CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-425

CROSS DISCIPLINE TEAM LEADER REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: April 26, 2006 (edited February 18, 2009)

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of Cardiovascular and Renal Products, HFD-110.

THROUGH: Dr. Norman Stockbridge, Division Director, Division of Cardiovascular and Renal Products, HFD-110.

TO: Dr. Robert Temple, Office Director, ODE-1

SUBJECT: Dronedarone Hydrochloride (Multaq®, SR33589B); Sanofi –aventis, U.S., Inc. as sponsor; NDA 21,913

This memo proposes that the two indications covered by the Sanofi aventis' submission dated 10 June 2005 are approvable but should not be approved at this time. The first indication is for the delay in recurrence of symptomatic atrial fibrillation in a population with previous events, who can be maintained in normal sinus rhythm for at least one hour. The second indication is for control of ventricular rate in patients who are not anticipated to be maintained in normal sinus rhythm.

The overwhelming impediment to drug approval is the results of the ANDROMEDA study. The ANDROMEDA study enrolled class II-IV (mostly II and III) NYHA patients with systolic dysfunction who had a recent hospitalization for CHF. That study was discontinued early because of an increase in mortality among those treated with dronedarone. The confidence interval for that study does not rule out a 4-fold increase in adverse mortality effect with dronedarone. Prior to any consideration for approval, the sponsor needs to define a population who can both benefit and also safely be treated with dronedarone. The sponsor also needs to propose an acceptable risk management program, which protect subjects with heart failure, prior to considering the marketing of dronedarone.

With respect to the indication, for the delay in recurrence of atrial fibrillation in patients who can sustain sinus rhythm for at least one hour, two studies demonstrate superiority of dronedarone at a dose of 400 mg BID to placebo. Dronedarone was superior to placebo in delaying the time to first recurrence of arrhythmia as well as the time to recurrence of the first symptomatic arrhythmia. The upper limit of dosing appears to be less than 800 mg BID based on the high dropout rate due to diarrhea as observed in the DAFNE study.

With respect to the indication, to control of ventricular rate in patients with chronic atrial fibrillation, a dose of 400 mg BID had a modest effect both on resting and exercise heart rate.

There was, however, no improvement in either exercise performance or symptom benefit among those treated with dronedarone.

The sponsor did not explore the entire usable dose range for this indication. A single regimen was studied that was equivalent to that studied for arrhythmia recurrence. There is no reason to believe that the dose for the two indications would be the same. It is unlikely, based on the modest effect on heart rate, that all subjects would be adequately controlled by this regimen. Furthermore, approximately 25% of those patients enrolled in this study discontinued within 4 months of starting therapy. It is unknown if lower doses would afford adequate benefit with an improved safety profile in the chronic atrial fibrillation population. Some additional analyses of the Holter-recordings performed to assess 24-hour heart rate in the ERATO study, particularly the heart rates at the end of the interdosing interval would be appropriate to assess whether the BID dose regimen is reasonable.

Dronedarone appears to be a carcinogen both in mice and rats. As assessed by the CAC, histiocytic sarcomas are increased in male mice and mammary carcinomas in females. In rats hemangiomas are increased. The mechanism for these tumors is unclear but may partly be a genotoxic effect, since S9 processed dronedarone produced a significant number of mutants in the Chinese hamster V79 fibroblast assay. The pattern of tumors seen with dronedarone differs from that of amiodarone where the only thyroid tumors were noted. Since dronedarone is meant for chronic use, the observed genotoxic effect for a long-term, symptom-based treatment, further nudges the risk-benefit calculation in a negative direction.

Since the drug is only approvable at this time, no attempts have been made to edit the label or make comments on the packaging. Comments to the sponsor, with the exception of those dealing with the label or packaging, by each of the disciplines are appended at the end of this review.

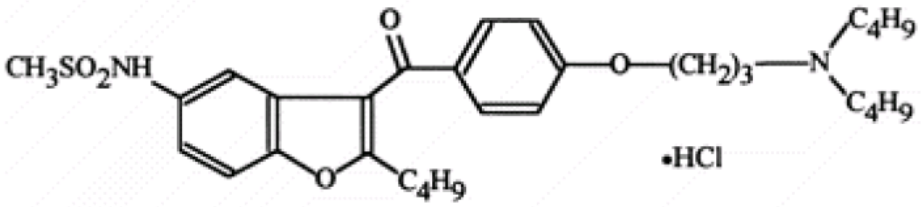
The sponsor's submissions as well as the following FDA reviews were consulted in the course of constructing this memo:

- Joint Medical Officer/Biostatistics review by Gail Moreschi, M.D., M.P.H., and Valeria Freidlin, Ph.D., dated 29 March 2006.
- Pharmacology Review by E. Hausner, D.V.M. (several), dated 3 March 2006. Memo by Kenneth Hastings, Dr.P.H., D.A.B.T., associate Director, OND, dated 4 April 2006.
- Biopharmaceutic review by R. Kumi, Ph.D., dated 30 March 2006.
- Chemistry Review by D.R. Lu, Ph.D. and W. Timmer, Ph.D., dated 7 April 2006 (2); Memo to file by R. Sood, dated 7 April 2006.
- DMETS Proprietary Trade name reviews by Laura Pincock, Pharm.D., dated 11 April, 2005; and Jinhee Jahng, Pharm.D., dated 4 October 2005 and 30 January 2006.
- Clinical Inspection by D. Tesch, Consumer Safety Officer, dated 15 March 2006.
- Environmental assessment (finding of no significant impact) by Bai Nguyen (based on contract review by Ruth Ganunis), dated 29 March 2006.
- Statistical review of carcinogenicity, by Jialu Zhang, Ph.D., dated 10 June 2005.

Chemistry:

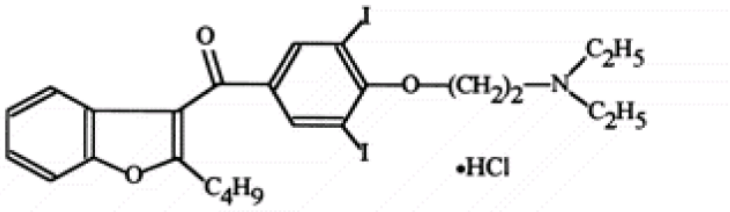
The structures of dronedarone and amiodarone both are shown in Figure 1. Dronedarone is structurally similar to amiodarone but is a methanesulfonamide derivative, contains a longer side chain on the tertiary amine and does not contain iodine on the phenyl ring.

Figure 1: Structure of dronedarone and amiodarone:



SR33589B/Dronedarone (MW=593)

Name (USAN): Dronedarone hydrochloride
Name (CAS): methanesulfonamide, N-(2-butyl-3-[43[(dibutylamino) propoxy]benzoyl]-5-benzofuranyl]-, monochloride
Molc. Formula: $C_{31}H_{45}ClN_2O_5S$
Molc Weight: 593.22 g/mol



Amiodarone (MW=682)

Formulation: Tablet, single strength of 400 mg.

The final formulation for dronedarone has evolved. The proposed to-be-marketed formulation contains poloxamer 407, a solubilizing agent that constitutes 6.15% of the weight of the formulation. The solubilizer was added to decrease the effect of food on the bioavailability of drug.

Drs. Timmer and Lu considered the proposed formulation as approvable. The chemists recommend an expiration shelf-life data for drug product of 18 months.

The comments they wish to transmit to the sponsor are located at the end of this review.

Quality and reliability of data:

The financial disclosure statement indicates one investigator Dr. Ruskin, a sub-investigator in the ADONIS study, had a disclosable financial interest. In addition five sub-investigators and one primary-investigator had incomplete financial disclosure information. The small number of investigators and sub-investigators who did not submit adequate financial disclosure information, when compared to the several hundred who declared no conflict, supports our acceptance of the data as valid.

The central ECG core laboratory for the two pivotal studies ADONIS and EURIDES, MDS Pharma services, was inspected. The inspectors considered the data as analyzed by this core-lab reliable.

The EER report dated 14 March 2006 was considered ACCEPTABLE.

Other issues:

The Trade name Multac or Multaq was found acceptable by DMETS. The environmental assessment was found to be of no significant impact (FONSI).

Mechanism of action:

Dronedarone has many biological activities. Despite structural similarities to amiodarone, and despite overlap in the nature of the channels both block, the affinity of the drugs for the receptors may not be proportional in across all effects. Both drugs, moreover, have complex metabolic patterns, with the contributions by the metabolites to total activities of the drug remaining an unknown.

Based on a series of *in vivo*, *in vitro* and *ex vivo* studies encompassing receptor binding, cell culture, explanted organs and whole animals, dronedarone interacts with a variety of ion channels as well as having other effects. The context for assessing the importance of binding to any receptor is related to the C_{max} concentrations of 0.14 μM in conjunction with the large fraction of drug that is protein bound (>99%).

Channel effects:

Sodium channels:

Dronedarone inhibits sodium channels as observed in guinea pig papillary muscle. This inhibition, as assessed by an inhibition of dV/dT_{max} is use-dependent, with properties consistent with sodium channel blockers of the Ib type. In human cardio-myocytes, dronedarone as measured by patch clamp methodology, inhibited sodium currents, with 27% inhibition at doses of 0.3 μM and 97% inhibition at doses of 3 μM.

Potassium channels:

Dronedarone has affinity for a broad array of potassium channels in guinea pig heart. The specific IC_{50} concentrations for binding to the various receptors are show below in Table 1 and human potassium receptors (Table 2). The IC_{50} for inhibition of potassium channels would suggest that dronedarone would likely prolong ventricular repolarization and only at higher concentrations would it bind to atrial-selective potassium channels kv1.5

Table 1: Binding of dronedarone to potassium channels in guinea pig heart receptors (in μM):

I_{kf}	I_{ks}	I_{ki}	I_{kf}	I_{KACH}	$I_{Ca\text{-}L}$	$I_{Ca\text{-}T}$
≤ 3	10	≥ 30	> 30	~0.01	0.18	> 30

Table 2: Binding IC_{50}) of dronedarone to human potassium channels (in μM):

hERG (CHO cells expressed)	hERG expressed in HEK cells	Kv1.5
0.53	0.059	2.7

Calcium channels:

In a series of studies using cell homogenates, the binding constants for dronedarone to calcium channels was dependent on the origin of these channels. Based on the IC_{50} values, dronedarone likely will have effects on the L-type calcium channel as well as the sodium/calcium exchanger. The origin of the channel and the specific IC_{50} were: calcium L-channel (guinea pig brain) 0.14 μM; (rat heart) 0.5 μM; calcium N-channel (rat brain) inactive; calcium channel from sarcoplasmic reticulum (rabbit muscle) inactive; sodium/calcium exchanger (dog heart) 82% inhibition at 1 μM and sodium-proton pump (chick heart) inactive at 10 μM.

Adrenergic receptors:

After two weeks of treatment with dronedarone, ranging from 50-150 mg/kg to rats, cardiac membrane preparations showed a down-regulation of beta adrenergic receptors in a dose-related manner. In mongrel dogs intravenous dronedarone at a dose of 5 mg/kg and greater, the drug inhibited adrenaline induced blood pressure increase (α-adrenergic receptor blocker). It also inhibited isoprenaline induced tachycardia at similar doses (β_1-adrenergic receptor blocker). Origin of receptor and (binding constants) were β_1-adrenergic receptor-rat heart (2.2 μM), β_2-adrenergic receptors- rat lung (70% inhibition at 30 μM), α_1-adrenergic receptor-rat heart (30 μM); α_2-adrenergic receptor-guinea pig brain (28 μM). Based on these binding measurements dronedarone preferentially binds to β_1-adrenergic receptors.

Adenylate cyclase activity:

Dronedarone inhibits the stimulation of adenyl cyclase formation in rat myocyte-preparations when the preparations are stimulated by isoprenaline. The effect does not simply appear to be blockage of the adrenergic receptor, since dronedarone also inhibited adenyl cyclase generation when the membrane preparations were stimulated by glucagons or secretin, that do not act through the beta-adrenergic receptor. Dronedarone, however, did not inhibit adenyl cyclase generation when the stimulus was at the level of the regulatory or catalytic subunit. The inhibition of dronedarone on adenyl cyclase was non-competitive in nature.

Cardiac effects in intact animals:

Electrophysiology:

In anesthetized dogs (5 per gender/dose) two doses of intravenous dronedarone were administered 60 minutes apart at each of three dose levels. Surface ECGs were collected and intracardiac intervals were measured. Effects, limited to those that appear dose-related (as a

percentage change from baseline), are shown below. The greatest effects are in lengthening the atrio-ventricular node effective refractory period and the Wenckebach cycle length.

Table 3: ECG and intracardiac intervals (as % change from baseline) in anesthetized dogs:

Parameter	1 mg/kg	2.5 mg/kg	5 mg/kg
Heart rate	-15	-23	-36
Sinus cycle length	15	31	59
Atrial-His time	12	34	65
Wenckebach cycle length	31	75	112
Atrial effective refractory period	12	18	14
Atrio-ventricular nodal effective refractory period	15	99	125
Ventricular effective refractory period	7	8	23
PQ interval	9	23	51
QT interval	9	15	19

Hemodynamics:

The application contains both acute intravenous effects as well as longer term administration of dronedarone. The model systems include rats, dogs and pigs. The most consistent finding was that dronedarone decreases dP/dT_{max}, seen across species and across duration of treatments. These effects are consistent with the ability of dronedarone to block sodium channels

Bioactivity of metabolites:

Two major metabolites (see figure below) SR 35012A and SR90154 were screened for binding to an assortment of receptors. The screen assessed binding to the following receptors (and their origin): β_1-adrenergic (rat heart), β_2-adrenergic receptor (rat lung), α_1-adrenergic receptor (rat heart), α_2-adrenergic (guinea pig brain), cholinergic muscarinic (rat heart), Purinergic A_1 (rat brain), L-type calcium channel (guinea-pig brain, rat heart) , N-type calcium channel (rat brain), sodium channel (rat brain and heart), K-channel , ATP-dependent (rat heart). Of note, there was no screen for K-channel receptor binding, for IK_r, IK_s or IK_o channels.

Figure 2: Major metabolites of dronedarone:

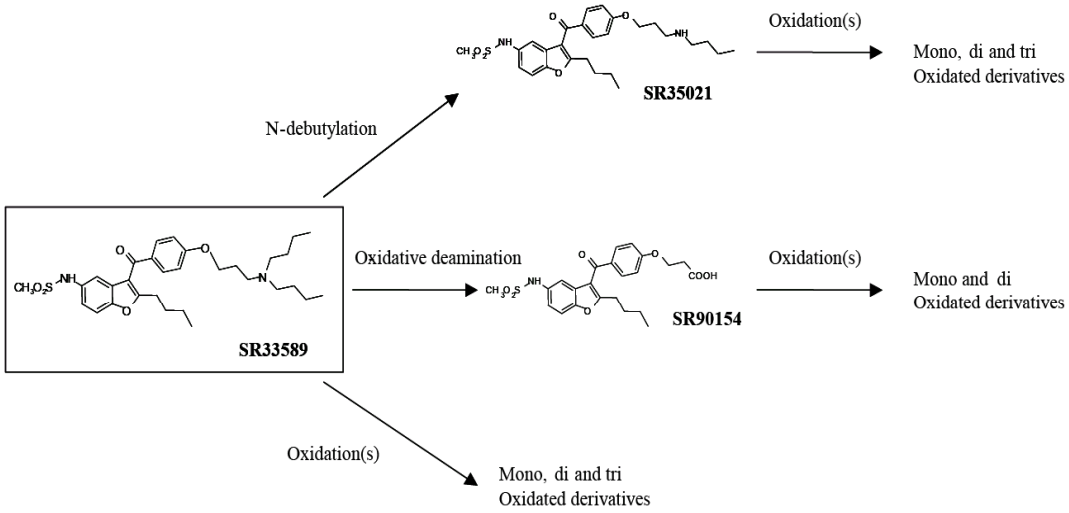


Figure (2.4.3.3) 1 - Major pathways of biotransformation of dronedarone

With respect to SR 35021A, the following receptors had EC_{50} of less than 10 μM: cholinergic muscarinic receptors (7.1 μM), L-type calcium channel (1.6 μM- brain and 3.5 μM- heart), sodium channel (1.4 μM) brain) and 7.2 μM (heart). The binding constants do not define whether the substrate is an agonist, antagonist or partial agonist nor does it define the magnitude of its effect at any receptor. For SR90154 all EC_{50} binding effects were at concentrations > 30 μM.

Carcinogenicity

In three repeat assays S9 processed dronedarone produced a significant increase in mutants in the Chinese hamster V79 fibroblasts.

The executive CAC met on 18 October 2005 to review the dronedarone mouse and rat carcinogenicity studies. The conclusions of the CAC were that the following findings were drug related: histocytic sarcomas in male mice, mammary adenocarcinoma in female mice and hemangiomas in male rats. The exposure to dronedarone, relative to the proposed human dose ranged from 4.6 in male rats to 8.2 in female mice. As suggested by Dr. Hausner, the mammary tumors as well as the alterations in cycling in female rats and dogs, may suggest changes mediated by an alteration in the hypothalamic-pituitary-endocrine axis.

Teratology

Dronedarone appears teratogenic in rats. Observations in the offspring include skeletal and external malformations in 17 out of 18 fetuses at a dose of 160 mg/kg (with some maternal toxicity) and 15 of 48 fetuses at a dose of at a dose of 80 mg/kg. Both these findings were observed in a preliminary dose-testing study. In the definitive study, at a dose of 100 mg/kg which was maternally toxic, approximately 90% (198/221) of the fetuses had external, organ-

system and/or skeletal abnormalities. No abnormalities were noted in the maternal group treated with 30 mg/kg. In the low dose group (10 mg/kg), there were reports of unilateral microopthalmia, and unilateral anopthalmia. In rabbit studies, two fetuses of different litters were profoundly deformed with craniofacial and laryngeal abnormalities.

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Other effects: Thyroid hormones, phospholipidosis.

Doses of dronedarone of 50, 100 or 150 mg/kg were studied in rats. In male rats dronedarone at doses of 150 mg/kg but not doses of 100 mg/kg or 50 mg/kg decreased T4, T4/T3 ratio. In the three-month toxicology studies in rats there were small increases in TSH both in male and female rats at a dose of 60 mg/kg daily.

Foamy macrophages were reported in various organs in rats. At dose of > 5 mg/kg (3 month study) these macrophages were reported in lungs as well as in other tissues.

Pharmacokinetics:

Biopharmaceutics:

Dronedarone demonstrated non-linearity in exposure relative to dose. On the first day of dosing the proportionate increase in the AUC was 2.8 in increasing the dose from 200 mg BID to 400 mg BID, and 2.7 in increasing the dose from 400 to 800 mg BID. The proportionate increase in AUC by dose was 2.8 fold on day 1. The proportionate increase were slightly greater at day 14.

Table 4: Dose-related pharmacokinetic parameters of dronedarone and SR35021 (BID-dosing) mean ± SD:

Parameter		Dronedarone			SR35021		
		200 mg	400 mg	800 mg	200 mg	400 mg	800 mg
Cmax µg/ml	Day 1	23.1 ± 38	67.2 ± 36	162 ± 40	20.8 ± 21	49.5 ± 25	109 ± 29
	Day 14	40.3± 30	111 ± 17	298 ± 13	41.2 ±27	107 ± 22	282 ± 21
t_{max} median (h)	Day 1	3	3	3	5	5	5
	Day 14	5	5	5	5	5	5
AUC $_{0-12}$ ng h/ml	Day 1	111 ± 24	310 ± 28	846 ± 27	123 ± 19	275 ± 23	668 ± 24
	Day 14	276 ± 23	798 ± 19	2510 ± 12	325 ± 21	882 ± 17	2680 ± 20
$T_{1/2\alpha}$ (h)	Day 1	10 ± 33	18 ± 56	20 ± 33	16 ± 28	19 ± 24	22 ± 22
	Day 14	27 ± 32	30 ± 29	31 ± 32	24 ± 14	21 ± 16	20 ± 8

Absolute bioavailability

The absolute bioavailability of a dronedarone when administered orally while fasted was 4%. The absolute bioavailability orally while fed was approximately 15%. Comparing fasted to low fat and fat-rich meals shows a steady increase in AUC as the fat-content of the meal increases.

Distribution:

Dronedarone is approximately 99% bound to plasma protein, predominantly to albumin. Following administration of intravenous dronedarone, the volume of distribution associated with the terminal half-life was 2500-3400 Liters.

Distribution study in animals:

In male rats, oral administration of carbonyl-14C SR33598 (total dose of 30 mg/kg) produced a broad tissue distribution of radioactivity. Aside from the GI tract, high

concentrations were noted in lungs, liver, kidneys, spleen and thyroid at 1 to 8 hours post dose. In pigmented rats, dronedarone appears to be concentrated at sites containing melanin.

Metabolism:
In vitro CYP assay:

Dronedarone, when assayed in *in vitro* liver microsomal preparations showed only minimal inhibitory effect on the CYP family of enzymes. Of the enzymes inhibited, dronedarone inhibited CYP2D6 with K_i values of approximately 5 μM and CYP3A4 with a Ki of approximately 40 μM. One of the metabolites of dronedarone, RS-335021 inhibits several CYP 450 isoforms with K_i values of less than 40 μM. This metabolite inhibits the following isoforms (with the K_i values): CYP2D6 (4.4μM), CYP3A4 (8.1 μM), CYP2C19 (11.2μM), CYP2C9 (18.3 μM), CYP1A2 (30.6 μM), CYP2A6 (32.7 μM).

Drug-Drug interactions:

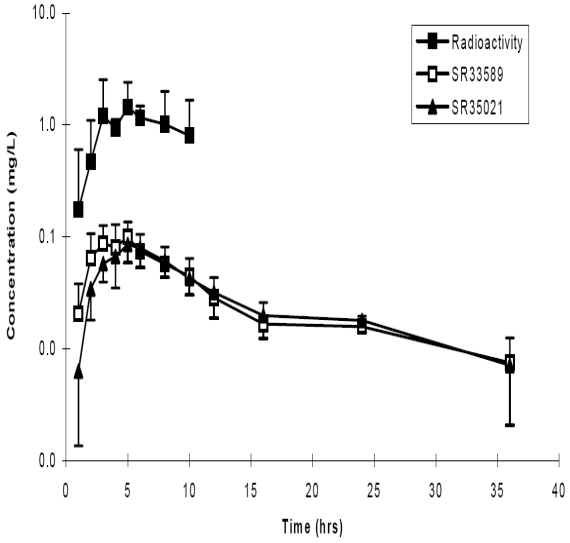
Several drug-drug interaction studies were performed with the results summarized in Table 24 of Dr. Kumi's review. Despite a lack of effect in the *in vitro* screen, dronedarone exposure is markedly increased in the presence of CYP3A4 inhibitors. Multiple dose ketoconazole (200 mg) increased Cmax and AUC of dronedarone at a 100 or 200 mg single dose, by 9 and 16 fold, respectively. It also seems that dronedarone acts a PGP inhibitor, increasing digoxin concentrations by 75% (C_{max}) and AUC by 150%.

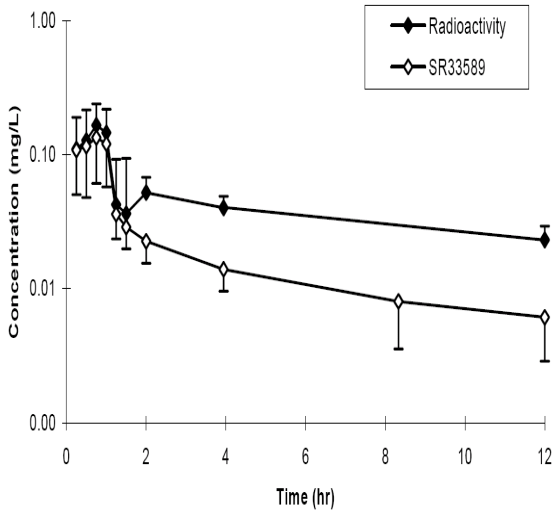
14C-tracer study in humans:

There were two 14C-labeled studies, one study with dronedarone administered orally and one intravenously. After oral administration, peak radioactivity occurs at approximately 4 hours. The concentration of the parent drug and one metabolite, SR 35021 accounts for only approximately 20% of the radioactivity (Figure 3). The specifics of the rest of the radioactivity remain unknown. The duration for which radioactivity was followed was only 10 hours and the terminal half-life of radioactivity after an oral dose cannot be determined with accuracy. After approximately 100 hours, nearly all the radioactivity was excreted in urine and feces, suggesting a functional half life of 25 hours for the metabolites of dronedarone (Figure 3).

After intravenous administration, the concentration of radioactivity and parent drug (SR33589) are equivalent shortly after drug administration (Figure 3). At about 2 hours, the concentrations appear to diverge, suggesting the generation of label-containing metabolites. The duration of observation (12 hours) does not allow an accurate assessment of the terminal radioactive half-life.

Figure 3: 14C-labeled dronedarone after oral (left) and intravenous (right) administration SR33589 is dronedarone:





Parameter (units)	Radioactivity[a,b]	SR33589[a]	SR35021[a]
C_{max} (mg/L)	1.75 (1.06)	0.10 (0.04)	0.09 (0.02)
t_{max} (h)	4.5 [c] (3 to 6) [d]	4.5 [c] (3 to 6) [d]	5.5 [c] (5 to 6) [d]
$t_{½}$ (h)	ND [e]	18.84 (4.01)	18.49 (2.57)
AUC_{0-t} (mg*h/L)	19.86 (29.85)	1.11 (0.41)	1.08 (0.34)
t (h)	11.0 (2.0)	36.0 (7.6)	40.8 (6.6)
AUC (mg*h/L)	ND	1.58 (0.39)	1.46 (0.34)
%(Extrapolated AUC /AUC)	ND	18.35 (6.54)	18.46 (4.43)

[a] Mean (±SD)
[b] Radioactivity is expressed as mg-equivalents where appropriate
[c] Median of all subjects
[d] Range for t_{max} from all subjects
[e] Not determined

Parameter (units)	Radioactivity[a,b]	SR33589[a]
C_{max} (mg/L)	0.17 (0.07)	0.14 (0.07)
t_{max} (h)	0.83 [c] (0.75 to 1.0) [d]	1.0 [c] (0.75 to 1.25) [d]
$t_{½}$ (h)	11.76 (5.78)	10.97 (5.21)
AUC_{0-t} (mg*h/L)	0.65 (0.32)	0.35 (0.15)
t (h)	17.33 (8.26)	17.33 (6.02)
AUC (mg*h/L)	0.95 (0.44)	0.49 (0.19)
%(Extrapolated AUC /AUC)	34.01 (8.56)	25.65 (11.48)

[a] Mean (±SD)
[b] Radioactivity is expressed as mg-equivalents where appropriate
[c] Median of all subjects
[d] Range for t_{max} from all subjects

Excretion:

Dronedarone label was excreted primarily in the feces. Of the tracer dose, 84% was eliminated in feces; 6% in urine. Full recovery of radioactivity required upward of 100 hours (Figure 4). There were more than of 30 metabolites detected in feces and urine. Approximately 20 of these metabolites each, reflect more than 1% of the tracer administered. A large fraction of these compounds were only partly characterized based ion mass spectroscopic fragmentation pattern. Only two of the metabolites SR35021 and SR90154 were screened through a series receptor binding assays (see above).

