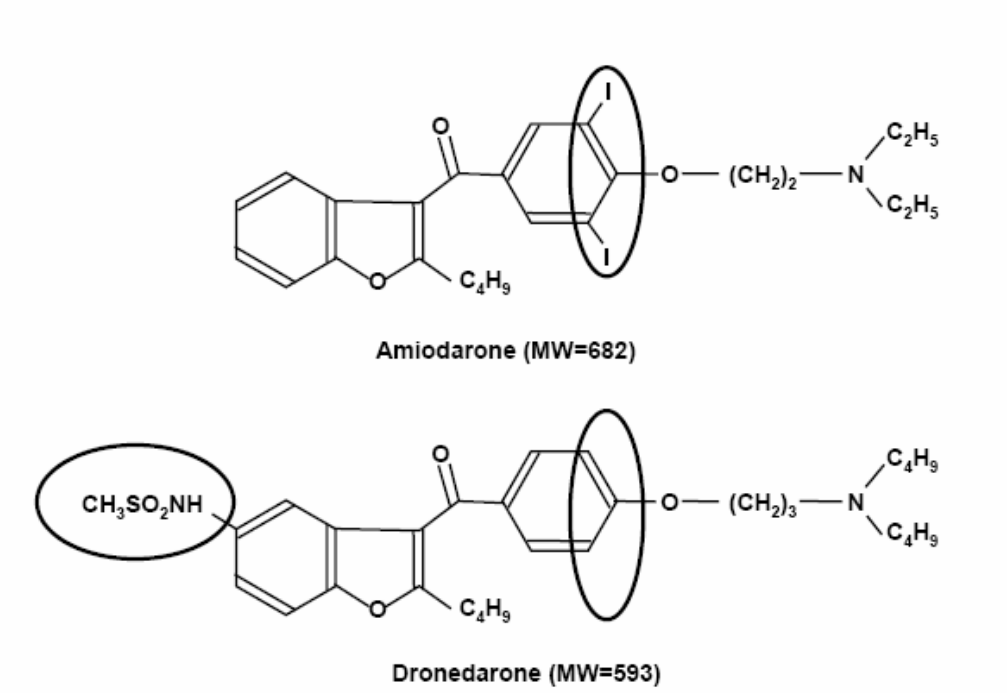
This briefing document presents:

- The preclinical evaluation of dronedarone (Section 2)
- An overview of the initial development program of dronedarone, including studies to control rate and rhythm and ANDROMEDA (Section 3)
- Results of the ATHENA trial specifically designed to evaluate the effect of dronedarone on the combined risk of cardiovascular hospitalization or death in patients with current or recent AF/AFL (Section 4).
- A discussion of ANDROMEDA and ATHENA (Section 5)
- A review of the safety profile of dronedarone in the pooled AF/AFL studies (Section 6)
- The risk evaluation and mitigation strategy (Section 7)
- A conclusion including an assessment of the benefit/ risk of dronedarone (Section 8).

2 PRECLINICAL EVALUATION OF DRONEDARONE

Dronedarone is a benzofuran derivative with an electrophysiological profile resembling that of amiodarone, but with different relative effects on individual ion channels and with structural modifications intended to minimize the non-cardiovascular adverse effects of amiodarone. Specifically, dronedarone was designed without iodine substituents to avoid the risk of thyroid side effects. In addition, dronedarone has a different pharmacokinetic profile with a shorter half-life and decreased lipophilicity owing to the introduction of methane-sulfonamyl group, leading to lower tissue accumulation compared with amiodarone (see Figure 2).

Figure 2 - Chemical structures of amiodarone and dronedarone



2.1 PRECLINICAL PHARMACOLOGY

Dronedarone demonstrates electrophysiological characteristics belonging to all 4 Vaughan-Williams classes of antiarrhythmic compounds. In cardiomyocytes, dronedarone reduced inward currents: rapid sodium channel (I_{Na} of human atrium, frequency-dependent inhibition of dV/dtmax in mammal heart) and L type and T-type calcium currents, outward K^+ currents: I_{K1}, I_{Kr}, I_{Ks}, and I_{KACh} and the pacemaker current I_f. It also inhibited currents of the human channels hERG (I_{Kr}) and Kv1.5 (I_{Kur}) stably transfected in Chinese Hamster ovarian cells.

Table 1 - IC_{50} of dronedarone on different ion channels in guinea pig

	I_{Kr}	I_{Ks}	I_{Kl}	I_f	I_{KACh}	$I_{Ca\text{-}L}$	$I_{Ca\text{-}T}$
Dronedarone	≤3	~10	≥30	>30	~0.01	0.18	>30

(µmol/L)

Dronedarone was effective in several animal models of AF. In low K^+ medium-induced models of AF, ex vivo treatment with dronedarone prevented AF in isolated guinea pig hearts. In electric burst-induced sustained AF in the dilated atrium of isolated rabbit heart, dronedarone restored sinus rhythm. In anesthetized dogs, dronedarone restored sinus rhythm in acetylcholine-induced AF. In vagally induced AF, dronedarone terminated AF and prevented its re-induction; the drug lengthened atrial effective refractory period (ERP) in a dose-dependent but frequency-independent manner.

Dronedarone was also active in several animal models of ventricular arrhythmia. Specifically, dronedarone reduced or suppressed arrhythmias induced by ouabain, ischemia and ischemia-reperfusion in the rat, dog and pig.

The hemodynamic profile of dronedarone was studied in dogs and pigs under anaesthetized or conscious conditions. When given intravenously, both dronedarone and amiodarone decreased arterial blood pressure (BP) and myocardial contractility (dP/dt_{max}) and increased left ventricular end diastolic pressure; coronary blood flow was transiently increased and femoral blood flow decreased. However, the LVEF and fractional shortening (echocardiographic measurements) of healed MI dogs were not modified after chronic oral treatment.

Dronedarone (intravenous [IV] or per os (by mouth) [PO]) displayed important antiadrenergic effects: it reduced the $\alpha 1$ adrenergic BP response to epinephrine and attenuated both the $\beta 1$ (tachycardic) and $\beta 2$ (hypotensive) responses to isoprenaline in anesthetized or conscious dogs.

Dronedarone was active in several animal models of atrial and ventricular arrhythmias. At the atrial level, dronedarone prevented or suppressed AF induced by low K^+ medium, electrical stimulation/atrial dilation and vagal stimulation. At the ventricular level, dronedarone reduced or suppressed arrhythmias induced by ouabain, ischemia and ischemia-reperfusion in several animal models (rat, dog or pig).

In summary, dronedarone exhibits an array of pharmacological activities at several well-defined molecular targets that may mediate and explain its clinical benefit in patients with cardiac arrhythmias.

2.2 PRE-CLINICAL SAFETY

Dronedarone was generally well tolerated in animals. The safety of dronedarone has been evaluated in a non-clinical testing program designed in accordance with the claimed indication in man, the intended route of administration, and duration of treatment. Since dronedarone was developed with the intent of eliminating the non-cardiovascular adverse effects of amiodarone, the program particularly focused on the potential for amiodarone-like toxic effects.

Phospholipidosis: After 14-day repeated administration to rats, dronedarone, unlike amiodarone, induced no phospholipid accumulation in the lung (up to 150 mg/kg) but induced slight non-dose dependent increases in liver phospholipid content. With dronedarone, as compared with historical data with amiodarone, slight reversible phospholipidosis was only seen in the rat at high doses. It was not observed in other species and not when dronedarone was administered by the IV route. Therefore, this effect was considered specific to the oral route and limited to the rat.

Thyroid: Thyroid changes observed with dronedarone (at 50 mg/kg/day in the 6-month rat study conducted at 0, 2, 10 and 50 mg/kg/day and at doses $\geq$ 15 mg/kg/day in the one-year dog study conducted at 0, 5, 15 and 45 mg/kg/day) were minor and differed markedly in nature and severity from those induced by amiodarone (historical comparison): only slight variations in hormone levels, ie, decrease in tri-iodothyronine (T3) with no effect on thyroid stimulating hormone (TSH), were observed as opposed to marked increases of thyroxine (T4) and TSH with

amiodarone. Also, there were no microscopic changes observed in the dog, only an increased incidence of columnar follicular epithelium in the rat. There was no increased incidence of thyroid tumors with dronedarone.

Phototoxicity: Dronedarone was slightly phototoxic in the guinea-pig at high doses, but was not photoallergic conversely to amiodarone which is strongly phototoxic.

Renal changes: Dronedarone administered at 0, 10 and 30 mg/kg/day in a dedicated male rat 14-day study did not alter renal blood flow or creatinine clearance. Only slight renal functional alterations (urinalysis modifications or very slight serum creatinine increase in the rat only (5 to 6% at 10 and 50 mg/kg/day in the 6-month study conducted at 0, 2, 10 and 50 mg/kg/day; highest increase of 15% in the 3-month study at the highest dose tested of 60 mg/kg/day) were observed throughout the toxicology program. These effects were minor and not associated with any microscopic change in the kidney in any of the studies and species.

Liver changes: Hepatic effects (isolated increases in transaminases and/or alterations in bilirubin as well as histopathological changes essentially in the biliary tract) were seen at high doses in short term studies in the rat and the dog. These were considered to be secondary to high dose toxicity as they did not occur in isolation but as part of a spectrum of signs of general toxicity and health deterioration. In addition in the rat these signs were observed at doses causing death or exceeding the maximal tolerated dose (MTD). The biochemical changes did not correlate with the histopathological findings which were considered to be linked more to the physicochemical properties of the compound. At lower doses and longer term treatment no consistent hepatic changes were observed and when present showed a lack of dose response and time dependency, with in addition, the presence of similar changes in control animals on certain studies.

Reprotoxicity: Dronedarone induced abnormalities in rat fetuses at the high dose of 100 mg/kg/day that also induced maternal toxicity, but not at 30 mg/kg/day in the embryofetal development study. At 100 mg/kg/day, there were slightly fewer viable fetuses, a higher number of resorptions as well as reduced fetal and placental weights. Abnormalities affecting external morphology, all major organ systems, and the skeleton were noted. In the pre- and post-natal study, the dose of 50 mg/kg/day was shown to be devoid of any significant effects on the fetus. Despite the absence of teratogenic effects in rabbits, in light of the findings in rats, and because the risk for humans is not known, the Sponsor recommends not to use the product during pregnancy.

Carcinogenic potential: In the oncogenic studies, the following findings were observed at the highest dose only (300 and 70 mg/kg/day in mice and rats, respectively) corresponding to 5- to 10-fold the clinical exposure:

- Increased incidence of mammary gland tumors in female mice. This effect was limited to one sex and one species and is considered to be linked to slight effects on hormone homeostasis (minimal increase in prolactin levels). This mechanism of tumor induction is known to be of low relevance in the development of human mammary neoplasms, which are also morphologically different from the mouse tumors observed (28);
- A slight increase in the incidence of histiocytic sarcoma in mice (statistically significant in males only) was observed. This finding was considered to be incidental, as the frequency

remained within the range of published historical data for a tumor known of marked variability in incidence. No tumor of this type was noted in the rat. The morphological tumor type is specific to the mouse and does not occur in man. In addition, there was no increase in the frequency of other hemolymphoreticular tumors in either the rat or mouse;

- Increased incidence of vaso-proliferative lesions in mesenteric lymph nodes was observed for both sexes in the rat and in the female mouse. In the rat, an increase in the background incidence of only benign changes (hemangioma) was seen. In the female mouse, a very low incidence (2 cases) of hemangioma and hemangiosarcoma was observed. The malignant changes (hemangiosarcoma), which were not statistically significant, were limited to one species and one sex. The benign changes in the rat were considered to be part of a reactive-proliferative process linked to accumulation of foamy macrophages containing dronedarone in the mesenteric lymph nodes. This rat specific accumulation is postulated to result in alterations of local blood flow and compound associated vasodilatation, leading to the reactive-proliferative process. These benign tumors are not considered to be precursors of malignant change.

Overall, dronedarone is not genotoxic and on weight of evidence the tumors seen in the carcinogenicity studies were incidental or considered to be of very low relevance for human beings. Therefore, sanofi-aventis believes that dronedarone does not pose any concern for carcinogenicity in man.

3 INITIAL CLINICAL DEVELOPMENT OF DRONEDARONE

The development of dronedarone for the management of patients with AF/AFL had three main phases. The first phase focused on characterizing the pharmacokinetic and pharmcodynamic properties of the drug in man; the second phase focused on an evaluation of its ability to achieve rate and rhythm control in patients with AF/AFL; and the third phase focused on the evaluation of the drug on morbidity and mortality.

The main studies of the clinical development program are shown in Table 2.

Table 2 - Dronedarone clinical development program with main studies

Study Type and ID	N	Dose Regimen	Population	Objectives
Clinical Pharmacology				
TDR2395	52	800-1600 mg OD 400-800 mg BID vs. placebo	Healthy subjects	Tolerability/Pharmacodynamic ascending doses
TDR3549	41	800-1600 mg BID vs. placebo	Healthy subjects	Tolerability/Pharmacodynamic ascending doses
PDY5487	12	400 mg BID vs. placebo	Healthy subjects	Effect on serum creatinine
PDY5923	31	400 mg BID vs. placebo	Young healthy subjects	Effect on serum creatinine
PDY5850	33	400 mg BID vs. placebo	Elderly healthy subjects	Effect on serum creatinine
Other Populations				
ACT2401	124	400, 800 mg OD 600 mg BID vs. placebo	LV dysfunction	Safety/pharmacodynamic effects on patients with LVD
DRI3151 +LTS3841	73	600, 800, 1000 mg BID vs. placebo	ICD population	Prevention of ICD shocks
EFC4966/ ANDROMEDA	627	400 mg BID vs. placebo	Recent severe episode of CHF and LV dysfunction	Prevention of hospitalization for worsening heart failure or death in patients with unstable severe CHF with LVD
Dose Finding				
DRI3550/DAFNE	270	400, 600, 800 mg BID vs. placebo	AF	Efficacy and safety in AF cardioversion and maintenance of sinus rhythm
Efficacy in control of rate or rhythm in patients with AF/AFL				
EFC3153/EURIDIS	612	400 mg BID vs. placebo	AF/AFL	Maintenance of sinus rhythm in AF/AFL
EFC4788/ADONIS	625	400 mg BID vs. placebo	AF/AFL	Maintenance of sinus rhythm in AF/AFL
EFC4508/ERATO	174	400 mg BID vs. placebo	Permanent AF	Ventricular rate control
EFC4968/DIONYSOS	504	400 mg BID vs. amiodarone: 600mg OD for 28 days then 200 mg OD	AF, cardioversion and antiarrhythmic treatment indicated, and receiving anticoagulants.	Prevention of recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy
Efficacy in reduction of morbidity and mortality in patients with AF/AFL				
EFC5555/ATHENA	4628	400 mg BID vs. placebo	AF/AFL at high risk	Prevention of cardiovascular hospitalization or death from any cause in patients with AF/AFL

3.1 CLINICAL PHARMACOKINETICS

3.1.1 Absorption, Distribution, Metabolism, and Elimination

After oral administration in fed conditions in healthy subjects, dronedarone is well-absorbed (at least 70%); its absolute bioavailability is 15% due to significant first pass metabolism. Peak plasma concentrations of dronedarone are reached within 3 to 6 hours under fed conditions. At 400 mg BID, steady state levels of the drug are reached within 4 to 8 days of treatment, mean steady state dronedarone C_{max} ranges from 85 to 150 ng/mL and mean C_{trough} from 40 to 55 ng/mL, demonstrating limited fluctuation between peak and trough concentrations. The exposures and pharmacokinetic profiles of the main active circulating metabolite, SR35021, are approximately similar to those of dronedarone. Based upon exposure and activity in preclinical models, SR35021 may contribute to 10-30% of the pharmacological activity of dronedarone.

Dronedarone and SR35021 exposures increase with dose in a supra-dose proportional fashion. For a 2-fold increase in dose over the range of 200 to 800 mg BID, there is, on average, a 2.5- to 3.0-fold increase in dronedarone exposure. On repeated 400 mg BID dosing, steady state is reached within 4 to 8 days with an accumulation ratio for dronedarone and SR35021 ranging from 2.6 to 4.5.

Dronedarone and SR35021 exhibit high and nonsaturable protein binding (>98%) in human plasma. Both compounds bind primarily to albumin.

Dronedarone is extensively metabolized primarily by CYP3A4. The numerous metabolites observed are excreted primarily in feces. Renal excretion is a very minor route of elimination (6% of the dose) with no unchanged dronedarone excreted in urine. The steady state terminal elimination half-life of dronedarone is approximately 30 hours and that of SR35021 approximately 25 hours. Dronedarone is completely eliminated from plasma within 2 weeks after the last dose of 400 mg BID treatment.

The main circulating metabolites in man, the N-debutyl derivative hydrochloride SR35021A and the O-propanoic acid derivative, SR90154, have been studied. SR35021A displayed antiarrhythmic, electrophysiological and hemodynamic activities similar to those of dronedarone but was less potent (approximately 3 to 10 times) than its parent compound. SR90154 has very little or no activity.

3.1.2 Intrinsic and Extrinsic Factors in Pharmacokinetic Variability

Intrinsic Factors

The pharmacokinetics of dronedarone in patients with AF and the main sources of variability are consistent with those in healthy subjects. The variability in exposure (C_{max}, C_{trough}, area under the curve [AUC]) is modest in patients (CVs of 30% to 40%). The primary intrinsic sources of variability are gender, weight, and age. On average, female patients have dronedarone exposures 1.3-fold higher compared with male patients. In patients with bodyweight ≤ 60 kg, exposures are 1.4-fold higher compared with patients with bodyweight 60 to 100 kg. In patients ≥ 65years or ≥ 75 years of age, exposures are 1.2-fold and 1.4-fold higher compared with patients < 65 years

old. In patients, the exposure to the active metabolite is influenced by the same covariables as for the parent compound. CHF, renal function, and in particular, severe renal impairment do not significantly influence the pharmacokinetics of dronedarone in patients, once the effect of age, gender and weight are taken into account. As expected, moderate hepatic impairment modifies the pharmacokinetics of dronedarone, but only moderately: steady-state dronedarone exposure increased by 1.3-fold and active metabolite exposure decreased by 1.6- to 1.9-fold.

Extrinsic Factors

The primary extrinsic factors which impact the pharmacokinetics of dronedarone are food and co-medications which modulate CYP3A4.

Dronedarone was recommended to be taken with meal in all the efficacy/safety studies. While the impact of administration of dronedarone in the fasted state is significant (a 2-3 fold decrease in exposure) after single dose, the predicted impact of one administration of dronedarone in fasted state would only be a 30-40% decrease in exposure during a chronic treatment.

A large portion of the clearance of dronedarone is mediated by CYP3A4. The administration of a strong inhibitor of CYP3A4 (ketoconanzole) with a single 200 mg dose of dronedarone resulted in a 17 fold increase in dronedarone exposure. While the increase in exposure with ketoconazole would be expected to be less (5 to 8-fold) with repeated 400 mg BID doses of dronedarone, the use of any strong inhibitor of CYP3A4 was contraindicated in all clinical trials with dronedarone.

Moderate CYP3A4 inhibitors such as diltiazem, verapamil have a modest effect (1.5-fold) on dronedarone exposures with no significant change on the active metabolite. Under intensive (double strength, large volume, T.I.D) conditions, grapefruit juice increases dronedarone exposure by 3- fold. Strong CYP3A4 inducers decreased, by 5-fold, dronedarone exposure, with no change on the active metabolite.

Impact on multiple intrinsic and extrinsic factors

Based upon the population pharmacokinetic model of dronedarone, the impact of multiple intrinsic factors on the exposure of dronedarone can be assessed. Furthermore, the impact of additional extrinsic factors on top of one or more intrinsic factors can be assessed using clinical pharmacology interaction data obtained at the 400 mg dose in the BID. The results from this assessment indicated that even a combination of 2-3 factors would generally not be expected to increase exposures more than 2-3 fold.

Table 3 - Combined Effect of Intrinsic and Extrinsic Factors: Population at Risk of Higher Dronedarone Exposures

Parameters	Range	Dronedarone AUC_{0-12} ratio of mean exposures
Age	≥ 65 y vs < 65 y	1.2
	≥ 75 y vs < 65 y	1.4
Gender	Female vs Male	1.3
Weight	≤ 60 kg vs]60-100 kg[	1.4
Elderly (≥ 75 y) female with low weight (≤ 60 kg)		1.6
Elderly (≥ 75 y) female with low weight (≤ 60 kg) + CYP3A4 moderate inhibitor		2.4

3.1.3 Impact of dronedarone on concomitant medications

Dronedarone is a moderate inhibitor of CYP3A4, a weak inhibitor of CYP2D6, and has the potential to interact with substrates of those CYPs. It also has the potential to inhibit Pgp transport. Dronedarone has no significant potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2C8, or CYP 2B6. The potential impact of inhibition of CYP3A4, CYP2D6 and Pgp on commonly prescribed medications in this indication is described below:

CYP3A4

Statins: Dronedarone (400 mg BID) increased simvastatin and simvastatin acid exposure by 4-and 2-fold, respectively. Dronedarone could increase exposures of lovastatin, atorvastatin, and pravastatin within the same range as simvastatin. Significant interaction of dronedarone on statins that are not CYP3A4/P-gP substrates (fluvastatin and rosuvastatin) is unlikely.

Calcium antagonists: Dronedarone (400 mg BID) increased the exposure of verapamil by 1.4-fold, and nisoldipine by 1.5- fold. The modest effect of dronedarone on calcium anatagonists is consistent with the lower contribution of CYP3A4 to the total clearance of calcium antagonists when compared with statins.

CYP2D6

Beta-blockers: Dronedarone (800 mg daily dose) increased metoprolol exposure by 1.6-fold and propranolol exposure by 1.3-fold. Other beta-blockers that are metabolized by CYP2D6 (such as bisoprolol, carvedilol, nebivolol, timolol) could also have their exposure increased by dronedarone.

P-glycoprotein transporter (Pgp)

Digoxin: Dronedarone (400 mg BID) increased digoxin exposure by 2.5-fold by inhibiting P-gP transporter.

Clinical safety analyses of drug-drug interactions are present in Section 6.4.

Due to pharmacokinetic interactions and potential additional pharmacodynamic interactions, specific recommendations were given to investigators for concomitant use with calcium channel antagonists, beta-blockers, and digoxin; these recommendations are also reflected in the proposed labeling.

3.2 STUDIES TO EXPLORE MECHANISM FOR SERUM CREATININE INCREASE

Increase in serum creatinine with dronedarone 400 mg BID has been observed across the whole clinical development program. It occurred early after treatment initiation and reached a plateau after 7 days. Values returned to baseline within 1 week after treatment discontinuation (as noted in DAFNE, EURIDIS, and ADONIS).

The absence of evidence for kidney damage in animal toxicity studies associated with a rapid, stable, and reversible mild (10 µmol/L) mean increase in serum creatinine value, as repeatedly observed, did not suggest nephrotoxicity. Once the potential of dronedarone interference with the creatinine assay method was excluded, it was speculated that these observations were related to a pharmacodynamic interaction of the drug with the kidney. To clarify this, a specific study was performed in healthy subjects (Study PDY5487). In order to better characterize the time course of serum creatinine increase, two additional studies were conducted: one in young healthy male subjects (Study PDY5923) and one in elderly healthy male subjects with or without renal impairment (Study PDY5850).

Study PDY5487 demonstrated that the increase in creatinine plasma levels associated with dronedarone administration is due to a decrease in renal creatinine clearance without concomitant decrease in glomerular filtration (no modification in sinistrin clearance). This was also supported by the significant reduction in the clearance of the endogenous cation N-methylnicotinamide, especially when normalized to renal perfusion (p=0.007) (Table 4). Fourteen days after the last dronedarone dose, all parameters showing an interaction of dronedarone with tubular function were back to baseline values. Consequently, the significant decrease in the ratio of creatinine clearance over sinistrin clearance suggested inhibition of creatinine tubular secretion.

Table 4 - Percent changes from baseline in renal clearances - PDY5487

	Placebo D7/D-1 (%)	Dronedarone 400 mg bid D7/D-1 (%)	(D7/D-1)Dronedarone/(D7/D-1)Placebo ratio		
			Estimate (%)	95% CI (%)	P-value ANOVA
Sinistrin clearance	1.35	-2.11	-3.42	[-20.41,17.21]	0.7229
Creatinine clearance	4.91	-13.66	-17.70	[-31.68,-0.85]	0.0405
Creatinine clearance over sinistrin clearance	3.42	-11.80	-14.72	[-20.72,-8.25]	<.0001
PAH clearance	0.06	-5.72	-5.77	[-22.47,14.51]	0.5471
NMN clearance	-0.86	-17.74	-17.02	[-31.58, 0.65]	0.0581
NMN clearance over PAH clearance	-1.11	-12.75	-11.76	[-19.35, -3.45]	0.0068

P-value is the significance level of the hypothesis test: (Day7/Day-1) Dronedarone / (Day7/Day-1) Placebo ratio equals 1
D-1: baseline

Study PDY5923 showed that other parameters of kidney function (plasma renin activity, aldosterone, angiotensin II (A-II), cortisol, urea, uric acid, N^1-methylnicotinamide, sodium, and potassium) were not modified by dronedarone treatment. In this study, serum creatinine increase was observed within 2 days after administration in healthy subjects, and values remained stable during treatment and returned to baseline within 3 days after treatment discontinuation. Similar observations have been made in patients. In addition, the magnitude of the increase in serum creatinine has not been shown to be dependent on baseline kidney function in elderly male subjects (Study PDY5850). Also, a complementary population pharmacokinetic analysis (Study POH0204) confirmed that renal impairment and in particular severe renal impairment had no significant effect on dronedarone pharmacokinetics, once the effect of age, weight, and gender covariates was taken into account.

The description of renal adverse events in the whole AF/AFL population including ATHENA is provided in Section 6.

3.3 STUDIES OF DRONEDARONE TO CONTROL RATE OR RHYTHM IN PATIENTS WITH ATRIAL FIBRILLATION OR FLUTTER

The initial development of dronedarone focused on its efficacy for the control of rhythm and rate in patients with AF/AFL.

- The dose selected for these studies was based on findings from the **DAFNE** study (which evaluated three different doses of dronedarone, i.e., 400 mg BID, 600 mg BID, or 800 mg BID).
- The placebo-controlled **EURIDIS** and **ADONIS** studies demonstrated the ability of dronedarone 400 mg BID to maintain sinus rhythm in patients with a history of AF/AFL.
- The placebo-controlled **ERATO** study documented the ability of dronedarone 400 mg BID to control the ventricular rate in permanent AF.
- The **DIONYSOS** study compared the efficacy and safety of dronedarone and amiodarone on the prevention of arrhythmia recurrence in patients with AF.

3.3.1 DAFNE

The DAFNE trial was a multinational, multicenter, double-blind, parallel-group, placebo-controlled, study that was designed to compare 3 different doses of dronedarone with placebo for the maintenance of sinus rhythm following electrical cardioversion, in patients with AF. The primary objective was to assess the efficacy of several doses of dronedarone for the maintenance of sinus rhythm at 6 months in patients undergoing cardioversion for AF. The study was carried out in 50 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. Patient enrollment began in February 1999 and the last patient completed in July 2000.

3.3.1.1 Study Design

Patients were eligible for the study if they were 21 to 85 years old; had persistent AF (for at least 72 hours but less than 12 months); and had an indication for cardioversion and antiarrhythmic treatment. Patients were excluded if they had: AFL as the presenting arrhythmia; unstable angina pectoris (ischemic symptoms during the last 7 days or recent MI (≤ 6 weeks); AF associated with an acute reversible condition (e.g. alcohol intake, thyrotoxicosis, infection, recent i.e. ≤2 months cardiac surgery); plasma potassium <3.5 mmol/L and uncorrected or >5.5 mmol/L; congenital long QT syndrome; QT-interval >500 ms; history of TdP; bradycardia <50 bpm while awake; evidence on ECGs recorded in sinus rhythm of PR-interval ≥0.28 s or high degree atrioventricular (AV) block (2nd degree or higher), or significant sinus node disease without a permanent pacemaker implanted; antiarrhythmic therapy required for other arrhythmias; treatment with amiodarone for 5 or more days during the last 6 months (patients who received IV amiodarone for ≤ 5 days during the prior 6 months could be included after a wash-out period of 5 days); clinically overt CHF or NYHA class III or IV; LVEF less than 35% assessed by radionuclide angiography or echocardiography within the 4 weeks preceding the screening visit; potentially dangerous symptoms associated with AF such as angina pectoris, TIAs, stroke, syncope precluding the ethical administration of placebo; Wolff-Parkinson-White syndrome; presence of an implantable cardioverter defibrillator; more than two cardioversions in the last 6 months; contraindication to oral anticoagulants; evidence of clinically relevant hematologic, hepatic (alanine aminotransferase [ALT], aspartate aminotransferase (AST), bilirubin >2 times the laboratory upper limit), GI, renal (serum creatinine >150 μmol/L), pulmonary, endocrinologic (in particular thyroid) or psychiatric disease.

Patients fulfilling the entry criteria for the study were randomly assigned to either 400 mg twice daily, 600 mg twice daily, 800 mg twice daily or placebo, which were continued for 6 months. The 400 mg BID regimen was chosen as the lowest dose because this was the lowest dose that demonstrated electrophysiological effects in healthy subjects (as reflected by a prolongation of the PR interval and a slight prolongation of the QTc interval on the 12-lead ECG). The 800 mg BID regimen was chosen as the highest dose because it was associated with a significant prolongation of the QTc interval and was considered the highest dose that was likely to be well tolerated.

The BID regimen was selected for all dose levels of dronedarone to minimize peak to trough fluctuations while maximizing drug exposure and pharmacodynamic activity. For the same daily dose, dronedarone and SR35021 exposures (AUC0-24) were 1.1 to 1.6 fold higher for the BID regimen compared to the OD regimen, and there was limited fluctuations (2 to 3 fold) between peak and trough concentrations for a BID regimen.

All antiarrhythmic drugs were withdrawn for at least five plasma half-lives before the beginning of the study. Patients were started on an oral anticoagulant 3 weeks before cardioversion, and the anticoagulant was continued at least 4 weeks following cardioversion. Prohibited medications included antiarrhythmic drugs (Vaughan Williams class I and III), calcium antagonists with depressing effects on the sinus and AV node (e.g. diltiazem and verapamil), drugs known to prolong the QT-interval and all potent inhibitors of CYP450 3A4 such as ketoconazole.

The primary endpoint was time to first recurrence of AF after conversion to sinus rhythm. The secondary endpoints were: time to treatment failure (from randomization to first recurrence in

patients converted to sinus rhythm or to cardioversion failure for patients not converted), number of patients converted to sinus rhythm, number of patients with spontaneous conversion on treatment before cardioversion, ventricular rate during AF in case of recurrence.

Patients were followed for 6 months, in case of premature study drug discontinuation and a follow-up visit was conducted 10 days after study drug discontinuation.

3.3.1.2 Patient Enrollment and Disposition

A total of 270 patients were randomized in the trial: 66 to placebo, 76 to 400 mg BID, 66 to 600 mg BID, and 62 to 800 mg BID. Table 5 describes the disposition of patients in the study. Randomized and treated patients in AF at randomization who were already in or converted to sinus rhythm at V2 (Day 5 visit) represent the intent to treat maintenance (ITTM) population. Patients in per-protocol maintenance population (PPM) were those in ITTM population excluding all those without persistent (>72 h and <12 months) documented AF at randomization; with less than 4 days of study drug at the electrical cardioversion visit (V2) with compliance lower than 75%, without documentation of spontaneous or electrical conversion to sinus rhythm or AF recurrence, or using prohibited medication.

Table 5 – Patient Disposition - DAFNE

	Placebo	400 mg BID	600 mg BID	800 mg BID	Total
All treated	66	76	66	62	270
Intent-to-treat	66	76	66	61	269
Per protocol	64	69	61	54	248
Intent-to-treat maintenance (ITTM)	49	56	56	44	205
Per protocol maintenance (PPM)	48	54	54	43	199

Thirty of the 270 randomized patients ended study drug treatment prematurely, either due to an AE (23 patients), protocol deviations (4 patients), patient requests (2 patients), or other reason (1 patient). Premature termination occurred in 1 placebo patient (1.5%) and in 5 patients (6%), 6 patients (9.1%), and 18 patients (29%) in the 400mg BID, 600 mg BID and 800 mg BID groups respectively. The difference among groups in the number of premature permanent discontinuations was significant ($p < 0.0001$).

3.3.1.3 Patient Characteristics

The duration of treatment was longer in the dronedarone 400 mg BID group than in the placebo group, likely due to the efficacy of this dronedarone dose. Demographic data for the per-protocol maintenance population (PPM) are presented by treatment group in Table 6.

Table 6 - Demographic Characteristics: Per Protocol Maintenance Population - DAFNE

Parameter		Placebo (N=48)	Dronedarone 400 mg BID (N=54)	Dronedarone 600 mg BID (N=54)	Dronedarone 800 mg BID (N=43)
Age (years)	n	48	54	54	43
	Median	67	66	63	64
	Mean	65.6	64.0	63.7	62.3
	SD	8.4	13.0	8.7	11.7
	Min - Max	46 - 80	24 - 81	39 - 78	29 - 79
Age (years) [n(%)]	<65	19 (39.6%)	24 (44.4%)	30 (55.6%)	22 (51.2%)
	[65-75[	20 (41.7%)	18 (33.3%)	14 (25.9%)	17 (39.5%)
	>=75	9 (18.8%)	12 (22.2%)	10 (18.5%)	4 (9.3%)
Weight (kg)	n	48	54	54	43
	Median	80.0	81.5	82.0	81.5
	Mean	80.82	81.80	83.38	84.35
	SD	12.99	13.78	16.65	14.41
	Min - Max	54.5 - 120.0	54.0 - 119.9	54.0 - 136.0	62.0 - 135.0
Gender [n(%)]	Male	38 (79.2%)	31 (57.4%)	38 (70.4%)	29 (67.4%)
	Female	10 (20.8%)	23 (42.6%)	16 (29.6%)	14 (32.6%)
Race [n(%)]	Caucasian	48 (100.0%)	54 (100.0%)	54 (100.0%)	43 (100.0%)

Table 7 - Number (%) of Patients by Presence of Structural Heart Disease and Cardiovascular History - Per Protocol Maintenance Population - DAFNE

Variable	Placebo N=48 n (%)	Dronedarone 400 mg BID N=54 n (%)	Dronedarone 600 mg BID N=54 n (%)	Dronedarone 800 mg BID N=43 n (%)
Structural heart disease[a]	32 (66.7)	28 (51.9)	30 (55.6)	25 (58.1)
Ischemic heart disease	13 (27.1)	11 (20.4)	10 (18.5)	9 (20.9)
Congestive heart failure	11 (22.9)	8 (14.8)	13 (24.1)	5 (11.6)
Valvular dysfunction	24 (50)	19 (35.2)	17 (31.5)	16 (37.2)
Cardiac arrhythmias	3 (6.3)	8 (14.8)	6 (11.1)	5 (11.6)
Arterial hypertension	27 (56.3)	28 (51.9)	27 (50)	19 (44.2)

a: Includes CHF and/or ischemic heart disease and/or valvular dysfunction

3.3.1.4 Efficacy results

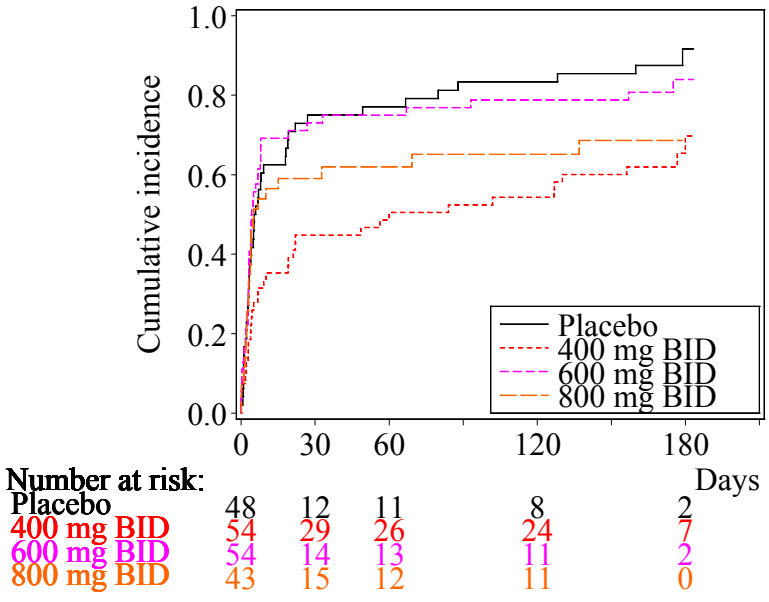
Primary Analysis

The primary objective of the study was to evaluate the relation between dose and the time to first recurrence of AF, but the study observed no dose effect for maintenance of sinus rhythm (p=0.7188). The longest median time to first AF recurrence was 60 days in the dronedarone 400 mg BID group, compared to 5 days in the placebo group (see Table 8 and Figure 3).

Table 8 – Time to AF Recurrence (Days) - Per Protocol Maintenance Population - DAFNE

Parameters	Statistics	Placebo N=48	400 mg BID N=54	600 mg BID N=54	800 mg BID N=43
Time to AF recurrence					
Duration in sinus rhythm (days)	Median	5.32	59.92	4.31	5.18
	Minimum	0.028	0.059	0.002	0.089
	Maximum	183.5	193.6	183.5	178.5
Risk versus placebo	Risk ratio		0.45	0.95	0.68
	95% CI		0.28 / 0.72	0.62 / 1.45	0.42 / 1.11

Figure 3 - Time from conversion to adjudicated first AF recurrence within 6 months – Per-protocol Maintenance Population - DAFNE



Note: Kaplan-Meier cumulative incidence curves

Post-hoc analyses

Post-hoc analysis revealed a significant treatment effect for time to recurrence of AF in the 400 mg BID group in both the PPM population (p=0.0010) and in the ITTM population (p=0.0007). The effects seen in the 600 mg BID group and 800 mg BID group were not significant.

Secondary/additional analyses

Time to AF treatment failure**.** Consistent with the analysis of time to AF recurrence, the longest median time to AF treatment failure was observed in the PP (per-protocol) population in the 400 mg BID group, 24.16 days, compared to 9.23 days in the placebo group. No dose effect was observed. Post-hoc analysis showed a treatment effect for time to AF treatment failure in the 400 mg BID group, both in the ITT analysis (p=0.0010) as well as in the PP analysis (p=0.0008).

