

Parameter		Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Age (years)	n	208	417	625
	Median	65	66	66
	Mean	63.0	64.6	64.1
	SD	11.4	11.3	11.4
	Min - Max	30 - 87	20 - 88	20 - 88
Age (years)[n(%)]	<65	104 (50.0 %)	186 (44.6 %)	290 (46.4 %)
	[65-75[80 (38.5 %)	149 (35.7 %)	229 (36.6 %)
	>=75	24 (11.5 %)	82 (19.7 %)	106 (17.0 %)
Height (cm)	n	204	410	614
	Median	173	175	175
	Mean	172.7	173.1	173.0
	SD	10.6	10.9	10.8
	Min - Max	142 - 200	138 - 198	138 - 200
Weight (Kg)	n	208	417	625
	Median	85.7	86.8	86.4
	Mean	87.81	88.61	88.34
	SD	19.27	19.88	19.67
	Min - Max	51.0 - 167.7	35.0 - 185.9	35.0 - 185.9
Gender [n(%)]	Male	140 (67.3 %)	293 (70.3 %)	433 (69.3 %)
	Female	68 (32.7 %)	124 (29.7 %)	192 (30.7 %)
Race [n(%)]	Caucasian	199 (95.7 %)	391 (93.8 %)	590 (94.4 %)
	Black	3 (1.4 %)	9 (2.2 %)	12 (1.9 %)
	Asian / Oriental	0 (0.0 %)	4 (1.0 %)	4 (0.6 %)
	Other	6 (2.9 %)	13 (3.1 %)	19 (3.0 %)

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Table 28- Summary of demographic characteristics

Symptoms:

Incidences of AF/AFL-related symptoms in the 3 months prior to screening were as follows:

- palpitations, 66.4% in the dronedarone group and 69.1% in the placebo group;
- dizziness, 37.4% and 40.1%, respectively;
- fatigue, 65.9% and 57.5%, respectively;
- chest pain, 28.1% and 24.2%, respectively;
- dyspnea, 59.0% and 51.7%, respectively.

In both groups, the intensity of symptoms was most frequently only moderate or mild.

It is noted that symptoms are usually why a patients seeks medical care in AF/AFL. These are nonspecific symptoms and could relate to a number of different underlying medical conditions.

Heart rate (HR):

The summary of HR, assessed in AF/AFL prior to randomization, is presented in the following table.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
n	198	401	599
Median	99	101	100
Mean	106.3	104.9	105.3
SD	32.3	30.8	31.3
Min - Max	54 - 199	45 - 215	45 - 215

(page 57 EFC4788)

Table 29- Summary of heart rate (bpm) at the time of last 12-lead ECG prior to randomization

Antiarrhythmics:

In the randomized and treated patients population, 66.9% of patients in the dronedarone group and 67.3% in the placebo group, had taken previous antiarrhythmic treatment for AF/AFL.

In 22.6% of study patients, a previous antiarrhythmic drug was stopped due to lack of efficacy. The most frequently used antiarrhythmic were amiodarone (34.1% and 33.7% in dronedarone and placebo patients, respectively), sotalol (20.4% and 25.5%, respectively), Class IC (16.8% and 18.8%, respectively), respectively, Class III (13.2% and 9.1%, respectively), and Class IA (10.3% and 10.1%, respectively).

Cardiovascular history:

In the following table the cardiovascular history is summarized.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Hypertension	97 (46.6 %)	242 (58.0 %)	339 (54.2 %)
Structural heart disease ^a	94 (45.6 %)	199 (48.5 %)	293 (47.6 %)
Coronary heart disease	44 (21.2 %)	104 (24.9 %)	148 (23.7 %)
Clinically relevant valvular heart disease including mitral valve prolapse	42 (20.2 %)	86 (20.6 %)	128 (20.5 %)
Dilated cardiomyopathy	19 (9.1 %)	34 (8.2 %)	53 (8.5 %)
Pacemaker (only if still in place)	13 (6.3 %)	31 (7.4 %)	44 (7.0 %)
Rheumatic heart disease	8 (3.8 %)	18 (4.3 %)	26 (4.2 %)
Hypertrophic cardiomyopathy	4 (1.9 %)	13 (3.1 %)	17 (2.7 %)
Implantable cardioverter defibrillator (ICD) (only if still in place)	2 (1.0 %)	6 (1.4 %)	8 (1.3 %)
Congenital heart disease	1 (0.5 %)	4 (1.0 %)	5 (0.8 %)

Structural heart disease = coronary heart disease and/or clinically relevant abnormalities at baseline echocardiography

^a Because of missing values, percentages were calculated using N=206 for placebo and N=410 for dronedarone group
 (page 58 EFC4788)

Table 30- Summary of cardiovascular history

Other baseline cardiovascular findings from a 2D-echocardiogram and physical examination are in the following table.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
2D-echocardiogram			
Left ventricular ejection fraction (%)			
n	195	394	589
Median	60.0	60.0	60.0
Mean	57.21	57.91	57.68
SD	12.24	11.23	11.57
Min - Max	5.5 - 82.0	5.0 - 83.0	5.0 - 83.0
< 35 %	14 / 195 (7.2 %)	15 / 394 (3.8 %)	29 / 589 (4.9 %)
>= 35 %	181 / 195 (92.8 %)	379 / 394 (96.2 %)	560 / 589 (95.1 %)
Cardiovascular clinical examination			
Patients with left CHF	36 (17.3 %)	78 (18.7 %)	114 (18.2 %)
NYHA Class I (Potential)	10 (4.8 %)	28 (6.7 %)	38 (6.1 %)
NYHA Class II (Mild)	26 (12.5 %)	50 (12.0 %)	76 (12.2 %)

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Table 31- Summary of baseline cardiology status

The following table summarizes baseline vital signs.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Systolic blood pressure (mmHg)			
n	208	417	625
Median	130	130	130
Mean	129.8	130.8	130.4
SD	17.4	17.3	17.3
Min - Max	90 - 194	94 - 200	90 - 200
Diastolic blood pressure (mmHg)			
n	208	417	625
Median	76	76	76
Mean	75.7	76.3	76.1
SD	9.1	10.0	9.7
Min - Max	56 - 100	50 - 120	50 - 120
Heart rate (bpm)			
n	208	416	624
Median	64	64	64
Mean	65.4	66.8	66.3
SD	10.6	11.3	11.1
Min - Max	46 - 100	47 - 152	46 - 152

Note: After 3 minutes in supine position. Heart rate measured with a stethoscope for at least 15 seconds

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Table 32- Summary of baseline vital signs

The difference between the heart rate on physical exam and ECG can easily be explained by the occurrence of not all the heart beats being transmitted in AF/AFL.

Concomitant medication

Patients who received not permitted concomitant medications from the day of first study drug intake up to the day of last study drug intake are summarized in the following table.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Total forbidden concomitant medications	33 (15.9%)	69 (16.5%)	102 (16.3%)
Vaughan-Williams class I or III antiarrhythmic drugs ^a	6 (2.9%)	17 (4.1%)	23 (3.7%)
Amiodarone	19 (9.1%)	19 (4.6%)	38 (6.1%)
Drugs which can cause Torsades de Pointes	30 (14.4%)	65 (15.6%)	95 (15.2%)
Potent inhibitors of CYP3A4	2 (1.0%)	7 (1.7%)	9 (1.4%)
Substrates of CYP3A4 with a narrow therapeutic margin	1 (0.5%)	2 (0.5%)	3 (0.5%)

Note: Creams, spray and lozenges are not taken into account

^a Including Sotalol and excluding Amiodarone

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Table 33- Number (%) of patients who received not permitted concomitant medication

The sponsor states that excluding patients who either stopped amiodarone the day of randomization (the protocol allowed amiodarone to be stopped the day of randomization) or started a not permitted concomitant medication on the day of study drug discontinuation, the number of patients who received not permitted concomitant medication was only 44 (10.6%) and 14 (6.7%) in the dronedarone and placebo groups, respectively.

The following table summarizes the number and percentage of patients who received specific permitted concomitant medications.

	Placebo (N=208)	Dronedarone 800 mg (N=417)	Total (N=625)
Total other specific concomitant medications	207 (99.5%)	411 (98.6%)	618 (98.9%)
Beta blocking agents (except Sotalol)	114 (54.8%)	208 (49.9%)	322 (51.5%)
ACE inhibitors or Angiotensin II receptor antagonists	96 (46.2%)	194 (46.5%)	290 (46.4%)
ACE inhibitors	80 (38.5%)	151 (36.2%)	231 (37.0%)
Angiotensin II receptor antagonists	21 (10.1%)	56 (13.4%)	77 (12.3%)
Digitalis	53 (25.5%)	94 (22.5%)	147 (23.5%)
Digoxin	53 (25.5%)	94 (22.5%)	147 (23.5%)
Calcium antagonists with heart rate lowering effects ^a	55 (26.4%)	103 (24.7%)	158 (25.3%)
Diuretics	65 (31.3%)	150 (36.0%)	215 (34.4%)
Spironolactone	4 (1.9%)	23 (5.5%)	27 (4.3%)
Diuretics other than Spironolactone	65 (31.3%)	149 (35.7%)	214 (34.2%)
Oral anticoagulant	149 (71.6%)	298 (71.5%)	447 (71.5%)
Chronic antiplatelet therapy	88 (42.3%)	191 (45.8%)	279 (44.6%)
Statins	79 (38.0%)	168 (40.3%)	247 (39.5%)
Metabolized by CYP3A4	57 (27.4%)	129 (30.9%)	186 (29.8%)
Not metabolized by CYP3A4	27 (13.0%)	58 (13.9%)	85 (13.6%)
Moderate inhibitors of CYP3A4	58 (27.9%)	105 (25.2%)	163 (26.1%)
NSAID	43 (20.7%)	101 (24.2%)	144 (23.0%)

^a Restricted to Diltiazem, Verapamil
 (page 62 EFC4788)

Table 34 - Number (%) of patients who received specific permitted concomitant medications

As expected in AF/AFL patients, the most frequently prescribed drugs were oral anticoagulants, and beta-blocking agents.

6.1.4.2.3 Analysis of primary endpoint

The results of the primary analysis are summarized below.

	Placebo (N=208)	Dronedarone 800 mg (N=417)
Number of patients with adjudicated first AF/AFL recurrence within 12 months from randomization	146	246
Median time in days (95% CI)	59 ([22;96])	158 ([80;252])
Relative risk ^a	0.725	
95% CI ^a	[0.590;0.890]	
Log-rank's test result (p-value)	0.0017	

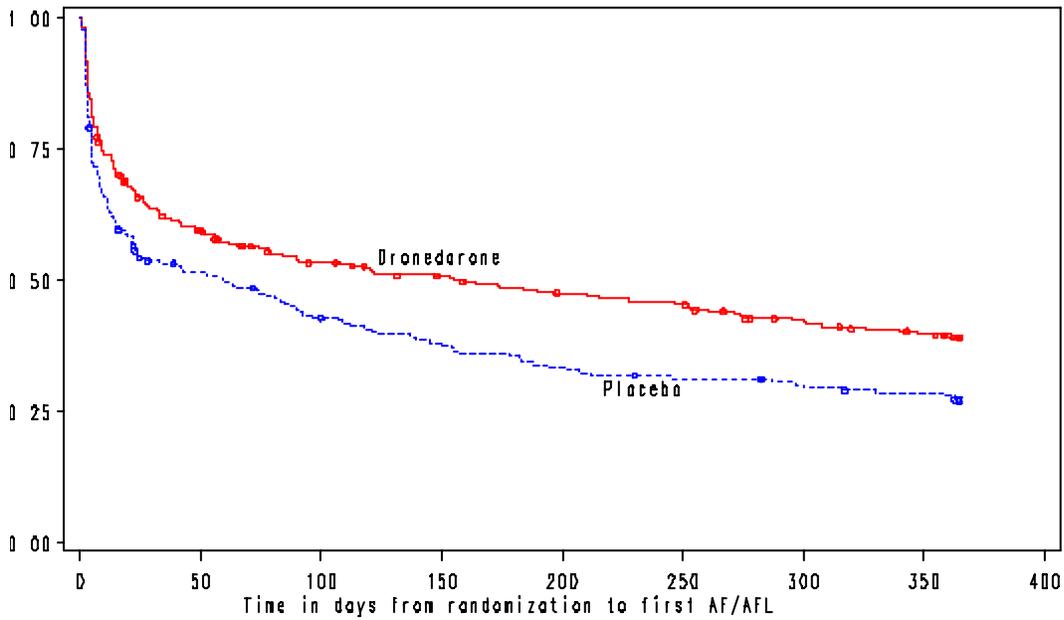
^a Determined from Cox regression model confirmed by Dr. Valeria Freidlin (page 63 EFC4788)

Table 35- Unadjusted analysis of first AF/AFL recurrence within 12 months

Dronedarone significantly lowered, by 27.5%, the risk of first recurrence of AF/AFL within the 12-month study period compared to placebo in the randomized and treated patients population. The median time from randomization to adjudicated first AF/AFL recurrence in the dronedarone group was 2.7-fold longer than in the placebo group.

At 12 months, taking into account patients censored over time, 61.1% of dronedarone patients had experienced a first AF/AFL recurrence, compared to 72.8% of placebo patient. However, earlier in the protocol (page 50) the sponsor states “It was expected that 60% of patients on placebo in this trial would have an AF/AFL recurrence.” Therefore, dronedarone does not do much better than what was expected from the placebo population.

Below are the cumulative incidence curves showing this.



(figure provided by Dr. Valeria Freidlin)

Figure 6- Primary efficacy endpoint, time to first AF/AFL

Baseline covariates analysis

The adjusted relative risks based on baseline prognostic factors are summarized for the primary endpoint in the following table.

Prognostic factor	Risk	Adjusted relative risk ^a		
		Relative risk	95% CI	p-value
Treatment	Dronedarone / Placebo	0.714	[0.581;0.879]	0.0014
Convsr	Yes / No	1.587	[1.257;2.005]	0.0001
Amio	Yes / No	1.185	[0.926;1.516]	0.178
Shd	Yes / No	0.862	[0.703;1.059]	0.157

^a Determined from Cox regression model

Convsr: electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization

Amio: chronic treatment with amiodarone preceding randomization

Shd: structural heart disease

(page 65 EFC4788)

Table 36- Adjusted relative risk for adjudicated first AF/AFL recurrence within 12 months by prognostic factors.

This above table shows that treatment effect was significant when adjusted for pre-specified baseline prognostic factors. The recurrence rate was 1.587 times higher in patients with electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization than in other patients (p = 0.0001).

Relative risks in each prognostic factor subcategory (yes/no) are summarized for the primary endpoint in the following table.

Prognostic factor	Category	Number of patients				Unadjusted relative risk ^a Dronedarone/Placebo		
		Placebo		Dronedarone 800 mg		Relative risk	95% CI	p-value
		N	Nb of events	N	Nb of events			
Convsr	Yes	46	40	90	61	0.652	[0.436;0.973]	0.03627
	No	162	106	327	185	0.756	[0.596;0.961]	0.02209
Amio	Yes	43	35	82	48	0.549	[0.355;0.851]	0.0073
	No	165	111	335	198	0.779	[0.617;0.983]	0.03540
Shd	Yes	94	64	199	117	0.773	[0.570;1.049]	0.098
	No	112	80	211	123	0.685	[0.517;0.909]	0.0087

^a Determined from Cox regression model

Convsr: electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization

Amio: chronic treatment with oral amiodarone preceding randomization

Shd: structural heart disease

(page 65 EFC4788)

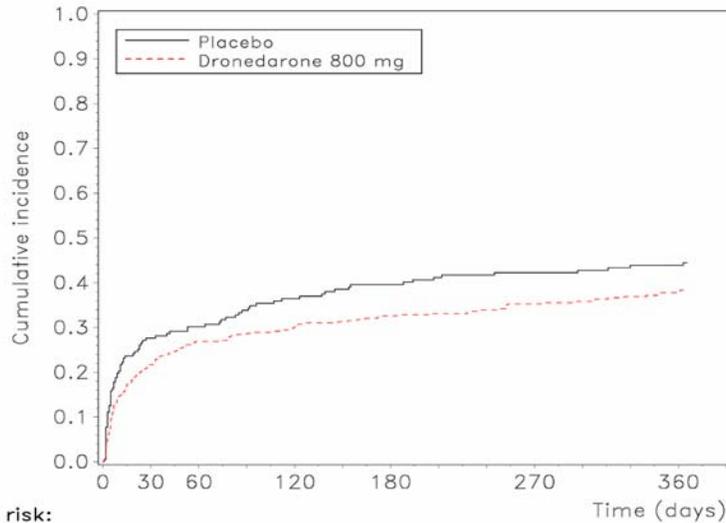
Table 37- Unadjusted relative risk for adjudicated first AF /AFL recurrence within 12 months by prognostic factor subcategories

The above table shows that being converted by electrical cardioversion, ibutilide infusion or overdrive pacing prior to randomization was of benefit for the dronedarone patients. Also, the use of chronic oral amiodarone preceding randomization and the lack of structural heart disease decreased the risk of the occurrence of AF/AFL in this group.

6.1.4.2.4 Secondary efficacy endpoints

6.1.4.2.4.1 Symptomatic AF/AFL among adjudicated first AF/AFL recurrence

The adjudicated first AF/AFL recurrence was associated with symptoms in about 62% of patients, consistently in both groups as shown in the Prentice cumulative incidence curves below.



Nb exposed at risk:	0	30	60	120	180	270	360
Placebo	208	105	96	77	67	58	49
Dronedarone 800 mg	417	260	228	200	183	162	137

Competing events: symptomatic adjudicated first AF/AFL recurrence and asymptomatic adjudicated first AF/AFL recurrence
 (page 68 EFC4788)

Figure 7- Prentice cause-specific cumulative incidence curves for adjudicated first AF/AFL recurrence – randomized and treated patients population

Dronedarone significantly delayed the time to symptomatic adjudicated first AF/AFL recurrence within 12 months from randomization (Log-rank test, $p = 0.021$).

6.1.4.2.4.2. Ventricular rate assessed at time of adjudicated first AF/AFL recurrence

The following table summarizes HR assessed at the time of adjudicated first AF/AFL recurrence.

	Placebo (N=208)	Dronedarone 800 mg (N=417)
TTEM recording ECG method		
n	102	188
Median	114	101
Mean	116.6	104.6
SD	31.9	27.1
Min - Max	56 - 226	57 - 173
Whatever recording ECG method		
n	146	246
Median	105	100
Mean	110.6	102.7
SD	32.2	28.3
Min - Max	55 - 226	46 - 217

Note: Heart rate values obtained on only 1 RR interval are not taken into account
 (page 69 EFC4788)

Table 38- Summary of heart rate (bpm) assessed at time of adjudicated first AF/AFL recurrence during study period up to Day 365 – randomized and treated patients population

The sponsor states that at time of first recurrence dronedarone patients had significantly lower mean HR based on the TTEM method, $p = 0.0009$, ANOVA. However, this statistician differs stating that analysis based on the subgroup (TTEM method) was not prespecified. Therefore, analysis based on all data (all ECG's submitted) should be used. This analysis showed that dronedarone was only numerically ($p = 0.078$) better than placebo relative to heart rate.

Also, it is important to note that clinically the heart rate should be lowered to a range of 60 to 80 bpm in order to be considered improved. Therefore, the mean rate of 102 is far from what is clinically considered improved.

6.1.4.2.4.3. Time between steady state and adjudicated first AF/AFL recurrence

The following table summarizes the unadjusted analysis of time from Day 5 midnight to the adjudicated first AF/AFL recurrence in the modified randomized and treated patients population.