Figure 4: Time course of label excretion after oral dose of dronedarone:

Table (8.2.1.3) 1 - Mean recovery of radioactivity in urine, feces and expired air from six healthy male subjects following oral administration of 800 mg (6.63 MBq) of ^{14}C-SR33589B

Excretion (% of dose)			
Urine	**Feces**	**Expired air**	**Total**
5.8 ± 1.2	83.9 ± 5.1	0.0 ± 0.0	89.7 ± 4.7

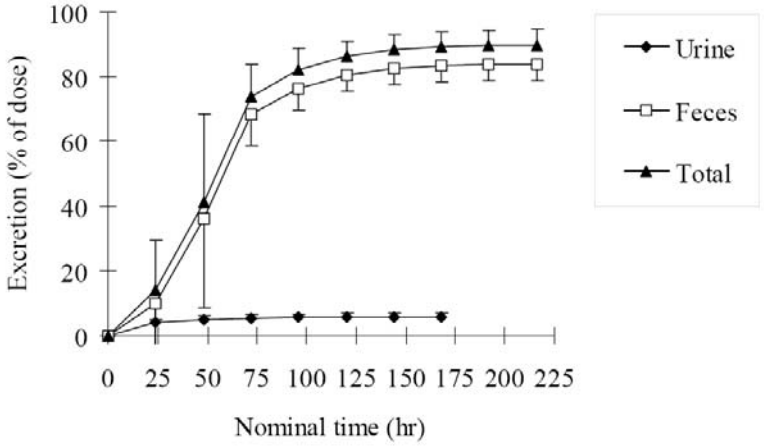


Figure (8.2.1.3) 1 - Mean cumulative excretion (±SD) of radioactivity in urine and feces from six healthy male subjects following oral administration of 800 mg (6.63 MBq) of ^{14}C-SR33589B

Specific populations:

After an 800 mg QD dose, the C_{max} for elderly (age 65-80 years, mean 70-72 years) was 15% higher on day 1 and 30% higher on day 17, than young males (age 25-40 years, mean 29 years). The C_{max} for elderly females was approximately 90% higher on day 1 and day 17 than young males. For AUC, elderly males had an increase of approximately 30% relative to young males. Elderly females had an increase of approximately 100% on days 1 and 17 compared to young males.

Japanese males appeared to have lower clearances than their Caucasian counterparts at a dose of 400 mg (cross-study comparisons). There was no information with respect to the kinetics in African-Americans.

There were no studies in patients with hepatic impairment that have been completed. One study POP5829 is ongoing.

Efficacy:

Dronedarone at a dose of 400 mg BID, administered with food, demonstrated a prolongation to the time of recurrence of atrial fibrillation in two placebo-controlled randomized studies, EURIDES[1] and ADONIS[2]. The studies were performed concurrently,

[1] European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone in patients for the Maintenance of Sinus Rhythm.-EFC3153

[2] American-Australian-African Trial with Dronedarone in patients for the maintenance of Sinus rhythm-EFC4788

under the same protocol. The core lab that performed the analyses of ECGs, TTEMs (transtelephonic electrocardiogram monitoring) and laboratory measurements was the same for both studies.

The differences in studies were the geographical areas from which populations were recruited. In the EURIDES study the population enrolled was derived from l2 countries: Netherlands, Germany, Poland, Hungary, Italy, France, Czech Republic, Belgium, Spain, Denmark, Finland and the United Kingdom; in the ADONIS study the populations were derived from: USA, Canada, Australia, Argentina and South Africa.

Patients were eligible for enrollment if, within the previous 3 months, they had an episode of atrial fibrillation or flutter and were in sinus rhythm for at least 1 hour at the time of randomization. Notable exclusion criteria included NYHA class III or greater heart failure and previous failure of amiodarone treatment. Proscribed medications included drugs with Vaughn-Williams Class I and/or III antiarrhythmic activity, drugs known to provoke torsades de pointes and potent CYP3A4 inhibitors. Anticoagulants were to be administered and monitored as per study site or published guidelines.

At baseline, each of the patients was given and instructed how to use TTEM device, as well as the best position to place that monitor for observing p-waves. The TTEM devices were to be used at specified times to capture the ongoing rhythm: days 2, 3, and 5, month 3, 5, 7 and 10, as well as when the subjects felt symptoms consistent with past fibrillation events. Standard 12-lead ECGs were recorded at the following specified times: day 1, 7, 14 and 21 as well as month 2, 4, 6, 9 and 12. Both TTEMs and 12-lead ECGs were to be repeated 10 minutes apart. The recurrence of an atrial fibrillation or flutter would be defined by the demonstration that the arrhythmia was present on the two measurements. If the arrhythmia was only present on the second of the measurements, even if subsequent ECGs failed to demonstrate an arrhythmia, the subject had met the endpoint.

At the time of an ECG or TTEM transmission[3] to the core lab, the lab queried the subject about the following five symptoms (palpitations, dizziness, fatigue, chest pain or dyspnea) as well as their intensity.

After baseline determinations, subjects were randomized in a 2:1 ratio to either dronedarone 400 mg BID or placebo. The dose was to be taken with or shortly after breakfast and dinner.

[3] The timing of the recording and transmission of the TTEM was not necessarily closely linked. The ability to transmit the information was dependent on the working hours of the core lab as well the availability of a translator to query symptoms, if required by the patient's native language. The TTEM could have several ECGs in memory that would be transmitted concurrently. The maximum memory capacity of the TTEM was 6 recording. Consequently, only three episodes (with 10-minute replicates) could be captured before capacity was reached. Once down-loaded, the TTEM erased the tracing and additional recording space became available. At the time of transmission the patient was asked about the presence of six symptoms suggestive of recurrence of an arrhythmia. Since the patient did not fill out a diary, the recall of symptoms, perhaps several days after the event, relies on recall to an inordinate extent.

The primary study endpoint was time that normal sinus rhythm was lost, as judged by the initial time of recurrence of atrial fibrillation or flutter. This endpoint was assessed in the randomized and treated patient population with the comparison performed by a 2-sided Log-rank asymptotic test. The cumulative incidence functions for each treatment were calculated using the nonparametric Kaplan-Meier estimate. The relative risk, with 95% confidence interval was estimated using the Cox model with treatment group as the only factor. In addition to the primary analysis, per protocol and a covariate analyses were planned. The specific covariates were type of conversion of the last event (electrical, ibutalide use or overdrive pacing), chronic amiodarone use prior to enrollment and the presence of structural heart disease.

Secondary endpoints were:

- Time to recurrence in the presence of symptoms, assessed through a survival of competing risk analyses.
- Ventricular rate at the time of primary endpoint, analyzed by a 2-way ANOVA with treatment and ECG as covariates
- The time from attaining steady state of dronedarone to the time of the adjudicated first event. The statistical methodology was as used for the primary analysis.

Since the studies were carried out in a similar manner the disposition of patients, the characteristics of the patients, and outcomes for both studies will be tabulated together.

Patient disposition:

The disposition of the patients from both the ADONIS and EURIDIS study are shown in Table 5. In both studies the randomization was 2:1, dronedarone: placebo. There was a higher rate of discontinuation for adverse events among those treated with dronedarone compared to placebo-treated patients. Selected demographics, baseline conditions and concomitant medications are shown in Table 6.

Table 5: Disposition of subjects in ADONIS and EURIDIS:

	ADONIS		EURIDIS	
Screened	731		680	
Screening failures	102		65	
Randomized	629		615	
Not treated	4		6	
Randomized and treated	625		612	
	Placebo	Dronedarone	Placebo	Dronedarone
	208	417	201	411
Completed Therapy or end point	172 (83%)	336 (81%)	176 (88%)	344 (84%)
Discontinued	36 (17%)	81 (19%)	25 (12%)	67 (16%)
Endpoint of lack of efficacy	3 (1%)	1 (<1%)	0	0
AE	16 (8%)	45 (11%)	13 (6%)	36 (9%)
Compliance	4 (25)	3 (1%)	0	0
Patient's request	8 (4%)	21 (5%)	11 (5.5%)	27 (6.6%)
Other	5 (2%)	10 (2%)	1 (<1%)	4 (1%)

.

Table 6: Demographics, baseline cardiovascular disease and selected treatments for ADONIS and EURIDIS:

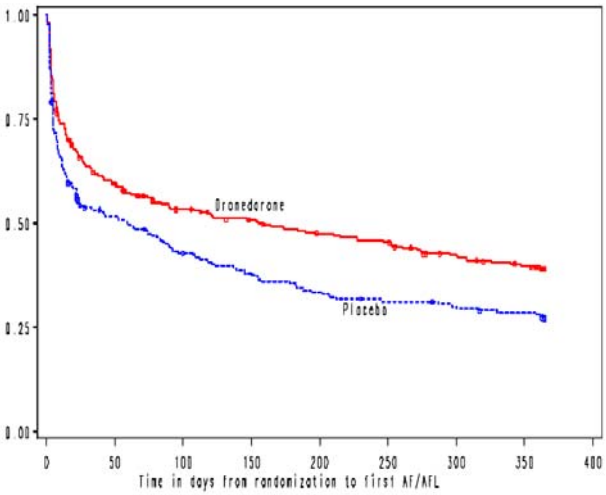
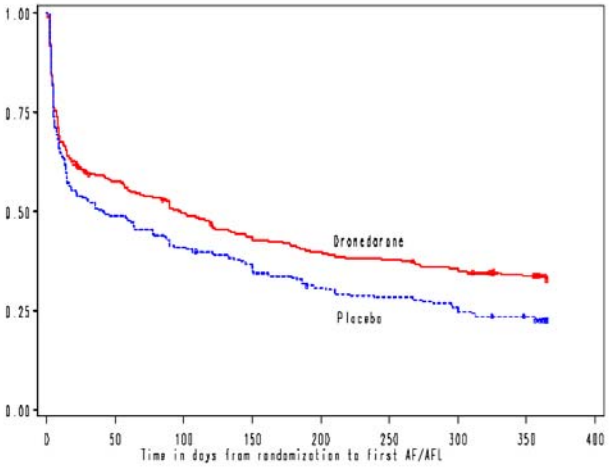
	ADONIS		EURIDIS	
	Placebo	Dronedarone	Placebo	Dronedarone
N=	208	417	201	411
Age in years (mean ±SD)	63 ± 11	65 ± 11	61 ± 11	62 ± 10
<65 N (%)	104 (50%)	186 (45%)	111 (55%)	338 (55%)
65-75 N (%)	80 (39%)	149 (36%)	76 (38%)	215 (35%)
≥ 75 N (%)	24 (12%)	82 (20%)	14 (7%)	59 (10%)
Weight in Kg (mean ± SD	88 ± 19	89 ± 20	86 ± 15	83 ± 14
Gender N- Male (%)	140 (67%)	293 (70%)	140 (70%)	285 (69%)
Race non-Caucasian N (%)	9 (4%)	26 (6%)	0	2 (<1%)
Concomitant cardiac disease, N (%)				
Hypertension	97 (47%)	242 (58%)	108 (54%)	255 (62%)
Structural heart disease	94 (46%)	199 (49%)	65 (33%)	149 (36%)
Coronary heart disease	44 (21%)	104 (25%)	31 (15%)	91 (22%)
Valvular heart disease (includes MVP)	42 (20%)	86 (21%)	19 (10%)	50 (12%)
Dilated cardiomyopathy	19 (9%)	34 (8%)	11 (6%)	16 (4%)
Functional pacemaker	13 (6%)	31 (8%)	7 (4%)	33 (8%)
Rheumatic heart disease	8 (4%)	18 (4%)	6 (3%)	7 (2%)
Hypertrophic cardiomyopathy	4 (2%)	13 (3%)	8 (4%)	10 (2%)
ICD,	2 (1%)	6 (1%)	3 (1%)	0
Congenital heart disease	1 (< 1%)	4 (1%)	2 (1%)	9 (2%)
LVEF (2-D Echo) mean ± SD	57 ± 12	58 ± 11	60 ± 9	60 ± 10
NYHA Class II	26 (13%)	50 (12%)	21 (10%)	46 (11%)
Baseline medications, N (%)				
Beta blockers excluding sotalol	114 (55%)	208 (50%)	124 (62%)	245 (60%)
ACEI and/or ARB	96 (46%)	194 (47%)	94 (47%)	215 (52%)
Digitalis	55 (26%)	94 (23%)	55 (27%)	79 (19%)
Diltiazem or verapamil	55 (25%)	103 (25%)	23 (11%)	36 (9%)
Diuretics	65 (31%)	150 (36%)	60 (30%)	121 (29%)
Spironolactone	4 (2%)	23 (6%)	14 (7%)	10 (2%)
Oral anticoagulants	149 (72%)	298 (72%)	142 (71%)	273 (66%)
Anti-platelet drugs	88 (42%)	191 (46%)	64 (32%)	135 (33%)
Statins	79 (38%)	168 (40%)	52 (26%)	95 (23%)

The two groups were reasonable well balanced. There were differences however, in the baseline demographics that include: the presence of hypertension, structural and coronary heart disease, which was more frequent in the dronedarone group. Approximately 90% of those enrolled were NYHA class I.

Primary efficacy outcome for time to first arrhythmic recurrence and the secondary outcome of time to first symptomatic arrhythmia recurrence, indicate a superiority of dronedarone to placebo in both studies.

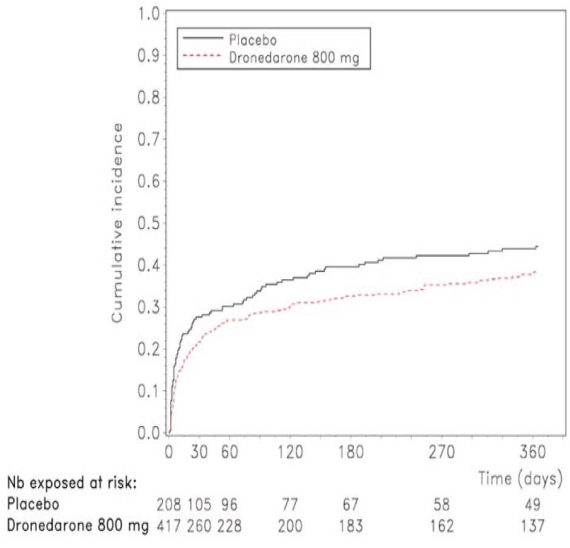
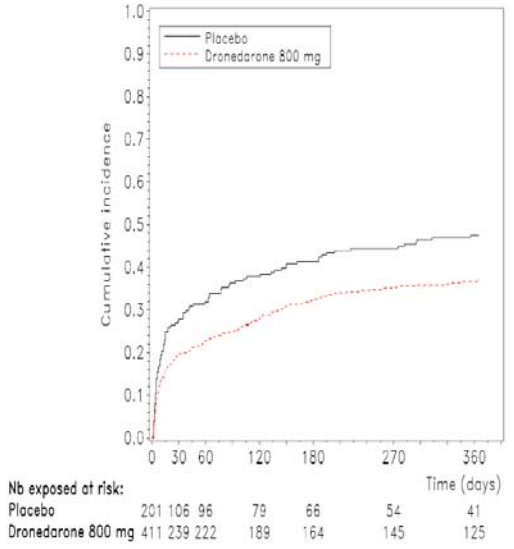
The Kaplan-Meier curve for the recurrence –free time for both ADONIS and EURIDIS is shown below. There was an approximately 27% decrease in risk of arrhythmia recurrence in the dronedarone relative to placebo patients.

Figure 5: Time course for recurrence of arrhythmia ADONIS (left) and EURIDIS (right), with corresponding p-values:

ADONIS	EURIDIS
 (figure provided by Dr. Valeria Freidlin) Figure 6- Primary efficacy endpoint, time to first AF/AFL	 (Figure provided by Dr. Valeria Freidlin) Figure 9- Primary efficacy endpoint, time to first AF/AFL
Relative risk (Cox Regression Model) [95%CI] 0.725 [0.59-0.89]	Relative risk (Cox Regression Model) [95%CI] 0.743 [0.57-0.96]

There was a statistically significant difference, comparing dronedarone to placebo, in the time to first symptomatic events (Figure 6). The sponsor also indicated a significant difference in time to recurrence after steady state for both ADONIS and EURIDIS (data not re-analyzed by FDA).

Figure 6: Time to first symptomatic recurrence in ADONIS (left) and EURIDIS (right), and p-values:

ADONIS	EURIDIS
	
Log rank test p=0.021	Log rank test p=0.0037

Ventricular rate at time of recurrence:

The heart rate at the time of first adjudicated recurrence is shown below. In both the ADONIS and EURIDIS study this heart rate was lower among those treated with dronedarone. Only in the EURIDIS study was effect significant. In neither study was the mean heart rate at the time of recurrence in what one would consider acceptable control (60-80 bpm).

Table 7; ventricular rate at time of recurrence in ADONIS (left) and ADONIS (right):

	ADONIS		EURIDIS	
	Placebo	Dronedarone	Placebo	Dronedarone
Heart rate	111 ± 32	103 ± 28	112 ± 29	100 ± 25
	P=0.078		P<0.001	

Choice of dose:

The only empirical data for the choice of both the dose of dronedarone (800 mg daily) with food is derived solely from the DAFNE[4] study. This study was a multinational, multicenter, double-blind, parallel-arm, placebo-controlled study comparing dronedarone versus placebo, in patients currently in atrial fibrillation who are planned for cardioversion. Patients were started on medication either placebo, or dronedarone at a dose of 400, 600 or 800 mg BID. The primary endpoint was time to recurrence of atrial fibrillation. The primary statistical analysis was the dose-response effect to the time recurrence of atrial fibrillation in those who could be cardioverted or who spontaneously reverted to normal sinus rhythm. The analytic plan assessed doses as evenly spaced parameters, using a Cox's model. The analytic plan included two baseline covariates in addition to dose; presence of structural heart disease and duration of current episode of atrial fibrillation.

Of the 270 subjects who were randomized and received blinded medication 205 were eventually cardioverted (electrical or pharmacologic) or spontaneously reverted to sinus rhythm and entered the intent to treat maintenance phase. Of these patients, there was no overall dose response in the time to recurrence of atrial fibrillation (p=0.7). Despite the overall lack of significant effect in the truncated population, the sponsor suggested that the 400 mg BID dose separated itself from the two higher doses. There was a substantially larger drop out rate that appeared dose-related, but was particularly evident at the 1600 mg dose.

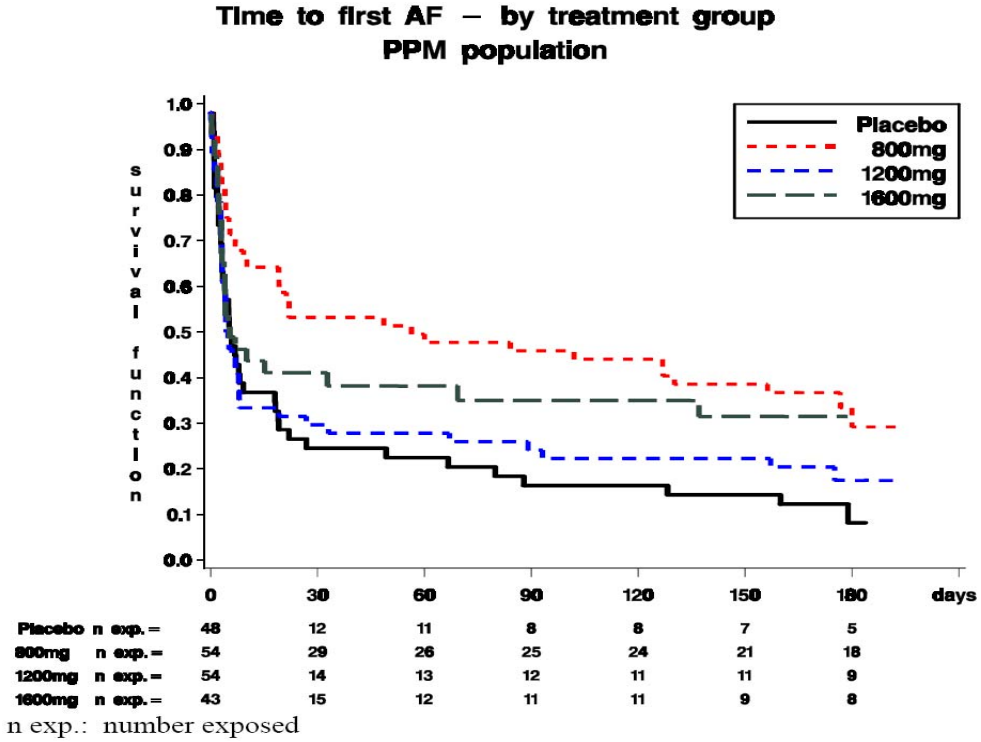
[4] Dronedarone Atrial Fibrillation study after Electrical cardioversion-DRI3550

Table 8: Disposition of patients in the DAFNE study:

Population	Placebo	Dronedarone (daily dose divided BID)			Total
		800 mg	1200 mg	1600 mg	
Randomized	66	76	66	62	270
In NSR at baseline	0	0	0	1	1
Randomized and treated	66	76	66	61	269
Adverse event	0	3	5	15	23
Patient request	1	0	1	0	2
Protocol Deviation	0	2	0	2	2
Other	0	0	0	1	1
Cardioversion failures	17	16	7	11	51
Entered Maintenance	49	56	56	44	205
Adverse event	0	1	3	10	14
Patient request	1	0	0	0	1
Protocol Deviation	0	0	0	0	0
Other	0	0	0	1	1
Completed	48	55	53	33	189

The time course to recurrence of first arrhythmia is shown below. The significance as tabulated by the sponsor is immediately following. Overall there was no dose effect (p=0.7).

Figure 7: Recurrence of arrhythmia in DAFNE for those in sinus rhythm by spontaneous conversion or pharmacologic/electrical methods when entering the maintenance phase:



n exp.: number exposed

The data as submitted do not rule out that higher of lower doses than 400 mg BID would be a reasonable anti-arrhythmic dose. The usable dose range for dronedarone is therefore, uncertain.

Indication of rate control:

The ERATO[5] study enrolled patients with symptomatic atrial fibrillation with a resting ventricular rate ≥ 80 BPM, for which cardioversion was not considered. Notable exclusion criteria included grade III or IV NYHA heart failure. Subjects had 24 hour Holters performed at baseline and day 14. Exercise testing, by graded cycle ergometry was also performed at baseline and day 14.

Primary endpoint:

The primary endpoint was the change in heart rate, averaged over 24 hours, as assessed by Holter. This rate was analyzed by an analysis of covariance taking into account as covariates, treatment and baseline medications that could alter heart rate, as well as demographic factors such as age and baseline heart rate.

Secondary end point included:

- The decrease in ventricular rate during sub-maximal and maximal symptom limited exercise test compared to baseline without decreasing exercise performance. Exercise performance was estimated by measurement of the maximum work load reached and the gas exchange variables.

- The decrease in mean ventricular rate measured by 24-hours at 4 months.

At each of the monthly visits, the subject filled out the Bubien and Kay patient symptom questionnaire. This questionnaire asked the patient about sixteen symptoms potentially related to the underlying atrial fibrillation. The questions attempted to capture the frequency and intensity of these symptoms over the previous thirty-day period. Frequency was assessed by summing the scores of the sixteen symptoms with 0= never to 4= always. Severity for each of the 16 symptoms was graded from 0= never to 3=extreme.

The study enrolled 185 patients. Those patients enrolled from one study site were excluded. Of the remaining 174 subjects, 89 received placebo and 85 dronedarone at a dose of 400 mg BID. There were 79 and 68 completers in the placebo and dronedarone groups, respectively. There were 10 and 17 discontinuations in the placebo and dronedarone group respectively, with 9 in placebo and 13 in the dronedarone attributed by the sponsor to adverse events.

Underlying cardiovascular disease was similar in the two treatments. The most common disease (and %) were: hypertension (48%), structural heart disease (38%), valvular disease (17%) and coronary artery disease (17%). Of those enrolled approximately 28% were NYHA class II. Approximately 87% were taking oral anticoagulants and 15% chronic anti-platelet therapy. Medications to control heart rate, with the exception of calcium antagonists, were similar in the two treatment groups and included beta-blockers (53%) and digitalis (43%).

[5] Efficacy and safety of dronedarone for the control of ventricular rate during atrial fibrillation. EFC 4508.

Calcium antagonists (verapamil or diltiazem) were used in 17% of placebo and 29% of dronedarone groups. It is unclear if patients were on maximal doses of those drugs which offer some rate control prior to the start of randomized treatment. Since there are pharmacokinetic effects of dronedarone with CYP2D6 (β-blockers), CYP3A4 (verapamil and diltiazem) and PGP (digoxin) substrates, the possibility that some of the heart rate effects may be a consequence of dronedarone's effect on these concomitant therapies cannot be dismissed.

Comparing dronedarone to placebo there was a -11.7 beat per minute difference on average heart rate throughout the 24-hour Holter on the day 14 assessments ($p < 0.0001$). There was also a decrease in maximal heart rate on exercise ergometry at day 14 of -25 bpm ($p < 0.001$). There was a change in heart rate at the final 4-month assessment -8.8 bpm ($p< 0.001$). There were however, no differences in duration of exercise performance (-0.12 minutes) p= NS, gas-exchange variables or Bubien and Kay frequency or severity scores.

Since only one dose regimen of dronedarone was studied for rate control, it is not possible to determine if better rate control would result from higher doses or a more benign safety profile with adequate rate control could be achieved by the use of lower doses.

Interdosing interval:

Based on pharmacokinetic considerations the BID dose interval appears appropriate. Below are some data from the ADONIS, EURIDIS, ANDROMEDA and ERATO studies from population PK sampling (adopted from Dr. Kumi's Table 8). For each study C_{min} was > 50% of C_{max}.

Table 9: C_{max} and C_{min} for dronedarone concentrations in the EURIDIS, ADONIS, ERATO and ANDROMEDA studies.

		EURIDIS	ADONIS	ANDROMEDA	ERATO
Dronedarone	C_{max} (ng/ml)	106 (50)	98 (64)	101 (54)	92 (107)
	C_{min} (ng/ml)	66 (56)	60 (58)	65 (66)	56 (56)
SR35021	C_{max} (ng/ml)	59 (45)	53 (51)	61 (500	50 (56)
	C_{min} (ng/ml)	40 (44)	38 (46)	36 (62)	38 (33)

With respect to the ERATO study any dynamic effect on heart rate at the interdosing interval that could be analyzed for an effect at the interdosing interval. This information was not supplied.

Safety:

Exposure:

The exposure among those enrolled into the atrial fibrillation/flutter or rate control studies are shown below. The studies include DAFNE, ERATO, EURIDIS and ADONIS. The ANDROMEDA study will be described separately.

Table 10: Exposure information atrial fibrillation studies:

	Placebo	Dronedarone		
		400 mg BID	600 mg BID	800 mg BID
N=	564	989	66	62
Mean days ± SD	205 ± 141	240 ± 142	64 ± 76	57 ± 71
Patient-years	316.7	650.3	11.6	9.7
Exposure at day				
30	446	833	23	23
180	316	661	12	9
360	100	283	0	0
Patients with TEAE (per patient year)	340 (1.1)	660 (1.0)	42 (3.6)	45 (5.9)
Serious TEAE (per patient year)	79 (0.25)	133 (0.20)	4 (0.34)	8 (0.82)
Deaths* (per patient year)	3 (0.009)	9 (0.014)	0	0
Patients discontinued (per patient year)	34 (0.10)	96 (0.15)	4 (0.34)	14 (1.4)
* Deaths from first dose till ten days after last dose.				

The numbers of patient-year exposure for dronedarone is approximately double that of placebo. There were a reasonable number of dronedarone subjects treated for approximately 1 year (360 days). There appears to be a dose response relationship, when correcting for patient exposure when considering TEAE and serious TEAE. Deaths within 10-days of completing treatment, when normalized to patient exposure, were greater in the dronedarone group.

Deaths-atrial fibrillation studies :

The following are the description of the deaths associated with the Afib studies. The numbers that I get differ from the numbers in the above table. Overall there were 7 (0.22 per patient year) deaths among those randomized to placebo and 15 among those treated with dronedarone 400 mg BID (0.23 per patient year). One placebo patient died from sudden death. There were four patients who were currently on dronedarone who died sudden deaths. The small number of events is neither alarming nor reassuring for the use of dronedarone in this population.