Number of patients converted to sinus rhythm. The frequency of conversion without electrical cardioversion showed a significant dose effect in the per-protocol analysis; conversion to sinus rhythm was seen in 5.80%, 8.20%, and 14.81% of patients in the 400 mg BID, 600 mg BID, and 800 mg BID groups, respectively, as compared with 3.13% of placebo patients (p=0.0261). Results were similar in the intention-to-treat analysis. Electrical conversion was equally successful across the four treatment groups; the frequencies of successful electrical cardioversion in the per-protocol analysis population were: 77.3% (400 mg BID), 87.9% (600 mg BID), and 76.6% (800 mg BID) and 73.0% (placebo).

Success of cardioversion. In both the per-protocol and intention-to-treat analyses no statistically significant dose effect was observed in the number of shocks or in the energy necessary to obtain sinus rhythm.

Ventricular rate in case of recurrence. In the PPM population, there was a significant difference between groups for ventricular rate in case of recurrence of AF (p=0.0001). When compared with placebo, the ventricular response was lower in all three dronedarone groups, both in the PPM and ITTM analyses.

The ventricular rate control effect of dronedarone evaluated at the time of AF recurrence in DAFNE is presented in Table 9.

Table 9 - Ventricular Rate (bpm) in Case of Recurrence - Per Protocol Maintenance Population - DAFNE

Ventricular rate (bpm)	Statistics	Placebo	400 mg BID	600 mg BID	800 mg BID	p-value [a]
Observed value	N	43	35	44	28	0.0001
	Mean	102.9	89.7	83.6	85.1	
	SD	21.9	20.5	17.3	21.1	
	Median	99.0	90.0	82.5	79.0	
	Minimum	71	52	52	52	
	Maximum	151	141	122	143	
Adjusted difference	Mean		-13.2	-19.2	-17.8	
versus placebo	95% CI		-22.2 / -4.1	-27.8 / -10.7	-27.5 / -8.1	

a: analysis of variance (ANOVA)

Symptoms associated with AF and intensity. The proportion of symptomatic patients was similar in the four treatment groups at day 1 and day 5-8 in the PPM and ITTM analyses.

Safety results. The trial revealed evidence of a dose-response relationship particularly for diarrhea, which was seen in 2.0% of the placebo group, 2.6% of the 400 mg BID group, 7.6% of the 600 mg BID group and 27.4% of the 800 mg BID group.

3.3.1.5 Study Conclusion and dose selection

Among the three doses evaluated, the 400 mg BID dose of dronedarone was associated with the greatest efficacy and least toxicity. This finding was noteworthy since in clinical pharmacology studies, the 400 mg BID dose was the lowest dose of dronedarone that produced consistent changes in the 12 lead ECG (prolongation of the PR interval and slight prolongation of the QTc interval). As a result, this dose was selected as the therapeutic dose for future studies.

The 400 mg BID dose was shown to be effective for rhythm and rate control in EURIDIS/ADONIS, and ERATO and was further selected for the ATHENA study. The appropriateness of the 400 mg BID dose was confirmed in the ATHENA study, overall and in patients with intrinsic (age, gender and weight) and extrinsic (food and CYP3A4 inhibitors) factors known to increase systemic exposure to dronedarone (Section 4).

3.3.2 EURIDIS and ADONIS

The EURIDIS and ADONIS trials were sister studies, identical in design, which were carried out as pivotal trials to demonstrate the 1-year efficacy of dronedarone (400 mg BID) in the maintenance of normal sinus rhythm after electrical, pharmacological, or spontaneous conversion of AF/AFL. As opposed to DAFNE, patients in the two studies were required to be in sinus rhythm at randomization.

EURIDIS and ADONIS differed only in the location where the studies were conducted. The EURIDIS trial was carried out in 65 centers in 12 countries: Netherlands, Germany, Poland,

Hungary, Italy, France, Czech Republic, Belgium, Spain, Denmark, Finland and United Kingdom. Patient enrollment began in November 2001 and the last patient completed in August 2003. The ADONIS trial was carried out in 101 centers in 5 countries: USA, Canada, Australia, South Africa and Argentina. Patient enrollment began in November 2001 and the last patient completed in September 2003.

3.3.2.1 Study Design for EURIDIS and ADONIS

Patients were eligible for the study if they were aged 21 years or greater, in sinus rhythm for at least 1 hour at the time of randomization, and had at least one ECG-documented episode of AF/AFL in the last 3 months. Patients were excluded if they had a documented episode of AF/AFL that did not persist beyond 10 days after an acute condition known to cause AF/AFL (eg, alcohol intake, thyrotoxicosis, infection, MI, pericarditis, pulmonary embolism, cardiac surgery); a history of TdP; bradycardia <50 bpm at the screening ECG; PR-interval ≥ 0.28 second at screening; high degree AV block (second degree or higher), or significant sinus node disease (documented pause of 3 seconds or more) without a permanent pacemaker implanted; treatment with other Class I or III antiarrhythmic drugs; clinically overt CHF with NYHA Class III or IV at the time of randomization; ongoing potentially dangerous symptoms when in AF/AFL (such as angina pectoris, TIAs, stroke, syncope); patients in whom amiodarone (prescribed for sinus rhythm maintenance) had been discontinued for inefficacy; patients in whom 3 or more Class I or III antiarrhythmic drugs (prescribed for sinus rhythm maintenance) had been discontinued for inefficacy; patients known to have AF/AFL continuously for more than 12 months; hypokalemia (plasma potassium <3.5 mmol/L) or hypomagnesemia (plasma magnesium <0.7 mmol/L); and clinically relevant hematologic, hepatic ALT, AST, bilirubin >2 times the upper limit of normal (ULN) at screening], GI, renal [serum creatinine ≥ 150 μmol/L (ie, 1.7 mg/dL) at screening], pulmonary, endocrinologic (in particular thyroid) or psychiatric disease.

Patients fulfilling the entry criteria for the study were randomly assigned to either 400 mg twice daily or placebo (in a 2:1 ratio), which were continued for 12 months.

The detection of recurrences of AF/AFL was based on a centralized review of transtelephonic ECG monitoring and 12-lead ECGs. All potential endpoints were adjudicated by a group of four senior cardiologists of the ECG Corelab.

During the course of the study, use of following drugs was prohibited: Vaughan-Williams-Singh Class I and III antiarrhythmic drugs (including sotalol), drugs which can cause TdP(eg phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides), grapefruit juice and all potent inhibitors of CYP450 3A4, such as ketoconazole, itraconazole, cyclosporin, clarithromycin, erythromycin, nefazodone, and ritonavir.

The primary endpoint was time from randomization to first adjudicated AF/AFL recurrence (defined as an episode lasting 10 minutes or more as indicated by two consecutive 12-lead ECGs or transtelephonic electrocardiogram monitoring (TTEM) tracings recorded approximately 10 minutes apart and both showing AF/AFL). Secondary endpoints were mean heart rate at time of first adjudicated AF/AFL recurrence (12-lead ECG or TTEM) and time from randomization to symptomatic first AF/AFL episode.

The planned treatment duration for each patient was 12 months. The follow-up visit was done 10-15 days after study drug discontinuation. In case of premature study drug discontinuation, if the patient reached the primary endpoint and stopped treatment, the study was considered completed. If not, follow-up visits according to the protocol schedule had to be performed until the patient reached the primary endpoint.

3.3.2.2 Patient Enrollment and Disposition

EURIDIS Trial

A total of 552 patients were planned, but 615 patients were randomized into the trial; 612 patients were randomized and treated: 201 to placebo and 411 to dronedarone. The primary analysis of efficacy was performed in this randomized and treated patient population.

The number of patients who permanently discontinued the study drug before the scheduled end of treatment (EOT) was similar among treatment groups (16.3% in the dronedarone group and 12.4% in the placebo group).

ADONIS Trial

A total of 552 patients were planned, but 629 patients were randomized into the trial; 625 patients were randomized and treated: 208 to placebo and 417 to dronedarone. The primary analysis of efficacy was performed in this randomized and treated patient population.

The number of patients who permanently discontinued the study drug was similar among treatment groups (19.4% in the dronedarone group and 17.3% in the placebo group).

3.3.2.3 Patient Characteristics

The demographic characteristics of patients in the EURIDIS and ADONIS studies and in the pooled population are displayed in Table 10.

A summary of specific medications at baseline in all randomized and treated patients in the EURIDIS and ADONIS studies study is presented in Table 11.

Table 10 – Demographic characteristics – Randomized and treated patients - EURIDIS & ADONIS

Parameter		EURIDIS		ADONIS		Pooled	
		Placebo (N=201)	Dronedarone 400mg BID (N=411)	Placebo (N=208)	Dronedarone 400mg BID (N=417)	Placebo (N=409)	Dronedarone 400mg BID (N=828)
Age (years)	n	201	411	208	417	409	828
	Median	63	63	65	66	63	65
	Mean	61.3	62.3	63.0	64.6	62.2	63.5
	SD	10.7	10.0	11.4	11.3	11.1	10.7
	Min - Max	32 - 82	23 - 86	30 - 87	20 - 88	30 - 87	20 – 88
Age (years) [n(%)]	<65	111 (55.2%)	227 (55.2%)	104 (50.0%)	186 (44.6%)	215 (52.6%)	413 (49.9%)
	[65-75[	76 (37.8%)	139 (33.8%)	80 (38.5%)	149 (35.7%)	156 (38.1%)	288 (34.8%)
	>=75	14 (7.0%)	45 (10.9%)	24 (11.5%)	82 (19.7%)	38 (9.3%)	127 (15.3%)
Weight (kg)	n	198	408	208	417	406	825
	Median	85.0	83.0	85.7	86.8	85.0	85.0
	Mean	86.43	83.84	87.81	88.61	87.14	86.25
	SD	14.78	14.39	19.27	19.88	17.22	17.53
	Min - Max	61.0 - 168.0	50.0 - 165.0	51.0 - 167.7	35.0 - 185.9	51.0 - 168.0	35.0 - 185.9
Gender [n(%)]	Male	140 (69.7%)	285 (69.3%)	140 (67.3%)	293 (70.3%)	280 (68.5%)	578 (69.8%)
	Female	61 (30.3%)	126 (30.7%)	68 (32.7%)	124 (29.7%)	129 (31.5%)	250 (30.2%)
Race [n(%)]	Caucasian	201 (100.0%)	409 (99.5%)	199 (95.7%)	391 (93.8%)	400 (97.8%)	800 (96.6%)
	Black	0 (0.0%)	0 (0.0%)	3 (1.4%)	9 (2.2%)	3 (0.7%)	9 (1.1%)
	Asian/Oriental	0 (0.0%)	2 (0.5%)	0 (0.0%)	4 (1.0%)	0 (0.0%)	6 (0.7%)
	Other	0 (0.0%)	0 (0.0%)	6 (2.9%)	13 (3.1%)	6 (1.5%)	13 (1.6%)

Table 11 - Baseline intake of specific medications – Randomized and treated patients – EURIDIS & ADONIS

	EURIDIS		ADONIS		Pooled	
	Placebo (N=201)	Dronedarone 400 mg BID (N=411)	Placebo (N=208)	Dronedarone 400 mg BID (N=417)	Placebo (N=409)	Dronedarone 400 mg BID (N=828)
Oral anticoagulant	133 (66.2%)	247 (60.1%)	138 (66.3%)	270 (64.7%)	271 (66.3%)	517 (62.4%)
Beta blocking agents	92 (45.8%)	212 (51.6%)	89 (42.8%)	168 (40.3%)	181 (44.3%)	380 (45.9%)
Beta blocking agents (except Sotalol)	91 (45.3%)	209 (50.9%)	87 (41.8%)	162 (38.8%)	178 (43.5%)	371 (44.8%)
ACE inhibitors or A II receptor antagonists	86 (42.8%)	193 (47.0%)	84 (40.4%)	171 (41.0%)	170 (41.6%)	364 (44.0%)
ACE inhibitors	73 (36.3%)	161 (39.2%)	71 (34.1%)	134 (32.1%)	144 (35.2%)	295 (35.6%)
A II receptors antagonist	14 (7.0%)	35 (8.5%)	13 (6.3%)	39 (9.4%)	27 (6.6%)	74 (8.9%)
Chronic antiplatelet therapy	41 (20.4%)	112 (27.3%)	76 (36.5%)	160 (38.4%)	117 (28.6%)	272 (32.9%)
Statins	40 (19.9%)	80 (19.5%)	56 (26.9%)	137 (32.9%)	96 (23.5%)	217 (26.2%)
Metabolized by CYP3A4	24 (11.9%)	52 (12.7%)	44 (21.2%)	109 (26.1%)	68 (16.6%)	161 (19.4%)
Not metabolized by CYP3A4	17 (8.5%)	30 (7.3%)	13 (6.3%)	28 (6.7%)	30 (7.3%)	58 (7.0%)
Diuretics	50 (24.9%)	98 (23.8%)	49 (23.6%)	118 (28.3%)	99 (24.2%)	216 (26.1%)
Diuretics (other than spironolactone)	48 (23.9%)	95 (23.1%)	49 (23.6%)	116 (27.8%)	97 (23.7%)	211 (25.5%)
Spironolactone	12 (6.0%)	9 (2.2%)	2 (1.0%)	15 (3.6%)	14 (3.4%)	24 (2.9%)
Digitalis	41 (20.4%)	64 (15.6%)	36 (17.3%)	82 (19.7%)	77 (18.8%)	146 (17.6%)
Digoxin	31 (15.4%)	42 (10.2%)	36 (17.3%)	82 (19.7%)	67 (16.4%)	124 (15.0%)
Digitalin	9 (4.5%)	20 (4.9%)	0 (0.0%)	0 (0.0%)	9 (2.2%)	20 (2.4%)
Digitalis other than Digoxin or Digitalin	1 (0.5%)	2 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	2 (0.2%)
Moderate inhibitors of CYP3A4	15 (7.5%)	28 (6.8%)	37 (17.8%)	79 (18.9%)	52 (12.7%)	107 (12.9%)
Calcium antagonists with heart rate lowering effects (a)	15 (7.5%)	28 (6.8%)	36 (17.3%)	78 (18.7%)	51 (12.5%)	106 (12.8%)
NSAID	10 (5.0%)	9 (2.2%)	28 (13.5%)	62 (14.9%)	38 (9.3%)	71 (8.6%)

(a) Restricted to diltiazem, verapamil and bepridil.

NSAID=nonsteroidal anti-inflammatory drug.

3.3.2.4 Efficacy Results

EURIDIS Trial

Primary Analysis. When compared with placebo, treatment with dronedarone significantly decreased (by 22%) the risk of first recurrence of AF/AFL within the 12-month study period in the randomized and treated population. The median time from randomization to the first adjudicated recurrence of AF/AFL was 2.3-fold longer in the dronedarone group than in the placebo group. At 12 months, taking into account patients who were censored over time, AF/AFL recurred in 67.1% of dronedarone-treated patients as compared with 77.5% of placebo-treated patients. These results were confirmed in the on-treatment analysis in the per protocol population (log-rank, p = 0.0131).

The results of the primary efficacy analysis are summarized in Table 12.

Table 12 - Time to adjudicated first recurrence of AF/AFL within 12 months after randomization – Randomized and treated patients - EURIDIS

	Placebo (n=201)	Dronedarone 800 mg (n=411)
Median time in days (95% CI)	41 (16, 87)	96 (61, 133)
Relative risk (dronedarone / placebo)[a] (95% CI)	0.784 [0.644 – 0.955]	
Log-rank p-value	0.01383	

a: determined from Cox regression model

Symptomatic AF/AFL among adjudicated first AF/AFL recurrence. First recurrences of AF/AFL were associated with symptoms in 55.1% of patients in the dronedarone group, as compared with 61.3% in the placebo group. Dronedarone significantly delayed the time to the first *symptomatic* recurrence of AF/AFL within 12 months from randomization (log rank, p = 0.0055).

Ventricular rate assessed at time of adjudicated first AF/AFL recurrence. At time of first recurrence, dronedarone-treated patients had significantly lower mean heart rates: 102.3 bpm on dronedarone versus 117.5 bpm on placebo (p<0.0001).

ADONIS Trial

Primary Analysis. When compared with placebo, treatment with dronedarone significantly decreased (by 27.5%) the risk of first recurrence of AF/AFL within the 12-month study period in the randomized and treated population. The median time from randomization to the first adjudicated recurrence of AF/AFL was 2.7-fold longer in the dronedarone group than in the placebo group. At 12 months, taking into account patients who were censored over time, AF/AFL recurred in 61.1% of dronedarone-treated patients as compared with 72.8% of placebo-treated patients. These results were confirmed in the on-treatment analysis in the per protocol population (log-rank, p = 0.0018).

The results of the primary efficacy analysis are summarized in Table 13.

Table 13 - Time to adjudicated first recurrence of AF/AFL within 12 months after randomization – Randomized and treated patients - ADONIS

	Placebo (n=208)	Dronedarone 800 mg (n=417)
Median time in days (95% CI)	59 (22, 96)	158 (80, 252)
Relative risk (dronedarone / placebo)[a] (95% CI)	0.725 [0.590 – 0.890]	
Log-rank p-value	0.0017	

a: determined from Cox regression model

Symptomatic AF/AFL among adjudicated first AF/AFL recurrences. First AF/AFL recurrence was associated with symptoms in 61% of patients in placebo and 62.6% the in dronedarone 400 mg BID groups. Dronedarone significantly delayed the time to symptomatic first recurrence of AF/AFL within 12 months from randomization (log-rank, p = 0.021).

Ventricular rate assessed at time of adjudicated first AF/AFL recurrence. At time of first recurrence, dronedarone-treated patients had significantly lower mean heart rates: 104.6 beats/min on dronedarone versus 116.6 beats on placebo (p = 0.0009).

Pooled Analysis of EURIDIS and ADONIS

The EURIDIS and ADONIS trials were designed as identical studies carried out in the same time period, and the two trials both demonstrated the efficacy of dronedarone. The results from the two trials were pooled in order to enhance the precision of the estimates of drug efficacy.

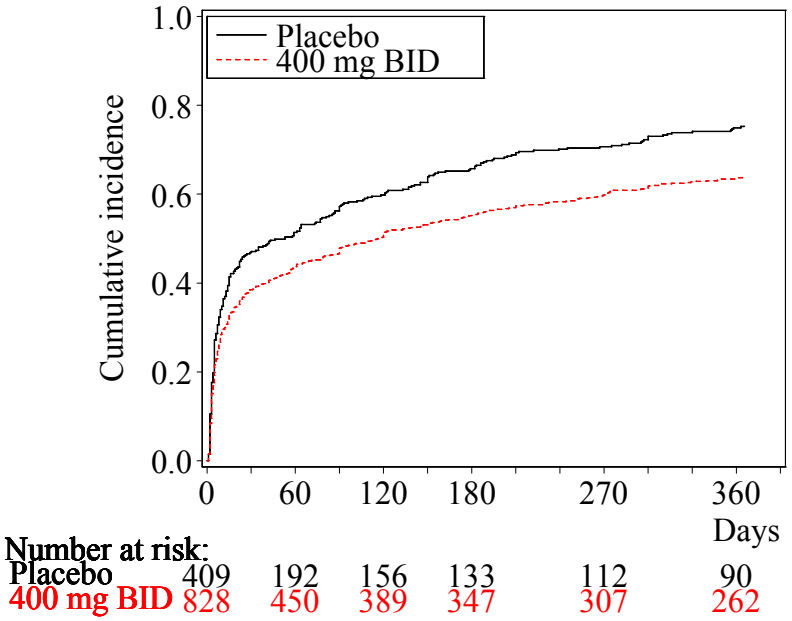
In the pooled analysis, dronedarone (400 mg BID) given for 12 months reduced the risk of a first recurrence of AF/AFL by 25% and more than doubled the median time to recurrence (p=0.00007) (Table 14). At 12 months, 64.1% of dronedarone 400 mg BID-treated patients were estimated (Kaplan-Meier) to have experienced a first AF/AFL recurrence, compared to 75.2% of placebo-treated patients (Figure 4).

Table 14 - Time to adjudicated first recurrence of AF/AFL within 12 months after randomization – Randomized and treated patients - EURIDIS & ADONIS

	EURIDIS		ADONIS		Pooled	
	Placebo (N=201)	Dronedarone 400 mg BID (N=411)	Placebo (N=208)	Dronedarone 400 mg BID (N=417)	Placebo (N=409)	Dronedarone 400 mg BID (N=828)
Number of patients with endpoints	155	272	146	246	301	518
Median time in days 95% CI	41 [16;87]	96 [61;133]	59 [22;96]	158 [80;252]	53 [23;81]	116 [89;150]
Relative risk with 95% CI[a]	0.784 [0.644;0.955]		0.725 [0.590;0.890]		0.753 [0.653;0.868]	
Log-rank test result (p-value)	0.01383		0.0017		0.00007	

(a) Determined from Cox regression model.
Note: Unadjusted analysis

Figure 4 - Time to adjudicated first AF/AFL recurrence within 12 months – Randomized and treated patients – pooled EURIDIS & ADONIS



Note: Kaplan-Meier cumulative incidence curves

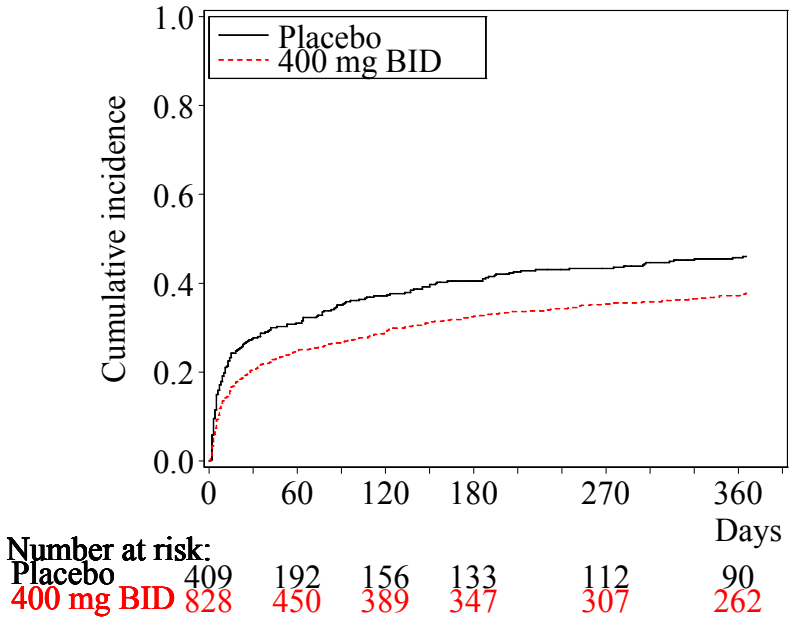
Treatment with dronedarone also reduced the proportion of patients who experienced a symptomatic recurrence from 46% to 38% (p = 0.0003) (see Table 15). The adjudicated first AF/AFL recurrence was associated with symptoms in 58.7% (304/518) of patients in the dronedarone 400 mg BID group (55.1% in EURIDIS, 62.6% in ADONIS), versus 61.1% (184/301) in the placebo group (61.3% in EURIDIS, 61.0% in ADONIS) (Figure 5).

Table 15 - Number (%) of patients with symptomatic adjudicated first recurrence of AF/AFL within 12 months – Randomized and treated patients - EURIDIS & ADONIS

	EURIDIS		ADONIS		Pooled	
	Placebo N= 201	Dronedarone 400 mg BID N= 411	Placebo N= 208	Dronedarone 400 mg BID N= 417	Placebo N= 409	Dronedarone 400 mg BID N= 828
Number of patients with endpoints	95	150	89	154	184	304
Prentice estimate % of patients with endpoint at 12 months	47.5	37.1	44.5	38.3	46.0	37.7
Log-rank p-value	0.0055		0.02139		0.0003	

Note: Four patients (2 enrolled in EURIDIS, 2 enrolled in ADONIS), without indication of whether the first adjudicated recurrence was symptomatic, were considered asymptomatic.

Figure 5 - Time to symptomatic adjudicated first AF/AFL recurrence within 12 months - Randomized and treated patients - EURIDIS & ADONIS



Note: Prentice cumulative incidence curves

In addition, patients had significantly lower heart rate on dronedarone 400 mg BID at the time of the first AF or AFL recurrence as compared to placebo (mean heart rate on transtelephonic ECG: 103.4 vs. 117.1, p <0.0001, pooled EURIDIS and ADONIS data).

Importantly, in a post hoc analysis, in both the EURIDIS and ADONIS trials, treatment with dronedarone was associated with a notable trend for a lower risk of death or first cardiovascular hospitalization, i.e., 27% lower risk in the EURIDIS trial and 11% lower risk in the ADONIS trial. Pooled analysis of the data from both trials showed a 20% reduction in the risk of death or cardiovascular hospitalization (relative risk 0.80 [95% CI: 0.591, 1.094]) (see Table 16).

Table 16 - Time from randomization to first cardiovascular hospitalization or death – Randomized and treated patients - EURIDIS & ADONIS

Studies	Number of Patients with Endpoint		Relative Risk [95% CI] [(a)]
	Placebo	Dronedarone 400mg BID	
EURIDIS	35 / 201	54 / 411	0.730 [0.477, 1.118]
ADONIS	29 / 208	57 / 417	0.890 [0.569, 1.392]
Pooled EURIDIS and ADONIS	64 / 409	111 / 828	0.804 [0.591, 1.094]

(a) Relative Risk from Cox model is adjusted on study

Table 17 shows that this 20% risk reduction was largely related to a reduction in the risk of cardiovascular hospitalization, since the proportion of deaths was similar in the placebo and dronedarone groups in these two sister trials.

Table 17 - Time from randomization to death from any cause during the on-study period – Randomized and treated patients - EURIDIS & ADONIS

Studies	Number of patients with endpoint		Relative Risk [95% CI] [a]
	Placebo	Dronedarone 400mg BID	
EURIDIS	0 / 201	2 / 411	NA
ADONIS	5 / 208	9 / 417	0.794 [0.266, 2.370]

(a) Determined from Cox regression model
(b) Relative Risk from Cox model is adjusted on studies

Safety data on pooled AF/AFL studies with dronedarone 400 mg BID are provided in Section 6.

3.3.2.5 Conclusions

When considered individually or as pooled data, the findings of two identical trials, the EURIDIS and ADONIS trials, demonstrated that one-year's treatment with dronedarone (400 mg BID) significantly decreased the risk of first recurrence of AF/AFL; doubled the median time from randomization to the first recurrence of AF/AFL; reduced the risk of first recurrence of symptomatic episodes of these arrhythmias; slowed the ventricular response in patients whose atrial arrhythmia recurred; and was associated with a lower risk of hospitalization for cardiovascular reasons. This consistent pattern of efficacy over a prolonged period suggested that dronedarone might have favorable effects on important cardiovascular outcomes in patients who present with a current or recent history of AF/AFL.

3.3.3 ERATO (rate control study)

The ERATO trial was a multicenter, double-blind, randomized, parallel-group, placebo controlled study to evaluate the efficacy of dronedarone 400 mg BID given for 6 months in controlling the ventricular rate in patients with symptomatic permanent AF at rest. The trial was carried out in 35 centers in 9 countries: Belgium, Czech Republic, France, Italy, Netherlands, Poland, Spain,

Sweden and Switzerland. Patient enrollment began in August 2002 and the last patient completed in June 2004.

3.3.3.1 Study Design

Patients were eligible for the study if they were aged 21 years or greater; had permanent AF (for at least 6 months); were symptomatic from their AF (any arrhythmia-related symptoms including palpitations); had a resting ventricular rate ≥ 80 bpm; and were not considered candidates for cardioversion. Patients were excluded if they had unstable angina pectoris [ischemic symptoms during the last 7 days or recent MI (< 6 weeks)]; history of TdP; plasma potassium <3.5 mmol/L at screening; third degree AV block on the screening ECG while in AF or documentation of PR-interval on ECGs previously recorded while in sinus rhythm >0.28 seconds or high degree AV block (2nd degree or higher), or significant sinus node disease (documented pause of 3 seconds or more) without a permanently implanted pacemaker; clinically overt CHF [NYHA class III or IV] at randomization; treatment with amiodarone during the 2 months preceding randomization; treatment with other antiarrhythmic drugs; clinically relevant hematologic, hepatic [ALT, AST>2 times the ULN at screening], GI, renal (serum creatinine >220 μmol/L at screening), pulmonary, endocrinologic (in particular thyroid) or psychiatric disease; participation in another clinical study in which the patient was currently taking an investigational drug (under development) or using an investigational device; or previous participation in this study or in other dronedarone studies.

Eligible patients were randomized to receive dronedarone or placebo (1:1 ratio) for 6 months.

During the course of the study, patients were not allowed to receive amiodarone, Vaughan-Williams-Singh Class I and III antiarrhythmic drugs (including sotalol), all drugs that can cause TdP (eg some phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides), or potent inhibitors of CYP3A4 such as ketoconazole, itraconazole, cyclosporin, clarithromycin, erythromycin, nefazodone, ritonavir and grapefruit juice.

The primary endpoint was change from baseline in mean heart rate measured by 24-Hour Holter at Day 14. Secondary endpoints were change from baseline and vs. placebo in ventricular rate (and exercise duration) during exercise test on Day 14, change from baseline and vs. placebo in mean Heart Rate measured by 24-H Holter at 4 months.

All patients were to be followed for 6 months, even if the study drug was prematurely discontinued.

3.3.3.2 Patient Enrollment and Disposition

A total of 160 patients were planned, but 174 patients were randomized into the trial: 89 to placebo and 85 to dronedarone. All patients received randomized treatment and were considered for primary analysis.

Other analyses were conducted on the per protocol population, which excluded 24 patients (28.2%) in the dronedarone group and 23 patients (25.8%) in the placebo group, due to

missing data. There was no significant difference between treatment groups in number of patients discontinuing study drug treatment (17 in the dronedarone group and 10 in the placebo group).

3.3.3.3 Patient Characteristics

A summary of demographic charateristics of all randomized patients is presented in Table 18.

Table 18 - Summary of demographic characteristics - All randomized patients - ERATO

Parameter		Placebo (N=89)		Dronedarone 400 mg BID (N=85)	
Age (years)	n	89		85	
	Median	67		65	
	Mean	66.4		65.2	
	SD	9.5		10.5	
	Min - Max	39 - 86		31 - 86	
Age (years) [n(%)]	<65	34	(38.2%)	38	(44.7%)
	[65-75[	38	(42.7%)	33	(38.8%)
	>=75	17	(19.1%)	14	(16.5%)
Weight (kg)	n	89		85	
	Median	84.0		83.0	
	Mean	85.08		83.32	
	SD	16.25		15.57	
	Min - Max	54.0 - 133.2		48.0 - 122.0	
Gender [n(%)]	Male	62	(69.7%)	58	(68.2%)
	Female	27	(30.3%)	27	(31.8%)
Race [n(%)]	Caucasian	88	(98.9%)	84	(98.8%)
	Black	1	(1.1%)	1	(1.2%)

A summary of cardiovascular history in all randomized patients in the ERATO study is presented in Table 19.

Table 19 - Number (%) of patients according to cardiovascular history - All randomized patients - ERATO

	Placebo (N=89)	Dronedarone 400 mg BID (N=85)
Hypertension	41/ 89 (46.1%)	44/ 85 (51.8%)
Structural heart disease	34/ 85 (40.0%)	31/ 82 (37.8%)
Clinically relevant valvular heart disease including mitral valve prolapse	16/ 89 (18.0%)	14/ 85 (16.5%)
Coronary heart disease	14/ 89 (15.7%)	16/ 85 (18.8%)
Dilated cardiomyopathy	10/ 89 (11.2%)	8/ 85 (9.4%)
Pacemaker (only if still in place)	8/ 89 (9.0%)	9/ 85 (10.6%)
Rheumatic heart disease	2/ 89 (2.2%)	5/ 85 (5.9%)
Hypertrophic cardiomyopathy	0/ 89 (0.0%)	4/ 85 (4.7%)
Congenital heart disease	1/ 89 (1.1%)	2/ 85 (2.4%)
Implantable cardioverter defibrillator (ICD)	2/ 89 (2.2%)	0/ 85 (0.0%)

A summary of specific medications at baseline in all randomized patients in the ERATO study is presented in Table 20.

Table 20 - Number (%) of patients with specific medications present at baseline - All randomized patients - ERATO

	Placebo (N=89)	Dronedarone 400 mg BID (N=85)
Total patients with specific medications	89 (100.0%)	84 (98.8%)
Vaughan-Williams class I or III antiarrhythmic drugs (a)	0 (0.0%)	0 (0.0%)
Amiodarone	0 (0.0%)	0 (0.0%)
Drugs which can cause Torsades de Pointes	1 (1.1%)	0 (0.0%)
Potent inhibitors of CYP3A4	0 (0.0%)	0 (0.0%)
Substrates of CYP3A4 with a narrow therapeutic margin	0 (0.0%)	0 (0.0%)
Statins	20 (22.5%)	17 (20.0%)
Metabolized by CYP3A4	13 (14.6%)	13 (15.3%)
Not metabolized by CYP3A4	7 (7.9%)	4 (4.7%)
Digitalis	35 (39.3%)	30 (35.3%)
Digoxin	32 (36.0%)	27 (31.8%)
Digitalin	0 (0.0%)	0 (0.0%)
Digitalis other than Digoxin or Digitalin	3 (3.4%)	3 (3.5%)
Moderate inhibitors of CYP3A4	13 (14.6%)	19 (22.4%)
Calcium antagonists with heart rate lowering effects (b)	13 (14.6%)	19 (22.4%)
Beta blocking agents	41 (46.1%)	44 (51.8%)
Beta blocking agents (except Sotalol)	40 (44.9%)	42 (49.4%)
ACE inhibitors or A II receptor antagonist	40 (44.9%)	42 (49.4%)
ACE inhibitors	33 (37.1%)	31 (36.5%)
A II receptor antagonists	7 (7.9%)	11 (12.9%)
Spironolactone	8 (9.0%)	8 (9.4%)
NSAID	3 (3.4%)	3 (3.5%)
Diuretics (other than spironolactone)	30 (33.7%)	36 (42.4%)
Oral anticoagulant	79 (88.8%)	73 (85.9%)
Chronic antiplatelet therapy	9 (10.1%)	15 (17.6%)

(a) Including Sotalol and excluding Amiodarone
(b) Restricted to Diltiazem, Verapamil

3.3.3.4 Efficacy Results

Primary Analysis

The decrease from baseline in 24-hour Holter heart rate on day 14 was significantly more pronounced in the dronedarone group than in the placebo group (analysis of covariance

[ANCOVA], p<0.0001) (Table 21). Concurrent treatment with beta blockers, calcium antagonists and digitalis (each tested separately) had no significant effect on the primary endpoint analysis.

Table 21 - 24-hour Holter-monitored heart rate (bpm) – All randomized patients - ERATO

		Placebo (N=89)	Dronedarone 400 mg BID (N=85)
Baseline	Mean	90.6	86.5
	SEM	1.5	1.4
D14	Mean	90.2	76.2
	SEM	1.5	1.4
Change from baseline(a)	Mean	0.7	-11.0
	95%CI(b)	[-1.9;3.3]	[-13.5;-8.5]
Treatment effect(a)	Mean	-11.7	
	95%CI(b)	[-14.8;-8.5]	
	p-value(b)	$22x10^{-14}$	

(a) Change from baseline and treatment effect (difference between dronedarone 400 mg BID and placebo groups) are adjusted for baseline heart rate value, age and type of baseline standard treatment (beta-blocker, heart rate lowering calcium antagonist, digitalis).
(b) Following multiple imputation technique using Rubin's rule [4(4.7%) dronedarone and 2(2.2%) placebo patients had missing data at baseline and were evaluated on Day 14, 5(5.9%) dronedarone and 5(5.6%) placebo patients were evaluated at baseline and had missing data on Day 14, and 1(1.2%) dronedarone patient had missing data at baseline and on Day 14].

Secondary / Additional Analyses

Duration of maximal exercise (main secondary endpoint). In the all randomized patient population, changes from baseline to day 14 in maximal exercise duration were not significantly different between the two groups.

Heart rate during exercise test. The changes from baseline to day 14 in heart rate at sub-maximal and maximal exercise were significantly greater in the dronedarone group than in the placebo group (submaximal: -25.6 bpm versus –2.2 bpm, respectively; maximal: -27.4 bpm versus -2.9 bpm, respectively; ANCOVA, p<0.0001 for the all randomized patient population with non-missing endpoint evaluation). In the all randomized population, the presence of digitalis at baseline had a significant effect on the day 14 change from baseline in heart rate at sub-maximal exercise (-6.9 bpm; ANCOVA, p=0.0151).

Heart rate evaluated by the 24-hour Holter at 4 months. In the all randomized patient population, the change from baseline to month 4 in heart rate was significantly greater in the dronedarone group than in the placebo group (-10.1 bpm versus -1.3 bpm, ANCOVA, p<0.0001).

Dronedarone safety profile is presented in Section 6, based on the pooled safety database of the 5 studies conducted in the target population of AF/AFL.

3.3.3.5 Conclusions

The findings of the ERATO trial demonstrate that dronedarone (400 mg BID) reduces the ventricular rate of patients with permanent AF, thus (together with the results of the other placebo-controlled trials) establishing that the drug has the ability to control both rate and rhythm in patients with AF.

3.3.4 DIONYSOS

The DIONYSOS trial was a multicenter, randomized, double-blind, parallel-arm study to compare the efficacy and safety of dronedarone (400 mg BID) versus amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) for at least 6 months for the maintenance of sinus rhythm in patients with AF. The trial was carried out in 112 centers in 23 countries: Argentina, Australia, Austria, Belgium, Canada, Chile, China, Czech Republic, Estonia, Finland, France, Germany, Italy, Mexico, Morocco, Netherlands, Poland, Republic of Korea, Russia, Sweden, Tunisia, Turkey, United States. Patient enrollment began in June 2007 and the last patient completed in October 2008.

This study was initiated during the conduct of the ATHENA study to meet a request from the European Medicines Agency (EMEA) for a study with an active comparator. The analysis of the DIONYSOS trial has recently been completed, a study report has been submitted to the FDA in February 2009 but the results of the trial may have not yet been formally reviewed by the FDA.