	Placebo (N=146)	Dronedarone 800 mg (N=327)
Number of patients with adjudicated first AF/AFL recurrence within 12 months from randomization	87	161
Median time in days (95% CI)	152 ([104;292])	342 ([248;..])
Relative risk ^a	0.743	
95% CI ^a	[0.572;0.964]	
Log-rank's test result (p-value)	0.02443	

^a Determined from Cox regression model confirmed by Dr. Valeria Freidlin)
 (page 70 EFC4788)

Table 39- Unadjusted analysis of time from steady state to adjudicated first AF/AFL recurrence within 12 months from randomization

Dronedarone significantly lowered, by 26%, the risk of recurrence of AF/AFL considered between Day 5 midnight and 12 months post randomization. The median time to adjudicated first AF/AFL recurrence in the dronedarone group was 2.3-fold longer than in the placebo group.

6.1.4.2.4.4. Pharmacokinetics

The steady state of dronedarone and SR35021 plasma concentrations was reached by Day 7. The PK characteristics of dronedarone and its major active circulating metabolite SR35021 in the patients of the present study, as well as the effect of gender, age and CYP3A4 moderate inhibitor were consistent with those already reported in healthy subjects or patients. This is discussed in the pharmacokinetic review.

6.1.4.2.5. The Adonis Study Conclusions

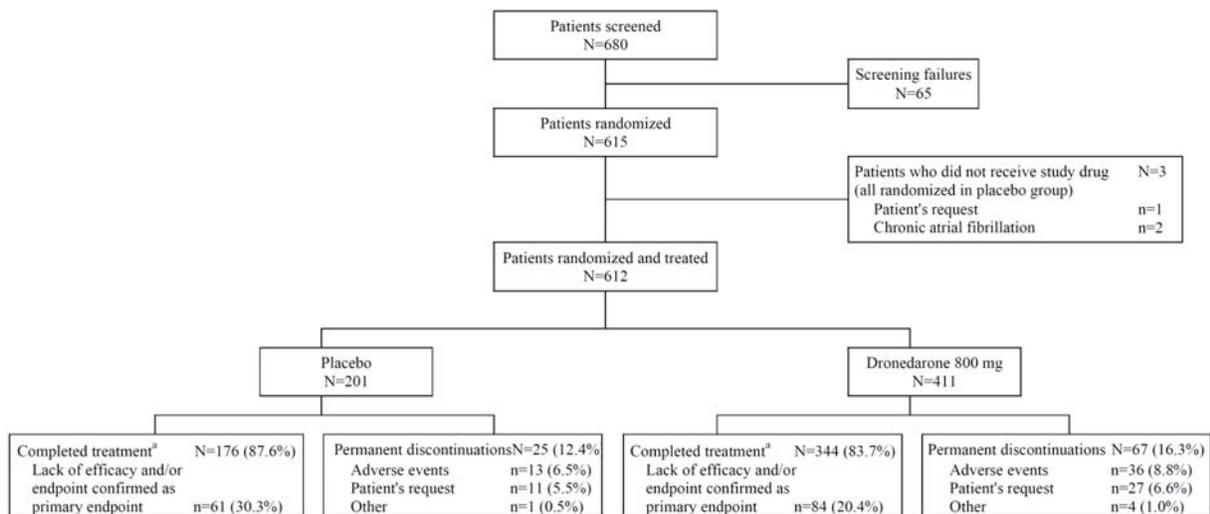
Dronedarone 800 mg daily (400 mg BID) significantly delayed the first AF/AFL recurrence. It also delayed the symptomatic first recurrence. However, these reviewers disagree with the Sponsor that dronedarone significantly reduced ventricular rate at the time of first recurrence.

6.1.4.3. EURIDIS (EFC3153)

This study is essentially identical to the ADONIS.

6.1.4.3.1. Overview

This multinational study was conducted in 65 active centers in 12 European countries between November 2001 and August 2003. The following figure provides a disposition of the patients. There was no statistically significant difference between the treatment groups in the number of premature permanent discontinuations.



a: including patients for whom lack of efficacy and/or endpoint was reported (and endpoint confirmed by adjudication) as the main reason
 (page 51 EFC3153)

Figure 8- Disposition of patients

The demographic data for the randomized and treated patients are summarized in the table below.

Parameter		Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
Age (years)	n	201	411	612
	Median	63	63	63
	Mean	61.3	62.3	62.0
	SD	10.7	10.0	10.2
	Min - Max	32 - 82	23 - 86	23 - 86
Age (years)[n(%)]	<65	111 (55.2 %)	227 (55.2 %)	338 (55.2 %)
	[65-75[76 (37.8 %)	139 (33.8 %)	215 (35.1 %)
	>=75	14 (7.0 %)	45 (10.9 %)	59 (9.6 %)
Height (cm)	n	195	407	602
	Median	175	173	173
	Mean	174.6	172.9	173.4
	SD	9.3	9.9	9.8
	Min - Max	152 - 200	148 - 213	148 - 213
Weight (Kg)	n	198	408	606
	Median	85.0	83.0	84.0
	Mean	86.43	83.84	84.68
	SD	14.78	14.39	14.55
	Min - Max	61.0 - 168.0	50.0 - 165.0	50.0 - 168.0
Gender [n(%)]	Male	140 (69.7 %)	285 (69.3 %)	425 (69.4 %)
	Female	61 (30.3 %)	126 (30.7 %)	187 (30.6 %)
Race [n(%)]	Caucasian	201 (100 %)	409 (99.5 %)	610 (99.7 %)
	Asian / Oriental	0 (0.0 %)	2 (0.5 %)	2 (0.3 %)

Table 40- Summary of demographic characteristics

6.1.4.3.2. Medical history

Symptoms:

Incidences of AF/AFL-related symptoms in the 3 months prior to screening were as follows:

- palpitations, 65.0% in the dronedarone group and 66.7% in the placebo group;
- dizziness, 30.2% and 29.4%, respectively;
- fatigue, 46.2% and 42.8%, respectively;
- chest pain, 23.1% and 24.9%, respectively;
- dyspnea, 44.5% and 41.3%, respectively.

In both groups, the intensity of symptoms were most frequently moderate or mild.

Heart rate:

The summary of HR, assessed in AF/AFL prior to randomization, is presented in the following table.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
n	195	394	589
Median	99	97	98
Mean	103.3	102.2	102.6
SD	31.6	28.8	29.8
Min - Max	45 - 198	51 - 187	45 - 198

Note: Heart rate values obtained on only 1 RR interval are not taken into account
 (page 55 EFC3153)

Table 41- Summary of heart rate (bpm) at the time of last 12-lead ECG in AF/AFL prior to randomization

Antiarrhythmics:

In the randomized and treated patients population, 79.3% of patients in the dronedarone group and 78.6% in the placebo group, had taken previous antiarrhythmic treatment for AF/AFL. In 39.5% of study patients, a previous antiarrhythmic drug was stopped due to lack of efficacy. The most frequently used antiarrhythmics were Class II (33.3% and 30.3% in dronedarone and placebo patients, respectively), sotalol (31.4% and 29.4%, respectively), Class IC (29.2% and 34.3%, respectively), and amiodarone (24.6% and 27.9%, respectively).

6.1.4.3.3. Cardiovascular history

The cardiovascular history of randomized and treated patients is summarized in the following table.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
Hypertension	108 (53.7 %)	255 (62.0 %)	363 (59.3 %)
Structural heart disease ^a	65 (33.3 %)	149 (36.3 %)	214 (35.4 %)
Coronary heart disease	31 (15.4 %)	91 (22.1 %)	122 (19.9 %)
Clinically relevant valvular heart disease including mitral valve prolapse	19 (9.5 %)	50 (12.2 %)	69 (11.3 %)
Pacemaker (only if still in place)	7 (3.5 %)	33 (8.0 %)	40 (6.5 %)
Dilated cardiomyopathy	11 (5.5 %)	16 (3.9 %)	27 (4.4 %)
Hypertrophic cardiomyopathy	8 (4.0 %)	10 (2.4 %)	18 (2.9 %)
Rheumatic heart disease	6 (3.0 %)	7 (1.7 %)	13 (2.1 %)
Congenital heart disease	2 (1.0 %)	9 (2.2 %)	11 (1.8 %)
Implantable cardioverter defibrillator (ICD) (only if still in place)	3 (1.5 %)	0 (0.0 %)	3 (0.5 %)

Structural heart disease = coronary heart disease and/or clinically relevant abnormalities at baseline echocardiography

^a Because of missing values, percentages were calculated using N=195 for placebo group and N=410 for dronedarone group
 (page 56 EFC3153)

Table 42- Summary of the cardiovascular history

In the above table differences can be seen among the two groups in regards to hypertension, coronary artery disease, and clinically relevant heart disease including mitral valve prolapse. A summary of the baseline cardiology status is shown on the following table.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
2D-echocardiogram			
Left ventricular ejection fraction (%)			
n	191	400	591
Median	60.0	60.0	60.0
Mean	59.83	59.57	59.65
SD	9.37	10.25	9.97
Min - Max	20.0 - 84.0	15.0 - 93.4	15.0 - 93.4
< 35 %	2 / 191 (1.0 %)	8 / 400 (2.0 %)	10 / 591 (1.7 %)
>= 35 %	189 / 191 (99.0 %)	392 / 400 (98.0 %)	581 / 591 (98.3 %)
Cardiovascular clinical examination			
Patients with left CHF	37 (18.4 %)	65 (15.8 %)	102 (16.7 %)
NYHA Class I (Potential)	16 (8.0 %)	19 (4.6 %)	35 (5.7 %)
NYHA Class II (Mild)	21 (10.4 %)	46 (11.2 %)	67 (10.9 %)

(page 57 EFC3153)

Table 43- Summary of baseline cardiology status

The summary of the baseline vital signs are provided in the table below.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
Systolic blood pressure (mmHg)			
n	200	411	611
Median	130	130	130
Mean	131.4	134.5	133.4
SD	17.0	17.4	17.3
Min - Max	92 - 181	90 - 192	90 - 192
Diastolic blood pressure (mmHg)			
n	200	411	611
Median	80	80	80
Mean	79.1	80.7	80.2
SD	9.7	9.1	9.3
Min - Max	50 - 100	50 - 101	50 - 101
Heart rate (bpm)			
n	199	411	610
Median	64	65	64
Mean	66.8	67.3	67.1
SD	11.3	11.9	11.7
Min - Max	48 - 127	47 - 130	47 - 130

(page 58 EFC3151)

Table 44- Summary of baseline vital signs

6.1.4.3.4. Concomitant medication

Patients who received not permitted concomitant medications from the day of first study drug intake up to the day of last study drug intake are summarized in the following table.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
Total forbidden concomitant medications	26 (12.9%)	43 (10.5%)	69 (11.3%)
Vaughan-Williams class I or III antiarrhythmic drugs ^a	8 (4.0%)	20 (4.9%)	28 (4.6%)
Amiodarone	17 (8.5%)	24 (5.8%)	41 (6.7%)
Drugs which can cause Torsades de Pointes	26 (12.9%)	42 (10.2%)	68 (11.1%)
Potent inhibitors of CYP3A4	0 (0.0%)	3 (0.7%)	3 (0.5%)
Substrates of CYP3A4 with a narrow therapeutic margin	0 (0.0%)	3 (0.7%)	3 (0.5%)

Note: Creams, spray and lozenges are not taken into account

^aIncluding Sotalol and excluding Amiodarone

(page 59 EFC3153)

Table 45- Number (%) of patients who received not permitted concomitant medication

Excluding patients who either stopped amiodarone the day of randomization (the protocol allowed amiodarone to be stopped the day of randomization) or started a not permitted concomitant medication on the day of study drug discontinuation, the number of patients who

received not permitted concomitant medications was only 14 (3.4%) and 6 (3.0%) in the dronedarone and placebo groups, respectively.

In the following table are the number and percent of patients who received permitted concomitant medications.

	Placebo (N=201)	Dronedarone 800 mg (N=411)	Total (N=612)
Total other specific concomitant medications	196 (97.5%)	395 (96.1%)	591 (96.6%)
Beta blocking agents (except Sotalol)	124 (61.7%)	245 (59.6%)	369 (60.3%)
ACE inhibitors or Angiotensin II receptor antagonists	94 (46.8%)	215 (52.3%)	309 (50.5%)
ACE inhibitors	79 (39.3%)	176 (42.8%)	255 (41.7%)
Angiotensin II receptor antagonists	22 (10.9%)	50 (12.2%)	72 (11.8%)
Digitalis	55 (27.4%)	79 (19.2%)	134 (21.9%)
Digoxin	42 (20.9%)	51 (12.4%)	93 (15.2%)
Digitalin	12 (6.0%)	24 (5.8%)	36 (5.9%)
Digitalis other than Digoxin or Digitalin	1 (0.5%)	4 (1.0%)	5 (0.8%)
Calcium antagonists with heart rate lowering effects ^a	23 (11.4%)	36 (8.8%)	59 (9.6%)
Diuretics	60 (29.9%)	121 (29.4%)	181 (29.6%)
Spironolactone	14 (7.0%)	10 (2.4%)	24 (3.9%)
Diuretics other than Spironolactone	58 (28.9%)	119 (29.0%)	177 (28.9%)
Oral anticoagulant	142 (70.6%)	273 (66.4%)	415 (67.8%)
Chronic antiplatelet therapy	64 (31.8%)	135 (32.8%)	199 (32.5%)
Statins	52 (25.9%)	95 (23.1%)	147 (24.0%)
Metabolized by CYP3A4	28 (13.9%)	59 (14.4%)	87 (14.2%)
Not metabolized by CYP3A4	29 (14.4%)	44 (10.7%)	73 (11.9%)
Moderate inhibitors of CYP3A4	23 (11.4%)	36 (8.8%)	59 (9.6%)
NSAID	19 (9.5%)	31 (7.5%)	50 (8.2%)

^a Restricted to Diltiazem, Verapamil
 (page 60 EFC 3153)

Table 46- Number (%) of patients who received specific permitted concomitant medications

6.1.4.3.5. Primary endpoint

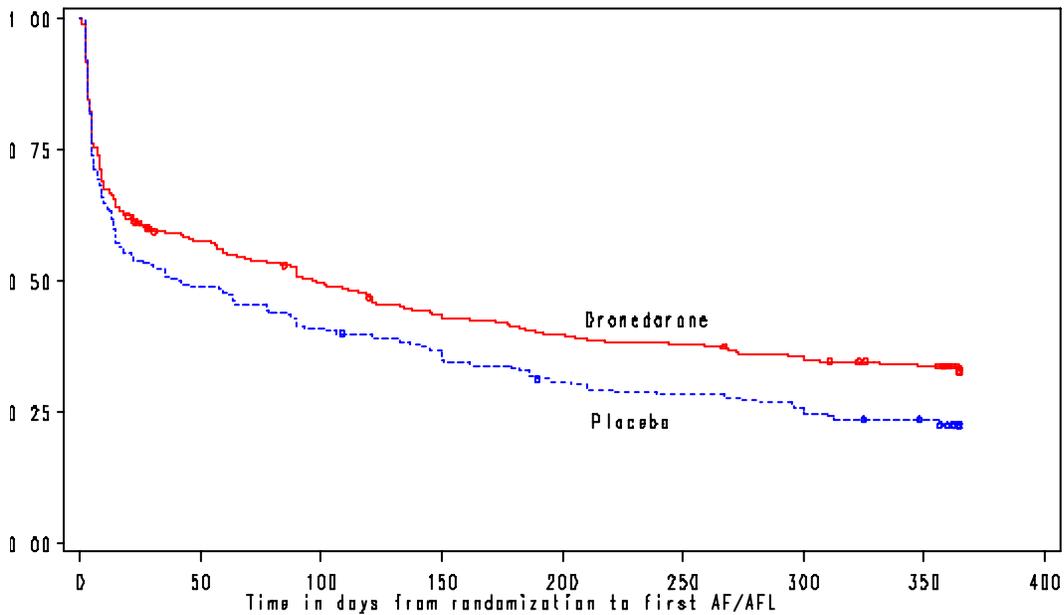
The results of the primary analysis of the primary endpoint are in the following table.

	Placebo (N=201)	Dronedarone 800 mg (N=411)
Number of patients with adjudicated first AF/AFL recurrence within 12 months from randomization	155	272
Median time in days (95% CI)	41 ([16;87])	96 ([61;133])
Relative risk (Dronedarone / Placebo) ^a	0.784	
95% CI ^a	[0.644;0.955]	
Log-rank's test result (p-value)	0.01383	

^a Determined from Cox regression model and confirmed by Dr. Valeria Freidlin
 (page 61 EFC3153)

Table 47- Unadjusted analysis of time to adjudicated first AF/AFL recurrence within 12 months

Dronedarone significantly lowered, by 22%, the risk of first recurrence of AF/AFL within the 12-month study period compared to placebo in the randomized and treated patients population. The median time from randomization to adjudicated first AF/AFL recurrence in the dronedarone group was 2.3-fold longer than in the placebo group. This is also shown in the figure below.



(Figure provided by Dr. Valeria Freidlin)

Figure 9- Primary efficacy endpoint, time to first AF/AFL

Secondary analysis of the primary endpoint

At 12 months of treatment (Prentice estimates), 65.5% of patients experienced a first AF/AFL recurrence in the dronedarone group as compared to 76.5% in the placebo group. Adjusted relative risks based on baseline prognostic factors are summarized for the primary endpoint in the following table.

Prognostic factor	Risk	Adjusted relative risk ^a		
		Relative risk	95% CI	p-value
Treatment	Dronedarone / Placebo	0.801	[0.656;0.978]	0.02959
Convsr	Yes / No	1.147	[0.942;1.397]	0.173
Amio	Yes / No	0.850	[0.651;1.109]	0.231
Shd	Yes / No	1.000	[0.819;1.221]	1.000

^a Determined from Cox regression model
 Convsr: electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization
 Amio: chronic treatment with amiodarone preceding randomization
 Shd: structural heart disease
 (page 63 EFC3153)

Table 48- Adjusted relative risk of time to adjudicated first AF/AFL recurrence within 12 months by prognostic factors

Treatment effect was significant when adjusted for pre-specified baseline prognostic factors. None of the 3 baseline prognostic factors had a significant effect on time to recurrence.

Relative risks in each prognostic factor subcategory (yes/no) are summarized for the primary endpoint in following table.

Prognostic factor	Category	Number of patients				Unadjusted relative risk ^a Dronedarone/Placebo		
		Placebo		Dronedarone 800 mg		Relative risk	95% CI	p-value
		N	Nb of events	N	Nb of events			
Convsr	Yes	75	59	153	105	0.823	[0.598;1.133]	0.233
	No	126	96	258	167	0.764	[0.594;0.982]	0.03567
Amio	Yes	32	25	66	41	0.688	[0.418;1.134]	0.143
	No	169	130	345	231	0.800	[0.645;0.992]	0.04166
Shd	Yes	65	51	149	100	0.814	[0.581;1.141]	0.233
	No	130	98	261	172	0.794	[0.620;1.018]	0.069

^a Determined from Cox regression model
 Convsr: electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization
 Amio: chronic treatment with amiodarone preceding randomization
 Shd: structural heart disease
 (page 63 EFC31532)

Table 49- Unadjusted relative risk to adjudicated first AF/AFL recurrence within 12 months by prognostic factor subcategories

6.1.4.3.6. Secondary endpoints

AF/AFL related symptoms

Two patients in the dronedarone group, without indication of whether the recurrence was symptomatic, were considered asymptomatic in this analysis. Adjudicated first AF/AFL recurrence was associated with symptoms in 55.1% of patients in the dronedarone group, versus 61.3% in the placebo group. At the end of treatment, the intensity of symptoms were reported as significantly lower in the dronedarone group.

Ventricular rate assessed at time of adjudicated first AF/AFL recurrence

The following table summarizes HR assessed at the time of adjudicated first AF/AFL recurrence.