Table 11: Summary of death in the atrial fibrillation database (ADONIS, EURIDIS, ERATO and DAFNE):

Study	Pt ID/Age/gender	Description
Placebo		
xERATO	528005004/70 y-o Male	Infiltrate noted day 44, diagnosed as malignant neoplasm. Patient D/C'd drug on day 57 and died day 102.
xEURIDIS	528011008/77 y-o female	Never treated, died 11 months later.
ADONIS	124024042/72 y-o. male	Sudden death day 117.
ADONIS	124028001/84 y-o female	Had two non-Q-wave MIs, died day 254 of circulatory collapse
ADONIS	8400020008/72 y-o male	Day 73 had dyspnea and hemoptysis. Day 79 diagnosed with bacteremia. Died day 82.
xADONIS	840036006/63 y-o male	Day 140 heart failure worsened. Day 152 developed renal failure and became dialysis dependent. Medications D/C'd. Died 62 days later.
ADONIS	840040010/ 69 y-o Female	Hospitalized day 13 for chest pain (musculoskeletal). Day 15 had CVA. Died day 16.
Dronedarone		
xDAFNE	22050008/77 y-o male	Episode of trauma (ran over by tractor). Meds D/C'd. Died 4 weeks later.
ERATO	250004003/31 y-o female	Family history of early sudden death (father age 35, brother age 19). She was S/P surgery to correct ostium primum defect. Died day 8 from sudden death.
ERATO	528009007/75 y-o male	UTI day 163, medication D/C's day 169. Died day175.
xEURIDIS	528005001/85 y-o male	On day 282 had pacemaker implanted. Day 324 hospitalized for dyspnea. Died day 418 (94 days after drug D/C).
EURIDIS	528006007/77 y-o male	Died day 3 of sudden death.
EURIDIS	528011027/69 y-o male	Had MI day 310 (increased CPK and MB fraction). Lapsed into coma 2 days later and died.
ADONIS	32005005/ 79 y-o male	Hospitalized day 50 for fatigue and dyspnea (heart failure hx). V-fib on day 67 leading to death.
xADONIS	124011006/79 y-o male	History of CHF, CAD, HBP. Hospitalized day 3 for CHF. Hospitalized day 86 for AF. Med D/C and started on quinidine. Sudden death 8 weeks later.
ADONIS	124032005/77 y-o female	Had 2 episodes of pulmonary edema on days 60 and 89. On day 106 developed pulmonary edema and enterococcal septicemia. Died 12 days later.
ADONIS	710006002/83 y-o female	Sudden death on day 19. Baseline EF was 33%.
ADONIS	710006004/77 y-o female	Day 282 severe AF (associated with surgery to bunion). Day 299 chest pain with third degree A-V block. Developed cardiogenic shock and died.
xADONIS	84002004/86 y-o male	Day 132 diagnosed with metastatic liver and lung disease. Died day 224.
xADONIS	840004014/72 y-o female	Randomized but never received drug. Died from vertebral-basilar artery insufficiency (had events just prior to dosing).
xADONIS	84001006/64 y-o female	Had implantable defibrillator electively removed. Died 5 months post last dose of multiple myeloma.
ADONIS	840040011/48 y-o male	Obese, HBP, DM, had EF 27% at baseline. Died day 288 of sudden death.

X=unlikely to be related to study drug.

Deaths-ANDROMEDA:

The ANDROMEDA[6] study randomized 627 subjects (originally the study planned to enroll 1000 subjects) in a 1:1 ratio to either dronedarone 400 mg BID or placebo. The study was carried out in six Western European countries. It was prematurely discontinued seven months after randomization of the first patient due to an adverse mortality outcome in the dronedarone-treated patients.

The ANDROMEDA study enrolled subjects with symptomatic CHF (NYHA class II-IV), a wall motion index (WMI)[7] of $\leq$ 1.2 and requiring recent hospitalization and treatment with

[6] ANtiarrhythmic trial with DRONedarone in Moderate to severe CHF Evaluating morbidity DecreAse –EFC4966

[7] The wall motion index was determined by a central echocardiography laboratory after reading the baseline 2D-echocardiogram. The assessment averaged the segmental wall motion score over 16 segments. The individual scoring was as follows: Pronounced paradoxical motion (-1.0); slight paradoxical motion (-0.5); akinesia (0); pronounced hypokinesia (0.5); moderate hypokinesia (1.0); slight hypokinesia (1.5); normokinesis (2.0); slight hyperkinesia (2.5); pronounced hyperkinesia (3.0).

diuretics. The abnormal wall motion index reflects left ventricular dysfunction. According to the sponsor, multiplying the WMI by 30 approximates the EF. Notable exclusion criteria included recent myocardial infarction, recent decompensated heart failure (e.g., acute pulmonary edema, shock requiring pressors or acute MI), cardiomyopathy, or use of Vaughn-Williams Class I or III anti-arrhythmic agents.

There were 2402 patients screened, of which 650 were randomized and treated. The results of one center that enrolled 23 patients were excluded for poor quality control. Of the remaining 627 patients 317 were randomized to placebo and 310 to Dronedarone.

Selected baseline demographics are shown in Table 12.

Table 12: Demographics, cardiovascular history, cardiac status and selected concomitant medications in ANDORMEDA

Parameter	Placebo	Dronedarone
N=	317	310
Age, years (mean ± SD	69 ± 12	70 ± 12
Gender, Number male (%)	242 (76%)	230 (74%)
Race # non-Caucasian (%)	1 (<1%)	2 (1%)
Weight Mean ± SD, Kg	79 ± 19	78 ± 17
Cardiovascular history, selected, N=(%)		
Coronary heart disease	201 (63%)	266 (66%)
Valvular heart disease	175 (55%)	171 (55%)
Hypertension	107 (34%)	123 (40%)
Dilated cardiomyopathy	103 (33%)	79 (26%)
Diabetes mellitus	62 (20%)	73 (24%)
CABG	42 (13%)	57 (18%)
Severe ventricular arrhythmia	33 (10%)	33 (11%)
Stroke	31 (10%)	24 (8%)
Cardiac status		
Wall motion Index, mea ± SD	0.86 ± 0.23	0.90 ± 0.23
NYHA class (II/III/IV) (%/%/%)	118/186/13 (37%/59%/4%)	126/178/6 (41%/57%/3%)
Concomitant medications, selective, N (%)		
Diuretics	309 (98%)	297 (96%)
ACE-I/ARB	267 (84%)	274 (88%)
Chronic anti-platelet therapy	196 (62%)	203 (66%)
Oral anti-coagulants	102 (32%)	92 (28%)
Bet blockers (except sotalol)	191 (60%)	192 (62%)
Statins	97 (31%)	113 (57%)
Cardiac glycosides	101 (32%)	96 (31%)
Verapamil/diltiazem	12 (4%)	9 (3%)

In general, the two groups appear well matched at baseline. Those enrolled were largely male and nearly all Caucasian, most were NYHA class III failure. Given the underlying CHF, the fraction of patients using of diuretics and ACE-I/ARB are appropriate.

Although the primary endpoint of the study was composite of time to death or hospitalization for CHF, the DSMB recommended the discontinuation of the study because of an increase in the number of deaths in the placebo relative to the dronedarone-treated patients.

The relative risk for death and for the composite of death and hospitalization for adjudicated heart failure are shown below.

Figure 8 : Kaplan-Meier plots for death (left) and death or hospitalization for heart failure (right) in ANDROMEDA

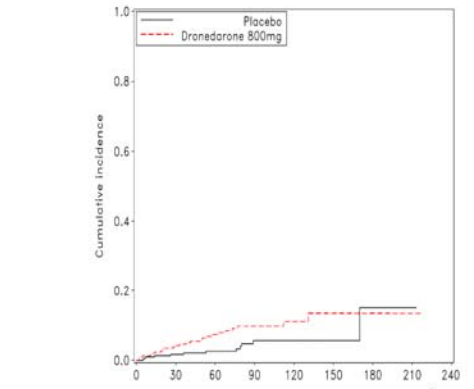


Figure (11.2.1) 1 - Kaplan-Meier cumulative incidence curves from randomization to death up to 16 January 2003- randomized and treated patients population excluding center 616004

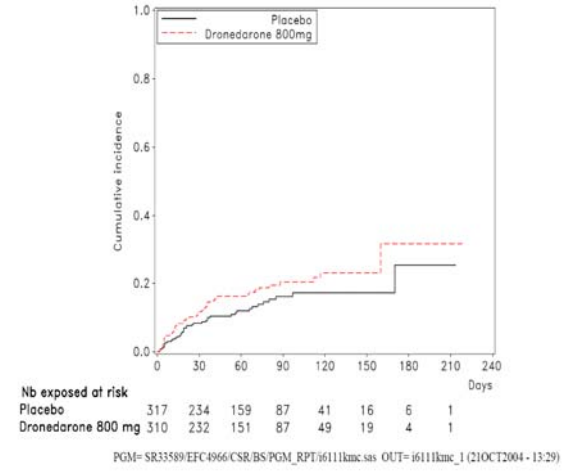


Figure (11.1.1) 1 - Kaplan-Meier cumulative incidence curves from randomization to death or hospitalization for worsening heart failure up to 16 January 2003- randomized and treated patients population excluding center 616004

Hazard ratios for several clinically meaningful measurements are shown Table 13. All Hazard ratios favor placebo. The upper CI for death extends beyond a factor of 4. The adjudicated cause of death is shown in Table14.

Table 13: Outcomes and statistical assessments for ANDROMEDA:

Parameter	Placebo N=317	Dronedarone N=310	Hazard ratio (95% CI	Log-rank p-value
Death	12	25	2.13 (1.1-4.2)	0.03
Died or hospitalized for worsening heart failure	40	53	1.38 (0.92-2.1)	0.12
Number hospitalized for worsening failure	31	39	Not calculated	0.27
Number hospitalized for cardiovascular reasons	50	71	Not calculated	0.02

Table 14: Adjudicated causes of death are shown below and (fraction of population) [fraction of deaths] ANDROMEDA:

	Placebo (N= 317)	Dronedarone (N=310)
Number of Events	12	25
Cardiovascular death	9 (3%) [75%]	24 (8%)[96%]
MI	2 (1%) [17%]	0
Worsening CHF	2 (1%)[17%]	10 (3%) [40%]
Documented arrhythmia	2 (1%) [17%]	6 (2%) [24%]
Procedure related	0	1 (<1%) [4%]
Other CV reason	0	2 (1%) [8%]
Presumed CV reason	3 (1%) [25%]	5 (2%) [20%]
Non-cardiovascular	2 (1%)[17%]	1 (< 1%) [4%]
Cancer	1 (< 15) [8%]	1 (< 1%) [4%]
Other	1 (<1%) [8%]	0
Non-adjudicated death	1 (<1%)[8%]	0

There was an increase in predominantly worsening heart failure deaths, but arrhythmia events were also increased.

The sponsor postulated that the increase in deaths in the dronedarone group in the ANDROMEDA study is a consequence of dronedarone's ability to inhibit creatinine secretion into the urine (see later). The sponsor further postulated that the patients with elevated creatinine would be more likely to have their ACE-I /ARB medication discontinued, losing the benefit of these treatments and predisposing to a negative mortality and hospitalization outcome.

The above postulated mechanism would suggest the following sequence of events. First, the subject would have an asymptomatic creatinine elevation, leading to the discontinuation of the ACE-I/ARB and only then would the patient be at risk for cardiac decompensation or death.

Although it is true that many dronedarone patients discontinued the ACE-I/ARB treatment than did placebo patients. Among those who died, there were few subjects whose creatinine increases was unrelated to either a cardiac or renal insult.

Discontinuations atrial fibrillation:

Table 15 contains a listing of Meddra terms applied to the discontinuations among those in the atrial fibrillation database. There did not appear to be substantial difference in comparing the placebo to dronedarone treatments. All 7 subjects who discontinued due to renal and urinary tract investigations were in the dronedarone treated group, consistent with the ability of dronedarone to alter creatinine measurements.

Table 15: Meddra terms for those discontinuing, limited to those > 5 events in the dronedarone 400 mg BID group in the atrial fibrillation database.

Meddra Term	Placebo	Dronedarone		
		400 mg BID	600mg BID	800 mg BID
Number exposed	564	989	66	62
Any event leading to discontinuation	34 (6%)	96 (10%)	4 (6%)	14 (23%)
Gastrointestinal (GI) Disorder	7 (1%)	16 (2%)	1 (1%)	7 (11%)
GI signs and symptoms	4 (1%)	7 (1%)	1 (1%)	3 (5%)
GI motility and defecation conditions	3 (1%)	4 (< 1%)	0	4 (7%)
Investigations	1 (<1%)	18 (2%)	0	2 (3%)
Renal and urinary tract investigations or urinalyses	0	7 (1%)	0	0
Hepatobiliary investigations	1 (< 1%)	5 (1%)	0	0
Cardiac disorders	10 (2%)	14 (1%)	2 (3%)	1 (2%)
Cardiac arrhythmias	4 (1%)	12 (1%)	1 (1%)	0
Nervous system disorders	6 (1%)	14 (1%)	0	1 (2%)
Neurological disorders	3 (1%)	9 (1%)	0	1(2%)
Skin and subcutaneous tissue disorders	3 (1%)	13 (1%)	0	1 (2%)
Epidermal and dermal conditions	2 (< 1%)	12 (1%)	0	1 (2%)
General disorders and administrative site conditions	2 (< 1%)	12 (1%)	1 (2%)	1 (2%)
General system disorders	1 (< 1%)	7 (1%)	1 (2%)	1 (2%)
Respiratory, thoracic and mediastinal disorders	2 (< 1%)	6 (1%)	0	0
Eye disorder	2 (< 1%)	5 (1%)	0	0

Overall adverse events atrial fibrillation:

Overall adverse events are shown below for any event limited to Meddra terms that contain more than 10 patients who were treated with the dronedarone 400 mg BID group. The bolded listings are those that appear more frequent in the dronedarone group and may be related to treatment.

Table 16: Meddra terms for overall adverse events in the atrial fibrillation database limited to major events:

Meddra Term	Placebo	Dronedarone		
		400 mg BID	600mg BID	800 mg BID
Number exposed	564	989	66	62
Any event leading to discontinuation	340 (60%)	660 (67%)	42 (64%)	45 (72%)
Gastrointestinal (GI) Disorder	**90 (16%)**	**188 (19%)**	**13 20%)**	**22 (36%)**
GI signs and symptoms	56 (10%)	112 (11%)	9 (14%)	9 (15%)
GI motility and defecation conditions	**37 (7%)**	**79 (8%)**	**5 (8%)**	**18 (29%)**
GI hemorrhage nec	2 (1%)	13 (1%)	1 (2%)	0
Infection and Infestations	**95 (17%)**	**194 (20%)**	**7 (11%)**	**7 (11%)**
Infections-pathogen class unspecified	**70 (12%)**	**155 (16%)**	**5 (8%)**	**5 (8%)**
Viral infectious disorder	24 (4%)	45 (5%)	1 (2%)	2 (3%)
Nervous system disorders	81 (14%)	144 (15%)	4 (6%)	6 (10%)
Neurological disorders	32 (6%)	77 (8%)	2 (3%)	4 (7%)
Headaches	40 (7%)	54 (6%)	2 (3%)	3 (5%)
Movement disorders (inc parkinsonism)	2 (< 1%)	10 (1%)	0	0
Investigations	**49 (9%)**	**133 (13%)**	**10 (15%)**	**8 (13%)**
Hepatobiliary investigations	13 (2%)	34 (3%)	3 (5%)	2 (3%)
Renal and urinary tract investigations or urinalyses	**3 (1%)**	**31 (3%)**	**2 (3%)**	**3 (5%)**
Enzyme investigations (nec)	5 (1%)	17 (2%)	0	0
Cardiac and vascular investigations (excl enzyme tests)	8 (1%)	11 (1%)	2 (3%)	2 (3%)
Physical examination topics	5 (1%)	12 (1%)	1 (2%)	1 (2%)
Hematology investigations	3 (1%)	13 (1%)	0	0
Endocrine investigations	5 (1%)	11 (1%)	1 (2%)	0
Cardiac disorders	**62 (11%)**	**123 (12%)**	**12 (18%)**	**13 (21%)**
Cardiac arrhythmias	26 (5%)	56 (6%)	3 (5%)	10 (16%)
Coronary artery disorders	21 (4%)	31 (3%)	0	1 (2%)
Heart failures	6 (1%)	24 (2%)	6 (9%)	2 (3%)
Cardiac disorders signs and symptoms	6 (1%)	11 (1%)	4 (6%)	3 (5%)
General disorders and administrative site conditions	60 (11%)	130 (12%)	6 (9%)	6 (10%)
General system disorders	**51 (9%)**	**115 (12%)**	**6 (9%)**	**5 (8%)**
Musculoskeletal and connective tissue disorders	61 (11%)	126 (13%)	2 (3%)	3 (5%)
Musculoskeletal and connective tissue disorders (nec)	**22 (4%)**	**61 (6%)**	**1 (2%)**	**1 (2%)**
Joint disorders	20 (4%)	52 (5%)	1 (2%)	2 (3%)
Muscle disorders	17 (3%)	28 (3%)	0	0
Respiratory, thoracic and mediastinal disorders	**58 (10%)**	**117 (12%)**	**2 (3%)**	**9 (15%)**
Respiratory disorders nec	37 (7%)	76 (8%)	1 (2%)	6 (10%)
Upper respiratory disorders (excl infections)	10 (2%)	21 (2%)	0	1 (2%)
Bronchial disorders (excl neoplasm)	7 (1%)	14 (1%)	1 (2%)	0
Lower respiratory tract disorders (excl obstruction and infect)	9 (2%)	13 (1%)	0	1 (2%)
Skin and subcutaneous tissue disorders	**36 (6%)**	**94 (10%)**	**4 (6%)**	**6 (10%)**
Epidermal and dermal conditions	**23 (4%)**	**73 (7%)**	**2 (3%)**	**3 (5%)**
Skin appendage conditions	10 (2%)	12 (1%)	1 (2%)	3 (5%)
Vascular disorders	35 (6%)	62 (6%)	1 (2%)	3 (5%)
Vascular hypertensive disorders	14 (3%)	25 (3%)	1 (2%)	1 (2%)
Increased and non-specific blood pressure	9 (2%)	14 (1%)	0	1 (2%)
Injury, poisoning and procedural complications	29 (5%)	57 (6%)	1 (2%)	2 (3%)
Injuries nec	23 (4%)	29 (3%)	1 (2%)	2 (3%)
Bone and joint injuries	4(1%)	10 (1%)	0	0
Psychiatric disorders	16 (3%)	52 (5%)	2 (3%)	1 (2%)

Sleep disorders and disturbances	9 (2%)	17 (2%)	1 (2%)	1 (2%)
Anxiety disorders and symptoms	4 (1%)	16 (2%)	1 (2%)	0
Depressed mood disorders and disturbances	2 (< 1%)	11 (1%)	0	0
Eye disorder	15 (3%)	29 (3%)	2 (3%)	2 (3%)
Vision disorders	6 (1%)	10 (1%)	1 (2%)	0
Metabolism and nutrition disorders	29 (5%)	28 (35)	3 (5%)	1 (2%)
Renal and urinary disorders	15 (3%)	26 (3%)	1 (2%)	0
Urinary tract signs and symptoms	13 (2%)	19 (2%)	0	0
Reproductive system and breast disorders	11 (2%)	24 (2%)	1 (2%)	1 (2%)
Ear and labyrinth disorders	5 (1%)	20 (2%)	3 (5%)	2 (3%)
Inner ear and 8th nerve cranial disorders	4 (1%)	16 (2%)	3 (5%)	2 (3%)
Neoplasms benign, malignant and unspecified	11 (2%)	22 (2%)	0	0
Endocrine disorders	9 (2%)	13 (1%)	0	1 (2%)
Thyroid gland disorders	9 (2%)	13 (1%)	0	1 (2%)
Blood and lymphatic system	**0**	**14 (1%)**	**0**	**0**

Thyroid:

Thyroid function measurements were measured frequently during the first month of treatment and every 1-3 months in the DAFNE, ADONIS and EURIDIS studies. Thyroid measurements were apparently not performed during the ERATO study.

There did not appear to be a strong signal in the shift-table that dronedarone provokes hypothyroidism (no increase in TSH) or hyperthyroidism (no increase in FT3).

Table 17: Thyroid measurements as shift table DAFNE, EURIDIS and ADONIS:

	FT3		FT4		TSH	
	increase	decreases	increase	decreases	increase	decreases
Dronedarone 400 mg BID	50/856 (5.8%)	15/856 (1.8%)	5/857 (0.6%)	7/857 (0.8%)	30/857 (3.5%)	28/857 (3.3%)
Placebo	38/439 (8.7%)	2/439 (0.5%)	9/439 (2.1%)	1/439 (0.2%)	16/439 (3.6%)	34/439 (7.7%)

Pulmonary toxicity

One subject # 348001007, a 72 year-old male enrolled in the EURIDIS study, had an adverse event of mild pulmonary fibrosis that led to discontinuation after 6 months of treatment. Baseline laboratory measurements including chest X-ray were listed as normal. Dr. C. Katalin head, radiology department Karolyi hospital, read side-by side, the baseline and end of treatment X-rays, and he concluded that the pulmonary fibrosis was present at the initial, baseline evaluation. The subject, however, did not have PFTs or a lung biopsy either at baseline or at the time of discontinuation, so that one can't definitively be sure that pulmonary fibrosis was present at baseline and if so, that it did not worsen during treatment.

There was an increase in events that might reflect early fibrosis. There were more adverse events listed as dyspnea and cough with dronedarone than with placebo. Whether these events are sentinel symptoms to early fibrosis or they reflect early heart failure (as an Ib sodium channel blocker, dronedarone is likely a negative inotrope) is unclear.

Mean duration of exposure to dronedarone is modest. Although there appears to be a reasonable numbers of subjects exposed for > 360 days, pulmonary fibrosis may take longer to become overt.

Renal clearance:

Dronedarone at a dose of 400 mg BID compared to placebo had a decrease in creatinine clearance of approximately 18%, with minimal differences in sinistrin (a non-cation substrate used to measure clearance). Dronedarone also inhibited clearance of N^1-methylnicotinamide (NMN) a substrate of the tubular organic cation transporter. Suggesting that the effect of dronedarone is on transport of cations and therefore could increase creatinine levels in the absence of a deleterious effect on renal function. There did not appear to any effect on renal blood flow (PAH clearance) or urinary 24-hour electrolyte excretion.

DMETS comments:

DMETS comments reflect concerns for labeling and the package insert. These issues will be revisited should an approval recommendation be made.

Biopharmaceutic comments:

Comments to Sponsor

- Please indicate when results from the hepatic impairment study, POP5820, will be submitted to the Agency. Without this information, the product labeling will be restrictive in this patient population
- You have not adequately addressed the issue of dose-response in the target population; therefore dosage adjustment is not feasible during dronedarone therapy.
- You have not provided sufficient permeability information to support dronedarone designation as BCS 2. Please provide all available information that demonstrate dronedarone is a high permeability compound.
- The dissolution methodology is acceptable, however, we do not agree with your dissolution specification. Based on the data provided the following specification is more appropriate: 1) Not less than 25 % and not more than 50 % is dissolved within 30 minutes 2) Q = 80 at 90 minutes
- In future submissions, any concentrations and/or subjects that have been excluded from the analysis should be maintained in the datasets. For this analysis, the sponsor identified 123 concentrations (from 10 subjects) as outliers and excluded these observations from the dataset.
- Please refer to the attached, revised label for detailed labeling recomendations

Chemistry comments:

IV. List Of Comments

A. Regarding the Drug Substance

1. Please add a particle size specification of D(0.9) and submit appropriate data.

B. Regarding the Drug Product

1. Please provide a labeled chromatogram from the ID / assay test via liquid chromatography (LC), which is actually a reverse-phase (RP) – HPLC based method.

2. Please restate the all assay specifications and test results as a percentage plus/minus a specific range.

3. Please remove the 'hydrochloride' from the label, package insert and carton(s). By convention, salts are not included in the established name.

   In addition Multaq® is expressed as the free base; that is, the drug contains 426 mg of dronedarone hydrochloride which corresponds to 400 mg dronedarone base. Hence inclusion of the term 'hydrochloride' is unnecessary.

4. The analytical method for uniformity of mass is Ph. Eur. 2.9.5. Please convert the test method to a USP/NF method.

5. Please submit the following information concerning the dissolution studies:

   a. All relevant dissolution data at 60 minutes for both the clinical and stability batches for the *film-coated tablet*.

   b. As in a) above, but for the *tablet core(s)*. (Note: The submission contains only disintegration data).

Medical officer comments:

1. The ongoing trial EFC5555 must show both efficacy and safety.
2. Other doses in the range of 50 mg to 800 mg should be investigated.

Additional comments:

1. Please submit an hour-by hour assessment of heart rate during the ERATO study to assess that the heart rate effects persist during the interdosing interval.
2. Please submit the CRFs for those who had asymptomatic elevated levels of creatinine during the ANDROMEDA study.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Abraham Karkowsky
2/19/2009 01:09:07 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 26, 2009

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of Cardiovascular and Renal Products, HFD-110.

TO Dr. Robert Temple, Director, ODE-1.

SUBJECT: Dronedarone Hydrochloride (Multaq®, SR33589B); Sanofi-aventis, U.S., Inc. as sponsor; NDA 22-425.

This memo is a follow-up to my original memo dated April 26, 2006 (edited on February 18, 2009) for NDA 21,913 which recommending an approvable action for dronedarone should the sponsor be able to demonstrate that a population can be defined which both benefited by treatment and which can be safely treated. This current memo largely consists of the CDTL memo of NDA #22-425 entered into DFS on February 19, 2009. Included in this current memo, however, are recommendations suggested by the advisory committee meeting of March 19, 2009 as well as pharmacology and biopharmaceutic studies that were not reviewed in the February 19, memo.

The current NDA # 22-425 differs in the original NDA number for dronedarone because it requests additional claims compared to those of NDA 21,913. The pivotal information in this submission is the results of the ATHENA study. The results of the ATHENA appear to define a population which derives benefit from dronedarone use and in whom safety was demonstrated.

In addition to the ATHENA study, the new clinical information summarized in this memo relates to the ANDROMEDA study. This latter study was previously reviewed. The sponsor halted the study for an adverse mortality outcome in the dronedarone-treated subjects. In this memo, I have included an analysis of those subjects who died during this study who were withdrawn from angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs), or were not treated with these classes of drugs at baseline. I have also added some additional analyses concerning the degree of heart failure among those who died during the ANDROMEDA study. It does not appear that the mortality excess, as observed in the ANDROMEDA study can be explained by a model in which subjects had asymptomatic creatinine increases which provoked discontinuation of ACE-I or ARB treatment and only then resulted in cardiac decompensation. Nearly all the events which provoked discontinuation of the ACE-I/ARB treatment appear to be acute exacerbations of either renal or cardiac disease at the time these drugs were discontinued.

The labeling recommendations are based on the results of the ATHENA study. This study randomized 4628 subjects, across 37 countries and 551 centers who had at least one previous episode of atrial fibrillation or flutter and one normal ECG (not necessarily in that order) within the last six months. Subjects were randomized in a 1:1 ratio to receive either dronedarone at a dose of 400 mg BID with food or placebo. For those who were not in sinus rhythm at the time of enrollment, the subject was to undergo an attempt at cardioversion.