3.3.4.1 Study Design

Patients were eligible for the study if they were aged 21 years or greater; had documented AF for more than 72 hours; had a need for cardioversion and antiarrhythmic treatment; and were receiving anticoagulants. Patients were excluded if they had a contraindication to oral anticoagulation; patients having received more than a total of twenty 200 mg tablets or more than 5 days IV of amiodarone in the past; previous (2 preceding months) or current participation in another clinical trial with an investigational drug (under development) or with an investigational device; clinically relevant hematological, hepatic ALT, AST >1.5 fold the ULNat randomization), GI, renal (serum creatinine >150 micromol/liter [µmol/L] (1.7 milligram/deciliter [mg/dL]) at randomization), pulmonary, endocrinologic, psychiatric, neurological or dermatological disease; serum potassium <3.5 millimol/liter (mmol/L) (in patients with hypokalemia, potassium deficiency was to be corrected before randomization) and uncorrected or >5.5 mmol/L before randomization; unstable angina pectoris (ischemic symptoms during the last 7 days) or recent MI (<6 weeks); documented episode of AF due to an acute condition (e.g., alcohol intake, thyrotoxicosis, acute infection, pericarditis, pulmonary embolism, cardiac surgery); history of TdP; first degree family history of sudden cardiac death below age 50 years in the absence of coronary heart disease; history of high degree AV block (2nd degree Mobitz 2 or higher), or significant sinus node disease (documented pause of 3 seconds or more) without a permanent pacemaker implanted; bradycardia <50 bpm on the last 12-lead ECG before randomization; clinically overt CHF with NYHA Class III or IV at the time of randomization; potentially dangerous symptoms when in AF such as angina pectoris, TIAs, stroke or syncope; patients known to have continuous AF for more than 12 months; Wolff-Parkinson-White Syndrome;

patients with AFL; patients with paroxysmal AF; long QT syndrome or QT- or QTc-interval ≥500 ms before randomization; treatment with other Class I or III antiarrhythmic drugs which could not be discontinued with the required washout period before the first study drug administration; hyperthyroidism or hypothyroidism; or other contraindications to amiodarone including hypersensitivity to iodine.

Eligible patients were randomized to receive (in a 1:1 ratio) dronedarone (400 mg BID) or amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) for at least 6 months.

During the course of the study, patients were not allowed to receive Vaughan William Class I and III antiarrhythmic drugs (including sotalol), drugs that can cause TdP (some phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides), potent inhibitors of CYP3A4 eg ketoconazole, itraconazole, cyclosporin, clarithromycin, erythromycin, nefazodone, ritonavir, grapefruit juice, or substrates of CYP3A4 with narrow therapeutic margin.

The primary endpoint was a composite endpoint of time to first AF recurrence or premature study drug discontinuation for intolerance or lack of efficacy. Patients were followed up until 190 days following the date of randomization for the last patient in the trial. In case of premature study drug discontinuation, the end-of-study visit was to be performed at 10-15 days after study drug discontinuation.

3.3.4.2 Patient Enrollment and Disposition

A total of 472 patients were planned, but 504 patients were randomized into the trial; all randomized patients received treatment: 249 to dronedarone and 255 to amiodarone. No patients were lost to follow-up.

The proportion of patients who discontinued treatment prematurely was higher in the dronedarone group (38.6%, 96 of 249 patients) compared with the amiodarone group (27.1%, 69 of 255 patients). More patients in the dronedarone group than in the amiodarone group discontinued treatment due to lack of efficacy (21.3% versus 5.5%), while more patients in the amiodarone group than in the dronedarone group discontinued due to AEs (17.6% versus 12.9%).

3.3.4.3 Patient Characteristics

The population of 504 patients had a mean age of 64.0 ± 10.7 years (mean ± SD). One third of patients were women (Table 22).

Table 22 - Summary of demographics and patient characteristics at baseline – All randomized and treated patients - DIONYSOS

	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg OD (N=255)
Age (years)		
n	249	255
Mean (SD)	64.4 (10.8)	63.7 (10.6)
Median	64.0	64.0
Min : Max	28 : 90	30 : 89
Age category [n(%)]		
n	249	255
< 65	125 (50.2%)	138 (54.1%)
[65 - 75[	76 (30.5%)	70 (27.5%)
≥ 75	48 (19.3%)	47 (18.4%)
Weight (kg)		
n	249	254
Mean (SD)	85.4 (17.6)	86.4 (18.2)
Median	82.5	86.0
Min : Max	46 : 162	48 : 157
Gender [n(%)]		
n	249	255
Male	176 (70.7%)	182 (71.4%)
Female	73 (29.3%)	73 (28.6%)
Race [n(%)]		
n	249	255
Caucasian/White	211 (84.7%)	212 (83.1%)
Black	0	3 (1.2%)
Asian/Oriental	37 (14.9%)	40 (15.7%)
Other	1 (0.4%)	0

Note: n corresponds to the count of patients with non missing data used for the calculation

A summary of cardiovascular history at baseline in all randomized and treated patients in the DIONYSOS study is presented in Table 23, lone AF represented 16.5% of the study population, and 21.6% of patients had a first episode of AF.

Table 23 - Number (%) of patients with cardiovascular history – All randomized and treated patients - DIONYSOS

	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg OD (N=255)
Hypertension	164 (65.9%)	173 (67.8%)
Structural heart disease	70 (28.1%)	74 (29.0%)
CHF	56 (22.5%)	53 (20.8%)
Valvular heart disease	52 (20.9%)	42 (16.5%)
Coronary heart disease	47 (18.9%)	43 (16.9%)
Lone atrial fibrillation	46 (18.5%)	37 (14.5%)
Non-rheumatic valvular heart disease	42 (16.9%)	38 (14.9%)
Dilated cardiomyopathy	25 (10.0%)	31 (12.2%)
Non-ischemic dilated cardiomyopathy	21 (8.4%)	23 (9.0%)
Pacemaker	15 (6.0%)	14 (5.5%)
Sinus bradycardia < 50 bpm / Sick sinus syndrome	15 (6.0%)	13 (5.1%)
Ischemic dilated cardiomyopathy	10 (4.0%)	17 (6.7%)
Cardiac valve surgery	15 (6.0%)	11 (4.3%)
Rheumatic valvular heart disease	16 (6.4%)	10 (3.9%)
Ablation for AF/AFL	11 (4.4%)	10 (3.9%)
Hypertrophic cardiomyopathy	9 (3.6%)	10 (3.9%)
Supra-ventricular tachycardia other than AF/AFL	9 (3.6%)	9 (3.5%)
Atrio-ventricular block above first degree	7 (2.8%)	9 (3.5%)
Implanted cardioverter defibrillator	8 (3.2%)	8 (3.1%)
Congenital heart disease	6 (2.4%)	8 (3.1%)
Ablation for other reason than AF/AFL	6 (2.4%)	7 (2.7%)
Sustained ventricular tachycardia	7 (2.8%)	6 (2.4%)
Ventricular fibrillation	7 (2.8%)	6 (2.4%)

Note: No missing data in each category.

A summary of baseline medications in all randomized and treated patients in the DIONYSOS study is presented in Table 24.

Table 24 - Summary of baseline medications – All randomized and treated patients - DIONYSOS

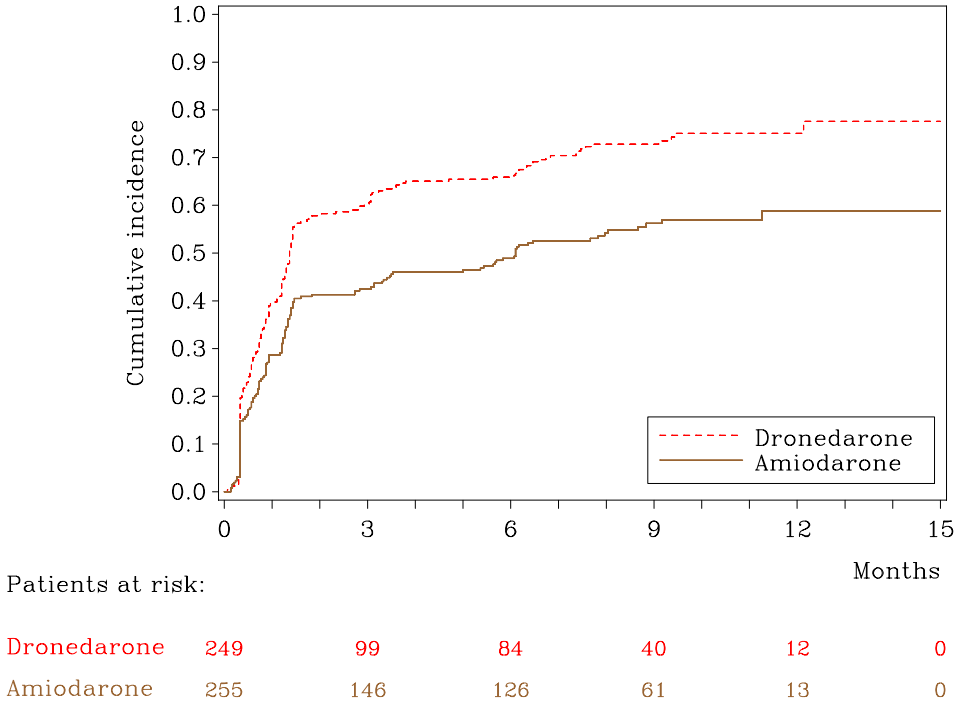
	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg OD (N=255)
Oral anticoagulant	241 (96.8%)	241 (94.5%)
Beta blocking agents (except sotalol)	152 (61.0%)	163 (63.9%)
ACE inhibitors or A II receptor antagonists	121 (48.6%)	139 (54.5%)
Diuretics	71 (28.5%)	79 (31.0%)
Diuretics (other than spironolactone)	67 (26.9%)	74 (29.0%)
Spironolactone	15 (6.0%)	19 (7.5%)
Statins	62 (24.9%)	61 (23.9%)
Statins - metabolized by CYP3A4	56 (22.5%)	54 (21.2%)
Statins - not metabolized by CYP3A4	7 (2.8%)	7 (2.7%)
Digitalis	53 (21.3%)	51 (20.0%)
Digoxin	46 (18.5%)	42 (16.5%)
Digitalin	7 (2.8%)	8 (3.1%)
Digitalis other than digoxin or digitalin	0	1 (0.4%)
Chronic antiplatelet therapy	33 (13.3%)	38 (14.9%)
Drugs interacting with creatinine tubular secretion/secreted at tubular level	22 (8.8%)	29 (11.4%)
Moderate inhibitors of CYP3A4	20 (8.0%)	17 (6.7%)
Calcium antagonists with heart rate lowering effects	20 (8.0%)	17 (6.7%)
NSAID	11 (4.4%)	10 (3.9%)

Note: Baseline medications are medications starting before the first study drug intake and stopping on or after the first study drug intake.

3.3.4.4 Efficacy results

The incidence of the primary efficacy endpoint defined as first recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy at 12 months was 75.1% in the dronedarone group and 58.8% in the amiodarone group (HR=1.589, 95% CI [1.275; 1.980] log-rank p-value<0.0001), with an early separation of the curves within the first 2 months post-randomization (Figure 6).

Figure 6 – Time to primary endpoint - All randomized and treated patients - DIONYSOS



Note: Kaplan-Meier cumulative incidence curve

Description of the components of the primary endpoint showed that recurrences of AF (including absence of conversion) were more frequent in the dronedarone group than in the amiodarone group, whereas premature study drug discontinuations due to intolerance were less frequent in the dronedarone group (Table 25).

Table 25 - Components of the primary endpoint– All randomized and treated patients - DIONYSOS

	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg OD (N=255)
Number of patients with endpoint	184 (73.9%)	141 (55.3%)
Af recurrence	158 (63.5%)	107 (42.0%)
Documented AF after conversion	91 (36.5%)	62 (24.3%)
Unsucessful electrical cardioversion	29 (11.6%)	16 (6.3%)
No spontaneous conversion and no electrical cardioversion on day 10 to day 28	38 (15.3%)	29 (11.4%)
Premature study drug discontinuation	26 (10.4%)	34 (13.3%)
Lack of efficacy	1 (0.4%)	0
Intolerance	25 (10.0%)	34 (13.3%)

Note: Primary endpoint is defined as recurrence of atrial fribrillation or premature study drug discontinuation for intolerance or lack of efficacy, according to investigator's judgment. Intolerance includes: discontinuations due to an AE and all discontinuations not due to administrative reasons.
For each patient, only the first component or primary endpoint is taken into account.

The primary safety analyses of the DIONYSOS trial are presented in detail in the safety section of this document (Section 6.5).

3.3.4.5 Conclusions

The findings of the DIONYSOS trial suggest that, in the doses administered, dronedarone is better tolerated but is not as effective as amiodarone in reducing the recurrence of AF. Additional comparative safety data of dronedarone vs. amiodarone are provided in Section 6.5.

3.4 STUDIES IN SPECIAL PATIENT POPULATIONS

Studies performed in non-AF/AFL populations helped to better delineate dronedarone's clinical profile. The ACT2401 study conducted in patients with severe LVD evaluated the safety of ascending doses of dronedarone up to 1200 mg daily. Studies DRI3151 and LTS3841 evaluated its effects in patients with ICD by recording numbers of shocks received over 1- and 6-month periods, respectively. The ANDROMEDA was desinged to evaluate the effect of dronedarone 400 mg BID on the risk of death or hospitalizations for worsening heart failure in patients hospitalized for decompensated heart failure.

3.4.1 Study in patients with left ventricular dysfunction (ACT2401)

The ACT2401 study was primarily conducted to evaluate the safety of ascending doses of dronedarone up to 1200 mg daily in 124 patients with severe LVD (LVEF ≤30%). Dronedarone 400 mg OD, 800 mg OD or 600 mg BID administered orally did not result in decreased LVEF, nor decreased exercise performance measured during a 6-minute walk test.

The incidence of AEs was similar between dronedarone groups and placebo (200 mg BID: 55.2%; 400 mg BID: 70.0%; 600 mg BID: 60.0%). One sudden death (on Day 17) was reported in the dronedarone 600 mg BID group. In this population with LVD, the incidence of any cardiac failure (ie, cardiac failure/cardiac failure left and right) was not different from placebo, ie, 3.3% in dronedarone 400 mg BID and 5 % in placebo groups. However, dyspnea and chest pain were more frequent in the dronedarone 400 mg BID (20.7%) group compared to the placebo (17.5%) group.

3.4.2 Studies in patients with Cardioverter/Defibrillator (DRI3151/LTS3841)

The DRI3151 study was a double-blind, multicenter, randomized (1:1), parallel arm, placebo-controlled study aimed at evaluating the safety and tolerability of three doses (600, 800, or 1000 mg BID) of dronedarone in an ICD population and the effect of dronedarone in preventing ICD intervention. Based on QTc effect of dronedarone, a higher dose range than in the AF population of the DAFNE study was deemed necessary, to favor efficacy in ventricular arrhythmia. The LTS3841 study was an extension of the DRI3151 study aimed at the evaluation of long-term safety and tolerability of dronedarone in ICD patients included in the DRI3151 study and for whom continuation of treatment with the study drug was warranted. The primary objective of the study was to assess whether dronedarone interacted with the function of the ICD. This study also gave the opportunity to determine the possible effect of dronedarone on ventricular arrhythmia documented by ICD interventions (shocks).

Of 73 treated patients, 54 received dronedonarone, and 19 received placebo in the DRI3151 study. A total of 47 patients completed this study. Of these 47 patients, 40 entered Study LTS3841 and were analyzed for safety. The results of this study showed a trend (p=0.058) for fewer appropriate ICD interventions over 7 months under dronedarone treatment vs. placebo, with no obvious dose-effect. These results also suggested that dronedarone can be safely administered in this type of patient.

The 1000 mg BID dose was prematurely discontinued due to poor GI tolerance (mainly diarrhea). There were no episodes of TdP reported in this study. In DRI3151, one patient taking dronedarone 1000 mg BID died during treatment at Day 3 from sudden death in a context of decompensated CHF (without any ICD evidence of arrhythmic event in the week preceding death). No death occurred during the 6 additional months in the 40 patients who continued.

3.4.3 Study in patients hospitalized for congestive heart failure within the last month (The ANDROMEDA trial)

The ANDROMEDA trial was a multicenter, double-blind, parallel-group, placebo-controlled study evaluated the effect of dronedarone 400 mg BID on the risk of hospitalizations for worsening heart failure or death, in a high risk population of patients with recently decompensated congestive heart failure. The trial was carried out in 72 centers in 6 European countries: Denmark, Hungary, the Netherlands, Norway, Poland, and Sweden. Patient enrollment began in June 2002 and the last patient completed in August 2003.

The ANDROMEDA trial was carried out with the knowledge that many drugs with antiarrhythmic properties had been shown to increase the risk of cardiovascular death in vulnerable populations (e.g., patients with significant structural heart disease or heart failure), presumably related to a proarrhythmic effect. However, previous trials had shown that amiodarone did not have significant proarrhythmic effects, and the long-term administration of amiodarone to patients with stable chronic heart failure had neither a favorable nor detrimental effect on mortality. Thus, the ANDROMEDA study was performed to evaluate the effect of dronedarone on long-term cardiovascular risks.

It is important to note that the ANDROMEDA trial was not specifically carried out in patients likely to receive the drug in clinical practice, i.e., those with AF/AFL. Instead, the patient population for ANDROMEDA consisted of patients who had the highest known long-term risk of cardiovascular death (i.e., those hospitalized for decompensated heart failure), whether or not they had an arrhythmia likely to respond favorably to treatment with dronedarone. This study provided the opportunity to evaluate the potential risk of a proarrhythmic effect with dronedarone, in patients most likely to be sensitive to such an effect.

3.4.3.1 Study Design and Conduct

Patients were eligible for the study if they were aged 18 years or greater; were hospitalized for the management of worsening heart failure at the time of randomization; had NYHA class II-IV symptoms requiring treatment with a diuretic; had had within the last month at least one episode of dyspnea or fatigue at rest or on slight exertion; and had a WMI $\leq$1.2 (equivalent to a LVEF

≤35%) as determined by a blinded central echocardiographic evaluation. Patients were excluded if they had acute pulmonary edema within 12 hours prior to start of study medication; cardiogenic shock requiring treatment with IV pressor agents or mechanical ventilation; uncorrected hemodynamically significant primary obstructive valvular disease; hemodynamically significant obstructive cardiomyopathy; acute MI during the 5-7 days preceding randomization; cardiac surgery or revascularization procedure during the month preceding randomization; planned major non-cardiac or cardiac surgery or procedures including surgery for valvular heart disease, coronary artery bypass graft, or cardiac transplantation; acute myocarditis or constrictive pericarditis; history of TdP; bradycardia <50 bpm and/or PR-interval ≥280 ms; QTc-interval >500 ms; significant sinus node disease (documented pause of at least 3 sec) or second or third degree AV block unless treated with a pacemaker; treatment with other class I or III anti-arrhythmic drugs; any illness or disorder other than heart failure that could preclude participation or severely limit survival including cancer with metastasis and organ transplantation requiring immune suppression; serum potassium <3.5 mmol/L; other conditions/circumstances likely to lead to poor treatment adherence (eg, history of poor compliance, alcohol or drug dependency, psychiatric illness, etc.); current participation in another clinical study in which the patient is currently taking an investigational drug (under development) or using an investigational device; or previous participation in this study or in other dronedarone studies.

Eligible patients were randomized (in a 1:1 ratio) to dronedarone or placebo for 12 months and were followed for the occurrence of death or adjudicated hospitalization for worsening heart failure (primary endpoint). The secondary endpoints were all-cause mortality (analyzed individually) and adjudicated hospitalization for worsening heart failure (analyzed individually).

The Steering Committee was responsible for the conduct of the trial but remained blinded to all study results. An independent data safety monitoring board (DSMB) closely monitored the safety of patients in the study. An independent and blinded Critical Events Committee (CEC) adjudicated the cause of death (cardiovascular death: MI, worsening CHF, documented arrhythmia, procedure related, other cardiovascular reason, presumed cardiovascular reason; noncardiovascular death) and mode of death (non sudden, or sudden witnessed or unwitnessed). This committee also adjudicated the reason for hospitalization (ie, cardiovascular: worsening heart failure or other cardiovascular reason; or noncardiovascular).

This study was to randomize a total of 1000 patients (500 patients per group) for a minimum follow-up of 12 months. However, seven months after study start (on January 16, 2003, after 627 patients had been randomized), the DSMB recommended termination of the trial because it had observed a higher number of deaths in patients randomized to dronedarone as compared with placebo. The mean duration of follow-up at the time was 2 months. The DSMB recommended that investigators schedule their patients for a final visit to discontinue their treatment, and then to follow-up each patient after 2 weeks and after 1, 3, and 6 months (i.e., up to 17 July 2003). During this entire follow-up period, investigators remained blinded to treatment.

3.4.3.2 Patient Enrollment and Disposition

A total of 1000 patients were planned, but 650 patients were randomized into the trial: 329 to placebo and 321 to dronedarone. Of these, 23 patients were enrolled at center 616004, but this

center was suspected of important data integrity issues, and therefore, the patients enrolled at this site were excluded from all analyses. As a result, there were 627 patients included in the final intention-to-treat analysis: 317 were randomized to placebo and 321 were randomized to dronedarone.

Overall, the number of permanent discontinuations before recommendation of the DSMB to stop the trial in the main analysis population was higher in the dronedarone group (28.1%) than in the placebo group (18.0%). Permanent discontinuations were mainly due to treatment-emergent AEs in both groups and were driven by cardiac failure and blood creatinine increase.

3.4.3.3 Patient Characteristics

All 627 randomized patients had severely impaired left ventricular function (corresponding to LVEF ≤ 35%) as required by protocol. A majority had NYHA Class II or III symptoms at randomization and all had been hospitalized for decompensated heart failure. At randomization, only one-fourth had AF at randomization (38% had a history of AF). Patients were receiving concomitant treatments appropriate for the treatment of chronic heart failure. A summary of demographic characteristics in the randomized and treated patients in the ANDROMEDA study is presented in Table 26.

Table 26 - Summary of demographic parameters - Randomized and treated patients - ANDROMEDA

Parameter		Placebo (N=317)	Dronedarone 400 mg BID (N=310)
Age (years)	n	317	310
	Median	72	71
	Mean	68.8	69.5
	SD	12.1	11.5
	Min - Max	27 - 96	33 - 90
Age (years) [n (%)]	<65	102 (32.2 %)	101 (32.6 %)
	[65;75[	93 (29.3 %)	92 (29.7 %)
	>=75	122 (38.5 %)	117 (37.7 %)
Weight (Kg)	n	314	308
	Median	77.5	78.0
	Mean	79.13	77.72
	SD	18.70	17.00
	Min - Max	36.8 - 188.7	37.5 - 147.0
Gender [n (%)]	Male	242 (76.3 %)	230 (74.2 %)
	Female	75 (23.7 %)	80 (25.8 %)
Race [n (%)]	Caucasian	316 (99.7 %)	308 (99.4 %)
	Black	1 (0.3 %)	0 (0.0 %)
	Asian / oriental	0 (0.0 %)	1 (0.3 %)
	Other [a]	0 (0.0 %)	1 (0.3 %)

a Other race = Greenland
Note: EFC4966/ANDROMEDA

Cardiovascular history in the randomized and treated patients in the ANDROMEDA study is presented in Table 27.

Table 27 - Number (%) of patients according to cardiovascular history – Randomized and treated patients - ANDROMEDA

	Placebo (N=317)	Dronedarone 400 mg BID (N=310)
Coronary heart disease	201/317 (63.4%)	206/310 (66.5%)
Valvular heart disease	175/317 (55.2%)	171/310 (55.2%)
Hypertension	107/317 (33.8%)	123/310 (39.7%)
Dilated cardiomyopathy	103/317 (32.5%)	79/310 (25.5%)
Diabetes mellitus	62/317 (19.6%)	73/310 (23.5%)
Coronary artery bypass grafting	42/317 (13.2%)	57/310 (18.4%)
Documented severe ventricular arrhythmia	33/317 (10.4%)	33/310 (10.6%)
Stroke	31/317 (9.8%)	24/310 (7.7%)
Percutaneous coronary revascularisation	26/317 (8.2%)	27/310 (8.7%)
Pacemaker	17/317 (5.4%)	21/310 (6.8%)
Alcohol induced cardiomyopathy	6/317 (1.9%)	13/310 (4.2%)
Hypertrophic cardiomyopathy	7/317 (2.2%)	11/310 (3.5%)
Congenital heart disease	0/317 (0.0%)	2/310 (0.6%)

Note: EFC4966/ANDROMEDA

A summary of echocardiography and cardiovascular clinical examination at baseline in the randomized and treated patients in the ANDROMEDA study is presented in Table 28.

Table 28 - Summary of echocardiography (LVEF) and cardiovascular clinical examination (NYHA Class) at baseline - Randomized and treated patients - ANDROMEDA

	Placebo (N=317)		Dronedarone 400 mg BID (N=310)	
Left ventricular ejection fraction (%)				
n	316		309	
Mean (SD)	25.9(6.9)		27.1(6.8)	
Median	27		30	
Min ; Max	9 ; 36		9 ; 36	
Cardiovascular clinical examination - NYHA classification	317	(100%)	310	(100%)
Class II	121	(38.2%)	131	(42.3%)
Class III	183	(57.7%)	173	(55.8%)
Class IV	13	(4.1%)	6	(1.9%)

Note: WMI is used to estimate LVEF, with LVEF = WMI * 30
Note: EFC4966/ANDROMEDA

In addition, 126 patients (39.7%) in the placebo group and 114 patients (36.8%) in the dronedarone group had a history of AF. Eighty five (85) patients (28%) in the placebo group and 72 (24.1%) in the dronedarone group had AF at randomization. Approximately two-third of the patients had coronary artery disease; about one-third had a history of hypertension and one-half had evidence of edema at randomization. Summaries of baseline creatinine and baseline creatinine clearance at baseline are presented in Table 29 and Table 30, respectively.

Table 29 - Summary of serum creatinine (µmol/L) at baseline – Randomized and treated patients - ANDROMEDA

	Placebo (N=317)	Dronedarone 400 mg BID (N=310)
n	310	303
Median	111	115
Mean	124.2	128.0
SD	53.7	43.8
Min - Max	55 - 738	61 - 321

Note: EFC4966/ANDROMEDA

Table 30 - Summary of baseline calculated creatinine clearance (mL/minute) - randomized and treated patients - ANDROMEDA

	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%)

Note: EFC4966/ANDROMEDA

A summary of patients according to intake of specific medications at baseline in the randomized and treated patients in the ANDROMEDA study is presented in Table 31.

Table 31 - Number (%) of patients according to intake of specific medications at baseline – Randomized and treated patients - ANDROMEDA

	Placebo (N=317)	Dronedarone 400 mg BID (N=310)
Diuretics	309 (97.5%)	297 (95.8%)
Diuretics (other than spironolactone)	302 (95.3%)	288 (92.9%)
Spironolactone	124 (39.1%)	131 (42.3%)
ACE inhibitors or A II receptor antagonists	267 (84.2%)	274 (88.4%)
ACE inhibitors	241 (76.0%)	242 (78.1%)
AII receptors antagonists	28 (8.8%)	36 (11.6%)
Chronic antiplatelet therapy	196 (61.8%)	203 (65.5%)
Beta blocking agents	192 (60.6%)	192 (61.9%)
Beta blocking agents (except sotalol)	191 (60.3%)	192 (61.9%)
Statins	97 (30.6%)	113 (36.5%)
Metabolized by CYP3A4	73 (23.0%)	94 (30.3%)
Not metabolized by CYP3A4	24 (7.6%)	20 (6.5%)
Digitalis	101 (31.9%)	96 (31.0%)
Digoxin	92 (29.0%)	84 (27.1%)
Digitalin	5 (1.6%)	7 (2.3%)
Digitalis other than digoxin or digitalin	6 (1.9%)	5 (1.6%)
Oral anticoagulant	102 (32.2%)	92 (29.7%)
Moderate inhibitors of CYP3A4	14 (4.4%)	10 (3.2%)
Calcium antagonists with heart rate lowering effects (a)	12 (3.8%)	9 (2.9%)
NSAID(s)	12 (3.8%)	8 (2.6%)

(a) Restricted to diltiazem, verapamil
Note: EFC4966/ANDROMEDA

3.4.3.4 Study Results

Primary Endpoint

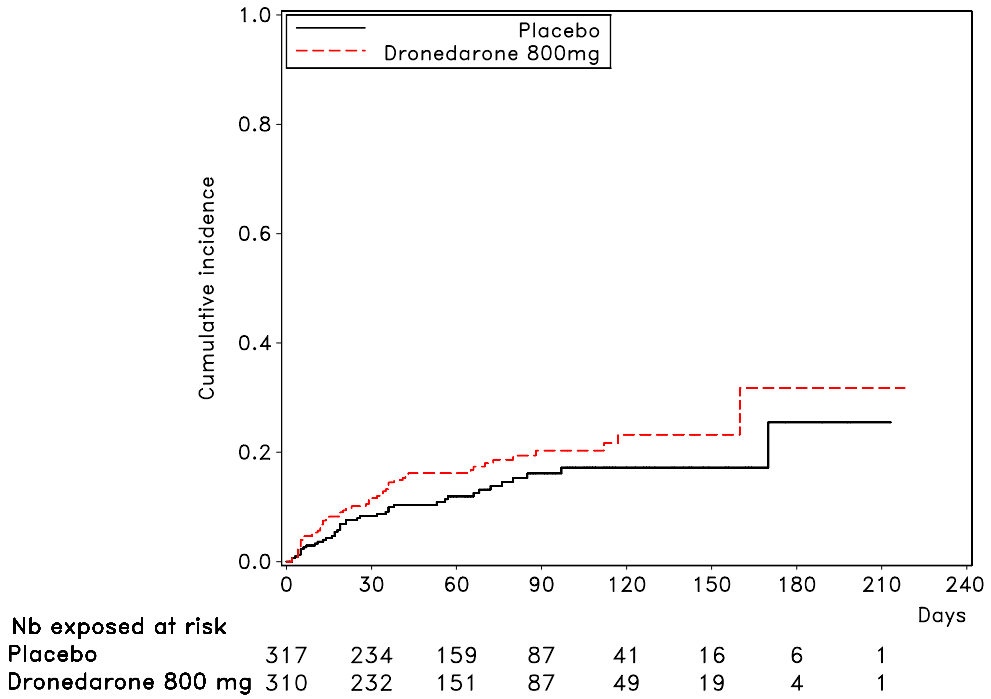
At the time of early study termination, there was a trend toward an increased risk of the primary endpoint (all-cause mortality and hospitalization for worsening heart failure) in the dronedarone group when compared with the placebo group (HR = 1.38, log-rank p=0.118) (Table 32 and Figure 7).

Table 32 – Time to death or hospitalization for worsening heart failure up to DSMB decision of study drug discontinuation- Randomized and treated patients - ANDROMEDA

	Placebo (n=317)	Dronedarone (n=310)
Number of patients who died or were 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 Cox regression model
Note: EFC4966/ANDROMEDA

Figure 7 - Time to death or hospitalization for worsening heart failure up to DSMB decision of study drug discontinuation- Randomized and treated patients - ANDROMEDA



Note: Kaplan-Meier cumulative incidence curves

Secondary Endpoints

The adverse trend on the primary endpoint was driven by an imbalance in the risk of death without an apparent difference in the risk of hospitalization for worsening heart failure (31 patients in placebo group and 39 patients in dronedarone group). Dronedarone was associated with a 2.13-fold increase in the risk of death (Table 33), whereas the time to first hospitalization for worsening heart failure was not significantly different between treatment groups (log rank test, p=0.271).

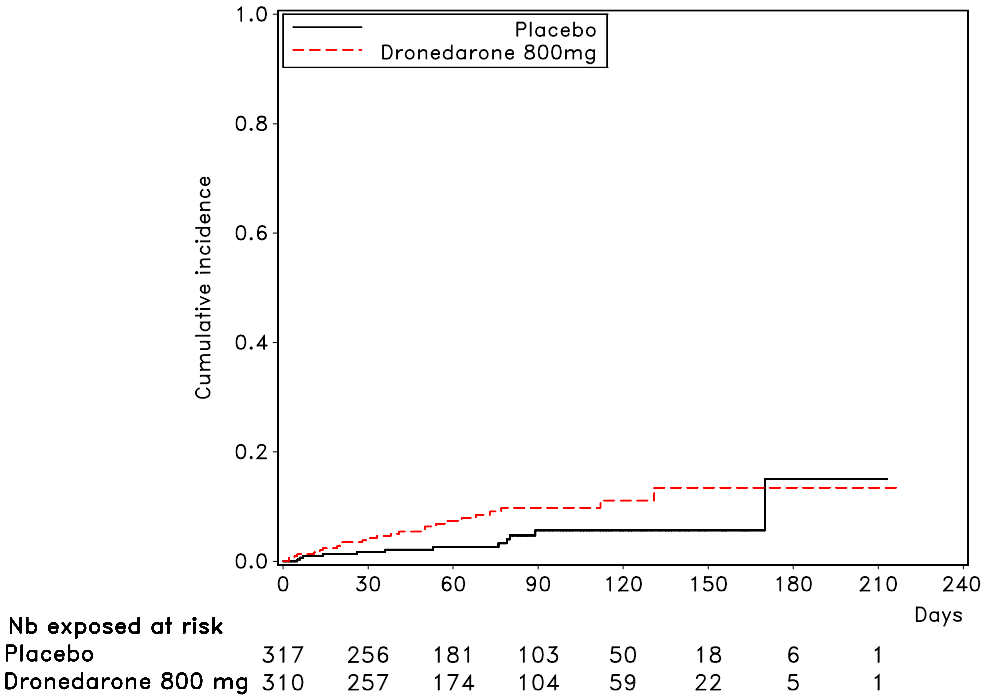
Table 33 - Time to death up to DSMB decision of study drug discontinuation - Randomized and treated patients - ANDROMEDA

	Placebo (n=317)	**Dronedarone 400 mg BID (n=310)**
Number of patients who died	12	25
Relative risk[a]	2.13	
95% CI[a]	[1.071 , 4.247]	
Log-rank test (p-value)	0.02717	

a Determined from unadjusted Cox regression model

The corresponding Kaplan-Meier plots are presented in Figure 8.

Figure 8 – Time to death up to DSMB decision of study drug discontinuation- Randomized and treated patients - ANDROMEDA



Note: Kaplan-Meier cumulative incidence curve

Excess mortality in the dronedarone group was due to an increase in cardiovascular death, in particular, a higher incidence of non-sudden death, especially death due to worsening heart failure (Table 34 and Table 35).

Table 34 - Adjudicated timing of cardiovascular death - ANDROMEDA

	Placebo (n=9)	Dronedarone 400 mg BID (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%)

Table 35 - Adjudicated primary cause of death - ANDROMEDA

	Placebo (n=12)	Dronedarone 400 mg BID (n=25)
Cardiovascular death	9	24
Myocardial infarction	2	0
Worsening heart failure	2	10
Documented arrhythmia	2	6
Procedure related	0	1
Other cardiovascular reason	0	2
Presumed cardiovascular reason	3	5
Noncardiovascular death	2	1
Cancer	1	1
Gangrene	1	0
Non-adjudicated death (a)	1	0

(a) The absence of documentation of the cause of death did not allow adjudication

No episodes of TdP were reported among the 8 cases of death that were adjudicated as a "documented arrhythmia" (6 dronedarone patients and 2 placebo patients). All 8 deaths were "sudden and witnessed".

Additional Analyses

The most common SOCs (with incidence ≥10% in at least 1 treatment group) were cardiac disorders (mainly cardiac failure), GI disorders (mainly Diarrhea), investigations (mainly blood creatinine increased), infections and infestations (mainly pneumonia in the placebo group), and respiratory, thoracic, and mediastinal disorders (mainly cough).

The overall rates of patients experiencing SAEs were not different between treatment groups, except for cardiac disorders (mainly cardiac failures) and the investigations (mainly blood creatinine increased) System Organ Classes.

These tables reveal an excess of reports of increased serum creatinine in patients treated with dronedarone. Although this increase may have been related to the increased frequency of heart failure in dronedarone-treated patients, excess reports of increased serum creatinine have been seen consistently in all dronedarone trials, most of which enrolled few patients with severe heart failure and noted no adverse effect of the drug on the heart or circulation (Section 3.2).

Subgroup analyses of the effect of dronedarone on the risk of death were performed based on selected baseline characteristics. These analyses indicate that the risk of death in dronedarone-treated patients was most apparent in patients with the most advanced heart failure (i.e., those with severe symptoms, very poor ventricular function – WMI < 1.0 corresponding to an ejection fraction < 30%), and compromised renal function (Table 36).

Table 36 - Unadjusted relative risk by prognostic factor subcategories of time to death up to DSMB decision of study drug discontinuation- Randomized and treated patients - ANDROMEDA

		Placebo		Dronedarone 400 mg BID		Unadjusted relative risk[a] Dronedarone/Placebo	
Prognostic factor	Category	N	Nb of events	N	Nb of events	Relative risk	95% CI
Baseline creatinine clearance	<50 ml/min	128	6	133	17	2.70	[1.065 ; 6.867]
	>=50 ml/min	179	5	168	6	1.36	[0.412 ; 4.492]
Baseline NYHA class	II	121	5	131	7	1.28	[0.405 ; 4.029]
	III or IV	196	7	179	18	2.77	[1.156 ; 6.625]
Baseline WMI	<1	181	4	145	15	4.60	[1.526 ; 13.868]
	>=1	136	8	165	10	1.05	[0.415 ; 2.674]

[a] Determined from Cox regression

An alternative explanation (as described in Section 3.2) is that dronedarone interferes with the secretion of creatinine by the renal tubules. This can explain why initiation of treatment with dronedarone is predictably accompanied by an increase in serum creatinine, which does not reflect a decline in glomerular function. However, in patients with severe heart failure who are routinely being treated with ACE inhibitors or ARBs, it is possible that the increase in serum creatinine could be attributed to treatment with ACE inhibitors or ARBs rather than to treatment with dronedarone. Conversely, it is conceivable that physicians might respond to the increase in serum creatinine by withdrawing treatment with the ACE inhibitor or ARB or by delaying or deferring the initiation of these drugs [ACE inhibitors and ARBs were started less frequently and were withdrawn more frequently in patients treated with dronedarone than in patients treated with placebo (Table 37)]. This hypothesis as well as others is discussed in section 5.

Table 37 - Use of ACE inhibitors and angiotensin-II receptor antagonists – Randomized and treated patients - ANDROMEDA

	Placebo (N=317)	Dronedarone (N=310)
Patients with ACE inhibitors or A-II receptor antagonists at baseline	267 (84.2%)	274 (88.4%)
Patients with ACE inhibitors or A-II receptor antagonists at baseline who did not interrupt these treatments	254 (80.1%)	237 (76.5%)
Patients who started ACE inhibitors or A-II receptor antagonists after baseline and who did not interrupt these treatments	27 (8.5%)	12 (3.9%)
Patients who discontinued treatment with ACE inhibitors or A-II receptor antagonists	18 (5.7%)	41 (13.2%)
Patients who were never treated with ACE inhibitors or A-II receptor antagonists	18 (5.7%)	20 (6.5%)

3.4.3.5 Study Conclusions

The ANDROMEDA trial reported an increased risk of death in high risk patients with decompensated heart failure treated with dronedarone, not attributed to a proarrhythmic effect of the drug. Therefore, the pattern of increased risk seen in ANDROMEDA differed from that seen in outcome trials with other (Class I and III) antiarrhythmic drugs and required further study.