	Placebo (N=201)	Dronedarone 800 mg (N=411)
TTEM recording ECG method		
n	117	199
Median	115	100
Mean	117.5	102.3
SD	29.1	24.7
Min - Max	70 - 204	53 - 173
Whatever recording ECG method		
n	154	269
Median	109	95
Mean	112.1	99.5
SD	29.4	25.0
Min - Max	62 - 204	53 - 173

Note: Heart rate values obtained on only 1 RR interval are not taken into account
 (page 67 EFC3153)

Table 50- Summary of heart rate (bpm) assessed at time of adjudicated first AF/AFL recurrence during study period up to Day 365

At time of first recurrence dronedarone patients had statistically lower mean HR (TTEM method, $p < 0.0001$, ANOVA; but this is not clinically significant as it is not within the acceptable rate at rest of 60 to 80 bpm.

Pharmacokinetics

Dronedarone significantly lowered, by 29%, the risk of recurrence of AF/AFL considered between Day 5 midnight and 12 months post randomization. The median time to adjudicated first AF/AFL recurrence in the dronedarone group was 1.8-fold longer than in the placebo group. The steady state of dronedarone and SR35021 plasma concentrations was reached by Day 7.

6.1.4.3.7. The Euridis Study Conclusions

Dronedarone 800 mg daily (400 mg BID) delayed the first symptomatic AF/AFL recurrence. Although it reduced the ventricular heart rate at the first recurrence, this was not clinically significant.

6.1.4.4. The ERATO Study (EFC4508)

This is a supportive study for ventricular rate control in permanent atrial fibrillation.

6.1.4.4.1. Primary endpoint

The results of the primary analysis of the primary endpoint are shown in following table.

		Placebo (N=89)	Dronedarone 800 mg (N=85)
Baseline	Mean	90.6	86.5
	SEM	1.5	1.4
D14	Mean	90.2	76.2
	SEM	1.5	1.4
Change from baseline(a)	Mean	0.7	-11.0
	95%CI(b)	[-1.9;3.3]	[-13.5;-8.5]
Treatment effect(a)	Mean	-11.7	
	95%CI(b)	[-14.8;-8.5]	
	p-value(b)	22x10 ⁻¹⁴	

(a) Change from baseline and treatment effect (difference between Dronedarone 800 mg and Placebo groups) are adjusted for baseline heart rate value, age and type of baseline standard treatment (beta-blocker, heart rate lowering calcium antagonist, digitalis)

(b) Following multiple imputation technique using Rubin's rule [4 (4.7%) dronedarone and 2 (2.2%) placebo patients had missing data at baseline and were evaluated on Day 14, and 5 (5.9%) dronedarone and 5 (5.6%) placebo patients were evaluated at baseline and had missing data on Day 14, 1 (1.2%) dronedarone patient had missing data at baseline and on Day 14]
 (page 57 EFC4508)

Table 51- 24-hour Holter heart rate (bpm)

The decrease from baseline in 24-hour Holter HR on Day 14 in the dronedarone group was significantly more pronounced than the change from baseline observed in the placebo group (ANCOVA, p<0.0001). The presence/absence at baseline of beta blockers, calcium antagonists and digitalis (each tested separately) had no significant effect on the primary endpoint analysis. However, this was not supported in the ADONIS and EURIDIS trials above.

6.1.4.4.2. Ventricular rate during exercise

		Placebo (N=89)	Dronedarone 800 mg (N=85)
Baseline	N	87	82
	Mean	131.6	124.6
	SEM	2.9	2.3
D14	N	84	75
	Mean	130.0	103.3
	SEM	2.9	2.3
Change from baseline(a)	N	84	74
	Mean	-2.2	-25.6
	95%CI	[-6.7;2.4]	[-30.1;-21.1]
Treatment effect(a)	Mean	-23.4	
	95%CI	[-28.9;-17.9]	
	p-value	25x10 ⁻¹⁵	

(a) Change from baseline and treatment effect (difference between Dronedarone 800 mg and Placebo groups) are adjusted for baseline heart rate value, age and type of baseline standard treatment (beta-blocker, heart rate lowering calcium antagonist, digitalis)
 (page 59 EFC4508)

Table 52- Heart rate at sub-maximal exercise (bpm)

		Placebo (N=89)	Dronedarone 800 mg (N=85)
Baseline	N	88	84
	Mean	162.4	152.6
	SEM	3.6	2.9
D14	N	86	76
	Mean	159.6	129.7
	SEM	3.7	3.1
Change from baseline(a)	N	86	76
	Mean	-2.9	-27.4
	95%CI	[-8.0;2.3]	[-32.5;-22.3]
Treatment effect(a)	Mean	-24.5	
	95%CI	[-30.8;-18.3]	
	p-value	1x10 ⁻¹²	

(a) Change from baseline and treatment effect (difference between Dronedarone 800 mg and Placebo groups) are adjusted for baseline heart rate value, age and type of baseline standard treatment (beta-blocker, heart rate lowering calcium antagonist, and digitalis)
 (page 59 EFC4508)

Table 53- Heart rate at maximal exercise (bpm)

6.1.4.4.3. The Erato Study Conclusions

Dronedarone 800 mg daily (400 mg BID) significantly decreased HR at steady state (Day 14) and long term (Month 4), compared with placebo. On Day 14, while decreases from baseline in HR at sub-maximal and maximal exercise were significantly greater with dronedarone versus

placebo, the changes from baseline in maximal exercise duration were not different between the 2 treatment groups. This study confirms the lack of efficacy of dronedarone in ventricular rate control in patients with atrial fibrillation.

6.1.4.5. The DAFNE Study (DRI3550)

This was a dose-ranging study of the efficacy and safety of dronedarone for the maintenance of sinus rhythm in patients undergoing cardioversion for atrial fibrillation.

6.1.4.5.1. Results

There was no statistically significant dose effect was observed in the number of shocks or in the energy necessary to obtain sinus rhythm.

Comparison	Cox's model results p-value		
	Treatment group	Covariate SHD	Covariate AFD
800 mg versus placebo	0.0010	0.4137	0.6043
1200 mg versus placebo	0.8106	0.5019	0.3439
1600 mg versus placebo	0.1209	0.0860	0.0923

SHD = presence of structural heart disease, AFD = duration of the current AF episode
 (page 79 DRI3550)

Table 54- Time to Atrial Fibrillation Recurrence - Comparison of Each Treatment Group versus Placebo:

A highly statistically significant treatment effect was observed in the 800 mg group (p = 0.0010). No statistically significant effects were observed in the covariate analysis of SHD or AFD.

6.1.4.5.1 Conclusions

In this study there was no dronedarone dose effect for maintenance of sinus rhythm. The lack of dose effect cannot be explained by any pharmacokinetic related issues. However, dronedarone 800 mg/day (400 mg. b.i.d.) was superior to placebo for this endpoint. The sponsor should consider the implementation of another controlled study with a wider dose range (e.g. 50mg bid to 800mg).

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

In the Andromeda Study among the patients on the study drug dronedarone, there were more deaths, more hospitalizations and more hospitalizations for acute cardiovascular reasons than in the patients on placebo. Although the Sponsor attributes this increase in mortality and morbidity to the lack of ACE inhibitors or Angiotensin II receptor antagonists in the dronedarone patients, these reviewers do not concur with the sponsor's conclusions. The percentage for both groups receiving ACE inhibitors or Angiotensin II receptor antagonists was similar, dronedarone 93.5% and placebo 94.3%, during the study.

In the Adonis study dronedarone 800 mg daily (400 mg BID) significantly delayed the first AF/AFL recurrence. It also delayed the symptomatic first recurrence. However, these reviewers disagree with the sponsor that dronedarone significantly reduced ventricular rate at the time of first recurrence. In the Euridis study which was identical to the Adonis, dronedarone 800 mg daily (400 mg BID) delayed the first symptomatic AF/AFL recurrence. Although it reduced the ventricular heart rate at the first recurrence, this was not clinically significant.

In the Erato study dronedarone 800 mg daily (400 mg BID) significantly decreased HR at steady state (Day 14) and long term (Month 4), compared with placebo. On Day 14, while decreases from baseline in HR at sub-maximal and maximal exercise were significantly greater with dronedarone versus placebo, the changes from baseline in maximal exercise duration were not different between the 2 treatment groups. This study confirms the lack of efficacy for dronedarone in ventricular rate control in atrial fibrillation.

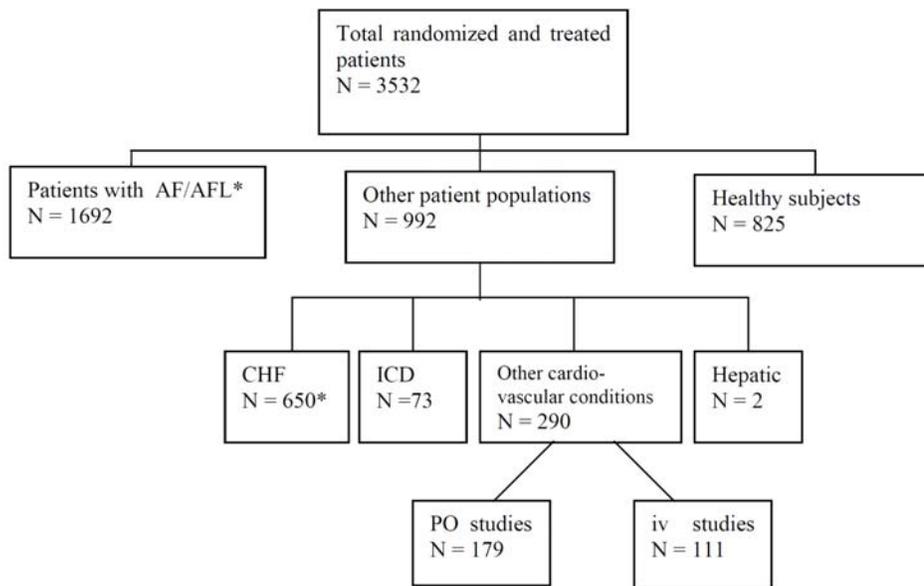
In the Dafne study there was no dronedarone dose effect for maintenance of sinus rhythm. The lack of dose effect cannot be explained by any pharmacokinetic related issues. However, dronedarone 800 mg/day (400 mg b.i.d.) was superior to placebo for the maintenance of sinus rhythm. We concur with Dr. Williams, recommendations that the sponsor should consider the implementation of another controlled study with a wider dose range (e.g. 50mg bid to 800mg).

Before dronedarone can be shown to be safe and efficacious, the Athena Study (EFC5555) must be completed with favorable results. This study, "A Placebo-Controlled, Double-blind, Parallel Arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of Cardiovascular Hospitalization or Death from any cause in patients with atrial fibrillation/atrial flutter (AF/AFL)," plans to enroll almost 4000 patients 70 years old or older.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This safety review is essentially divided into three sections: The Andromeda Study which included patients with congestive heart failure (CHF), the studies pertaining to atrial fibrillation/flutter (AF/AFL), and the studies in normal volunteers. An overview of all the studies included for safety is shown in the following diagram.



*23 patients in EFC4966/ANDROMEDA and 11 patients in EFC4508/ERATO, from centers 616004 and 616003 respectively, are counted in this figure; hereafter they are excluded from all analyses presented (unless otherwise specified) due to a major violation in GCP which raised doubts about the integrity of the data from these centers. (page 312 Module 2.7.4 Summary)

Figure 10- Overall disposition of subjects/patients in the completed clinical studies

7.1.1 Deaths

7.1.1.1. Deaths in the ANDROMEDA study (EFC4966)

The primary objective of this study was to evaluate whether dronedarone reduces death from any cause or hospitalizations for worsening heart failure in patients with moderate to “severe” congestive heart failure (CHF) and left ventricular dysfunction (LVD), when added to usual evidence-based treatments for CHF, over a minimum period of 12 months as compared to placebo. A secondary objective was to evaluate whether dronedarone reduces death from any cause. Another secondary objective was whether dronedarone reduces arrhythmic/sudden death.

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

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

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

^a Determined from unadjusted Cox regression model
 (page 67 EFC4966)

Table 55- Analysis of time from randomization to death or hospitalization for worsening of heart failure up to January 16, 2003 (excluding center 616004)

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

The analysis of time from randomization to death or hospitalization for worsening of heart failure up to January 16, 2003 (excluding center 616004) is also shown in the Kaplan-Meier cumulative incidence curve below.

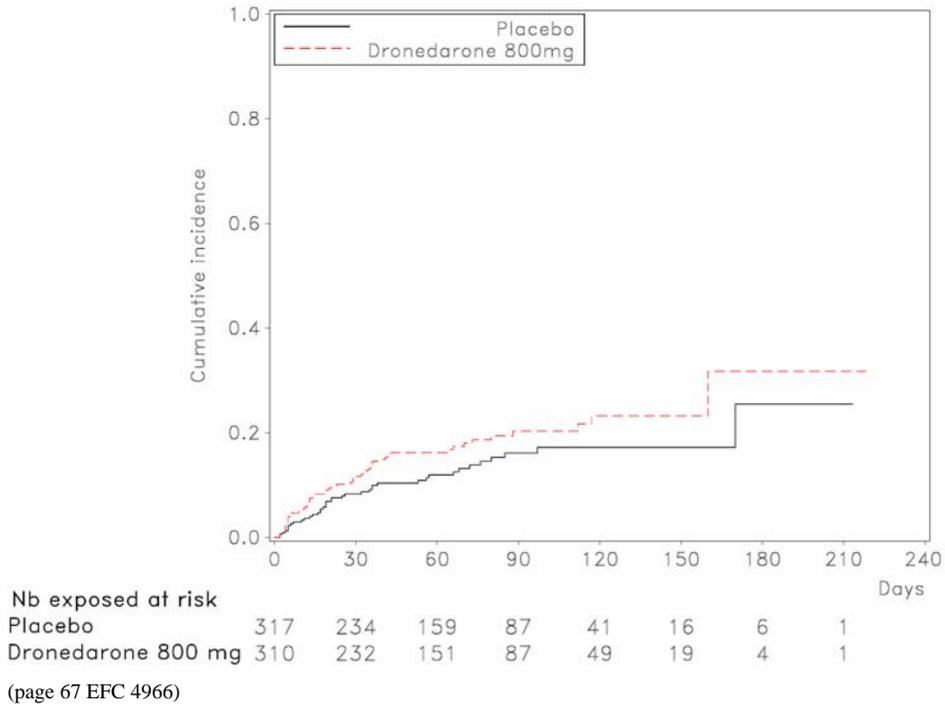


Figure 11- Kaplan-Meier incidence curves to January 16, 2003 (excluding c. 616004)

Secondary supportive analysis of primary endpoint

The adjusted relative risks based on prognostic factors for the primary endpoint are summarized in the following table.

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

Note: intake of medications has been analyzed as time dependent variable

^a Determined from Cox regression model

^b Creatinine clearance estimate using Cockcroft formula

^c Excluding Sotalol

^d WMI is used to estimate LVEF, with LVEF = WMIx30 (5)

(page 68 EFC4966)

Table 56- Post hoc adjusted relative risk of death or hospitalization for worsening of heart failure by prognostic factors up to January 16, 2003 (excluding center 616004)

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

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

^a Determined from Cox regression

^b No intake is co-medication either never taken or prematurely stopped (i.e. prior to endpoint or censoring date)

^c Excluding Sotalol
 (page 70 EFC4966)

Table 57- Unadjusted relative risk of death or hospitalization for worsening heart failure by prognostic factors up to January 16, 2003 (excluding center 616004)

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

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

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

Table 58- Analysis of time from randomization to death or hospitalization for worsening heart failure up to 16 January 2003, including center 616004

7.1.1.1.2. Death from any cause

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

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

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

Table 59- Analysis of death up to January 16, 2006, (excluding center 616004)

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

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

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

(page 73 EFC4966)

Table 60- Number (%) of patients according to adjudicated primary cause of death up to January 16, 2003 (excluding center 616004)

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

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

(page 73) EFC4966)

Table 61- Number (%) of patients according to adjudicated timing of cardiovascular deaths up to January 16, 2003 (excluding center 616004)

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

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

Note: intake of medications has been analyzed as time dependent variable

^a Determined from Cox regression model

^b Creatinine clearance estimate using Cockcroft formula

^c Excluding Sotalol

^d WMI is used to estimate LVEF, with LVEF = WMIx30 (5)

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Table 62- Post hoc adjusted relative risk of death by prognostic factors up to January 16, 2003 (excluding center 616004)

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

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

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

^a Determined from Cox regression

^b No intake is co-medication either never taken or prematurely stopped (i.e. prior to endpoint or censoring date)

^c Excluding Sotalol
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Table 63- Unadjusted relative risk by prognostic factor subcategories for death up to January 16, 2003, (excluding center 616004)

The analysis performed 6 months after discontinuation of inclusions and ongoing study

drug treatment, July 17, 2003, showed a similar number of deaths in both treatment groups: 42 patients in the dronedarone group, and 39 in the placebo group. The cumulative incidence curves are presented in the figure below. The number of deaths due to worsening heart failure was similar in both treatment groups: 15 patients in the dronedarone group, and 13 in the placebo group. To these reviewers the significance of this is unknown.

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

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

(page 3202, Appendix 16.2.6.2.2.1.1.7 EFC4966)

Table 64- Summary of local primary cause of death January 16, 2003, per protocol population

The above table shows the dronedarone patients had an increase in sudden death (probably an arrhythmia) and also shows a worsening of congestive heart failure. According to the Sponsor, among the arrhythmic/sudden deaths there were no reported cases of torsades de pointes.