Subjects were to be elderly (over 70 years old). Initially, however, they could be any age but have additional risk factors for the development of cardiovascular events. A subsequent amendment modified the enrollment criteria to require subjects to be over 75 with the history of atrial fibrillation (AFib) or atrial flutter (AFl) as above, or over 70 with the same history but have one additional cardiovascular risk factor. Notable exceptions for enrollment included a history of chronic atrial fibrillation. Subjects were to be followed for one year after the last subject enrolled.

The primary endpoint of the study, time to first cardiovascular hospitalization or death, was highly significant favoring dronedarone ($p< 10^{-7}$). The primary secondary analysis, all-cause death was not significant but numerically favored of dronedarone ($p=0.2$). Several of these deaths that were captured occur at time points after to the proposed cut-off date. Most of those post-cut-off events occurred in the placebo group, making the lean on mortality slightly less convincing.

Since the primary secondary endpoint, all-cause death, was not significant, the other two secondary endpoints should be considered as exploratory.

With respect to cardiovascular hospitalizations, this result highly favors dronedarone. The significance is driven entirely by the AFib/AFl hospitalizations. The underlying reason that subjects were hospitalized for AFib/AFl is unclear. There is too little information collected on the CRF to adequately tease out AFib/AFl events whose manifestation is other than for AFib e.g., heart failure.

With respect to cardiovascular deaths, the Steering Committee, which was composed of five independent cardiologist and three sponsor's representatives, assessed the nature of death. The broad outline of what constitutes a cardiovascular death appears somewhat arbitrary and in some cases irrelevant to events that would likely be preventable in this population. It is unclear if the new analysis of cause-specific mortality events adds clarity to assessing the benefit of dronedarone or the analysis merely allows for a second attempt at defining a mortal benefit.

Should only a small number of events be reclassified from cardiovascular to non-cardiovascular in the placebo-treated subjects, or from non-cardiovascular to cardiovascular in the dronedarone treated group, nominal significance would be lost, particularly when the analysis excludes those events, which occurred after the cut-off time. Furthermore, the results of the ATHENA study with respect to cardiovascular

outcomes are so discrepant with the results from the ANDROMEDA study, that caution should be exercised in asserting dronedarone as having a mortal benefit.

I find the results of EURIDIS, ADONIS (previously reviewed) and ATHENA coupled with that of ANDROMEDA as consistent with the conclusion that dronedarone is a useful antiarrhythmic to delay recurrence of symptoms associated with the underlying arrhythmia and to prevent atrial fibrillation hospitalizations or more specifically cardiovascular hospitalization attributable to atrial fibrillation. The results are not convincing that, dronedarone prevents other morbid or mortal outcomes.

The sponsor has also shared with us the top-line results of the DIONYSOS study. This study has not yet been reviewed but based on the sponsor's assessment the effectiveness of dronedarone in preventing atrial fibrillation is substantially less than that of amiodarone.

In summary, based on the results of the ADONIS and EURIDIS studies previously reviewed and based on the prevention of hospitalization in the ATHENA study, dronedarone should be approved for the delay recurrence of symptomatic events and decrease hospitalization for atrial fibrillation, in a population likely to have recurrence of AFib. Because of the adverse mortality effect that was observed in the ANDROMEDA study, despite the favorable lean in the ATHENA study, no mortality claim should be granted.

Safety concerns, based on the outcome of the ANDROMEDA study, strongly indicate that individuals with Class III or IV NYHA heart failure should be precluded from its use. The tricky issue is how to control those whose heart failure transitions into NYHA class III from less severe degrees of heart failure.

Labeling concerns were discussed at the above mentioned advisory committee to be included within labeling are:

- A boxed warning for patients with more than minimal degrees of heart failure
- (b) (4) [redacted]
- Safety issues related to drug interaction are to be included. These safety issues consist of:
  - Interactions with Digoxin
  - Interactions with warfarin
  - Alteration in concentrations based on food effects and use of CYP3A4 inhibitors
  - Acute and static alterations in creatinine clearances.

A risk management plan still needs to be constructed and agreed upon. It is likely that an acceptable Med-Guide will be the rate limiting step for approval.

The final establishment evaluation report (EER) is still pending and approval will be dependent on accepting the facilities as acceptable.

This review is largely based on the joint clinical-statistical review by Gail Moreschi M.D., MPH, FACP (clinical) and Valeria Freidlin, Ph.D., (statistics).

Additional information consulted in the preparation of this review is derived from the following memos:

- Chemistry review by Donghao (Robert) Lu, Ph.D. dated 18 February 2009.
- Pharmacology reviews by Elizabeth Hausner, D.V.M., dated10 December 2008 and a response to Sanofi-aventis' submission, the review date was 6 February 2009.
- Proprietary name review by Jinhee Lee PharmD., safety evaluator dated 13 January 2009
- DSI reports by Tejashri Purchit-Sheth dated 24 December 2008 (Dr. Yuri Shubik, St Petersburg, Russia); dated 24 December 2008 (Dr. Valadmir Babarich, M.D.); and 15 January 2009 (Dr. Vratislav Dedek, Czech Republic).

In addition to the above memos, previously reviewed information as included in the reviews described in my review for NDA 21, 913 are pertinent to this application and were consulted when necessary.

Data quality:

Three sites that recruited subjects for the ATHENA study Dr. Yuri Shubik, St. Petersburg, Russia; Dr. Valadmir Babarich, M.D.; and Dr. Vratislav Dedek, Czech Republic were inspected for the integrity of the data generated and collected at their clinical sites. The data from all sites were considered as adhering to the specified protocol and deemed reliable.

Chemistry review:

The chemist considered the application as acceptable. The label, however, should be labeled as "Dronedarone" versus "Dronedarone hydrochloride", to accurately define the substance that is described by the 400 mg dose. Storage recommendations were slightly altered from "up to 25◦ C" to "25◦ C". As noted above, the EER is still pending.

Proprietary name review:

The Division of Medication Error Prevention and Analysis had no objection to the proprietary name Multaq™.

Pharmacology review:

The sponsor submitted both data and arguments to mitigate the carcinogenicity labeling as recommended by the Division's pharmacologist. The CAC had previously reviewed the carcinogenicity findings and considered the following findings as drug related.

- An increase in the incidence of adenocarcinomas in mammary gland of female mice.

- An increase in histiocytic sarcomas in mice, and
- An increase in vaso-proliferative lesions in the mesenteric lymph nodes of rats and female mice.

(b) (4) With respect to the mammary tumors observed in mice, the sponsor submits both a single dose and 28 day dose study in mice. Prolactin levels were indeed significantly increased in mice treated with dronedarone compared to controls. There was an approximate factor of 4 increase after single dose and an approximately factor of 3 after 28 days of dronedarone treatment. Dr. Hausner noted that the sponsor had not assessed whether there are or are not prolactin increases in humans. (b) (4) (b) (4)

In considering the incidence of histiocytic sarcomas in mice, the sponsor suggested that, frequency of these tumors lie within the historical controls. Although the incidence of hemangiomas in rats approached 40% of the animals, there was some support that this frequency had been observed in previous experience.

The sponsor also suggests that the incidence of hemangiomas was related to altered blood flow with the build up of foamy macrophages that subsequently obstruct flow leading to the observed lesions. The sponsor in two studies was unable to demonstrate that blood flow was altered.

Dr. Hausner, based on the multiple mechanisms needed to explain away the three different observed drug-associated tumors, did not find the explanation as sufficient to mitigate the CACs assessment of drug-associated carcinogenicity. I concur.

Biopharmaceutics:

There were three studies included in this submission:

- Study POP5820 explored the kinetics of dronedarone in hepatic-impaired subjects compared to normal healthy individuals.
- Study PDY5850 explored the effect of dronedarone on the changes in serum creatinine in elderly subjects.
- Study MIH0138 examined the effect of dronedarone's metabolite SR35021 on CYP enzymes in an in vitro assay.

Study (POP5820) compared the pharmacokinetics of dronedarone in patients with moderate hepatic dysfunction [Child-Pugh class B of 7 to 9 (n=9, hepatic-impaired and n=9 normal)], treated with the proposed 400 mg BID dose administered with food. The AUC for dronedarone after 7 days of 400 mg BID dosing was approximately 30% higher for the hepatic-impaired subjects, the AUC based on the unbound fraction was nearly double that of the profile in healthy individuals. The coefficient of variation in the measured parameters was approximately double in the hepatic-impaired subjects. The high variability points to several of the small number of subjects having very high levels of dronedarone.

Conversely, the metabolite SR35021 displayed lower C_{max} and AUC in the subjects with hepatic impairment compared to the healthy volunteers. The coefficient of variation was also increased in the population with hepatic impairment.

Since there is no smaller dose than 400 mg of dronedarone and since the dronedarone tablet is not scored, it is not possible to recommend a smaller starting dose. Should one treat patients with atrial fibrillation and moderately impaired hepatic function, with dronedarone, particular attention should be made to ECG effects (QT_C), Digoxin levels and alteration serum creatinine. The DAFNE study explored doses of dronedarone up to 1600 mg daily (with non linear kinetics this dose should result in exposures in excess of the exposure to hepatic-impaired patients). Consequently, a blanket prohibition of the use of dronedarone in a moderate hepatic-impaired patient appears unwarranted. Patients with more severe hepatic dysfunction, in the absence of at least kinetic information should not be treated with dronedarone.

Study PDY5850 explored the effect of dronedarone on serum creatinine function in elderly patients. The study collected data on 29 subjects and these subjects were stratified based on the calculated (Cockroft-Gault formula) moderate CLcr between 30-50 ml/min (n=6); mild CLcr > 50 to 80 ml/min (n=7); and normal CLcr > 80 ml/min (N=6). The mean age in the dronedarone subjects ranged from 66 (normal group) to 74 (moderate group).

In the elderly with moderate decreases in renal function, creatinine values increased between day 2 and 3 and reached a plateau of an increase of approximately 10% greater than baseline. The increase in creatinine values re-approached baseline after approximately 3 days off drug.

Study MIH0138 was an in vitro study of the metabolite SR35021 and its route of degradation. The study explored the metabolism of SR35021 with several different metabolizing model systems. When SR35021 was incubated with supersomes (insect cells transfected with human CYP genes), CYP3A4 and CYP2D6 appears to be the only two human CYP enzymes that degrade this metabolite.

In human microsomes preparations, however, the two CYP enzymes CYP 3A4 and CYP2D6 contributed only 22% and 6% of the degradation of SR35021, respectively, when assessed with and without potent specific inhibitors (quinidine and ketoconazole, respectively). It should be noted that there was substantial degradation of dronedarone in these preparations but the mechanism of degradation is obscure.

Clinical-Statistical:

ANDROMEDA study:

This description of the ANDROMEDA study and the results that are included in this review were copied and pasted from the review for NDA 21-913. This review, however, includes new analyses of those who died and were either on no ACE-I or ARB

at baseline or who discontinued these medications, and the relationships of mortal events to both NYHA class and WMI at baseline.

The ANDROMEDA[1] study randomized 627 subjects (originally the study planned to enroll 1000 subjects) in a 1:1 ratio to either dronedarone 400 mg BID with food or placebo. The study was carried out in six Western European countries. It was prematurely discontinued, seven months after the randomization of the first subject, because of an adverse mortality outcome in the dronedarone-treated compared to placebo-treated subjects.

The ANDROMEDA study enrolled subjects with symptomatic CHF (NYHA class II-IV), a wall motion index (WMI)[2] of ≤ 1.2 and requiring recent hospitalization and treatment with diuretics. The abnormal wall motion index reflects left ventricular dysfunction. According to the sponsor, multiplying the WMI by 30 approximates the EF. Notable exclusion criteria included recent myocardial infarction, recent decompensated heart failure (e.g., acute pulmonary edema, shock requiring pressors or acute MI), cardiomyopathy, or use of Vaughn-Williams Class I or III anti-arrhythmic agents.

There were 2402 patients screened, of which 650 were randomized and treated. The results from one center that enrolled 23 subjects, was excluded for poor quality control. Of the remaining 627 subjects 317 were randomized to placebo and 310 to dronedarone.

Selected baseline demographics are shown in Table 1.

Table 1: Demographics, cardiovascular history, cardiac status and selected concomitant medications in ANDORMEDA

Parameter	Placebo	Dronedarone
N=	317	310
Age, years; Mean ± SD	69 ± 12	70 ± 12
Gender: Number male (%)	242 (76%)	230 (74%)
Race: # non-Caucasian (%)	1 (<1%)	2 (1%)
Weight: Mean ± SD, Kg	79 ± 19	78 ± 17
Cardiovascular history, selected, N= (%)		
Coronary heart disease	201 (63%)	266 (66%)
Valvular heart disease	175 (55%)	171 (55%)
Hypertension	107 (34%)	123 (40%)
Dilated cardiomyopathy	103 (33%)	79 (26%)
Diabetes mellitus	62 (20%)	73 (24%)
CABG	42 (13%)	57 (18%)
Severe ventricular arrhythmia	33 (10%)	33 (11%)
Stroke	31 (10%)	24 (8%)

[1] ANtiarrhythmic trial with DRONedarone in Moderate to severe CHF Evaluating morbidity DecreAse –EFC4966.

[2] The wall motion index was determined by a central echocardiography laboratory after reading the baseline 2D-echocardiogram. The assessment averaged the segmental wall motion score over 16 segments. The individual scoring was as follows: Pronounced paradoxical motion (-1.0); slight paradoxical motion (-0.5); akinesia (0); pronounced hypokinesia (0.5); moderate hypokinesia (1.0); slight hypokinesia (1.5); normokinesis (2.0), slight hyperkinesia (2.5); pronounced hyperkinesia (3.0).

Cardiac status		
Wall motion Index, mean ± SD	0.86 ± 0.23	0.90 ± 0.23
NYHA class (II/III/IV) (%/%/%)	118/186/13 (37%/59%/4%)	126/178/6 (41%/57%/3%)
Concomitant medications, selective, N (%)		
Diuretics	309 (98%)	297 (96%)
ACE-I/ARB	267 (84%)	274 (88%)
Chronic anti-platelet therapy	196 (62%)	203 (66%)
Oral anti-coagulants	102 (32%)	92 (28%)
Beta-blockers (except sotalol)	191 (60%)	192 (62%)
Statins	97 (31%)	113 (37%)
Cardiac glycosides	101 (32%)	96 (31%)
Verapamil/diltiazem	12 (4%)	9 (3%)

In general, the two groups appear well matched at baseline. Those enrolled were largely male and nearly all Caucasian, most were in NYHA class III failure. Given the underlying CHF, the fraction of subjects using of diuretics and ACE-I/ARB are appropriate.

Although the primary endpoint of the study was composite of time to death or hospitalization for CHF, the DSMB recommended the discontinuation of the study because of an increase in the number of deaths in the dronedarone-treated relative to the placebo-treated subjects. The relative risk for death and for the composite of death and hospitalization for adjudicated heart failure are shown below.

Figure 1 : Kaplan-Meier plots for death (left) and death or hospitalization for heart failure (right) in ANDROMEDA

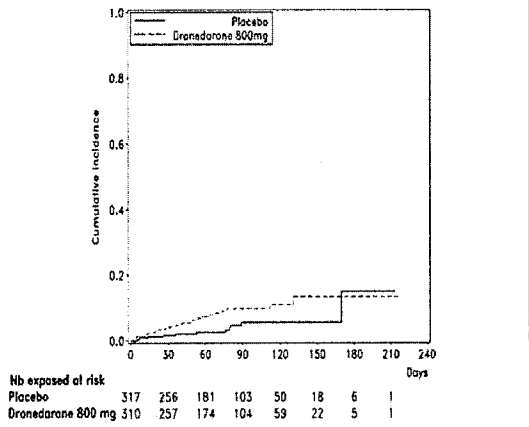


Figure (11.2.1) 1 - Kaplan-Meier cumulative incidence curves from randomization to death up to 16 January 2003- randomized and treated patients population excluding center 616004

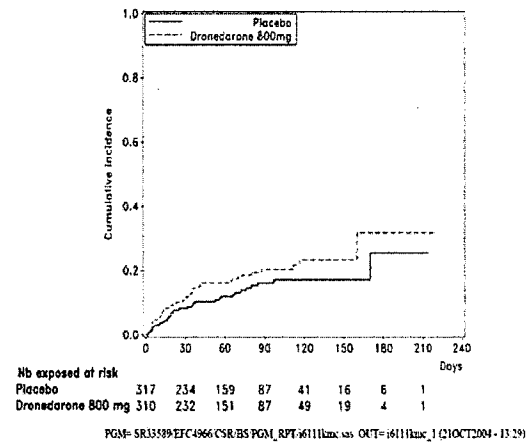


Figure (11.1.1) 1 - Kaplan-Meier cumulative incidence curves from randomization to death or hospitalization for worsening heart failure up to 16 January 2003- randomized and treated patients population excluding center 616004

Hazard ratios for several clinically meaningful measurements are shown in Table 2. All Hazard ratios favor placebo. The upper CI for death extends beyond a factor of 4. The adjudicated cause of death is shown in Table 3.

Table 2: Outcomes and statistical assessments for ANDROMEDA:

Parameter	Placebo N=317	Dronedarone N=310	Hazard ratio (95% CI	Log-rank p-value
Death	12	25	2.13 (1.1-4.2)	0.03
Died or hospitalized for worsening heart failure	40	53	1.38 (0.92-2.1)	0.12
Number hospitalized for worsening failure	31	39	Not calculated	0.27
Number hospitalized for cardiovascular reasons	50	71	Not calculated	0.02

Table 3: Adjudicated causes of death are shown below and (fraction of population) [fraction of deaths] ANDROMEDA:

	Placebo (N= 317)	Dronedarone (N=310)
Number of Events	12	25
Cardiovascular death:	9 (3%) [75%]:	24 (8%)[96%]:
MI	2 (1%) [17%]	0
Worsening CHF	2 (1%)[17%]	10 (3%) [40%]
Documented arrhythmia	2 (1%) [17%]	6 (2%) [24%]
Procedure related	0	1 (<1%) [4%]
Other CV reason	0	2 (1%) [8%]
Presumed CV reason	3 (1%) [25%]	5 (2%) [20%]
Non-cardiovascular	2 (1%)[17%]	1 (< 1%) [4%]
Cancer	1 (< 15) [8%]	1 (< 1%) [4%]
Other	1 (<1%) [8%]	0
Non-adjudicated death	1 (<1%)[8%]	0

The increase in mortality was predominantly attributed to worsening heart failure deaths, but arrhythmia deaths were also increased. Among those who died, the greatest increase in death for dronedarone subjects was NYHA Class III subjects. With respect to wall motion index, I have broken down the populations to capture approximately 25% in each cutoff. Most of the deaths occurred among those with the worst WMI.

Table 4 NYHA class and the risk of death in the ANDROMEDA study.

Placebo- NYHA	Dronedarone-NYHA
NYHA II- 5/118 (4.2%)	NYHA II-7/126 (5.6%)
NYHA III- 7/186 (3.8%)	NYHA III-17/178 (9.6%)
NYHA IV-0/13 (0%)	NYHA IV-1/6 (17%)

Table 5 Wall motion index (WMI) at baseline and the risk of death-ANDROMEDA study

Placebo-WMI	Dronedarone-WMI
0.3-0.7= 0/115 (0%)	0.3-0.7= 9/84 (10.7%)
0.8-0.9= 4/77 (5.2%)	0.8-0.9= 6/65 (9.2%)
1.0-1.0 =5/67 (7.4%)	1.0-1.0 =1/75 (1.3%)
1.1-1.2= 3/73 (4.1%)	1.1-1.2= 9/95 (9.4%)

The sponsor postulated that the increase in deaths in the dronedarone group in the ANDROMEDA study is a consequence of dronedarone's ability to inhibit creatinine secretion into the urine, these subjects with elevated creatinine would be more likely to have their ACE-I /ARB medication discontinued, losing the benefit of these treatments and predisposing to a negative mortality and hospitalization outcome.

The above postulated mechanism would suggest the following sequence of events. First, the subject would have an asymptomatic creatinine elevation leading to the discontinuation of the ACE-I/ARB and only then would the patient be at risk for cardiac decompensation or death.

Although more dronedarone subjects discontinued the ACE-I/ARB treatment than did placebo subjects, among those who died, there were few subjects whose creatinine increases were unrelated to either a cardiac or renal insult. The percentage of subjects who were treated with dronedarone who died was substantially higher whether they were not treated with ACE-I/ARBs at baseline or discontinued from these medications. The relationship between ACE-I/ARB use status and mortal events is shown below.

Table 6: Outcome of ANDROMEDA based on ACE-I/ARB status

	Placebo	Dronedarone
Number enrolled	317	310
Number not on ACE-I /ARB at baseline (A)	50	36
Number who died (% of A)	1 (2%)	6 (16%)
Number on ACE-I/ARB at baseline and throughout (B)	255	255
Number on B who died (% B)	10 (4%)	10 (4%)
Number who discontinued from ACE-I/ARB (C)	12	19
Number who died (% C)	1 (8%)	9 (47%)

There were 12 placebo subjects and 25 dronedarone-treated subjects who died. Of these deaths, nine of the placebo subjects and 24 of the dronedarone subjects died of cardiovascular events. Among the subjects in the placebo group who died, one death occurred in a subject who never received ACE-I or ARB. In the dronedarone group there were six subjects who died in this category. Among the subjects who were treated and remained on ACE-I/ARB, deaths were the same in both groups.

The capsular summaries for these subjects who were treated with dronedarone and were discontinued from the ACE-I or ARB are provided below. None of these events can be interpreted as an asymptomatic creatininemia, provoking the discontinuation of ACE-I /ARB treatments.

Dronedarone subjects:
Subject # 208 103009 was an 81 year-old female with a history of myocardial infarction and chronic atrial fibrillation. Her NYHA was Class III. She was hospitalized for increased blood creatinine but received a glucose infusion (was it really glucose + insulin for hyperkalemia?) and transfusions. The subject died 11 days after admission from worsened heart failure. The hospitalization death was attributed to worsened CHF.

Subject 208116008 was a 66 year-old female with a history of myocardial infarction and dilated cardiomyopathy. She was hospitalized on (b) (4) (6 days after randomization) for interstitial nephropathy. She stopped her ACE-I (trandolapril) one day after admission. She required hemodialysis beginning two days after admission. She died one week after admission. At admission she had elevated serum K+ (5.9 mEq/L) and increased weight gain.

Subject 208126010 was a 70 year-old male with a cardiac history of hypertrophic cardiomyopathy. The subject was admitted after approximately 4 weeks of treatment with dronedarone for unstable angina for a CABG procedure. Cozaar was stopped during this hospitalization. The subject had an MI two days after the discontinuation of the Cozaar and he died about a week later. The MI preceded ventricular tachycardia and the need for a mechanical surrogate heart.

Subject 208137001 was an 87 year-old male with a history of coronary artery disease and NYHA class III. The subject was admitted two weeks after enrollment for increase in creatinine and worsening heart failure. Ramipril was discontinued two days later. The subject died two months later from worsening heart failure. There was one intervening hospitalization for worsening failure and palpitations.

Subject 578304006 was a 77 year-old female with a history of coronary artery disease, myocardial infarction, mitral regurgitation and diabetes mellitus. She discontinued Cozaar on (b) (4) and died on (b) (4) from metastatic disease.

Subject 616002003 was a 56 year-old male with idiopathic dilated cardiomyopathy and chronic atrial fibrillation. The subject was admitted and had among other conditions, worsening renal function, and heart failure, which required assisted ventilation. The subject died during that hospitalization (2 1/2 weeks after admission). Quinapril was discontinued at the time of the hospitalization.

Subject 752211001 was an 82 year-old male with a history of coronary artery disease, myocardial infarction, mitral regurgitation and atrial fibrillation. The subject was admitted approximately one week after enrollment for among other reasons worsening heart failure and pneumonia. The subject discontinued ramipril after the subject was admitted. The subject died approximately 5 weeks later from worsening heart failure.

Subject 752215002 was admitted for worsening heart failure after about 3 days of dronedarone treatment and had ramipril discontinued at that time. The subject was admitted approximately two weeks later for worsening heart failure and died during that hospitalization.

Subject 752220004 was a 79 year-old female with a history of myocardial infarction. She was in sinus rhythm and NYHA class III at randomization. She was hospitalized approximately 3 weeks later for worsening heart failure and her ramipril was stopped during that hospitalization. She died 1 ¾ months later from worsening heart failure.

Aside from the one subject who died from a metastatic process, all subjects who discontinued their ACE-I or ARB treatments were symptomatic either with renal or cardiac decompensation at the time of discontinuation.

The ATHENA[3] study:

This study was a double-blind, placebo-controlled study comparing dronedarone to placebo in subjects who had both an ECG demonstrating atrial fibrillation and one demonstrating normal sinus rhythm within 6 months (in either order) of enrollment. The original enrollment criteria required subjects, in addition, to be over 70 years old or to have one of the following risk factors: (hypertension, diabetes, prior CVA, left atrial diameter greater than 50 mm by M-mode echocardiography or left ventricular ejection fraction less than 0.40 by 2D echocardiography). The protocol was amended to alter the enrollment criteria to those who had the above document ECG rhythms and who were over 75 years old or those who were over 70 and also had one of the above noted risk factors. Ostensibly, the reason for this change was to more closely align the age range of this study with that of the AFFIRM[4] study and the SPORTIF studies[5].

Notable exclusions from the study included subjects in permanent atrial fibrillation, subjects with unstable cardiovascular status including those who have pulmonary edema (within 12 hours), require pressors (within 4 weeks), or subjects with GFR < 10 ml/min. Concomitant precluded medications included include Vaughan-Williams class I and III antiarrhythmic drugs. Subjects were stratified based on center and the presence or absence of atrial fibrillation/atrial flutter at the time of randomization.

The pre-specified endpoint of the study was time to first cardiovascular hospitalizations or death. Subjects were to be followed for the duration of the study which was to be 12 months after the enrollment of the last subject. For those who completed the study the data were to be right censored at that time.

The primary method of analysis is a 2-sided Log-rank asymptotic test at a level of 0.05. The cumulative incidence function in each treatment group was to be calculated using a non-parametric Kaplan-Meier estimate with a Cox proportional Hazard model to estimate the Hazard ratio.

The primary secondary endpoint is all cause mortality. If the difference in death was statistically significant, other secondary endpoints, first hospitalization for cardiovascular reasons and cardiovascular deaths would be analyzed. The cardiovascular nature of either a hospitalization or death was left to the investigator who filled out a check-box form. There was no pre-specified adjudication committee nor was a complete description of the event available to this reviewer to assess the validity of the

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[3] 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 patENts with Atrial fibrillation/atrial flutter (AF/AFL).

[4] Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control I patients with atrial fibrillation. N Eng J Med 2002; 347: 1825-33.

[5] Ford GA, Choy AM, Deedwania P, Karalis DG, Lindholm CJ, Pluta W, Frison, L, Olsson SB, and on behalf of the SPORTIF III,V Investigators. Direct Thrombin Inhibition and Stroke Prevention in Elderly Patients With Atrial Fibrillation: Experience From SPORTIF III and V Trials. Stroke 2007 38: 2965-2971.

cause-specific events. An amendment to the protocol transferred the responsibility for categorizing mortal events to the Steering Committee (after 85 deaths had already occurred). The Steering Committee consisted of 5 independent cardiologists and 3 members of the sponsor. Subjects were followed throughout the study even after the first cardiovascular hospitalization or discontinuation of therapy. An interim look for efficacy/futility was included after 485 subjects achieved the end point.

The study planned to originally enroll 3700 subjects in order to achieve 970 total events. An amendment was submitted August, 2006 (this was early in the study) to increase the sample size to 4300 subjects in order to have a better chance to demonstrate a benefit on mortality. The sponsor notes that the decision to change the size of the study was based on a blinded assessment of mortal events. The final study size, however, was substantially larger (4628).