The excess risk of death in dronedarone-treated patients was most apparent in patients with the most advanced heart failure (i.e., those with severe symptoms, very poor ventricular function; WMI < 1.0, corresponding to an ejection fraction of < 30%) and compromised renal function.

The ANDROMEDA trial raises the possibility that dronedarone might increase the risk of heart failure in highly vulnerable patients. Both dronedarone and amiodarone are known to exert negative inotropic effects in animal models, but despite this finding, amiodarone is not believed to exert cardiodepressant effects in the clinical setting, and dronedarone did not decrease ejection fraction or impair exercise tolerance in patients with LVD (see description of the ACT2401 trial in section 3.4.1). Since the ANDROMEDA trial raised the possibility that dronedarone-induced changes in serum creatinine that might lead physicians to reduce their use of ACE inhibitors and ARBs in patients with severe heart failure, investigators in future studies with dronedarone were advised not to rely on changes in serum creatinine following initiation of treatment with the drug to justify decisions regarding changes in the use of ACE inhibitors or ARBs.

4 EFFECT OF DRONEDARONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH ATRIAL FIBRILLATION OR FLUTTER: THE ATHENA STUDY

The ATHENA study was a prospective, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to evaluate the long-term effect of dronedarone 400 mg BID versus placebo on the combined risk of all-cause mortality and cardiovascular hospitalization in patients with a recent or current history of AF/AFL.

The study was carried out in 551 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, and United States. Patient enrollment began in June 2005, and the last patient completed in March 2008.

4.1 STUDY CONCEPTUALIZATION

The ATHENA study was designed to accomplish two goals:

1. *To determine if dronedarone's favorable effects in patients with AF/AFL (demonstrated in the DAFNE, EURIDIS, ADONIS and ERATO trials) could result in a long-term reduction in the risk of major adverse cardiovascular events.* In the past, development programs for drugs for AF had traditionally focused on the control of the arrhythmia and associated symptoms, and thus, little was known about the effect of available drugs on the natural history of patients with the disease. Patients with AF/AFL generally had several associated cardiovascular disorders that influenced their morbidity and mortality (hypertension, coronary artery disease, cardiomyopathy), and the influence of most antiarrhythmic drugs on the course of these associated conditions was not known. A large-scale, long-term outcomes trial with dronedarone (ATHENA) could therefore, provide unique insights into therapeutic role of this drug in patients with AF/AFL.

Importantly, in the two major trials carried out to demonstrate the efficacy of dronedarone for the control of AF recurrence (EURIDIS and ADONIS), treatment with dronedarone was associated with a lower risk of death or first cardiovascular hospitalization, i.e., 27% lower risk in the EURIDIS trial and 11% lower risk in the ADONIS trial post-hoc analysis. Pooled analysis of the data from both trials showed a 20% reduction in the risk of death or cardiovascular hospitalization (relative risk 0.804 [95% CI: 0.591, 1.094]) post-hoc analysis (Section 3.3.2.4, Table 16).

2. *To clarify and further elucidate the effect of dronedarone on the risk of death in patients likely to receive the drug in clinical practice.* The increased mortality risk in ANDROMEDA was seen in patients with decompensated heart failure (largely without AF/AFL) who had been studied primarily to evaluate the drug's safety even though most of the patients in the study did not have a specific therapeutic indication for the drug. All of the patients were clinically unstable, having been hospitalized for the management of worsening heart failure, and half of the patients still had evidence of fluid retention at the time of entry into the study. Such patients might be uniquely sensitive to treatment with a drug with even modest negative inotropic effects. Indeed, although

large-scale long-term trials with amiodarone (CHF-STAT and SCD-HeFT) demonstrated no overall increase in the risk of death in patients with stable chronic heart failure, dronedarone may have adversely affected patients with the most severe symptoms in the ANDROMEDA study. Subgroup analysis of the results of the ANDROMEDA trial (see section 3.4.3.4) also suggested that the increased risk with dronedarone was most apparent in patients with the most severely depressed ventricular or renal function (see Table 36). In addition, the effect of dronedarone on serum creatinine may have caused investigators in the ANDROMEDA trial to selectively withhold the use of ACE inhibitors and ARBs in dronedarone-treated patients.

The ATHENA trial was a large-scale, long-term trial that was designed to achieve both goals by evaluating the effects of dronedarone on the risk of death or cardiovascular hospitalization in patients receiving the drug for the treatment of AF/AFL. The trial included patients with stable heart failure but excluded hospitalized patients who were clinically decompensated. Furthermore, investigators were given specific guidance not to withhold the use of ACE inhibitors and ARBs in patients who experience increases in serum creatinine related to the initiation of treatment with dronedarone.

4.2 ATHENA STUDY DESIGN AND METHODOLOGY

The intent of the ATHENA trial was to enroll a wide spectrum of patients with AF/AFL, similar to that seen in clinical practice. However, in order to achieve the number of events needed to test the primary hypothesis of the study, the inclusion criteria were similar to those of the AFFIRM study (12).

Specifically, patients were randomized into the study if they had had AF/AFL within the prior 6 months but were now in sinus rhythm; cardioversion could have been spontaneously achieved or following a procedure such as electrical cardioversion (or overdrive pacing) or administration of an antiarrhythmic drug. Patients could also be randomized if they were in AF/AFL at the start of the study, if there was a plan for the patient to undergo cardioversion after appropriate anticoagulation during the follow-up period. All patients were to be treated according to standard of care. Although patients in permanent AF were excluded at the time of randomization, some patients who were in AF/AFL at randomization were never documented to convert to sinus rhythm at ECGs collected during follow-up visits and thus were considered permanently in AF/AFL during the course of the study.

In addition to the requirement for AF/AFL, patients were also required to have at least one additional risk factor for the occurrence of a major cardiovascular event. In the original protocol, this could be achieved (1) if patients were at least 70 years old and had no additional risk factors; or (2) if patients were less than 70 years old and had one of the following:

- Hypertension (taking antihypertensive drugs of at least 2 different classes)
- Diabetes
- Prior cerebrovascular accident (stroke or TIA) or systemic embolism
- Left atrium diameter greater than or equal to 50 mm by M-Mode echocardiography

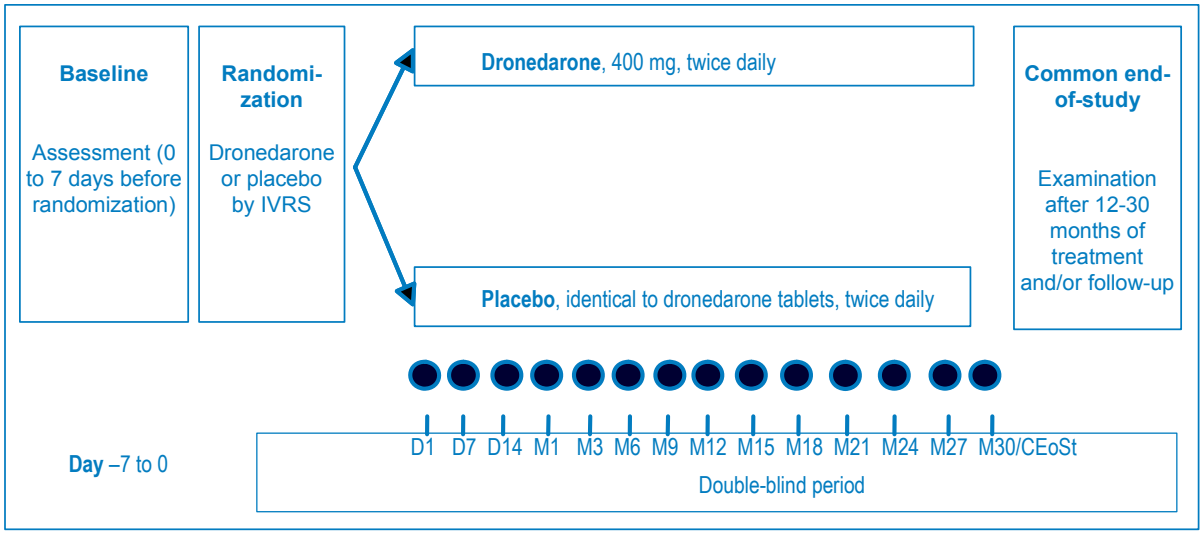
- LVEF less than 0.40 by 2D-echocardiography

A protocol amendment implemented in March 2006 changed the determining age from 70 years to 75 years, i.e., patients could enter the trial if they had none of the five risk factors if they were at least 75 years old; at least one risk factor was required if they were younger than 75 years.

Patients were excluded from participation in the study if they had permanent AF at randomization; an unstable hemodynamic condition such as acute pulmonary edema within 12 hours prior to start of study medication; cardiogenic shock; treatment with IV pressor agents or mechanical ventilation; class IV heart failure within 4 weeks; uncorrected, hemodynamically significant primary obstructive valvular disease; hemodynamically significant obstructive cardiomyopathy; a cardiac operation or revascularization procedure within 4 weeks preceding randomization; acute myocarditis or constrictive pericarditis; bradycardia <50 bpm and/or PR-interval ≥ 0.28 sec on the last 12-lead ECG; significant sinus node disease (documented pause of 3 seconds or more) or second or third degree AV block unless treated with a pacemaker; need of a prohibited concomitant medication, including the requirement for Vaughan-Williams Class I and III antiarrhythmic drugs; plasma potassium <3.5 mmol/L; calculated glomerular filtration rate (GFR) at baseline <10 mL/min using the Cockroft Gault formula; 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; any non-cardiovascular illness or disorder that could preclude participation or severely limit survival including cancer with metastasis and organ transplantation requiring immune suppression; or previous (within 2 months) or current participation in another clinical trial with an investigational drug (under development) or with an investigational device.

The ATHENA study design is presented in Figure 9.

Figure 9 - ATHENA: Study Design



After a screening period of ≤ 7 days to determine if patients fulfilled the entry criteria, all patients randomized (1:1) were followed at planned visits, whether or not study drug was discontinued, until a common study end date visit, which was to be 1 year after the last patient was randomized.

In addition to dronedarone, usual standard therapy (eg, calcium antagonists, beta-blockers, digoxin, and oral anticoagulants) for the patient's cardiac condition could be administered according to published guidelines.

Investigators were given specific instructions on the management of increases in serum creatinine. If a mild or moderate asymptomatic increase in creatinine was observed after beginning treatment with the study medication, the investigator was advised to use clinical judgment, taking into account that this increase might be related to an inhibitory effect of dronedarone on the renal tubular secretion of creatinine. Depending on the patient's condition and symptoms, an increase in serum creatinine should not reflexly trigger the discontinuation of treatment with angiotensin-converting enzyme (ACE)-inhibitors or A-II receptor antagonists. Treatment with the study drug could be temporarily interrupted in case of doubt, and then, the study drug could be reintroduced as soon as possible once any concern was resolved.

This study was monitored by an independent Data Monitoring Committee (Drs. Raymond Lipicky, Marvin Konstam, and Thomas Fleming).

The pre-specified primary endpoint for the ATHENA trial was the time from randomization to first occurrence of hospitalization for cardiovascular reason or death from any cause. Secondary clinical endpoints included: time from randomization to death from any cause; time to first hospitalization for cardiovascular reasons; and time to cardiovascular death, as reported by investigators.

Hospitalizations were classified as cardiovascular when the reported main cause corresponded to one of the items of a prespecified list: atherosclerosis related (if not otherwise specified); MI or unstable angina; stable angina pectoris or atypical chest pain; syncope, TIA or stroke (except intracranial hemorrhage); AF and other supraventricular rhythm disorders; non-fatal cardiac arrest; cardiovascular surgery except cardiac transplantation; implantation of a pacemaker, ICD or any other cardiac device; transcutaneous coronary, cerebrovascular or peripheral procedure; BP related (hypotension, hypertension; except syncope); cardiovascular infection; major bleeding (requiring two or more units of blood or any intracranial hemorrhage); pulmonary embolism or deep vein thrombosis; worsening heart failure, including pulmonary edema or dyspnea of cardiac origin; ventricular extrasystoles, ventricular tachycardia (VT) (non-sustained and sustained), ventricular fibrillation or other ventricular arrhythmia. Other causes of hospitalizations were classified as non cardiovascular. The main cause of hospitalizations was determined by the site investigator and was not adjudicated. In contrast, the Steering Committee classified deaths in a blinded manner using the following categories: noncardiovascular, vascular noncardiac, cardiac nonarrhythmic, and cardiac arrhythmic.

All efficacy analyses were carried out according to the ITT principle and included all randomized patients (whether they took their study medication) and all assessments from randomization to the final follow-up visit/last contact date (which was to occur on or beyond the common study end date, prespecified to occur 12 months after the last patient randomized) or the date of death, whichever came earlier. The primary analysis was the comparison in all randomized patients (ITT population) of the time from randomization to the primary endpoint between the two treatment groups using a 2-sided log-rank asymptotic test. This same approach was used for analysis of all secondary endpoints. In order to protect the global type I error of 5%, a hierarchical procedure was to be applied to the secondary efficacy endpoints. "All deaths whatever the cause" was to be

tested first. If results from this first test were significant, then testing of "cardiovascular hospitalization" was to be performed. If the results of this second test were significant, then "cardiovascular death" was to be tested.

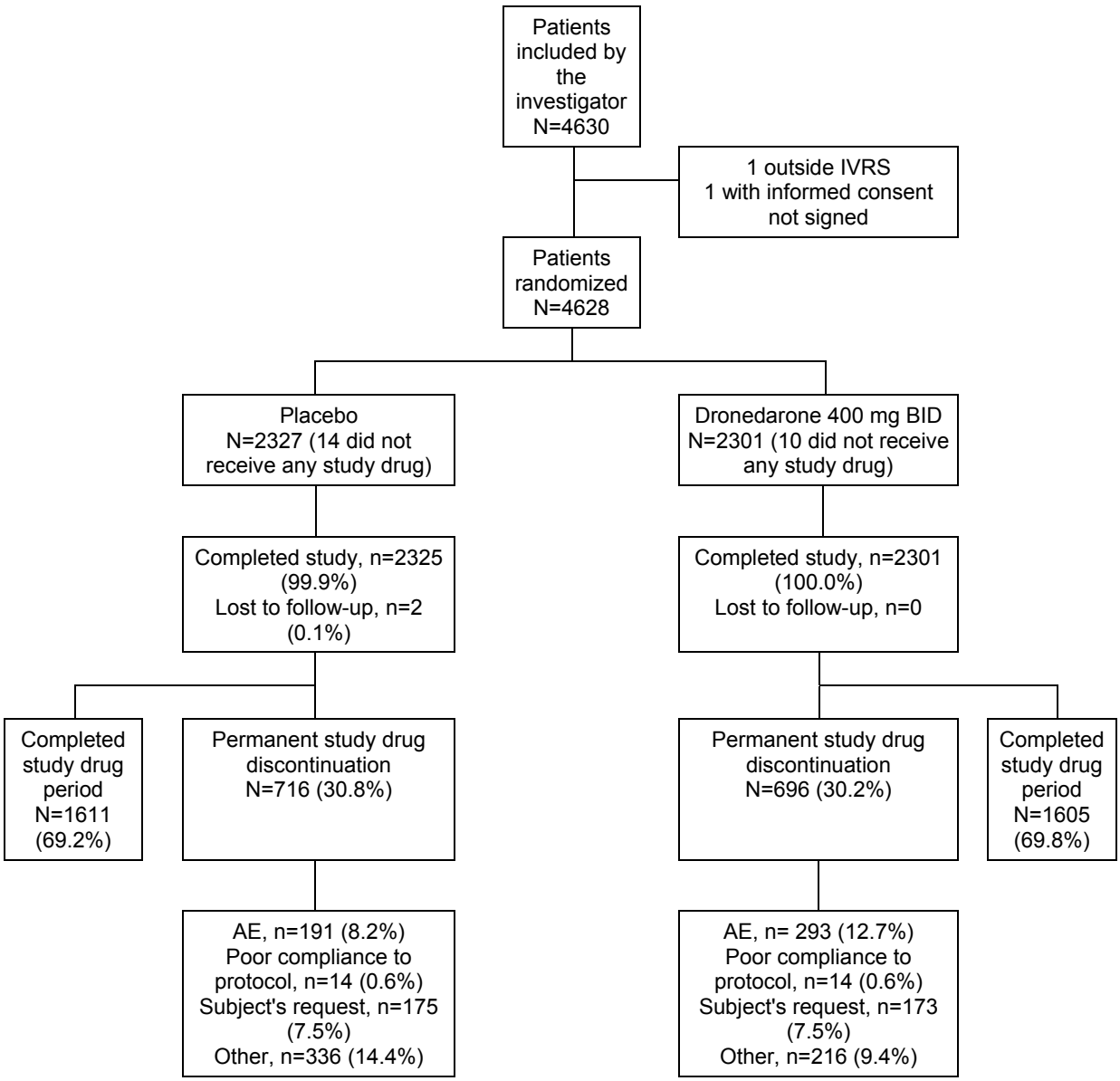
The sample size for the ATHENA trial was calculated from the following assumptions. Based on the pooled results of EURIDIS and ADONIS studies, the 1-year placebo-group cardiovascular hospitalization rate was anticipated to be 20%, and it was anticipated that dronedarone would be associated with a 20% decrease in risk at 1 year. If dronedarone had no favorable or adverse effect on all-cause mortality, the overall decrease in risk for the primary endpoint would be 15% at 1 year. Under these assumptions and considering a 1-year recruitment and a minimum follow-up of 1 year (average follow-up 1.5 years), 970 patients reaching the primary endpoint would give 80% power to test the superiority of dronedarone over placebo (using a 2-sided 5% level). It was originally anticipated that 1850 patients per group (3700 in total) would be needed to evaluate the protocol-specified primary objective. However, during the course of the study, blinded review of the overall death rate revealed a lower than expected risk of mortality, and therefore, the size of the trial was increased to 4300 patients (2150 per group).

4.3 PATIENT ENROLLMENT AND DISPOSITION

A total of 4628 patients were randomized: 2301 in the dronedarone 400 mg BID group and 2327 in the placebo group. Duration of follow-up was similar in both treatment groups, with a mean (SD) of 614.4 (148.3) days in the dronedarone 400 mg BID group and 613.9 (153.7) days in the placebo group. Median duration of follow-up was 650 and 653 days, respectively (ie, 22 months. Two patients in the placebo group and none in the dronedarone group were lost to follow-up. All other patients were followed until the last visit/contact, that occurred on or beyond the common study end date (30 December 2007), unless they died before.

There was no difference in the number of premature permanent treatment discontinuations between groups. More patients in the dronedarone 400 mg BID group discontinued treatment due to AEs (mainly GI). More patients in the placebo group discontinued treatment for "other" reasons, which were mainly related to lack of efficacy (eg, AF/AFL recurrence or need for an alternative antiarrhythmic agent). Exposure to treatment was similar in both groups, with a mean (SD) of 483.3 (253.6) days in the dronedarone 400 mg BID group and 484.9 (248.5) days in the placebo group. Median duration of treatment was 539 and 540 days, respectively. The disposition of patients is summarized in Figure 10.

Figure 10 - Patient disposition – ATHENA



4.4 PATIENT CHARACTERISTICS

The treatment groups were well balanced for demographic characteristics. In both treatment groups, more than 40% of the patients were ≥ 75 years old (Table 38).

Table 38 - Baseline demographic characteristics – All randomized patients (ITT population) - ATHENA

Parameter		Placebo (N=2327)		Dronedarone 400 mg BID (N=2301)	
Age (years)	n	2327		2301	
	Median	73		73	
	Mean	71.7		71.6	
	SD	9.0		8.9	
	Min - Max	33 - 95		23 - 97	
Age (years) [n(%)]	<65	442	(19.0%)	431	(18.7%)
	[65-75[	907	(39.0%)	923	(40.1%)
	>=75	978	(42.0%)	947	(41.2%)
Weight (kg)	n	2327		2301	
	Median	79.2		79.5	
	Mean	80.54		80.35	
	SD	17.78		17.18	
	Min - Max	31.0 – 208.2		33.0 – 168.2	
Gender [n(%)]	Male	1289	(55.4%)	1170	(50.8%)
	Female	1038	(44.6%)	1131	(49.2%)
Race [n(%)]	Caucasian	2072	(89.0%)	2065	(89.7%)
	Black	31	(1.3%)	19	(0.8%)
	Asian/Oriental	154	(6.6%)	150	(6.5%)
	Other	70	(3.0%)	67	(2.9%)
	- Hispanic	56	(80.0%)	48	(71.6%)
	- Latin	12	(17.1%)	13	(19.4%)
	- Other	2	(2.9%)	6	(9.0%)

Medical history at baseline was well balanced between treatment groups as was cardiovascular history at baseline. Approximately 60% of patients in both treatment groups had a history of structural heart disease (Table 39).

Patients could be included either while in sinus rhythm or in AF/AFL. Three quarters of the patients were in sinus rhythm at the time of randomization but had a history of AF/AFL. One quarter was in AF/AFL at the time of randomization as per stratification factor.

Table 39 - Number (%) of patients by cardiovascular history at baseline – All randomized patients (ITT population) - ATHENA

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Hypertension	1996/ 2327 (85.8%)	1999/ 2301 (86.9%)
Structural heart disease[a]	1402/ 2304 (60.9%)	1330/ 2281 (58.3%)
Tachycardia	797/ 2327 (34.3%)	752/ 2301 (32.7%)
Coronary heart disease	728/ 2327 (31.3%)	661/ 2301 (28.7%)
Non-rheumatic valvular heart disease	354/ 2327 (15.2%)	331/ 2301 (14.4%)
Pacemaker	243/ 2327 (10.4%)	214/ 2301 (9.3%)
Lone atrial fibrillation[b]	139/ 2318 (6.0%)	140/ 2297 (6.1%)
Ischemic dilated cardiomyopathy	118/ 2327 (5.1%)	92/ 2301 (4.0%)
Ablation for AF/AFL	106/ 2327 (4.6%)	90/ 2301 (3.9%)
Supra-ventricular tachycardia other than AF/AFL	98/ 2327 (4.2%)	97/ 2301 (4.2%)
Cardiac valve surgery	95/ 2327 (4.1%)	80/ 2301 (3.5%)
Non-ischemic dilated cardiomyopathy	84/ 2327 (3.6%)	82/ 2301 (3.6%)
Hypertrophic cardiomyopathy	50/ 2327 (2.1%)	45/ 2301 (2.0%)
Implanted cardioverter defibrillator	43/ 2327 (1.8%)	42/ 2301 (1.8%)
Rheumatic valvular heart disease	29/ 2327 (1.2%)	51/ 2301 (2.2%)
Sustained ventricular tachycardia[c]	19/ 2327 (0.8%)	21/ 2301 (0.9%)
Congenital heart disease	16/ 2327 (0.7%)	21/ 2301 (0.9%)
Ablation for other reason than AF/AFL	17/ 2327 (0.7%)	12/ 2301 (0.5%)
Ventricular fibrillation	12/ 2327 (0.5%)	12/ 2301 (0.5%)

[a]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 CHF

[b]Lone atrial fibrillation: patients without hypertension and without structural heart disease

[c]VT that lasted more than 30 seconds

Approximately 30% of patients in both treatment groups had CHF, ie, either a LVEF <35% or a left CHF NYHA Class I or greater. About 4% of patients were NYHA Class III at the time of enrollment (Table 40).

Table 40 - Baseline cardiovascular examination – All randomized patients (ITT population) - ATHENA

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
2D-Echocardiogram - Left ventricular ejection fraction (%)		
N	2281	2263
Mean	57.31	57.36
SD	11.25	10.95
LVEF<35%	87 / 2281 (3.8%)	92 / 2263 (4.1%)
LVEF>=35%	2194 / 2281 (96.2%)	2171 / 2263 (95.9%)
Cardiovascular clinical examination		
Patients with left CHF	693 (29.8%)	672 (29.2%)
NYHA classification [n(%)]		
Class I	178 (7.6%)	208 (9.0%)
Class II	406 (17.4%)	373 (16.2%)
Class III	109 (4.7%)	91 (4.0%)
LVEF < 35% and/or NYHA class I or above		
Yes	723 (31.1%)	694 (30.2%)
No	1568 (67.4%)	1578 (68.6%)

The treatment groups were well balanced for baseline medication use (Table 41). Prior and concomitant medications were in line with the current standard of care, with a broad use of rate control drugs including beta blockers, calcium antagonists, digitalis, and appropriate anticoagulation use. About 70% of patients also received ACE inhibitors/AII receptor antagonists.

Table 41 - Baseline medications – All randomized patients (ITT population) - ATHENA

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Beta blocking agents (except sotalol)	1641 (70.5%)	1628 (70.8%)
Calcium antagonists with heart rate lowering effects	307 (13.2%)	331 (14.4%)
Digitalis	308 (13.2%)	321 (14.0%)
Oral anticoagulant	1384 (59.5%)	1403 (61.0%)
Low dose of aspirin (<= 365 mg)	1019 (43.8%)	1018 (44.2%)
Other chronic antiplatelet therapy*	166 (7.1%)	126 (5.5%)
ACE inhibitors or A II receptor antagonists	1602 (68.8%)	1614 (70.1%)
Diuretics	1265 (54.4%)	1227 (53.3%)
Diuretics other than spironolactone	1224 (52.6%)	1187 (51.6%)
Spironolactone	136 (5.8%)	148 (6.4%)
Statins	914 (39.3%)	878 (38.2%)
Statins metabolized by CYP3A4	755 (32.4%)	737 (32.0%)
Statins not metabolized by CYP3A4	166 (7.1%)	147 (6.4%)
Drugs interacting with the creatinine tubular secretion	237 (10.2%)	229 (10.0%)
Moderate inhibitors of CYP3A4	226 (9.7%)	214 (9.3%)
NSAID	123 (5.3%)	114 (5.0%)

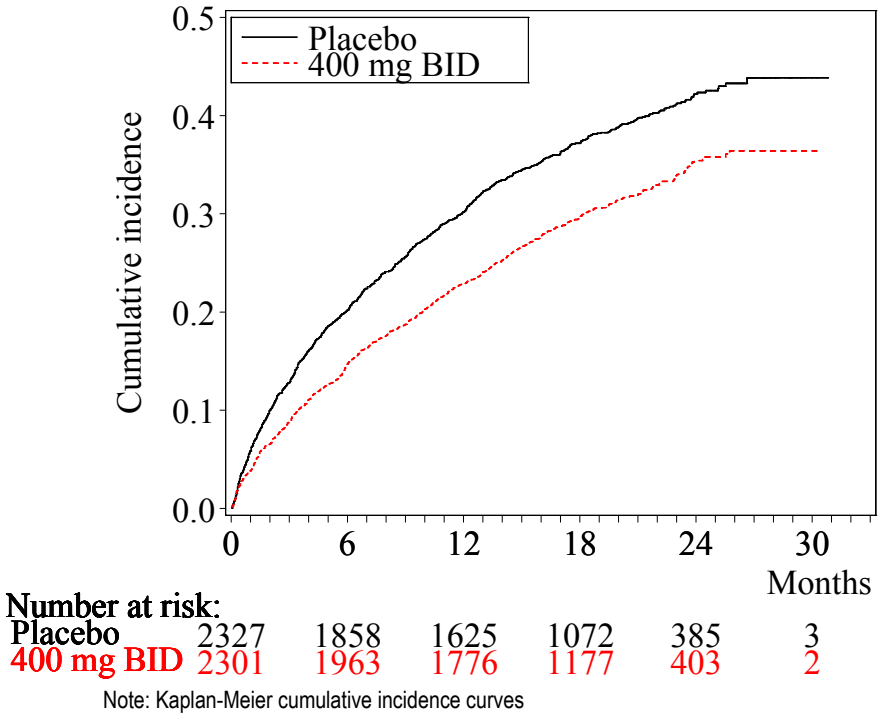
*other than low dose aspirin

4.5 STUDY RESULTS

4.5.1 Primary endpoint: Reduction of risk of cardiovascular hospitalization or all cause death

By ITT, there were 917 cardiovascular hospitalizations or death in the placebo group but only 734 cardiovascular hospitalizations or deaths in the dronedarone group. Treatment with dronedarone 400 mg BID was associated with a 24.2% reduction of the combined risk of cardiovascular hospitalization or all cause-death ($p=2 \times 10^{-8}$; HR [95%CI] 0.758 [0.688 - 0.835]) when compared to placebo (Figure 11).

Figure 11 - Time to first cardiovascular hospitalization or death from any cause: All randomized patients (ITT population) - ATHENA



Note: Kaplan-Meier cumulative incidence curves

4.5.2 Secondary endpoints of ATHENA

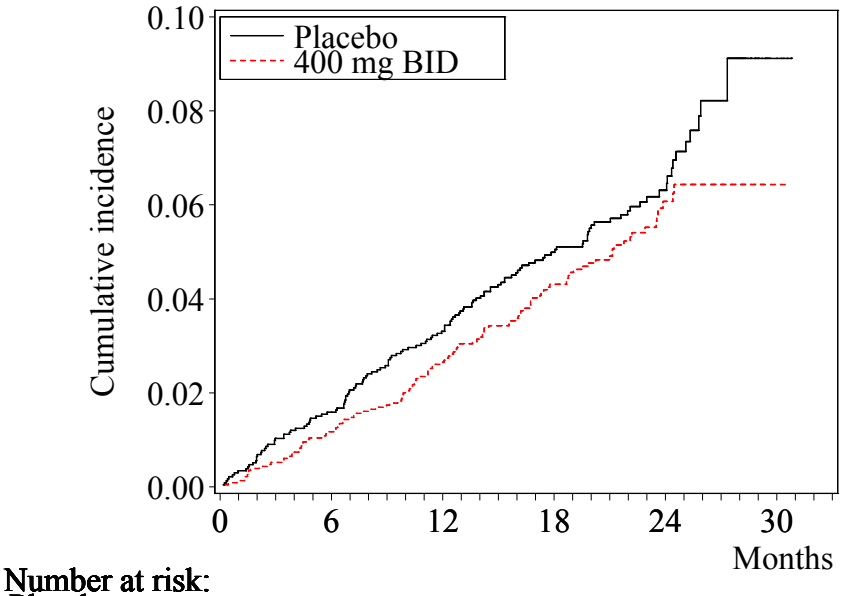
The secondary endpoints are presented in the prespecified hierarchical order described in Section 4.2.

4.5.2.1 Deaths from any cause

In the ATHENA study, there were numerically fewer deaths for any reasons in the dronedarone group (n=116, 5.0%) when compared with the placebo group (n=139, 6.0%). This difference reflected a nonsignificant 15.6% reduction of risk in dronedarone-treated patients (p=0.1758; HR [95%CI] 0.844 [0.660 - 1.080]) (Figure 12). Importantly, the upper bound of the 95% CI of 1.08 effectively excluded any clinically meaningful increase in the risk of death as a result of treatment with dronedarone in the ATHENA population.

Although the analysis of all cause death did not achieve statistical significance, the prespecified subsequent analyses of cardiovascular hospitalizations and cardiovascular death are provided in Section 4.5.2.2 and Section 4.5.2.3 for descriptive purposes.

Figure 12 – Cumulative incidence of death from any cause – All randomized patients (ITT population) - ATHENA



Number at risk:

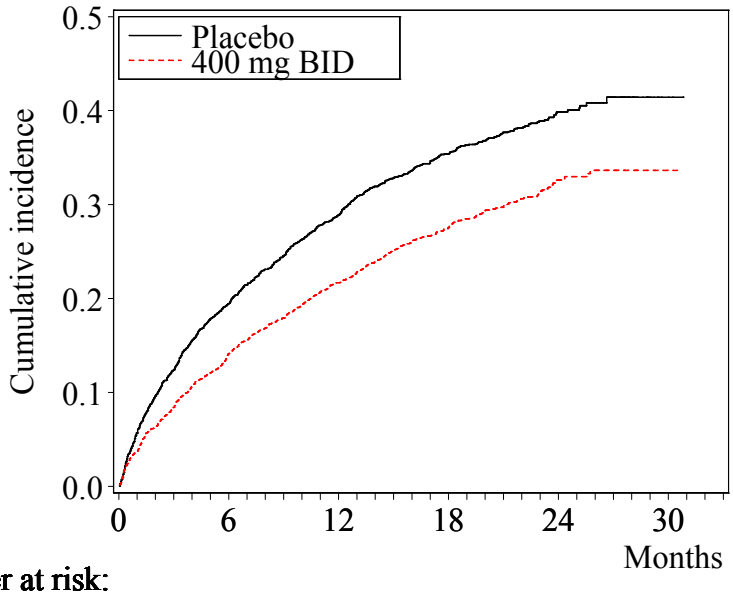
Placebo	2327	2290	2250	1629	636	7
400 mg BID	2301	2274	2240	1593	615	4

Note: Kaplan-Meier cumulative incidence curves

4.5.2.2 Cardiovascular hospitalizations

Dronedarone 400 mg BID reduced time to first cardiovascular hospitalization by 25.5% (HR [95%CI] 0.745 [0.673 - 0.824]) compared to placebo. The reduction in cardiovascular hospitalization (Figure 13) was not accompanied by an increase in non-cardiovascular hospitalization (Figure 14).

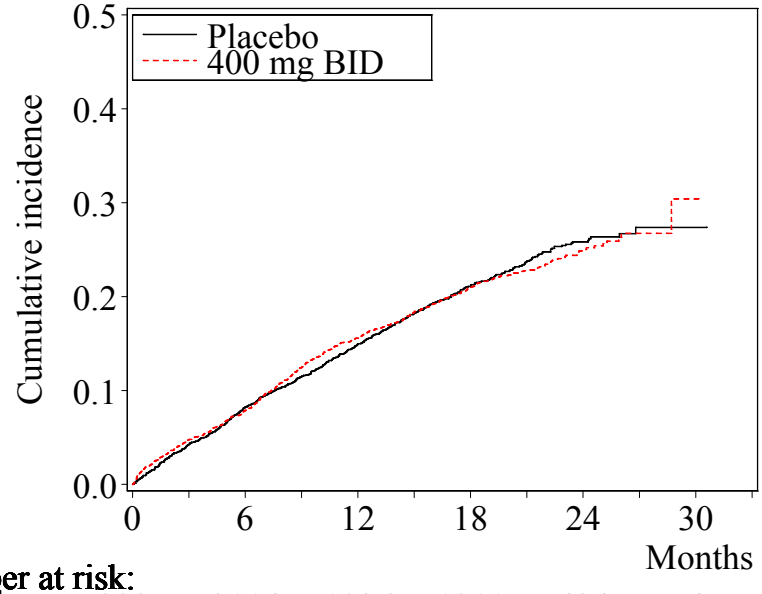
Figure 13 – Time to first cardiovascular hospitalizations - All randomized patients (ITT population) - ATHENA



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

Note: Kaplan-Meier cumulative incidence curves

Figure 14 – Time to first non-cardiovascular hospitalizations - All randomized patients (ITT population)–ATHENA



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

Note: Kaplan-Meier cumulative incidence curves

Descriptive analyses of the endpoint of cardiovascular hospitalizations

Examination and comparison of the relative risk reductions demonstrated that the decrease in the number of cardiovascular hospitalizations seen with dronedarone was due to a reduction in several contributors, including hospitalizations for AF or other supraventricular rhythm disorders, hospitalizations for MI or unstable angina, hospitalizations for stroke or TIA, and hospitalizations for worsening heart failure.

Table 42 - Main reason for first cardiovascular hospitalization - All randomized patients (ITT population) - ATHENA

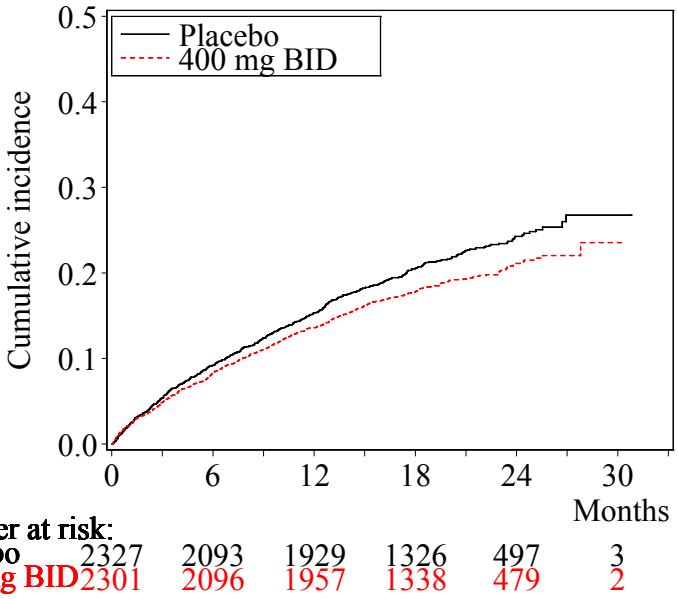
	Placebo (N=2327)		Dronedarone (N=2301)		HR (95% CI)
Any cardiovascular hospitalization	859	(36.9%)	675	(29.3%)	0.745 [0.673 – 0.824]
Atherosclerosis related (if not otherwise specified)	8	(0.3%)	11	(0.5%)	1.282 [0.516 – 3.187]
Myocardial infarction or unstable angina	61	(2.6%)	48	(2.1%)	0.742 [0.508 – 1.083]
Stable angina pectoris or atypical chest pain	41	(1.8%)	45	(2.0%)	1.042 [0.682 – 1.591]
Syncope	24	(1.0%)	21	(0.9%)	0.836 [0.465 – 1.501]
TIA or stroke (except intracranial hemorrhage)	35	(1.5%)	28	(1.2%)	0.751 [0.457 – 1.235]
Atrial fibrillation and other supraventricular rhythm disorders	457	(19.6%)	296	(12.9%)	0.616 [0.532 – 0.713]
Non-fatal cardiac arrest	2	(<0.1%)	3	(0.1%)	1.442 [0.241 – 8.632]
Cardiovascular surgery except cardiac transplantation	23	(1.0%)	21	(0.9%)	0.852 [0.472 – 1.540]
Implantation of a pacemaker, ICD or any other cardiac device	29	(1.2%)	32	(1.4%)	1.041 [0.630 – 1.721]
Transcutaneous coronary, cerebrovascular or peripheral procedure	31	(1.3%)	27	(1.2%)	0.817 [0.488 – 1.369]
Blood pressure related (hypotension, hypertension; except syncope)	21	(0.9%)	21	(0.9%)	0.949 [0.518 – 1.738]
Cardiovascular infection	0	(0%)	4	(0.2%)	NA
Major bleeding (requiring two or more units of blood or any intracranial hemorrhage)	24	(1.0%)	21	(0.9%)	0.816 [0.454 – 1.466]
Pulmonary embolism or deep vein thrombosis	3	(0.1%)	10	(0.4%)	3.159 [0.869 – 11.478]
Worsening heart failure, including pulmonary edema or dyspnea of cardiac origin	92	(4.0%)	78	(3.4%)	0.805 [0.595 – 1.089]
Ventricular extrasystoles	1	(<0.1%)	1	(<0.1%)	0.973 [0.061 – 15.560]
Ventricular tachycardia (non-sustained and sustained)	6	(0.3%)	6	(0.3%)	0.952 [0.307 – 2.951]
Ventricular fibrillation	1	(<0.1%)	1	(<0.1%)	0.943 [0.059 – 15.083]
Other ventricular arrhythmia	0	(0%)	1	(<0.1%)	NA

Note: first cardiovascular hospitalization according to pre specified main reason per the Investigator.