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

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

(page 3224 Appendix 16.2.6.2.2.1.7. EFC4966)

Table 65- Summary of local primary cause of death February 16, 2003, per protocol population

7.1.1.1.3 Listing of all deaths among patients receiving dronedarone in Andromeda Study

Table 66- Deaths among patients receiving dronedarone in Andromeda Study

TABLE 13.9.2 - Listing of all deaths - randomized and treated patients population (treatment as received - Dronedarone 800 mg)

Patient number	Last study drug intake (Day#)	Death Date(Day#)	Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208101019	2003-01-17(2)	e 2003-11-14(303)						
208102001	* 2003-01-17(129)	c 2003-02-02(145)	P 3 General disorders and administration site conditions	Death (Death)	2003-02-02(145)	No	Presumed cardiovascular reason	Sudden death unwitnessed
208102003	2002-09-17(2)	e 2003-11-18(429)						
208102007	2002-10-13(12)	a b 2002-10-14(13)	T 2 General disorders and administration site conditions	Sudden death (Sudden death - unwitnessed)	2002-10-14(13)	No	Presumed cardiovascular reason	Sudden death unwitnessed
208103009	* 2002-10-14(20)	a b 2002-10-14(20)	T 2 Cardiac disorders	Cardiac failure (Worsening chf)	2002-10-14(20)	No	Worsening CHF	Non sudden death
208103017	2002-12-16(33)	a b 2002-12-16(33)	T 2 General disorders and administration site conditions	Sudden death (Sudden dead)	2002-12-16(33)	No	Documented arrhythmia	Sudden death witnessed
208104007	2003-01-17(36)	c 2003-02-16(66)	T 2 Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-12-16(4)	No	Worsening CHF	Non sudden death
208105002	2002-08-27(8)	d 2003-02-18(183)	P 2 Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-12-27(130)	No	Worsening CHF	Non sudden death

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Table 66- continued

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208105003	*	2002-10-15(41)	b	2002-11-01(58)	T 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-10-23(49)	No	Worsening CHF	Non sudden death
208106011		2002-11-13(3)	a b	2002-11-14(4)	T 2	Gastrointestinal disorders	Mesenteric occlusion (Mesentery thrombosis)	2002-11-14(4)	No	Other cardiovascular reason	Non sudden death
208108003		2003-01-17(139)	d	2003-06-07(280)	P 4	Cardiac disorders	Cardiac failure (Progression in heart failure)	2003-06-01(274)	No	Worsening CHF	Non sudden death
208108006		2002-12-26(112)	a b	2002-12-26(112)	T 2	Cardiac disorders	Cardiac failure (Worsening chf)	2002-12-09(95)	No	Documented arrhythmia	Sudden death witnessed
208111002	*	2002-09-09(28)	a b	2002-09-09(28)	T 2	Cardiac disorders	Ventricular tachycardia (Ventricular tachycardia (cardiac arrest (death)))	2002-09-07(26)	No	Documented arrhythmia	Sudden death witnessed
208112001		2002-09-11(30)	a b	2002-09-11(30)	T 2	General disorders and administration site conditions	Sudden death (Sudden death)	2002-09-11(30)	No	Presumed cardiovascular reason	Sudden death un-witnessed

Continued
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Table 66- continued

(continued)

Patient number		Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208112010		2002-11-01(5)	a b	2002-11-01(5)	T 2	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2002-11-01(5)	No	Presumed cardiovascular reason	Sudden death unwitnessed
208114018		2003-01-17(45)	a c	2003-01-21(49)	T 2	Cardiac disorders	Cardiac failure (Worsening of heart failure)	2003-01-14(42)	No	Worsening CHF	Non sudden death
208114019		2003-01-17(40)	c	2003-02-04(58)	T 3	Cardiac disorders	Acute myocardial infarction (Ami worsening heart failure)	2003-01-24(47)	No	Procedure related	Non sudden death
208116008		2002-11-04(5)	a b	2002-11-10(11)	T 2	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2002-11-10(11)	No	Presumed cardiovascular reason	Sudden death witnessed
208116011		2003-01-05(18)	c	2003-02-08(52)	P 3	Cardiac disorders	Cardiac failure (Worsening chf)	2003-02-01(45)	No	Presumed cardiovascular reason	Non sudden death
208118003		2003-01-01(45)	d	2003-07-01(226)	P 4	Cardiac disorders	Cardiogenic shock (Cardiogenic shock)	2003-06-29(224)	No	Presumed cardiovascular reason	Non sudden death
208121014		2003-01-15(2)	c	2003-01-27(14)	T 3	Renal and urinary disorders	Renal tubular disorder (Acute tubular interstitial nephropathy)	2003-01-17(4)	No	Worsening CHF	Non sudden death

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Table 66- continued

Patient number	Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208124007	2002-12-13(1)	d	2003-06-05(175)	P 4	Cardiac disorders	Acute myocardial infarction (Acute myocardial infarct)	2003-06-05(175)	No	Presumed cardiovascular reason	Sudden death unwitnessed
208126005	2003-01-17(155)	d	2003-06-14(303)	P 4	Cardiac disorders	Cardiac failure (Worsening heart failure)	2003-06-13(302)	No	Presumed cardiovascular reason	Non sudden death
208126010	2002-12-15(33)	a b	2002-12-23(41)	T 2	Cardiac disorders	Myocardial ischaemia (Ischaemic heart disease)	2002-12-09(27)	No	Procedure related	Non sudden death
208128001	2003-01-17(134)	d	2003-03-27(203)	P 4	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm malignant (Lung cancer)	2003-03-27(203)	No	Cancer	
208129004	2002-09-09(19)	a b	2002-09-09(19)	T 2	Cardiac disorders	Ventricular fibrillation (Possibly ventricular fibrillation)	2002-09-09(19)	Yes	Documented arrhythmia	Sudden death witnessed
208129009	2003-01-16(73)	e	2003-07-22(260)	P 5	General disorders and administration site conditions	Death (Dead at admission to hospital)	2003-07-22(260)	No	Presumed cardiovascular reason	Sudden death unwitnessed

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Table 66- continued

Patient number	Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208130011	2003-01-16(43)	e	2003-07-23(231)	P 4	Infections and infestations	Sepsis (Sepsis)	2003-07-04(212)	No	Primary infection disease	
208131001	* 2002-10-02(21)	b	2002-10-19(38)	P 2	Cardiac disorders	Cardiac disorder (Terminal heart disease)	2002-10-19(38)	No	Worsening CHF	Non sudden death
208131003	2002-12-12(63)	d	2003-03-10(151)	P 4	Cardiac disorders	Cardiac arrest (Asystole)	2003-03-10(151)	No	Documented arrhythmia	Sudden death witnessed
208131011	2003-01-16(7)	c	2003-02-06(28)	T 2	Nervous system disorders	Cerebrovascular accident (Apoplexia cerebri)	2003-01-14(5)	No	Stroke	Non sudden death
208133010	* 2003-01-15(6)	a c	2003-01-21(12)	T 2	Nervous system disorders	Cerebrovascular accident (Stroke / apoplexia cerebri)	2003-01-14(5)	No	Stroke	Non sudden death
208137001	2002-10-31(81)	b	2002-12-20(131)	T 2	Investigations	Blood creatinine increased (Increased creatinin)	2002-08-19(8)	No	Worsening CHF	Non sudden death
		b	2002-12-20(131)	P 2	Cardiac disorders	Cardiac failure (Worsening of heart failure)	2002-12-17(128)	No	Worsening CHF	Non sudden death

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Table 66- continued

Patient number	Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug###	Adjudication Main reason	Timing
208137006	2003-01-16(18)	a c	2003-01-20(22)	T 3	General disorders and administration site conditions	Sudden death (Sudden death, found dead in his chair, in hospital, section showed pneumonia)	2003-01-20(22)	No	Primary infection disease	
528002004	2003-01-16(94)	d	2003-05-27(225)	P 4	Cardiac disorders	Ventricular fibrillation (Ventricle fibrillation)	2003-05-27(225)	No	Documented arrhythmia	Sudden death witnessed
578304003	2002-10-09(13)	a b	2002-10-10(14)	T 2	Cardiac disorders	Cardiac failure (Increasing heart failure)	2002-10-09(13)	No	Worsening CHF	Non sudden death
578304006	2003-01-10(72)	a b	2003-01-15(77)	T 2	Infections and infestations	Bronchitis (Bronchitis)	2002-12-19(50)	No	Cancer	
616002003	2002-10-21(21)	b	2002-11-22(53)	T 2	Cardiac disorders	Cardiac failure (Worsening of heart failure)	2002-10-22(22)	Yes	Worsening CHF	Non sudden death
		b	2002-11-22(53)	T 2	Respiratory, thoracic and mediastinal disorders	Respiratory failure (Respiratory insufficiency)	2002-10-25(25)	No	Worsening CHF	Non sudden death
616004012	I * 2003-01-16(50)	c	2003-02-15(80)	P 3	Cardiac disorders	Cardiopulmonary failure (Cardio-pulmonary insufficiency)	2003-02-04(69)	No	Procedure related	Non sudden death

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Table 66- continued

Patient number	Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug###	Adjudication Main reason	Timing
752206001	2002-12-12(71)	a b	2002-12-14(73)	T 2	Gastrointestinal disorders	Peritonitis (Peritonitis)	2002-12-12(71)	No	Other cardiovascular reason	Non sudden death
752210007	2002-12-20(12)	a b	2002-12-28(20)	T 2	General disorders and administration site conditions	Sudden death (Sudden death)	2002-12-28(20)	No	Presumed cardiovascular reason	Non sudden death
752211001	2002-12-11(42)	a b	2002-12-19(50)	T 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-11-20(21)	No	Worsening CHF	Non sudden death
752213001	2002-10-11(1)	a b	2002-10-12(2)	T 2	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2002-10-12(2)	Yes	Documented arrhythmia	Sudden death witnessed
752215002	2002-11-27(50)	a b	2002-11-27(50)	T 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-11-13(36)	No	Worsening CHF	Non sudden death
752215004	2002-11-19(2)	a b	2002-11-19(2)	T 2	Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-11-19(2)	No	Worsening CHF	Non sudden death

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Table 66- continued

Patient number	Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
752220003	2002-12-14(68)	a b	2002-12-14(68)	T 2	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2002-12-14(68)	No	Documented arrhythmia	Sudden death witnessed
752220004	2002-12-16(62)	a b	2002-12-16(62)	T 2	Cardiac disorders	Cardiac failure (Worsening chf)	2002-12-13(59)	No	Worsening CHF	Non sudden death

Note: For all deaths, only AEs leading to death are listed. Deceased patients with no AE leading to death are also listed.

Day 1 is the day of first study drug intake, ## As assessed by the investigator, *: Patient excluded from per-protocol population, I: Patient from center 616004, N: AE occurred before 1st admin., T: AE occurred between 1st admin. and last admin. + 10 days, P: AE occurred after last admin. + 10 days, 2: AE occurred between 1st admin. and 16/01/2003, 3: AE occurred between 17/01/2003 and 17/02/2003, 4: AE occurred between 18/02/2003 and 17/07/2003, 5: AE occurred after 17/07/2003, a: Death between 1st admin. and last admin. + 10 days, b: Death between 1st admin. and 16/01/2003, c: Death between 17/01/2003 and 17/02/2003, d: Death between 18/02/2003 and 17/07/2003, e: Death after 17/07/2003
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7.1.1.1.4 Deaths among the patients receiving placebo

Table 67- List of deaths among the patients receiving placebo

Patient number	Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208102009	2002-11-18(39)	b	2002-12-29(80)	T 2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer (Malignant prostate cancer)	2002-11-18(39)	No	Cancer	
208102019	2003-01-22(14)	d	2003-05-29(141)							
208103002	2002-07-28(4)	a b	2002-07-29(5)	T 2	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2002-07-29(5)	No	Myocardial infarction	Non sudden death
208103005	2002-09-09(13)	c	2003-01-17(143)							
208103011	2002-10-15(6)	a b	2002-10-15(6)	T 2	General disorders and administration site conditions	Asthenia (Weakness)	2002-10-14(5)	No	Worsening CHF	Sudden death witnessed
		a b	2002-10-15(6)	T 2	Cardiac disorders	Cardiac arrest (Asystole)	2002-10-15(6)	No	Worsening CHF	Sudden death witnessed
208103024	2003-01-17(12)	d	2003-05-15(130)	P 4	General disorders and administration site conditions	Sudden death (Sudden death)	2003-05-15(130)	No	Documented arrhythmia	Sudden death unwitnessed

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Table 67- continued

Patient number	Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208105005	2002-12-08(75)	d	2003-03-16(173)	P 4	Vascular disorders	Hypotension (Hypotension)	2003-03-12(169)	No	Worsening CHF	Non sudden death
		d	2003-03-16(173)	P 4	Cardiac disorders	Cardiac failure (Worsening heart failure)	2003-03-12(169)	No	Worsening CHF	Non sudden death
208105007	2003-01-17(66)	c	2003-02-12(92)	T 3	Cardiac disorders	Cardiac failure (Worsening heart failure)	2003-01-20(69)	No	Worsening CHF	Non sudden death
208106002	2003-01-17(157)	d	2003-03-11(210)	N	Investigations	Blood creatinine increased (High p-creatinimum 347 mcmol/l)	2002-08-13(0)	No	Worsening CHF	Non sudden death
		d	2003-03-11(210)	P 4	Cardiac disorders	Cardiac failure (Worsening chf)	2003-03-04(203)	No	Worsening CHF	Non sudden death
208107002	2002-12-03(89)	d	2003-04-23(230)							
208107011	2003-01-16(36)	d	2003-03-25(104)	P 4	Metabolism and nutrition disorders	Diabetic foot (Worsening of diabetic wound)	2003-03-06(85)	No	Presumed cardiovascular reason	Sudden death witnessed
208110007	2003-01-17(121)	e	2003-07-27(312)	P 5	Cardiac disorders	Cardiac failure (Worsening heart failure)	2003-07-26(311)	No	Worsening CHF	Non sudden death

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Table 67- continued

Patient number	Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208111015	2003-01-16(39)	d	2003-03-20(102)	P 4	Vascular disorders	Hypotension (Hypotension)	2003-03-18(100)	No	Worsening CHF	Non sudden death
		d	2003-03-20(102)	P 4	Respiratory, thoracic and mediastinal disorders	Pulmonary oedema (Pulmonary oedema)	2003-03-19(101)	No	Worsening CHF	Non sudden death
208111015	2003-01-16(39)	d	2003-03-20(102)	P 4	Cardiac disorders	Cardiac failure (Worsening heart failure)	2003-03-19(101)	No	Worsening CHF	Non sudden death
208112009	2003-01-17(82)	d	2003-03-08(132)	P 4	Cardiac disorders	Cardiac arrest (Cardiac arrest)	2003-03-08(132)	No	Documented arrhythmia	Sudden death witnessed
208114005	2002-12-21(75)	a b	2002-12-22(76)	T 2	Vascular disorders	Gangrene (Bed sore leading to gangrene right foot)	2002-10-29(22)	No	Other non cardiovascular reason	
208114016	2003-01-17(58)	a c	2003-01-20(61)	T 3	Cardiac disorders	Ventricular fibrillation (Ventricular fibrillation)	2003-01-20(61)	No	Documented arrhythmia	Sudden death witnessed
208114020	2003-01-17(30)	d	2003-04-07(110)	P 4	Cardiac disorders	Ventricular fibrillation (Ventricular fibrillation)	2003-04-07(110)	No	Documented arrhythmia	Sudden death witnessed

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Table 67- continued

Patient number	Last study drug intake (Day#)		Death Date(Day#)	Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208115007	2003-01-17(52)	e	2003-07-31(247)	P 4 Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm (Right side central lung tumor with compression of trachea)	2003-07-15(231)	No	Presumed non cardiovascular reason	
208117015	* 2003-01-17(3)	d	2003-03-28(73)	P 4 Cardiac disorders	Cardiac failure congestive (Increasing congestive heart failure)	2003-03-20(65)	No	Worsening CHF	Non sudden death
208119008	2002-12-09(26)	d	2003-03-03(110)	P 4 General disorders and administration site conditions	Sudden death (Sudden death)	2003-03-03(110)	No	Presumed cardiovascular reason	Sudden death witnessed
208120001	2002-09-03(20)	d	2003-04-20(249)						
208121004	* 2002-10-25(12)	c	2003-01-25(104)	P 2 Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to central nervous system (Metastasis cerebrum)	2003-01-12(91)	No	Cancer	
208125008	2003-01-17(45)	d	2003-06-06(185)	P 4 General disorders and administration site conditions	Sudden death (Sudden death)	2003-06-06(185)	No	Presumed cardiovascular reason	Sudden death unwitnessed

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Table67- continued

Patient number	Last study drug intake (Day#)		Death Date(Day#)	Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Rela study drug##	Adjudication Main reason	Timing
208126003	2002-12-31(170)	a b	2002-12-31(170)	T 2 Cardiac disorders	Cardiac arrest (Cardiac arrest)	2002-12-31(170)	No	Documented arrhythmia	Sudden death witnessed
208126009	* 2002-12-03(36)	d	2003-02-21(116)	P 4 Cardiac disorders	Cardiac arrest (Cardiac arrest)	2003-02-21(116)	No	Worsening CHF	Non sudden death
208126011	2003-01-09(53)	a b	2003-01-09(53)	T 2 Cardiac disorders	Cardiac arrest (Cardiac arrest)	2003-01-09(53)	No	Presumed cardiovascular reason	Sudden death unwitnessed
208131002	2002-12-24(78)	a b	2002-12-25(79)	T 2 Cardiac disorders	Cardiac failure (Worsening heart failure)	2002-12-12(66)	No	Worsening CHF	Non sudden death
208132004	* 2003-01-17(82)	d	2003-04-27(182)	P 4 Injury, poisoning and procedural complications	Femur fracture (Collum femoris fracture)	2003-04-22(177)	No	Worsening CHF	Non sudden death
208133009	* 2003-01-14(5)	d	2003-05-11(122)	P 4 Cardiac disorders	Cardiac arrest (Cardiac arrest)	2003-05-11(122)	No	Documented arrhythmia	Sudden death witnessed
348002004	XXXX-XX-XX(13)	a b	2002-12-02(13)	T 2 Cardiac disorders	Myocardial infarction (Myocardial infarction)	2002-12-02(13)	No	Myocardial infarction	Non sudden death

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Table 67- continued

TABLE 13.7.2-1 - LISTING OF ALL DEATHS - RANDOMIZED PATIENTS POPULATION (TREATMENT AS RECEIVED - PER-PROTOCOL) (CONTINUED)

Patient number	Last study drug intake (Day#)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Relevant study drug##	Adjudication Main reason	Timing
348003004	2003-01-17(80)	a c	2003-01-25(88)	T 3	Cardiac disorders	Cardiac failure (Worsening of congestive heart failure)	2003-01-20(83)	No	Worsening CHF	Non sudden death
578303001	2003-01-17(137)	d	2003-05-06(246)	P 4	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2003-05-05(245)	No	Myocardial infarction	Non sudden death
578307002	2003-01-13(36)	a b	2003-01-13(36)	T 2	General disorders and administration site conditions	Sudden death (Sudden death)	2003-01-13(36)	No	Presumed cardiovascular reason	Sudden death unwitnessed
616002008	* 2002-12-13(26)	a b	2002-12-13(26)	T 2	General disorders and administration site conditions	Sudden death (Sudden death)	2002-12-13(26)	Yes	Presumed cardiovascular reason	Sudden death unwitnessed
752205003	2003-01-17(65)	d	2003-03-05(112)	P 4	Vascular disorders	Shock (Circulation failure due to heart failure and multiple infarctions)	2003-03-03(110)	No	Worsening CHF	Non sudden death
752206002	2002-10-31(22)	b	2003-01-06(89)							
752206005	2003-01-16(57)	d	2003-02-25(97)	P 3	Cardiac disorders	Cardiac failure (Worsening chf)	2003-02-11(83)	No	Worsening CHF	Non sudden death

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Table 67- continued

TABLE 13.7.2-1 - LISTING OF ALL DEATHS - RANDOMIZED PATIENTS POPULATION (TREATMENT AS RECEIVED - PER-PROTOCOL) (CONTINUED)

Patient number	Last study drug intake (Days)		Death Date(Day#)		Primary system organ class	Preferred term (verbatim)	Onset Date(Day#)	Relevant study drug##	Adjudication Main reason	Timing
752210005	2003-01-02(35)	d	2003-05-19(172)	P 4	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2003-05-19(172)	No	Myocardial infarction	Non sudden death
752215003	2002-10-21(7)	a b	2002-10-21(7)	T 2	General disorders and administration site conditions	Sudden death (Sudden death)	2002-10-21(7)	No	Documented arrhythmia	Sudden death witnessed
752216002	2003-01-16(65)	d	2003-06-01(201)	P 4	General disorders and administration site conditions	Multi-organ failure (Multi organ failure probably due to liver malignancy)	2003-05-29(198)	No	Cancer	
752217002	2003-01-16(56)	a c	2003-01-20(60)	T 3	General disorders and administration site conditions	Multi-organ failure (Multi organ failure)	2003-01-20(60)	No	Worsening CHF	Non sudden death

Note: For all deaths, only AEs leading to death are listed. Deceased patients with no AE leading to death are also listed. # Day 1 is the day of first study drug intake, ## As assessed by the investigator, *: Patient excluded from per-protocol population, I: Patient from center 616004, N: AE occurred before 1st admin., T: AE occurred between 1st admin. and last admin. + 10 days, P: AE occurred after last admin. + 10 days, 2: AE occurred between 1st admin. and 16/01/2003, 3: AE occurred between 17/01/2003 and 17/02/2003, 4: AE occurred between 18/02/2003 and 17/07/2003, 5: AE occurred after 17/07/2003, a: Death between 1st admin. and last admin. + 10 days, b: Death between 1st admin. and 16/01/2003, c: Death between 17/01/2003 and 17/02/2003, d: Death between 18/02/2003 and 17/07/2003, e: Death after 17/07/2003

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7.1.2 Other Serious Adverse Events

7.1.2.1. Patients in the ANDROMEDA Study

The following table provides an overview of the Treatment Emergent Adverse Events (TEAE) during this study.