The study randomized 2327 subjects to placebo and 2301 to dronedarone 400 mg BID. There were 551 study centers from 37 countries (Eastern and Western Europe, South America, North America, Middle East and Asia).

The disposition of subjects within the study and the demographics of those enrolled are shown below.

Figure 2: Disposition of subjects in the ATHENA study

Placebo	Dronedarone
Total Randomized N=4628	
Randomized N= 2327	Randomized N=2301
Completed study N=2325 Lost to follow-up N=2	Completed study N= 2301 Lost to follow-up N= 0
Completed on drug N= 1611 Discontinued drug but followed N=716 Reason for discontinuation: Adverse event N= 191 Poor compliance N= 14 Subject's request N=175 Other N =336	Completed on drug N= 1605 Discontinued drug but followed N=696 Reason for discontinuation: Adverse event N= 293 Poor compliance N= 14 Subject's request N=173 Other N=216

The demographics of those enrolled per sponsor are shown below:

Table 7: Demographics of those enrolled in the ATHENA study

Parameter	Placebo (n=2327)	Dronedarone (n=2301)
Age, years mean ± SD	72 ± 9.0	72 ± 8.9
Gender [male/female] (% female)	[1289/1038][(45%)	[1170/1131] (49%)
Race [Caucasian/black/Asian/Other] (%Caucasian)	[2072/31/154/70] (89%)	2065/19/150/70 (89%)
Cardiovascular history N (%)		
Hypertension	1996 (86%)	1999 (87%)
Structural heart disease	1402 (61%)	1330 (58%)
Tachycardia	797 (34%)	752 (33%)
Coronary heart disease	728 (31%)	661 (29%)
Non-rheumatic valvular heart disease	354 (15%)	331 (14%)
Pacemaker	243 (10%)	214 (9%)
Lone atrial fibrillation	139 (6%)	140 (6%)
Ischemic dilated cardiomyopathy	118 (5%)	92 (4%)
Ablation for AFib/AFl	106 (5%)	90 (4%)
Supraventricular tachycardia not AFib/AFl	98 (4%)	97 (4%)
Previous cardiac valve surgery	95 (4%)	80 (4%)
Non-ischemic dilated cardiomyopathy	84 (4%)	80 (4%)
Hypertrophic cardiomyopathy	50 (2%)	45 (2%)
Other history N (%)		
Hypercholestrolemia	1002 (43%)	1034 (45%)
Dyslipidemia	778 (33%)	756 (33%)
NIDDM	398 (17%)	423 (18%)
Chronic pulmonary disease	314 (14%)	297(13%)
Hypothyroidism	227 (10%)	263 (11%)
Malignant neoplasm	192 (8%)	165 (7%)
Embolic or thrombotic disease	159 (7%)	175 (8%)
Syncope	140 (6%)	154 (7%)
Hyperthyroidism	100 (4%)	154 (7%)
Chronic renal failure	83 (4%)	85 (4%)
Other parameters N (%)		
Number of subjects in atrial fibrillation/flutter at randomization per stratification factor (%)	586 (25%)	569 (25%)
Left atrial diameter (2D –echocardiogram), mean ±SD	44 ± 7.0	44 ± 6.8
Left ventricular ejection fraction (%) 2-D echocardiogram, mean ± SD	57 ± 11	57 ± 11
NYHA class III	109 (5%)	91 (4%)

There were some differences in the baseline demographic characteristics of the two groups. In particular, there were more females, less structural heart disease (coronary heart disease and/or dilated cardiomyopathy and/or non-ischemic dilated cardiomyopathy), less coronary heart disease, more hypercholestolemia, in the dronedarone treated group. The mean ejection fraction in this study was at 57%, there were few subjects who were NYHA class III and the overlap between this population and that of the ANDROMEDA study is likely minimal. Some concomitant therapies are shown below.

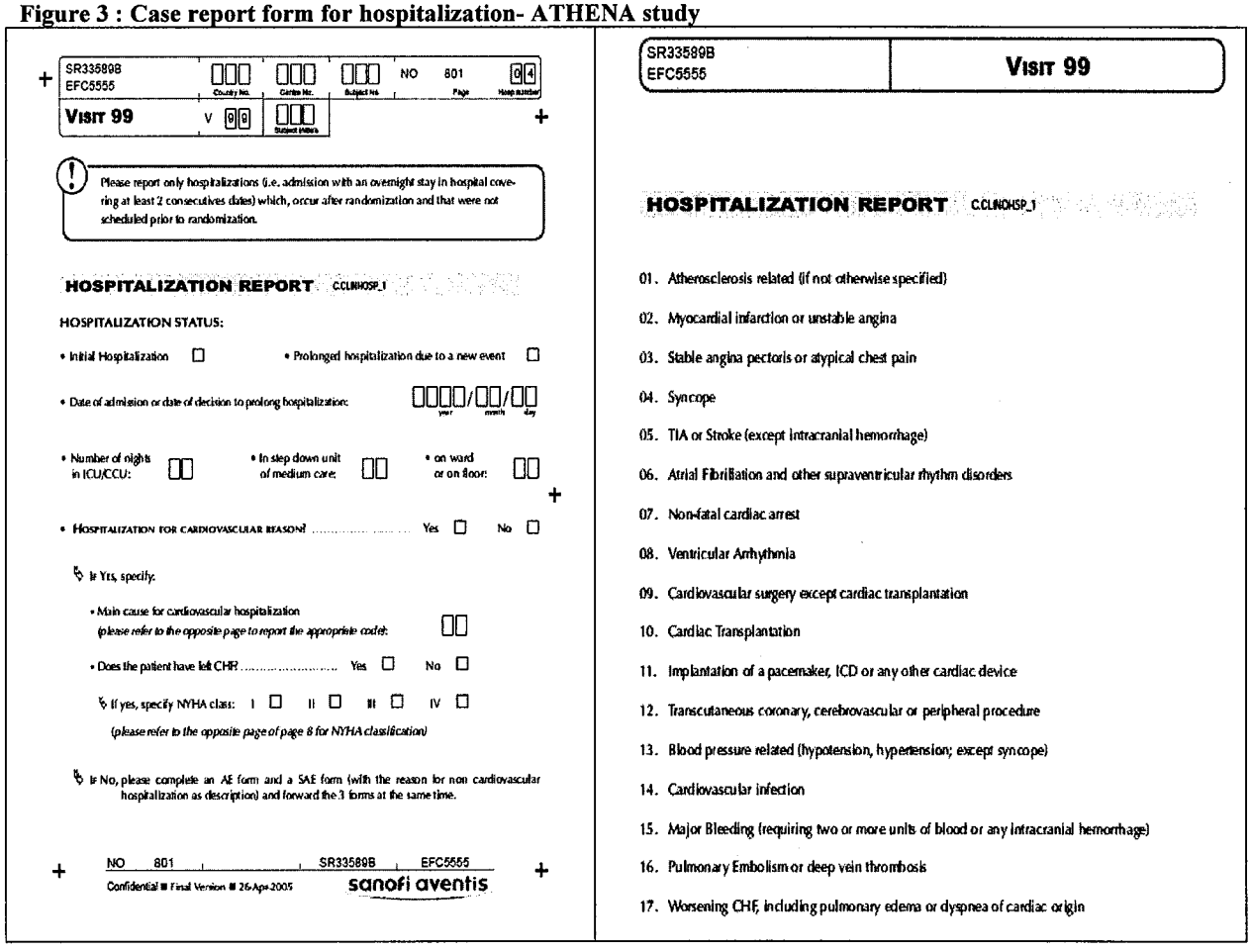
Table 8; Baseline medication for those enrolled in the ATHENA study N (%)

Beta blockers	1860 (80%)	1785 (78%)
ACE inhibitors/angiotensin II receptor antagonists	1800 (77%)	1771 (77%)
Oral anticoagulants	1643 (71%)	1601 (70%)
Spironolactone	136 (6%)	148 (6%)
Diuretics	1522 (65%)	1492 (65%)
Digitalis	574 (25%)	468 (20%)
Calcium antagonists (non-dihydropyridine)	490 (21%)	459 (20%)
Statins	1131 (49%)	1044 (45%)

Baseline medication seems reasonably well balanced between treatments. There were more subjects in the placebo group treated with beta blockers at baseline.

Before describing the outcome of the study, it is perhaps appropriate to describe how the information was captured. The following data were the entirety of the information collected as part of the CRF. The information that was collected was skeletal and forced a categorization that may not have been totally accurate.

Figure 3 : Case report form for hospitalization- ATHENA study



SR33589B EFC5555 — VISIT 99

Please report only hospitalizations (i.e. admission with an overnight stay in hospital covering at least 2 consecutives dates) which, occur after randomization and that were not scheduled prior to randomization.

HOSPITALIZATION REPORT CCLINHOSP_1

HOSPITALIZATION STATUS:

- Initial Hospitalization ☐
- Prolonged hospitalization due to a new event ☐
- Date of admission or date of decision to prolong hospitalization: ☐☐☐☐/☐☐/☐☐ (year/month/day)
- Number of nights in ICU/CCU: ☐☐ | in step down unit of medium care: ☐☐ | on ward or on floor: ☐☐
- HOSPITALIZATION FOR CARDIOVASCULAR REASON? ..... Yes ☐ No ☐

If Yes, specify:

- Main cause for cardiovascular hospitalization (*please refer to the opposite page to report the appropriate code*): ☐☐
- Does the patient have left CHF ..... Yes ☐ No ☐

If yes, specify NYHA class: I ☐ II ☐ III ☐ IV ☐

(*please refer to the opposite page of page 8 for NYHA classification*)

If No, please complete an AE form and a SAE form (with the reason for non cardiovascular hospitalization as description) and forward the 3 forms at the same time.

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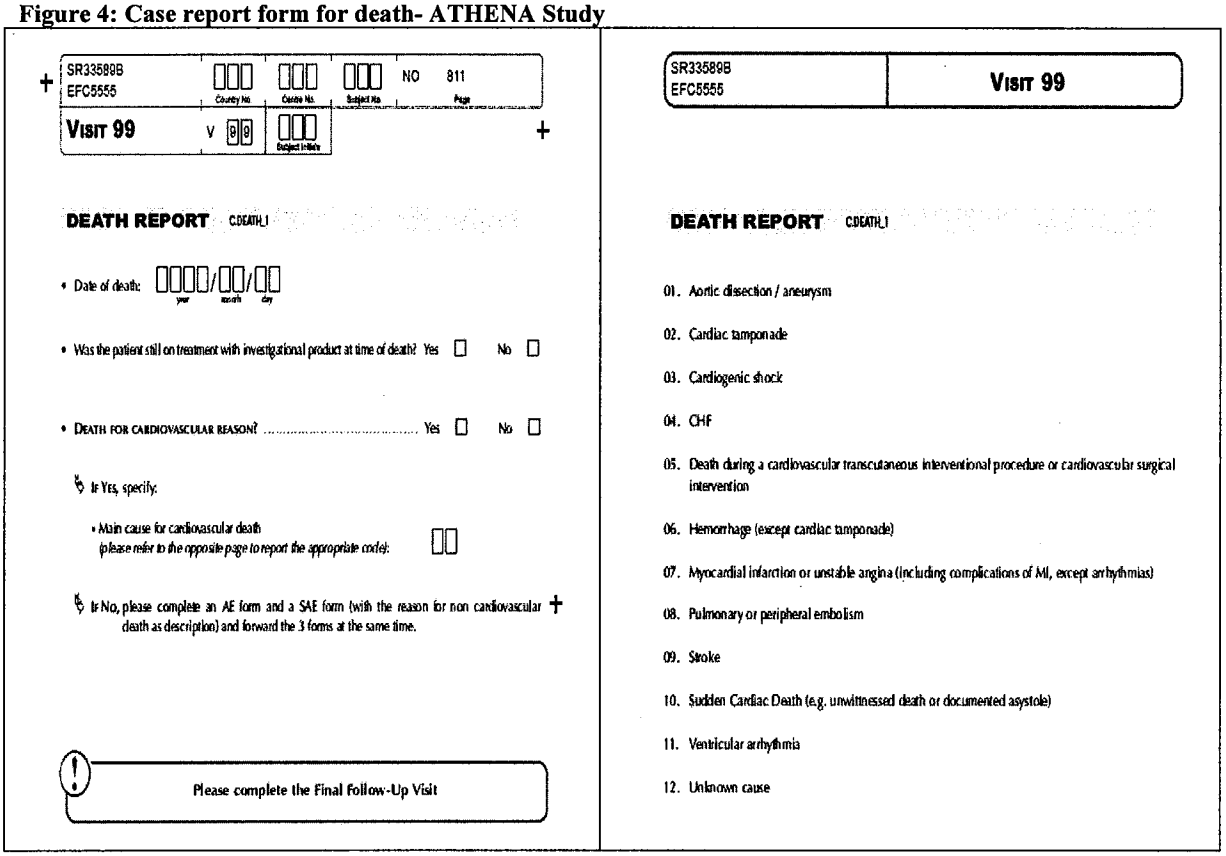
HOSPITALIZATION REPORT CCLINOHSP_1

01. Atherosclerosis related (if not otherwise specified)
02. Myocardial infarction or unstable angina
03. Stable angina pectoris or atypical chest pain
04. Syncope
05. TIA or Stroke (except intracranial hemorrhage)
06. Atrial Fibrillation and other supraventricular rhythm disorders
07. Non-fatal cardiac arrest
08. Ventricular Arrhythmia
09. Cardiovascular surgery except cardiac transplantation
10. Cardiac Transplantation
11. Implantation of a pacemaker, ICD or any other cardiac device
12. Transcutaneous coronary, cerebrovascular or peripheral procedure
13. Blood pressure related (hypotension, hypertension; except syncope)
14. Cardiovascular infection
15. Major Bleeding (requiring two or more units of blood or any intracranial hemorrhage)
16. Pulmonary Embolism or deep vein thrombosis
17. Worsening CHF, including pulmonary edema or dyspnea of cardiac origin

Figure 4: Case report form for death- ATHENA Study



SR33589B
EFC5555

Country No. | Centre No. | Subject No. | NO 811 Page

VISIT 99 V 99 Subject Initials

DEATH REPORT CDEATH_I

- Date of death: ____/__/__ year month day
- Was the patient still on treatment with investigational product at time of death? Yes ☐ No ☐
- DEATH FOR CARDIOVASCULAR REASON? ..... Yes ☐ No ☐

If Yes, specify:

- Main cause for cardiovascular death
  (please refer to the opposite page to report the appropriate code): ☐☐

If No, please complete an AE form and a SAE form (with the reason for non cardiovascular death as description) and forward the 3 forms at the same time.

Please complete the Final Follow-Up Visit

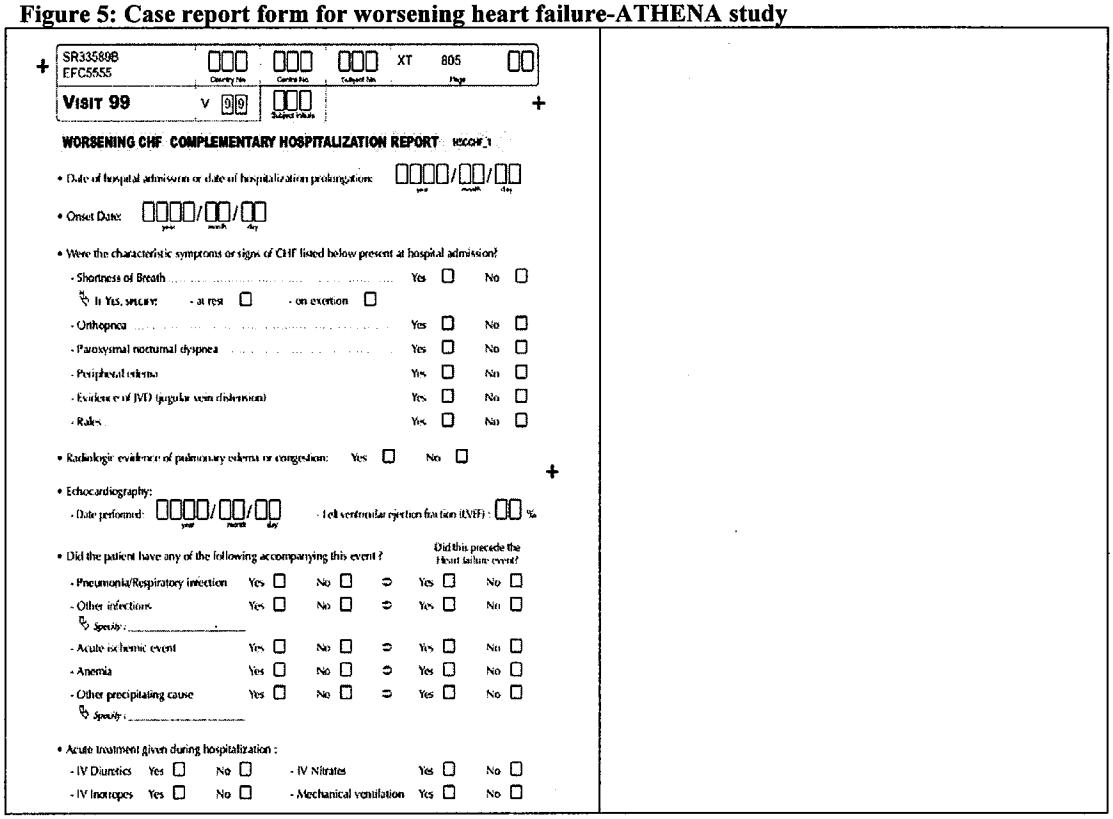
SR33589B
EFC5555

VISIT 99

DEATH REPORT CDEATH_I

01. Aortic dissection / aneurysm
02. Cardiac tamponade
03. Cardiogenic shock
04. CHF
05. Death during a cardiovascular transcutaneous interventional procedure or cardiovascular surgical intervention
06. Hemorrhage (except cardiac tamponade)
07. Myocardial infarction or unstable angina (including complications of MI, except arrhythmias)
08. Pulmonary or peripheral embolism
09. Stroke
10. Sudden Cardiac Death (e.g. unwitnessed death or documented asystole)
11. Ventricular arrhythmia
12. Unknown cause

Figure 5: Case report form for worsening heart failure-ATHENA study



SR33589B
EFC5555
Country No. Centre No. Subject No. XT 805 Page

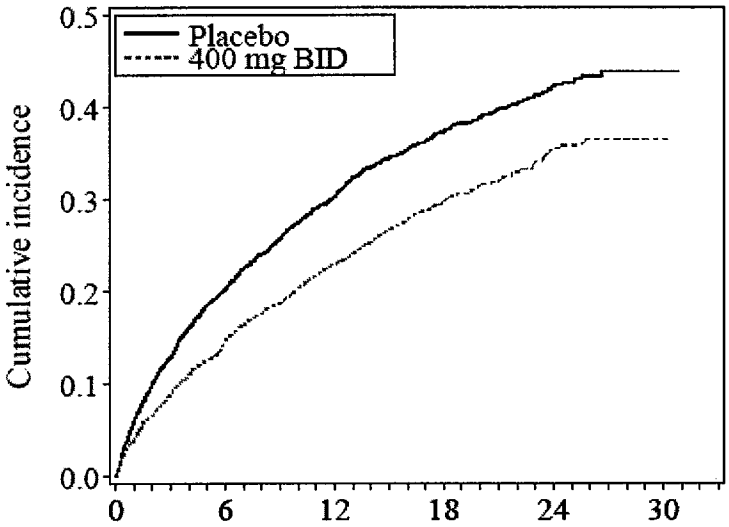
VISIT 99 V 99 Subject Visit No.

WORSENING CHF COMPLEMENTARY HOSPITALIZATION REPORT HOSCHF_1

- Date of hospital admission or date of hospitalization prolongation: ____/__/__ (year/month/day)
- Onset Date: ____/__/__ (year/month/day)
- Were the characteristic symptoms or signs of CHF listed below present at hospital admission?
  - Shortness of Breath ..... Yes ☐ No ☐
    - If Yes, specify: - at rest ☐ - on exertion ☐
  - Orthopnea ..... Yes ☐ No ☐
  - Paroxysmal nocturnal dyspnea ..... Yes ☐ No ☐
  - Peripheral edema Yes ☐ No ☐
  - Evidence of JVD (jugular vein distension) Yes ☐ No ☐
  - Rales Yes ☐ No ☐
- Radiologic evidence of pulmonary edema or congestion: Yes ☐ No ☐
- Echocardiography:
  - Date performed: ____/__/__ (year/month/day) - Left ventricular ejection fraction (LVEF): __ %
- Did the patient have any of the following accompanying this event? / Did this precede the Heart failure event?
  - Pneumonia/Respiratory infection Yes ☐ No ☐ ⇒ Yes ☐ No ☐
  - Other infection Yes ☐ No ☐ ⇒ Yes ☐ No ☐
    - Specify: _____
  - Acute ischemic event Yes ☐ No ☐ ⇒ Yes ☐ No ☐
  - Anemia Yes ☐ No ☐ ⇒ Yes ☐ No ☐
  - Other precipitating cause Yes ☐ No ☐ ⇒ Yes ☐ No ☐
    - Specify: _____
- Acute treatment given during hospitalization :
  - IV Diuretics Yes ☐ No ☐ - IV Nitrates Yes ☐ No ☐
  - IV Inotropes Yes ☐ No ☐ - Mechanical ventilation Yes ☐ No ☐

The primary metric of efficacy in the study was first episode of either cardiovascular hospitalization or death. The Kaplan-Meier curves for this metric are as per sponsor and are shown below. The difference between the two groups is highly significant (P<<0.0001). The relative risk comparing dronedarone to placebo was 0.76.

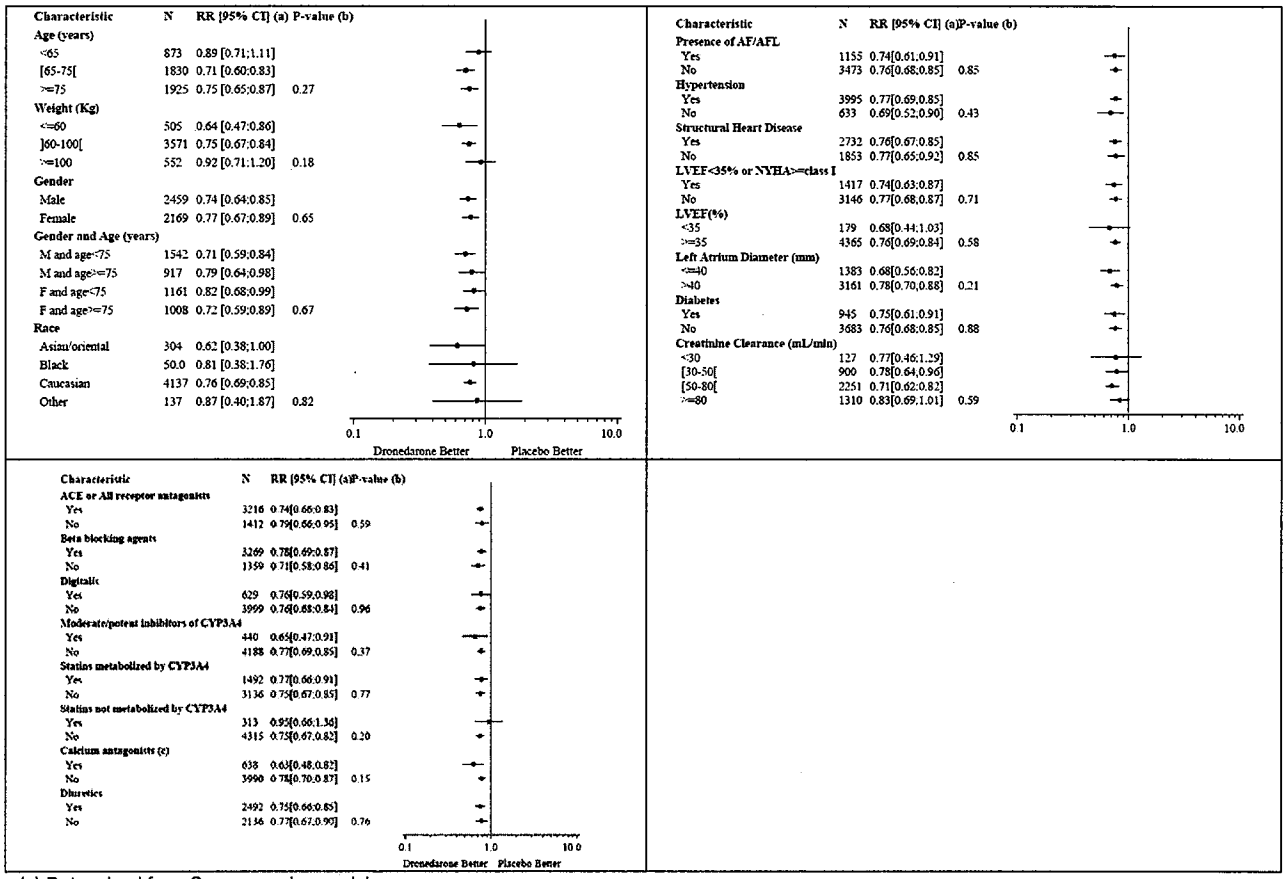
Figure 6: Kaplan-Meier cumulative incidence curves from randomization to first cardiovascular hospitalization or death from any cause-all randomized subjects



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

Forest plots for subgroup do not indicate any heterogeneity base on the following baseline demographic characteristics.

Figure 7: Forest plot based on baseline characteristics-ATHENA study



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

The Hazard ratio for the US sites was similar to the overall study effect Hazard ratio 0.81 [95% CI, 0.68, 0.96].

Secondary endpoints:
All cause mortality:

The primary secondary endpoint is all cause death. The sponsor notes that there were 139 deaths in the placebo group and 116 deaths in the dronedarone group. The sponsor's analysis indicates that this result was not statistically significant. The sponsor's analysis captures six deaths that occurred after the 12-month follow-up period. The last subject was enrolled on December 30, 2006. In essence all events occurring after December 29, 2007 should not have been included in this analysis. Of the additional six events which were captured after this cut-off date 5 were placebo-treated subjects and one a dronedarone-treated subject. Excluding these subjects there were 134 events in the placebo group and 115 in the dronedarone group. The Log-rank test p-value was 0.23.

Hospitalization for cardiovascular reasons:

Since all-cause mortality was not significant and was the first secondary endpoint, all subsequent endpoints should be considered only as exploratory.

The second and subordinate secondary endpoint was time to first cardiovascular hospitalization. The results are shown below. There was clearly a decrease in the rate of first cardiovascular hospitalization in the dronedarone group (N=675) compared to the placebo group (N=859). The nominal Hazard ratio and confidence intervals are 0.75 (0.68, 0.82). The specific reasons for hospitalization are shown below.