Further evidence that the reduction in the risk of cardiovascular hospitalization was not attributable entirely to a reduction in the risk of hospitalization for supraventricular arrhythmias is provided by an analysis of the effect of dronedarone on the risk of first cardiovascular hospitalization not due to a supraventricular arrhythmia (defined as the time to a first cardiovascular hospitalization not reported as AF or another supraventricular rhythm disorder, with censoring of any prior occurrence of hospitalization for AF). Dronedarone was associated with a 14.5% reduction in the risk of a first cardiovascular hospitalization not due to a

supraventricular arrhythmia (HR [95% CI] 0.855 [0.753 - 0.972]) (Table 43). As noted below, the lower number of non-AF/AFL hospitalizations on dronedarone was mainly due to fewer hospitalizations for worsening heart failure, MI or unstable angina, or stroke or TIA (Table 43; Figure 15).

Figure 15 – Time to first non-AF/AFL cardiovascular hospitalization - All randomized patients (ITT population) - ATHENA



Note: Kaplan-Meier cumulative incidence curves

Table 43 - Main reason for first non-AF/AFL cardiovascular hospitalization - All randomized patients (ITT population) - ATHENA

	Placebo (N=2327)		Dronedarone (N=2301)		HR (95% CI)
Any non-AF cardiovascular hospitalization	511	(22.0%)	438	(19.0%)	0.855 [0.753 – 0.972]
Atherosclerosis related (if not otherwise specified)	10	(0.4%)	11	(0.5%)	1.094 [0.464 – 2.575]
Myocardial infarction or unstable angina	71	(3.1%)	52	(2.3%)	0.730 [0.511 – 1.045]
Stable angina pectoris or atypical chest pain	53	(2.3%)	51	(2.2%)	0.962 [0.655 – 1.412]
Syncope	28	(1.2%)	23	(1.0%)	0.822 [0.474 – 1.427]
TIA or stroke (except intracranial hemorrhage)	43	(1.8%)	32	(1.4%)	0.742 [0.469 – 1.172]
Non-fatal cardiac arrest	2	(<0.1)	3	(0.1%)	1.504 [0.251 – 9.000]
Cardiovascular surgery except cardiac transplantation	28	(1.2%)	24	(1.0%)	0.853 [0.495 – 1.472]
Implantation of a pacemaker, ICD or any other cardiac device	56	(2.4%)	46	(2.0%)	0.819 [0.555 – 1.210]
Transcutaneous coronary, cerebrovascular or peripheral procedure	40	(1.7%)	31	(1.3%)	0.773 [0.484 – 1.235]
Blood pressure (hypotension, hypertension, not syncope)	26	(1.1%)	25	(1.1%)	0.960 [0.554 – 1.662]
Cardiovascular infection	0	(0%)	4	(0.2%)	NA
Major bleeding (requiring two or more units of blood or any intracranial hemorrhage)	28	(1.2%)	27	(1.2%)	0.960 [0.566 – 1.628]
Pulmonary embolism or deep vein thrombosis	4	(0.2%)	11	(0.5%)	2.713 [0.864 – 8.521]
Worsening heart failure, including pulmonary edema or dyspnea of cardiac origin	113	(4.9%)	89	(3.9%)	0.787 [0.596 – 1.039]
Ventricular extrasystoles	1	(<0.1)	1	(<0.1)	1.005 [0.063 – 16.062]
Ventricular tachycardia (non-sustained and sustained)	7	(0.3%)	6	(0.3%)	0.857 [0.288 – 2.550]
Ventricular fibrillation	1	(<0.1)	1	(<0.1)	0.997 [0.062 – 15.940]
Other ventricular arrhythmia	0	(0%)	1	(<0.1)	NA

Further analysis of the hospitalizations for AF or other supraventricular rhythm disorders (Table 44) indicated that the vast majority of these admissions were not related to the need for electrical cardioversion. Among patients experiencing at least one hospitalization for AF/AFL during the on-study period (510 in placebo and 335 in dronedarone 400 mg BID), most were not associated with electrical cardioversions (cardioversion took place in only 138/510 [27.1%] hospitalizations for AF/AFL in the placebo group and in 89/335 [26.6%] hospitalizations for AF/AFL in dronedarone group).

To further characterize the hospitalizations for AF, information was collected regarding the occurrence of electrical cardioversion or the occurrence of heart failure during each hospitalization for AF. The following four subsets were defined: cardioversion without heart failure; cardioversion with heart failure; no cardioversion and no heart failure; and heart failure but no cardioversion.

As shown in Table 44, less than 20% of cardiovascular hospitalizations for AF or other supraventricular rhythm disorder were associated with a cardioversion alone (i.e. with no associated heart failure). As a result, the decision for these hospitalizations was not primarily driven by a motivation to restore sinus rhythm. Instead, a substantial number (approximately 40%) of these hospitalizations were associated with heart failure, even though they were classified primarily as being related to the occurrence of AF or other supraventricular rhythm disorder. Hence, many of the hospitalizations for AF and other supraventricular rhythm disorders were associated with worsening of other serious cardiovascular conditions but were not classified or analyzed under these conditions.

Table 44 - First AF/AFL cardiovascular hospitalization according to presence/absence of CHF and presence/absence of cardioversion at first hospitalization - All randomized patients (ITT population) - ATHENA

	Placebo (N= 2327)	Dronedarone (N= 2301)	Relative risk with 95 % CI	Log-rank p-value
Patients with at least one AF/AFL hospitalization	510 (21.9%)	335 (14.6%)	0.626 [0.546 - 0.719]	<.0001
Patients with cardioversion and no CHF reported during first AF/AFL hospitalization	96 (4.1%)	63 (2.7%)	0.625 [0.455 - 0.859]	0.0035
Patients with cardioversion and CHF reported during first AF/AFL hospitalization	42 (1.8%)	26 (1.1%)	0.592 [0.363 - 0.966]	0.0339
Patients with no cardioversion and no CHF reported during first AF/AFL hospitalization	208 (8.9%)	144 (6.3%)	0.660 [0.533 - 0.816]	0.0001
Patients with no cardioversion and CHF reported during first AF/AFL hospitalization	164 (7.0%)	102 (4.4%)	0.593 [0.463 - 0.760]	<.0001

The effect of dronedarone on the incidence of all (as opposed to first) cardiovascular hospitalizations (Table 45) were consistent with its effect on first cardiovascular hospitalizations. Treatment with dronedarone was associated with a lower number of hospitalizations for AF and other supraventricular rhythm disorders as well as a lower number of non-AF/AFL

hospitalizations (i.e., fewer hospitalizations for worsening heart failure, MI or unstable angina, or stroke or TIA).

Table 45 - Number of all cardiovascular hospitalizations according to pre specified main reason per the investigator - All randomized patients (ITT population) - ATHENA

	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
All cardiovascular hospitalizations	1596	1177
Atrial fibrillation and other supraventricular rhythm disorders	829	514
Worsening CHF, including pulmonary edema or dyspnea of cardiac origin	184	165
Myocardial infarction or unstable angina	113	71
Implantation of a pacemaker, ICD or any other cardiac device	83	65
Stable angina pectoris or atypical chest pain	72	69
TIA or stroke (except intracranial hemorrhage)	64	46
Transcutaneous coronary, cerebrovascular or peripheral procedure	55	52
Cardiovascular surgery except cardiac transplantation	47	38
Major bleeding (requiring two or more units of blood or any intracranial hemorrhage)	33	41
Blood pressure related (hypotension, hypertension; except syncope)	40	30
Syncope	33	32
Atherosclerosis related (if not otherwise specified)	20	17
Pulmonary embolism or deep vein thrombosis	6	15
Ventricular tachycardia (non-sustained and sustained VT)	10	8
Non-fatal cardiac arrest	2	6
Cardiovascular infection	0	5
Ventricular fibrillation	2	1
Ventricular extrasystoles	1	1
Cardiac transplantation	1	0
Other ventricular arrhythmia	0	1

The total number of days in the hospital for any reason during the study was decreased by 18.6% in the dronedarone group during the on-treatment period. This was primarily due to a 26% decrease in the number of days in the hospital for a cardiovascular reason ($p=1.01 \times 10^{-7}$) without an increase in the number of days in the hospital for a noncardiovascular reason. The median duration of each cardiovascular hospitalization was 4 nights in both treatment groups, indicating that the reduction in the number of days in the hospital for a cardiovascular reason was not associated with a longer duration of these hospitalizations. The total duration of days in intensive care units/critical care units (ICU/CCU) was reduced significantly (Table 46).

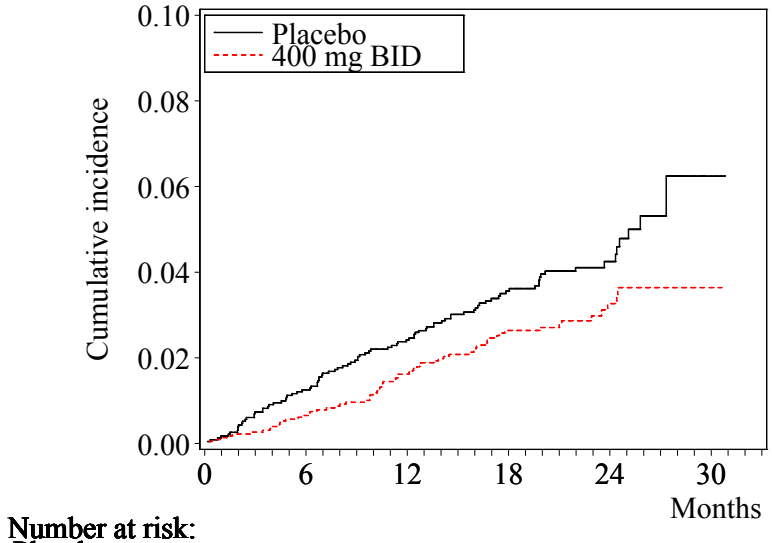
Table 46 - Duration of hospitalization according to the level of care – All randomized patients (ITT population) - ATHENA

	Cardiovascular hospitalization		All-cause hospitalization	
	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)	Placebo (N=2327)	Dronedarone 400 mg BID (N=2301)
Total number of patients with at least one hospitalization	859 (36.9%)	675 (29.3%)	1142 (49.1%)	964(41.9%)
Total number of nights	11344	8316	17670	14217
Median duration of admission	4.0	4.0	5.0	5.0
In ICU/CCU	1488	878	1969	1372
Median	2.0	2.0	2.0	2.0
In step down unit of medium care	2093	1242	2979	1843
Median	3.0	3.0	3.0	3.0
On ward or on floor	7763	6196	12722	11002
Median	5.0	5.0	5.0	5.0

4.5.2.3 Cardiovascular deaths

Treatment with dronedarone was associated with a 30.2% lower risk of cardiovascular death (HR [95%CI] 0.698 [0.509; 0.958]) when compared to placebo (Figure 16).

Figure 16 – Time to cardiovascular death - All randomized patients (ITT population) - ATHENA



Note: Kaplan-Meier cumulative incidence curves

As noted in the table below, the reduction of cardiovascular death with dronedarone 400 mg BID was mainly due to a reduction in the risk of sudden cardiac deaths and stroke (Table 47).

Table 47 - Main reason for cardiovascular death - All randomized patients (ITT population) - ATHENA

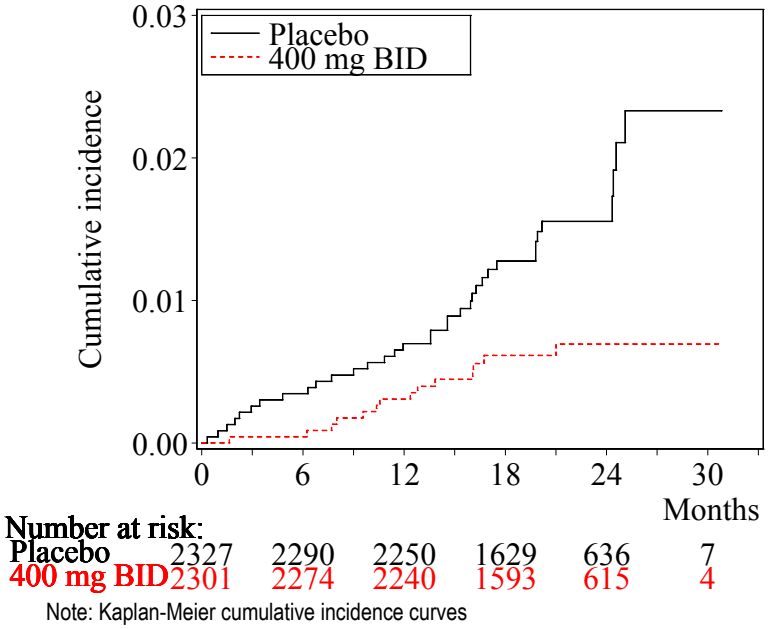
	Placebo (N=2327)		Dronedarone 400 mg BID (N=2301)	
Any cardiovascular death	94	(4.0%)	65	(2.8%)
Aortic dissection/aneurysm	0	(0%)	1	(<0.1%)
CHF	10	(0.4%)	13	(0.6%)
Cardiogenic shock	2	(<0.1%)	5	(0.2%)
Death during a cardiovascular transcutaneous interventional procedure or cardiovascular surgical intervention	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 (eg, 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%)

Note: pre-specified main reason, Investigator's judgment

Descriptive analyses of the endpoint of cardiovascular death

Dronedarone significantly lowered by 59.5% (p=0.0031; HR [95%CI] 0.405 [0.218 - 0.752]) the risk of sudden cardiac deaths compared to placebo, as determined by the site investigator. Kaplan-Meier cumulative curves from randomization to the occurrence of sudden cardiac death are shown below (Figure 17).

Figure 17 – Time to sudden cardiac death – All randomized patients (ITT population) - ATHENA



Note: Kaplan-Meier cumulative incidence curves

In line with the above data on sudden cardiac death, an independent classification of deaths by the Steering Committee (using a modified Hinkle and Thaler classification) confirmed the reduction of cardiac/arrhythmic deaths in the dronedarone group compared with placebo (Table 48). This classification also confirmed that the risk of non-cardiovascular death was not increased by active treatment.

Table 48 - Summary of death classification per Steering Committee - All randomized patients (ITT population) - ATHENA

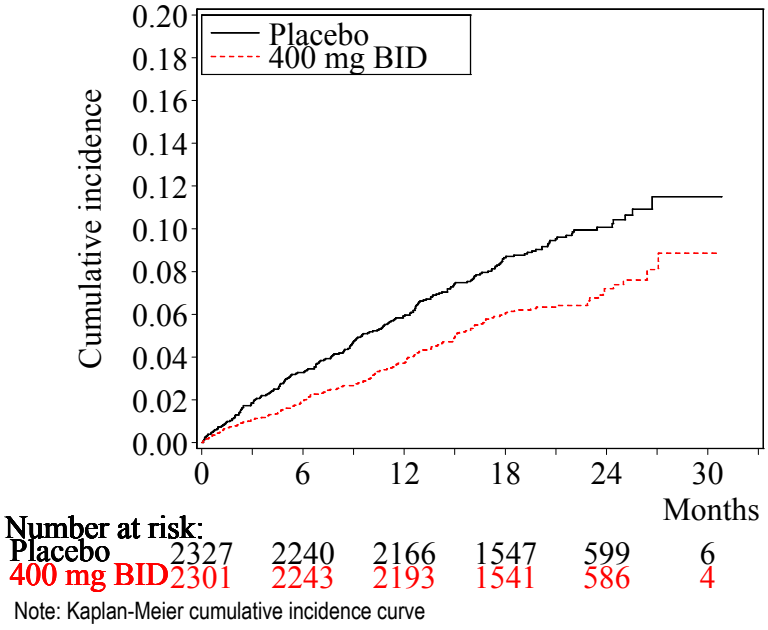
	Placebo (N=2327)		Dronedarone 400 mg BID (N=2301)	
Number of deaths(a)	139	(6.0%)	116	(5.0%)
Cardiac/arrhythmic	48	(2.1%)	26	(1.1%)
Cardiac/nonarrhythmic	18	(0.8%)	17	(0.7%)
Nonvascular	49	(2.1%)	53	(2.3%)
Vascular/non-cardiac	24	(1.0%)	20	(0.9%)

(a) One additional cardiac/non-arrhythmic death was reported in the placebo group beyond the study period during which data were no longer collected systematically

4.5.3 Other exploratory endpoints

In order to further characterize the effects of dronedarone, the commonly used composite endpoint of cardiovascular death, acute coronary syndrome (ACS) or stroke was analyzed using the data from the ATHENA trial. Dronedarone was associated with a 31.9% reduction in the risk of cardiovascular death, ACS or stroke (p=0.0003; HR [95% CI] 0.681 [0.552 - 0.839]) (Figure 18)

Figure 18 – Time to cardiovascular death or stroke or acute coronary syndrome - All randomized patients (ITT population) - ATHENA



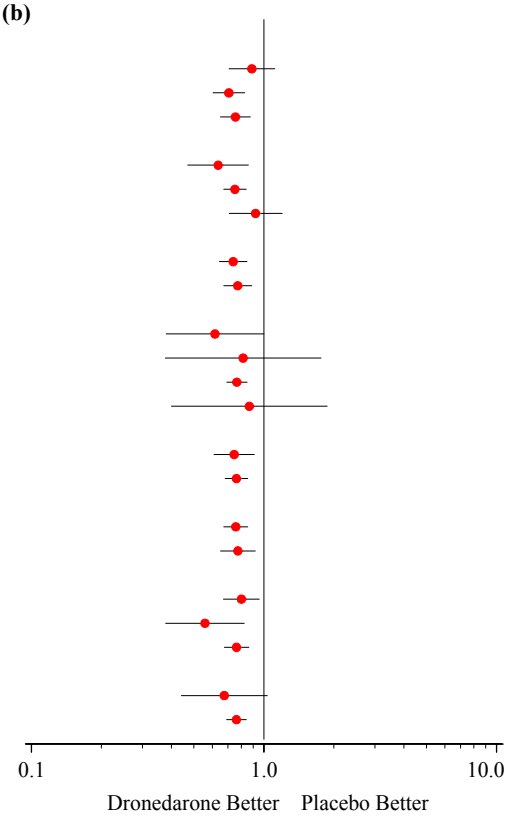
Note: Kaplan-Meier cumulative incidence curve

4.5.4 Effect of Intrinsic and extrinsic factors on the primary endpoint of cardiovascular hospitalization or death from any cause

The effect of dronedarone to reduce the risk of all-cause mortality and cardiovascular hospitalization was seen consistently across all subgroups evaluated, as shown in the figures below (Figure 19, Figure 20).

Figure 19 - Time to first cardiovascular hospitalization or death from any cause according to baseline characteristics - All randomized patients (ITT population) – ATHENA

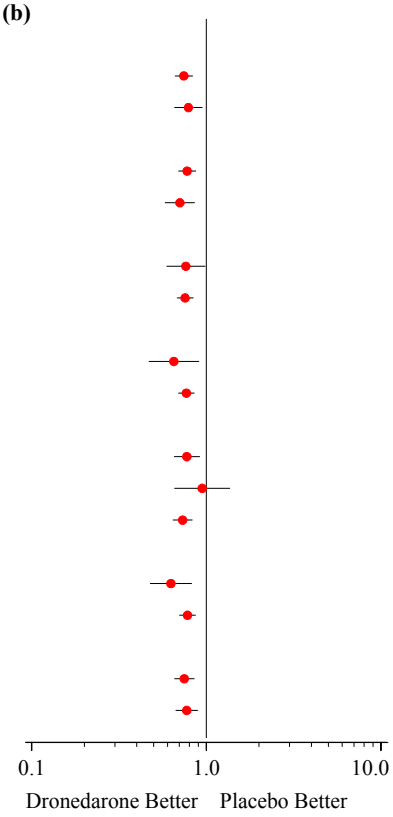
Characteristic	N	RR [95% CI] (a)	P-value (b)
Age (years)			
<65	873	0.89[0.71;1.11]	
[65-75[	1830	0.71[0.60;0.83]	
>=75	1925	0.75[0.65;0.87]	0.27
Weight (Kg)			
<=60	505	0.64[0.47;0.86]	
]60-100[	3571	0.75[0.67;0.84]	
>=100	552	0.92[0.71;1.20]	0.18
Gender			
Male	2459	0.74[0.64;0.85]	
Female	2169	0.77[0.67;0.89]	0.65
Race			
Asian/oriental	304	0.62[0.38;1.00]	
Black	50	0.81[0.38;1.76]	
Caucasian	4137	0.76[0.69;0.85]	
Other	137	0.87[0.40;1.87]	0.82
Presence of AF/AFL			
Yes	1155	0.74[0.61;0.91]	
No	3473	0.76[0.68;0.85]	0.85
Structural Heart Disease			
Yes	2732	0.76[0.67;0.85]	
No	1853	0.77[0.65;0.92]	0.85
NYHA			
Class I or II	1165	0.80[0.67;0.96]	
Class III	200	0.56[0.38;0.82]	
No CHF	3263	0.76[0.68;0.86]	0.22
LVEF(%)			
<35	179	0.68[0.44;1.03]	
>=35	4365	0.76[0.69;0.84]	0.58



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

Figure 20 – Time to first cardiovascular hospitalization or death from any cause according to baseline medications - All randomized patients (ITT population) – ATHENA

Characteristic	N	RR [95% CI] (a)	P-value (b)
ACE or All receptor antagonists			
Yes	3216	0.74[0.66;0.83]	
No	1412	0.79[0.66;0.95]	0.59
Beta blocking agents			
Yes	3269	0.78[0.69;0.87]	
No	1359	0.71[0.58;0.86]	0.41
Digitalis			
Yes	629	0.76[0.59;0.98]	
No	3999	0.76[0.68;0.84]	0.96
Moderate/potent inhibitors of CYP3A4			
Yes	440	0.65[0.47;0.91]	
No	4188	0.77[0.69;0.85]	0.37
Statins			
Only statins metabolized by CYP3A4	1479	0.77[0.66;0.91]	
Other statins	313	0.95[0.66;1.36]	
No statins	2836	0.73[0.64;0.83]	0.39
Calcium antagonists (c)			
Yes	638	0.63[0.48;0.82]	
No	3990	0.78[0.70;0.87]	0.15
Diuretics			
Yes	2492	0.75[0.66;0.85]	
No	2136	0.77[0.67;0.90]	0.76

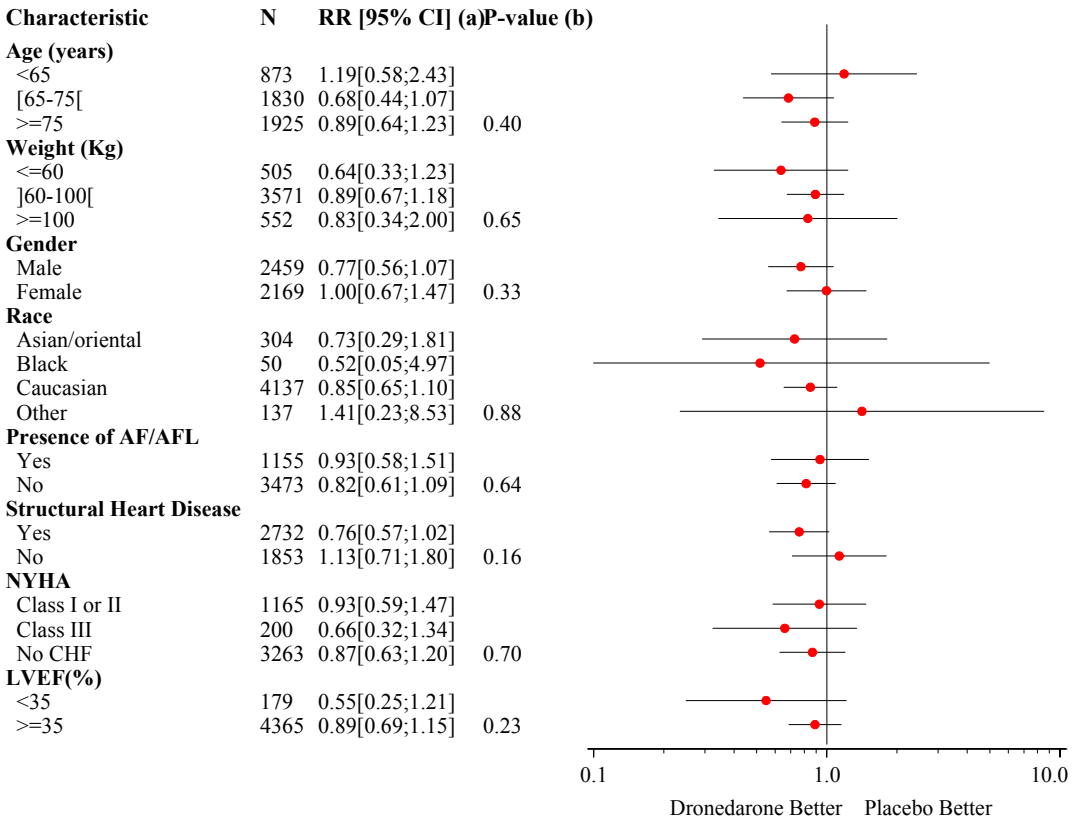


a: Determined from Cox regression model
b: P-value of interaction between baseline medications and treatment based on Cox regression model
c: Calcium antagonists with heart rate lowering effects restricted to diltiazem, verapamil and bepridil

4.5.5 Effect of Intrinsic and extrinsic factors on the endpoint of all deaths

The neutral effect of dronedarone 400 mg BID on the endpoint of death from any cause was consistent in most subgroups (Figure 21 and Figure 22). The significant interaction with diuretics could either be a play of chance or related to different patient profile (i.e. those with diuretics or without) or related to the pharmacological activity of dronedarone on potassium homeostasis. Indeed a small (< 0.1 mmol/L) and stable increase in plasma potassium in patients receiving dronedarone was observed and may interact with the risk of death in patients concomitantly treated with diuretics.

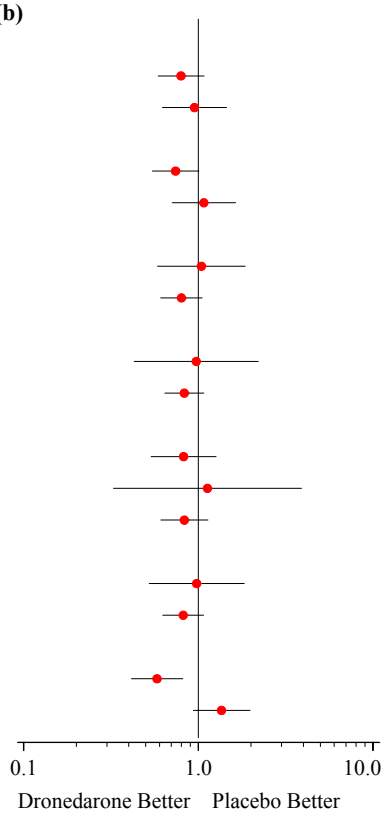
Figure 21 – Time to deaths from any cause according to baseline characteristics – all randomized patients (ITT population) - ATHENA



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

Figure 22 – Time to deaths from any cause according to baseline medications - All randomized patients (ITT population) – ATHENA

Characteristic	N	RR [95% CI] (a)	P-value (b)
ACE or All receptor antagonists			
Yes	3216	0.80[0.59;1.08]	
No	1412	0.95[0.62;1.45]	0.51
Beta blocking agents			
Yes	3269	0.74[0.55;1.01]	
No	1359	1.08[0.71;1.64]	0.16
Digitalis			
Yes	629	1.04[0.58;1.86]	
No	3999	0.80[0.61;1.05]	0.40
Moderate/potent inhibitors of CYP3A4			
Yes	440	0.97[0.43;2.21]	
No	4188	0.83[0.64;1.08]	0.72
Statins			
Only statins metabolized by CYP3A4	1479	0.82[0.54;1.26]	
Other statins	313	1.13[0.33;3.90]	
No statins	2836	0.83[0.61;1.14]	0.88
Calcium antagonists (c)			
Yes	638	0.98[0.52;1.83]	
No	3990	0.82[0.63;1.07]	0.62
Diuretics			
Yes	2492	0.58[0.41;0.81]	
No	2136	1.36[0.93;1.98]	0.00



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

4.6 CLINICAL BENEFIT OF DRONEDARONE IN AF/AFL PATIENTS

As noted earlier in this section, the ATHENA study was designed to accomplish two goals:

1. *To determine if dronedarone's favorable effects in patients with AF/AFL (demonstrated in the DAFNE, EURIDIS, ADONIS and ERATO trials) could result in a long-term reduction in the risk of major adverse cardiovascular events.*

The ATHENA trial demonstrated that long-term treatment of patients with AF/AFL with dronedarone was associated with a highly significant 24% reduction in the combined risk of all-cause mortality or cardiovascular hospitalization, on top of standard care. The reduction in risk was related to a significant reduction in the risk of cardiovascular death and a significant reduction in the risk of cardiovascular hospitalization. This finding confirmed the observations in the EURIDIS and ADONIS trials, which observed that dronedarone was associated with a 20% lower risk of all-cause mortality and cardiovascular hospitalization, as illustrated in Table 49.

Table 49 - Time from randomization to first cardiovascular hospitalization or death, by study

Studies	Number of patients with endpoint Placebo	Dronedarone 400mg BID	Relative Risk [95% CI] (a)
DAFNE	2 (N=49)	2 (N=56)	0.627[0.085;4.621]
EURIDIS	35 (N=201)	54 (N=411)	0.730[0.477;1.118]
ADONIS	29 (N=208)	57 (N=417)	0.890[0.569;1.392]
ERATO	4 (N=89)	3 (N=85)	0.808[0.181;3.612]
ATHENA	917 (N=2327)	734 (N=2301)	0.758[0.688;0.835]
AF/AFL Population (b)	**987 (N=2874)**	**850 (N=3270)**	**0.762[0.694;0.835]**

(a) Determined from Cox regression model
(b) Relative Risk from Cox model is adjusted on study

2. *To clarify and further elucidate the effect of dronedarone on the risk of death in patients likely to receive the drug in clinical practice.*

The increased mortality risk in ANDROMEDA was seen in patients with decompensated heart failure (largely without AF/AFL), and its findings raised concerns that dronedarone might increase the risk of death when used in patients with AF/AFL in clinical practice. The findings of the ATHENA trial (which focused on patients with AF/AFL and excluded patients with decompensated heart failure) indicated with a high degree of confidence that dronedarone did not increase the risk of death. The upper bound of 1.08 effectively excluded a meaningful increase in the risk of death when dronedarone is administered to patients eligible for the ATHENA trial and likely to receive the drug in clinical practice. This upper bound is consistent when looking across all studies in patients with AF/AFL (Table 50).

Table 50 - Time from randomization to death from any cause during the on-study period, by study

Studies	Number of patients with endpoint Placebo	Dronedarone 400mg BID	Relative Risk [95% CI] (a)
DAFNE	0 (N=66)	0 (N=76)	NA
EURIDIS	0 (N=201)	2 (N=411)	NA
ADONIS	5 (N=208)	9 (N=417)	0.794[0.266-2.370]
ERATO	1 (N=89)	1 (N=85)	1.066[0.067-17.046]
ATHENA	139 (N=2311)	116 (N=2293)	0.841[0.657-1.076]
AF/AFL Population (b)	**145 (N=2875)**	**128 (N=3282)**	**0.849[0.668-1.077]**

(a) Determined from Cox regression model
(b) Relative Risk from Cox model is adjusted on studies
Unadjusted analysis

5 DISCUSSION OF ANDROMEDA AND ATHENA

5.1 DISCREPANT RESULTS IN ANDROMEDA AND ATHENA

Sanofi-aventis carried out two large-scale trials to evaluate the long-term effect of dronedarone on the risk of major adverse cardiovascular events. The ANDROMEDA trial reported that dronedarone 400 mg BID was associated with an increased risk of death, which was primarily due to an increased risk of cardiovascular death (primarily due to worsening heart failure). The ATHENA trial reported that dronedarone 400 mg BID was associated with a decreased risk of death and cardiovascular hospitalization, which was due to both a decrease in the risk of cardiovascular hospitalization and a decrease in the risk of cardiovascular death (primarily due to a decrease in the risk of sudden death). It is important to reconcile these highly discrepant results in order to define the appropriate role of dronedarone in the management of patients with AF/AFL.

Sanofi-aventis explored several possibilities in an effort to explain the discrepant results of the ANDROMEDA and ATHENA trials. These possibilities included:

(1) differences in the types of patients;

(2) differences in the use of ACE inhibitors and ARBs; and

(3) differences in the reliability of the findings.

5.2 DIFFERENCES IN THE TYPES OF PATIENTS ENROLLED IN THE ANDROMEDA AND ATHENA TRIALS

The ANDROMEDA and ATHENA trials enrolled two distinctly different types of patients because the two trials had different objectives. Specifically, the ANDROMEDA trial was conceptualized primarily as a study sought to enroll clinically unstable patients with advanced heart disease who might be most likely to demonstrate a proarrhythmic effect of dronedarone (if one existed). Most patients did not have AF/AFL, and thus, most would not be candidates for treatment with the drug if it were to become commercially available for the treatment of AF/AFL. In contrast, the ATHENA trial was conceptualized primarily as an efficacy study and sought to enroll patients likely to receive the drug in clinical practice, i.e., those with recent or current AF/AFL. Although most of the patients in the ATHENA trial had structural heart disease, they were clinically stable.

The presence or absence of clinical stability was the primary feature that distinguished the patients enrolled in the ANDROMEDA and ATHENA trials. Both trials enrolled patients with low ejection fractions or with class II or III heart failure; however, these patients had been hospitalized for worsening heart failure in the ANDROMEDA trial but were stable outpatients in the ATHENA trial. Further analyses (summarized below) indicated that patients with a low ejection fraction or with class III heart failure responded differently in the two trials.

5.2.1 Response of Patients With a Low Ejection Fraction in the ANDROMEDA and ATHENA Trials

A depressed LVEF (approximately < 35%) was present in all 627 patients in the ANDROMEDA trial and in 179 patients (4%) in the ATHENA trial. The following table summarizes the effect of dronedarone on all-cause mortality in this patient subgroup in the two trials.

Table 51 - Overview of death in patients with LVEF in ANDROMEDA and ATHENA

	ANDROMEDA Clinically unstable	ATHENA LVEF < 35% Clinically stable	ATHENA LVEF ≥ 35% Clinically stable
Total number of patients	627	179	4365
Number of patients on placebo	317	87	2194
Number of patients on dronedarone	310	92	2171
Total number of events	37	26	227
Number of events on placebo	12	16	121
Number of events on dronedarone	25	10	106
Relative risk of death (95% CI)	2.13 [1.07-4.25]	0.55 [0.25-1.21]	0.89 [0.69 – 1.15]

- All-cause mortality was significantly increased by dronedarone in the clinically unstable patients with an ejection fraction < 35% enrolled in the ANDROMEDA trial. However, patients with a similar ejection fraction enrolled in the ATHENA trial did not show an increased risk of death with dronedarone; in fact, the upper bound of the 95% CI in this subgroup was 1.21, thereby excluding a clinically meaningful increase in the risk of death in clinically stable patients. Of note, in the ATHENA trial, the effect of dronedarone on the risk of death was similar whether patients had an ejection fraction ≥ 35% or < 35%; indeed, a numerically larger benefit was seen in the subgroup with the most compromised left ventricular function. These findings indicated that clinical stability is a determinant of the effect of dronedarone, but ejection fraction is not a determinant as long as the patients are clinically stable.

5.2.2 Response of Patients With Moderate-to-Severe Symptoms of Heart Failure in the ANDROMEDA and ATHENA Trials

Class III-IV symptoms of heart failure were present at the time of randomization in 337 patients in the ANDROMEDA trial and in 200 patients in the ATHENA trial (all were class III). The following table summarizes the effect of dronedarone on all-cause mortality in this patient subgroup in the two trials.

Table 52 - Overview of death in class III or IV patients in ANDROMEDA and ATHENA

	ANDROMEDA Class III-IV Clinically unstable	ATHENA Class III Clinically stable	ATHENA All Others Clinically stable
Total number of patients	375	200	4428
Number of patients on placebo	196	109	2218
Number of patients on dronedarone	179	91	2210
Total number of events	25	33	222
Number of events on placebo	7	21	118
Number of events on dronedarone	18	12	104
Relative risk of death (95% CI)	2.77 [1.16-6.63]	0.66 [0.32-1.34]	0.89 [0.68 – 1.16]

All-cause mortality was significantly increased by dronedarone in the clinically unstable patients with class III-IV symptoms of heart failure enrolled in the ANDROMEDA trial. However, patients with a similar NYHA functional class enrolled in the ATHENA trial did not show an increased risk of death with dronedarone; in fact, the upper bound of the 95% CI in this subgroup was 1.34, thereby excluding a clinically meaningful increase in the risk of death in clinically stable patients. Of note, in the ATHENA trial, the effect of dronedarone on the risk of death was similar whether patients had class III symptoms or whether they had no or mild (class II) symptoms of heart failure; indeed, a numerically larger benefit was seen in the subgroup with more severe symptoms. These findings indicated that clinical stability is a determinant of the effect of dronedarone, but functional class is not a determinant as long as the patients are clinically stable.

5.2.3 Response of Patients with Atrial Fibrillation in the ANDROMEDA and ATHENA Trials

History of AF was present in 240 patients in the ANDROMEDA trial and 1155 patients in the ATHENA trial were in AF/AFL at randomization. The following table summarizes the effect of dronedarone on all-cause mortality in this patient subgroup in the two trials.