	Placebo (N=317)		Dronedarone 400 mg BID (N=310)	
Patients with any TEAE (a)	214	(67.5%)	220	(71.0%)
Patients with any serious TEAE	118	(37.2%)	128	(41.3%)
Deaths (b)	12	(3.8%)	25	(8.1%)
Patients permanently discontinued study drug for any TEAE (a)(c)(d)	28	(8.8%)	58	(18.7%)

(a) Including SAEs

(b) Patients who died from first study drug intake up to the 16 January 2003

(c) According to the 'End of treatment' form

(d) Whatever the period

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Table 68- Overview of main treatment emergent events [number (%) of patients] up to January 16, 2003

This table show that among the patients treated with dronedarone there were more treatment emergent adverse events, more patients with serious treatment emergent adverse events, more deaths, and more patients who permanently discontinued their drug for treatment emergent adverse events compared to placebo.

Hospitalization for worsening of heart failure

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

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

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Table 69- Analysis of time to first hospitalization for worsening of heart failure up to January 16, 2003 (excluding center 616004)

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

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

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Table 70- Number (%) of patients according to adjudicated primary cause of the first hospitalization for acute cardiovascular reasons up to January 16, 2003 (excluding c.616004)

Among patients with a recent “severe” episode of CHF, there were marked differences in frequency between the dronedarone treated patients and the placebo group for cardiac disorders, GI disorders and laboratory findings. The most common treatment emergent adverse events (with incidence $\geq 10\%$ in at least 1 treatment group) in this population of patients with a recent severe episode of CHF were cardiac disorders, GI disorders, laboratory results, infections and infestations, and respiratory thoracic and mediastinal disorders. Among the TEAEs with an incidence $\geq 2\%$, there were more cardiac failure and blood creatinine increased in the dronedarone 400 mg BID group. This is shown in the following table.

Table 71- Number (%) of patients with TEAEs for preferred term with incidence $\geq 2\%$ in either treatment group presented by system organ class up to January 16, 2003

MedDRA (6.1) Organ Class Preferred term	Placebo (N=317)		Dronedarone 400 mg BID (N=310)	
Any Class any event	214	(67.5%)	220	(71.0%)
Cardiac disorders				
Any event	76	(24.0%)	105	(33.9%)
Cardiac failure	24	(7.6%)	46	(14.8%)
Angina pectoris	11	(3.5%)	12	(3.9%)
Ventricular tachycardia	3	(0.9%)	9	(2.9%)
Atrial fibrillation	12	(3.8%)	3	(1.0%)
Gastrointestinal disorders				
Any event	42	(13.2%)	65	(21.0%)
Diarrhoea	15	(4.7%)	26	(8.4%)
Nausea	9	(2.8%)	14	(4.5%)
Investigations				
Any event	28	(8.8%)	54	(17.4%)
Blood creatinine increased	7	(2.2%)	35	(11.3%)
Infections and infestations				
Any event	50	(15.8%)	46	(14.8%)
Pneumonia	23	(7.3%)	14	(4.5%)
Respiratory, thoracic and mediastinal disorders				
Any event	39	(12.3%)	46	(14.8%)
Cough	12	(3.8%)	15	(4.8%)
Dyspnoea	9	(2.8%)	9	(2.9%)
Nervous system disorders				
Any event	27	(8.5%)	28	(9.0%)
Dizziness	12	(3.8%)	11	(3.5%)
Vascular disorders				
Any event	11	(3.5%)	19	(6.1%)
Hypotension	4	(1.3%)	10	(3.2%)
Metabolism and nutrition disorders				
Any event	18	(5.7%)	18	(5.8%)
General disorders and administration site conditions				
Any event	17	(5.4%)	17	(5.5%)
Musculoskeletal and connective tissue disorders				
Any event	16	(5.0%)	15	(4.8%)
Skin and subcutaneous tissue disorders				
Any event	11	(3.5%)	14	(4.5%)
Renal and urinary disorders				
Any event	8	(2.5%)	14	(4.5%)
Psychiatric disorders				
Any event	9	(2.8%)	11	(3.5%)

Continued

Table 71- continued

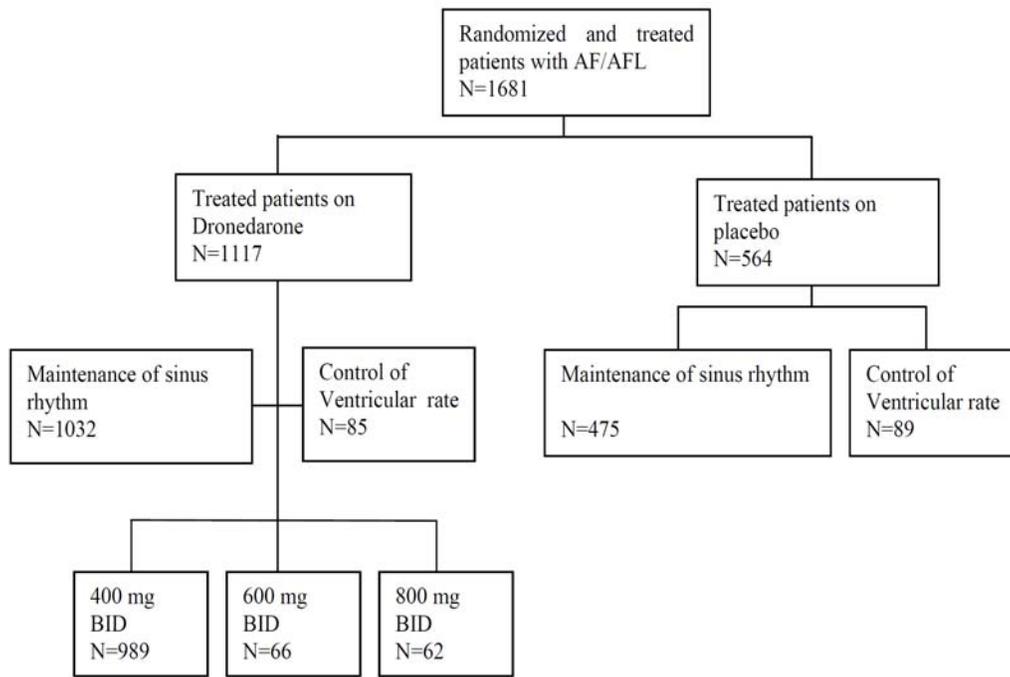
MedDRA (6.1) Organ Class Preferred term	Placebo (N=317)		Dronedarone 400 mg BID (N=310)	
Blood and lymphatic system disorders				
Any event	5	(1.6%)	11	(3.5%)
Anaemia	5	(1.6%)	10	(3.2%)
Injury, poisoning and procedural complications				
Any event	2	(0.6%)	9	(2.9%)
Reproductive system and breast disorders				
Any event	1	(0.3%)	4	(1.3%)
Eye disorders				
Any event	4	(1.3%)	2	(0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Any event	7	(2.2%)	1	(0.3%)
Ear and labyrinth disorders				
Any event	0	(0%)	1	(0.3%)
Surgical and medical procedures				
Any event	10	(3.2%)	0	(0%)
Hepatobiliary disorders				
Any event	6	(1.9%)	0	(0%)

Note: A patient can have AEs in more than one system organ class and in more than one preferred term (pages 361-2 Module 2.7.4 Summary)

7.1.1.2 Deaths in the AF/AFL Studies (ADONIS, EURIDIS, ERATO and DAFNE)

7.1.1.2.1. Baseline characteristics of AF/AFL patients

An overview of the all the patients in the AF/AFL program is shown in the diagram below.



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Figure 12- Patient disposition in patients with AF/AFL

The following table summarizes the number of randomized patients exposed to treatment according to study day in patients with AF/AFL.

Days	Placebo	Dronedarone 400 mg BID	Dronedarone 600 mg BID	Dronedarone 800 mg BID
D1	564	989	66	62
D30	446	833	23	23
D60	420	782	21	20
D120	374	724	19	16
D180	316	661	12	9
D270	235	546	0	0
D360	100	283	0	0

Note: Protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
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Table 72- Number of patients who were on study drug from Day 1 to Day 360

This clinical reviewer feels that only 283 patients treated for a year on a drug that will be utilized for a chronic illness is a very small number to evaluate safety of a new drug for patients that will be exposed long term. This may also be why the Sponsor did not see some of the side effects that are seen with amiodarone because of this low number of patients exposed to the drug for 360 days.

An overview of all the treated patients for AF /AFL is shown in the table below.

Parameter		Placebo (N=564)	Dronedarone 400 mg BID (N=989)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)	Total (N=1681)
Age (years)	n	564	989	66	62	1681
	Median	65	65	64	66	65
	Mean	63.3	63.6	64.2	63.7	63.5
	SD	10.7	10.8	8.6	10.8	10.7
	Min - Max	30 - 87	20 - 88	39 - 79	29 - 80	20 - 88
Age (years) [n(%)]	<65	274 (48.6%)	490 (49.5%)	34 (51.5%)	30 (48.4%)	828 (49.3%)
	[65-75[223 (39.5%)	344 (34.8%)	21 (31.8%)	24 (38.7%)	612 (36.4%)
	>=75	67 (11.9%)	155 (15.7%)	11 (16.7%)	8 (12.9%)	241 (14.3%)
Height (cm)	n	552	976	65	61	1654
	Median	173	173	172	171	173
	Mean	173.2	172.8	171.6	170.3	172.8
	SD	9.8	10.4	8.8	10.5	10.1
	Min - Max	142 - 200	138 - 213	141 - 190	147 - 209	138 - 213
Weight (kg)	n	561	986	66	61	1674
	Median	85.0	85.0	83.5	80.5	84.5
	Mean	86.17	85.80	84.39	83.03	85.76
	SD	16.76	17.09	16.31	14.49	16.86
	Min - Max	51.0 - 168.0	35.0 - 185.9	54.0 - 136.0	55.0 - 135.0	35.0 - 185.9
BMI (Kg/m ²) [n(%)]	<30	38 (69.2%)	649 (66.6%)	45 (69.2%)	40 (65.6%)	111 (67.6%)
	2	2	0	0	0	6
	>=30	17 (30.8%)	325 (33.4%)	20 (30.8%)	21 (34.4%)	536 (32.4%)
	0	0	0	0	0	0
	Missing	12	15	1	1	29
Gender [n(%)]	Male	38 (68.8%)	684 (69.2%)	48 (72.7%)	40 (64.5%)	116 (69.0%)
	8	8	0	0	0	0
	Female	17 (31.2%)	305 (30.8%)	18 (27.3%)	22 (35.5%)	521 (31.0%)
	6	6	0	0	0	0
Race [n(%)]	Caucasian	55 (98.2%)	960 (97.1%)	65 (98.5%)	62 (100.0%)	164 (97.6%)
	4	4	0	0	0	1
	Black	4 (0.7%)	10 (1.0%)	0 (0.0%)	0 (0.0%)	14 (0.8%)
	Asian/Orienta	0 (0.0%)	6 (0.6%)	1 (1.5%)	0 (0.0%)	7 (0.4%)
	l	0	0	0	0	0
	Other	6 (1.1%)	13 (1.3%)	0 (0.0%)	0 (0.0%)	19 (1.1%)

Note: protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
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Table 73- Summary of demographic characteristics of patients with AF/AFL

From this above table it is clear that the studied population was quite young compared to the population at large with the real risk, as the incidence of atrial fibrillation increases with each decade. Therefore, although there were not many deaths in these studies, it is not a representative population of the patients who may utilize this drug.

Another table showing how healthy the patients were in the AF/AFL studies is following. In the baseline cardiovascular examination there were no patients in moderate or severe CHF. In fact, almost all the patients had a LVEF \geq 35.

	Placebo (N=564)	Dronedarone 400 mg BID (N=989)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)	Total (N=1681)
2D-Echocardiogram - Left ventricular ejection fraction (%)					
n	531	944	65	59	1599
Median	60.0	60.0	55.0	55.0	60.0
Mean	57.48	58.17	54.29	53.68	57.62
SD	10.99	10.68	11.70	11.07	10.89
Min - Max	5.5 - 84.0	5.0 - 93.4	35.0 - 88.0	31.0 - 82.0	5.0 - 93.4
LVEF<35%	19 / 531 (3.6%)	25 / 944 (2.6%)	0 / 65 (0.0%)	1 / 59 (1.7%)	45 / 1599 (2.8%)
LVEF>=35%	511 / 531 (96.2%)	918 / 944 (97.2%)	65 / 65 (100.0%)	58 / 59 (98.3%)	1552 / 1599 (97.1%)
Cardiovascular clinical examination					
Patients with left CHF	122 (21.6%)	196 (19.8%)	17 (25.8%)	15 (24.2%)	350 (20.8%)
NYHA classification [n(%)]					
Class I (Potential)	41 (7.3%)	67 (6.8%)	10 (15.2%)	7 (11.3%)	125 (7.4%)
Class II (Mild)	81 (14.4%)	129 (13.0%)	7 (10.6%)	8 (12.9%)	225 (13.4%)

Note: protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
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Table 74- Number (%) of patients according to cardiovascular examination

7.1.1.2.2. Deaths of patients on dronedarone

The following table provides an overview of deaths during each time period. The incidence of deaths was similar in the dronedarone 400 mg BID and placebo groups during the study period.

Number of deaths	Placebo	Dronedarone 400 mg BID	Dronedarone 600 mg BID	Dronedarone 800 mg BID
Between randomization and 1st administration	1/568 (0.2%)	1/992 (0.1%)	0/ 66 (0.0%)	0/ 62 (0.0%)
On randomized and treated patients				
During treatment	3/564 (0.5%)	9/989 (0.9%)	0/ 66 (0.0%)	0/ 62 (0.0%)
95% CI	[0.1% - 1.5%]	[0.4% - 1.7%]	[0.0% - 5.4%]	[0.0% - 5.8%]
Post treatment up to the planned end of study	3/561 (0.5%)	3/980 (0.3%)	0/ 66 (0.0%)	0/ 62 (0.0%)
During study	6/564 (1.1%)	12/989 (1.2%)	0/ 66 (0.0%)	0/ 62 (0.0%)
95% CI	[0.4% - 2.3%]	[0.6% - 2.1%]	[0.0% - 5.4%]	[0.0% - 5.8%]
Reported after the planned end of study *	0	3	0	1

Note: One patient died during the screening period

Note: Patients from study center 616003 are excluded from results. No death occurred in this center

* Data no longer collected systematically

Note: protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
 (page 376 Module 2.7.4.)

Table 75- Number (%) of deaths according to analysis periods in patients with AF/AFL

Table 76- Listing of all deaths of patients treated with dronedarone

Patient Number	Last study drug intake date [day(a)]	Death		Characteristics of the adverse events related to death				
		Date [day(a)]		MedDRA (7.0) organ class	Preferred Term (Verbatim)	Onset date [day(a)]	Onset time	Relation to study drug(b)
Treatment as received: Dronedarone 400 mg BID								
003153528005001	2002-12-25(323)	2003-03-30(418)	(3)	Respiratory, thoracic and mediastinal disorders	Dyspnoea (Dyspnoea)	2002-12-26(324)	XX:XX	No

(Continued)

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Table 76- continued

Patient Number	Last study drug intake date(day(a))	Death		Characteristics of the adverse events related to death				
		Date [day(a)]		MedDRA (7.0) organ class	Preferred Term (Verbatim)	Onset date[day(a)]	Onset time	Relation to study drug(b)
003153528006007	2002-02-09(3)	2002-02-09(3)	(1)	General disorders and administration site conditions	Sudden death (Sudden death)	2002-02-09(3)	XX:XX	Yes
003153528011027	2003-05-08(310)	2003-05-10(312)	(1)	Cardiac disorders	Myocardial infarction (Myocardial infarction)	2003-05-08(310)	XX:XX	No
004508250004003	2003-04-01(8)	2003-04-01(8)	(1)	General disorders and administration site conditions	Sudden death (Sudden death)	2003-04-01(8)	13:15	Yes
004508528009007	2003-09-02(169)	2003-09-23(190)	(2)	Gastrointestinal disorders	Diverticular perforation (Perforated diverticulitis)	2003-09-08(175)	XX:XX	No
004788032005005	2002-10-26(66)	2002-10-27(67)	(1)	Cardiac disorders	Cardiac failure congestive (Congestive heart failure nyha iii)	2002-10-10(50)	11:00	No
	2002-10-26(66)	2002-10-27(67)	(1)	Cardiac disorders	Ventricular fibrillation (Ventricular fibrillation)	2002-10-27(67)	XX:XX	No
004788036002010	2002-05-23(95)	2002-05-23(95)	(1)	General disorders and administration site conditions	Sudden death (Sudden death)	2002-05-23(95)	09:05	Yes
004788124011006	2002-11-13(86)	2003-01-08(142)	(2)	General disorders and administration site conditions	Sudden cardiac death (Sudden cardiac death)	2003-01-08(142)	17:30	No
004788124032005	2002-06-29(66)	2002-08-20(118)	(3)	Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema (Acute pulmonary oedema)	2002-08-08(106)	XX:XX	No
	2002-06-29(66)	2002-08-20(118)	(3)	Infections and infestations	Enterococcal sepsis (Septicemia enterococcus)	2002-08-08(106)	13:08	No
004788710006002	2002-04-12(19)	2002-04-12(19)	(1)	General disorders and administration site conditions	Sudden death (Death)	2002-04-12(19)	13:00	No

(Continued)

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Table 76- continued

Patient Number	Last study drug intake date [day(a)]	Death		Characteristics of the adverse events related to death				
		Date [day(a)]		MedDRA (7.0) organ class	Preferred Term (Verbatim)	Onset date [day(a)]	Onset time	Relation to study drug(b)
004788710006004	2003-03-21(299)	2003-03-22(300)	(1)	Cardiac disorders	Atrioventricular block complete (Third degree heart block)	2003-03-21(299)	20:00	No
004788840002004	2002-09-19(221)	2002-09-22(224)	(1)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastatic neoplasm (Suspected metastatic liver + lung carcinoma- primary site unknown confirmed for ct scan)	2002-06-22(132)	XX:XX	No
004788840010006	2002-09-20(60)	2003-02-13(206)	(3)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Multiple myeloma (Multiple myeloma exacerbation)	2003-02-13(206)	XX:XX	No
004788840021013	2002-11-25(187)	2003-06-02(376)	(3)	Cardiac disorders	Cardiac failure congestive (Worsening congestive heart failure)	2003-05-24(367)	XX:XX	No
004788840040011	2003-03-XX(288)	2003-03-17(288)	(1)	General disorders and administration site conditions	Sudden death (Sudden death)	2003-03-17(288)	XX:XX	No
Treatment as received: Dronedarone 800 mg BID								
003550528005008	2000-04-17(162)	2000-05-13(188)	(2)	Injury, poisoning and procedural complications	Injury (Trauma)	2000-04-17(162)	XX:XX	No

(page 515 Clinical Summary, Module 2.7.4)

7.1.1.2.2. Deaths in patients treated on placebo

Table 77- Listing of all deaths for patients treated with placebo

Patient Number	Last study drug intake date [day(a)]	Death		Characteristics of the adverse events related to death				
		Date [day(a)]		MedDRA (7.0) organ class	Preferred Term (Verbatim)	Onset date [day(a)]	Onset time	Relation to study drug(b)
Treatment as received: Placebo								
004508528005004	2003-11-25(57)	2004-01-09(102)	(2)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bronchioloalveolar carcinoma (Diffuse broncho-alveolar cell carcinoma in both lungs)	2003-11-12(44)	XX:XX	No
004788124024042	2002-12-16(117)	2002-12-16(117)	(1)	General disorders and administration site conditions	Sudden death (Sudden death)	2002-12-16(117)	XX:XX	Yes
004788124028001	2002-08-29(206)	2002-10-16(254)	(2)	Vascular disorders	Circulatory collapse (Vascular collapse-not otherwise specified)	2002-10-16(254)	XX:XX	No
004788840002008	2002-10-04(82)	2002-10-04(82)	(1)	Cardiac disorders	Cardiac arrest (Death secondary to cardiac arrest - previously reported as hypertensive cardiomyopathy, previously reported as death)	2002-10-04(82)	14:57	Yes
004788840036006	2002-10-23(140)	2002-12-24(202)	(2)	Cardiac disorders	Cardiac failure congestive (Worsening congestive heart failure)	2002-10-23(140)	02:34	No
	2002-10-23(140)	2002-12-24(202)	(2)	Renal and urinary disorders	Renal insufficiency (Renal failure)	2002-11-04(152)	05:30	No
004788840040010	2002-05-27(15)	2002-05-28(16)	(1)	Nervous system disorders	Cerebrovascular accident (Cerebral vascular accident)	2002-05-27(15)	XX:XX	No

(a) Day related to first study drug as day 1

(b) As assessed by the investigator

(1) Death occurred from first study drug intake up to last study drug intake + 10 days

(2) Death occurred after last study drug intake + 10 days up to end of study date

(3) Death occurred after end of study date

No death after D365 but before end of study in EURIDIS/ADONIS

Note: Protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
 (pages 514-6 Module 2.7.4 Summary)

7.1.1.2.3. Other serious Adverse Events in Patients in the AF/AFL studies

There was a dose response for GI disorders with a difference in the incidence of GI disorders between the placebo (0.5%) and the dronedarone 400 mg BID group (1.9%). For cardiac disorders the overall incidence of SAEs was similar in the placebo and dronedarone 400 mg BID groups. In the dronedarone 400 mg group, GI hemorrhages and GI signs and symptoms accounted for most of the SAEs. Almost all of the patients who experienced GI hemorrhage in the dronedarone 400 mg BID group took an oral anticoagulant (OAC) concomitantly.