Table 9: Reason for first hospitalization in the ATHENA study

	Placebo (N=2327)	Dronedarone (N=2301)	HR (95%CI)[+]
Any Hospitalization	859 (37%)	675 (29%)	0.75 (0.67, 0.82)
Atrial fibrillation and other supraventricular rhythm disorders	457 (20%)	296 (13%)	0.62 (0.53,0.71)
Worsening heart failure, including pulmonary edema or dyspnea of cardiac origin	92 (4%)	78 (3%)	0.80 (0.6, 1.09)
Myocardial infarction or unstable angina	61 (3%)	48 (2%)	0.74 (0.51, 1.08)
Stable angina pectoris or atypical chest pain	41 (2%)	45 (2%)	1.04 (0.69, 1.6)
TIA or stroke (except intracranial hemorrhage)	35 (2%)	28 (1%)	0.75 (0.5, 1.5)
Transcutaneous coronary, cerebrovascular or peripheral procedure	31 (1%)	27 (1%)	0.82 (0.5, 1.4)
Implantation of a pacemaker, ICD or any other device	29 (1%)	32 (1%)	1.04 (0.6, 1.7)
Major bleeding (requiring two or more units of blood) or intracranial hemorrhage	24 (1%)	21 (1%)	0.82 (0.45, 1.5)
Syncope	24 (1%)	21 (1%)	0.83 (0.5, 1.5)
Cardiovascular surgery except cardiac transplantation	23 (1%)	21 (1%)	0.85 (0.5, 1.54)
Blood pressure related (hypotension-except syncope), hypertension	21 (1%)	21 (1%)	0.95 (0.5, 1.74)
Atherosclerosis-related (if not otherwise specified)	8 (< 1%)	11 (< 1%)	1.3 (0.5, 3.2)
Ventricular tachycardia (non-sustained and sustained)	6 (< 1%)	6 (< 1%)	0.95 (0.31, 2.96)
Pulmonary embolism or deep vein thrombosis	3 (< 1%)	10 (<1%)	3.2 (0.9,11.5)
Non fatal cardiac arrest	2 (<1%)	3 (<1%)	1.4 (0.2, 8.7)
Ventricular extrasystoles	1 (< 1%)	1 (<1%)	0.97 (0.06,15.6)
Ventricular fibrillation	1 (< 1%)	1 (<1%)	0.94 (0.06-15.1)
Cardiovascular infection	0	4 (0.2%)	????
Other ventricular arrhythmias	0	1 (< 1%)	????

[+] Nominal values

Nearly all the benefit in hospitalization is attributable to the decrease in atrial fibrillation hospitalizations. There was no specific case report form for atrial fibrillation hospitalization to further assess the underlying provocative symptoms.

With respect to heart failure hospitalizations, there were numerically more individuals who were hospitalized in the placebo group compared to the dronedarone group. Although the number of subjects hospitalized for CHF was numerically greater in the placebo group, the nature of the interventions required were more aggressive in the dronedarone group. Fewer subjects in the placebo group required any treatment including diuretics. Numerically more dronedarone groups were treated with IV nitroglycerin or inotropes. The number of subjects with class IV at any time was somewhat higher in the placebo group.

Table 10: Characterization of heart failure events- ATHENA study

Parameter	Placebo (N=2327)	Dronedarone (N=2301)
Number of subjects	130	112
Number of events	188	166
Interventions:		
None	40	26
Required diuretics	138	135
IV nitroglycerin	22	26
Inotropes	18	25
Mechanical ventilation	7	7
NYHA class IV at any time	52	41

Cause-specific mortality:

Before detailing the results for cause-specific mortality, it is appropriate to look at the CRF forms for cause-specific events. The concerns that are described here could be similarly applied the primary endpoint of cardiovascular hospitalizations plus all cause deaths. The results for the primary endpoint are so overwhelmingly positive, that it is unlikely that attributing a cardiovascular cause to the events would alter the conclusion.

For all cause mortality, however, since overall mortality was not significant, cause-specific mortality creates some problems. Let me first list the events that were so classified.

Table 11: Classification of cardiovascular or non-cardiovascular deaths in the ATHENA study

Classified as cardiovascular	Classified as non-cardiovascular.
Aortic dissection	Sepsis
Cardiogenic shock	Neoplasms
CHF	Asthenia
Death during intervention	Chronic obstructive pulmonary disease
Hemorrhage	Hepatitis (cytolytic, toxic)
MI unstable angina	Influenza
Pulmonary peripheral embolism	Interstitial lung disease
Stroke	Multi-organ failure
Sudden death	Edema
Unknown cause	Pneumonia
Ventricular fibrillation.	Pulmonary fibrosis
	Dementia
	Trauma (drowning , electrocution, crime, brain contusion)
	Renal failure
	Failure to thrive
	Death

I've highlighted those events that I think fit poorly in the category in which they are classified.

I have looked at several of the case report forms as well as narratives in an unblinded manner. The complete information available for writing the narratives was not available to this reviewer. The timing of the writing of the narratives relative to the time of unblinding of the study is not stated. I have only commented on a few cases, for which I think inconsistency was demonstrated. Since only a few reclassifications would

alter the nominal significance of cardiovascular events these descriptions are of importance. Although it is possible that there would be equal and opposite questionable classifications in the opposite direction, which strengthen the contention that cardiovascular events are mitigated by the use of dronedarone, my intent was to show that the causal assessment has substantial problems.

Among those classified as cardiovascular were 12 individuals whose death was classified as unknown; 6 in each treatment. There was one subject whose death was classified as "death" treated as non-cardiovascular (dronedarone). Some of these deaths, based on the death certificates (not submitted with the CRFs) are likely to be sudden cardiac deaths; others are possibly, some are truly unknown.

One subject #840106008 entered hospice care for Parkinson's disease, she was found dead. The death was attributed to a cardiovascular cause. Deaths of people who are anticipated to die within months were not to be considered as cardiovascular deaths.

Hemorrhagic deaths were classified as cardiovascular deaths. This classification appears unreasonable. There were 11 such hemorrhagic deaths, 6 in the dronedarone- and 5 in the placebo-treated group. Some of these events may be hemorrhagic strokes, other are major bleeds unrelated to the cardiovascular system.

A cerebral bleed as a consequence of trauma was sometimes classified as a cardiac event other time a non-cardiovascular event. There was one subject among the dronedarone-treated subjects with an event termed "brain contusion" and not considered a cardiovascular death. Below is the capsular summary of the two cases. I find the categorization of the event inconsistent. The information below was copied form the subject's narratives as written by the sponsor.

Subject number 246008008 (Treated with dronedarone –**classified as a brain contusion and not considered cardiovascular event**). This patient treated with low dose of aspirin and oral anticoagulant (international normalized ratio at 1.1), fell from his bicycle and became unconscious with profuse bleeding from nasopharynx, on Day 362. Skull fracture and large right subdural hematoma, massive edema of the brain with transtentorial and subfalcine herniation were observed on computed tomography scan. Furthermore he suffered from 3 rib fractures without pneumothorax. Despite poor prognosis, an emergency evacuation of subdural hematoma was performed. During this procedure the patient experienced an uncontrollable intracranial pressure increase leading to cerebral edema and the patient died the same day. No autopsy was performed.
Patient 528003011 treated with placebo (**treated as a cardiovascular event**). This patient, who was taking oral anticoagulants, was admitted to a Turkish hospital on Day 158 after falling and hitting his head during a visit to Turkey. The patient went into a coma due to subarachnoid and intracerebral bleeding, which was treated by a surgical decompensation. The investigational product was discontinued. On Day 169 the patient was transported back to the Netherland with a Glasgow coma scale of 6. Due to the poor (infaust) neurological prognosis, it was decided that neither resuscitation nor readmittance to the intensive care unit should be done in the future. The patient died in the hospital as a consequence of the initial event on Day 201.

One subject (in the dronedarone group) with a death defined as "edema" was classified as a non-cardiovascular death. The case report form however classified the subject as cardiovascular non-arrhythmic event. This subject should be classified as a cardiovascular death.

Patient 32012003 treated with dronedarone not counted as a cardiac death. This patient complained of vomiting, asthenia and anorexia leading to hospitalization and investigational product discontinuation on Day 156 (last intake). On admission, the patient presented with severe edema including ascites, hepatomegaly and pleural effusion. Despite a corrective treatment with furosemide and albumin the patient's status worsened and required assisted ventilation. On Day 190, the patient experienced bradycardia with cardiac arrest leading to death. The etiology of the ascites-edema syndrome was never established. No autopsy was performed.

There were 8 subjects who died due to pneumonia. In a cardiovascular at-risk population, the underlying cardiovascular disease is often the disease responsible. In at least several cases, the capsular summary sites the chest X-ray report as indicating pulmonary consolidation cannot rule-out failure. These subjects were classified as non-cardiac.

Respiratory failure was sometimes classified as non-cardiac. For example, subject 840135009, a dronedarone-treated patient, was admitted on (b) (4) for an aortic aneurism repair. The patient, while still ventilator dependent apparently had an exacerbation of COPD. The patient died. The cause of death was not attributed to a cardiovascular event (aneurism repair) but to respiratory failure.

There were 6 patients whose deaths were attributable to renal disease (either acute or chronic). Renal-related deaths may often be attributable to the underlying cardiovascular disease.

Dr. Freidlin calculated that if four placebo-treated patients had their CV deaths reclassified as non-cardiac (based on changing the cause nature of some of those assessed as unknown cause), the p-value would not be significant. As I noted above, there were 6 deaths that occurred after the nominal cut-off date, three in the placebo group were classified as cardiovascular; the one death in the dronedarone group was classified as non-cardiovascular.

The ostensible reason for categorizing the underlying cause of the deaths is to remove the noise that is engendered in capturing all causes of death. In this manner deaths that are non-preventable by antiarrhythmic therapy would not taint the prevention signal. What I am finding is that the inconsistency in the characterization of mortal events. The characterization of deaths adds a different form of noise. Given the small wiggle room, I don't see an analysis of cardiovascular mortality as convincing.

With respect to the steering committee's characterization of cardiovascular death, the table below shows their assessment.

Table 12: Characterization of cardiovascular death by the Steering Committee-ATHENA study

Type of death	Placebo	Dronedarone
Cardiovascular deaths	94	65
Aortic dissection aneurism	0	1
Congestive heart failure	10	13
Cardiogenic shock	2	5
Death during cardiac interventional procedure or cardiovascular surgical procedures	2	0
Hemorrhage (except cardiac tamponade)	5	6
Myocardial infarction or unstable angina	7	5
Pulmonary or peripheral embolism	6	2
Stroke	18	11
Sudden cardiac death	35	14
Unknown cause	6	6
Ventricular fibrillation	2	2
Ventricular tachycardia	1	0

Of note, there were substantially more neoplasm-related deaths in the dronedarone relative to the placebo group (25 versus 14).

Safety:

Duration of exposure:

The duration of exposure is shown below:

Table 13: Duration of safety exposure- ATHENA study

	Placebo(N=2327)	Dronedarone (N=2301)
Mean duration of exposure ± SD, days	485 ± 249	483 ± 254
Total patient-years	3071	3031

Deaths:

Deaths were captured above.

Discontinuations:

The reason for the temporary or permanent discontinuation of therapies (> 10 subjects in either group) is shown below and derived form sponsor's Table 37.

Table 14: Reason for drug discontinuation-ATHENA study (≥ 10 events in either treatment)

	Placebo (N=2313)	Dronedarone (N=2291)
Any	187 (8%)	290 (13%)
Gastrointestinal disorders	44 (2%)	90(4%)
Diarrhea	11 (< 1%)	37 (2%)
Nausea	6 (< 1%)	26 (1%)
Investigations	22 (1%)	58 (3%)
QT prolonged (electrocardiogram)	12 (1%)	33 (1%)
Blood creatinine increased	2 (<1%)	16 (1%)
General disorders and administration site conditions	26 (1%)	27 (1%)
Fatigue	5 (< 1%)	11(<1%)
Skin and subcutaneous disorders	13 (1%)	27 (1%)
Nervous system disorders	18 (1%)	25 (1%)
Dizziness	7 (< 1%)	11 (< 15)
Cardiac disorders	13 (1%)	23 (1%)
Bradycardia	1 (<1%)	10 (< 1%)
Musculoskeletal and connective tissue disorders	13 (1%)	16 (1%)
Respiratory and mediastinal disorders	16 (1%)	15 (1%)
Dyspnea	10 (<1%)	8 (< 1%)
Neoplasms benign and unspecified	8 (< 1%)	13 (1%)
Psychiatric disorders	10 (< 1%)	6 (< 1%)

There were more drug discontinuations in the dronedarone group largely manifest as by gastrointestinal events; in particular more subjects diarrhea. Cardiac events which led to discontinuation included QT prolongation and bradycardia.

Overall adverse events are shown below:

Table 15; Adverse events in the ATHENA study (≥2% events in any treatment)

	Placebo	Dronedarone
Any event	**1603 (69%)**	**1649 (72%)**
Gastrointestinal disorders	**508 (22%)**	**600 (26%)**
Diarrhea	**144 (6%)**	**223 (10%)**
Nausea	**72 (3%)**	**122 (5%)**
Vomiting	**27 (1 %)**	**49 (2 %)**
Infections and infestations	582 (25%)	542 (24%)
Urinary tract infections	64 (3%)	74 (3%)
Upper respiratory tract infections	83 (4%)	70 (3%)
Nasopharyngitis	75 (3%)	69 (3%)
Bronchitis	72 (3%)	67 (3%)
Pneumonia	71 (3%)	50 (2%)
General disorders and administrative site conditions	**356 (15%)**	**403 (18%)**
Edema peripheral	**119 (5%)**	**147 (6%)**
Fatigue	**90 (4%)**	**115 (5%)**
Asthenia	**47 (2%)**	**68 (3%)**
Chest pain	55(2%)	52(2%)
Musculoskeletal and connective tissue disorders	396 (17%)	381 (17%)
Back pain	80 (4%)	73 (3%)
Arthralgia	62 (3%)	64 (3%)
Pain in extremity	44 (2%)	50 (2%)
Nervous system disorder	381 (17%)	373 (16%)
Dizziness	146 (6%)	161 (7%)
Headache	84 (4%)	70 (3%)
Respiratory, thoracic and mediastinal disorders	337 (15%)	332 (15%)
Dyspnea	**97 (4%)**	**120 (5%)**
Cough	83 (4%)	83 (4%)
Investigations	206 (9%)	309 (13%)
Blood creatinine increased	31 (1%)	108 (5%)
INR increased	47 (2%)	48 (2%)
Cardiac disorders	**221 (10%)**	**260 (11%)**
Bradycardia	**28 (1%)**	**81 (4%)**
Skin and subcutaneous tissue disorders	**176 (7%)**	**237 (10%)**
Rash	**37 (2%)**	**60 (3%)**
Injury poisoning and procedural complications	227 (10%)	219 (10%)
Fall	70 (3%)	69 (3%)
Metabolism and nutrition disorders	203 (9%)	186 (8%)
Hypokalemia	62 (3%)	40 (2%)
Vascular disorders	193 (8%)	182 (8%)
Hypertension	89 (4%)	82 (3%)
Renal and urinary disorders	118 (5%)	116 (5%)
Eye disorders	106 (5%)	115 (5%)
Psychiatric disorders	131 (6%)	111 (5%)
Neoplasms benign and unspecified	118 (5%)	105 (5%)
Reproductive system and breast disorders	57 (3%)	61 (3%)
Ear and Labyrinth	70 (3%)	56 (3%)
Blood and lymphatic systems	65 (3%)	47 (2%)

The main differences suggesting an increase in adverse events in the dronedarone group are bolded. Gastrointestinal disorders were increased in the dronedarone treated subjects. Of note, is that among the events that are more prevalent in the dronedarone group are symptoms often associated with worsening heart failure including peripheral edema, dyspnea, fatigue and asthenia. Bradycardia was much more frequent in the dronedarone treated subjects. Among investigations there was an increase in the incidence of QT prolongation and bradycardia.

Summary of data:

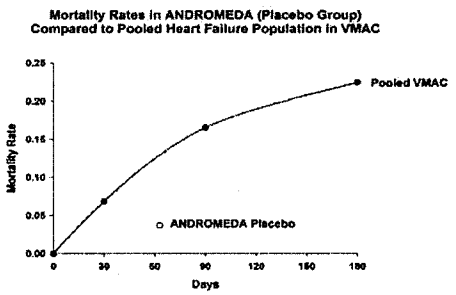
There are two studies pertinent to assess the mortal effects of dronedarone. The ANDROMEDA study was discontinued early because of an adverse mortality effect. The ATHENA study enrolled a different population. 70% of those enrolled into the ATHENA had no evidence of heart failure. Of the 30% who had heart failure, only 5% had NYHA grade III failure. The mean ejection fraction in the ATHENA study was approximately 57%. A comparison of those enrolled into ANDROMEDA and ATHENA is shown below. It would have been unethical to perform ATHENA if the two populations overlapped.

Table 16 Comparison of population in ANDROMEDA and ATHENA studies

Andromeda:	Athena:
• Population recently hospitalized or clinic visit for heart failure requiring at the minimum iv diuretics. • Age- 70; M =76% • Median wall motion index =0.9; • EF? • NYHA None/I/II/III/IV= 0%/0%/39%/58%/3%	• Elderly population with history of AFib/AFl and normal NSR • Age- 72; M=55% • Median wall motion index? • Mean EF= 57% • NYHA None/I/II/III/IV= 70%/8%/17%/5%/0%

The severity of heart failure in the ANDROMEDA study is difficult to quantify. Below is a comparison of the mortality of those who enrolled in the placebo group of ANDROMEDA compared to the mortality rates at 30 and 60 days as well as at 6 months in those who enrolled into the VMAC study. This study enrolled patients with decompensated heart failure who were treated with either nesiritide or nitroglycerin. The mortal event rate among those treated with placebo in the ANDROMEDA study is about 1/3 of the severely decompensated patient. Consequently, although those entered in the ANDROMEDA study were ill, they were not unstable in their status.

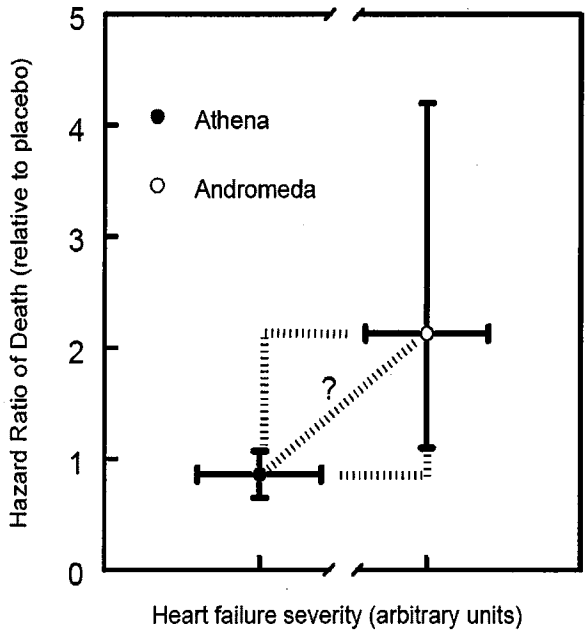
Figure 8 Mortality rate in the placebo cohort of the ANDROMEDA study compared to the mortality rate in the VMAC study



The sum of data concerning mortal outcomes is depicted in the cartoon below. The X-axis is an arbitrary scale reflecting the degree of heart failure. The Y-axis reflects the Hazard ratio. The yellow shaded area reflects the area where there is a decrease in mortal risk with dronedarone. There are two studies with markedly different outcomes. The mortality rate for the ANDROMEDA study was decidedly negative. The ATHENA study was modestly positive. The degree of heart failure in the two studies was

substantially different. The decision needs to be made where the cutoff from intolerable risk for the degree of benefit resides. The decision also needs to define a set of instructions for subjects whose heart failure status deteriorates while on dronedarone. The advisory committee suggested excluding patients either who have at baseline or during therapy, the following risks: NYHA class III or IV, an EF < 35% or who were hospitalized for heart failure. Although I have some misgivings that there is inadequate power in the number of patients ATHENA population to assume these groups can safely be treated, particularly when taking into account the outcomes in the ANDROMEDA study, I can accept these recommendations as reasonable.

Figure 9 Graph of total mortality in the two mortal-morbid studies (ANDROMEDA and ATHENA).



Conclusion: The application is approvable for the delay and recurrence of both atrial fibrillation and atrial flutter and to prevent cardiovascular hospitalization associated with atrial fibrillation. Patients with NYHA class III-IV, have an EF < 35% or had a recent hospitalization for heart failure or those during treatment who develop these risks should not be started on or if already on therapy should probably be discontinued from therapy.

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/s/

Abraham Karkowsky
3/25/2009 02:56:33 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 17, 2009

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of Cardiovascular and Renal Products, HFD-110.

TO: Cardiovascular and Renal Products Advisory Committee

SUBJECT: Dronedarone Hydrochloride (Multaq®, SR33589B); Sanofi –aventis, U.S., Inc. as sponsor; NDA 22-425.

This memo is a follow-up to my original memo dated April 26, 2006 (edited on February 18, 2009) for NDA 21,913 which recommending an approvable action for dronedarone, should the sponsor be able to demonstrate that a population can be defined which both benefited by treatment and which can be safely treated. The current NDA # 22-425 differs in the original NDA number for dronedarone because it requests additional claims compared to those of NDA 21,913. The pivotal information in this submission is the results of the ATHENA study. The results of the ATHENA appear to define a population which derives benefit from dronedarone use and in whom safety was demonstrated.

In addition to the ATHENA study, the new information summarized in this memo relates to the ANDROMEDA study. This study was previously reviewed. The sponsor halted the study for an adverse mortality outcome in the dronedarone treated subjects. In this memo, I have included an analysis of those subjects who died during this study who were withdrawn from angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs), or were not treated with these classes of drugs at baseline. It does not appear that the mortality excess, as observed in the ANDROMEDA study can be explained by a model in which subjects had asymptomatic creatinine increases which provoked discontinuation of ACE-I or ARB treatment and only then resulted in cardiac decompensation. All events which provoked discontinuation of the ACE-I/ARB treatment appear to be acute exacerbations of either renal or cardiac disease at the time these drugs were discontinued.

This review is largely based on the joint clinical-statistical review by Gail Moreschi M.D., MPH, FACP (clinical) and Valeria Freidlin, Ph.D., (statistics).

The ATHENA study randomized 4628 subjects, across 37 countries and 551 centers, who had one previous episode of atrial fibrillation or flutter and one normal ECG (not necessarily in that order), to receive either dronedarone at a dose of 400 mg BID with food or placebo in a 1:1 ratio. For those who were not in sinus rhythm at the

time of enrollment, the subject was to undergo an attempt at cardioversion. Subjects were to be elderly (over 70 years old). Initially, however, they could be any age but have additional risk factors for cardiovascular outcomes. A subsequent amendment modified the enrollment criteria to require subjects to be over 75 with the history of atrial fibrillation (AFib) or atrial flutter (AFL) as above, or over 70 with the same history but have one additional cardiovascular risk factor. Notable exceptions for enrollment included a history of chronic atrial fibrillation. Subjects were to be followed for one year after the last subject enrolled.

The primary endpoint of the study, time to first cardiovascular hospitalization or death, was highly significant favoring dronedarone. The primary secondary analysis, all-cause death was not significant but numerically favored of dronedarone (p=0.2). Several of these deaths that were captured occur at time points after to the proposed cut-off date. Most of those post-cut-off events occurred in the placebo group, making the lean on mortality slightly less convincing.

Since the primary secondary endpoint, all-cause death, was not significant, the other two secondary endpoints should be considered as exploratory.

With respect to cardiovascular deaths, the Steering Committee, which was composed of 5 independent cardiologist and three sponsor's representatives, assessed the nature of death. The broad outline of what constitutes a cardiovascular death appears somewhat arbitrary and in some cases irrelevant to events that would likely be preventable in this population. It is unclear if the new analysis of cause-specific mortality events adds clarity to the any benefit of dronedarone or the results merely allows for a second attempt at defining a mortal benefit.

Should only a small number of events be reclassified from cardiovascular to non-cardiovascular in the placebo-treated subjects, or from non-cardiovascular to cardiovascular in the dronedarone treated group, nominal significance would be lost, particularly when the analysis excludes those events, which occurred after the cut-off time. The results of the ATHENA study with respect to cardiovascular outcomes are so discrepant with the results from the ANDROMEDA study, that caution should be exercised in asserting dronedarone as having a mortal benefit.

With respect to cardiovascular hospitalizations, this result highly favors dronedarone. The significance is driven entirely by the AFib/AFl hospitalizations. The underlying reason that subjects were hospitalized for AFib/AFl is unclear.

I find the results of EURIDIS, ADONIS (previously reviewed) and ATHENA coupled with that of ANDROMEDA as consistent with the conclusion that dronedarone is a useful antiarrhythmic to delay recurrence of symptoms associated with the underlying arrhythmia and to prevent atrial fibrillation hospitalizations. The results are not convincing that, aside from hospitalization for atrial fibrillation, dronedarone prevents other morbid or mortal outcomes. I however, do not have adequate information at this time that efficacy applies both to the atrial fibrillation and atrial flutter populations, as

such, since the predominantly enrolled population is the AFib population, approval should be limited this group.

The sponsor has also shared with us the top-line results of the DIONYSIS study. This study has not yet been reviewed but based on the sponsor's assessment the effectiveness of dronedarone in preventing atrial fibrillation is substantially less than that of amiodarone.

In summary, based on the results of the ADONIS and EURIDIS studies previously reviewed and based on the prevention of hospitalization in the ATHENA study, dronedarone should be approved for the delay recurrence of symptomatic events and decrease hospitalization for atrial fibrillation, in a population likely to have recurrence of AFib. Because of the adverse mortality effect that was observed in the ANDROMEDA study, despite the favorable lean in the ATHENA study, no mortality claim should be granted.

Furthermore, based on the outcome of the ANDROMEDA study individuals with Class III or IV NYHA heart failure should be precluded from its use. The tricky issue is how to control those whose heart failure transitions into NYHA class III from less severe degrees of heart failure.

ANDROMEDA study:

This description of the ANDROMEDA study and the results that are included in this review were copied and pasted from the review for NDA 21-913. This review, however, contains a new analysis of those who died and were either on no ACE-I or ARB at baseline or who discontinued these medications.

The ANDROMEDA[1] study randomized 627 subjects (originally the study planned to enroll 1000 subjects) in a 1:1 ratio to either dronedarone 400 mg BID or placebo. The study was carried out in six Western European countries. It was prematurely discontinued seven months after the randomization of the first subject because of an adverse mortality outcome in the dronedarone-treated compared to placebo-treated subjects.

The ANDROMEDA study enrolled subjects with symptomatic CHF (NYHA class II-IV), a wall motion index (WMI)[2] of ≤ 1.2 and requiring recent hospitalization and treatment with diuretics. The abnormal wall motion index reflects left ventricular dysfunction. According to the sponsor, multiplying the WMI by 30 approximates the EF. Notable exclusion criteria included recent myocardial infarction, recent decompensated

[1] ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DecreAse –EFC4966.

[2] The wall motion index was determined by a central echocardiography laboratory after reading the baseline 2D-echocardiogram. The assessment averaged the segmental wall motion score over 16 segments. The individual scoring was as follows: Pronounced paradoxical motion (-1.0); slight paradoxical motion (-0.5); akinesia (0); pronounced hypokinesia (0.5); moderate hypokinesia (1.0); slight hypokinesia (1.5); normokinesis (2.0), slight hyperkinesia (2.5); pronounced hyperkinesia (3.0).

heart failure (e.g., acute pulmonary edema, shock requiring pressors or acute MI), cardiomyopathy, or use of Vaughn-Williams Class I or III anti-arrhythmic agents.

There were 2402 patients screened, of which 650 were randomized and treated. The results from one center that enrolled 23 subjects, was excluded for poor quality control. Of the remaining 627 subjects 317 were randomized to placebo and 310 to dronedarone.

Selected baseline demographics are shown in Table 1.