Table 53 - Overview of death in patients with AF in ANDROMEDA and ATHENA

	ANDROMEDA History of Atrial fibrillation Clinically unstable	ATHENA Atrial fibrillation at randomization Clinically stable	ATHENA No atrial fibrillation at randomization Clinically stable
Total number of patients	240	1155	3473
Number of patients on placebo	126	586	1741
Number of patients on dronedarone	114	569	1732
Total number of events	20	67	188
Number of events on placebo	6	35	104
Number of events on dronedarone	14	32	84
Relative risk of death (95% CI)	2.6 [1.0-6.7]	0.935 [0.58 – 1.51]	0.815 [0.61 – 1.09]

All-cause mortality was significantly increased by dronedarone in the clinically unstable patients with history of AF enrolled in the ANDROMEDA trial. However, patients with this arrhythmia at

baseline in the ATHENA trial did not show an increased risk of death with dronedarone. Of note, in the ATHENA trial, the effect of dronedarone on the risk of death was similar whether patients had AF at baseline or not. These findings indicated that clinical stability is a determinant of the effect of dronedarone, but the presence of AF is not a determinant as long as the patients are clinically stable.

5.2.4 Magnitude of Benefit of Dronedarone in High Risk Patients

The presence of moderate-to-severe LVD, moderate-to-severe symptoms of heart failure or AF increases the absolute level of cardiovascular risk. As a result, for any given reduction in relative risk, any drug that reduces cardiovascular morbidity and mortality can be expected to have a greater absolute benefit in high-risk patients than in low-risk patients. This principle applies to the risk reduction seen with dronedarone in the ATHENA trial.

- The absolute benefit on cardiovascular hospitalization or death at 2 years was 7.3% in patients with a LVEF < 35% at randomization versus 6.6% in the remainder of the study population. The absolute benefit on death from any cause at 2 years was 5.7% in patients with a LVEF < 35% versus 0% in the remainder of the study population.

- The absolute benefit on cardiovascular hospitalization or death at 2 years was 20.7% in patients with NYHA class III at randomization versus 6.0% in the remainder of the study population. The absolute benefit on death from any cause at 2 years was 5.9% in patients with NYHA class III at randomization versus -0.1% in the remainder of the study population.

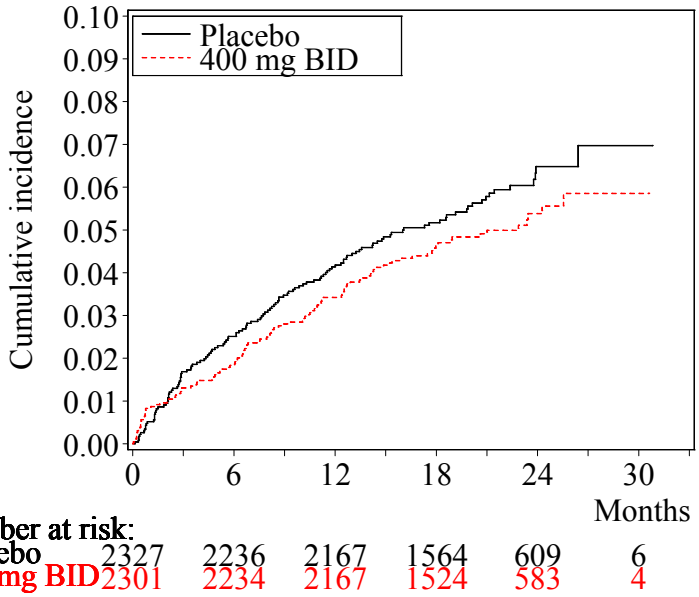
Hence, the exclusion of clinically stable patients with moderate-to-severe LVD or with moderate-to-severe symptoms of heart failure from treatment with dronedarone would prevent its therapeutic application from patients likely to show the greatest absolute benefit from treatment.

5.2.5 Outcome of Dronedarone-Treated Patients Who Develop Clinical Instability During Follow-up

If clinical stability is an important determinant of the effect of dronedarone on morbidity and mortality, it is relevant to evaluate whether dronedarone has an adverse effect on patients who were clinically stable at randomization but who develop clinical instability during follow-up.

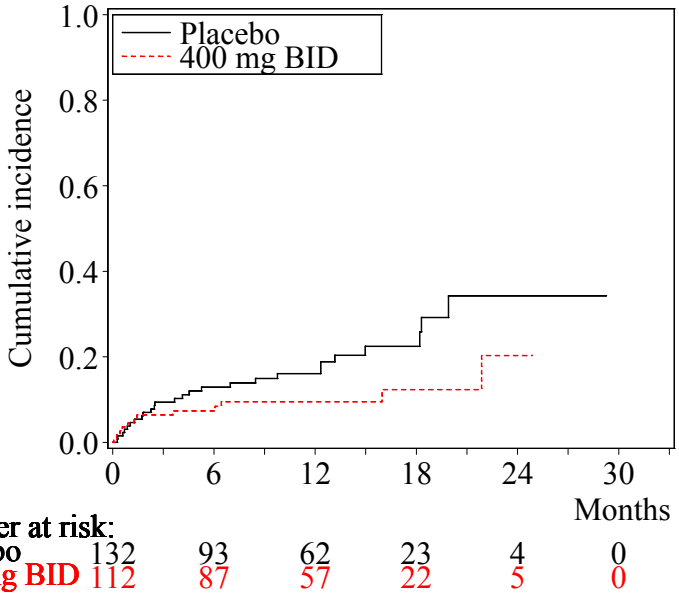
In the ATHENA trial, the risk of hospitalizations for heart failure was less in the dronedarone group when compared to the placebo group. An analysis of time to first hospitalization for heart failure included 132 events in the placebo group versus 112 events in the dronedarone group (HR 95% CI: 0.855 [0.665 - 1.100], Figure 23). The outcome of patients who were hospitalized for heart failure was consistent with the overall study population. Of note, the number of deaths was almost halved in the dronedarone group (12 over 112 patients) versus the placebo group (26 over 132 patients), a trend that approached significance (p=0.0515; HR [95% CI] 0.513 [0.259 - 1.017]) (Figure 24).

Figure 23 – Time to first hospitalization for congestive heart failure - All randomized patients (ITT population) - ATHENA



Note: Kaplan Meier cumulative incidence curves.

Figure 24 – Time to death from any cause from the day of first hospitalization for congestive heart failure up to end of study – All randomized patients (ITT population) with at least one CHF hospitalization – ATHENA

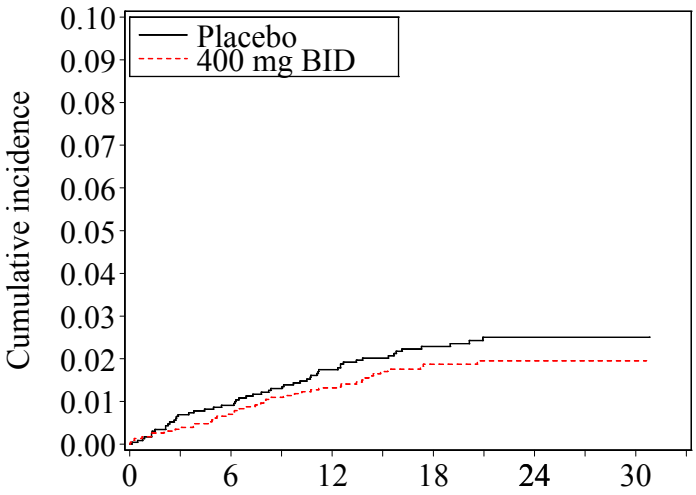


Note: All randomized patients with at least one CHF hospitalization during the study
Note: Kaplan Meier cumulative incidence curves

In addition, some patients in the ATHENA trial developed NYHA class IV symptoms at the time of a cardiovascular hospitalization; the number of such patients was less in the dronedarone group (42 patients) than in the placebo group (54 patients) (HR 95% CI: 0.782 [0.523 - 1.171], Figure 25). The outcome of patients who developed NYHA class IV symptoms was consistent with the

overall study population; the risk of death from any cause following the development of class IV symptoms was similar in the dronedarone and placebo groups (HR 95% CI: 0.869 [0.390; 1.936]).

Figure 25 - Time to first CHF class IV NYHA– All randomized patients, ATHENA (ITT)



Number at risk:						
Placebo	2327	2273	2220	1600	629	7
400 mg BID	2301	2261	2217	1567	607	4

Note: Kaplan-Meier cumulative incidence curves

These analyses suggest that, while treatment should not be initiated in clinically unstable or Class IV patients, dronedarone need not be stopped in patients who deteriorate clinically during the course of follow-up, as reflected by hospitalization for worsening heart failure or by worsening of functional Class to Class IV.

5.3 DIFFERENCES IN THE USE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS IN THE ANDROMEDA AND ATHENA TRIALS

Dronedarone interferes with the secretion of creatinine by the renal tubules, and thus, serum creatinine predictably increases in patients who are started on treatment with dronedarone. In patients with severe heart failure who are routinely being treated with ACE inhibitors or ARBs, physicians might attribute the increase in serum creatinine to treatment with ACE inhibitors or ARBs rather than to dronedarone. As a result, physicians might respond to the increase in serum creatinine by withdrawing treatment with the ACE inhibitor or ARB or by being particularly reluctant to initiate treatment with these drugs. In the ANDROMEDA trial, ACE inhibitors and ARBs were started less frequently and were withdrawn more frequently in patients treated with dronedarone than in patients treated with placebo (see Table 54).

Table 54 - Use of ACE Inhibitors and Angiotensin-II Receptor Blockers in ANDROMEDA

	Placebo (N=317)	Dronedarone (N=310)
Patients with ACE inhibitors or A-II receptor antagonists at baseline	267 (84.2%)	274 (88.4%)
Patients with ACE inhibitors or A-II receptor antagonists at baseline who did not interrupt these treatments	254 (80.1%)	237 (76.5%)
Patients who started ACE inhibitors or A-II receptor antagonists after baseline who did not interrupt these treatments	27 (8.5%)	12 (3.9%)
Patients who discontinued treatment with ACE inhibitors or A-II receptor antagonists	18 (5.7%)	41 (13.2%)
Patients who were never treated with ACE inhibitors or A-II receptor antagonists	18 (5.7%)	20 (6.5%)

This observation raised the possibility that this differential use of ACE inhibitors and ARBs in ANDROMEDA may have contributed to the increased risk of death in patients treated with dronedarone. Consequently, in the ATHENA trial, investigators were advised not to rely on changes in serum creatinine following initiation of treatment with the drug to justify decisions regarding changes in the use of ACE inhibitors or ARBs. It is therefore noteworthy that the use of ACE inhibitors and ARBs was similar in the placebo and dronedarone groups, and no increase in the risk of death was observed.

However, it is unlikely that the differential use of ACE inhibitors and ARBs in the ANDROMEDA study could explain the excess mortality seen in that trial. Meta-analyses of randomized clinical trials suggest that ACE inhibitors and ARBs reduce mortality by 20% in Class II-III symptoms and by 25-40% in patients with Class III-IV symptoms. The magnitude of these effects, when applied to 10-15% of patients in ANDROMEDA who were affected by the differential use of ACE inhibitors and ARBs, cannot explain the greater than 2-fold increase in mortality risk seen in that trial. This may explain why, when the magnitude of the dronedarone mortality effect is adjusted for the use of ACE inhibitors and ARBs, the excess risk of death attributable to dronedarone is not meaningfully altered.

5.4 DIFFERENCES IN THE RELIABILITY OF THE FINDINGS OF THE ANDROMEDA AND ATHENA TRIALS

In the development of new cardiovascular drugs, it has often been observed that a very large reduction in morbidity and mortality in a small study were not replicated in a large and adequately powered Phase III trial. In some cases, this discrepancy could be attributed to differences in the study population, drug dose or study conduct between the two studies. In other circumstances, however, the discrepancy between the Phase II and Phase III trials has been attributed to the inherent unreliability of the results of Phase II trials in assessing the effect of a new treatment on the risk of major clinical events.

Small trials are not designed to definitively evaluate the effect of a drug on the risk of major clinical events. Consequently, these studies generally record small numbers of clinical events

over relatively short periods of time, leading to estimates that are inherently imprecise and thus associated with very wide CIs. The unreliability of the findings of a small study can be emphasized in case of early termination of trial, thereby ensuring that any estimates will be based on a limited number of events and that the trial will be stopped at the point of maximal difference between the two treatments.

Just as large decreases in risk seen in small Phase II studies may not be replicated in large and adequately powered Phase III trials, it is possible that large increases in risk seen in trials with a small number of events may not be replicated in large-scale trials that are specifically designed to evaluate the effect of a drug on the risk of major clinical events. However, this latter possibility is unlikely to be tested in most drug development programs.

Sanofi-aventis decided to carry out the ATHENA trial, even though the ANDROMEDA trial raised substantial concerns about the safety of dronedarone. Of the two major outcome trials with dronedarone, it is apparent that the results of the ATHENA trial provide more reliable estimates of risk than the ANDROMEDA study. The ATHENA trial randomized 4628 patients who experienced 255 deaths over a mean follow-up period of 21 months. In contrast, the ANDROMEDA trial randomized only 627 patients who experienced 37 deaths over a mean follow-up period of only 2 months. Moreover, the ANDROMEDA trial (but not the ATHENA trial) was terminated early, further increasing the unreliability of any observed point estimates of a treatment effect.

The observations raise the possibility that the effects of dronedarone seen in the ANDROMEDA trial might not be replicated even if ANDROMEDA-type patients were evaluated in another trial. However, since the clinical unstable patients enrolled in the ANDROMEDA have not been evaluated in any subsequent trial, this possibility cannot be objectively evaluated.

5.5 CONCLUSIONS ON FINDINGS FROM ANDROMEDA AND ATHENA

The presence or absence of clinical stability was the primary feature that distinguished the patients enrolled in the ANDROMEDA and ATHENA trials. Both trials enrolled patients with low ejection fractions or with Class II or III heart failure; however, these patients had been hospitalized for worsening heart failure in the ANDROMEDA trial but were stable outpatients in the ATHENA trial. Further analyses indicated that patients with a low ejection fraction or with Class III heart failure responded differently in the two trials, supporting the finding that clinical instability was an important determinant of the effect of dronedarone but that ejection fraction or functional Class did not influence response to the drug in clinically stable patients.

These findings are highly relevant, since the exclusion of clinically stable patients with moderate-to-severe LVD or with moderate-to-severe symptoms of heart failure from treatment with dronedarone would effectively prevent its therapeutic application from patients likely to show the greatest absolute benefit from treatment.

Two other explanations for the discrepant results of the ANDROMEDA and ATHENA trials have been considered.

- One hypothesis is that the reluctance to use ACE inhibitors and ARBs in patients who experience an increase in serum creatinine with dronedarone may have deprived dronedarone-treated patients from a highly effective treatment for heart failure. Additional analyses, however, indicate that the differential use of ACE inhibitors and ARBs in a small proportion of patients could not account for the increase in risk observed in the ANDROMEDA trial.
- Another hypothesis is that the results of the ANDROMEDA trial may be unreliable because they were based on the analysis of a small number of events observed over a short period of time in a trial that was terminated early. These conditions are known to lead to highly imprecise estimates. However, since the clinically unstable patients enrolled in the ANDROMEDA have not been evaluated in any subsequent trial, this possibility cannot be objectively evaluated.

These observations suggest that differences in the clinical stability of patients at the time of randomization into the ANDROMEDA and ATHENA trials provides the most likely explanation for the observed differences in the effect of dronedarone in the two studies.

As a consequence, patients with worsening CHF or hospitalized for CHF within the last month should not be initiated with dronedarone and are therefore contraindicated in the proposed labeling.

6 SAFETY EVALUATIONS IN THE POOLED AF/AFL POPULATION

The clinical benefit of dronedarone in patients with AF or AFL is described in the preceding sections, with demonstration of a reduction in mortality and cardiovascular hospitalizations (see Section 4). Of note, in ATHENA (Section 4.2), cardiovascular hospitalizations and/or cardiovascular death were a component of the primary endpoint. They were not to be reported as SAEs so as to prevent dual reporting. Safety data of patients randomized while in unstable hemodynamic condition including NYHA Class IV CHF (ANDROMEDA) have been presented in Section 3.4.3.

The safety profile of dronedarone at the proposed therapeutic dose (400 mg BID), is further discussed in the following sequence:

- General safety profile of dronedarone across the pooled AF/AFL data, including renal and cardiac parameters, GI, skin disorders, with an exploration of intrinsic and extrinsic factors that might influence this profile (Section 6.1).
- Evaluation of cardiac disorders commonly observed with antiarrhythmic drugs, including proarrhythmic potential (Section 6.2).
- Due to chemical similarity with amiodarone, evaluation of specific events known to be associated with amiodarone (Section 6.3).
- Evaluation of drug-drug interactions with dronedarone (pharmacokinetic//pharmacodynamic) and potential for increased rate of specific adverse drug reaction (ADR) (Section 6.4).
- Comparative safety data with amiodarone from DIONYSOS (Section 6.5)

Exposure, disposition, demographics, and baseline characteristics

The safety profile of dronedarone 400 mg BID in patients with AF or AFL is documented from 5 placebo controlled studies: ATHENA, EURIDIS, ADONIS, ERATO and DAFNE. In these studies, a total of 6285 patients were randomized and treated. Of these, 3282 patients were treated with dronedarone 400 mg twice daily, and 2875 received placebo. The mean exposure across studies was 12 months. In ATHENA, the maximum follow-up was 30 months.

The summary of exposure in the pooled AF/AFL population is presented in Table 55 and Table 56.

Table 55 - Summary of study drug exposure – all randomized and treated patients with AF/AFL

	Placebo (N=2875)	Dronedarone 400 mg BID (N=3282)
Patient-years	3383.4	3684.5
Extent of exposure (month)		
n	2875	3282
Mean (SD)	14.1 (8.4)	13.5 (8.3)
Median	14.5	12.7
Min ; Max	0.0 ; 30.1	0.0 ; 29.8

Note: protocols : DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA

Table 56 - Summary of study drug exposure (number of patients, patient-months) according to specific time point – all randomized and treated patients with AF/AFL

	Placebo	Dronedarone 400 mg BID
Up to 3 months		
N	2414	2718
Patient-time	13364	14560
Up to 6 months		
N	2205	2517
Patient-time	6522	7132
Up to 12 months		
N	1812	1998
Patient-time	2965	3151
Up to 18 months		
N	1156	1145
Patient-time	1456	1445
Up to 24 months		
N	430	425
Patient-time	455	451

N corresponds to the cumulative number of patients exposed up to the associated time point
Note: protocols : DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA

A total of 1998 and 425 AF/AFL patients were treated with dronedarone 400 mg twice daily for 1 year and up to 2 years, respectively. Across the dronedarone 400 mg BID and placebo groups, demographic characteristics of the patients with AF or AFL were similar. The majority of patients were ≥65 years old, with a fair representation of elderly patients ≥75 years old (more than a third). Baseline characteristics were representative of the target AF/AFL population and similar in the dronedarone 400 mg BID and placebo groups. Approximately 80% of patients presented with hypertension. More than half of the patients had structural heart disease, and about one-third had coronary heart disease.

6.1 GENERAL SAFETY

The period of treatment emergence of AEs was kept consistent with the approach used in the individual studies. In the pooled AF/AFL population, TEAE were those AEs observed from the first administration of the study drug to the last administration + 10 days.

Common adverse events:

The overall incidence of patients with TEAEs was 70.4% vs. 67.5% in the dronedarone 400 mg bid and placebo groups, respectively. Table 57 presents the incidence of selected common TEAEs (high level terms with an incidence ≥ 2% in either treatment group) in each treatment group with adjusted relative risks (dronedarone 400 mg BID versus placebo) and 95% CIs. These are discussed in detail in subsequent sections.

The number (%) of patients with TEAEs for high level term with an incidence ≥ 2% in either treatment group presented by SOC, high level term (HLT) and preferred term (PT) excluding AF/AFL events in all randomized and treated patients with AF/AFL are summarized in Appendix 10, Table 63.

Table 57 - Incidence of common adverse events with adjusted relative risks (dronedarone 400 mg BID versus placebo) – All randomized and treated patients with AF/AFL

	Placebo (N = 2875)	Dronedarone 400 mg BID (N = 3282)	Relative risks (a) [95% CI] Dronedarone/Placebo
Renal function analyses	47 (1.6%)	158 (4.8%)	2.98[2.15- 4.11]
ECG investigations	18 (0.6%)	49 (1.5%)	2.47[1.47- 4.17]
Rate and rhythm disorders NEC	56 (1.9%)	124 (3.8%)	1.89[1.39- 2.59]
Rashes, eruptions and exanthems NEC	45 (1.6%)	87 (2.7%)	1.77[1.23- 2.54]
Nausea and vomiting symptoms	109 (3.8%)	198 (6.0%)	1.61[1.28- 2.03]
Diarrhoea (excl infective)	170 (5.9%)	295 (9.0%)	1.55[1.29- 1.86]
Asthenic conditions	158 (5.5%)	219 (6.7%)	1.29[1.06- 1.58]

(a) Relative risk from Cox model adjusted on study.
Note: protocols: DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA

Based on the above, in addition to the serum creatinine increase, the main AEs identified with dronedarone are diarrhea, nausea or vomiting, rash, and cardiac effects related to the pharmacodynamic profile of dronedarone (bradycardia, QT prolongation). In addition to those AEs of interest, rare events associated with dronedarone (i.e., with a higher incidence vs. placebo) were: dysgeusia (0.4% vs. <0.1%), ageusia (<0.1% vs. 0.0%), pruritus (1.3% vs. 0.9%), erythema (0.8% vs. 0.4%), eczema (0.6% vs. 0.3%), photosensitivity reaction (0.5% vs. <0.1%), and dermatitis (0.3% vs. 0.1%). These are included as ADRs in the proposed labeling and are not discussed further in this document.

Serious adverse events

The incidence of SAEs was similar across treatment groups (18.0% vs. 19.7% in the dronedarone 400 mg BID and placebo groups respectively). Table 58 summarizes treatment emergent SAEs (HLT ≥2% in at least 1 treatment group) according to Medical Dictionary for Regulatory Activities (MedDRA) organ classes. The SAEs were mainly related to infections and infestations, GI disorders, and cardiac disorders, with similar incidences in the dronedarone 400 mg BID and placebo groups. An overview of cardiovascular hospitalizations, which were reported as efficacy endpoints in the ATHENA study, is presented in Section 4.5.2.2.

Table 58 - Number (%) of patients with serious TEAEs for high level terms with incidence ≥2% in either treatment group (excludes AF/AFL events) – All randomized and treated patients with AF/AFL

MedDRA (10.1) Primary System Organ Class High Level Term(HLT) Preferred Term	Placebo (N=2875)		Dronedarone 400 mg BID (N=3282)	
Any class - Any event	567	(19.7%)	590	(18.0%)
Infections and infestations	137	(4.8%)	120	(3.7%)
HLT: Lower respiratory tract and lung infections	60	(2.1%)	51	(1.6%)
Pneumonia	46	(1.6%)	35	(1.1%)
Lobar pneumonia	7	(0.2%)	5	(0.2%)
Bronchitis	3	(0.1%)	4	(0.1%)
Bronchopneumonia	2	(<0.1)	4	(0.1%)
Bronchiectasis	0	(0%)	2	(<0.1)
Lower respiratory tract infection	1	(<0.1)	1	(<0.1)
Obstructive chronic bronchitis with acute exacerbation	2	(<0.1)	0	(0%)
Infective exacerbation of chronic obstructive airways disease	1	(<0.1)	0	(0%)
Pyothorax	1	(<0.1)	0	(0%)
Gastrointestinal disorders	71	(2.5%)	100	(3.0%)
HLT: Diarrhoea (excl infective)	4	(0.1%)	6	(0.2%)
Diarrhoea	4	(0.1%)	6	(0.2%)
Cardiac disorders	41	(1.4%)	60	(1.8%)
HLT: Heart failures nec	7	(0.2%)	15	(0.5%)
Cardiac failure	3	(0.1%)	8	(0.2%)
Cardiac failure congestive	4	(0.1%)	7	(0.2%)
Cardiogenic shock	0	(0%)	1	(<0.1)

Note: A patient can have AEs in more than one organ class
Note: Due to waiver in the ATHENA study, cardiovascular hospitalizations reported only as efficacy events are not reported in the table
Note: protocols DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA

Adverse events leading to permanent treatment discontinuation

Premature discontinuation due to AEs occurred in 11.8% and 7.7% in the dronedarone and placebo groups, respectively (Table 59). The most common reasons for discontinuation of therapy with dronedarone were GI disorders (3.2 % of patients in dronedarone 400 mg BID versus 1.8% in the placebo group). TEAEs of the GI SOC were the main reason for permanent discontinuation of dronedarone.

Among these events, “diarrhea excluding infective” and “nausea and vomiting symptoms” HLTs were reported most frequently. Gastrointestinal disorders are detailed in subsequent sections. The incidence of patients who permanently discontinued treatment due to TEAEs of the “Investigations” SOC was 2.3% under dronedarone 400 mg BID versus 0.8% under placebo, mostly ECG investigations and, in particular, prolonged QT-interval as described in the section below. The incidence of patients who permanently discontinued treatment due to TEAEs of the skin and subcutaneous tissue SOC was 1.2% in the dronedarone 400 mg BID versus 0.6% in the placebo group. TEAEs of this class are detailed in the section below.

Table 59 - Number (%) of patients with adverse events leading to permanent discontinuation for high level terms with an incidence ≥1% in either treatment group (excludes AF/AFL events) – All randomized and treated patients with AF/AFL

MedDRA (10.1) Primary System Organ Class High Level Term(HLT) Preferred Term	Placebo (N=2875)		Dronedarone 400 mg BID (N=3282)	
Any class - Any event	221	(7.7%)	386	(11.8%)
Gastrointestinal disorders	51	(1.8%)	106	(3.2%)
HLT: Diarrhoea (excl infective)	14	(0.5%)	42	(1.3%)
Diarrhoea	14	(0.5%)	41	(1.2%)
Diarrhoea haemorrhagic	0	(0%)	1	(<0.1)
HLT: Nausea and vomiting symptoms	9	(0.3%)	34	(1.0%)
Nausea	7	(0.2%)	29	(0.9%)
Vomiting	2	(<0.1)	10	(0.3%)
HLT: Gastrointestinal and abdominal pains (excl oral and throat)	6	(0.2%)	9	(0.3%)
Abdominal pain	4	(0.1%)	5	(0.2%)
Abdominal pain upper	2	(<0.1)	4	(0.1%)
Investigations	24	(0.8%)	76	(2.3%)
HLT: ECG investigations	14	(0.5%)	37	(1.1%)
Electrocardiogram QT prolonged	12	(0.4%)	36	(1.1%)
Electrocardiogram PR prolongation	0	(0%)	1	(<0.1)
Electrocardiogram abnormal	1	(<0.1)	0	(0%)
Electrocardiogram RR interval prolonged	1	(<0.1)	0	(0%)
HLT: Physical examination procedures	0	(0%)	2	(<0.1)
Weight decreased	0	(0%)	1	(<0.1)
Weight increased	0	(0%)	1	(<0.1)
Skin and subcutaneous tissue disorders	16	(0.6%)	40	(1.2%)
HLT: Pruritus nec	3	(0.1%)	6	(0.2%)
Pruritus	2	(<0.1)	3	(<0.1)
Rash pruritic	1	(<0.1)	3	(<0.1)
General disorders and administration site conditions	28	(1.0%)	38	(1.2%)
HLT: Asthenic conditions	16	(0.6%)	23	(0.7%)
Fatigue	6	(0.2%)	14	(0.4%)
Asthenia	6	(0.2%)	9	(0.3%)
Malaise	4	(0.1%)	1	(<0.1)
Nervous system disorders	24	(0.8%)	39	(1.2%)
HLT: Neurological signs and symptoms nec	8	(0.3%)	20	(0.6%)
Dizziness	7	(0.2%)	17	(0.5%)
Presyncope	1	(<0.1)	3	(<0.1)
Cardiac disorders	22	(0.8%)	37	(1.1%)
HLT: Ventricular arrhythmias and cardiac arrest	3	(0.1%)	8	(0.2%)
Ventricular extrasystoles	0	(0%)	4	(0.1%)
Ventricular tachycardia	1	(<0.1)	2	(<0.1)
Torsade de pointes	0	(0%)	1	(<0.1)
Ventricular fibrillation	0	(0%)	1	(<0.1)
Cardiac arrest	1	(<0.1)	0	(0%)
Ventricular arrhythmia	1	(<0.1)	0	(0%)
HLT: Heart failures nec	2	(<0.1)	5	(0.2%)
Cardiac failure	0	(0%)	4	(0.1%)
Cardiac failure congestive	2	(<0.1)	1	(<0.1)
Infections and infestations	7	(0.2%)	12	(0.4%)
HLT: Abdominal and gastrointestinal infections	1	(<0.1)	2	(<0.1)
Gastroenteritis	0	(0%)	2	(<0.1)
Abdominal abscess	1	(<0.1)	0	(0%)
Immune system disorders	0	(0%)	2	(<0.1)
HLT: Anaphylactic responses	0	(0%)	1	(<0.1)
Anaphylactic reaction	0	(0%)	1	(<0.1)
Anaphylactic shock	0	(0%)	0	(0%)

Note: A patient can have AEs in more than one organ class.

Note: In the ATHENA study, cardiovascular hospitalizations reported only as efficacy events are not reported in the table

Note: protocols DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA

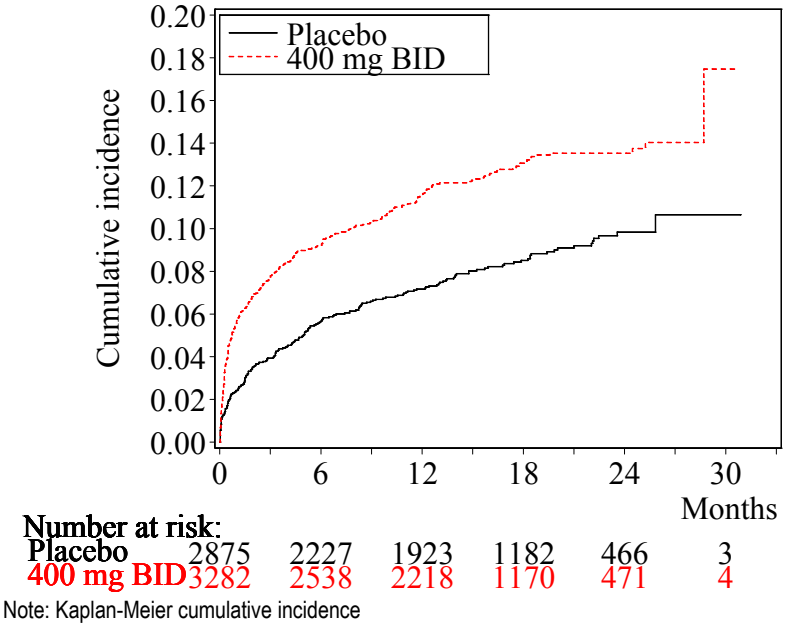
The analysis of time to first AE leading to permanent premature study drug discontinuation is presented in Table 60. As shown in Figure 26, the discontinuations due to an AE under dronedarone occurred early after treatment initiation.

Table 60 - Time to first adverse event leading to premature permanent study drug discontinuation during the on-treatment period – All randomized and treated patients with AF/AFL

	Placebo (N= 2875)	Dronedarone 400mg BID (N= 3282)
Number of events, n	221	386
Median survival (95% CI) (days)	NA	NA
Cumulative incidence of events at 6 months [95% CI]	5.7% [4.77% ; 6.53%]	9.2% [8.21% ; 10.24%]
Cumulative incidence of events at 1 year [95% CI]	7.2% [6.16% ; 8.17%]	11.6% [10.45% ; 12.75%]
Cumulative incidence of events at 2 years [95% CI]	9.8% [8.49% ; 11.17%]	13.5% [12.22% ; 14.84%]
Log-rank test p-value	63E-9	
Relative Risk with 95% CI (a)	1.589 [1.345 ; 1.877]	

(a) Determined from Cox regression model, adjusted on studies
Note: protocols : DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA

Figure 26 - Time to first adverse event leading to premature study drug discontinuation during the on-treatment period – All randomized and treated patients with AF/AFL



Note: Kaplan-Meier cumulative incidence

Intrinsic and extrinsic factors

In the AF/AFL population, interaction was tested between treatment effect (placebo or dronedarone 400 mg BID) and baseline prognostic factors (age, weight, gender, gender and age combined, race, hypertension, structural heart disease, LVEF <35% or NYHA Class I or above, LVEF, NYHA Class, diabetes, and creatinine clearance) for any TEAE, any SAEs, any AEs leading to premature permanent study drug discontinuation, GI SOC and skin and subcutaneous tissue SOC.

The testing of interactions between treatment and any of the intrinsic or extrinsic factors on the incidence of TEAEs and serious TEAEs did not suggest any excess of events in a particular subgroup. There was no interaction identified for TEAEs leading to premature permanent study drug discontinuation in most of the subgroups, with the exception of patients with heart failure who discontinued more frequently; the main reasons for discontinuation were GI disorders (diarrhea, nausea, and vomiting) and ECG investigations (QT prolonged), consistent with the overall AF/AFL population.

No interaction was identified between treatment and any of the extrinsic factors tested on the incidence of TEAEs, except for TEAEs leading to premature permanent study drug discontinuation, which were more frequent in patients receiving ACE inhibitors or AII receptor antagonists. The main reasons for discontinuation in this subgroup were consistent with the overall AF/AFL population: GI disorders (diarrhea, nausea, and vomiting) and ECG investigations (QT prolonged).

Safety parameters of interest

Renal parameters

The incidence of 'renal function analyses' TEAEs was greater in the dronedarone group (4.8%) compared to the placebo (1.6%) group, driven by reporting of blood creatinine increase. This is explained by the previously described effects of dronedarone on serum creatinine (Section 3.2).

In the pooled AF/AFL patient population, the number of patients having a continuous increase ≥10% from baseline until Day 5 (ie, not reaching a plateau) was higher in the dronedarone 400 mg BID (50.9%) group compared to the placebo group (20.6%). However, the number of patients with a further increase of creatinine after Day 5 was similar in both groups (40.8% on dronedarone vs. 47.4% on placebo). The higher rate of "blood creatinine increase" TEAEs reported in the dronedarone 400 mg BID (4.0% vs. 1.1%) was not associated with a parallel "increase in blood urea" TEAEs (1.0% vs. 0.6%), and is consistent with the mechanism described in Section 3.2.

Renal TEAEs were similar in incidence in the dronedarone (4.3%) and placebo (4.6%) groups. Acute renal failure was reported in 19 patients in the dronedarone group and in 7 patients in the placebo group. In the dronedarone group, 16 patients recovered without permanent study drug discontinuation, 1 patient recovered after permanent study drug discontinuation but with a concomitant diagnosis of myeloma, and 2 patients did not permanently discontinue study drug and died: 1 from CHF as the primary cause with low ejection fraction (35%) at baseline associated with a history of chronic renal failure and discontinued treatment with ACE inhibitors more than 6 months before death; and the second from "acute renal failure" who underwent dialysis. In the placebo group, 5 patients recovered without permanent study drug discontinuation, 1 patient recovered after permanent study drug discontinuation, and 1 patient did not permanently discontinue study drug and died from "exacerbation of chronic obstructive pulmonary disease." Since most cases in the dronedarone group recovered without permanent study drug discontinuation, the imbalance in reported cases of "acute renal failure" is likely to be mostly related to the effect of dronedarone on creatinine secretion and not to direct drug toxicity

Gastrointestinal disorders

Gastrointestinal disorders were reported in 24.1% of patients in the dronedarone 400 mg BID compared to 20.8% in the placebo group (with a difference between groups occurring early after treatment initiation). Among these, diarrhea was reported in 9.0% versus 5.9% and nausea and vomiting in 6.0% versus 3.8% in the dronedarone 400 mg BID and the placebo groups, respectively. Gastrointestinal disorders AEs (mostly "Diarrhea excluding infective" and "nausea and vomiting symptoms") were the main cause of permanent discontinuation of study drug in patients with AF or AFL.

Skin disorders

Skin and subcutaneous tissue disorders were reported in 10.2% and 7.4% in the dronedarone 400 mg BID and placebo groups, respectively. Rashes, eruptions and exanthemas were the only TEAEs reported with an incidence ≥ 2% in either treatment group (2.7% of patients in the dronedarone 400 mg BID group compared with 1.6% of patients in the placebo group). However, the majority of them were non-serious AEs and did not lead to permanent discontinuation of study drug in patients with AF or AFL .The incidence of severe skin events such as bullous conditions was very low and equal in the two treatment groups (<0.1%), with no reported case of toxic epidermal necrolysis or Stevens-Johnson syndrome.

6.2 CARDIAC DISORDERS INCLUDING PRO-ARRHYTHMIC POTENTIAL ASSESSMENT

Rate and rhythm disorders

Cardiac disorders (rate and rhythm disorders) were reported in 11.7% and 9.8% of patients in the dronedarone 400 mg BID and placebo groups, respectively. The difference was mainly due to bradycardia, which was reported in 3.3% versus 1.3%, consistent with the known pharmacodynamic effects of dronedarone. In the HLT category of heart failure (including cardiac failure, cardiac failure congestive, cardiac failure chronic, cardiogenic shock, and cardiopulmonary failure) events were reported similarly for the dronedarone 400 mg BID group (2.5%) and placebo (2.2%).

In addition, ventricular arrhythmia was at a low and similar incidence in both groups (0.8% versus 0.7%). A single case of TdP was reported after 10 months of treatment with dronedarone 400 mg BID, in a 67-year-old female patient. This patient had multiple cardiac diseases and other risk factors for TdP: prolonged QT interval at baseline, severe bradycardia, likely to be a sick sinus syndrome, and potassium level in the low range. More than 2 months after dronedarone discontinuation, episodes of VT were documented by the implantable cardioverter defibrillator.

Evaluation of ECG parameters

ECG-related AEs were reported with an incidence of 1.5% and 0.6% in the dronedarone 400 mg BID and the placebo groups, respectively. QT prolongation was reported in 1.3% of patients in the dronedarone 400 mg BID group and 0.5% in the placebo group, as expected due to the pharmacodynamic properties of dronedarone.

The effects of dronedarone 400 mg BID on ECG parameters were moderate across clinical trials. As expected from the pharmacodynamic properties of dronedarone, the incidences of low heart rate (≤ 50 bpm and decrease ≥ 15 bpm versus baseline [dronedarone 400 mg BID: 10.6%; placebo: 4.5%]) and QTc (Bazett correction) prolonged (>450 ms in males; >470 ms in females [dronedarone 400 mg BID: 27.6%; placebo: 18.7%]) was higher in the dronedarone 400 mg BID group when compared with the placebo group. On average, an increase in the mean QTcB of 10 msec was observed, consistent with the Vaughan-Williams Class III effect of dronedarone. An increase of about 2 msec was observed on the mean QRS-interval consistent with the Class I effect.

A decrease in heart rate of about -3 bpm and an increase in the PR-interval of about +8 msec were observed. These effects are consistent with the calcium antagonist and antiadrenergic properties of dronedarone.

The available data confirm that the pro-arrhythmic potential of dronedarone is very low.