One patient in the ADONIS study taking dronedarone 400 mg BID experienced an anaphylactic reaction, and 1 patient in the DAFNE study taking dronedarone 800 mg BID experienced an anaphylactic shock.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1. Patients in the AF/AFL studies

The overall incidence of AEs leading to permanent discontinuation of study drug was similar among all treatment groups, except for GI disorders and laboratory results (Investigations). Gastrointestinal disorders were the main reason for discontinuation in the dronedarone 800 mg BID group (11.3% of patients). The most frequent AEs (i.e., $\geq 1\%$) leading to permanent study drug discontinuation by high level group term (HLGT) in the dronedarone 400 mg BID group were cardiac arrhythmias, and epidermal and dermal conditions. However, their incidence was not different from that of placebo. There was a difference between placebo and dronedarone 400 mg BID groups for HLGT renal and urinary tract investigations and urinalyses.

There was an overall dose response observed in patients with any treatment-emergent adverse event (TEAE) and in patients who permanently discontinued study drug for any AE as shown in the following table.

	Placebo (N=564)	Dronedarone 400 mg BID (N=989)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)
Patients with any TEAE (a)	340 (60.3%)	660 (66.7%)	42 (63.6%)	45 (72.6%)
Patients with any serious TEAE	79 (14.0%)	133 (13.4%)	4 (6.1%)	8 (12.9%)
Deaths (b)	3 (0.5%)	9 (0.9%)	0 (0.0%)	0 (0.0%)
Patients permanently discontinued study drug for any AE (a)(c)(d)	34 (6.0%)	96 (9.7%)	4 (6.1%)	14 (22.6%)

(a) Including SAEs

(b) Deaths which occurred from first study drug intake up to last study drug intake plus 10 days

(c) According to 'End of treatment' form

(d) Events started before the first study drug intake were taken into account

Note: Protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)

(page 355 Module 2.7.4.)

Table 78- Overview of main treatment emergent events [number (%) of patients] excluding the occurrence of AF/AFL

A summary of AEs leading to permanent discontinuation of study drug according to MedDRA organ classes and preferred terms is provided in the following table.

MedDRA (7.0) Organ Class Preferred term	Placebo (N=564)	Dronedarone 400 mg BID (N=989)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)
Any Class any event	340 (60.3%)	660 (66.7%)	42 (63.6%)	45 (72.6%)
Gastrointestinal disorders				
Any event	90 (16.0%)	188 (19.0%)	13 (19.7%)	22 (35.5%)
Diarrhoea	23 (4.1%)	66 (6.7%)	5 (7.6%)	18 (29.0%)
Nausea	17 (3.0%)	39 (3.9%)	2 (3.0%)	5 (8.1%)
Abdominal pain upper	9 (1.6%)	20 (2.0%)	1 (1.5%)	1 (1.6%)
Abdominal pain	6 (1.1%)	19 (1.9%)	1 (1.5%)	2 (3.2%)
Vomiting	4 (0.7%)	17 (1.7%)	1 (1.5%)	2 (3.2%)
Dyspepsia	7 (1.2%)	13 (1.3%)	2 (3.0%)	0 (0%)
Infections and infestations				
Any event	95 (16.8%)	194 (19.6%)	7 (10.6%)	7 (11.3%)
Nasopharyngitis	18 (3.2%)	37 (3.7%)	3 (4.5%)	2 (3.2%)
Upper respiratory tract infection	6 (1.1%)	29 (2.9%)	0 (0%)	1 (1.6%)
Influenza	17 (3.0%)	25 (2.5%)	1 (1.5%)	2 (3.2%)
Nervous system disorders				
Any event	81 (14.4%)	144 (14.6%)	4 (6.1%)	6 (9.7%)
Headache	38 (6.7%)	52 (5.3%)	2 (3.0%)	3 (4.8%)
Dizziness	17 (3.0%)	34 (3.4%)	1 (1.5%)	3 (4.8%)
Investigations				
Any event	49 (8.7%)	133 (13.4%)	10 (15.2%)	8 (12.9%)
Blood creatinine increased	1 (0.2%)	22 (2.2%)	1 (1.5%)	0 (0%)
Hepatic enzyme increased	6 (1.1%)	12 (1.2%)	3 (4.5%)	1 (1.6%)
Blood urea increased	1 (0.2%)	4 (0.4%)	2 (3.0%)	2 (3.2%)
Electrocardiogram QT prolonged	0 (0%)	3 (0.3%)	1 (1.5%)	2 (3.2%)
Cardiac disorders				
Any event	62 (11.0%)	123 (12.4%)	12 (18.2%)	13 (21.0%)
Bradycardia	8 (1.4%)	26 (2.6%)	1 (1.5%)	4 (6.5%)
Angina pectoris	12 (2.1%)	20 (2.0%)	0 (0%)	1 (1.6%)
Palpitations	5 (0.9%)	11 (1.1%)	4 (6.1%)	3 (4.8%)
Cardiac failure congestive	4 (0.7%)	13 (1.3%)	3 (4.5%)	1 (1.6%)
Cardiac failure	3 (0.5%)	8 (0.8%)	3 (4.5%)	1 (1.6%)
Atrial tachycardia	7 (1.2%)	5 (0.5%)	0 (0%)	3 (4.8%)
General disorders and administration site conditions				
Any event	60 (10.6%)	130 (13.1%)	6 (9.1%)	6 (9.7%)
Oedema peripheral	23 (4.1%)	42 (4.2%)	1 (1.5%)	1 (1.6%)
Fatigue	14 (2.5%)	27 (2.7%)	3 (4.5%)	2 (3.2%)
Musculoskeletal and connective tissue disorders				
Any event	61 (10.8%)	126 (12.7%)	2 (3.0%)	3 (4.8%)
Back pain	9 (1.6%)	33 (3.3%)	0 (0%)	1 (1.6%)
Arthralgia	9 (1.6%)	31 (3.1%)	0 (0%)	1 (1.6%)
Pain in extremity	5 (0.9%)	21 (2.1%)	0 (0%)	0 (0%)

(Continued)

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Table 79- Number (%) of patients with TEAEs with incidence \geq 2% for all patients with AF/AFL

MedDRA (7.0) Organ Class Preferred term	Placebo (N=564)	Dronedarone 400 mg BID (N=989)	Dronedarone 600 mg BID (N=66)	Dronedarone 800 mg BID (N=62)
Respiratory, thoracic and mediastinal disorders				
Any event	58 (10.3%)	117 (11.8%)	2 (3.0%)	9 (14.5%)
Cough	8 (1.4%)	22 (2.2%)	1 (1.5%)	3 (4.8%)
Dyspnoea	12 (2.1%)	23 (2.3%)	0 (0%)	1 (1.6%)
Skin and subcutaneous tissue disorders				
Any event	36 (6.4%)	94 (9.5%)	4 (6.1%)	6 (9.7%)
Vascular disorders				
Any event	35 (6.2%)	62 (6.3%)	1 (1.5%)	3 (4.8%)
Hypertension	14 (2.5%)	24 (2.4%)	1 (1.5%)	1 (1.6%)
Injury, poisoning and procedural complications				
Any event	29 (5.1%)	57 (5.8%)	1 (1.5%)	2 (3.2%)
Psychiatric disorders				
Any event	16 (2.8%)	52 (5.3%)	2 (3.0%)	1 (1.6%)
Eye disorders				
Any event	15 (2.7%)	29 (2.9%)	2 (3.0%)	2 (3.2%)
Metabolism and nutrition disorders				
Any event	29 (5.1%)	28 (2.8%)	3 (4.5%)	1 (1.6%)
Hypokalaemia	3 (0.5%)	3 (0.3%)	2 (3.0%)	0 (0%)
Renal and urinary disorders				
Any event	15 (2.7%)	26 (2.6%)	1 (1.5%)	0 (0%)
Reproductive system and breast disorders				
Any event	11 (2.0%)	24 (2.4%)	1 (1.5%)	1 (1.6%)
Ear and labyrinth disorders				
Any event	5 (0.9%)	20 (2.0%)	3 (4.5%)	2 (3.2%)
Vertigo	1 (0.2%)	13 (1.3%)	3 (4.5%)	2 (3.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Any event	11 (2.0%)	22 (2.2%)	0 (0%)	0 (0%)
Endocrine disorders				
Any event	9 (1.6%)	13 (1.3%)	0 (0%)	1 (1.6%)
Blood and lymphatic system disorders				
Any event	0 (0%)	14 (1.4%)	0 (0%)	0 (0%)
Hepatobiliary disorders				
Any event	6 (1.1%)	7 (0.7%)	1 (1.5%)	0 (0%)
Surgical and medical procedures				
Any event	5 (0.9%)	8 (0.8%)	0 (0%)	0 (0%)
Immune system disorders				
Any event	2 (0.4%)	5 (0.5%)	1 (1.5%)	2 (3.2%)
Congenital, familial and genetic disorders				
Any event	0 (0%)	1 (0.1%)	0 (0%)	0 (0%)

Note: A patient can have AEs in more than one system organ class and in more than one preferred term
Note: Protocols: DRI3550 (DAFNE), EFC3153 (EURIDIS), EFC4788 (ADONIS), EFC4508 (ERATO)
(page 358 Module 2.7.4 Summary)

Table 79- continued

Among the TEAEs with an incidence $\geq 2\%$ (in at least 1 treatment group) there was a dose response, with a trend toward a higher incidence in dronedarone groups compared to placebo, for diarrhea, blood creatinine increased, blood urea increased, ECG QT-interval prolonged, palpitations, bradycardia and vertigo. Among the TEAEs with a dose response, there was a difference between placebo and dronedarone 400 mg BID for diarrhea, blood creatinine increased and vertigo. Considering the other TEAEs with an incidence $\geq 2\%$, only back pain and upper respiratory tract infection showed an apparent difference in incidence between placebo and the dronedarone 400 mg BID group.

Syncope were reported at a similar incidence in placebo (0.5%) and dronedarone 400 mg BID (0.7%) groups. The incidence of cerebrovascular accident or transient ischemic attack (TIA) in this population at risk for such events, was the same (0.2%) for TIA in both placebo and dronedarone 400 mg BID groups and for cerebrovascular accident was lower in dronedarone dose groups (0.1% in dronedarone 400 mg BID group, none in 600 mg BID and 800 mg BID group) compared to placebo (0.4%).

7.1.1.3. Deaths and Adverse events in normal volunteers

There were no significant adverse events or deaths in the volunteer studies or the drug interaction studies.

7.1.4 Immunogenicity

Not applicable.

7.1.5 Human Carcinogenicity

Not applicable.

7.1.6 Special Safety Studies

Not applicable.

7.1.7 Withdrawal Phenomena and/or Abuse Potential

Not applicable

7.1.8 Human Reproduction and Pregnancy Data

Not applicable.

7.1.9 Assessment of Effect on Growth

Not applicable.

7.1.10 Overdose Experience

Not applicable.

7.1.11 Postmarketing Experience

Not applicable.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

“The dose” was determined from the DAFNE trial. The Sponsor chose 400 mg B.I.D. although the Agency recommended a dosing sequence be made available. Doses from 50 mg. to 800 mg. should be investigated as discussed in Dr. Williams’ review of the DAFNE study.

8.2 Drug-Drug Interactions

The PK/PD drug interaction is shown in the following table from Dr. Kumi’s Review.

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

(page 7 Dr. Robert Kumi's Review)

Table 80- PK/PD drug-drug Interaction

8.3 Special Populations

From Dr. Robert Kumi's Review:

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

8.4 Pediatrics

The Sponsor requested March 9, 2005 a deferral of pediatric studies with dronedarone. The Division responded on April 1, 2005 to the sponsor's request, agreeing to a deferral of pediatric studies with dronedarone in patients less than 16 years of age for rhythm and rate

control in patients with atrial fibrillation/atrial flutter.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

A literature review of the available pharmacological treatments for AF/AFL was completed, as well as a review of amiodarone and the early studies pertaining to dronedarone.

8.7 Postmarketing Risk Management Plan

Not applicable.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

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

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

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

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

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

In these reviewers' opinion, the critical study is the ANDROMEDA Study which investigated patients with a previous episode of "severe" congestive heart failure (CHF). This study has clinical endpoints, death and hospitalizations, and not surrogate markers. The drug dronedarone statistically significantly ($p \leq 0.027$) increased the risk of death from any cause and the risk of hospitalization for acute cardiovascular reasons as compared to placebo.

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

9.2 Recommendation on Regulatory Action

NOT APPROVABLE

9.3 Labeling Review

To be completed in the future.

9.4 Comments to Applicant

There are two main comments for the Sponsor:

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.

10 APPENDICES

10.1 Review of Individual Study Reports

Study: ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity Decrease (ANDROMEDA), (EFC4966)

Study Dates: Planned dates were June 12, 2002 through August 19, 2003. However, the premature end of study drug treatment and randomizations was January 16, 2003. These patients were studied for an additional 6 months, to July 17, 2003.

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

Design: A multicenter, multinational, double-blind, randomized, parallel-group, placebo-controlled study of the efficacy of dronedarone 800 mg daily (400 BID), for reducing death or hospitalizations for worsening of heart failure in patients with symptomatic CHF (NYHA class II – IV) and moderate to severe systolic LVD defined as $WMI \leq 1.2$.

In addition to the blinded Steering Committee (SC) responsible for the conduct of the trial, a central, independent data safety monitoring board (DSMB) monitored the safety of patients in the study, and an independent, blinded Critical Events Committee (CEC) adjudicated the causes of deaths and hospitalizations.

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

Objectives:

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

Secondary objectives were to evaluate whether dronedarone:

- reduces death from any cause;
- reduces hospitalization for worsening heart failure;
- reduces hospitalization for acute cardiovascular reasons;
- reduces arrhythmic/sudden death;
- is effective in maintaining sinus rhythm in the target population.

Both the safety and tolerability of dronedarone versus placebo patients were to be evaluated.

Pharmacokinetic objective:

Dronedarone and SR35021 plasma levels at steady state were documented.

Interim analysis

The safety of patients included in the study will be monitored by the DSMB. No efficacy interim analysis for the study was planned.

Number of patients evaluated:

Planned: 1,000

Main analysis population: Randomized: 627; Treated: 627; Efficacy: 627 Safety: 627

On January 16, 2003, 7 months after randomization of the first patient, the inclusion of patients into the study was discontinued following a recommendation of the Data Safety Monitoring Board (DSMB), because of the higher number of deaths observed in the patients randomized to dronedarone compared to placebo. Following a second safety analysis (February 17, 2003), the DSMB recommended follow-up of mortality, major clinical events, and renal function for all the patients up to July 17, 2003 (6 months after the end of inclusions).

All patients randomized in center 616004 (n = 23) were excluded by the Sponsor from the main analysis population due to a major violation in good clinical practice (GCP) violation documented in this center, raising doubts about the integrity of the data provided by this center.

Inclusion criteria:

- a) Age 18 years;
- b) patients hospitalized with symptomatic CHF, current New York Heart Association (NYHA) class II-IV, requiring treatment with a diuretic, who had had within the last month at least 1 episode of dyspnea or fatigue at rest, or on slight exertion, corresponding to NYHA class III or IV;
- c) wall motion index (WMI) 1.2, determined by a blinded central evaluation of a recorded standard echocardiography, equivalent to a left ventricular ejection fraction (LVEF) 35%.

Exclusion criteria:

- a) acute pulmonary edema within 12 hours prior to start of study medication;
- b) cardiogenic shock, treatment with intravenous pressor agents or patients on respirator
- c) uncorrected hemodynamically significant primary obstructive valvular disease;
- d) hemodynamically significant obstructive cardiomyopathy;
- e) acute MI during the 7 days preceding randomization (changed to 5 days following Amendment No. 1);
- f) a cardiac operation or revascularization procedure [except percutaneous coronary intervention (PCI) following Amendment No. 1] during the month preceding randomization;
- g) planned major non-cardiac or cardiac surgery or procedures including surgery for valvular heart disease, coronary artery bypass graft (CABG), or on urgent cardiac transplantation list;
- h) acute myocarditis or constrictive pericarditis;
- i) history of torsades de pointes;

- j) bradycardia <50 bpm and/or PR-interval 280 ms at screening (at randomization following Amendment No. 1);
- k) QTc-interval >500 ms at screening (at randomization following Amendment No. 1);
- l) significant sinus node disease or second or third degree atrioventricular block (AV block) unless treated with a pacemaker;
- m) treatment with other class I or III anti-arrhythmic drugs;
- n) any illness or disorder other than CHF that could preclude participation or severely limit survival;
- o) pregnant women or women of child-bearing potential not on adequate birth control;
- p) breastfeeding women;
- q) serum potassium <3.5 mmol/L;
- r) other conditions/circumstances likely to lead to poor treatment adherence;
- s) current participation in another clinical study in which the patient is currently taking an investigational drug or using an investigational device;
- t) need of a concomitant medication that was prohibited in this study;
- u) previous participation in this study or in other dronedarone studies.