Table 1: Demographics, cardiovascular history, cardiac status and selected concomitant medications in ANDORMEDA

Parameter	Placebo	Dronedarone
N=	317	310
Age, years (mean ± SD	69 ± 12	70 ± 12
Gender: Number male (%)	242 (76%)	230 (74%)
Race: # non-Caucasian (%)	1 (<1%)	2 (1%)
Weight: Mean ± SD, Kg	79 ± 19	78 ± 17
Cardiovascular history, selected, N= (%)		
Coronary heart disease	201 (63%)	266 (66%)
Valvular heart disease	175 (55%)	171 (55%)
Hypertension	107 (34%)	123 (40%)
Dilated cardiomyopathy	103 (33%)	79 (26%)
Diabetes mellitus	62 (20%)	73 (24%)
CABG	42 (13%)	57 (18%)
Severe ventricular arrhythmia	33 (10%)	33 (11%)
Stroke	31 (10%)	24 (8%)
Cardiac status		
Wall motion Index, mean ± SD	0.86 ± 0.23	0.90 ± 0.23
NYHA class (II/III/IV) (%/%/%)	118/186/13 (37%/59%/4%)	126/178/6 (41%/57%/3%)
Concomitant medications, selective, N (%)		
Diuretics	309 (98%)	297 (96%)
ACE-I/ARB	267 (84%)	274 (88%)
Chronic anti-platelet therapy	196 (62%)	203 (66%)
Oral anti-coagulants	102 (32%)	92 (28%)
Beta-blockers (except sotalol)	191 (60%)	192 (62%)
Statins	97 (31%)	113 (57%)
Cardiac glycosides	101 (32%)	96 (31%)
Verapamil/diltiazem	12 (4%)	9 (3%)

In general, the two groups appear well matched at baseline. Those enrolled were largely male and nearly all Caucasian, most were in NYHA class III failure. Given the underlying CHF, the fraction of subjects using of diuretics and ACE-I/ARB are appropriate.

Although the primary endpoint of the study was composite of time to death or hospitalization for CHF, the DSMB recommended the discontinuation of the study because of an increase in the number of deaths in the dronedarone-treated relative to the placebo-treated subjects. The relative risk for death and for the composite of death and hospitalization for adjudicated heart failure are shown below.

Figure 1 : Kaplan-Meier plots for death (left) and death or hospitalization for heart failure (right) in ANDROMEDA

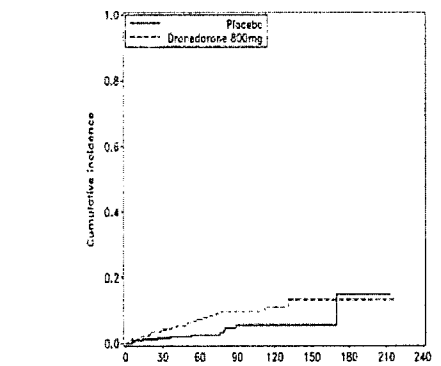

Figure (11.2.1) 1 - Kaplan-Meier cumulative incidence curves from randomization to death up to 16 January 2003- randomized and treated patients population excluding center 616004

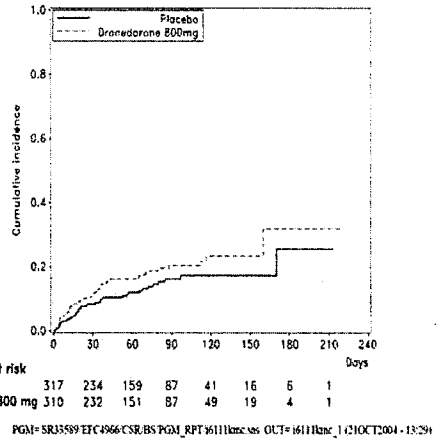

Figure (11.1.1) 1 - Kaplan-Meier cumulative incidence curves from randomization to death or hospitalization for worsening heart failure up to 16 January 2003- randomized and treated patients population excluding center 616004

Hazard ratios for several clinically meaningful measurements are shown in Table 2. All Hazard ratios favor placebo. The upper CI for death extends beyond a factor of 3. The adjudicated cause of death is shown in Table 3.

Table 2: Outcomes and statistical assessments for ANDROMEDA:

Parameter	Placebo N=317	Dronedarone N=310	Hazard ratio (95% CI	Log-rank p-value
Death	12	25	2.13 (1.1-4.2)	0.03
Died or hospitalized for worsening heart failure	40	53	1.38 (0.92-2.1)	0.12
Number hospitalized for worsening failure	31	39	Not calculated	0.27
Number hospitalized for cardiovascular reasons	50	71	Not calculated	0.02

Table 3: Adjudicated causes of death are shown below and (fraction of population) [fraction of deaths] ANDROMEDA:

	Placebo (N= 317)	Dronedarone (N=310)
Number of Events	12	25
Cardiovascular death:	9 (3%) [75%]:	24 (8%)[96%]:
MI	2 (1%) [17%]	0
Worsening CHF	2 (1%)[17%]	10 (3%) [40%]
Documented arrhythmia	2 (1%) [17%]	6 (2%) [24%]
Procedure related	0	1 (<1%) [4%]
Other CV reason	0	2 (1%) [8%]
Presumed CV reason	3 (1%) [25%]	5 (2%) [20%]
Non-cardiovascular	2 (1%)[17%]	1 (< 1%) [4%]
Cancer	1 (< 15) [8%]	1 (< 1%) [4%]
Other	1 (<1%) [8%]	0
Non-adjudicated death	1 (<1%)[8%]	0

The increase in mortality was predominantly attributed to worsening heart failure deaths, but arrhythmia deaths were also increased.

The sponsor postulated that the increase in deaths in the dronedarone group in the ANDROMEDA study is a consequence of dronedarone's ability to inhibit creatinine secretion into the urine, these subjects with elevated creatinine would be more likely to have their ACE-I /ARB medication discontinued, losing the benefit of these treatments and predisposing to a negative mortality and hospitalization outcome.

The above postulated mechanism would suggest the following sequence of events. First, the subject would have an asymptomatic creatinine elevation leading to the discontinuation of the ACE-I/ARB and only then would the patient be at risk for cardiac decompensation or death.

Although more dronedarone subjects discontinued the ACE-I/ARB treatment than did placebo subjects, among those who died, there were few subjects whose creatinine increases were unrelated to either a cardiac or renal insult. The percentage of subjects who were treated with dronedarone who died was substantially higher whether they were not treated with ACE-I/ARBs at baseline or discontinued from these medications. The relationship between ACE-I/ARB use status and mortal events is shown below.

Table 4: Outcome of ANDROMEDA based on ACE-I/ARB status

	Placebo	Dronedarone
Number enrolled		
Number not on ACE-I /ARB at baseline (A)	50	36
Number who died (% of A)	1 (2%)	6 (16%)
Number on ACE-I/ARB at baseline (B)	267	274
Number on B who died (% B)	10 (4%)	10 (4%)
Number who discontinued from ACE-I/ARB (C)	12	19
Number who died (% C)	1 (8%)	9 (47%)

There were 12 placebo subjects and 25 dronedarone-treated subjects who died. Of these deaths, nine of the placebo subjects and 24 of the dronedarone subjects died of cardiovascular events. Among the subjects in the placebo group who died, one death occurred in a subject who never received ACE-I or ARB. In the dronedarone group there were six subjects who died in this category. Among the subjects who were treated and remained on ACE-I/ARB, deaths were the same in both groups.

The capsular summaries for these subjects who were treated with dronedarone and were discontinued from the ACE-I or ARB are provided below. None of these events can be interpreted as an asymptomatic creatininemia, provoking the discontinuation of ACE-I /ARB treatments.

Dronedarone subjects:
Subject # 208 103009 was an 81 year-old female with a history of myocardial infarction and chronic atrial fibrillation. Her NYHA was Class III. She was hospitalized for increased blood creatinine but received a glucose infusion (was it really glucose + insulin

for hyperkalemia?) and transfusions. The subject died 11 days after admission from worsened heart failure. The hospitalization death was attributed to worsened CHF.

Subject 208116008 was a 66 year-old female with a history of myocardial infarction and dilated cardiomyopathy. She was hospitalized on (b) (4) (6 days after randomization) for interstitial nephropathy. She stopped her ACE-I (trandolapril) one day after admission. She required hemodialysis beginning two days after admission. She died one week after admission. At admission she had elevated serum K+ (5.9 mEq/L) and increased weight gain.

Subject 208126010 was a 70 year-old male with a cardiac history of hypertrophic cardiomyopathy. The subject was admitted after approximately 4 weeks of treatment with dronedarone for unstable angina for a CABG procedure. Cozaar was stopped during this hospitalization. The subject had an MI two days after the discontinuation of the Cozaar and he died about a week later. The MI preceded ventricular tachycardia and the need for a mechanical heart.

Subject 208137001 was an 87 year-old male with a history of coronary artery disease and NYHA class III. The subject was admitted two weeks after enrollment for increase in creatinine and worsening heart failure. Ramipril was discontinued two days later. The subject died two months later from worsening heart failure. There was one intervening hospitalization for worsening failure and palpitations.

Subject 578304006 was a 77 year-old female with a history of coronary artery disease, myocardial infarction, mitral regurgitation and diabetes mellitus. She discontinued Cozaar on (b) (4) and died on (b) (4) from metastatic disease.

Subject 616002003 was a 56 year-old male with idiopathic dilated cardiomyopathy and chronic atrial fibrillation. The subject was admitted and had among other conditions, worsening renal function, and heart failure, which required assisted ventilation. The subject died during that hospitalization (2 1/2 weeks after admission). Quinapril was discontinued at the time of the hospitalization.

Subject 752211001 was an 82 year-old male with a history of coronary artery disease, myocardial infarction, mitral regurgitation and atrial fibrillation. The subject was admitted approximately one week after enrollment for among other reasons worsening heart failure and pneumonia. The subject discontinued ramipril after the subject was admitted. The subject died approximately 5 weeks later from worsening heart failure.

Subject 752215002 was admitted for worsening heart failure after about 3 days of dronedarone treatment and had ramipril discontinued at that time. The subject was admitted approximately two weeks later for worsening heart failure and died during that hospitalization.

Subject 752220004 was a 79 year-old female with a history of myocardial infarction. She was in sinus rhythm and NYHA class III at randomization. She was hospitalized

approximately 3 weeks later for worsening heart failure and her ramipril was stopped during that hospitalization. She died 1 ¾ months later from worsening heart failure.

Aside from the one subject who died from a metastatic process, all subjects who discontinued their ACE-I or ARB treatments were symptomatic either with renal or cardiac decompensation at the time of discontinuation.

The ATHENA[3] study:

This study was a double-blind, placebo-controlled study comparing dronedarone to placebo in subjects who had both an ECG demonstrating atrial fibrillation and one demonstrating normal sinus rhythm within 6 months (in either order) of enrollment. The original enrollment criteria required subjects, in addition, to be over 70 years old or to have one of the following risk factors: (hypertension, diabetes, prior CVA, left atrial diameter greater than 50 mm by M-mode echocardiography or left ventricular ejection fraction less than 0.40 by 2D echocardiography). The protocol was amended to alter the enrollment criteria to those who had the above document ECG rhythms and who were over 75 years old or those who were over 70 and also had one of the above noted risk factors. Ostensibly, the reason for this change was to more closely align the age range of this study with that of the AFFIRM[4] study and the SPORTIF studies[5].

Notable exclusions from the study included subjects in permanent atrial fibrillation, subjects with unstable cardiovascular status including those who have pulmonary edema (within 12 hours), require pressors (within 4 weeks), or subjects with GFR < 10 ml/min. Concomitant precluded medications included include Vaughan-Williams class I and III antiarrhythmic drugs. Subjects were stratified based on center and the presence or absence of atrial fibrillation/atrial flutter at the time of randomization.

The pre-specified endpoint of the study was time to first cardiovascular hospitalizations or death. Subjects were to be followed for the duration of the study which was to be 12 months after the enrollment of the last subject. For those who completed the study the data were to be right censored at that time.

The primary method of analysis is a 2-sided Log-rank asymptotic test at a level of 0.05. The cumulative incidence function in each treatment group was to be calculated using a non-parametric Kaplan-Meier estimate with a Cox proportional Hazard model to estimate the Hazard ratio.

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[3] 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 patENts with Atrial fibrillation/atrial flutter (AF/AFL).

[4] Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control I patients with atrial fibrillation. N Eng J Med 2002; 347: 1825-33.

[5] Ford GA, Choy AM, Deedwania P, Karalis DG, Lindholm CJ, Pluta W, Frison, L, Olsson SB, and on behalf of the SPORTIF III,V Investigators. Direct Thrombin Inhibition and Stroke Prevention in Elderly Patients With Atrial Fibrillation: Experience From SPORTIF III and V Trials. Stroke 2007 38: 2965-2971.

The primary secondary endpoint is all cause mortality. If the difference in death was statistically significant, other secondary endpoints, cardiovascular deaths and first hospitalization for cardiovascular reasons would be analyzed. The cardiovascular nature of either a hospitalization or death was left to the investigator who filled out a check-box form. There was no pre-specified adjudication committee nor was a complete description of the event available to this reviewer to assess the validity of the cause-specific events. An amendment to the protocol transferred the responsibility for categorizing mortal events to the Steering Committee (after 85 deaths had already occurred). The Steering Committee consisted of 5 independent cardiologists and 3 members of the sponsor. Subjects were followed throughout the study even after the first cardiovascular hospitalization or discontinuation of therapy. An interim look for efficacy/futility was included after 485 subjects achieved the end point.

The study planned to originally enroll 3700 subjects in order to achieve 970 total events. An amendment was submitted August, 2006 (this was early in the study) to increase the sample size to 4300 subjects in order to have a better chance to demonstrate a benefit on mortality. The sponsor notes that the decision to change the size of the study was based on a blinded assessment of mortal events.

The study randomized 2327 subjects to placebo and 2301 to dronedarone 400 mg BID. There were 551 study centers from 37 countries (Eastern and Western Europe, South America, North America, Middle East and Asia).

The disposition of subjects within the study and the demographics of those enrolled are shown below.

Figure 2: Disposition of subjects in the ATHENA study

Placebo	Dronedarone
Total Randomized N=4628	
Randomized N= 2327	Randomized N=2310
Completed study N=2325 Lost to follow-up N=2	Completed study N= 2301 Lost to follow-up N= 0
Completed on drug N= 1611 Discontinued drug but followed N=716 Reason for discontinuation: Adverse event N= 191 Poor compliance N= 14 Subject's request N=175 Other N =336	Completed on drug N= 1605 Discontinued drug but followed N=696 Reason for discontinuation: Adverse event N= 293 Poor compliance N= 14 Subject's request N=173 Other N=216

The demographics of those enrolled per sponsor are shown below:

Table 5: Demographics of those enrolled in the ATHENA study

Parameter	Placebo (n=2327)	Dronedarone (n=2301)
Age, years mean ± SD	72 ± 9.0	72 ± 8.9
Gender [male/female] (% female)	[1289/1038[(45%)	[1170/1131] (49%)
Race [Caucasian/black/Asian/Other] (%Caucasian)	[2072/31/154/70] (89%)	2065/19/150/70 (89%)
Cardiovascular history N (%)		
Hypertension	1996 (86%)	1999 (87%)
Structural heart disease	1402 (61%)	1330 (58%)
Tachycardia	797 (34%)	752 (33%)
Coronary heart disease	728 (31%)	661 (29%)
Non-rheumatic valvular heart disease	354 (15%)	331 (14%)
Pacemaker	243 (10%)	214 (9%)
Lone atrial fibrillation	139 (6%)	140 (6%)
Ischemic dilated cardiomyopathy	118 (5%)	92 (4%)
Ablation for AFib/AFl	106 (5%)	90 (4%)
Supraventricular tachycardia not AFib/AFl	98 (4%)	97 (4%)
Previous cardiac valve surgery	95 (4%)	80 (4%)
Non-ischemic dilated cardiomyopathy	84 (4%)	80 (4%)
Hypertrophic cardiomyopathy	50 (2%)	45 (2%)
Other history N (%)		
Hypercholestrolemia	1002 (43%)	1034 (45%)
Dyslipidemia	778 (33%)	756 (33%)
NIDDM	398 (17%)	423 (18%)
Chronic pulmonary disease	314 (14%)	297(13%)
Hypothyroidism	227 (10%)	263 (11%)
Malignant neoplasm	192 (8%)	165 (7%)
Embolic or thrombotic disease	159 (7%)	175 (8%)
Syncope	140 (6%)	154 (7%)
Hyperthyroidsm	100 (4%)	154 (7%)
Chronic renal failure	83 (4%)	85 (4%)
Other parameters N (%)		
Number of subjects in atrial fibrillation/flutter at randomization per stratification factor (%)	586 (25%)	569 (25%)
Left atrial diameter (2D –echocardiogram)	44 ± 7.0	44 ± 6.8
Left ventricular ejection fraction (%) 2-D echocardiogram	57 ± 11	57 ± 11
NYHA class III	109 (5%)	91 (4%)

There were some differences in the baseline demographic characteristics of the two groups. In particular, there were more females, less structural heart disease (coronary heart disease and/or dilated cardiomyopathy and/or non-ischemic dilated cardiomyopathy), less coronary heart disease, more hypercholestolemia, in the dronedarone treated group. The mean ejection fraction in this study was at 57%, there were few subjects who were NYHA class III and the overlap between this population and that of the ANDROMEDA study is likely minimal. Some concomitant therapies are shown below.

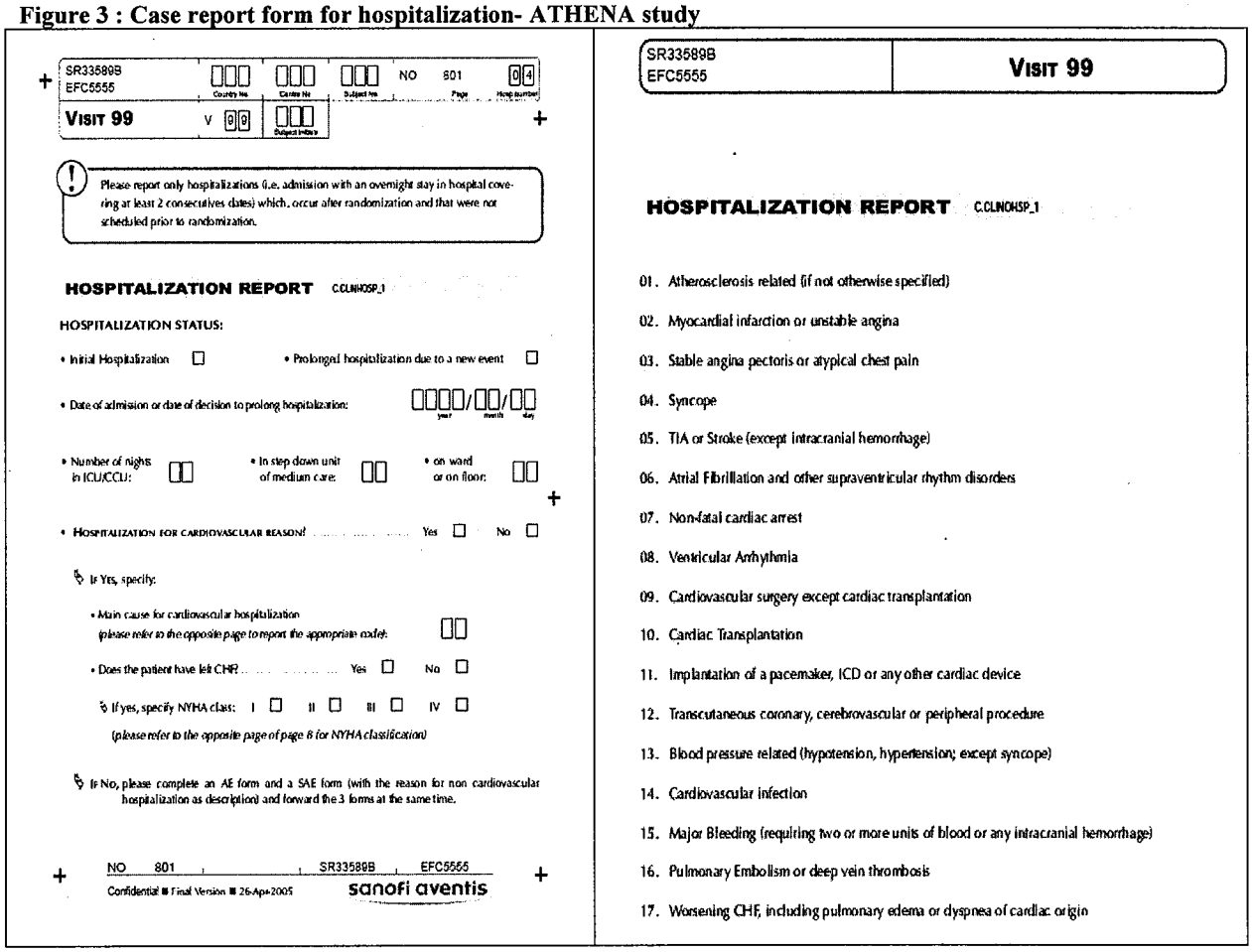
Table 6; Baseline medication for those enrolled in the ATHENA study N (%)

Beta blockers	1860 (80%)	1785 (78%)
ACE inhibitors/angiotensin II receptor antagonists	1800 (77%)	1771 (77%)
Oral anticoagulants	1643 (71%)	1601 (70%)
Spironolactone	136 (6%)	148 (6%)
Diuretics	1522 (65%)	1492 (65%)
Digitalis	574 (25%)	468 (20%)
Calcium antagonists (non-dihydropyridine)	490 (21%)	459 (20%)
Statins	1131 (49%)	1044 (45%)

Baseline medication seems reasonably well balanced between treatments. There were more subjects in the placebo group treated with beta blockers at baseline.

Before describing the outcome of the study, it is perhaps appropriate to describe how the information was captured. The following data were the entirety of the information collected as part of the CRF. The information that was collected was skeletal and forced a categorization that may not have been totally accurate.

Figure 3 : Case report form for hospitalization- ATHENA study



SR33589B
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VISIT 99 V 00

NO 801 04

Please report only hospitalizations (i.e. admission with an overnight stay in hospital covering at least 2 consecutives dates) which, occur after randomization and that were not scheduled prior to randomization.

HOSPITALIZATION REPORT C.CLINHOSP_1

HOSPITALIZATION STATUS:

- Initial Hospitalization ☐
- Prolongal hospitalization due to a new event ☐
- Date of admission or date of decision to prolong hospitalization: ☐☐☐☐/☐☐/☐☐ (year / month / day)
- Number of nights in ICU/CCU: ☐☐
- In step down unit of medium care: ☐☐
- on ward or on floor: ☐☐
- HOSPITALIZATION FOR CARDIOVASCULAR REASON? Yes ☐ No ☐

If Yes, specify:

- Main cause for cardiovascular hospitalization *(please refer to the opposite page to report the appropriate code)*: ☐☐
- Does the patient have left CHF? Yes ☐ No ☐

If yes, specify NYHA class: I ☐ II ☐ III ☐ IV ☐

(please refer to the opposite page of page 8 for NYHA classification)

If No, please complete an AE form and a SAE form (with the reason for non cardiovascular hospitalization as description) and forward the 3 forms at the same time.

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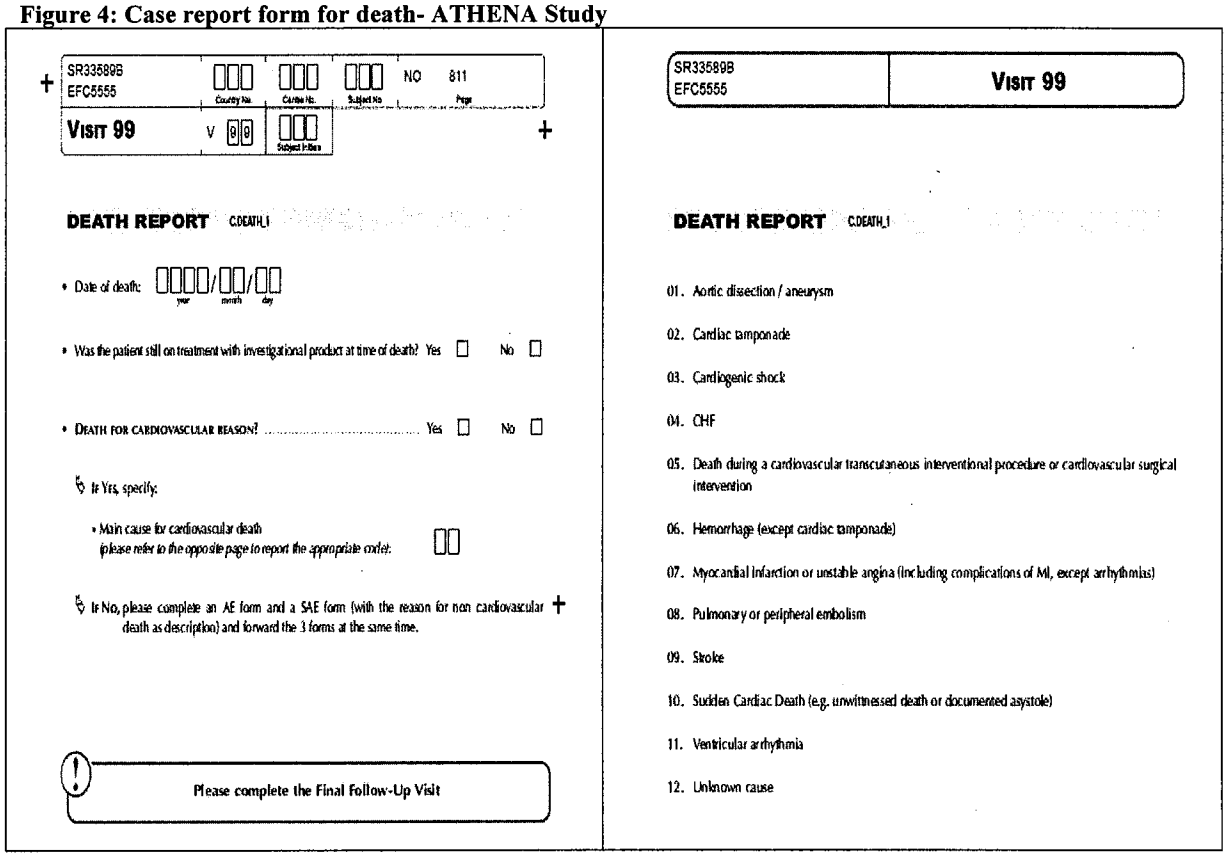
VISIT 99

HOSPITALIZATION REPORT C.CLINOHSP_1

01. Atherosclerosis related (if not otherwise specified)
02. Myocardial infarction or unstable angina
03. Stable angina pectoris or atypical chest pain
04. Syncope
05. TIA or Stroke (except intracranial hemorrhage)
06. Atrial Fibrillation and other supraventricular rhythm disorders
07. Non-fatal cardiac arrest
08. Ventricular Arrhythmia
09. Cardiovascular surgery except cardiac transplantation
10. Cardiac Transplantation
11. Implantation of a pacemaker, ICD or any other cardiac device
12. Transcutaneous coronary, cerebrovascular or peripheral procedure
13. Blood pressure related (hypotension, hypertension; except syncope)
14. Cardiovascular infection
15. Major Bleeding (requiring two or more units of blood or any intracranial hemorrhage)
16. Pulmonary Embolism or deep vein thrombosis
17. Worsening CHF, including pulmonary edema or dyspnea of cardiac origin

Figure 4: Case report form for death- ATHENA Study



SR33589B
EFC5555
Country No. Centre No. Subject No. NO 811 Page
VISIT 99 V 99 Subject Initials

DEATH REPORT C.DEATH_I

- Date of death: ____/__/__ year month day
- Was the patient still on treatment with investigational product at time of death? Yes ☐ No ☐
- DEATH FOR CARDIOVASCULAR REASON? ..... Yes ☐ No ☐

If Yes, specify:

- Main cause for cardiovascular death
  (please refer to the opposite page to report the appropriate code): ☐☐

If No, please complete an AE form and a SAE form (with the reason for non cardiovascular death as description) and forward the 3 forms at the same time.

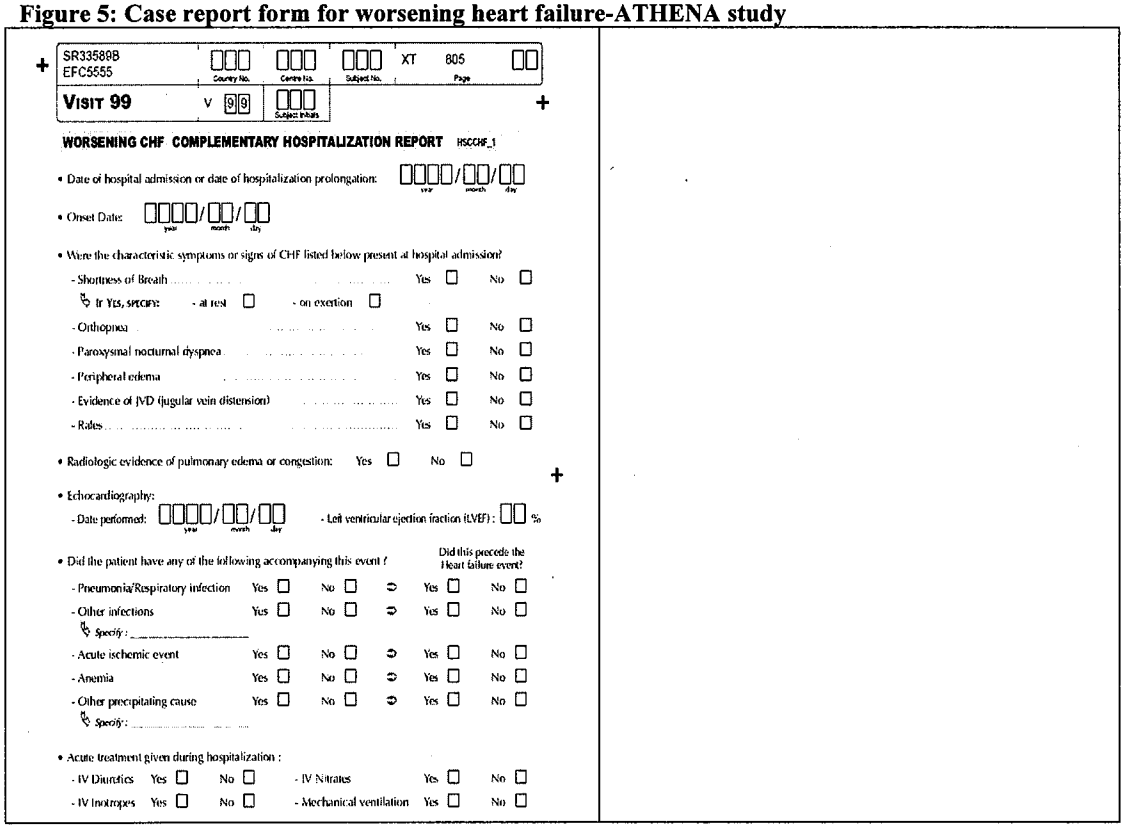
Please complete the Final Follow-Up Visit

SR33589B
EFC5555
VISIT 99

DEATH REPORT C.DEATH_I

01. Aortic dissection / aneurysm
02. Cardiac tamponade
03. Cardiogenic shock
04. CHF
05. Death during a cardiovascular transcutaneous interventional procedure or cardiovascular surgical intervention
06. Hemorrhage (except cardiac tamponade)
07. Myocardial infarction or unstable angina (including complications of MI, except arrhythmias)
08. Pulmonary or peripheral embolism
09. Stroke
10. Sudden Cardiac Death (e.g. unwitnessed death or documented asystole)
11. Ventricular arrhythmia
12. Unknown cause

Figure 5: Case report form for worsening heart failure-ATHENA study



SR33589B EFC5555 — Country No. — Centre No. — Subject No. — XT 805 — Page

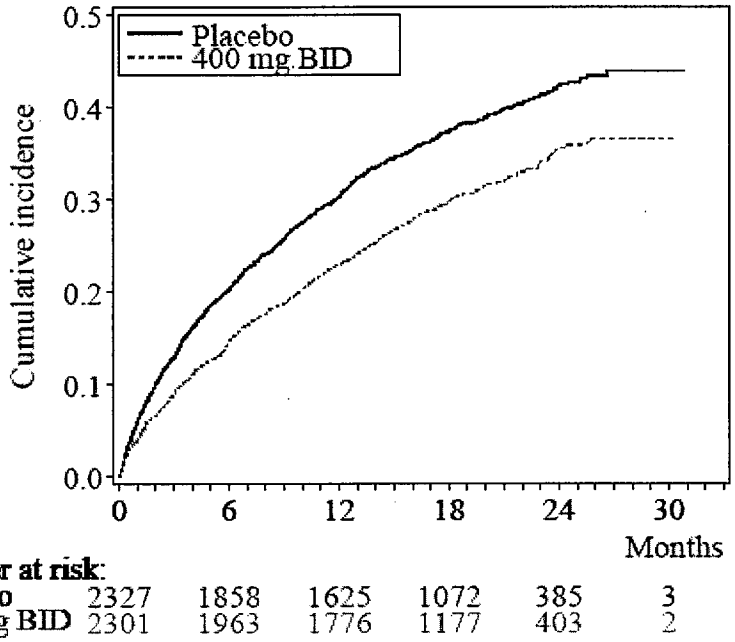
VISIT 99 V 99 — Subject Initials

WORSENING CHF COMPLEMENTARY HOSPITALIZATION REPORT HSCCHF_1

- Date of hospital admission or date of hospitalization prolongation: ☐☐☐☐/☐☐/☐☐ (year/month/day)
- Onset Date: ☐☐☐☐/☐☐/☐☐ (year/month/day)
- Were the characteristic symptoms or signs of CHF listed below present at hospital admission?
  - Shortness of Breath ..... Yes ☐ No ☐
    - If YES, SPECIFY: - at rest ☐ - on exertion ☐
  - Orthopnea ..... Yes ☐ No ☐
  - Paroxysmal nocturnal dyspnea ..... Yes ☐ No ☐
  - Peripheral edema ..... Yes ☐ No ☐
  - Evidence of JVD (jugular vein distension) ..... Yes ☐ No ☐
  - Rales ..... Yes ☐ No ☐
- Radiologic evidence of pulmonary edema or congestion: Yes ☐ No ☐
- Echocardiography:
  - Date performed: ☐☐☐☐/☐☐/☐☐ (year/month/day) - Left ventricular ejection fraction (LVEF): ☐☐ %
- Did the patient have any of the following accompanying this event? / Did this precede the Heart failure event?
  - Pneumonia/Respiratory infection Yes ☐ No ☐ ⇒ Yes ☐ No ☐
  - Other infections Yes ☐ No ☐ ⇒ Yes ☐ No ☐
    - Specify: _____
  - Acute ischemic event Yes ☐ No ☐ ⇒ Yes ☐ No ☐
  - Anemia Yes ☐ No ☐ ⇒ Yes ☐ No ☐
  - Other precipitating cause Yes ☐ No ☐ ⇒ Yes ☐ No ☐
    - Specify: _____
- Acute treatment given during hospitalization:
  - IV Diuretics Yes ☐ No ☐ - IV Nitrates Yes ☐ No ☐
  - IV Inotropes Yes ☐ No ☐ - Mechanical ventilation Yes ☐ No ☐

The primary metric of efficacy in the study was first episode of either cardiovascular hospitalization or death. The Kaplan-Meier curves for this metric are as per sponsor and are shown below. The difference between the two groups is highly significant ($P<<0.0001$). The relative risk comparing dronedarone to placebo was 0.76.

Figure 6: Kaplan-Meier cumulative incidence curves from randomization to first cardiovascular hospitalization or death from any cause-all randomized subjects

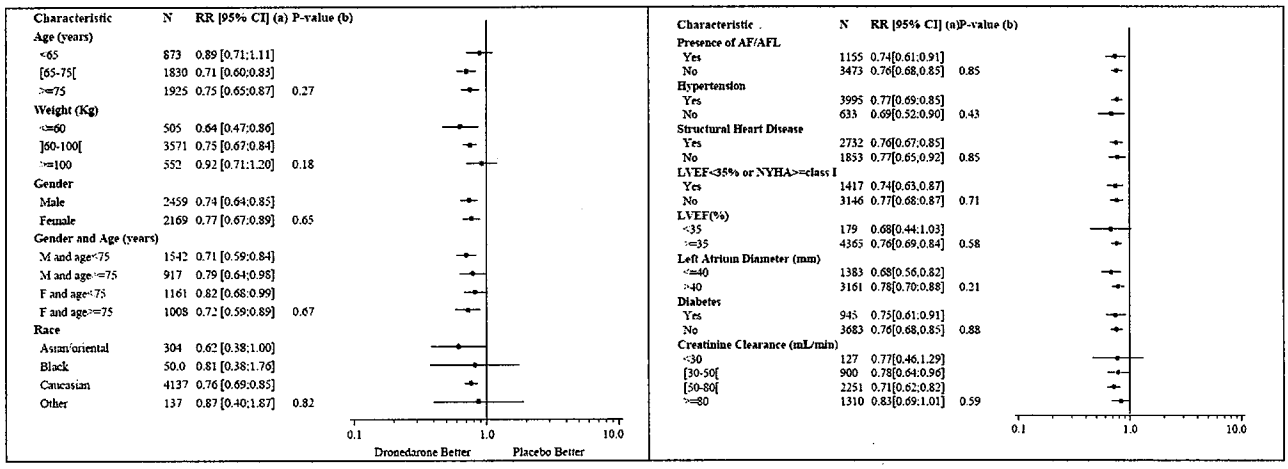


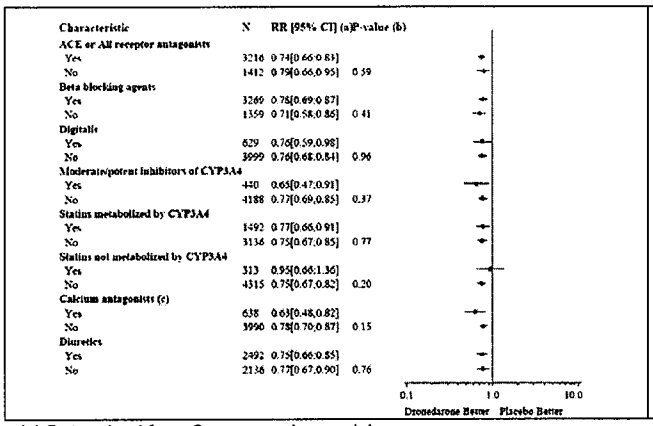
Number at risk:

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

Forest plots for subgroup do not indicate any heterogeneity base on the following baseline demographic characteristics.

Figure 7: Forest plot based on baseline characteristics-ATHENA study





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

The Hazard ratio for the US sites was similar to the overall study effect Hazard ratio 0.81 [95% CI, 0.68, 0.96].

Secondary endpoints:
All cause mortality:

The primary secondary endpoint is all cause death. The sponsor notes that there were 139 deaths in the placebo group and 116 deaths in the dronedarone group. The sponsor's analysis indicates that this result was not statistically significant. The sponsor's analysis captures six deaths that occurred after the 12-month follow-up period. The last subject was enrolled on December 30, 2006. In essence all events occurring after December 29, 2007 should not have been included in this analysis. Of the additional six events which were captured after this cut-off date 5 were placebo-treated subjects and one a dronedarone-treated subject. Excluding these subjects there were 134 events in the placebo group and 115 in the dronedarone group. The Log-rank test p-value was 0.23.

Cause-specific mortality:

Since all-cause mortality was not significant and was the first secondary endpoint, all subsequent endpoints should be considered only as exploratory.

Before detailing the results for cause-specific mortality, it is appropriate to look at the CRF forms for cause-specific events. The concerns that are described here could be similarly applied the primary endpoint of cardiovascular hospitalizations plus all cause deaths. The results for the primary endpoint are so overwhelmingly positive, that it is unlikely that attributing a cardiovascular cause to the events would alter the conclusion.

For all cause mortality, however, since overall mortality was not significant, cause-specific mortality creates some problems. Let me first list the events that were so classified.

Table 7: Classification of cardiovascular or non-cardiovascular deaths in the ATHENA study

Classified as cardiovascular	Classified as non-cardiovascular.
Aortic dissection	Sepsis
Cardiogenic shock	Neoplasms
CHF	Asthenia
Death	Chronic obstructive pulmonary disease
Death during intervention	Hepatitis (cytolytic, toxic)
Hemorrhage	Influenza
MI unstable angina	Interstitial lung disease
Pulmonary peripheral embolism	Multi-organ failure
Stroke	Edema
Sudden death	Pneumonia
Unknown cause	Pulmonary fibrosis
Ventricular fibrillation.	Dementia
	Trauma (drowning , electrocution, crime, brain contusion)
	Renal failure
	Failure to thrive

I've highlighted those events that I think fit poorly in the category in which they are classified.

I have looked at several of the case report forms as well as narratives in an unblinded manner. The complete information available for writing the narratives was not available to this reviewer. The timing of the writing of the narratives relative to the time of unblinding of the study is not stated. I have only commented on a few cases, for which I think inconsistency was demonstrated. Since only a few reclassifications would alter the nominal significance of cardiovascular events these descriptions are of importance. Although it is possible that there would be equal and opposite questionable classifications in the opposite direction, which strengthen the contention that cardiovascular events are mitigated by the use of dronedarone, my intent was to show that the causal assessment has substantial problems.

Among those classified as cardiovascular were 12 individuals whose death was classified as unknown; 6 in each treatment. There was one subject whose death was classified as "death" also treated as cardiovascular (dronedarone). Some of these deaths, based on the death certificates (not submitted with the CRFs) are likely to be sudden cardiac deaths; others are possibly, some are truly unknown.

One subject #840106008 entered hospice care for Parkinson's disease, she was found dead. The death was attributed to a cardiovascular cause.

Hemorrhagic deaths were classified as cardiovascular deaths. This classification appears unreasonable. There were 11 such hemorrhagic deaths, 6 in the dronedarone- and 5 in the placebo-treated group. Some of these events may be hemorrhagic strokes, other are major bleeds unrelated to the cardiovascular system.

A subdural hematoma as a consequence of trauma was sometimes classified as a cardiac event other time a non-cardiovascular event. There was one subject among the dronedarone-treated subjects with an event termed "brain contusion" and not considered

a cardiovascular death. Below is the capsular summary of the two cases. I find the categorization of the event inconsistent. The information below was copied form the subject's narratives as written by the sponsor.

Subject number 246008008 (Treated with dronedarone –**classified as a brain contusion and not considered cardiovascular event**). This patient treated with low dose of aspirin and oral anticoagulant (international normalized ratio at 1.1), fell from his bicycle and became unconscious with profuse bleeding from nasopharynx, on Day 362. Skull fracture and large right subdural hematoma, massive edema of the brain with transtentorial and subfalcine herniation were observed on computed tomography scan. Furthermore he suffered from 3 rib fractures without pneumothorax. Despite poor prognosis, an emergency evacuation of subdural hematoma was performed. During this procedure the patient experienced an uncontrollable intracranial pressure increase leading to cerebral edema and the patient died the same day. No autopsy was performed.
Patient 528003011 treated with placebo (**treated as a cardiovascular event**). This patient, who was taking oral anticoagulants, was admitted to a Turkish hospital on Day 158 after falling and hitting his head during a visit to Turkey. The patient went into a coma due to subarachnoid and intracerebral bleeding, which was treated by a surgical decompensation. The investigational product was discontinued. On Day 169 the patient was transported back to the Netherland with a Glasgow coma scale of 6. Due to the poor (infaust) neurological prognosis, it was decided that neither resuscitation nor readmittance to the intensive care unit should be done in the future. The patient died in the hospital as a consequence of the initial event on Day 201.

One subject (in the dronedarone group) with a death defined as "edema" was classified as a non-cardiovascular death. The case report form however classified the subject as cardiovascular non-arrhythmic event. This subject should be classified as a cardiovascular death.

Patient 32012003 treated with dronedarone not counted as a cardiac death. This patient complained of vomiting, asthenia and anorexia leading to hospitalization and investigational product discontinuation on Day 156 (last intake). On admission, the patient presented with severe edema including ascites, hepatomegaly and pleural effusion. Despite a corrective treatment with furosemide and albumin the patient's status worsened and required assisted ventilation. On Day 190, the patient experienced bradycardia with cardiac arrest leading to death. The etiology of the ascites-edema syndrome was never established. No autopsy was performed.

There were 8 subjects who died due to pneumonia. In a cardiovascular at-risk population, the underlying cardiovascular disease is often the disease responsible. In at least several cases, the capsular summary sites the chest X-ray report as indicating pulmonary consolidation cannot rule-out failure. These subjects were classified as non-cardiac.

Respiratory failure was sometimes classified as non-cardiac. For example, subject 840135009, a dronedarone-treated patient, was admitted on (b) (4) for an aortic aneurism repair. The patient, while still ventilator dependent apparently had an exacerbation of COPD. The patient died. The cause of death was not attributed to a cardiovascular event (aneurism repair) but to respiratory failure.

There were 6 patients whose deaths were attributable to renal disease (either acute or chronic). Renal-related deaths may often be attributable to the underlying cardiovascular disease.

Dr. Freidlin calculated that if four placebo-treated patients had their CV deaths reclassified as non-cardiac (based on changing the cause nature of some of those assessed as unknown cause), the p-value would not be significant. As I noted above, there were 6 deaths that occurred after the nominal cut-off date, three in the placebo group were classified as cardiovascular; the one death in the dronedarone group was classified as non-cardiovascular.

The ostensible reason for categorizing the underlying cause of the deaths is to remove the noise that is engendered in capturing all causes of death. In this manner deaths that are non-preventable by antiarrhythmic therapy would not taint the prevention signal. What I am finding is that the inconsistency in the characterization of mortal events. The characterization of deaths adds a different form of noise. Given the small wiggle room, I don't see an analysis of cardiovascular mortality as convincing.

With respect to the steering committee's characterization of cardiovascular death, the table below shows their assessment.

Table 8: Characterization of cardiovascular death by the Steering Committee-ATHENA study

Type of death	Placebo	Dronedarone
Cardiovascular deaths	94	65
Aortic dissection aneurism	0	1
Congestive heart failure	10	13
Cardiogenic shock	2	5
Death during cardiac interventional procedure or cardiovascular surgical procedures	2	0
Hemorrhage (except cardiac tamponade)	5	6
Myocardial infarction or unstable angina	7	5
Pulmonary or peripheral embolism	6	2
Stroke	18	11
Sudden cardiac death	35	14
Unknown cause	6	6
Ventricular fibrillation	2	2
Ventricular tachycardia	1	0

Of note, there were substantially more neoplasms-related deaths in the dronedarone relative to the placebo group (25 versus 14).

Hospitalization for cardiovascular reasons:

The third and subordinate secondary endpoint was time to first cardiovascular hospitalization. The results are shown below. There was clearly a decrease in the rate of first cardiovascular hospitalization in the dronedarone group (N=675) compared to the placebo group (N=859). The nominal Hazard ratio and confidence intervals are 0.75 (0.68, 0.82). The specific reasons for hospitalization are shown below.

Table 9: Reason for first hospitalization in the ATHENA study

	Placebo (N=2327)	Dronedarone (N=2301)	HR (95%CI)+
Any Hospitalization	859 (37%)	675 (29%)	0.75 (0.67, 0.82)
Atrial fibrillation and other supraventricular rhythm disorders	457 (20%)	296 (13%)	0.62 (0.53,0.71)
Worsening heart failure, including pulmonary edema or dyspnea of cardiac origin	92 (4%)	78 (3%)	0.80 (0.6, 1.09)
Myocardial infarction or unstable angina	61 (3%)	48 (2%)	0.74 (0.51, 1.08)
Stable angina pectoris or atypical chest pain	41 (2%)	45 (2%)	1.04 (0.69, 1.6)
TIA or stroke (except intracranial hemorrhage)	35 (2%)	28 (1%)	0.75 (0.5, 1.5)
Transcutaneous coronary, cerebrovascular or peripheral procedure	31 (1%)	27 (1%)	0.82 (0.5, 1.4)
Implantation of a pacemaker, ICD or any other device	29 (1%)	32 (1%)	1.04 (0.6, 1.7)
Major bleeding (requiring two or more units of blood) or intracranial hemorrhage	24 (1%)	21 (1%)	0.82 (0.45, 1.5)
Syncope	24 (1%)	21 (1%)	0.83 (0.5, 1.5)
Cardiovascular surgery except cardiac transplantation	23 (1%)	21 (1%)	0.85 (0.5, 1.54)
Blood pressure related (hypotension-except syncope), hypertension	21 (1%)	21 (1%)	0.95 (0.5, 1.74)
Atherosclerosis-related (if not otherwise specified)	8 (< 1%)	11 (< 1%)	1.3 (0.5, 3.2)
Ventricular tachycardia (non-sustained and sustained)	6 (< 1%)	6 (< 1%)	0.95 (0.31, 2.96)
Pulmonary embolism or deep vein thrombosis	3 (< 1%)	10 (<1%)	3.2 (0.9,11.5)
Non fatal cardiac arrest	2 (<1%)	3 (<1%)	1.4 (0.2, 8.7)
Ventricular extrasystoles	1 (< 1%)	1 (<1%)	0.97 (0.06,15.6)
Ventricular fibrillation	1 (< 1%)	1 (<1%)	0.94 (0.06-15.1)
Cardiovascular infection	0	4 (0.2%)	????
Other ventricular arrhythmias	0	1 (< 1%)	????

+ Nominal values

Nearly all the benefit in hospitalization is attributable to the decrease in atrial fibrillation hospitalizations. There was no specific case report form for atrial fibrillation hospitalization to further assess the underlying provocative symptoms.

With respect to heart failure hospitalizations, there were numerically more individuals who were hospitalized in the placebo group compared to the dronedarone group. Although the number of subjects hospitalized for CHF was numerically greater in the placebo group, the nature of the interventions required were more aggressive in the dronedarone group. Fewer subjects in the placebo group required any treatment including diuretics. Numerically more dronedarone groups were treated with IV nitroglycerin or inotropes. The number of subjects with class IV at any time was somewhat higher in the placebo group.

Table 10: Characterization of heart failure events- ATHENA study

Parameter	Placebo (N=2327)	Dronedarone (N=2301)
Number of subjects	130	112
Number of events	188	166
Interventions:		
None	40	26
Required diuretics	138	135
IV nitroglycerin	22	26
Inotropes	18	25
Mechanical ventilation	7	7
NYHA class IV at any time	52	41

Safety:

Duration of exposure:

The duration of exposure is shown below:

Table 11: Duration of safety exposure- ATHENA study

	Placebo(N=2327)	Dronedarone (N=2301)
Mean duration of exposure ± SD, days	485 ± 249	483 ± 254
Total patient-years	3071	3031

Deaths:

Deaths were captured above.

Discontinuations:

The reason for the temporary or permanent discontinuation of therapies (> 10 subjects in either group) is shown below and derived form sponsor's Table 37.

Table 12: Reason for drug discontinuation-ATHENA study (≥ 10 events in either treatment)

	Placebo (N=2313)	Dronedarone (N=2291)
Any	187 (8%)	290 (13%)
Gastrointestinal disorders	44 (2%)	90(4%)
Diarrhea	11 (< 1%)	37 (2%)
Nausea	6 (< 1%)	26 (1%)
Investigations	22 (1%)	58 (3%)
QT prolonged (electrocardiogram)	12 (1%)	33 (1%)
Blood creatinine increased	2 (<1%)	16 (1%)
General disorders and administration site conditions	26 (1%)	27 (1%)
Fatigue	5 (< 1%)	11(<1%)
Skin and subcutaneous disorders	13 (1%)	27 (1%)
Nervous system disorders	18 (1%)	25 (1%)
Dizziness	7 (< 1%)	11 (< 15)
Cardiac disorders	13 (1%)	23 (1%)
Bradycardia	1 (<1%)	10 (< 1%)
Musculoskeletal and connective tissue disorders	13 (1%)	16 (1%)
Respiratory and mediastinal disorders	16 (1%)	15 (1%)
Dyspnea	(<1%)	8 (< 1%)
Neoplasms benign and unspecified	8 (< 1%)	13 (1%)
Psychiatric disorders	10 (< 1%)	6 (< 1%)

There were more drug discontinuations in the dronedarone group largely manifest as by gastrointestinal events; in particular more subjects diarrhea. Cardiac events which led to discontinuation included QT prolongation and bradycardia.

Overall adverse events are shown below:

Table 13; Adverse events in the ATHENA study (≥2% events in any treatment)

	Placebo	Dronedarone
Any event	**1603 (69%)**	**1649 (72%)**
Gastrointestinal disorders	**508 (22%)**	**600 (26%)**
Diarrhea	**144 (6%)**	**223 (10%)**
Nausea	**72 (3%)**	**122 (5%)**
Vomiting	**27 (1 %)**	**49 (2 %)**
Infections and infestations	582 (25%)	542 (24%)
Urinary tract infections	64 (3%)	74 (3%)
Upper respiratory tract infections	83 (4%)	70 (3%)
Nasopharyngitis	75 (3%)	69 (3%)
Bronchitis	72 (3%)	67 (3%)
Pneumonia	71 (3%)	50 (2%)
General disorders and administrative site conditions	**356 (15%)**	**403 (18%)**
Edema peripheral	**119 (5%)**	**147 (6%)**
Fatigue	**90 (4%)**	**115 (5%)**
Asthenia	**47 (2%)**	**68 (3%)**
Chest pain	55(2%)	52(2%)
Musculoskeletal and connective tissue disorders	396 (17%)	381 (17%)
Back pain	80 (4%)	73 (3%)
Arthralgia	62 (3%)	64 (3%)
Pain in extremity	44 (2%)	50 (2%)
Nervous system disorder	381 (17%)	373 (16%)
Dizziness	146 (6%)	161 (7%)
Headache	84 (4%)	70 (3%)
Respiratory, thoracic and mediastinal disorders	337 (15%)	332 (15%)
Dyspnea	**97 (4%)**	**120 (5%)**
Cough	83 (4%)	83 (4%)
Investigations	206 (9%)	309 (13%)
Blood creatinine increased	31 (1%)	108 (5%)
INR increased	47 (2%)	48 (2%)
Cardiac disorders	**221 (10%)**	**260 (11%)**
Bradycardia	**28 (1%)**	**81 (4%)**
Skin and subcutaneous tissue disorders	**176 (7%)**	**237 (10%)**
Rash	**37 (2%)**	**60 (3%)**
Injury poisoning and procedural complications	227 (10%)	219 (10%)
Fall	70 (3%)	69 (3%)
Metabolism and nutrition disorders	203 (9%)	186 (8%)
Hypokalemia	62 (3%)	40 (2%)
Vascular disorders	193 (8%)	182 (8%)
Hypertension	89 (4%)	82 (3%)
Renal and urinary disorders	118 (5%)	116 (5%)
Eye disorders	106 (5%)	115 (5%)
Psychiatric disorders	131 (6%)	111 (5%)
Neoplasms benign and unspecified	118 (5%)	105 (5%)
Reproductive system and breast disorders	57 (3%)	61 (3%)
Ear and Labyrinth	70 (3%)	56 (3%)
Blood and lymphatic systems	65 (3%)	47 (2%)

The main differences suggesting an increase in adverse events in the dronedarone group are bolded. Gastrointestinal disorders were increased in the dronedarone treated subjects. Of note, is that among the events that are more prevalent in the dronedarone group are symptoms often associated with worsening heart failure including peripheral edema, dyspnea, fatigue and asthenia. Bradycardia was much more frequent in the dronedarone treated subjects. Among investigations there was an increase in the incidence of QT prolongation and bradycardia.

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/s/

Abraham Karkowsky
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