6.3 EVALUATION OF ADVERSE EVENTS ASSOCIATED WITH CHEMICALLY RELATED COMPOUND (AMIODARONE)

An evaluation of AEs known to be associated with amiodarone showed that, unlike amiodarone, dronedarone did not reveal endocrinological, hepatobiliary, neurological or pulmonary toxicity in the pooled AF/AFL population.

Thyroid: Thyroid hormones were monitored in three studies in patients with AF or AFL: DAFNE, EURIDIS, and ADONIS. The percentage of patients with an increase and/or decrease outside of normal range in free triiodothyronine (FT3), free thyroxine (FT4), or TSH was similar in the dronedarone 400 mg BID group and the placebo group, with no evidence of a safety signal for thyroid toxicity. Specific thyroid AEs commonly observed with amiodarone were assessed for the pooled data from the five AF/AFL studies using a combination of selected events including investigation abnormalities. Similar incidence was observed in the dronedarone 400 mg BID (1.5%) and the placebo groups (1.3%).

Liver:

- Laboratory evaluation:

Liver enzymes were measured in 4 studies in AF/AFL patients: DAFNE, EURIDIS, ADONIS, and ERATO (enzymes not collected in ATHENA). Overall, the percentages of patients with abnormalities in laboratory hepatic tests (ALT or AST >2 ULN, >3 ULN, or >5 ULN; or ALP >1.5 ULN; or total bilirubin ≥ 34 μmol/L) were similar in the dronedarone 400 mg BID and placebo groups. At the proposed therapeutic dose of dronedarone (400 mg BID), the mean changes from baseline in ALT and AST were similar to those observed in the placebo group.

Table 59 - Number (%) of patients with at least one postbaseline PCSA in liver function (AST, ALT) up to the end of treatment + 10 days - all randomized and treated patients with AF/AFL

Period	Parameter	PCSA criteria	Placebo (N=564)	Dronedarone 400 mg BID (N=989)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)
On-treatment	ALT (SGPT-ALAT)	> 2 ULN	34/559 (6.1%)	57/979(5.8%)	16/66(24.2%)	6/56(10.7%)
		> 3 ULN	11/559 (2.0%)	24/979(2.5%)	3/66(4.5%)	2/56(3.6%)
		> 5 ULN	5/559 (0.9%)	8/979(0.8%)	1/66(1.5%)	0/56(0.0%)
	AST (SGOT-ASAT)	> 2 ULN	16/558 (2.9%)	24/979(2.5%)	1/66(1.5%)	1/56(1.8%)
		> 3 ULN	6/558 (1.1%)	10/979(1.0%)	1/66(1.5%)	0/56(0.0%)
		> 5 ULN	0/558 (0.0%)	5/979(0.5%)	0/66(0.0%)	0/56(0.0%)

- Adverse events:

The overall incidences of TEAEs, serious TEAEs and TEAEs leading to permanent study drug discontinuation reported in the MedDRA SOC "hepatobiliary disorders" and in the HLT "liver function analyses" were similar in the dronedarone 400 mg BID (1.6%) and the placebo (1.5%) groups. Among the hepatobiliary disorders in the "hepatocellular damage and hepatitis" HLT, two cases were reported as SAEs with an outcome of death, one case of hepatitis toxic (preferred term) in the dronedarone 400 mg BID group with ALT >3ULN and Total Bilirubin >2ULN suggestive of autoimmune acute hepatitis, and one case of cytolytic hepatitis in a context of severe cardiac disease was reported in the placebo group. Pooled data from five AF/AFL studies showed similar incidence of specific hepatic events included in the SOC 'Hepatobiliary disorders' and the standard MedDRA query (SMQ) "Liver related investigation signs and symptoms" in the dronedarone 400 mg BID (2.9%) and the placebo (2.5%) groups.

Ophthalmic: In the DAFNE study, ophthalmologic examinations by slit lamp were conducted at screening, Day 90, and Day 180, in order to verify the absence of corneal deposits. There was no dose response and no difference between treatment groups for ophthalmic tolerability. Based on data pooled from all AF/AFL studies, the incidence of AEs in the eye disorders SOC did not differ between dronedarone 400 mg BID (4.4%) and placebo (4.2%). Corneal deposits were reported in very few patients (1/3282 patients in the dronedarone 400 mg BID group and 2/2875 patients in the placebo group).

Pulmonary: In the AF/AFL population, the frequency of severe pulmonary events included in the SMQ "interstitial lung disease" was similar (0.2 % in both dronedarone 400 mg BID and placebo groups). One reported case of "Interstitial lung disease" with fatal outcome in a 71-year-old female patient was assessed as possibly related to dronedarone by the investigator. This

patient had been treated with amiodarone for more than 2 years prior to starting dronedarone. About 9 months after dronedarone initiation, interstitial inflammation with organizing pneumonia (bronchiolitis obliterans organizing pneumonia-type) was diagnosed based on transbronchial biopsy. Despite treatment with corticoids, the patient died 1 month later. Possible alternative causes included infectious organizing pneumonia (most likely), cryptogenic, or connective tissue disease.

Neurological: Specific neurological AEs known to be associated with amiodarone were assessed for the pooled data from five AF/AFL studies using a combination of selected events. Similar overall incidence was observed in the dronedarone 400 mg BID (2.7%) and the placebo (2.5%) groups. Peripheral neuropathies were reported at a low incidence in both the dronedarone 400 mg BID and the placebo groups. Vision disorders were reported with the incidence of 1.3% and 1.1% in the dronedarone 400 mg BID and the placebo groups. Of note, the incidence of vision blurred was 0.6% in both treatment groups. No case of optic neuritis was reported in the dronedarone 400 mg BID versus 1 case in the placebo group.

Skin and subcutaneous tissue disorders: Specific skin and subcutaneous tissues disorders known to be associated with amiodarone were observed with a higher incidence in the dronedarone 400 mg BID group compared with the placebo group (4.0% vs. 2.1%) and were mainly rash (2.2% vs. 1.5%), photosensitivity reaction (0.5% vs. <0.1%), and erythema (0.4% vs. 0.2%).

6.4 DRUG-DRUG INTERACTIONS

The clinical implication of the drug-drug interaction potential (pharmacokinetic and pharmacodynamic) of dronedarone was thoroughly evaluated in the dronedarone development program as described in Section 3.1.3. Specific attention was given to medications commonly prescribed in the target population of patients with AF/AFL. A significant proportion of patients with AF or AFL received beta-blockers (65.7% placebo, 63.7% dronedarone 400 mg BID), oral anticoagulants (62.4% placebo, 62.9% dronedarone 400 mg BID), statins metabolized by CYP3A4 (29.3% placebo, 28.2% dronedarone 400 mg BID), digitalis (15.4% placebo, 16.0% dronedarone 400 mg BID), or calcium antagonists with heart-rate-lowering effects (12.9% placebo, 13.9% dronedarone 400 mg BID). Specific safety analyses of events known to occur with coadministered drugs both at baseline and during treatment were performed. Results of both analyses were consistent.

During the course of the clinical development, specific instructions were given to Investigators to manage the use of concomitant drugs likely to interact with dronedarone. These instructions are reflected in the proposed labeling.

Drug-drug interactions were evaluated on the overall TEAEs. In addition a specific analysis of adverse drugs reactions known to be observed with drugs that could potentially interact with dronedarone was conducted (eg, ACE inhibitors/AII receptor antagonists, beta-blockers, digitalis, moderate/potent CYP3A4 inhibitors, statins metabolized or not metabolized by CYP3A4, calcium antagonists with heart-rate-lowering effects, and diuretics).

Regarding events commonly associated with beta-blockers (hypotension, bradycardia, cardiac failure), no interaction has been identified between beta-blockers and treatment with dronedarone 400 mg BID with the exception of bradycardia.

The incidences of TEAEs associated with statin toxicity (rhabdomyolysis and myopathy) were low and similar in both dronedarone 400 mg BID and placebo groups, regardless of concomitant intake of statins metabolized by CYP3A4.

A slight increase in the incidence of diarrhea, nausea, and vomiting symptoms was observed when dronedarone was associated with digitalis. Digitalis/digoxin intoxication TEAEs were more frequently reported in the dronedarone 400 mg BID group compared to the placebo group. Interaction between dronedarone 400 mg and digitalis/digoxin was not demonstrated with regards to other signs/symptoms of digoxin toxicity (bradycardia and ventricular arrhythmia).

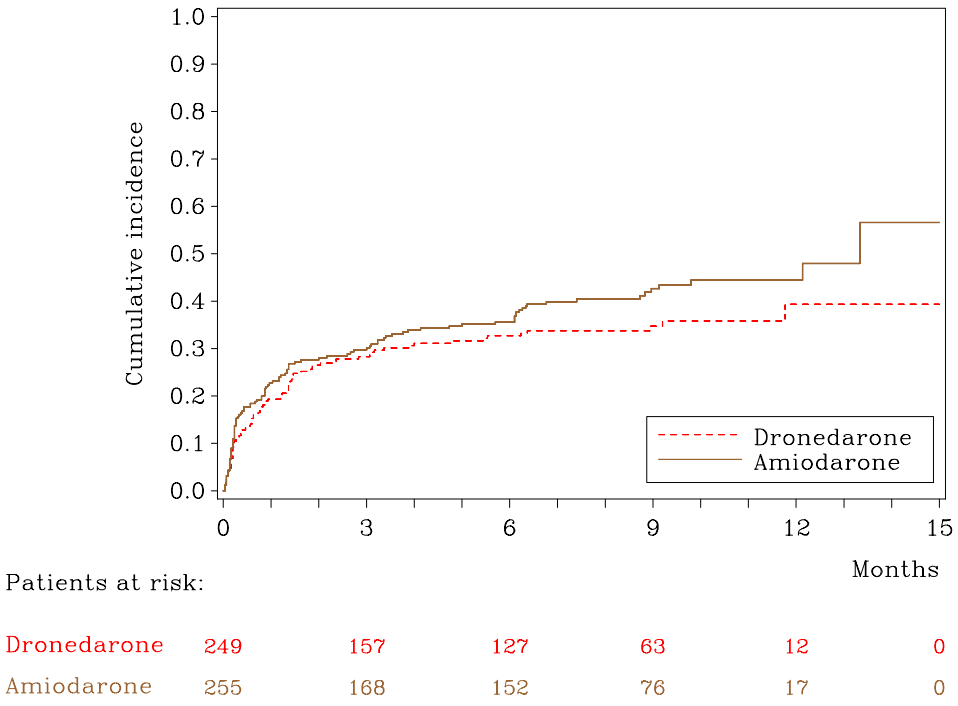
Consistent with the interaction study performed in healthy subjects, an increase in mean change from baseline in digoxin concentration was observed at Day 14 (ATHENA: +50%; ERATO: +41.4%) in patients concomitantly receiving digitalis and dronedarone. After Day 14, mean changes from baseline were lower, indicating a probable adjustment of digitalis doses according to digoxin concentration as recommended in the protocols.

Specific analyses conducted with oral anticoagulants or calcium antagonists with heart-rate-lowering effects did not show any safety concerns.

6.5 COMPARATIVE SAFETY DATA WITH AMIODARONE IN THE DIONYSOS STUDY

In DIONYSOS, a main safety endpoint was defined as the time to first occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye or GI specific events or premature study drug discontinuation following any AE. The main safety variable was analyzed up to the last drug intake plus 10 days (on-treatment period). The incidence for this pre-specified endpoint was 39.3% and 44.5% in the dronedarone and the amiodarone groups, respectively, after 12 months of treatment (HR=0.80, 95% CI=0.60; 1.07, log-rank p-value=0.13) (Figure 27).

Figure 27 – Time to first study drug intake to main safety endpoint - All randomized and treated patients - DIONYSOS



Note: Kaplan-Meier cumulative incidence curve
First main safety endpoint is defined as the occurrence of the following treatment emergent event whichever comes first: thyroid, pulmonary, neurological, skin, eye or GI specific events, or premature study drug
discontinuation due to any AE, or liver enzymes (AST/ALT) above 2xULN and more than 0.5xULN from the baseline value.

The analysis of GI AEs confirmed that these were driven by diarrhea (dronedarone 400 mg BID: 9.2%; amiodarone: 3.1%), none of them was serious.

The reduction in the incidence of the main safety endpoint was driven by a reduction of thyroid, neurological, skin, and ocular effects. When analyzed individually as predefined, the following was shown (Table 61):

- For thyroid disorders, an 84.2% relative risk reduction (p=0.0006) was observed in the dronedarone group compared to amiodarone. The majority of cases were hypothyroidisms: 4 amiodarone patients had hyperthyroidism vs. none in the dronedarone group.
- For neurological events, an 87.6% relative reduction (p<0.0001) in sleep disorders and tremor was observed in the dronedarone group compared to amiodarone.
- Fewer photosensitivity reactions and ocular AEs were also observed in the dronedarone group compared to amiodarone.

Table 61 - Analysis of time from first study drug intake to first specific event - All randomized and treated patients - DIONYSOS

	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg OD (N=255)
Thyroid event	3	20
Log-rank test p-value[a]	0.0006	-
Relative risk (95% CI)[b]	0.158 (0.047 to 0.533)	-
Neurological event	3	24
Log-rank test p-value[a]	$49x10^{-6}$	-
Relative risk (95% CI)[b]	0.124 (0.037 to 0.413)	-
Skin event (photosensitivity reaction)	3	5
Log-rank test p-value[a]	0.541	-
Relative risk (95% CI)[b]	0.642 (0.153 to 2.688)	-

a Pairwise Log-rank test of homogeneity between treatment group as actually received
b Estimated using Cox proportional Hazard Model with treatment group as actually received as the factor
Note: Kaplan-Meier estimates
Note: First skin event is defined as the first occurrence of the following treatment emergent event: photosensitivity reaction.

No pulmonary events, such as interstitial lung disease, hypersensitivity pneumonitis, or interstitial/alveolar pneumonitis, were reported during this short-term study.

The incidence of serious TEAEs of the "Hepatobiliary disorders" SOC was 0.8% (2 patients) in both treatment groups. Two cases presented with ALT>3 ULN and Total Bilirubin >2ULN were reported in the dronedarone group: one case of acute hepatocellular injury suspected to be due to hepatic ischemia secondary to transient low cardiac output and one case of mixed liver injury occurring in the context of pancreatic cancer leading to death. In the amiodarone group, one case of cholangitis and one case of acute cholecystitis were reported as serious TEAEs.

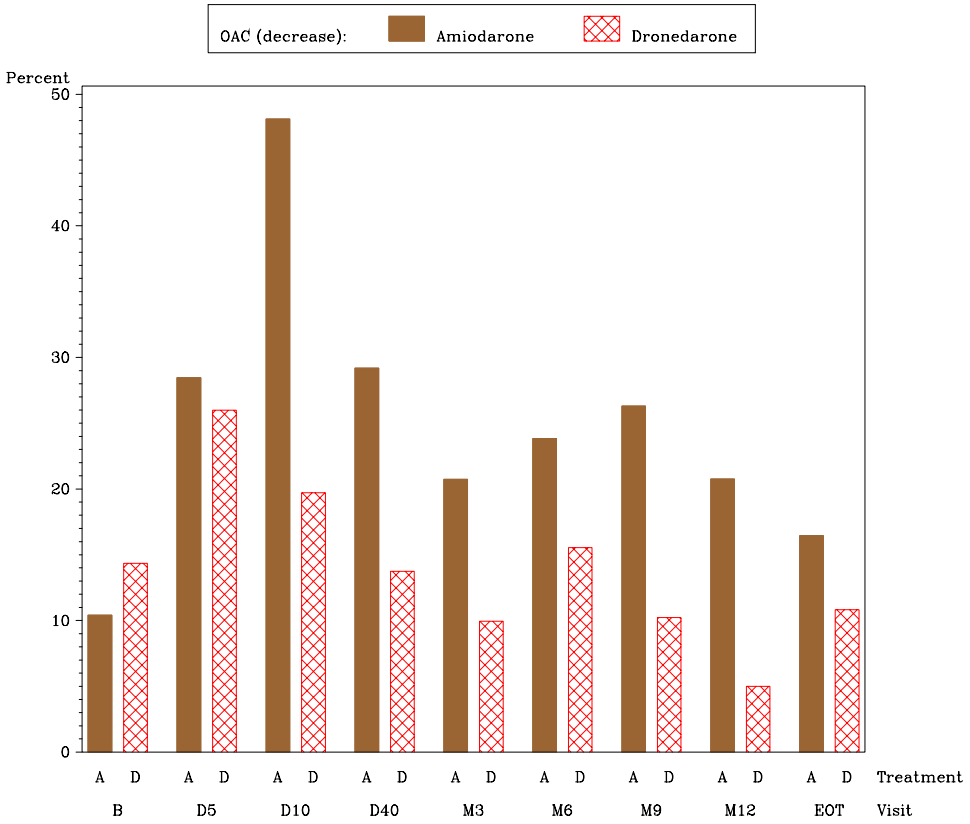
The overall incidence of TEAEs was lower in the dronedarone group compared with the amiodarone group (60.6% versus 67.5%). The incidence of AEs leading to premature permanent study drug discontinuation was also lower in the dronedarone group than in the amiodarone group (12.9% vs. 17.6%). The incidence of serious TEAEs was similar in both groups (13.7% in the dronedarone group, 14.5% in the amiodarone group). The number of deaths during the on-treatment period was 2 (0.8%) and 5 (2.0%) in the dronedarone and the amiodarone groups, respectively. The total number of deaths during the on-study period was 4 (1.6%) and 7 (2.7%) in the dronedarone and the amiodarone groups, respectively.

No cases of TdP were reported during the study. The proportion of patients with a QTcB-interval above 500 msec in the dronedarone group was half that of patients of the amiodarone group (10.9% and 20.5%, respectively). A higher proportion of patients was reported with bradycardia and conduction disorders in the amiodarone group compared to dronedarone. Bradycardia, auriculo-ventricular block, or intraventricular block led to premature study drug discontinuation in patients in the amiodarone but not in the dronedarone group.

Systolic and diastolic BPs were consistently lower during treatment with dronedarone than during treatment with amiodarone. High systolic BP values (≥160 mmHg and increase from baseline ≥20 mmHg) were reported in 9.6% of patients in the dronedarone group versus 28.0% in the amiodarone group. High diastolic blood pressure values (≥110 mmHg and increase from baseline ≥10 mmHg) were reported in 0.4% of patients in the dronedarone group versus 6.7% in the amiodarone group.

There was an interaction between amiodarone and anticoagulation with a higher proportion of patients with supratherapeutic INR levels despite more frequent dose adjustments in the amiodarone group compared to dronedarone. The need for a decrease in the dose of oral anticoagulant over the first days of treatment was less frequent in the dronedarone group compared to the amiodarone group (Figure 28).

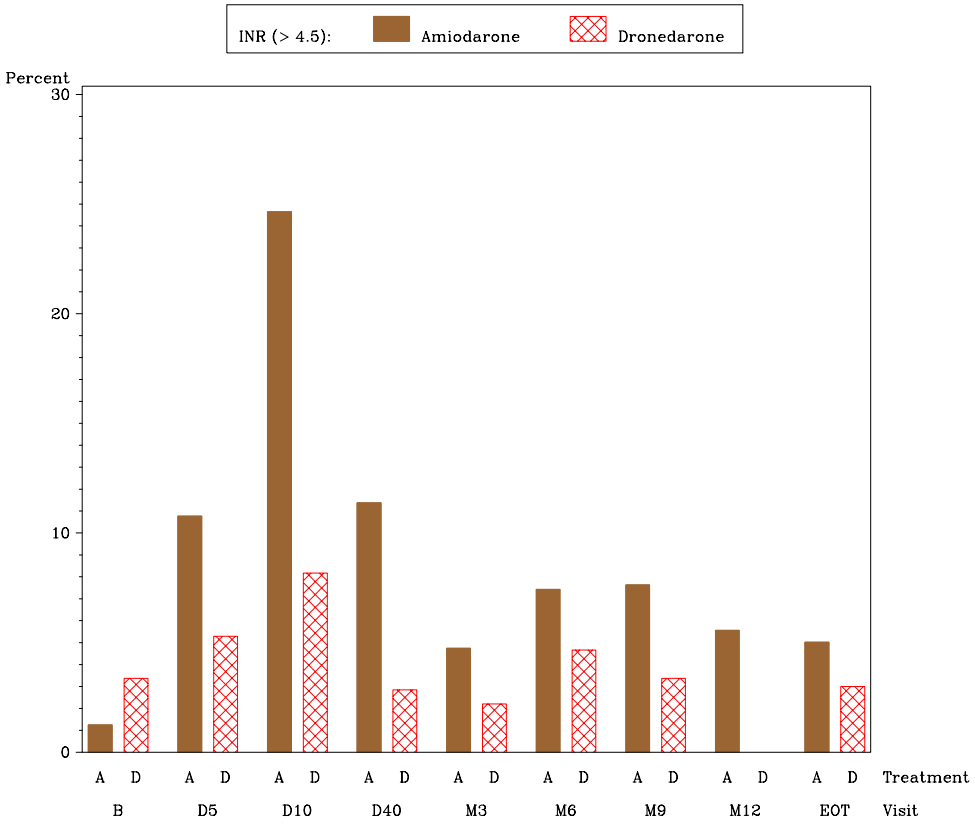
Figure 28 - Percentage of patients with decrease in oral anticoagulant dose over time for the maximum INR value - All randomized and treated patients - DIONYSOS



B: Baseline; EOT: End of Treatment (Last post baseline assessment before or on EOT)
Only scheduled time points are considered

The proportion of patients with an INR above 4.5 (considered dangerous because of the risk of bleeding) was lower in the dronedarone compared to the amiodarone group and this throughout the study (Figure 29).

Figure 29 - Percentage of patients with with INR >4.5 over time for the maximum INR value – All randomized and treated patients - DIONYSOS



B: Baseline
EOT: End of Treatment (Last post baseline assessment before or on EOT)
Only scheduled time points are considered

Low hemoglobin values were more frequently reported in the amiodarone group (4.7%) than in the dronedarone group (1.3%). The risk of hemorrhage was decreased by 50% in the dronedarone group compared to amiodarone (HR 95% CI: 0.504 [0.266 – 0.954]). Of note, one intracranial hemorrhage was reported in a patient receiving oral anticoagulant in the amiodarone group.

Digoxinemia were similar in both treatment groups.

There were more patients with thyroid function abnormalities, including FT3, FT4 and TSH, in the amiodarone group compared to dronedarone (Table 62).

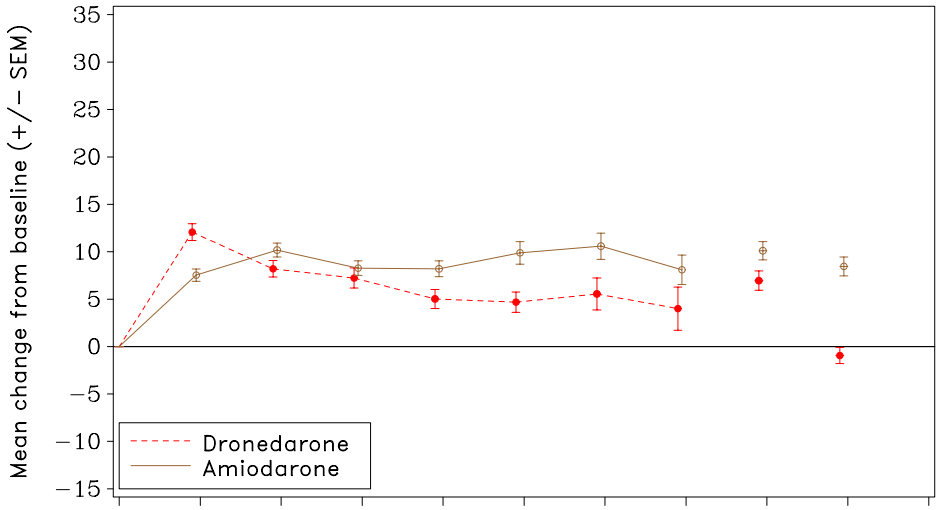
Table 62 - Number (%) of patients with increase and/or decrease outside normal range in thyroid function parameters up to the last study drug intake +10 days - All randomized and treated patients - DIONYSOS

Outside normal range n/N(%)	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg OD (N=255)
FT3 (pmol/L)		
Increase outside normal range [a]	7/240 (2.9%)	3/238 (1.3%)
Decrease outside normal range [b]	43/240 (17.9%)	141/238 (59.2%)
Increase and/or decrease outside normal ranges	50/240 (20.8%)	143/238 (60.1%)
FT4 (pmol/L)		
Increase outside normal range [a]	10/240 (4.2%)	78/238 (32.8%)
Decrease outside normal range [b]	9/240 (3.8%)	7/238 (2.9%)
Increase and/or decrease outside normal ranges	19/240 (7.9%)	85/238 (35.7%)
TSH (mIU/L)		
Increase outside normal range [a]	21/240 (8.8%)	69/238 (29.0%)
Decrease outside normal range [b]	7/240 (2.9%)	12/238 (5.0%)
Increase and/or decrease outside normal ranges	25/240 (10.4%)	81/238 (34.0%)

Note: Denominator refers to patients with post baseline value for the parameter
a N to H and/or L to H: highest post-baseline value up to last study drug intake + 10 days compared to baseline
b N to L and/or H to L: lowest post-baseline value up to last study drug intake + 10 days compared to baseline
L: low, N: normal, H: high with respect to laboratory ranges
For patients with missing baseline assessment, only their post-baseline assessments are taken into account

At baseline, the creatinine serum levels were similar, 88.9 ± 18.2 and 86.3 ± 19.3 µmol/L in the dronedarone and amiodarone groups respectively. A similar moderate increase in creatinine serum levels of about 10 µmol/L was observed in the two groups during the duration of the study drug administration. However, while a rapid decrease to baseline values was observed in the dronedarone group at the end of study visit occurring 10-15 days after study drug discontinuation, no return to baseline values was observed in the amiodarone group. Mean changes from baseline in serum creatinine are plotted in Figure 30.

Figure 30 - Mean changes from baseline (±SEM) over time in serum creatinine (µmol/L) - All randomized and treated patients - DIONYSOS



	B	D5	D10	D40	M3	M6	M9	M12	EOT	EOS
Number of patients:										
Dronedarone	241	234	209	215	196	166	105	46	238	240
Amiodarone	250	245	220	217	206	191	128	52	249	249

B: Baseline; EOT: End of Treatment (Last post baseline assessment before or on EOT); EOS: End of study (Last post baseline assessment)
Only scheduled time points are considered

7 RISK EVALUATION AND MITIGATION STRATEGY

Risk Management is an iterative process of assessing and optimizing a product's benefit-risk balance in clinical practice, often employing a Risk Evaluation and Mitigation Strategy (REMS) as described in Title IX of the Prescription Drug User Fee Act IV (PDUFA IV). The following describes the sanofi-aventis' current proposal for achieving the goals of the dronedarone REMS program.

Elements of the program are under review by FDA and will be finalized in consultation with FDA after the Advisory Committee panel convenes.

7.1 GOALS

The goals of the proposed REMS are to:

- Prevent use in patients with worsening CHF or hospitalized for CHF within the last month
- Prevent the concomitant use of potent CYP3A4 inhibitors
- Encourage appropriate early serum creatinine testing per product label

7.2 STRATEGY AND TOOLS

7.2.1 Strategy

The dronedarone REMS is designed to:

- Identify and educate targeted stakeholders to minimize risk and optimize benefit
- Support safe use in appropriate patient populations
- Assess and continuously improve program performance

7.2.2 Target Stakeholders

Market Research surveys in the US show that treatments for AF/AFL are most often initiated by cardiologists or internal medicine specialists, in both in-patient and out-patient settings. Family practice physicians and other care givers subsequently follow the treatment on a long-term basis and may renew it. Consequently, the dronedarone REMS is being developed to target the following key stakeholders: cardiologists (including electrophysiologists), internal medicine specialists and family practice physicians who treat AF and their staff including nurse practitioners and physicians' assistants. These stakeholders, as well as hospital and retail pharmacists, will receive risk communication, education, and other management support, adapted to their role in the patient's treatment pathway. Additionally, patients will receive education and support tools.

7.2.3 REMS Elements

The REMS tools are being developed to reinforce labeling and support appropriate patient selection, avoid drug-drug interactions, encourage early laboratory testing and counsel patients about managing the risks of dronedarone. In addition to the full product label, stakeholders will be provided with tools, education, and management support to reinforce key safety messages.

7.2.3.1 Medication Guide

The Medication Guide provides information directly to patients regarding the safe use of dronedarone, thus reinforcing information conveyed by their prescribing physicians and dispensing pharmacists. As outlined in the proposed REMS, steps will be taken to ensure that a Medication Guide is provided each time dronedarone is dispensed to a patient.

7.2.3.2 Other Patient Tools

The Patient Brochure has been designed to be used as an aid during patient counseling by physicians. Like the Medication Guide, it is written in low-health literacy language for ease of communication and is meant to remind patients of the most important safety considerations during dronedarone therapy. The brochure contains a tear-off reminder card for the patient to show his/her doctor, pharmacist or other care provider each time they receive a new medication.

7.2.3.3 Communication Plan

The Core component of Multaq® REMS is a Communication Plan that includes education, outreach and support to reinforce the goals of the REMS. In addition to the Package Insert, sanofi-aventis will provide HCPs with the educational materials listed below:

- Health Care Provider Introductory Letter
- Physician Information Sheet
- Pharmacist Information Sheet
- Shared Care Letter
- Other active management support

7.2.3.4 Distribution of Materials

Once the dronedarone REMS is approved, the educational materials will be mailed to the key stakeholders. Additionally, HCPs will have the ability to download copies of the educational materials from the product website or call the sanofi-aventis' Medical Information department to request additional materials.

7.3 ASSESSMENT PLAN

Surveys and existing databases will be used to evaluate the effectiveness of the REMS tools. The overall objectives of the dronedarone REMS assessment plan are to:

- Measure knowledge, attitudes and behaviors of prescribers/patients on REMS messages
- Assess medication guide distribution compliance
- Assess compliance with program goals e.g., appropriate patient selection, co-prescribing of contraindicated medications
- Monitor occurrence and management of targeted adverse events

In the development of drug utilization survey protocols, sanofi-aventis has specifically focused on the surveillance of the utilization of dronedarone in patients with CHF.

Formal assessments of the REMS will be provided to the FDA at 12 months, 18 months, 3 years and 7 years after product launch. If required following these assessments, recommendations for how to improve the effectiveness of the REMS program will be discussed with FDA.

8 OVERALL CONCLUSION: BENEFIT-RISK ASSESSMENT

Atrial fibrillation is the most common sustained arrhythmia in the US population. For most of the last century antiarrhythmic drugs have been used to control the rate or rhythm in these patients, without evidence of favorable impact on the natural history of this disease. Many drugs used to treat AF had proarrhythmic effects. Rate control strategies allowed the arrhythmia to persist, although the long-term consequences of persistent arrhythmia were not known. Despite rate control, patients with AF/AFL remain at a markedly increased risk of cardiovascular hospitalizations and cardiovascular death.

Dronedarone is a benzofuran derivative with an electrophysiological profile resembling that of amiodarone, but with different relative effects on individual ion channels and with structural modifications intended to minimize the non-cardiovascular adverse effects of amiodarone. Specifically, dronedarone was designed with the same basic chemical structure as amiodarone but with a methane-sulfonamyl group (leading to a shorter half-life and decreased lipophilicity, thereby lowering tissue accumulation of the drug and minimizing the risk of end-organ toxicity) and without iodine substituents (thus avoiding the risk of thyroid side effects). Sanofi-aventis developed dronedarone with the intent of replicating the effects of the antiarrhythmic drug, amiodarone, but minimizing the significant toxicity that characterizes the use of amiodarone.

The initial development of dronedarone focused on its efficacy for the control of rhythm and rate in patients with AF/AFL.

- The DAFNE trial indicated that 400 mg BID of dronedarone was associated with greater efficacy and less toxicity than higher doses of the drug. Administration of this dose for 6 months reduced by the risk of arrhythmia recurrence by 55% (P=0.001). This finding was noteworthy, since in clinical pharmacology studies, the 400 mg BID dose was the lowest dose of dronedarone that produced changes in the 12-lead ECG.

- The placebo-controlled EURIDIS and ADONIS studies demonstrated the ability of dronedarone 400 mg BID to maintain sinus rhythm in patients with a history of AF/AFL. Dronedarone reduced the risk of arrhythmia recurrence by 22% in the EURIDIS trial (p=0.0138) and by 27% in the ADONIS trial (p=0.0017). Dronedarone doubled the median time from randomization to the first recurrence of AF/AFL; reduced the risk of first recurrence of symptomatic episodes of these arrhythmias; and slowed the ventricular response in patients whose atrial arrhythmia recurred. Importantly, pooled analysis of the EURIDIS and ADONIS trials showed a 20% reduction in the risk of death or cardiovascular hospitalization (HR [95% CI] 0.804 [0.591, 1.094]).

- The placebo-controlled ERATO study documented the ability of dronedarone 400 mg BID to control the ventricular rate in permanent AF. Treatment with dronedarone significantly attenuated the ventricular rate, both at rest and during exercise.

- The DIONYSOS study compared the efficacy and safety of dronedarone and amiodarone on the prevention of combined endpoint arrhythmia recurrence or premature study drug discontinuation in patients with AF/AFL. Recurrences of AF were more frequent in the dronedarone group than in the amiodarone group, whereas premature study drug discontinuations due to intolerance were more frequent in the amiodarone group than in the dronedarone group.

While these studies demonstrated that dronedarone could effectively manage the arrhythmia in patients with AF, they also suggested (in a post-hoc pooled analysis of EURIDIS and ADONIS) clinically meaningful benefit to the patient with atrial fibrillation, by reducing the risk of cardiovascular hospitalization or death.

The ATHENA study demonstrated for the first time that long-term treatment with an antiarhythmic drug could reduce morbidity-mortality, on top of standard care. In this 4628-patient trial,

- Treatment with dronedarone 400 mg BID was associated with a 24% reduction of the combined risk of cardiovascular hospitalization or all cause-death ($p=2 \times 10^{-8}$; HR [95%CI] 0.758 [0.688 - 0.835]) when compared with placebo. This reduction was due to both a lower number of both cardiovascular hospitalizations and cardiovascular deaths and was consistent across all evaluated subgroups.
- Treatment with dronedarone reduced time to first cardiovascular hospitalization by 25.5% (HR [95%CI] 0.745 [0.673 – 0.824]) compared with placebo. The decrease in the number of cardiovascular hospitalizations seen with dronedarone was due to a reduction in several contributors, including hospitalizations for AF or other supraventricular rhythm disorders, hospitalizations for MI or unstable angina, hospitalizations for stroke or TIA, and hospitalizations for worsening heart failure. The reduction of cardiovascular hospitalizations was consistent across all evaluated patient subgroups.
- Treatment with dronedarone was associated with a 30% lower risk of cardiovascular death (HR [95%CI] 0.698 [0.509; 0.958]) when compared with placebo. The reduction of cardiovascular death with dronedarone 400 mg BID was mainly due to a reduction in the risk of sudden cardiac deaths and stroke and was consistent across all evaluated subgroups.

- There were numerically fewer deaths for any reasons in the dronedarone group (n=116, 5.0%) when compared with the placebo group (n=139, 6.0%). This difference reflected a trend for a 15.6% reduction of risk in dronedarone-treated patients (HR [95%CI] 0.844 [0.660 - 1.080]). Importantly, the upper bound of the 95% CI of 1.08 effectively excluded any clinically meaningful increase in the risk of death as a result of treatment with dronedarone in the ATHENA population.

The results of the ATHENA trial provide reassurance about the long-term use of dronedarone, especially in light of the concerns raised by the results of the ANDROMEDA trial. Additional analyses indicated that the presence or absence of clinical stability was the primary feature that distinguished the patients enrolled in the ANDROMEDA trial from those enrolled in the ATHENA trial. Both trials enrolled patients with low ejection fractions or with Class II or III heart failure; however, ANDROMEDA patients had been hospitalized for worsening heart failure while stable outpatients were enrolled in the ATHENA trial. Further analyses indicated that patients with a LVEF or with Class III heart failure responded differently in the two trials. This reinforces the conclusion that clinical instability rather than that ejection fraction or functional class was an important determinant of the treatment response to dronedarone. These findings are relevant, since the exclusion of clinically stable patients with moderate-to-severe LVD or with moderate-to-severe symptoms of heart failure from treatment with dronedarone would prevent its therapeutic application from patients likely to show the greatest absolute benefit from treatment.

Treatment with dronedarone 400 mg BID was well tolerated for long periods of time. The main clinical adverse events identified with dronedarone are diarrhea, nausea or vomiting and rash. Dronedarone produces electrocardiographic changes consistent with its pharmacodynamic activity; there is no evidence of a proarrhythmic effect of dronedarone; one case of TdP was identified in the entire clinical development program.

Increase in serum creatinine (mean increase 10 μmol/L) has been observed with dronedarone 400 mg BID across the AF/AFL clinical development program. It occurred early after treatment initiation and reached a plateau after 7 days; values returned to baseline within 1 week after treatment discontinuation. This increase is related to inhibition of the renal tubular secretion of creatinine, and has also been observed with other drugs such as cimetidine, trimethoprim and amiodarone.

Importantly, an evaluation of the adverse events known to occur with amiodarone showed that, unlike amiodarone, dronedarone was not associated with endocrinological, neurological or pulmonary toxicity. In the recently completed DIONYSOS study that compared dronedarone with amiodarone, dronedarone was associated with a markedly reduced risk of thyroid disorders; sleep disorders and tremor; and fewer episodes of bleeding due to less interference with oral anticoagulants.

Regarding drug-drug interactions, drugs potentially interacting with dronedarone from a pharmacokinetic or pharmacodynamic point of view were allowed in the AF/AFL clinical program. The potential impact of these interactions on patients' safety was evaluated by reviewing specific adverse events that could be induced by these interactions. These safety analyses provided assurance that recommendations given in clinical studies for the use of beta-blockers, calcium channel inhibitors, digitalis, and statins were adequate for the clinical management of the documented interactions.

In conclusion the benefit/risk of dronedarone for the treatment in patients with AF/AFL is positive. This supports the proposed indication for dronedarone (MULTAQ®):

MULTAQ® is indicated in patients with either a recent history of or current atrial fibrillation or flutter and with associated risk factors. MULTAQ® has been shown to decrease the combined risk of cardiovascular hospitalization or death.

MULTAQ® is contraindicated in patients with worsening CHF or hospitalized for CHF within the last month. Labeling will also include instructions on management of interacting drugs as well as interpretation of serum creatinine increase. The proposed REMS aims at preventing the use of dronedarone in the contraindicated CHF population, the concomitant use of potent CYP3A4 inhibitors as well as encouraging early serum creatinine testing as per labeling.