Figure 13- Amended Study Flowchart

Time	D-6 to D1 (Screening) ¹	D1	D5±2 ¹¹	M1±7D	M3±14D	M6±14D	M9±14D	M12±14D	M15±14D	M18±14D	M21±14D	M24±14D	EOS Visit ⁸
Inclusion/Exclusion Criteria	x	x											
Informed Consent	x	x											
Demographic data	x												
Medical history ⁶	x												
2D-echocardiography ⁴	x												
Chest X-ray ¹⁰	x												
12-lead ECG	x	x	x	x	x	x	x	x	x	x	x	x	x
NYHA	x	x	x	x	x	x	x	x	x	x	x	x	x
Laboratory 1 ⁷	(B-HCG, SB3) ³	H1, SB2	SB3	H1, SB2	SB3	H1, SB2	SB3	H1, SB2	SB3	SB2		H1, SB2	SB3
Laboratory 2 ¹¹	DIG ⁷	DIG	DIG	DIG	DIG	DIG	DIG	DIG		DIG		DIG	DIG
PK at trough ⁵			x			x							
Vital signs ⁸		x	x	x	x	x	x	x	x	x	x	x	x
IVRS call		x				x		x		x		x	
Dispense study medication		x		x	x	x	x	x	x	x	x		
Drug accountability				x	x	x	x	x	x	x	x	x	x
Symptoms ²		x	x	x	x	x		x		x		x	
Adverse event reporting & concomitant drugs	x	x	x	x	x	x	x	x	x	x	x	x	x
Endpoints		x	x	x	x	x	x	x	x	x	x	x	x

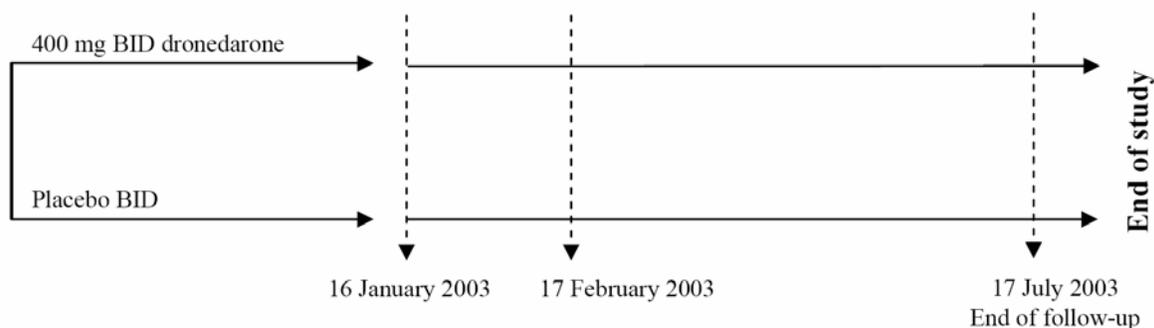
(from Appendix 1, page 236 of Study EFC4966)

Amended Study Flowchart Footnotes:

- 1) Full screening data will be recorded on the screening visit CRF for randomized patients, in non randomized patients only demographic data and reason(s) for noninclusion will be collected in a screening log
- 2) CHF and Arrhythmia related symptoms will be collected in the CRF
- 3) SB3, DIG, B-HCG in women (pregnancy test, can be replaced by urine test) assessed locally
- 4) Echocardiography assessed centrally for WMI
- 5) Must be done just before dosing in approximately 50% of patients. In addition to this, several blood samples (pre-dose, 2h, 4h, 6h, 8h, 10h and 12h postdose) will be taken in a subgroup of about 30 patients recruited at selected centers at M1. One of these samples will be collected as close as possible to the time of 12-lead ECG recording.
- 6) Includes medical history, previous therapy
- 7) Biology Laboratory Tests: see section in protocol body
- 8) Vital signs include: sitting or supine blood pressure and at randomization weight and height

- 9) End of study (EOS) visit to be completed as close as possible to 1 year treatment of last patient (end of the study)
- 10) Can be performed one month before to one week after randomization
- 11) SB3 should be done preferably on D3 whenever possible
- 12) Laboratory 2, only in patients receiving DIGOXIN.

Figure 14- Main timepoints implemented following January 16, 2003



(from EFC4966 page 28)

Investigational Plan

All potentially eligible patients at each site were to undergo an echocardiography to confirm their eligibility. Eligible patients were randomly allocated to dronedarone treatment or placebo in a 1:1 ratio, in addition to the standard treatment necessary for their condition. Three amendments were written for this study, Amendment No. 1, dated June 26, 2002; Amendment No. 2, dated January 15, 2003; and Amendment No. 3, dated March 7, 2003.

Protocol Amendment 1; dated June 26, 2002:

Reasons for the Amendment:

- Given the high incidence of cardiovascular deaths, including sudden deaths, in the target population, these adverse events are to be considered as expected, for regulatory purposes. Their reporting as serious adverse event (SAEs) is not changed.
- Exclusion of patients with recent acute myocardial infarction is brought from 7 to 5 days to facilitate recruitment.
- Clarifications are given concerning some additional points.

Additional exclusion criteria were included as cited above. Sudden deaths, are to be considered as expected, nevertheless they will always be reported as serious adverse events (SAEs). Changes occurred to the flow chart.

Protocol Amendment 2; dated January 15, 2003:

Reasons for Amendment:

A number of unexpected renal events and/or cardiac failures was noted when reviewing the serious adverse events. Based on an evaluation of individual serious adverse events and a blinded analysis of serum creatinine, the Steering Committee has decided to implement the following changes to ensure patients' safety in the ANDROMEDA study.

To improve patient's safety by:

- paying closer attention to the renal function both with respect to eligibility (exclude patients with poor renal function at baseline because they would not tolerate a further deterioration in renal function) and following renal function more closely in enrolled patients with the purpose of permanently stopping treatment with study medication if the renal function deteriorates.
- routinely measuring serum digoxin (se-digoxin) in participants receiving treatment with digoxin.

The investigator must discontinue study medication if one or more of the following are found:

- PR interval > 0.35 sec or 2° or 3° AV block unless patient has a pacemaker
- Symptomatic bradycardia
- New bundle branch block or increase in QRS duration > 50% compared to baseline
- ECG documented sustained ventricular tachycardia, or TdP.

Study drug will also be permanently discontinued if there is a decrease of creatinine clearance > 20% compared to baseline. For patients already enrolled in the study at the time of the implementation of this amendment (Amendment # 2) the study drug will be permanently discontinued if on the last available laboratory result the creatinine clearance is less than 24 ml/min or reduced by more than 20% compared to baseline. In all patients in whom study drug is discontinued because of decreased creatinine clearance, this parameter will be monitored after study drug discontinuation, at least at week 1, 2 and 4.

Also, changes were made to the study flow chart.

Protocol Amendment 3; March 7, 2003

Reason for the Amendment:

The Steering Committee also decided based on the DSMB's recommendations to maintain a 6-month follow-up of patients after the study drug discontinuation. The objective of this follow-up was to optimize patients' safety and to provide more data for explanatory analyses. It will be done in blinded conditions to avoid possible bias in data collection and will be focused on survival, major clinical events and renal function.

Amendment N°2 of the study protocol dated from January 15th 2003 finalized the day before the DSMB meeting was never circulated nor submitted and is superseded by the present amendment.

Patients must be followed up for 6 months after study treatment discontinuation. In addition to the visits already mentioned in the Letters of instructions to investigators, patients will be seen at least twice: 3 and 6 months following study treatment discontinuation.

Double blind will be maintained during the follow-up period in order to ensure an unbiased collection of data. At the request of the Steering Committee a preliminary statistical analysis will be conducted by a statistician appointed by the Sponsor, in order to understand the reasons leading to premature discontinuation. This analysis will be done once the endpoints have been adjudicated by the Central Event Committee, and after validation of the prospectively defined Statistical Analysis Plan. Full unblinding will occur when all the data has been validated.

The Investigator could discontinue study medication if 1 or more of the following were found:

- PR interval >350 ms or second or third degree AV block unless patient had a pacemaker;
- symptomatic bradycardia;
- new bundle branch block or increase in QRS duration >50% compared to baseline;
- electrocardiogram (ECG) documented sustained ventricular tachycardia (VT), or torsades de pointes;
- other cardiac or non-cardiac AEs which in the Investigator's opinion would be potentially threatening to the patient's safety.

Concomitant therapy

Not permitted therapy:

Vaughan Williams Class I and III anti-arrhythmic drugs (including the beta-blocking agent sotalol) could not be administered during the study and were to be withdrawn for at least 5 plasma half-lives (except for amiodarone) prior to the first administration of study drug.

Patients on amiodarone therapy could be randomized in the study as soon as amiodarone administration was permanently stopped but an ECG was to be performed about 4 hours after administration of study drug to verify good tolerability.

All concomitant drugs which caused torsades de pointes were contraindicated. Such drugs include some phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides.

Given the involvement of the cytochrome (CYP) 450 3A4 in the metabolism of dronedarone, the concomitant use of grapefruit juice and all potent inhibitors of CYP450 3A4, such as ketoconazole, itraconazole, cyclosporin, clarithromycin, erythromycin, nefazodone and ritonavir, were prohibited. Other drugs which are CYP450 3A4 substrates and have a narrow therapeutic margin, were to be avoided.

Permitted therapy:

No patient was deprived of any necessary therapy as a consequence of participating in this study. It was important that the participants received all accepted evidence-based treatments in accordance with national or international guidelines, such as anti-thrombotic therapy, anti-coagulation, adequate heart failure treatment including diuretics, Angiotensin converting enzyme (ACE) inhibitor or angiotensin II (AII) receptor antagonists in case of poor tolerability, beta-blockers and medication for rate control in patients with AF/FL.

Calcium antagonists with depressant effects on the sinus and AV node (e.g., diltiazem and verapamil) could be used, but with caution, as they could potentiate the depressant effects on conduction. Beta-blockers could also be used with caution. Digoxin could, if necessary, be co-administrated with caution. An interaction study had shown that dronedarone at the dose of 400 mg daily increases plasma levels of digoxin by an average of 30%. Therefore it was expected that patients required and would best tolerate lower doses of digoxin than usual.

If oral anticoagulation was indicated, the international normalized ration (INR) was monitored as required. No interaction between warfarin and dronedarone had been documented in Study INT3353.

An interaction study had shown that dronedarone could increase 4-fold the plasma concentrations of simvastatin, a CYP450 3A4 substrate. The clinical consequences of this PK interaction could not be predicted but the risk of rare side effects such as rhabdomyolysis could be increased.

Cardiovascular examination

A baseline echocardiography was performed in order to select a population with a reduced LVEF. To be eligible, central, blinded evaluation of the screening echocardiography had to confirm a WMI ≤ 1.2 . No follow-up echocardiographies were planned in the study.

Efficacy assessments

The main efficacy assessments were recordings of death from any cause, or hospitalization for worsening heart failure. Resuscitated cardiac arrest and/or cardiac transplantation were not counted as death in this study. The CEC-adjudicated hospitalizations for worsening heart failure were considered.

Primary efficacy variable:

The primary efficacy endpoint was death from any cause or hospitalization for worsening heart failure.

Secondary efficacy variables:

Secondary endpoints were:

- death from any cause;
- adjudicated hospitalization for worsening heart failure;
- adjudicated hospitalization for acute cardiovascular reasons;
- adjudicated arrhythmic/sudden death;
- AF/AFL.

General statistical approach

All statistical analyses were performed using two-sided tests and/or two-sided confidence intervals (CIs). Unless otherwise specified, Fisher's exact tests were used for qualitative parameters.

Continuous parameters were summarized using mean, standard deviation (SD), median, minimal and maximal values. Categorical parameters were summarized using counts and percentages. In summary tables, patients with missing data were presented when relevant; they were excluded from the calculation of percentages, unless otherwise specified.

Two dates were used as reference dates (Day 1) according to the purpose of the analysis: the date of randomization (efficacy analyses) and the date of first study drug intake (safety analyses). Computed duration expressed in days was calculated as the difference between start and end date plus 1 day.

All statistical summaries and analyses were generated using SAS version 8.2 on unix environment.

Analysis population

Patients were analyzed for efficacy and safety according to the treatment actually received. A patient was considered actually treated with dronedarone as soon as he/she received a tablet of dronedarone.

There were 3 analysis populations.

1. Randomized and treated patients

The randomized and treated patients population corresponds to all randomized patients who received at least 1 study drug administration, either dronedarone or placebo. This population was used for analyses of efficacy and safety parameters.

2. Randomized and treated patients excluding center 616004

Because a major violation in GCP was detected in center 616004, raising doubts about the integrity of the data provided by this center, patients from this center were excluded by the Sponsor from the randomized and treated patients population, due to potentially unreliable data which might have decreased the sensitivity of the analysis of the primary and other safety endpoints. Thus, the main efficacy analysis population was the randomized and treated patients excluding center 616004. This population was also used for all safety analyses.

3. Per-protocol population

The per-protocol (PP) population was all randomized and treated patients, excluding patients from center 616004, or those with a major protocol deviation.

Periods of analysis

Three periods were defined for efficacy and safety analyses according to the main cut-off dates of the trial: “Up to January 16, 2003”, “Up to February 17, 2003” and “Up to July 17, 2003”.

Primary efficacy endpoint

The primary efficacy endpoint was the time to death from any cause or time to hospitalization for worsening heart failure, whichever was earlier.

All deaths were adjudicated except those without a SAE form documenting the AE leading to death. However, all deaths, even if non-adjudicated, were taken into account in the analysis. All hospitalizations declared by the Investigators before February 17, 2003 were adjudicated, except those occurring before randomization, or those which were judged 'planned' by the Study Coordinating Center. Only adjudicated hospitalizations were taken into account in the analysis.

Primary analysis

The primary analysis was based on the "Randomized and treated patients excluding center 616004" population up to January 16, 2003.

The primary analysis was the comparison of the 2 treatment groups using a 2-sided Log-rank asymptotic test (level of significance 0.05). Cumulative incidence functions in each treatment group were calculated using non-parametric Kaplan-Meier estimate as well as the corresponding 95% CIs (with Greenwood's variance) at specified time point.

Cox's proportional hazard model was used to estimate the hazard ratio (labeled in tables "Relative risk") with 95% CIs, if the validity of proportional hazards assumptions was confirmed graphically. The original protocol states that the primary and secondary analyses will not include covariates (Appendix 16.1.1, Sections 10.7.1.2.3 and 10.7.2.2).

Patients with no primary endpoint up to January 16, 2003 were right-censored at the latest date with complete information (on hospitalization and alive status) obtained either on "last contact form" or at the last visit performed, or on January 16, 2003 whichever came first.

Secondary analyses

The primary analysis was also performed up to February 17, 2003. The censoring process was the same as that described for the primary analysis considering the February 17, 2003 cut-off date instead of January 16, 2003.

The Sponsor's post hoc covariate analyses:

The Sponsor submitted post hoc covariate analyses that were not prespecified in the original protocol.

The primary efficacy endpoint was analyzed by the Sponsor using the following covariates: baseline weight, creatinine clearance, WMI, NYHA status, and concomitant intake (up to date of endpoint or censoring) of beta-blocker, digitalis, spironolactone, ACE inhibitors or AII receptor antagonists. First, a Cox proportional hazard model was used with all covariates (intake of concomitant medication was included as time dependent covariates) in order to adjust the treatment effect to variables with possible influence on the endpoint. Then, a Cox proportional hazard model was performed for each subcategory defined by these covariates; in these univariate analyses, intake of co-medication is intake up to the endpoint or censoring date whenever the co-medication started. Kaplan-Meier cumulative incidence curves have been done for each subcategory of the more significant covariates among those defined above. This analysis was performed on the periods "Up to January 16, 2003" and "Up to February 17, 2003".

Sensitivity analysis and per-protocol analysis:

A sensitivity analysis including patients randomized in the Polish center 616004 was done on the periods “Up to January 16, 2003” and “Up to February 17, 2003”.

An “on-treatment” analysis was performed in the PP population using a competing risks analysis with model of cause-specific hazards. Competing events were the time of primary endpoint from randomization and the time of last study drug intake plus 10 days. The cumulative incidence functions were calculated separately for the 2 treatment groups with the nonparametric Prentice estimate. The 2 treatment groups were compared for primary endpoint using a 2-sided Log-rank asymptotic test.

Secondary efficacy endpoints

In all time-dependent analyses, the censoring process for secondary endpoints was the same as that described for the primary endpoint. The analyses were performed on the 3 populations unless otherwise specified. An “on-treatment” analysis was performed in the PP population with the same analytical method used for the primary efficacy parameter.

Death from any cause

The analysis consisted of the comparison of the 2 treatment groups using a 2-sided Log-rank asymptotic test. Cumulative incidence functions in each treatment group were calculated using the non-parametric Kaplan-Meier estimate as well as the corresponding 95% CIs (with Greenwood’s variance) at specified time point. Cox’s proportional hazard model was used to estimate the hazard ratio (labeled in tables “Relative risk”) with 95% CIs.

Arrhythmic/sudden deaths

Deaths were considered as arrhythmic deaths when adjudicated as ‘Documented arrhythmia’. Sudden deaths were those checked ‘sudden death unwitnessed’ or ‘sudden death witnessed’ in the death adjudication form. The time from randomization to an arrhythmic or a sudden death was analyzed with the same method as that described above for the endpoint ‘death from any cause’.

Hospitalization for worsening heart failure

The cumulative incidence of first hospitalization for worsening heart failure (adjudication) considering death from any cause as a competing risk was estimated by treatment group and compared by Log-rank test.

The duration in days of the first hospitalization was summarized as a quantitative variable and compared using a Wilcoxon test.

Hospitalizations for acute cardiovascular reasons

The same analyses as those described for the criterion ‘Hospitalization for worsening heart failure’ were performed for all adjudicated hospitalizations.

Atrial fibrillation/atrial flutter occurrence

Two different analyses were performed according to rhythm status at randomization:

- Patients in AF/AFL at randomization: the analyses focused on cardioversions (spontaneous or electrical);
- Patients in sinus rhythm at randomization: cumulative incidence of AF/AFL recurrence was calculated using Kaplan-Meier estimates.

10.1.2 American-Australian-African trial with DronedarONE In atrial fibrillation or flutter patients for maintenance of Sinus rhythm (ADONIS): EFC4788

Study Dates: November 17, 2001 to September 25, 2003

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

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

Study Design: This was a multicenter, multinational, double-blind, parallel-group study which compared the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological, or spontaneous conversion of atrial fibrillation/ atrial flutter (AF/AFL).

Objectives

Primary efficacy objective: The primary objective was to assess the efficacy of dronedarone versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL.

Secondary objectives were:

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

Secondary pharmacokinetic objectives:

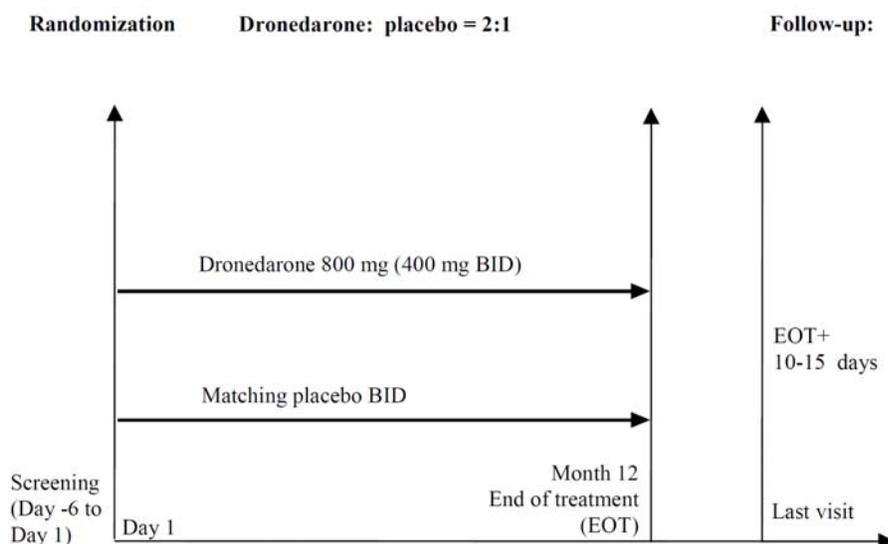
The PK objective was to document dronedarone and SR35021, the main metabolite, trough plasma levels at steady state and to describe the PK of the selected dose in the target population.

Study Design:

This was a multicenter, multinational, double-blind, parallel-group, placebo-controlled, phase 3 study. A total of 552 patients in normal sinus rhythm at randomization, with an ECG-documented history of an AF/AFL episode within the last 3 months, converted electrically, pharmacologically, or spontaneously, were to be randomized.

If, following randomization, AF/AFL recurred, it was recommended that the patient remain in the study according to the following conditions:

- if AF/AFL was not transient, electrical cardioversion while on study drug could be performed to restore sinus rhythm; this applied in particular to the first 5 days following randomization, the time necessary for study drug levels to reach steady state;
- if there was no indication for cardioversion the patient could remain on study drug while in AF/AFL in particular to benefit from the heart rate (HR)-lowering properties of the study drug.



(page 25 EFC4788)

Figure 15- Overall study design

Amendments:

Three amendments were issued for this study.

Amendment No.1, September 12, 2001, was introduced before the inclusion of any patients. In this Amendment the duration of study participation was revised, the definition of the primary efficacy population was changed, and the time window (12 months from randomization) for the observation of the primary endpoint was clarified.

Amendment No. 2, June 26, 2002, added specifications and recommendations regarding patient safety.

Amendment No. 3, March 3, 2003, gave further instructions regarding concomitant medications and safety.

Central laboratory/electrocardiogram Corelab

A central laboratory/electrocardiogram (ECG) Corelab, MDS Pharma Services, 95560 Baillet-en-France, was responsible for the following:

- reception and interpretation of transtelephonic electrocardiogram monitoring (i.e., TTEM) tracings recorded and transmitted by patients by phone;
- reading of 12-lead ECG tracings recorded by the investigational sites;
- adjudication of the primary endpoint by a group of 4 senior cardiologists;
- collection of frozen pharmacokinetic (PK) samples from the sites, storage and periodic transfer of the frozen samples to Sanofi-Synthelabo;
- assessment of biological safety parameters.

The procedure for central reading, and for the adjudication of the primary endpoint, was validated by an international expert in the field of cardiac arrhythmia

Randomization center

The S-Clinica Randomization center, B1050 Brussels, Belgium, provided the interactive voice response system (IVRS) for the following functions:

- randomization of patients using a stochastic minimization procedure;
- reallocation of treatments at Month 6 (M6);
- treatment replacement;
- recording of permanent study drug discontinuation;
- determination of investigational product needs;
- unblinding of treatment.

Steering Committee

The Steering Committee (SC) consisted of 9 members, 8 international experts in the field of cardiac arrhythmia, 1 of whom was the chairman, and 1 member from the Sponsor.

The main functions of the SC were:

- to provide advice on scientific and clinical aspects of the study protocol and related documents;
- to oversee the good conduct of the study, as well as its analysis and scientific reporting;
- to resolve policy issues that might be encountered during the study.

The SC members, who were blinded in regards to treatment groups, met to review and discuss the study at regular intervals.

Data safety monitoring board

The independent data safety monitoring board (DSMB) included 3 members:

2 international experts in cardiac arrhythmia and 1 in clinical pharmacology, who was the chairman.

The primary responsibility of the DSMB was to protect the welfare of patients participating in the study, through:

- immediate reviews of serious adverse events (SAEs) leading to death;
- regular review of monthly line listings using the Council for international organization of medical sciences (CIOMS) format;
- biannual review of the complete safety database;

- interim analysis of the primary efficacy endpoint when half of the expected events had been observed;
- recommendations based on reviews, to the SC and the Sponsor, in regards to protocol modifications, study continuation, or early study termination (conclusion forms).

Two parallel groups of patients were allocated according to central randomization to dronedarone 400 mg BID or placebo. Placebo was selected to document efficacy in the absence of a widely recognized first-line therapy for maintenance of sinus rhythm in AF/AFL patients. In order to appropriately document safety, randomization was performed in a 2 (dronedarone): 1 (placebo) ratio to maximize the number of patients on study drug, and follow-up was prolonged up to 12 months.

The detection of AF/AFL recurrences was based on a centralized review of transtelephonic electrocardiogram monitoring (TTEM) and 12-lead electrocardiogram (ECG) with adjudication of the first AF/AFL recurrence by a group of 4 senior cardiologists of ECG Corelab.

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

Exclusion criteria:

- a) women of childbearing potential not on adequate birth control: Pregnant women and breast-feeding women could not be included (Amendment No. 1);
- b) documented AF/AFL episode motivating inclusion in the study starting and not persisting beyond 10 days after an acute condition known to cause AF/AFL (e.g., alcohol intake, thyrotoxicosis, infection, myocardial infarction, pericarditis, pulmonary embolism, cardiac surgery);
- c) history of torsades de pointes;
- d) bradycardia <50 bpm at the screening ECG;
- e) PR-interval > 0.28 seconds at screening;
- f) high degree atrioventricular (AV) block (2nd degree or higher), or significant sinus node disease (documented pause of 3 seconds or more) without a permanent pacemaker implanted;
- g) treatment with other Class I or III antiarrhythmic drugs;
- h) clinically overt congestive heart failure (CHF) with New York Heart Association (NYHA) Class III or IV at the time of randomization;
- i) clinically relevant hematologic, hepatic [alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin >2 times the upper limit of normal at screening], gastrointestinal (GI), renal [serum creatinine > 150 µmol/L (i.e., 1.7 mg/dL) at screening], pulmonary, endocrinologic (in particular thyroid) or psychiatric disease;
- j) ongoing potentially dangerous symptoms when in AF/AFL such as angina pectoris, transient ischemic attacks, stroke, syncope, as judged by the Investigator;
- k) patients in whom amiodarone prescribed for sinus rhythm maintenance was discontinued for inefficacy;
- l) patients in whom 3 or more Class I or III antiarrhythmic drugs prescribed for sinus rhythm maintenance were discontinued for inefficacy;

- m) patients known to have chronic AF/AFL defined as continuous AF/AFL for more than 12 months;
- n) patients in whom a contraindicated concomitant treatment was mandatory;
- o) patients thought to be unable to use the TTEM system as scheduled in the study protocol;
- p) patients unable to sign an informed consent;
- q) hypokalemia (plasma potassium <3.5 mmol/L) and hypomagnesemia (plasma magnesium <0.7 mmol/L) had to be corrected before inclusion (Amendment No. 1).

Prior and concomitant therapy

Not permitted:

Vaughan-Williams-Singh Class I and III antiarrhythmic drugs (including sotalol) other than the study drug were not to be administered during the study and had to be withdrawn for at least 5 plasma half-lives prior to the first study drug administration.

Patients on nonchronic (including intravenous) amiodarone or chronic amiodarone therapy (defined as a cumulative dose of 20 or more 200 mg tablets in the last 2 months) could be randomized as soon as amiodarone was stopped. In these patients, an ECG was to be performed about 4 hours after the first study drug administration to verify good tolerability.

All concomitant drugs which can cause torsades de pointes were contraindicated. Such drugs include some phenothiazines, cisapride, bepridil, tricyclic antidepressants, and certain oral macrolides.

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

Permitted:

Calcium antagonists with depressant effects on the sinus and AV node (e.g., diltiazem and verapamil) could be used with caution, as a potentiation of the depressant effects on conduction is possible.

Beta-blockers could be used with caution (except sotalol which was contraindicated) as a potentiation of the depressant effects is possible: concomitant administration was to start with low doses of beta-blockers and increased only after ECG verification confirming good tolerability.

Digoxin, if necessary, could be concomitantly administered with caution (concomitant administration had to start with low doses of digoxin, and digoxin plasma levels monitored locally, especially at the beginning of the coadministration): an interaction study (INT2634) has shown that dronedarone at the dose of 400 mg daily increases digoxin plasma levels by an average of 30%.

If oral anticoagulation was indicated, the international normalized ratio (INR) to be monitored locally, although no interaction between warfarin and dronedarone had been documented.

An interaction study has shown that dronedarone can increase 4-fold the plasma concentrations of simvastatin, a CYP450 3A4 substrate. The clinical consequences of this PK interaction cannot be predicted, the risk of rare side effects such as rhabdomyolysis could be increased. In case of unexplained muscle pain, tenderness, or weakness occurring during concomitant therapy with a statin, the patients were to consult the Investigator immediately. The statin and the study drug were to be discontinued if myopathy was diagnosed or suspected (cf. Amendment No. 2).

The study flow chart is following.

Table 81- Study flow chart

	Screening D-6 to D1	D1 ⁱ	D7 ±2	D14 ±3	D21 ±3	M2 ±5D	M4 ±5D	M6 ±5D	M9 ±5D	M12 ±5D ^m	EOT ^g	EOT+ (10-15) D ^h
Informed consent	X											
Medical history ^a	X											
Cardiovascular examination	X											
Notification of symptoms ^b	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs ^c	X	X	X	X	X	X	X	X	X	X	X	X ^l
12-lead ECG ^k	X	X	X	X	X	X	X	X	X	X	X	X ^l
Laboratory tests ^d	B1,B2, B3		B2		B1,B2, B3		B1,B2, B3		B1,B2, B3		B1,B2, B3	
PK			X ^f		X ^f		X ^f		X ^f		X ^f	
Chest X-ray	X							X			X	
2D-echocardiogram	X											
IVRS calls ^j		X						X			X	
Randomization		X										
Dispense study drug		X				X	X	X	X			
Treatment with study drug		←-----→										
TTEM ^e		←-----→										
Adverse events & concomitant drugs	←-----	-----→										

- a: Includes: cardiovascular history, review of ECGs
 - b: Palpitations, dizziness, fatigue, chest pain, dyspnea
 - c: Weight, supine blood pressure and HR
 - d: B1: full blood count [red blood cells (RBC), white blood cells (WBC) with differential, platelets]
 B2: glucose, electrolytes (Na+, K+, Cl-, Ca++, Mg++), urea, creatinine, AST, ALT, gamma-glutamyl transferase (GGT), CPK, alkaline phosphatase, bilirubin
 B3: free triiodothyronine, free thyroxine (FT3, FT4), thyroid stimulating hormone (TSH; ultra sensitive method), triglycerides, cholesterol
 - e: Transtelephonic ECG monitoring (TTEM x 2 10 minutes apart) in case of symptoms and at the following times: Days 2, 3, 5, M3, M5, M7, M10
 - f: PK: sampling for study drug assay just before morning dosing (trough) and in case of AE leading to drug discontinuation
 - g: EOT visit at M12 after randomization or following premature discontinuation
 - h: The follow-up (EOT + 10 to 15 days) visit was to take place 10 to 15 days after study drug discontinuation
 - i: Baseline (just before first study drug administration)
 - j: IVRS
 - k: If the 12-lead ECG shows the first AF/AFL recurrence, a second recording was done 10 minutes after the first
 - l: TTEM instead of 12-lead ECG and vital signs not collected if telephone visit
 - m: Replaced by the EOT visit if patient still on treatment
- (page 33 EFC4788)

Efficacy assessments

Atrial fibrillation:

Atrial fibrillation is defined as the absence of P-waves and fine oscillations of the electrocardiographic baseline (fibrillatory waves) associated with an irregular ventricular rhythm (except in paced patients).

Atrial flutter:

Atrial flutter is defined by a characteristic regular flutter wave pattern (F-waves) with an atrial rate between 240 to 360 bpm.

Assessments for the primary endpoint:

The primary endpoint of the study was the time from randomization to first documented AF/AFL recurrence defined as an episode lasting 10 minutes or more, as indicated by 2 consecutive 12-lead ECG or TTEM tracings recorded approximately 10 minutes apart and both showing AF/AFL. The ECG Corelab centralized the reception of TTEMs and 12-lead ECGs and adjudicated the primary endpoint by reviewing tracings.

12-lead electrocardiogram:

At each visit, the Investigator recorded a 12-lead ECG. If this ECG showed the first AF/AFL recurrence, a second ECG was recorded 10 minutes after the first in order to confirm that the primary endpoint was reached.

All ECGs required by the study protocol were sent to the ECG Corelab for central reading which included: underlying rhythm, HR, PR-, QRS-, QT-, QTc-intervals. Results were then communicated to the centers by the Corelab.

Transtelephonic electrocardiogram monitoring:

Enrolled patients were given a transtelephonic electrocardiogram monitoring (TTEM) device for the duration of the study. Patients were asked to record their ECG at times planned and in case of symptoms that might be related to cardiac arrhythmia. Each time, 2 tracings (10 minutes apart) were to be recorded. After recording, the patient was to call the ECG Corelab to transmit the tracings by phone. Tracings were analyzed by the ECG Corelab for rhythm and HR.

Symptoms:

The presence of symptoms (palpitations, dizziness, fatigue, chest pain, dyspnea) was to be reported, each time an ECG (12-lead or TTEM) was recorded. If any symptom was present, the patient was considered as symptomatic.

At each visit, the presence and details of symptoms since last visit, were recorded independently of the AF/AFL status of the patient.

Atrial fibrillation/AFL and AF/AFL-related symptoms were not to be reported as AEs unless 1 or more of the seriousness criteria were met.

Twelve-lead electrocardiogram

Twelve-lead ECGs were recorded using the investigational center's own equipment. All ECGs were assessed for heart rhythm, HR, PR-, QRS-, QT-, and QTc-interval was derived using the Bazett and Fridericia formulae (QTcB and QTcF).

Clinical laboratory assessments

Blood samples were drawn according to the schedule provided in the study flow chart, prepared and sent to the Central laboratory. The following parameters were determined:

- liver function: ALT, AST, alkaline phosphatase, GGT, total bilirubin;
- renal function: creatinine, urea;
- electrolytes: calcium, chloride, potassium, sodium, magnesium;
- metabolism: glucose, CPK, total cholesterol, triglycerides;
- WBC: basophils, eosinophils, lymphocytes, monocytes, neutrophils, WBC count;
- RBC and platelets: RBC count, platelet count;
- endocrinology: FT3, FT4, TSH.

Chest X-ray

Although pulmonary side effects are not expected with dronedarone, in case of new onset clinical or X-ray abnormalities, the patients were to be seen by a lung specialist; lung function tests could be performed, looking for a restrictive pattern with impaired CO-transfer.

Cardiovascular examination

A cardiovascular examination was performed at screening to verify eligibility, and included NYHA classification assessment.

2D-echocardiogram

The echocardiogram was performed at screening to measure the following parameters: left atrium diameter, end-diastolic, end-systolic left ventricular diameters, end-diastolic septal and posterior wall myocardial thickness, left ventricular ejection fraction (LVEF), and valvular abnormalities as per Amendment No. 1.

According to the Sponsor, the TTEM and 12-lead ECG procedures used in this study allowed thorough documentation of arrhythmias as cardiac rhythm was documented during the study both at predefined intervals and in the case of symptoms.

Efficacy variables

The primary efficacy variable was the time in days elapsed between randomization and the first documented AF/AFL recurrence within 12 months from randomization. An AF/AFL recurrence was defined as an episode lasting 10 minutes or more, as indicated by 2 consecutive 12-lead ECGs or TTEM tracings recorded approximately 10 minutes apart, both showing AF/AFL, and

confirmed by the ECG Corelab responsible for the adjudication of the first recurrence based on the analysis of all ECGs and/or TTEMs.

The secondary efficacy variables were the following:

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

Pharmacokinetic assessments:

Trough (just before dosing) plasma concentrations of dronedarone (SR33589) and SR35021 were planned to be assessed in all patients, at steady state at visits Day 7 ± 2, Day 21 ± 3, M4 ± 5 days, M9 ± 5 days and M12 ± 5 days.

General statistical approach:

All statistical analyses were performed using two-sided tests and/or two-sided confidence intervals (CIs). Unless otherwise specified, Fisher's exact tests were used for qualitative parameters.

Continuous parameters were summarized using mean, standard deviation (SD), median, minimal and maximal values. Categorical parameters were summarized using counts and percentages.

Analysis populations:

Patients were analyzed for efficacy and for safety according to the treatment group assigned by the IVRS at randomization, i.e., as randomized.

Randomized and treated patients population (Intent-to-treat, ITT)

The randomized and treated patients population corresponds to the all randomized patients who received at least 1 study drug administration, either dronedarone or placebo.

Per-protocol population

The per-protocol population (PP) corresponds to the randomized and treated patients with no major protocol deviations and who had not reached the primary efficacy endpoint between randomization and the first study drug intake.

Primary efficacy endpoint:

For all analyses on the primary endpoint, only the results of the adjudication were taken into account. The primary efficacy endpoint was the time in days from the randomization to the adjudicated first AF/AFL recurrence within 12 months post randomization.

Primary analysis

The primary analysis was the comparison of the 2 treatment groups using a 2-sided Log-rank asymptotic test. A Type I error of 0.0492 was considered due to the interim analysis conducted when half of the expected events had been accumulated. Cumulative incidence functions in each

treatment group were calculated using the nonparametric Kaplan-Meier estimate as well as the corresponding 95% CIs (with Greenwood's variance estimated) at each scheduled time point. The hazard ratio (labeled in tables "Relative risk") with the 95% CI, was estimated using the Cox model with treatment group as the only factor.

Patients with no documented AF/AFL recurrence up to the end of study or up to Day 365 whichever came first, were considered as right-censored data.

Secondary analyses

Competing risks analysis on the per-protocol population:

An 'on-treatment' analysis was performed in the PP population using a competing risks analysis with model of cause-specific hazards. Competing events were: the time of adjudicated first AF/AFL recurrence within 12 months from randomization and the time of last study drug intake plus 10 days. The cumulative incidence functions were calculated separately for the 2 treatment groups with the nonparametric Prentice estimate. 95% CIs for cumulative adjudicated first AF/AFL recurrence event incidence were computed at each scheduled time point [Keiding and Andersen formula with delta method's variance estimated]. The 2 treatment groups were compared for adjudicated first AF/AFL recurrence event using a 2-sided Log-rank asymptotic test.

Baseline covariate analysis:

The primary efficacy endpoint was further analyzed using the following 3 binary baseline prognostic factors for recurrence of AF/AFL, to examine if treatment effect varied with subgroup or covariate:

- electrical cardioversion, ibutilide infusion or overdrive pacing for the last AF/AFL episode in the 5 days prior to randomization;
- chronic treatment with amiodarone;
- structural heart disease: structural heart disease was considered present if the patient has coronary heart disease and/or clinically relevant abnormalities at baseline echocardiography.

In the randomized and treated patients population, for each prognostic factor category, Kaplan-Meier cumulative incidence curves were provided per treatment group and hazard ratio (with 95% CI) was estimated using the Cox model. In order to test the treatment effect adjusted for covariate prognostic factors, a Cox model with the treatment group and the 3 prognostic factors as covariates was used.

In the PP population, an unadjusted "on-treatment" analysis was done using the competing risk method as described in the above subsection (competing risks analysis in the PP population). For each prognostic factor subcategory, Prentice cumulative incidence curves were provided per treatment group.

Secondary efficacy endpoints:

Analysis of AF/AFL-related symptoms

The analyses were performed in the randomized and treated patient population. Patients reported to be symptomatic at the time of the primary endpoint were summarized.

The primary endpoint was investigated according to presence/absence of symptoms through a survival competing risks analysis with a model of cause-specific hazards. The competing events were the time of symptomatic primary endpoint and the time of asymptomatic primary endpoint. The cumulative incidence functions were calculated separately for the 2 treatment groups with nonparametric Prentice estimate. The 2 treatment groups were compared for presence of symptoms using a 2-sided Log-rank asymptotic test.

Atrial fibrillation/AFL-related symptoms collected in the CRF at each visit (patients not necessarily in confirmed AF/AFL) were described according to intensity. An intensity index was calculated for each patient and summarized by visit; the 2 treatment groups were compared using a nonparametric Wilcoxon's rank test.

Analysis of ventricular rate at time of primary endpoint

Ventricular rate (obtained on 2 or more consecutive RR intervals on ECG) assessed at the time of the primary endpoint was analyzed in the randomized and treated patients population (modified randomized and treated patients population), as a continuous variable; first whatever the ECG method (12-lead ECG/TTEM) and considering only patients for whom primary endpoint was detected on TTEM. The 2 treatment groups were compared using a 2-way ANOVA with treatment group, ECG recording method, and their interaction.

10.1.3 SR33589B: EUROpean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS)

Study Dates: 19 November 2001 through 14 August 2003

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

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

Overall study design and plan:

This study was identical to the ADONIS Study except that it was a European trial with 65 active centers in 12 countries: Netherlands, Germany, Poland, Hungary, Italy, France, Czech Republic, Belgium, Spain, Denmark, Finland and United Kingdom.

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