9 REFERENCES

1. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. Circulation. 2003 Aug 12;108(6):711-6.
2. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998;82(8A):2N-9N.
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285(18):2370-5.
4. Ryder KM, Benjamin EJ. Epidemiology and significance of atrial fibrillation. Am J Cardiol 1999;84(9A):131R-138R.
5. Sawhney NS, Feld GK. Diagnosis and Management of Typical Atrial Flutter. Med Clin N Am. 2008;92:65-85.
6. Nattel S, Hadjis T, Talajic M. The treatment of atrial fibrillation. An evaluation of drug therapy, electrical modalities and therapeutic considerations. Drugs 1994;48(3):345-71.
7. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (Cast) Investigators. N Engl J Med 1989;321:406-12.
8. Roden DM. Risks and benefits of antiarrhythmic therapy. N Engl J Med 1994;331(12):785-91.
9. Waldo AL, Camm AJ, deRuyter H, Freidman PL, MacNeil DJ, Pauls JF et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The Sword investigators. Survival with oral d-sotalol. Lancet 1996;348:7-12.
10. Fuster V, Ryden LE. ACC/AHA/ESC Practice Guidelines: ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. J Am Coll Cardiol. 2001;38(4): 1266i-Ixx.
11. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation-Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. Lancet 2000;356:1789-94.
12. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB et al. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347(23):1825-33.
13. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347(23):1834-40.

14. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL; Atrial Fibrillation and Congestive Heart Failure Investigators. N Engl J Med. 2008 Jun 19;358(25):2667-77.

15. Chirinos JA, Castrellon A, Zambrano JP, Jimenez JJ, Jy W, Horstman LL, Willens HJ et al. Digoxin use is associated with increased platelet and endothelial cell activation in patients with nonvalvular atrial fibrillation. Heart Rhythm. 2005 May;2(5):525-9.

16. Nainggolan, Lisa. AF/CHF trial: rate as good as rhythm control for AF in heart failure [Internet]. Heartwire; 2007 November 6 [cited 2008 February 26]. Available from http://www.the heart.org/viewArticle.do?primaryKey=825357. (Accessed 24 April 2008).

17. Sotacor SPC (Date of revision February 2006). electronic Medicines Compendium (eMC). http://emc.medicines.org.uk (accessed 14 May 2008).

18. Benditt DG, Williams JH, Jin J, Deering TF, Zucker R, Browne K et al. Maintenance of sinus rhythm with oral d,l-sotalol therapy in patients with symptomatic atrial fibrillation and/or atrial flutter. d,l-Sotalol Atrial Fibrillation/Flutter Study Group. Am J Cardiol 1999;84(3):270-7.

19. Roy D, Talajic M, Dorian P, Connolly S, Eisenberg MJ, Green M, Kus T, Lambert J, Dubuc M, Gagné P, Nattel S, Thibault B. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. N Engl J Med. 2000 Mar 30;342(13):913-20

20. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomized trials. Lancet 1997;350:1417-24.

21. Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 2005;352:1861-72.

22. Bialy D, Lehmann H, Schumacher DN, Steinman RT, Meissner MD. Hospitalization for arrhythmias in the United States: importance of atrial fibrillation. J Am Coll Cardiol 1992;19(3):41A-1.

23. Morbidity and Mortality: 2007 chart book on cardiovascular, heart and lung diseases. National Institutes for Health; National Heart, Lung and Blood Institute. Available from: http://www.nhlbi.nih.gov/resources/docs/07a-chtbk.pdf. (accessed 24 April 2008).

24. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation 1998;98:946-52.

25. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. Arch Intern Med. 1998 Feb 9;158(3):229-34.

26. Nieuwlaat R, Prins MH, Le Heuzey JL, Vardas PE, Aliot E, Santini M et al. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on Atrial Fibrillation. Eur Heart J. 2008;29(9):1181-9.

27. Mehra R. Global public health problem of sudden cardiac death. J Electrocardiol. 2007;40(6 Suppl):S118-22.

28. Hummer M and Huber J. Hyperprolactinaemia and antipsychotic therapy in schizophrenia Current Medical Research and Opinions 2004; 20, N°2 p189-197.

10 APPENDIX : SUPPORTIVE SAFETY DATA

Table 63 - Number (%) of patients with TEAEs for high level term with an incidence ≥2% in either treatment group presented by system organ class, high level term and preferred term excluding AF/AFL events – all randomized and treated patients with AF/AFL

MedDRA (10.1) Primary System Organ Class High Level Term(HLT) Preferred Term	Placebo (N=2875)		Dronedarone 400 mg BID (N=3282)		Dronedarone 600 mg BID (N=66)		Dronedarone 800 mg BID (N=62)		Placebo Patient-years (N=3383)		Dronedarone 400 mg BID Patient-years (N=3684)	
Any class - Any event	1941	(67.5%)	2311	(70.4%)	42	(63.6%)	45	(72.6%)	1941	(57.4%)	2311	(62.7%)
Gastrointestinal disorders	599	(20.8%)	791	(24.1%)	13	(19.7%)	22	(35.5%)	599	(17.7%)	791	(21.5%)
HLT : Diarrhoea (excl infective)	170	(5.9%)	295	(9.0%)	5	(7.6%)	18	(29.0%)	170	(5.0%)	295	(8.0%)
Diarrhoea	168	(5.8%)	294	(9.0%)	5	(7.6%)	18	(29.0%)	168	(5.0%)	294	(8.0%)
Diarrhoea haemorrhagic	2	(<0.1)	2	(<0.1)	0	(0%)	0	(0%)	2	(<0.1)	2	(<0.1)
HLT : Nausea and vomiting symptoms	109	(3.8%)	198	(6.0%)	3	(4.5%)	7	(11.3%)	109	(3.2%)	198	(5.4%)
Nausea	89	(3.1%)	161	(4.9%)	2	(3.0%)	5	(8.1%)	89	(2.6%)	161	(4.4%)
Vomiting	31	(1.1%)	66	(2.0%)	1	(1.5%)	2	(3.2%)	31	(0.9%)	66	(1.8%)
Retching	1	(<0.1)	1	(<0.1)	0	(0%)	0	(0%)	1	(<0.1)	1	(<0.1)
HLT : Gastrointestinal and abdominal pains (excl oral and throat)	80	(2.8%)	115	(3.5%)	2	(3.0%)	2	(3.2%)	80	(2.4%)	115	(3.1%)
Abdominal pain upper	44	(1.5%)	60	(1.8%)	1	(1.5%)	1	(1.6%)	44	(1.3%)	60	(1.6%)
Abdominal pain	31	(1.1%)	53	(1.6%)	1	(1.5%)	2	(3.2%)	31	(0.9%)	53	(1.4%)
Abdominal pain lower	5	(0.2%)	2	(<0.1)	0	(0%)	0	(0%)	5	(0.1%)	2	(<0.1)
Abdominal tenderness	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)	0	(0%)
HLT : Gastrointestinal atonic and hypomotility disorders nec	63	(2.2%)	61	(1.9%)	1	(1.5%)	0	(0%)	63	(1.9%)	61	(1.7%)
Constipation	45	(1.6%)	44	(1.3%)	1	(1.5%)	0	(0%)	45	(1.3%)	44	(1.2%)
Gastrooesophageal reflux disease	19	(0.7%)	16	(0.5%)	0	(0%)	0	(0%)	19	(0.6%)	16	(0.4%)
Infrequent bowel movements	0	(0%)	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)
HLT : Dyspeptic signs and symptoms	32	(1.1%)	52	(1.6%)	2	(3.0%)	0	(0%)	32	(0.9%)	52	(1.4%)
Dyspepsia	28	(1.0%)	48	(1.5%)	2	(3.0%)	0	(0%)	28	(0.8%)	48	(1.3%)
Eructation	0	(0%)	3	(<0.1)	0	(0%)	0	(0%)	0	(0%)	3	(<0.1)
Epigastric discomfort	4	(0.1%)	1	(<0.1)	0	(0%)	0	(0%)	4	(0.1%)	1	(<0.1)

Table 63 - Number (%) of patients with TEAEs for high level term with an incidence ≥2% in either treatment group presented by system organ class, high level term and preferred term excluding AF/AFL events – all randomized and treated patients with AF/AFL

MedDRA (10.1) Primary System Organ Class High Level Term(HLT) Preferred Term	Placebo (N=2875)	Dronedarone 400 mg BID (N=3282)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)	Placebo Patient-years (N=3383)	Dronedarone 400 mg BID Patient-years (N=3684)
Infections and infestations	674 (23.4%)	739 (22.5%)	7 (10.6%)	7 (11.3%)	674 (19.9%)	739 (20.1%)
HLT : Upper respiratory tract infections	257 (8.9%)	258 (7.9%)	3 (4.5%)	4 (6.5%)	257 (7.6%)	258 (7.0%)
Nasopharyngitis	93 (3.2%)	106 (3.2%)	3 (4.5%)	2 (3.2%)	93 (2.7%)	106 (2.9%)
Upper respiratory tract infection	89 (3.1%)	99 (3.0%)	0 (0%)	1 (1.6%)	89 (2.6%)	99 (2.7%)
Sinusitis	47 (1.6%)	37 (1.1%)	0 (0%)	1 (1.6%)	47 (1.4%)	37 (1.0%)
Pharyngitis	11 (0.4%)	11 (0.3%)	0 (0%)	1 (1.6%)	11 (0.3%)	11 (0.3%)
Rhinitis	12 (0.4%)	7 (0.2%)	0 (0%)	0 (0%)	12 (0.4%)	7 (0.2%)
Tracheobronchitis	4 (0.1%)	4 (0.1%)	0 (0%)	0 (0%)	4 (0.1%)	4 (0.1%)
Acute sinusitis	5 (0.2%)	3 (<0.1)	0 (0%)	0 (0%)	5 (0.1%)	3 (<0.1)
Acute tonsillitis	2 (<0.1)	1 (<0.1)	0 (0%)	0 (0%)	2 (<0.1)	1 (<0.1)
Tracheitis	1 (<0.1)	1 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	1 (<0.1)
Laryngitis	6 (0.2%)	0 (0%)	0 (0%)	0 (0%)	6 (0.2%)	0 (0%)
Chronic sinusitis	2 (<0.1)	0 (0%)	0 (0%)	0 (0%)	2 (<0.1)	0 (0%)
Chronic tonsillitis	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Peritonsillar abscess	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Tonsillitis	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
HLT : Lower respiratory tract and lung infections	170 (5.9%)	171 (5.2%)	1 (1.5%)	0 (0%)	170 (5.0%)	171 (4.6%)
Bronchitis	80 (2.8%)	91 (2.8%)	1 (1.5%)	0 (0%)	80 (2.4%)	91 (2.5%)
Pneumonia	75 (2.6%)	61 (1.9%)	0 (0%)	0 (0%)	75 (2.2%)	61 (1.7%)
Lobar pneumonia	9 (0.3%)	8 (0.2%)	0 (0%)	0 (0%)	9 (0.3%)	8 (0.2%)
Bronchopneumonia	2 (<0.1)	8 (0.2%)	0 (0%)	0 (0%)	2 (<0.1)	8 (0.2%)
Lower respiratory tract infection	8 (0.3%)	6 (0.2%)	0 (0%)	0 (0%)	8 (0.2%)	6 (0.2%)
Lung infection	2 (<0.1)	3 (<0.1)	0 (0%)	0 (0%)	2 (<0.1)	3 (<0.1)
Bronchiectasis	2 (<0.1)	2 (<0.1)	0 (0%)	0 (0%)	2 (<0.1)	2 (<0.1)
Pneumonia primary atypical	0 (0%)	2 (<0.1)	0 (0%)	0 (0%)	0 (0%)	2 (<0.1)
Infective exacerbation of chronic obstructive airways disease	1 (<0.1)	1 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	1 (<0.1)
Obstructive chronic bronchitis with acute exacerbation	3 (0.1%)	0 (0%)	0 (0%)	0 (0%)	3 (<0.1)	0 (0%)
Pyothorax	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
HLT : Urinary tract infections	97 (3.4%)	120 (3.7%)	0 (0%)	0 (0%)	97 (2.9%)	120 (3.3%)
Urinary tract infection	66 (2.3%)	89 (2.7%)	0 (0%)	0 (0%)	66 (2.0%)	89 (2.4%)
Cystitis	21 (0.7%)	22 (0.7%)	0 (0%)	0 (0%)	21 (0.6%)	22 (0.6%)
Pyelonephritis chronic	6 (0.2%)	5 (0.2%)	0 (0%)	0 (0%)	6 (0.2%)	5 (0.1%)
Pyelonephritis	1 (<0.1)	4 (0.1%)	0 (0%)	0 (0%)	1 (<0.1)	4 (0.1%)
Urethritis	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Pyelonephritis acute	3 (0.1%)	0 (0%)	0 (0%)	0 (0%)	3 (<0.1)	0 (0%)
HLT : Influenza viral infections	59 (2.1%)	68 (2.1%)	1 (1.5%)	2 (3.2%)	59 (1.7%)	68 (1.8%)
Influenza	59 (2.1%)	68 (2.1%)	1 (1.5%)	2 (3.2%)	59 (1.7%)	68 (1.8%)

Table 63 - Number (%) of patients with TEAEs for high level term with an incidence ≥2% in either treatment group presented by system organ class, high level term and preferred term excluding AF/AFL events – all randomized and treated patients with AF/AFL

MedDRA (10.1) Primary System Organ Class High Level Term(HLT) Preferred Term	Placebo (N=2875)	Dronedarone 400 mg BID (N=3282)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)	Placebo Patient-years (N=3383)	Dronedarone 400 mg BID Patient-years (N=3684)
General disorders and administration site conditions	416 (14.5%)	533 (16.2%)	7 (10.6%)	6 (9.7%)	416 (12.3%)	533 (14.5%)
HLT : Asthenic conditions	158 (5.5%)	219 (6.7%)	4 (6.1%)	3 (4.8%)	158 (4.7%)	219 (5.9%)
Fatigue	104 (3.6%)	142 (4.3%)	3 (4.5%)	2 (3.2%)	104 (3.1%)	142 (3.9%)
Asthenia	49 (1.7%)	74 (2.3%)	0 (0%)	0 (0%)	49 (1.4%)	74 (2.0%)
Malaise	11 (0.4%)	16 (0.5%)	1 (1.5%)	1 (1.6%)	11 (0.3%)	16 (0.4%)
Prostration	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
HLT : Oedema nec	156 (5.4%)	207 (6.3%)	2 (3.0%)	1 (1.6%)	156 (4.6%)	207 (5.6%)
Oedema peripheral	142 (4.9%)	189 (5.8%)	1 (1.5%)	1 (1.6%)	142 (4.2%)	189 (5.1%)
Oedema	14 (0.5%)	18 (0.5%)	0 (0%)	0 (0%)	14 (0.4%)	18 (0.5%)
Face oedema	4 (0.1%)	2 (<0.1)	1 (1.5%)	0 (0%)	4 (0.1%)	2 (<0.1)
Pitting oedema	1 (<0.1)	2 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	2 (<0.1)
Localised oedema	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
HLT : Pain and discomfort nec	91 (3.2%)	93 (2.8%)	0 (0%)	2 (3.2%)	91 (2.7%)	93 (2.5%)
Chest pain	61 (2.1%)	63 (1.9%)	0 (0%)	1 (1.6%)	61 (1.8%)	63 (1.7%)
Non-cardiac chest pain	22 (0.8%)	26 (0.8%)	0 (0%)	1 (1.6%)	22 (0.7%)	26 (0.7%)
Pain	8 (0.3%)	6 (0.2%)	0 (0%)	0 (0%)	8 (0.2%)	6 (0.2%)
Discomfort	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Nervous system disorders	460 (16.0%)	518 (15.8%)	4 (6.1%)	6 (9.7%)	460 (13.6%)	518 (14.1%)
HLT : Neurological signs and symptoms nec	176 (6.1%)	208 (6.3%)	1 (1.5%)	3 (4.8%)	176 (5.2%)	208 (5.6%)
Dizziness	160 (5.6%)	189 (5.8%)	1 (1.5%)	3 (4.8%)	160 (4.7%)	189 (5.1%)
Presyncope	11 (0.4%)	9 (0.3%)	0 (0%)	0 (0%)	11 (0.3%)	9 (0.2%)
Dizziness postural	10 (0.3%)	9 (0.3%)	0 (0%)	0 (0%)	10 (0.3%)	9 (0.2%)
Head discomfort	0 (0%)	2 (<0.1)	0 (0%)	0 (0%)	0 (0%)	2 (<0.1)
Dizziness exertional	1 (<0.1)	1 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	1 (<0.1)
HLT : Headaches nec	124 (4.3%)	123 (3.7%)	2 (3.0%)	3 (4.8%)	124 (3.7%)	123 (3.3%)
Headache	121 (4.2%)	123 (3.7%)	2 (3.0%)	3 (4.8%)	121 (3.6%)	123 (3.3%)
Sinus headache	3 (0.1%)	1 (<0.1)	0 (0%)	0 (0%)	3 (<0.1)	1 (<0.1)
Musculoskeletal and connective tissue disorders	457 (15.9%)	514 (15.7%)	2 (3.0%)	2 (3.2%)	457 (13.5%)	514 (14.0%)
HLT : Musculoskeletal and connective tissue signs and symptoms nec	194 (6.7%)	232 (7.1%)	1 (1.5%)	1 (1.6%)	194 (5.7%)	232 (6.3%)
Back pain	89 (3.1%)	106 (3.2%)	0 (0%)	1 (1.6%)	89 (2.6%)	106 (2.9%)
Pain in extremity	49 (1.7%)	71 (2.2%)	0 (0%)	0 (0%)	49 (1.4%)	71 (1.9%)
Musculoskeletal pain	33 (1.1%)	29 (0.9%)	0 (0%)	0 (0%)	33 (1.0%)	29 (0.8%)
Neck pain	22 (0.8%)	16 (0.5%)	0 (0%)	0 (0%)	22 (0.7%)	16 (0.4%)
Musculoskeletal chest pain	16 (0.6%)	16 (0.5%)	0 (0%)	0 (0%)	16 (0.5%)	16 (0.4%)
Flank pain	3 (0.1%)	9 (0.3%)	0 (0%)	0 (0%)	3 (<0.1)	9 (0.2%)
Musculoskeletal discomfort	5 (0.2%)	8 (0.2%)	0 (0%)	0 (0%)	5 (0.1%)	8 (0.2%)
Limb discomfort	1 (<0.1)	3 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	3 (<0.1)

Table 63 - Number (%) of patients with TEAEs for high level term with an incidence ≥2% in either treatment group presented by system organ class, high level term and preferred term excluding AF/AFL events – all randomized and treated patients with AF/AFL

MedDRA (10.1) Primary System Organ Class High Level Term(HLT) Preferred Term	Placebo (N=2875)		Dronedarone 400 mg BID (N=3282)		Dronedarone 600 mg BID (N=66)		Dronedarone 800 mg BID (N=62)		Placebo Patient-years (N=3383)		Dronedarone 400 mg BID Patient-years (N=3684)	
Musculoskeletal stiffness	4	(0.1%)	2	(<0.1)	0	(0%)	0	(0%)	4	(0.1%)	2	(<0.1)
Sensation of heaviness	3	(0.1%)	1	(<0.1)	1	(1.5%)	0	(0%)	3	(<0.1)	1	(<0.1)
Mobility decreased	0	(0%)	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)
HLT : Joint related signs and symptoms	82	(2.9%)	115	(3.5%)	0	(0%)	0	(0%)	82	(2.4%)	115	(3.1%)
Arthralgia	68	(2.4%)	87	(2.7%)	0	(0%)	0	(0%)	68	(2.0%)	87	(2.4%)
Joint swelling	13	(0.5%)	28	(0.9%)	0	(0%)	0	(0%)	13	(0.4%)	28	(0.8%)
Joint stiffness	1	(<0.1)	3	(<0.1)	0	(0%)	0	(0%)	1	(<0.1)	3	(<0.1)
Respiratory, thoracic and mediastinal disorders	397	(13.8%)	450	(13.7%)	2	(3.0%)	9	(14.5%)	397	(11.7%)	450	(12.2%)
HLT : Breathing abnormalities	159	(5.5%)	184	(5.6%)	0	(0%)	2	(3.2%)	159	(4.7%)	184	(5.0%)
Dyspnoea	116	(4.0%)	149	(4.5%)	0	(0%)	1	(1.6%)	116	(3.4%)	149	(4.0%)
Dyspnoea exertional	29	(1.0%)	28	(0.9%)	0	(0%)	0	(0%)	29	(0.9%)	28	(0.8%)
Sleep apnoea syndrome	16	(0.6%)	11	(0.3%)	0	(0%)	0	(0%)	16	(0.5%)	11	(0.3%)
Hyperventilation	0	(0%)	2	(<0.1)	0	(0%)	1	(1.6%)	0	(0%)	2	(<0.1)
Nocturnal dyspnoea	1	(<0.1)	1	(<0.1)	0	(0%)	0	(0%)	1	(<0.1)	1	(<0.1)
Orthopnoea	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)	0	(0%)
Pickwickian syndrome	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)	0	(0%)
Tachypnoea	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)	0	(0%)
HLT : Coughing and associated symptoms	99	(3.4%)	116	(3.5%)	1	(1.5%)	3	(4.8%)	99	(2.9%)	116	(3.1%)
Cough	91	(3.2%)	105	(3.2%)	1	(1.5%)	3	(4.8%)	91	(2.7%)	105	(2.9%)
Haemoptysis	8	(0.3%)	7	(0.2%)	0	(0%)	0	(0%)	8	(0.2%)	7	(0.2%)
Productive cough	3	(0.1%)	6	(0.2%)	0	(0%)	0	(0%)	3	(<0.1)	6	(0.2%)
Allergic cough	0	(0%)	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)
Investigations	253	(8.8%)	441	(13.4%)	10	(15.2%)	8	(12.9%)	253	(7.5%)	441	(12.0%)
HLT : Renal function analyses	47	(1.6%)	158	(4.8%)	2	(3.0%)	2	(3.2%)	47	(1.4%)	158	(4.3%)
Blood creatinine increased	32	(1.1%)	130	(4.0%)	1	(1.5%)	0	(0%)	32	(0.9%)	130	(3.5%)
Blood urea increased	18	(0.6%)	34	(1.0%)	2	(3.0%)	2	(3.2%)	18	(0.5%)	34	(0.9%)
Renal function test abnormal	0	(0%)	9	(0.3%)	0	(0%)	0	(0%)	0	(0%)	9	(0.2%)
Blood creatine increased	1	(<0.1)	2	(<0.1)	0	(0%)	0	(0%)	1	(<0.1)	2	(<0.1)
Glomerular filtration rate decreased	1	(<0.1)	2	(<0.1)	0	(0%)	0	(0%)	1	(<0.1)	2	(<0.1)
Blood creatinine decreased	0	(0%)	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)
Creatinine renal clearance decreased	0	(0%)	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)
Creatinine urine increased	0	(0%)	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)
Renal function test	0	(0%)	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)

Table 63 - Number (%) of patients with TEAEs for high level term with an incidence ≥2% in either treatment group presented by system organ class, high level term and preferred term excluding AF/AFL events – all randomized and treated patients with AF/AFL

MedDRA (10.1) Primary System Organ Class High Level Term(HLT) Preferred Term	Placebo (N=2875)	Dronedarone 400 mg BID (N=3282)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)	Placebo Patient-years (N=3383)	Dronedarone 400 mg BID Patient-years (N=3684)
HLT : ECG investigations	18 (0.6%)	49 (1.5%)	2 (3.0%)	2 (3.2%)	18 (0.5%)	49 (1.3%)
Electrocardiogram QT prolonged	14 (0.5%)	44 (1.3%)	1 (1.5%)	2 (3.2%)	14 (0.4%)	44 (1.2%)
Electrocardiogram PR prolongation	0 (0%)	4 (0.1%)	1 (1.5%)	0 (0%)	0 (0%)	4 (0.1%)
ECG signs of myocardial ischaemia	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Electrocardiogram abnormal	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Electrocardiogram QRS complex abnormal	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Electrocardiogram QRS complex prolonged	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Electrocardiogram RR interval prolonged	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
HLT : Liver function analyses	27 (0.9%)	45 (1.4%)	3 (4.5%)	2 (3.2%)	27 (0.8%)	45 (1.2%)
Hepatic enzyme increased	7 (0.2%)	11 (0.3%)	3 (4.5%)	1 (1.6%)	7 (0.2%)	11 (0.3%)
Gamma-glutamyltransferase increased	5 (0.2%)	15 (0.5%)	0 (0%)	0 (0%)	5 (0.1%)	15 (0.4%)
Alanine aminotransferase increased	5 (0.2%)	9 (0.3%)	0 (0%)	0 (0%)	5 (0.1%)	9 (0.2%)
Transaminases increased	7 (0.2%)	8 (0.2%)	0 (0%)	0 (0%)	7 (0.2%)	8 (0.2%)
Aspartate aminotransferase increased	2 (<0.1)	3 (<0.1)	0 (0%)	0 (0%)	2 (<0.1)	3 (<0.1)
Liver function test abnormal	0 (0%)	3 (<0.1)	0 (0%)	0 (0%)	0 (0%)	3 (<0.1)
Blood bilirubin increased	3 (0.1%)	1 (<0.1)	0 (0%)	1 (1.6%)	3 (<0.1)	1 (<0.1)
Ammonia increased	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Transaminases abnormal	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Cardiac disorders	282 (9.8%)	383 (11.7%)	12 (18.2%)	13 (21.0%)	282 (8.3%)	383 (10.4%)
HLT : Rate and rhythm disorders nec	56 (1.9%)	124 (3.8%)	1 (1.5%)	4 (6.5%)	56 (1.7%)	124 (3.4%)
Bradycardia	36 (1.3%)	107 (3.3%)	1 (1.5%)	4 (6.5%)	36 (1.1%)	107 (2.9%)
Tachycardia	12 (0.4%)	8 (0.2%)	0 (0%)	0 (0%)	12 (0.4%)	8 (0.2%)
Nodal rhythm	0 (0%)	7 (0.2%)	0 (0%)	0 (0%)	0 (0%)	7 (0.2%)
Arrhythmia	1 (<0.1)	2 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	2 (<0.1)
Nodal arrhythmia	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Extrasystoles	3 (0.1%)	0 (0%)	0 (0%)	0 (0%)	3 (<0.1)	0 (0%)
Cardiac flutter	2 (<0.1)	0 (0%)	0 (0%)	0 (0%)	2 (<0.1)	0 (0%)
Bradyarrhythmia	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Tachyarrhythmia	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
HLT : Heart failures nec	64 (2.2%)	83 (2.5%)	6 (9.1%)	2 (3.2%)	64 (1.9%)	83 (2.3%)
Cardiac failure	24 (0.8%)	42 (1.3%)	6 (9.1%)	2 (3.2%)	24 (0.7%)	42 (1.1%)

Table 63 - Number (%) of patients with TEAEs for high level term with an incidence ≥2% in either treatment group presented by system organ class, high level term and preferred term excluding AF/AFL events – all randomized and treated patients with AF/AFL

MedDRA (10.1) Primary System Organ Class High Level Term(HLT) Preferred Term	Placebo (N=2875)	Dronedarone 400 mg BID (N=3282)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)	Placebo Patient-years (N=3383)	Dronedarone 400 mg BID Patient-years (N=3684)
Cardiac failure congestive	38 (1.3%)	35 (1.1%)	0 (0%)	0 (0%)	38 (1.1%)	35 (1.0%)
Cardiac failure chronic	2 (<0.1)	5 (0.2%)	0 (0%)	0 (0%)	2 (<0.1)	5 (0.1%)
Cardiogenic shock	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Cardiopulmonary failure	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
HLT : Supraventricular arrhythmias	35 (1.2%)	54 (1.6%)	1 (1.5%)	4 (6.5%)	35 (1.0%)	54 (1.5%)
Sinus bradycardia	14 (0.5%)	33 (1.0%)	0 (0%)	0 (0%)	14 (0.4%)	33 (0.9%)
Supraventricular tachycardia	4 (0.1%)	7 (0.2%)	1 (1.5%)	1 (1.6%)	4 (0.1%)	7 (0.2%)
Atrial tachycardia	9 (0.3%)	5 (0.2%)	0 (0%)	3 (4.8%)	9 (0.3%)	5 (0.1%)
Supraventricular extrasystoles	6 (0.2%)	4 (0.1%)	0 (0%)	0 (0%)	6 (0.2%)	4 (0.1%)
Sinus tachycardia	3 (0.1%)	4 (0.1%)	0 (0%)	0 (0%)	3 (<0.1)	4 (0.1%)
Sick sinus syndrome	1 (<0.1)	3 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	3 (<0.1)
Supraventricular tachyarrhythmia	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
HLT : Ischaemic coronary artery disorders	58 (2.0%)	53 (1.6%)	0 (0%)	1 (1.6%)	58 (1.7%)	53 (1.4%)
Angina pectoris	42 (1.5%)	38 (1.2%)	0 (0%)	1 (1.6%)	42 (1.2%)	38 (1.0%)
Angina unstable	7 (0.2%)	7 (0.2%)	0 (0%)	0 (0%)	7 (0.2%)	7 (0.2%)
Myocardial infarction	3 (0.1%)	4 (0.1%)	0 (0%)	0 (0%)	3 (<0.1)	4 (0.1%)
Myocardial ischaemia	3 (0.1%)	4 (0.1%)	0 (0%)	0 (0%)	3 (<0.1)	4 (0.1%)
Acute myocardial infarction	3 (0.1%)	1 (<0.1)	0 (0%)	0 (0%)	3 (<0.1)	1 (<0.1)
HLT : Cardiac signs and symptoms nec	48 (1.7%)	45 (1.4%)	4 (6.1%)	3 (4.8%)	48 (1.4%)	45 (1.2%)
Palpitations	46 (1.6%)	44 (1.3%)	4 (6.1%)	3 (4.8%)	46 (1.4%)	44 (1.2%)
Cyanosis	2 (<0.1)	1 (<0.1)	0 (0%)	0 (0%)	2 (<0.1)	1 (<0.1)
HLT : Ventricular arrhythmias and cardiac arrest	11 (0.4%)	22 (0.7%)	2 (3.0%)	1 (1.6%)	11 (0.3%)	22 (0.6%)
Ventricular tachycardia	4 (0.1%)	10 (0.3%)	1 (1.5%)	1 (1.6%)	4 (0.1%)	10 (0.3%)
Ventricular extrasystoles	4 (0.1%)	9 (0.3%)	1 (1.5%)	0 (0%)	4 (0.1%)	9 (0.2%)
Accelerated idioventricular rhythm	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Torsade de pointes	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Ventricular fibrillation	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Cardiac arrest	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Ventricular arrhythmia	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Ventricular flutter	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)

Table 63 - Number (%) of patients with TEAEs for high level term with an incidence ≥2% in either treatment group presented by system organ class, high level term and preferred term excluding AF/AFL events – all randomized and treated patients with AF/AFL

MedDRA (10.1) Primary System Organ Class High Level Term(HLT) Preferred Term	Placebo (N=2875)	Dronedarone 400 mg BID (N=3282)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)	Placebo Patient-years (N=3383)	Dronedarone 400 mg BID Patient-years (N=3684)
HLT : Cardiac conduction disorders	13 (0.5%)	20 (0.6%)	0 (0%)	2 (3.2%)	13 (0.4%)	20 (0.5%)
Atrioventricular block first degree	6 (0.2%)	12 (0.4%)	0 (0%)	1 (1.6%)	6 (0.2%)	12 (0.3%)
Bundle branch block right	1 (<0.1)	2 (<0.1)	0 (0%)	1 (1.6%)	1 (<0.1)	2 (<0.1)
Atrioventricular block complete	2 (<0.1)	2 (<0.1)	0 (0%)	0 (0%)	2 (<0.1)	2 (<0.1)
Atrioventricular block second degree	2 (<0.1)	1 (<0.1)	0 (0%)	0 (0%)	2 (<0.1)	1 (<0.1)
Bundle branch block left	1 (<0.1)	1 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	1 (<0.1)
Atrioventricular block	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Av dissociation	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)
Sinoatrial block	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Skin and subcutaneous tissue disorders	212 (7.4%)	334 (10.2%)	4 (6.1%)	6 (9.7%)	212 (6.3%)	334 (9.1%)
HLT : Rashes, eruptions and exanthems nec	45 (1.6%)	87 (2.7%)	1 (1.5%)	1 (1.6%)	45 (1.3%)	87 (2.4%)
Rash	42 (1.5%)	73 (2.2%)	1 (1.5%)	1 (1.6%)	42 (1.2%)	73 (2.0%)
Rash maculo-papular	2 (<0.1)	5 (0.2%)	0 (0%)	0 (0%)	2 (<0.1)	5 (0.1%)
Rash generalised	1 (<0.1)	5 (0.2%)	0 (0%)	0 (0%)	1 (<0.1)	5 (0.1%)
Rash macular	1 (<0.1)	5 (0.2%)	0 (0%)	0 (0%)	1 (<0.1)	5 (0.1%)
Injury, poisoning and procedural complications	256 (8.9%)	271 (8.3%)	0 (0%)	2 (3.2%)	256 (7.6%)	271 (7.4%)
HLT : Non-site specific injuries nec	101 (3.5%)	100 (3.0%)	0 (0%)	1 (1.6%)	101 (3.0%)	100 (2.7%)
Fall	79 (2.7%)	74 (2.3%)	0 (0%)	0 (0%)	79 (2.3%)	74 (2.0%)
Road traffic accident	7 (0.2%)	14 (0.4%)	0 (0%)	0 (0%)	7 (0.2%)	14 (0.4%)
Post-traumatic pain	4 (0.1%)	9 (0.3%)	0 (0%)	0 (0%)	4 (0.1%)	9 (0.2%)
Excoriation	6 (0.2%)	7 (0.2%)	0 (0%)	0 (0%)	6 (0.2%)	7 (0.2%)
Traumatic haematoma	5 (0.2%)	6 (0.2%)	0 (0%)	0 (0%)	5 (0.1%)	6 (0.2%)
Arthropod bite	3 (0.1%)	5 (0.2%)	0 (0%)	0 (0%)	3 (<0.1)	5 (0.1%)
Injury	1 (<0.1)	1 (<0.1)	0 (0%)	1 (1.6%)	1 (<0.1)	1 (<0.1)
Wound	0 (0%)	2 (<0.1)	0 (0%)	0 (0%)	0 (0%)	2 (<0.1)
Arthropod sting	4 (0.1%)	1 (<0.1)	0 (0%)	0 (0%)	4 (0.1%)	1 (<0.1)
Animal bite	1 (<0.1)	1 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	1 (<0.1)
Traumatic arthritis	1 (<0.1)	1 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	1 (<0.1)
Open wound	2 (<0.1)	0 (0%)	0 (0%)	0 (0%)	2 (<0.1)	0 (0%)
Animal scratch	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Snake bite	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Soft tissue injury	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Traumatic haemorrhage	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
Traumatic ulcer	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)	0 (0%)
HLT : Skin injuries nec	71 (2.5%)	52 (1.6%)	0 (0%)	0 (0%)	71 (2.1%)	52 (1.4%)
Contusion	51 (1.8%)	36 (1.1%)	0 (0%)	0 (0%)	51 (1.5%)	36 (1.0%)
Skin laceration	21 (0.7%)	12 (0.4%)	0 (0%)	0 (0%)	21 (0.6%)	12 (0.3%)
Scratch	1 (<0.1)	3 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	3 (<0.1)
Subcutaneous haematoma	1 (<0.1)	1 (<0.1)	0 (0%)	0 (0%)	1 (<0.1)	1 (<0.1)
Skin injury	0 (0%)	1 (<0.1)	0 (0%)	0 (0%)	0 (0%)	1 (<0.1)

Table 63 - Number (%) of patients with TEAEs for high level term with an incidence ≥2% in either treatment group presented by system organ class, high level term and preferred term excluding AF/AFL events – all randomized and treated patients with AF/AFL

MedDRA (10.1) Primary System Organ Class High Level Term(HLT) Preferred Term	Placebo (N=2875)		Dronedarone 400 mg BID (N=3282)		Dronedarone 600 mg BID (N=66)		Dronedarone 800 mg BID (N=62)		Placebo Patient-years (N=3383)		Dronedarone 400 mg BID Patient-years (N=3684)	
Vascular disorders	226	(7.9%)	241	(7.3%)	1	(1.5%)	3	(4.8%)	226	(6.7%)	241	(6.5%)
HLT : Vascular hypertensive disorders nec	103	(3.6%)	87	(2.7%)	1	(1.5%)	1	(1.6%)	103	(3.0%)	87	(2.4%)
Hypertension	103	(3.6%)	86	(2.6%)	1	(1.5%)	1	(1.6%)	103	(3.0%)	86	(2.3%)
Essential hypertension	0	(0%)	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)
Systolic hypertension	0	(0%)	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)
Diastolic hypertension	1	(<0.1)	0	(0%)	0	(0%)	0	(0%)	1	(<0.1)	0	(0%)
Metabolism and nutrition disorders	232	(8.1%)	214	(6.5%)	3	(4.5%)	1	(1.6%)	232	(6.9%)	214	(5.8%)
HLT : Potassium imbalance	87	(3.0%)	78	(2.4%)	2	(3.0%)	0	(0%)	87	(2.6%)	78	(2.1%)
Hypokalaemia	65	(2.3%)	43	(1.3%)	2	(3.0%)	0	(0%)	65	(1.9%)	43	(1.2%)
Hyperkalaemia	22	(0.8%)	35	(1.1%)	1	(1.5%)	0	(0%)	22	(0.7%)	35	(1.0%)
Ear and labyrinth disorders	74	(2.6%)	77	(2.3%)	3	(4.5%)	2	(3.2%)	74	(2.2%)	77	(2.1%)
HLT : Inner ear signs and symptoms	50	(1.7%)	58	(1.8%)	3	(4.5%)	2	(3.2%)	50	(1.5%)	58	(1.6%)
Vertigo	36	(1.3%)	43	(1.3%)	3	(4.5%)	2	(3.2%)	36	(1.1%)	43	(1.2%)
Tinnitus	9	(0.3%)	13	(0.4%)	0	(0%)	0	(0%)	9	(0.3%)	13	(0.4%)
Vertigo positional	3	(0.1%)	2	(<0.1)	0	(0%)	0	(0%)	3	(<0.1)	2	(<0.1)
Motion sickness	2	(<0.1)	1	(<0.1)	0	(0%)	0	(0%)	2	(<0.1)	1	(<0.1)

Note: A patient can have AEs in more than one organ class

Note: In the ATHENA study, cardiovascular hospitalizations reported only as efficacy events are not reported in the table

Note: protocols : DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA