22 December 2011
EMA/905311/2011

Assessment report for MULTAQ

Review under Article 20 of **Regulation (EC) No 726/2004**

International Non-proprietary Name: dronedarone

Procedure number: EMEA/H/C/1043/A-20/005

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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1. Background information on the procedure

Dronedarone is an anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds including amiodarone. Dronedarone demonstrates electrophysiological characteristics belonging to all 4 Vaughan-Williams classes of anti-arrhythmic compounds: it blocks sodium channels, exhibits non-competitive antiadrenergic activity, prolongs action potential duration and refractory periods, and it has calcium antagonist properties.

Multaq was initially approved for use in adult clinically stable patients with history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate, and was granted a marketing authorisation according to the centralised procedure on 26 November 2009. At that time, the clinical trial considered pivotal for the granting of the marketing authorisation (ATHENA) showed a statistically significant benefit for dronedarone as an antiarrhythmic agent in AF patients in terms of rhythm and rate control, when compared to placebo.

In December 2010, two life-threatening cases of liver failure requiring liver transplantation were reported, which triggered a comprehensive analysis of all available data on potential hepatic toxicity of dronedarone. As a consequence the CHMP recommended in January 2011 that there was a need to introduce new warnings and precautions in the Summary of Product Characteristics (SPC) to ensure that patients' liver function is tested before initiation of treatment, closely monitored during treatment, and treatment is stopped if there are signs of potential liver damage.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the CHMP on 21 January 2011 to assess the above concerns and its impact on the benefit/risk for Multaq, and to give its opinion on measures necessary to ensure the safe and effective use of Multaq, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

On 7 July 2011, whilst the review on hepatic safety of dronedarone was ongoing, the MAH informed the CHMP of the premature termination of the PALLAS study (a randomised, double-blind, placebo-controlled, parallel group trial for assessing the clinical benefit of dronedarone 400 mg BID on top of standard therapy in patients with permanent atrial fibrillation and additional risk factors). This decision was based on the recommendations of the Data Monitoring Committee which reviewed the unblinded data and concluded that there was a highly significant excess of events in the dronedarone group for both the co-primary outcomes as well as all hospitalisations and heart failure events, with no evidence of benefit in other secondary endpoints.

On 8 July 2011, the European Commission extended the scope of the ongoing review under Article 20 to allow consideration of other data, including the new data from the PALLAS study, prior to the adoption of an opinion on the benefit-risk balance of Multaq.

2. Scientific discussion

The clinical development of dronedarone included 5 placebo-controlled atrial fibrillation/atrial flutter trials: DAFNE, EURIDIS, ADONIS, ERATO and ATHENA. These studies, which demonstrated the rhythm and rate-control properties of dronedarone, were assessed within the marketing authorisation application and served as the basis for the granting of the marketing authorisation of Multaq.

In EURIDIS/ADONIS, dronedarone 400 mg BID significantly lowered (by 25%) the risk of first recurrence of AF/AFL within the 12-month study period compared to placebo. The results of ERATO showed a significant effect on mean heart rate compared to baseline at rest in the dronedarone group, compared to placebo, when measured after 14 days of treatment. The ATHENA study was a large multicenter, double-blind, randomised, parallel-arm study in more than 4000 haemodynamically stable patients in which the primary endpoint of incidence of CV hospitalisation or death from any cause was significantly reduced in patients administered dronedarone 400 mg when compared to placebo. The results were mainly driven by the number of CV hospitalisations, particularly AF-related hospitalisations. In addition, a significant decrease was observed in the secondary outcome of incidence of cardiovascular death. The results of ATHENA thus addressed concerns with the previous ANDROMEDA study, where a negative effect on mortality was seen on a haemodynamically unstable population for which a clear contraindication was required.

The results of the DIONYSOS study comparing the efficacy and safety of dronedarone versus amiodarone for the maintenance of sinus rhythm in patients with AF showed that dronedarone is less effective as an anti-arrhythmic than amiodarone, but safer in terms of thyroid and neurological adverse events.

Multaq is currently marketed in more than 30 countries worldwide. Cumulative patient exposure through to 30 June 2011 is estimated to be around 215 000 patient-years.

In July 2011 the PALLAS study (a randomised, double-blind, placebo-controlled, parallel group trial for assessing the clinical benefit of dronedarone 400 mg BID on top of standard therapy in patients with permanent atrial fibrillation and additional risk factors) was prematurely terminated due to a highly significant excess of events in the dronedarone group for both the co-primary outcomes as well as all hospitalisations and heart failure events, with no evidence of benefit in other secondary endpoints.

2.1. Clinical aspects

2.1.1. Cardiovascular safety

The data on the below analyses of the PALLAS study have a data cut-off of 2 August 2011 with 64% of events adjudicated.

The PALLAS study

Design: Prospective, randomized, double blind, parallel group, international, multicenter trial evaluating the effects of dronedarone 400 mg BID versus placebo (ratio 1:1) in patients with permanent atrial fibrillation and additional risk factors.

Objectives: The primary objective of this trial was to demonstrate the efficacy of dronedarone in preventing major cardiovascular events (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death) or unplanned cardiovascular hospitalization or death from any cause in patients with permanent atrial fibrillation and additional risk factors.

Study population
Patients in permanent atrial fibrillation defined by the presence of all of the following criteria:
- Availability of one 12-lead ECG not more than 14 days prior to randomization, showing that the patient is in AF/AFL.
- Documentation showing that the patient was in AF/AFL at least 6 months prior to randomization
- No evidence of sinus rhythm in the period between these two documentations of atrial fibrillation
- Patient and physician decision to allow AF to continue without further efforts to restore sinus rhythm.

Main Inclusion criteria
- Patients ≥ 65 years with at least one of the following risk factors or combination of risk factors:
- Coronary artery disease
- Prior stroke or TIA
- Symptomatic heart failure
- Left ventricular ejection fraction less than or equal to 0.40
- Peripheral arterial occlusive disease
- Patients ≥ 75 years or older with both hypertension and diabetes mellitus

Main Exclusion Criteria
- Patients in paroxysmal atrial fibrillation
- Patients in persistent atrial fibrillation without a decision to allow atrial fibrillation to continue without further efforts to restore sinus rhythm
- Patients with heart failure of NYHA class IV or recent unstable NYHA class III.

Study Endpoints
Co-primary Endpoints
• Composite endpoint of first stroke, systemic arterial embolism, myocardial infarction or cardiovascular death
• Composite endpoint of first unplanned cardiovascular hospitalization or death from any cause

Secondary Endpoint
• Cardiovascular death

All deaths, strokes, systemic arterial embolisms and myocardial infarctions, all heart failure hospitalizations as well as all other unplanned cardiovascular hospitalizations up to the first not refuted unplanned cardiovascular hospitalization were adjudicated by a blinded committee.

Duration of study period (per patient)
The common study end date anticipated based on the projected blind number of events to reach 844 co-primary events not refuted by adjudication (stroke, systemic arterial embolism, myocardial infarction or cardiovascular death) was not less than 3 months after the last patient randomized.

The design of the study is depicted in the following figure:

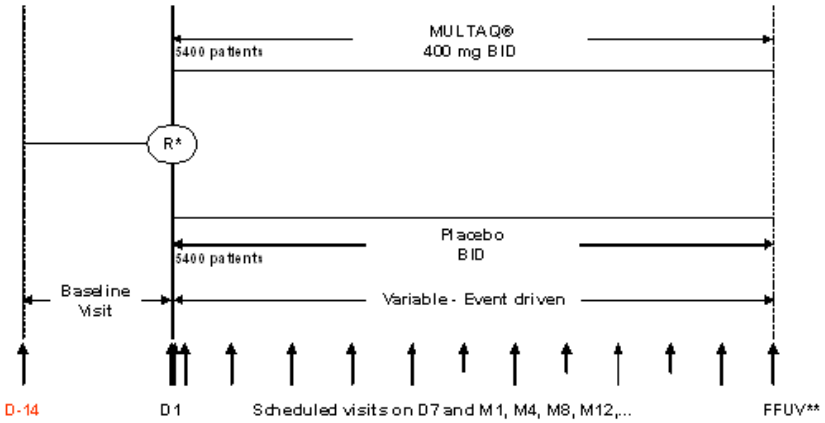

Figure 1 Design of the PALLAS study

Patient Disposition
The first patient was randomized on 19 July 2010 and 3149 patients out of the 10800 planned were enrolled. The main demographic characteristics of the PALLAS are presented in table 1. Data shows that the treatment arms were balanced.

Table 1 Demographic data of recruited patients

			A		B	
	n	Percent	n	Percent	n	Percent
Randomized	3149	100%	1577	100%	1572	100%
Baseline information available	3065	100%	1538	100%	1527	100%
Age: number	3065	100%	1538	100%	1527	100%
65<= and < 75	1481	48.3%	742	48.2%	739	48.4%
>= 75	1583	51.6%	796	51.8%	787	51.5%
Sex: number	3063	99.9%	1538	100%	1525	99.9%
Male	1993	65.1%	993	64.6%	1000	65.6%
Female	1070	34.9%	545	35.4%	525	34.4%
Ethnicity: number	3060	99.8%	1536	99.9%	1524	99.8%
Black	29	0.9%	14	0.9%	15	1.0%
European	2466	80.6%	1244	81.0%	1222	80.2%
Asian	116	3.8%	58	3.8%	58	3.8%
Arab	9	0.3%	5	0.3%	4	0.3%
Native Latin	385	12.6%	189	12.3%	196	12.9%
Other	55	1.8%	26	1.7%	29	1.9%

A= placebo, B=dronedarone

Tables 2 and 3 show the CV risk factors and $CHADS_2$ score of the recruited patients at baseline, respectively. Around 20% of the patients had a LVEF ≤40%. Results show that the recruited patients were a moderate to high risk group with two-thirds of recruited patients having a $CHADS_2$ score of 2 or 3, and around 27% of the patients having history of prior stroke or TIA.

Table 2 Risk Factors for primary composite outcomes at inclusion

			A		B	
	n	Percent	n	Percent	n	Percent
Randomized	3149	100%	1577	100%	1572	100%
Eligibility information available	3038	100%	1529	100%	1509	100%
Risk factors: number	3038	100%	1529	100%	1509	100%
0	37	1.2%	26	1.7%	11	0.7%
1	2116	69.7%	1072	70.1%	1044	69.2%
2	684	22.5%	322	21.1%	362	24.0%
>=3	201	6.6%	109	7.1%	92	6.1%
Risk factors: Coronary artery disease	1245	41.0%	623	40.8%	622	41.2%
Prior stroke or TIA	819	27.0%	423	27.7%	396	26.2%
Symptomatic heart failure	502	16.5%	245	16.0%	257	17.0%
LVEF <=40%	619	20.4%	307	20.1%	312	20.7%
Peripheral arterial occlusive disease	368	12.1%	193	12.6%	175	11.6%
Age >= 75 years with hypertension and diabetes	568	18.7%	270	17.7%	298	19.7%

A= placebo, B=dronedarone

Table 3 $CHADS_2$ score at baseline

			A		B	
	n	Percent	n	Percent	n	Percent
Randomized	3149	100%	1577	100%	1572	100%
Baseline information available	3065	100%	1538	100%	1527	100%
CHADS2 score: Number	3036	99.1%	1524	99.1%	1512	99.0%
0	49	1.6%	21	1.4%	28	1.9%
1	331	11.1%	155	10.3%	176	11.9%
2	995	33.3%	513	34.1%	482	32.5%
3	938	31.4%	456	30.3%	482	32.5%
4	523	17.5%	281	18.7%	242	16.3%
5	165	5.5%	82	5.5%	83	5.6%
6	35	1.2%	16	1.1%	19	1.3%
0, 1	380	12.5%	176	11.5%	204	13.5%
>3	723	23.8%	379	24.9%	344	22.8%

A= placebo, B=dronedarone

The most frequently reported cardiovascular co-morbidities included hypertension (82.5%), myocardial infarction (25.2%), percutaneous coronary intervention (18.6%) and ischemic stroke (17.2%); the distribution was balanced between the treatment arms. Around 68% of the patients had heart failure with NYHA II: 67.5% (n= 1417) and NHYA III: 11.5% (n=242). Table 4 shows that in the patient group with LVEF $\leq$40% (n=619) 467 patients did not have symptomatic HF vs. 152 who did.

Table 4 Heart failure and LVEF ≤40 %

				Overall		A		B	
				n	%	n	%	n	%
Heart failure info available				3065	100.0	1538	100.0	1527	100.0
LVEF <=40%	Symptomatic HF	NYHA: II/III	History HF						
No	No	No	No	900	29.4	461	30.0	439	28.7
			Yes	345	11.3	169	11.0	176	11.5
		Yes	No	41	1.3	24	1.6	17	1.1
			Yes	810	26.4	411	26.7	399	26.1
	Yes	No	No	4	0.1	2	0.1	2	0.1
			Yes	26	0.8	8	0.5	18	1.2
		Yes	Yes	320	10.4	156	10.1	164	10.7
Yes	No	No	No	36	1.2	14	0.9	22	1.4
			Yes	84	2.7	45	2.9	39	2.6
		Yes	No	7	0.2	1	0.1	6	0.4
			Yes	340	11.1	168	10.9	172	11.3
	Yes	No	Yes	11	0.4	4	0.3	7	0.5
		Yes	No	1	0.0	.	.	1	0.1
			Yes	140	4.6	75	4.9	65	4.3

A= placebo, B=dronedarone

Other relevant medical history included hypercholesterolemia, diabetes mellitus, and chronic renal impairment reported in 56.2%, 35.5%, and 9.3% of the patients respectively, with comparable distribution between the treatment arms.

The majority of the patients had received an anti-thrombotic medication (aspirin: 27.9% or vitamin K antagonists: 82.4%). For rate control, 87.5% of the patients were administered medications such as beta-blockers (73.6%) and to a lesser extent digoxin (32.6%) or calcium channel blockers (9.5%). The combination of beta-blockers and digoxin was used in 22.2% of the patients. The majority of patients (75.6%) had received anti-hypertensives mainly: diuretics 67%, dihydropyridine calcium channel blockers (19.6%) or an alpha blocker (7.6%); with around 11.5% administered both a diuretic and a calcium channel blocker. Other medications recorded at baseline were angiotensin-converting enzyme inhibitors (51.5%), angiotensin-receptor blockers (24.9%) and statins (56.3%). The high rate of co-administered CV drugs supports the high risk level of the recruited patients.

Patient discontinuation

There was a significantly higher incidence of patient discontinuation in the dronedarone arm compared to placebo (HR=2.41; CI 95%: 1.91-3.04). The frequency of discontinuation in this study is comparable to what is reported in the current summary of product characteristics. The main cause of discontinuation was adverse event (71.5% dronedarone vs 51.8% placebo).

Table 5 Causes of Permanent discontinuations

			A		B	
	n	Percent	n	Percent	n	Percent
Randomized	3149	100%	1577	100%	1572	100%
Early discontinuation of study drug	338	10.7%	110	7.0%	228	14.5%
Patient decision to permanently discontinue the treatment	248	72.5%	86	76.8%	162	70.4%
Reason for treatment discontinuation: adverse event	220	65.1%	57	51.8%	163	71.5%
Poor compliance to protocol	11	3.3%	7	6.4%	4	1.8%
Lost to follow-up	1	0.3%	0	0.0%	1	0.4%
Contraindicated therapy required	4	1.2%	1	0.9%	3	1.3%
Uncontrolled symptomatic AF	2	0.6%	1	0.9%	1	0.4%
Other	100	29.6%	44	40.0%	56	24.6%
Missing	2	0.1%	1	0.1%	1	0.1%

A=placebo, B=dronedarone

Efficacy results
There was a significantly higher incidence in both co-primary endpoints reported in the dronedarone group compared to placebo [composite of stroke, MI, systemic embolism and CV death, HR=2.16 (95%CI: 1.17-3.00; p=0.0117); composite of time to first CV hospitalization or death, HR=1.62 (95%CI: 1.20-2.17; p=0.0013)].

Table 6 Primary events during the study

	Adjudication status 2 August[a]				
	Total	P	D	Hazard ratio (95% CI)	p-value
Time to first stoke, MI, SE, CV death	47	15	32	2.16 (1.17 – 3.99)	0.0117
Time to first CV hospitalization or death	186	72	114	1.62 (1.20 – 2.17)	0.0013
Components of primary endpoints					
Time to death	23	7	16	2.31 (0.95 – 5.62)	0.0568
Time to CV death	21	6	15	2.53 (0.98 – 6.53)	0.0462
Time to first stroke	25	8	17	2.14 (0.92 – 4.96)	0.0689
Time to first MI	6	3	3	1.01 (0.20 – 5.01)	0.9886
Time to first SE	1	0	1	NA	
Time to first unplanned CV hospitalization	172	68	104	1.56 (1.15 – 2.12)	0.0039
Tertiary endpoints					
Time to first hospitalization for HF[b]	51	16	35	2.21 (1.22 – 3.99)	0.0070
Time to first heart failure (any episode)[c]	113	33	80	2.49 (1.66 – 3.74)	<0.0001

P=placebo, D=dronedarone

The separation of the two Kaplan-Meier curves (dronedarone versus placebo) on the 2 coprimary endpoints is observed from the first two weeks of treatment and progresses over time. The main events that drove the early separation of the curves were stroke (dronedarone=9; placebo=0) and hospitalization for heart failure (dronedarone=11; placebo=1).

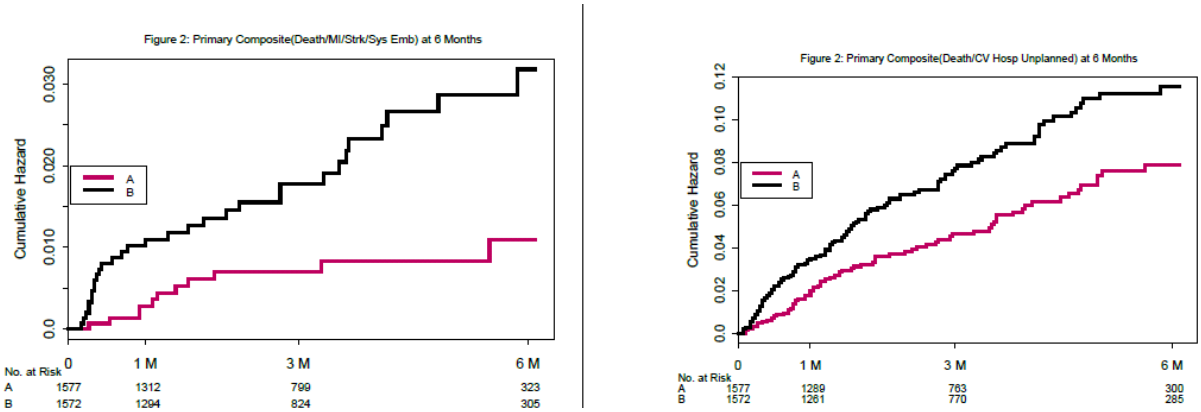

Figure 2 Kaplan-Meier curves for the primary composite (stroke, MI, systemic embolism and CV death) and the primary composite (death/CV unplanned hospitalization)
A=placebo, B=dronedarone

Overall, the results were mainly driven by a higher incidence of cardiovascular deaths, heart failure and stroke in the dronedarone as compared to the placebo group.

Cardiovascular death

More cases of CV death were reported in the dronedarone arm (n=15) than the placebo arm (n=6). These were mainly arrhythmic deaths or presumed cardiovascular deaths.

Table 7 Causes of CV deaths

Causes of death	Placebo	Dronedarone
	6	15
Cardiac arrhythmic	2	9
Heart failure	0	1
Other cardiac causes	2	0
Stroke	0	1
Other vascular	0	1
Presumed CV	2	3

An analysis of baseline characteristics with regard to cardiovascular medical history was performed. All point estimates of the HRs were ≥1 regardless of the covariates. Although the HR may sometimes be numerically higher in the absence or presence of certain covariates at baseline, the 95% confidence intervals always overlap and the interaction p-value is not significant except for NYHA class. However, no specific trend was observed and the number of events in some sub-groups (e.g. no CHF, class I and class III) is very low.

An analysis of baseline characteristics with regard to cardiovascular medications identified a single interaction at baseline. More cardiovascular deaths were reported in patients who were taking digoxin at baseline [HR=11.2 (95%CI: 1.43-85.8; p=0.015)]. This is consistent with a multivariate analysis done on all deaths that showed an interaction between treatment and digoxin use.

Table 8 Multivariate analysis on time from randomization to all cause death – PALLAS

Risk factor	Hazard ratio (95% CI)	p-value	Interaction with treatment p=
Treatment	2.35 (0.96,5.70)	0.060	-
Digoxin	2.58 (1.13,5.90)	0.024	0.092
INR<2 or no Vitamin K antagonist	3.31 (1.40, 7.84)	0.007	0.596

P<0.10 is significant

Among the patients who experienced cardiovascular death, 1 out of 6 patients in the placebo group and 11 out of 15 in the dronedarone group were receiving digoxin at baseline.

Digoxin has a narrow therapeutic index, some patients experiencing toxicity even when within the recommended range. It is generally recommended to keep digoxin serum levels within a range of 0.8-2 ng/mL. Although it is possible that a PK interaction between dronedarone and digoxin exists, resulting in a doubling of digoxin level in high risk patients leading to an arrhythmic death, in the individual cases of death due to cardiac arrhythmia levels were not higher than 2 ng/mL. Only one patient had a serum level of digoxin at day 7 of 3.8 ng/ml, but his death was not classified as arrhythmogenic. An alternative explanation could be that the patients on digoxin treatment might have had more serious dysfunction, digoxin not only being given for rate control but also for a positive inotropic effect.

Heart failure

The main results of this endpoint are shown below.

Table 9 Results of time to first hospitalization for heart failure in PALLAS

	Adjudication status 2 August[a]				
	Total	P	D	Hazard ratio (95% CI)	p-value
Time to first hospitalization for HF	51	16	35	2.21 (1.22 – 3.99)	0.0070
Time to first heart failure (any episode)	113	33	80	2.49 (1.66 – 3.74)	<0.0001

P=placebo, D=dronedarone

The analysis of baseline characteristics with regard to cardiovascular medical history on first hospitalization for HF showed that all hazard ratios were ≥1 regardless of the covariates. The interaction p-value is not significant except for coronary artery disease (CAD) (p=0.081). This result needs to be interpreted with caution because of the large number of analyses conducted without adjustment of the alpha risk for the multiplicity of tests.

In particular, there is no physiopathological reason to explain why dronedarone would have a more significant negative inotropic effect in patients with CAD. Although this could be an indirectly related variable (patients with coronary artery disease are more likely to have a low LVEF and therefore a higher risk of negative inotropic effect from dronedarone). The analysis specifically looking at LVEF does not support this as patients with low LVEF ≤40% did not have a higher risk of hospitalization due to HF.

With analysis on any type of heart failure, a significant interaction p-value was also observed for CAD (p=0.048)]. In addition, a significant p-value of interaction was found for the following risk factors: symptomatic HF at baseline, hypertension, history of stroke or TIA, CHADS2 score ≤2 or >2 and left atrium diameter; with, as compared to placebo, a high incidence of events in patients without hypertension, without history of stroke, with a CHADS2 score ≤2 or with a left atrium diameter >40 mm.

Overall, the results of the analyses presented above are consistent with the multivariate analysis done on any HF that found 10 risk factors to be predictive of the risk of any HF, some of them being closely related (eg symptomatic HF and NYHA class III). There was some evidence of interactions between treatment and hypertension, symptomatic heart failure at baseline, and coronary heart disease (p-values from 0.05 to 0.09).

Table 10 Multivariate analysis on time from randomization to first heart failure (any type) – PALLAS

Risk factor	Hazard ratio (95% CI)	p-value	Interaction with treatment p=
Treatment	2.44 (1.62,3.66)	<0.0001	-
CHD	1.69 (1.17,2.46)	0.006	0.087
PAOD	2.24 (1.39,3.62)	0.001	0.842
History of HF	1.62 (0.98,2.69)	0.061	0.725
Symptomatic HF	2.06 (1.31,3.23)	0.002	0.067
NYHA Class III	1.94 (1.14,3.29)	0.014	0.550
CHADS2 score >2	2.09 (1.34,3.27)	0.001	0.264
Calcium channel blocker	2.45 (1.50,4.00)	0.0004	0.560
Age >75 yr	1.65 (1.10,2.43)	0.016	0.224
Digoxin	0.63 (0.41,0.96)	0.034	0.258
Hypertension	0.60 (0.37,0.99)	0.044	0.057

P<0.10 is significant

Overall, the risk factors for which a significant effect was observed are related to the disease itself and its associated risk factors in a population with permanent AF.

Ischemic stroke

There were 17 patients in the dronedarone group and 8 patients in the placebo group who experienced a stroke while on study medication. In the dronedarone group, 9/17 strokes occurred within the first 2 weeks of treatment, whereas the majority of the strokes in the placebo group occurred after month 1. After 2 weeks, the proportion of patients who had a stroke was comparable between treatment groups.

No significant interaction was observed between treatment and relevant covariates at baseline except with digoxin use; a trend was observed for patients with less risk factors at baseline (age <75 years, CHADS2 score ≤2, no history of stroke) or with an INR ≤3 or no vitamin K antagonist (VKA).

Using the multivariate analysis, three risk factors were found to be predictive of time to first stroke: age <75 years, CHF NYHA class III, and INR<2 or no VKA. There was no evidence of any interactions with treatment.

Table 11 Multivariate analysis on time from randomization to first stroke – PALLAS

Risk factor	Hazard ratio (95% CI)	p-value	Interaction with treatment p=
Treatment	2.16 (0.93,5.02)	0.072	-
Age>75	0.47 (0.20,1.10)	0.081	0.697
NYHA Class III	3.07 (1.21,7.76)	0.018	0.360
INR<2 or No Vitamin K Antagonist	2.28 (1.02,5.13)	0.045	0.393

P<0.10 is significant

Data showed that overall, a large proportion of the PALLAS study population received anticoagulant and/or antithrombotic medications as per protocol and guidelines recommendation, and this appeared similar in both groups. However, dronedarone treated patients experiencing a stroke in the PALLAS study appeared to have suboptimal anticoagulation. Only 11/17 patients experiencing a stroke in the dronedarone group were on oral anticoagulants, compared to 6/7 patients in the placebo group. Among the patients with a $CHADS_2$ score >2 and no VKA at baseline, 1 patient in the dronedarone group experienced stroke versus 0 in the placebo group. In addition, a baseline INR below 2.0 was documented in 45.5% of dronedarone treated patients who experience a stroke versus 33.3% of placebo treated patients.

For those patients who experienced stroke, the median time in therapeutic range (TTR) was largely inferior in the dronedarone group (49.7%) as compared to the placebo group (61.0%). This is consistent with the results observed on time with INR<2 (median 36.8% versus 8.6% respectively). In addition, a TTR <50% was observed in 5 patients in the dronedarone group versus 1 in the placebo group. Among the 9 events that occurred within the first 2 weeks, most of the cases had INR values below 2 or fluctuating (no value at time of event).

Because of the anti-arrhythmic properties of dronedarone, it would be possible that even in this permanent AF population there may have been intermittent conversion to normal sinus rhythm. In the placebo group 16/1577 (1.0%) compared to 42/1573 in the dronedarone group (2.7%) developed sinus rhythm during the study (HR=2.678; 95%CI=1.506 to 4.763). If, for most of the other patients, the ECG performed at hospital admission for stroke did not show sinus rhythm, a transient conversion to sinus rhythm during the study cannot be excluded. However this theory is not further supported by individual data of the patients who did get a stroke (sinus rhythm was recorded in 1 patient treated with dronedarone at the time of hospital admission for stroke).

Safety Results

Adverse events (AEs) were generally in line with the known adverse event profile of dronedarone, with diarrhoea, nausea and vomiting, fatigue and asthenia as the most frequent. Rate and rhythm disorders were also reported with a higher frequency in the dronedarone group (n=47; 3.0% vs n=11; 0.7%), mainly driven by cases of bradycardia. AEs related to coagulation and bleeding analysis were also reported with higher frequency in the dronedarone group (n=13; 0.8% vs n=5; 0.3%), driven by INR increase (12 out of 13 cases). Overall, rates of SAEs, discontinuations, and deaths related to bleeding events were not imbalanced between treatment arms.

AEs related to renal function were more frequently reported in the dronedarone group (dronedarone n= 36; 2.3% vs 4 cases: 0.3%). Of these, 14 cases in the dronedarone group and 4 in the placebo group were classified as serious renal failure. One serious case in the dronedarone group had a fatal outcome, compared to none in the placebo group. Most of the serious cases developed in the context of heart failure.

Table 12 Treatment emergent adverse events reported under the high level term of 'renal function analysis' - PALLAS study

High level term (HLT) Preferred term (PT)	Placebo (N=1577)	Dronedarone (N=1572)
Renal function analyses	4 (0.3%)	36 (2.3%)
Blood creatinine increased	4 (0.3%)	31 (2.0%)
Blood urea increased	0	6 (0.4%)
Cystatin c increased	0	2 (0.1%)
Glomerular filtration rate decreased	0	2 (0.1%)
Creatinine renal clearance decreased	0	1 (<0.1%)
Glomerular filtration rate abnormal	0	1 (<0.1%)
Renal function test abnormal	0	1 (<0.1%)

Of note, in clinical studies an increase in plasma creatinine has been observed with dronedarone. This is explained by a reduction of tubular secretion of creatinine without an effect on glomerular filtration rate, and is not indicative of deterioration of renal function.

Breathing abnormalities were reported more frequently in the dronedarone arm (n=62) in comparison to the placebo arm (n=25).

Table 13 Adverse events reported under the high level term of 'breathing abnormalities'- PALLAS study - 30 June 2011

High level term (HLT) Preferred Term (PT)	Placebo (N=1577)	Dronedarone (N=1572)
Breathing abnormalities	25	62
Dyspnoea	17	53
Dyspnoea exertional	4	7
Sleep apnoea syndrome	3	2
Orthopnoea	0	2
Respiratory distress	1	0

The majority of patients with breathing abnormalities were reported to have dyspnea or exertional dyspnea (placebo 21/25 and dronedarone 59/62).

There were 2 serious adverse events of dyspnea and respiratory distress in the placebo group and 1 serious adverse event of dyspnoea in the dronedarone group, all 3 events were reported as 'not related to investigational product'. Of the patients in the placebo group with adverse events of dyspnea, 2 patients also reported CHF during the study and none reported interstitial lung disease (ILD). Of the patients in the dronedarone group with adverse events of dyspnea, 2 patients also reported CHF during the study and none reported ILD.

The reported dyspnea events did not seem to be associated with a diagnosed heart failure. Further review of the patient profiles available for the dronedarone group revealed that a majority (35/62) of the patients had concurrent symptoms of either fluid retention, or required adjustment of a diuretic or other medication/intervention, experienced an increase in the NYHA functional classification, or experienced a concurrent illness that contributed to 1 of the events under breathing abnormalities. A review of the patient profiles available for the placebo group revealed similar findings for 7 of the 25 patients.

In the PALLAS study, liver function tests (ALT, AST, and total bilirubin) were to be monitored at baseline, day 7 and months 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 22, 28, and 34, as well as at the final follow-up visit. More dronedarone-treated patients than placebo patients reported hepatobiliary adverse events in the PALLAS study, 4.0% versus 1.8% respectively. The most common event was

alanine aminotransferase increased, 1.6% on dronedarone and 0.6% on placebo. The only serious event in the placebo group was alanine aminotransferase elevation. In the dronedarone group acute hepatic failure, hepatitis, acute cholecystitis, and cholelithiasis were also serious.

Table 14 Overview of treatment emergent Liver related investigations, signs and symptoms or treatment emergent adverse events (TEAE) in SOC hepatobiliary disorders

	Placebo (N=1577)	Dronedarone (N=1572)
Patients with any TEAE	28 (1.8%)	63 (4.0%)
Patients with any serious TEAE.	3 (0.2%)	11 (0.7%)
Patients with any TEAE leading to Death	0	0
Patients permanently discontinued study drug for any AE	3 (0.2%)	9 (0.6%)

PGM=DEVOPS/SR33589/EFC11405/CIR_01/REPORT/PGM/teae_liveroverview_s_t.sas OUT=REPORT/OUTPUT/teae_liveroverview_s_t_i.rtf (28JUL2011 - 17:29)

Results showed an increase in the mean (5.3) and median (2.0) ALT within 7 days of initiation of dronedarone and AST showed and increase in the mean (1.6) within 7 days and median (1.0) within 16 to 45 days. There were no such increases in the placebo group. Bilirubin mean and median showed no change in either group.

A greater percentage of patients in the dronedarone group had ALT elevations >3 ULN and >5 ULN, while increases >10 ULN were more evenly distributed. The frequencies are the same for total bilirubin. The onset for most of the adverse events was within the first 30 days (hazard ratio = 2.42, 95%CI = 1.55-3.78, p=0001). Only 4.4% of patients in the dronedarone group with CHF or hepatic event experienced two conditions simultaneously, and none in the placebo group.

ALT ≥3 ULN was an AE with prespecified monitoring, and it occurred more frequently in the dronedarone group than in the placebo group (n=27; 1.7% vs n=9; 0.6%). More of the events in the dronedarone group were serious, 10 compared to 1 in the placebo group.

Overall, rates of SAEs, discontinuations, and deaths related to bleeding events were not different between the dronedarone group when compared to the placebo group. No trends were evident for specific bleeding event Preferred Terms (PT) or among specific System Organ Classes (SOC).

Table 15 Overview of treatment emergent haemorrhage event - All randomized patients in the PALLAS study as of June 30, 2011

	Placebo (N=1577)		Dronedarone (N=1572)	
Patients with any TEAE	30	(1.9%)	32	(2.0%)
Patients with any serious TEAE.	6	(0.4%)	9	(0.6%)
Patients with any TEAE leading to death	0		1	(<0.1%)
Patients permanently discontinued study drug for any AE	1	(<0.1%)	1	(<0.1%)

Comparison between the PALLAS and ATHENA studies

As shown in table 16, in the population of patients with permanent AF included in the PALLAS study the proportion of patients with coronary artery disease, age ≥75 years (in particular with associated hypertension and diabetes), prior stroke or TIA, CHF, LVEF ≤40%, was higher than in the ATHENA population. All these are important recognized risk factors associated with poorer prognosis in patients with heart disease.

Table 16 Baselines characteristics of the PALLAS and ATHENA populations

	ATHENA (overall)		PALLAS	
	Placebo	Dronedarone	Placebo	Dronedarone
Age, mean	71.7	71.6		
Age, 65-75 yr	39%	40.1%	48.2%	48.4%
Age, ≥75 yr	42%	41.2%	51.8%	51.5%
Gender, male	55.4%	50.8%	64.6%	65.6%
Risk factors, number				
0	60.9%	63.5%	1.7%	0.7%
1	33.2%	31.1%	70.1%	69.2%
2	5.2%	4.9%	21.1%	24.0%
≥3	0.7%	0.5%	7.1%	6.1%
Risk factors				
Coronary artery disease	31.3%	28.7%	40.8%	41.2%
Prior stroke or TIA	7.1%	7.3%	27.7%	26.2%
Symptomatic heart failure			16.0%	17.0%
LVEF ≤40%	4.7%	4.2%	20.1%	20.7%
PAOD			12.6%	11.6%
Age ≥75 years with hypertension and diabetes	2.7%	2.1%	17.7%	19.7%
Patients with CHF	29.8%	29.2%	68.5%	69.1%
Class I	7.6%	9.0%	13.9%	14.9%
Class II	17.4%	16.2%	46.9%	46.0%
Class III	4.7%	4.0%	7.6%	8.2%

The results obtained in both ATHENA and PALLAS on the 2 coprimary endpoints of PALLAS, and their components (cardiovascular death and stroke), as well as on time to first hospitalization for HF and on time to any heart failure are summarized in the table below. Further analysis shows that using the investigated endpoints in PALLAS, significant benefit would still be shown in the ATHENA population.

Table 17 Main efficacy results - PALLAS and ATHENA studies

	ATHENA		PALLAS	
Time to first stroke, MI, SE, CV death[a]	0.681	(0.552 – 0.839)	2.16	(1.17 – 3.99)
Time to CV death	0.698	(0.509 – 0.958)	2.53	(0.98 – 6.53)
Time to first stroke	0.660	(0.455 – 0.957)	2.14	(0.92 – 4.96)
Time to first ACS	0.711	(0.521 – 0.97)		
Time to first MI			1.01	(0.20 – 5.01)
Time to first CV hospitalization or death	0.758	(0.688 – 0.835)	1.62	(1.20 – 2.17)
Time to death	0.844	(0.660 – 1.080)	2.31	(0.95 – 5.62)
Time to first CV hospitalization	0.745	(0.673 – 0.824)	1.56	(1.15 – 2.12)
Time to first hospitalization for heart failure	0.855	(0.665 – 1.100)	2.21	(1.22 – 3.99)
Time to first heart failure (any)[b]	1.080	(0.923 – 1.265)	2.49	(1.66 – 3.74)

In the ATHENA study, analyses of time to cardiovascular death, time to first stroke or heart failure (first hospitalisation or any heart failure) by baseline cardiovascular medical history or baseline cardiovascular medications did not find significant interactions with treatment effect.

PALLAS study overview and discussion

The PALLAS study was performed in a group of patients different than that of the currently approved indication for dronedarone, with permanent AF and more risk factors. There was no significant difference between both arms of the study with regards to baseline characteristics. As in the case of the previous ANDROMEDA study, it was discontinued prematurely because the HR of the primary endpoint was significantly increased in the dronedarone group compared to placebo (first composite of

stroke, myocardial infarction, systemic embolism or cardiovascular death, HR=2.16 (95%CI: 1.17-3.99; p=0.0117); second composite of first unplanned cardiovascular hospitalization and death from any cause, HR=1.62 (95%CI: 1.20-2.17; p=0.0013). Time to first CV death, time to first stroke and time to first CV hospitalization were reported with HR=2.53 (95%CI: 0.98-6.53); HR=2.14 (95%CI: 0.92-4.96) and HR=1.56 (95%CI: 1.15-2.12), respectively.

This imbalance of events is observed within 2 weeks of dronedarone administration due to a higher incidence of stroke and first hospitalisation for HF. No single risk factor was consistently shown to statistically impact the different outcomes; some analyses showed possible links to NYHA class, LVEF ≤ 35%, history of HF and CAD. However, baseline characteristics of the population clearly indicated that the PALLAS population was associated with more risk factors and poorer prognosis than the patients with non-permanent AF recruited in the ATHENA study, and for which dronedarone is currently approved. The prevalence of the different co-morbidities in the ATHENA trial was lower than that in the PALLAS trial. Further analysis shows that using the investigated endpoints in PALLAS, significant benefit would still be shown in the ATHENA population. No consistent risk factors were shown to negatively impact these benefits.

The likely cause of the higher reported heart failure cases in the dronedarone group could be the negative inotropic effect of dronedarone in particular when co-administered with beta-blockers or non-dihydropyridine calcium channel blockers in predisposed patients. A possible contributing factor of the increased CV mortality in the dronedarone group could be the PK interaction between dronedarone and digoxin in susceptible patients, but this could not be proven and is not supported by the data from the ATHENA study. The use of digoxin per se might indicate a more serious haemodynamic dysfunction. The increased stroke incidence could be related to under utilization of oral anticoagulants in the dronedarone group, although a direct relationship could not be established.

Based on the data from the PALLAS study on renal safety, it would be appropriate to provide further information to prescribers on what degree of elevation of serum creatinine may be expected, and timepoints at which the tests should be performed in order to allow distinction between cases of elevated serum creatinine due to inhibition of tubular creatinine secretion (where a plateau would be reached) and cases of 'true' renal failure (where serum creatinine would continue to increase).

2.1.2. Hepatic safety

Clinical trial data

As of 31 July 2010, the dronedarone clinical program included an assessment of 67 controlled studies, involving a total of 9067 patients and healthy subjects. Of these, 5317 received dronedarone.

In the pool of placebo-controlled clinical studies conducted in patients with AF/AFL, the incidence of hepatic adverse events observed in patients receiving dronedarone was similar to that observed with placebo.

Table 18 Overview of the SOC 'hepatobiliary disorders' and SMQ 'liver related investigation signs ans symptoms' adverse events (number [%] of patients) - all randomised and treated patients with AF/AFL

	Placebo (N=2875)		Dronedarone 400 mg BID (N=3282)	
Treatment emergent adverse events	73	(2.5%)	95	(2.9%)
Serious treatment emergent adverse events	29	(1.0%)	28	(0.9%)
Adverse events leading to premature study drug discontinuation	7	(0.2%)	10	(0.3%)
Serious treatment emergent adverse events leading to hospitalization	26	(0.9%)	28	(0.9%)
Serious treatment emergent adverse events leading to death	2	(<0.1%)	1	(<0.1%)

Note: Selected events using : System organ class "HEPATOBILIARY DISORDERS" or SMQ "LIVER RELATED INVESTIGATIONS SIGNS and SYMPTOMS" broad + narrow selection
Note: protocols : DRI3550/DAFNE, EFC3153/EURIDIS, EFC4788/ADONIS, EFC4508/ERATO, EFC5555/ATHENA
PGM=DEVOPS/SR33589/OVERALL/NDAQSMHR_P/REPORT/PGM/i7AEEDAae_aehepat_overview.sas
OUT=REPORT/OUTPUT/i7AEEDAae_aehepat_overview_i.rtf (18MAR2011 - 16:15)

Table 19 Number (%) of patients with at least 1 potentially clinically significant abnormality in liver function (AST, ALT) - on-treatment period (post-baseline up to the end of treatment plus 10 days)- all randomized and treated patients with AF/AFL (except ATHENA)

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

ULN: Upper Limit of Normal

PGM= SR33589/OVERALL/SCSMHR/BS/PGM RPT/i8AEEDbiooutlivgr.sas OUT= OUTPUT/I8AEED biooutpcsalivgr.html (07MAY2008 - 10:43) - Denominator refers to patients with post baseline value for the parameter

The DIONYSOS study was a comparative study with amiodarone 600 mg/200 mg.

Amiodarone is a lipophilic drug that concentrates in and is metabolized by the liver. Long-term treatment with oral amiodarone can cause a full spectrum of hepatic side effects, from an asymptomatic increase in transaminase levels, observed frequently (i.e., up to 46.8% of patients), to less frequent chronic symptomatic liver toxicity such as nonalcoholic steatosis, which can lead to cirrhosis. The typical oral amiodarone toxicity is usually detected in studies lasting more than one year. Overall, in patients treated with amiodarone, the incidence of hepatic disorders varies depending on the definition of outcome of interest, follow-up time, and maintenance dose, among other factors.

The table below presents an overview of the SOC 'hepatobiliary disorders' and SMQ 'liver related investigation signs and symptoms' in DIONYSOS. The incidence in the dronedarone group was higher (8.8%) than in the amiodarone group (5.5%).The proportion of serious events was the same in the 2 groups, and the proportion of hepatic events leading to hospitalization was lower in the dronedarone group, with no deaths in either group. The majority of these events were liver function analysis abnormalities occurring in 7.2% and 4.3% of patients in the dronedarone and amiodarone groups, respectively.

Table 20 Overview of SOC 'hepatobiliary disroders' and SMQ 'liver investigation signs and symptoms' adverse events (number [%] of patients) - all randomised and treated patients in DIONYSOS

	Dronedarone 400 mg BID (N=249)		Amiodarone 600 mg/200 mg OD (N=255)	
Treatment emergent adverse events	22	(8.8%)	14	(5.5%)
Serious treatment emergent adverse events	2	(0.8%)	2	(0.8%)
Adverse events leading to premature study drug discontinuation	7	(2.8%)	6	(2.4%)
Serious treatment emergent adverse events leading to hospitalization	0	(0.0%)	2	(0.8%)
Serious treatment emergent adverse events leading to death	0	(0.0%)	0	(0.0%)

PGM= SR33589/EFC4968/NDAMHR P/BS/PGM RPT/i7DIOeventHepat.sas OUT= OUTPUT/I7DIO eventHepat.html (04MAR2009 - 11:41)

Note: Selected events using: SMQ "liver related investigation signs and symptoms" or SOC "hepatobiliary disorders" broad + narrow selection

Note: Protocols: EFC4968 (DIONYSOS)

AE = adverse event; BID = twice daily; OD = once daily, TEAE = treatment-emergent; SMQ = standard MedDRA query; SOC = system organ class

In DIONYSOS, a specific predefined analysis of patients with at least one increase in transaminase levels, defined as alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) more than 2 x the upper limit of normal (ULN) and more than 0.5 x ULN from the baseline value, was conducted. This parameter was monitored as a component of the predefined main safety endpoint, the other components being thyroid, neurologic, skin, eye, and gastrointestinal events. The results were

comparable in the dronedarone and the amiodarone groups, with no increased incidence in the dronedarone group compared with amiodarone and no evidence of an earlier occurrence.

The incidence of increased ALT/AST, defined as at least one value above 2, 3, or 5 x ULN, in the placebo and dronedarone groups in all clinical studies (except ATHENA) shows a high degree of variability across studies but with no statistical significant evidence of an increased risk with dronedarone compared with placebo group.

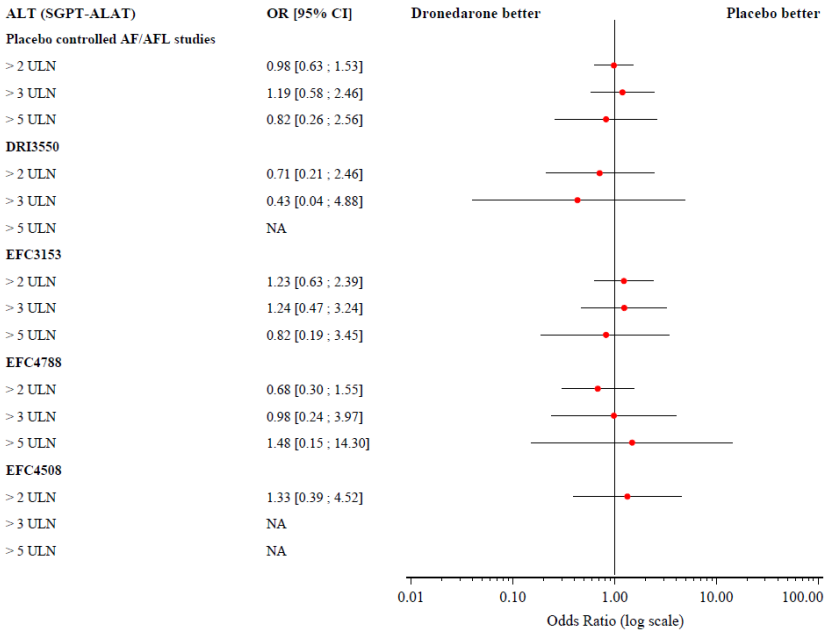

Figure 3 Odds ratio (dronedarone 400 mg BID versus placebo) and 95% confidence interval for incidence of potentially clinically significant abnormalities in ALT – all randomised and treated patients in placebo-controlled AF/AFL studies except ATHENA

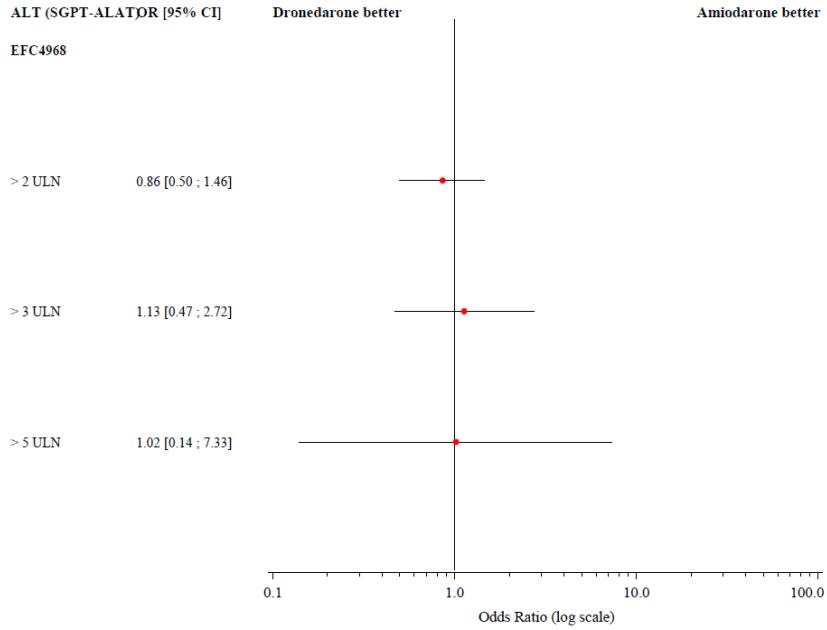

Figure 4 Odds ratio (dronedarone 400 mg BID versus amiodarone 600/200 mg OD) and 95% confidence interval for the incidence of potentially clinically significant abnormalities for ALT – all randomised and treated patients in DIONYSOS

The different study designs, and in particular the difference in the number of blood samples for ALT/AST assessment may have contributed to the difference in the incidence of ALT/AST abnormalities.

The incidence of hepatic events (i.e., adverse event or ALT ≥5 x ULN), together with their odds ratios, in the placebo and dronedarone groups in all clinical studies conducted in patients with AF/AFL show that there is a high degree of variability across studies, with no evidence of an increased risk with dronedarone compared with placebo, as none of the confidence intervals excluded 1.

In DIONYSOS, a greater number of adverse events occurred in the dronedarone group than in the amiodarone group. However, the corresponding odds ratio (1.67 [95% CI: 0.83; 3.34]) does not allow to conclude that there is a significant difference between the 2 agents with respect to hepatic events.

Overall, in patients treated with amiodarone, the incidence of hepatic disorders varied depending on the definition of outcome of interest, follow-up time, and maintenance dose, among other factors. The low incidence of liver adverse events reported in the amiodarone group in DIONYSOS may be explained by the relatively short follow-up period (median 7 months).

This may explain why dronedarone could appear similar to placebo in the placebo-controlled studies and similar to amiodarone in DIONYSOS. It should be noted that the duration of follow-up in dronedarone-placebo studies was not longer than in DIONYSOS.

A quantitative analysis of changes from baseline in ALT and AST was performed for all clinical studies excluding ATHENA (in which there was no systematic monitoring of ALT/AST). No significant change from baseline was observed when compared with controls. No significant effect was demonstrated between dronedarone and either amiodarone or placebo.

In the PALLAS study, mean and median ALT changed from baseline within 7 days of initiation of dronedarone by 5.3 and 2.0 x ULN, respectively. Mean AST changed from baseline by 1.6 x ULN within 7 days and median AST by 1.0 x ULN within 16 to 45 days. There were no such increases in the placebo group. Bilirubin mean and median showed no change in either group. The increases in ALT and AST persisted throughout treatment. More patients in the dronedarone group had potentially clinically significant abnormalities for ALT and AST. The frequencies are the same for total bilirubin. There were more hepatic events in the dronedarone group (63) than in the placebo group (28) and the onset for most of them was within the first 30 days (HR=2.42; 95%CI=1.55-3.78, p=0001). Congestive heart failure appeared to be a risk factor for hepatobiliary events. There were 6 patients with both a hepatic event and CHF and 3 patients with CHF before the hepatic event in the dronedarone group.

Post-marketing data

In the period from launch of dronedarone to 30 June 2011, a total of 725 cases pertaining to liver disorders and coded either under the SOC Hepatobiliary disorders or the HLGT Hepatobiliary Investigations have been reported, with an estimated exposure of 215 000 patient years.

Among these 725 cases, 391 cases were assessed as serious. Hepatocellular injury (n=174) was reported most frequently followed by jaundice (n=34) and hepatitis (n=33). In the investigations SOC, the top five terms reported were alanine aminotransferase increased (n=198), Gamma-glutamyltransferase increased (n=160), aspartate aminotransferase increased (n=158), transaminases increased (n=136) and hepatic enzyme increased (n=120).

Of the 168 serious cases with known times of onset, 91 had an onset within 30 days of initiating dronedarone. More than half of the 184 cases with known peak ALT had a peak ALT>10 ULN (102/184). Of these 55 had an onset within 30 days, 35 had an onset >30 days and for 12 the onset was unknown.

The following table summarizes the two cases where a hepatic transplant was needed. In both cases the investigation could not find an alternative explanation for the hepatocellular injury developed.

Table 21 Cases of serious hepatic injury leading to liver transplantation

Age / Sex	Preferred Terms	Comments
69 / female	Acute hepatic failure, Asthenia, Jaundice, Chromaturia, Abdominal pain, Hepatic encephalopathy, Hepatocellular injury	Onset 5.5 months, ALT 62.9 ULN, hepatocellular injury, history of hypertension and coronary artery disease, atrial fibrillation, concomitant statin, presented with hepatic encephalopathy, total bilirubin 28 mg / dL, and required a liver transplant. 4-5 months later she was discharged for further rehabilitation. Workup failed to reveal an alternative explanation.
72/ female	Hepatic failure, Hepatic enzyme increased, Blood bilirubin increased, Coagulopathy, International normalised ratio increased	Onset 6 months, ALT 76 ULN, hepatocellular injury, history of paroxysmal atrial fibrillation, Sjogren's syndrome, presented with weakness abdominal pain and increased Coumadin levels, bilirubin 6.3 mg, dL, developed acute liver failure requiring transplantation, biopsy showed fulminant hepatitis with 75-80% hepatocyte loss. She recovered within 2 months. Workup failed to reveal an alternative explanation

Pharmacokinetic and non-clinical data

In comparison with amiodarone, dronedarone has a different pharmacokinetic profile with a shorter half-life and decreased lipophilicity owing to the introduction of methane-sulfonamyl group, leading to lower tissue accumulation.

Table 22 Comparative pharmacokinetic data of dronedarone and amiodarone

	Amiodarone	Dronedarone
Bioavailability	46 ± 22%	15%
Protein binding	99.9%	99.7%
Metabolism	primarily CYP3A4	primarily CYP3A4
Major metabolites	Desethylamiodarone (activity similar to amiodarone in animals)	SR35021, N-debutyl metabolite (10% to 30% activity) SR90154, O-propanoic acid
Half-life	25±12 days	1.25 days
Time to steady-state	130 to 535 days	4 to 8 days
Mean steady-state Cmax value	2 to 3.5 µM (at 400 mg daily)	0.15 to 0.3 µM (at 400 mg BID)
Liver/plasma ratio (rats treated at 50 mg/kg/d)	11	2.5
Elimination	primarily metabolism and biliary excretion, minimal excretion in urine	primarily metabolism and biliary excretion, no renal excretion

A preclinical program was initiated to investigate the potential mechanisms of hepatotoxicity induced by dronedarone using amiodarone as a comparator. Since the cellular alterations noted in vitro are not fully predictive of hepatic injury in vivo, additional in vivo studies will be performed to better understand the potential liver toxicity of dronedarone.

Preliminary data available during this review indicated that dronedarone and its metabolites were cytotoxic to rat primary hepatocytes, impaired the mitochondrial respiration and triggered the generation of superoxide anions. In comparison with amiodarone, dronedarone, its mono-debutyl metabolite and the desethyl metabolite of amiodarone were more cytotoxic. The deaminodibutyl carboxy metabolite of dronedarone was not cytotoxic. It also appeared that glutathione plays only a

minor role in dronedarone's cytotoxic mechanism. Impairment of mitochondrial respiration occurred by uncoupling and inhibition, for amiodarone and its desethyl metabolite at all concentrations tested, whereas for dronedarone and two metabolites (mono-N-debutyl and deaminodibutyl carboxy) uncoupling occurred at low concentrations and inhibition through another mechanism at high concentration.

In addition dronedarone and two metabolites were inducers of phospholipidosis. In the assay performed amiodarone was more potent than dronedarone, and desethylamiodarone was more potent than mono-debutyldronedarone and deaminodibutyl carboxydronedarone.

Data currently available on studies conducted in rats and dogs receiving dronedarone for 2 weeks shows no signs suggestive of toxicity mediated by an immune response. However the data available is limited so the potential for an immune-related mechanism of toxicity needs be further evaluated.

Hypoxia

Hypoxic hepatitis tends to occur in patients with a profile of cardiac disease, coronary artery disease, arrhythmia, episode of arterial hypotension (not required), episode of respiratory failure (not required). It has a better prognosis with less risk of fatal liver failure even when blood clotting tests are altered.

Given the current indication of dronedarone, there is a reasonable possibility that it will be given to patients who are at high risk of hemodynamic instability, particularly during the initiation of therapy before their arrhythmia is controlled. Published literature confirms that all three patterns of liver injury (hepatocellular, mixed or cholestatic) may occur in such situations. In patients with a profile of cardiac disease, findings from the literature show that, when available information is present, ischemia and/or congestion of the liver could be one of the plausible explanations for the hepatic signs.

Co-administration of potentially hepatotoxic drugs

Adverse event cases pertaining to liver disorders have been analysed for presence of at least one concomitant or co-suspect drug. In a number of cases (including serious and non serious) at least one concomitant or co-suspect drug was found, including widely used drugs in this patient population such as oral anticoagulants, beta-blockers, calcium-channel antagonists, ACE inhibitors, lipid-lowering drugs or diuretics. Due to the limitations of post-marketing data, precise treatment dates for these drugs were rarely provided, but in most instances it was assumed that they had been used as long term treatment. The limited information available in most cases makes it difficult to assess the role of the drug interaction.

Auto-immune co-morbidity

The dronedarone cumulative safety data up to the 31 January 2011 included 27 reported cases in patients with an autoimmune disorder (e.g. Sjögren's syndrome, systemic lupus erythematosus, diabetes mellitus type I, autoimmune thyroiditis including Grave's disease and Hashimoto's thyroiditis, Crohn's disease/ulcerative colitis, glomerulonephritis) listed as concomitant disease or in the medical history. Among the 27 cases retrieved, only 4 serious cases reported a hepatobiliary disorder. This information is not suggestive that the presence of an auto-immune disease would increase the risk or seriousness of an hepatotoxic reaction induced by dronedarone.

Time to onset

The postmarketing liver safety events of greatest interest occurred between 1 and 6 months from initiation of treatment with dronedarone. In particular, the two cases which have been associated with liver transplantation exhibited a delay of 5-6 months. Similarly, the case with the highest causality grade (classified as 'probable' by a panel of liver experts) exhibited the same delay (case without liver failure).

Thirty (30) cases of hepatocellular injury with an onset within 30 days of dronedarone initiation were reported up to 31 January 2011. Follow-up information for these cases was received until 30 June 2011. Of the 30 serious cases, 13 were in males and 17 were in females, the mean age was 71 years (range from 45 to 86 years). There were 7 cases with ALT >20 times the upper limit of normal (ULN) and 9 with ALT between 10 and 20 x ULN. The table below is a summary of the cases by peak ALT elevation as the multiple of ULN, and the day of onset.

Table 23 ALT elevation and time of onset

	ALT ≥ 20 ULN	ALT≥ 10 -<20 ULN	ALT ≥5 - <10 ULN	ALT <5 ULN	ALT UNK ULN
Day 1				1	
Day 2	1	3		1	
Day 3		1	1		1
Day 5	1				
Day ≤7	2	1	1		1
Day 8-15	1	1	2		
Day 16-30	2	3	3	2	1

Eleven of the 15 cases with onset within ≤7 days of dronedarone initiation appeared to have hypoxic hepatitis based on a history of or adverse event of congestive heart failure, reported LVEF ≤25%, shock, hypotension, hypovolemia (dehydration), or AST >ALT. Ischemic hepatitis accounted for 2 of 4 cases from day 8 to 15 and 6 of 11 from day 16 to 30. There were additional confounding factors such as previous amiodarone treatment or concomitant statin administration in 7 cases. One of the cases had too limited information to allow interpretation. A total of 22 patients recovered or were recovering, 2 had not recovered, 4 died (3 of shock related to infection and 1 of unknown cause).

Most of the cases of post-marketing hepatocellular injury with an onset of less than or equal to 30 days may have alternate explanations, however there does seem to exist a pattern of association between early hepatocellular injury due to ischemic hepatitis and heart failure, given that 50% of the post-marketing cases had an onset of ≤7 days. ALT elevations in the PALLAS study showed a similar pattern.

Hepatic safety overview and discussion

The incidence of serious hepatic events with dronedarone does not seem to differ from the placebo-controlled studies. In a study comparing dronedarone with amiodarone, the incidence of hepatic events was similar. However, because of the small duration of follow-up in most placebo-controlled studies, the risk of hepatic disorders for dronedarone may actually be higher than what is observed and, in any case, does not seem to be lower than that of amiodarone.

Mechanistic *in vitro* toxicology studies indicate that dronedarone and its metabolites is cytotoxic to rat primary hepatocytes, impairs the mitochondrial respiration and triggers the generation of superoxide anions. In addition dronedarone and two metabolites (mono-N-debutyl and deaminodibutyl carboxy) are inducers of phospholipidosis.

The currently available evidence does not indicate that liver toxicity as observed in patients and animals is immune-mediated. However, not all potential pathways related to immune-mediated hepatotoxicity have yet been studied. Further investigations, including planned and ongoing studies on the formation of reactive metabolites and a toxicogenomic study need to be performed.

Several risk minimisation activities were implemented following a CHMP review in January 2011. This led to a recommendation that initial monitoring of liver enzymes should be done before the start of treatment, followed by monthly monitoring for six months, at months 9 and 12, and periodically thereafter.

When considering the cumulative experience, the 2 liver transplant cases have remained exceptional in their clinical setting and outcome. For none of them causal relationship with dronedarone could be clearly evidenced or ruled out (both were considered possibly/probably related by the expert consultants).

The latest analysis of cases of hepatotoxicity with an onset within 30 days of starting treatment indicates that 50% of the events occur during the first 7 days of treatment. Therefore patients on dronedarone require closer monitoring of liver enzymes during the first month of treatment. The CHMP considers that additional pharmacovigilance activities are required to provide clarification on the mechanism of hepatotoxicity, and therefore the MAH will conduct non clinical mechanistic studies, surveillance and pharmacoepidemiological studies, a pharmacogenomic study and extend existing nested case-control studies to further elucidate this issue. These additional pharmacovigilance activities have been included in the Risk Management Plan.

2.1.3. Pulmonary safety

Clinical trial data

Up to 6 June 2011, clinical trials with dronedarone included 9097 patients and healthy subjects, of which 5346 received dronedarone. No cases of interstitial lung disease (ILD) or pulmonary toxicity were identified in healthy volunteers exposed to dronedarone. In placebo-controlled studies in 6285 patients with atrial fibrillation/atrial flutter, 0.6% (21/3282) of patients in the dronedarone group had pulmonary events of interest, including 3 cases of ILD, 2 of pneumonitis and 2 of pulmonary fibrosis, versus 0.8% (22/ 2875) of patients treated with placebo who developed pulmonary events of interest, including 1 case of ILD, 1 of pulmonary toxicity, 1 of pneumonitis and 2 of pulmonary fibrosis. All 3 patients with ILD in the dronedarone group had a history of prior exposure to amiodarone. There was no case of ILD, pulmonary fibrosis or pulmonary toxicity reported in 2812 patients exposed to dronedarone in other studies and indications.

As of 30 June 2011, the incidence of pulmonary toxicity events in the PALLAS study was 0.4% in the dronedarone group and 0.6% in the placebo group. Pneumonitis and pulmonary fibrosis were reported by 1 patient (each) in the placebo group. None of these preferred terms were reported in the dronedarone group.

Post marketing data

There have been post-marketing reports of ILD in patients treated with dronedarone. Until 6 June 2011, a total of 40 cases of suspected ILD, including 5 with fatal outcome, had been reported post-marketing in a timeframe which corresponds to approximately 195,000 patient-years of exposure. Of these 40 cases, most had confounding factors such as CHF, infection, chronic renal failure and other underlying diseases. In 20 cases, the main confounding factor was previous exposure to amiodarone, with reported knowledge of prior amiodarone pneumonitis in 9 cases. Causal involvement of dronedarone mainly based on chronology of facts was considered as possible in 5 cases and probable in 1 case of ILD. In some of the cases reported close temporal relationship, dechallenge and rechallenge were noted.

Pre-clinical data

Based on the mechanism of action, there are similarities between dronedarone and amiodarone with respect to pulmonary toxicity. Amiodarone-induced pulmonary toxicity is characterized by alveolitis and interstitial inflammation and followed by pulmonary fibrosis. These changes are caused by amiodarone itself, or by its active metabolite N-desethylamiodarone, which also exhibits cytotoxicity and tends to accumulate in the lung more intensively than amiodarone. The underlying pathophysiology is not completely clear, but several mechanisms have been implicated[1]. Of these mechanisms, phospholipidosis, cytotoxicity and apoptosis have received attention as primary causes of amiodarone-induced pulmonary toxicity.

Dronedarone has a different pharmacokinetic profile to that of amiodarone, with a shorter half-life and decreased lipophilicity leading to lower tissue accumulation. The lower accumulation of dronedarone in the lung would suggest a lower potential of dronedarone to induce lung toxicity *in vivo*. In preclinical studies, the effects of dronedarone on the lung have been observed in rats, mice, dogs and guinea pigs. In rats, toxicological findings in the lungs were limited to phospholipidosis at 3-6 times of clinical exposure levels. No compound-related histopathological findings were noted in the lungs of mice and dogs treated orally in the tested dose range (>7 up to >20 times human exposure, respectively). These data point to a sufficient safety margin for humans. However, this margin may be debatable, considering that not only dronedarone but also two of its metabolites have cytotoxic properties. There is insufficient information on whether there is a dose-response relationship for the pulmonary effects observed with dronedarone in rats and dogs.

[1] Kapatou E et al. Amiodarone attenuates apoptosis, but induces phospholipidosis in rat alveolar epithelial cells, J Physiol Pharmacol 6, 671-677, 2010.

Preliminary results of ongoing studies on the potential of dronedarone on hepatoxicity also point to similarities on toxic effects of dronedarone and amiodarone at cellular level (phospholipidosis, cellular toxicity, mitochondrial toxicity). Further investigations on the formation of reactive metabolites are ongoing however, from the data obtained so far, it can be concluded that the potential of dronedarone (and two of its metabolites) and amiodarone (and one of its metabolites) to induce phosphoslipidosis and cell death by mitochondrial disruption is an important risk factor of these drugs, that may not only contribute to the development of hepatotoxicity, but also to the development of pulmonary fibrosis. From available preclinical data it is not possible to estimate whether this risk is higher for dronedarone than for amiodarone. There is insufficient information about the possible mechanisms by which dronedarone can cause pulmonary toxicity and about the similarities and differences with amiodarone in these aspects.

Pulmonary safety overview and discussion

In the PALLAS study, pulmonary toxicity was observed less frequently in the dronedarone group compared with placebo. The remaining trials also did not indicate higher risk of pulmonary toxicity associated to dronedarone. However, cases have been reported in the post-marketing setting and in some cases close temporal relationship, dechallenge and rechallenge were observed. This is suggestive of an association with dronedarone. While some of the cases may be confounded by previous amiodarone use, in other reports there was no history of amiodarone use. The pre-clinical data available is insufficient to clarify the effect of dronedarone in respect of pulmonary toxicity, but it is possible that amiodarone and dronedarone share the same mechanism of toxicity.

2.2. Pharmacovigilance

Risk management plan

The applicant submitted an updated risk management plan.

Summary of the risk management plan:

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Heart Failure (including use in patients with unstable hemodynamic conditions with history of, or current heart failure or left ventricular systolic dysfunction)	Routine pharmacovigilance Dronedarone utilization program to assess the effectiveness of risk minimisation activities	Labeling: Contraindication to use these patients in section 4.3 of the SmPC and Special warnings and precautions for use in section 4.4 of the SmPC Additional risk minimisation program : Direct Healthcare Professional Communication letter, Prescriber Checklist and Multaq Information Card.
Permanent atrial fibrillation defined as an AF duration ≥ 6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician	Routine pharmacovigilance Dronedarone utilization program to assess the effectiveness of risk minimisation activities	Labeling: contraindication to use in these patients in section 4.3 of the SmPC and Special warnings and precautions for use in section 4.4 of the SmPC. Additional risk minimisation program: Direct Healthcare Professional Communication letter, Prescriber Checklist and Multaq Information Card.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Drug-Drug Interactions with potent CYP3A4 inhibitors	Routine pharmacovigilance EU Cross-sectional surveys (CRONOS) THIN and LabRx® repeated utilization studies Dronedarone utilization program to assess the effectiveness of risk minimisation activities	Labeling: Coadministration with strong CYP3A4 inhibitors is contraindicated in section 4.3 of the SmPC. Section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC provides the pharmacokinetic information about this interaction. For grapefruit juice (CYP3A4 inhibitor): Section 4.2, 4.4 and 4.5 of the SmPC indicate that "patients should be warned to avoid grapefruit juice beverages while taking dronedarone" Additional risk minimisation program: Direct Healthcare Professional Communication letter, Prescriber Checklist and Multaq Information Card.
Hepatotoxicity	Routine pharmacovigilance, Pharmacogenomics evaluation through planned genomic substudies Surveillance and pharmaco-epidemiologic studies in EU and US EU Cross-sectional surveys (CRONOS) THIN (UK) and NHI (US) nested case-control studies. Dronedarone utilization program to assess the effectiveness of risk minimisation activities	Labeling: Contraindication in section 4.3 of the SmPC in patients with liver toxicity related to the previous use of amiodarone, as well as severe hepatic impairment section 4.3. In addition, special warnings and precautions for use in section 4.4 of the SmPC. Additional risk minimisation program: Direct Healthcare Professional Communication letter, Prescriber Checklist and Multaq Information Card.
Pulmonary-interstitial lung disease (ILD)	Routine pharmacovigilance	Labeling: Contraindication to use in patients with lung toxicity related to the previous use of amiodarone in section 4.3 of the SmPC. In addition, in section special warnings and precautions for use in section 4.4 of the SmPC. Additional risk minimisation program: Direct Healthcare Professional Communication letter, Prescriber Checklist and Multaq Information Card.
Important potential risks		
Renal failure	Routine pharmacovigilance Dronedarone utilization program to assess the effectiveness of risk minimisation activities	Labeling: Contraindication in patients with severe renal impairment in section 4.3 of the SmPC. In addition, special warnings and precautions for use in section 4.4 of the SmPC. Additional risk minimisation program: Direct Healthcare Professional Communication letter, Prescriber Checklist and Multaq Information Card.
Inappropriate anticoagulation	Routine pharmacovigilance Dronedarone utilization program to assess the effectiveness of risk minimisation activities	Labeling: Special warnings and precautions for use in section 4.4 of the SmPC: Additional risk minimisation program: Direct Healthcare Professional Communication letter, Prescriber Checklist and Multaq Information Card.
Drug-Drug Interactions with digitalis, calcium antagonists with heart rate lowering	Routine pharmacovigilance EU Cross-sectional surveys (CRONOS) THIN and LabRx® repeated utilization studies	Labeling: Special warnings and precautions for use in section 4.4 of the SmPC. Section 4.5 Interaction with other medicinal products and other forms of interaction of the SmPC provides the pharmacokinetic information about these interactions. Additional risk minimisation program: Direct Healthcare Professional

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
properties, beta-blockers, statins, tacrolimus and sirolimus, potent CYP3A4 inducers, warfarin, dabigatran.	Dronedarone utilization program to assess the effectiveness of risk minimisation activities	Communication letter, Prescriber Checklist and Multaq Information Card.
Amiodarone-like effects: photosensitivity disorders and pigmentation disorders (extended to severe skin disorders), neuropathy (including Optic Neuropathy)	Routine pharmacovigilance	No minimization action is proposed as there is no evidence of such risks with the use of dronedarone.
Prolactin-induced mammary carcinogenesis (preclinical finding)	Routine pharmacovigilance	No minimization action proposed, as not confirmed ADR.
Important missing information		
Effect in pregnancy	Routine pharmacovigilance	Labeling: Use during pregnancy and in women of childbearing potential not using contraception is not recommended as per section 4.6 Fertility, pregnancy and lactation of the SmPC. Information about the existence of findings in animals is provided in section 5.3 Preclinical safety date of the SmPC.
Effect in lactation	Routine pharmacovigilance,	Labeling: Section 4.6 Fertility, pregnancy and lactation of the SmPC indicates that a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Multaq therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Information about excretion of dronedarone and its metabolites in breast milk in animals is provided.
Effect in severe hepatic impairment	Routine pharmacovigilance	Labeling: Use in severe hepatic impairment is contraindicated in Section 4.3 of the SmPC. Information about the lack of data in this sub-population is provided in Section 4.2 Posology and method of administration of the SmPC.
Effect in children (potential off-label use)	Routine pharmacovigilance, THIN and LabRx® repeated utilization studies	Labeling: Section 4.2 Posology and method of administration of the SmPC states: "The safety and efficacy of Multaq® in children aged below 18 years of age have not yet been established. No data are available."

The following additional risk minimisation activities were required:

- Direct Healthcare Professional Communication,
- Revised Multaq Information Card.
- Prescriber Checklist.

In addition, a drug utilization program will be conducted to collect data on the use of dronedarone and assess the effectiveness of risk minimisation activities. A protocol for this study should be submitted to the CHMP by end of 2011, and after endorsement by the Committee interim reports shall be submitted regularly with the PSURs. The PSUR cycle has also been amended to reflect the continued requirement for six-monthly submissions.

2.3. Product information

The CHMP recommended amendments to be introduced in the summary of product characteristics (SPC), Annex II and package leaflet. Within the summary of product characteristics, sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 were updated.

3. Overall discussion and benefit/risk assessment

Benefits of dronedarone at time of approval included rate and rhythm control properties in patients with non-permanent AF, including patients with some risk factors such as the elderly and patients with hypertension. No increased mortality was observed and there was even a benefit in terms of reduction in cardiovascular death. The interaction profile of dronedarone with commonly used cardiovascular medications (beta-blockers, digoxin) appeared manageable with adequate monitoring. The main limitation recognized for this dataset was the under-representation of patients with NYHA III and LVEF ≤35%; therefore it was recommended not to use dronedarone in these patients. Patients with unstable NYHA III and IV were contraindicated. The results of DIONYSOS were useful because they allowed direct comparison with the use of amiodarone. Dronedarone was considered to have lower efficacy than amiodarone, but its safety profile was more favorable due to the lower incidence of thyroid, neurological, skin and ocular adverse events. Appropriate warnings were included in the product information, and pharmacovigilance activities and risk minimization measures were put in place in relation to important safety issues: management of the signal of serum creatinine increase, drug-drug interactions, use in patients in unstable hemodynamic condition, monitoring for amiodarone-like effects.

The new data that became available recently on the hepatic toxicity of dronedarone raised serious concerns on its safety profile. There is reason to consider that dronedarone and amiodarone may share the same mechanism for hepatotoxicity, although data currently available does not allow concluding on how the two compare in this respect. Several risk minimisation activities were implemented following a CHMP review in January 2011. This led to a recommendation that monitoring of liver enzymes should be done before the start of treatment, followed by monthly monitoring for six months, at months 9 and 12, and periodically thereafter. The latest analysis of cases of hepatotoxicity with an onset within 30 days of treatment initiation indicates that 50% of the events occur during the first 7 days. Therefore patients on dronedarone require closer monitoring of liver enzymes during the first month of treatment. The CHMP considers that additional pharmacovigilance activities are required to provide clarification on the mechanism of hepatotoxicity, and therefore the MAH will conduct non clinical mechanistic studies, surveillance and pharmacoepidemiological studies, a pharmacogenomic study and extend existing nested case-control studies to further elucidate this issue. These additional pharmacovigilance activities have been included in the Risk Management Plan.

The association of dronedarone with cases of pulmonary toxicity with dronedarone was also assessed. Cases have been reported in the post-marketing setting, and in some cases there is information on temporal relationship, dechallenge and rechallenge suggestive of a causal association. Experimental data seems to be suggestive of a mechanism similar to that of amiodarone, although again it can not be estimated whether this risk is higher for dronedarone than for amiodarone or *vice versa*. Patients on dronedarone should be closely monitored for any changes in pulmonary function.

Whilst the review of the hepatic and pulmonary toxicity was ongoing, the results of the PALLAS study became available. The PALLAS study was performed in a group of patients different than that of the currently approved indication for dronedarone, with permanent AF and more risk factors. There was no significant difference between both arms of the study with regards to baseline characteristics. As in the case of the previous survival study ANDROMEDA, it was discontinued prematurely because the hazard ratio (HR) of the primary endpoint was significantly increased in the dronedarone group compared to placebo (first composite of stroke, myocardial infarction, systemic embolism or cardiovascular death, HR=2.16 (95%CI: 1.17-3.99; p=0.0117); second composite of first unplanned cardiovascular hospitalization and death from any cause, HR=1.62 (95%CI: 1.20-2.17; p=0.0013). Time to first CV

death, time to first stroke and time to first CV hospitalization were reported with HR=2.53 (95%CI: 0.98-6.53); HR=2.14 (95%CI: 0.92-4.96) and HR=1.56 (95%CI: 1.15-2.12), respectively.

This imbalance of events is observed from the first 2 weeks of dronedarone administration due to a higher incidence of stroke and first hospitalisation for HF. No single risk factor was consistently shown to statistically impact the different outcomes; some analyses showed possible links to NYHA class, LVEF ≤35%, history of HF and coronary artery disease. However, baseline characteristics of the population clearly indicate that the PALLAS population had more risk factors and poorer prognosis than the patients with non-permanent AF recruited in ATHENA study, and for which dronedarone is currently approved. The prevalence of the different co-morbidities in the ATHENA trial was lower than that in the PALLAS trial. Further analysis shows that using the investigated endpoints in PALLAS, significant benefit would still be shown in the ATHENA population. No consistent risk factors were shown to negatively impact these benefits.

The likely cause of the higher reported heart failure cases in the dronedarone group of PALLAS could be the negative inotropic effect of dronedarone in particular when co-administered with beta-blockers or non-dihydropyridine calcium channel blockers in predisposed patients. A possible contributing factor of the increased CV mortality in the dronedarone group could be the PK interaction between dronedarone and digoxin in susceptible patients, but this could not be proven and is not supported by the data from the ATHENA study. The use of digoxin per se might indicate a more serious haemodynamic dysfunction. The increased stroke incidence could be related to under utilization of oral anticoagulants in the dronedarone group, although a direct relationship could not be established.

The Scientific Advisory Group (SAG) on Cardiovascular issues was consulted and was of the opinion that, although the new information significantly impacts the benefit-risk balance of the product and its use should be restricted, there is still a place for dronedarone in clinical practice as an alternative to existing antiarrhythmic drugs. Compared to amiodarone, dronedarone may have shown to be less effective with similar hepatic and pulmonary toxicity, but because of absence of serious thyroid and skin adverse events it may still be considered as a therapeutic option in a restricted patient population under close monitoring. The majority of SAG experts were of the opinion that treatment should be initiated by specialists.

The Committee considered that the negative results of PALLAS seem to confirm and extend the previously reported detrimental effects in heart failure patients. It is recognized that this study was carried out in patients with permanent AF and with a high rate of heart failure or left ventricular dysfunction, in whom Multaq would not be indicated or would even be contraindicated according to the current Summary of Product Characteristics. However, this may still have implications for the use of dronedarone in clinical practice. Atrial fibrillation is a continuum, progressing from short, rare episodes to longer and more frequent attacks and over time many patients will develop sustained forms with decline in myocardial function.

In order to reflect the findings of the PALLAS study, dronedarone should be contraindicated in patients with permanent atrial fibrillation. In addition, the currently existing contraindication for patients with unstable NYHA class III and IV heart failure should be expanded to include any patient in unstable haemodynamic conditions, history or current heart failure and left ventricular systolic dysfunction.

Based on the data from the PALLAS study on renal safety, it would be appropriate to provide further information to prescribers on the degree of elevation of serum creatinine may be expected, and timepoints at which the tests should be performed in order to allow distinction between cases of elevated serum creatinine due to inhibition of tubular creatinine secretion (where a plateau would be reached) and cases of 'true' renal failure (where serum creatinine would continue to increase).

In relation to hepatotoxicity, given that a significant percentage of the cases will have very early onset, more frequent monitoring of liver enzymes during the early phases of treatment is necessary. During treatment patients also need to be monitored for pulmonary adverse events. It is likely that amiodarone and dronedarone share the same mechanism for hepatic and pulmonary toxicity, so there is potential for cumulative toxicity when switching from amiodarone to dronedarone due to the long half life of amiodarone. Limited information is available on the switch and it is therefore recommended that it is done with caution and under specialist supervision. Elderly patients with multiple co-morbidities may be at increased risk and therefore require particular attention.

It is recognized that there is a medical need for therapeutic alternatives for AF prevention, in particular in younger patients who are often symptomatic and in whom atrial fibrillation may reoccur despite

treatment. Clinically, this prevention is often trial and error before the optimal treatment is found. Flecainide, propafenone and sotalol are all known to be arrhythmogenic. Adequate ECG monitoring is therefore needed when these agents are used, not only at initiation but also during treatment. In addition, these drugs may also have negative inotropic effects. Dronedarone has the advantage of a lower pro-arrhythmic potential. It is recognised that very limited data exists to allow comparison of the different anti-arrhythmic agents. The DYONISOS study showed that amiodarone is more effective than dronedarone, whilst dronedarone is safer in certain aspects. The data currently available suggests that dronedarone shares the hepatic and pulmonary toxicity already known for amiodarone, however it still retains advantages mainly due to the lower incidence of thyroid, neurological, ocular and skin disorders. Dronedarone may therefore be of particular relevance for patients developing thyroid, neurological, ocular and skin disorders as a consequence of amiodarone use.

The existence of comparative efficacy and safety data between the different anti-arrhythmics would facilitate the clear identification of the exact patient population who can derive greater benefit from dronedarone treatment. However, this information not being available, the Committee considered that the therapeutic indication of Multaq needs to be significantly revised to ensure that it is only used after consideration of other anti-arrhythmic agents. It should also not be used in patients with permanent AF or in patients with heart failure or left ventricular systolic dysfunction.

Even by restricting the use of dronedarone as described, patients will require close monitoring for very serious adverse reactions and to ensure that they remain within the approved indication. It is therefore considered appropriate that the initiation and monitoring of therapy be done by a specialist and that Multaq becomes subject to restricted medical prescription. In addition the MAH will put in place a programme for assessing the use of dronedarone and the effectiveness of the risk minimisation measures, and report back to the Committee regularly on the findings.

Having reviewed all the available data on hepatic and pulmonary toxicity, as well as the data from the PALLAS study, the Committee recommended the restriction of the therapeutic indication of dronedarone and a number of changes to the Summary of Product Characteristics, Annex II and Package Leaflet.

The Committee also agreed on additional pharmacovigilance activities to further clarify the risk of hepatic and pulmonary toxicity. The Committee endorsed additional risk minimisation activities such as the sending out of a DHPC to communicate the outcome of the present review, and the development of a continuous medical information programme for prescribers.

The Committee, in view of the above mentioned restrictions and need for monitoring of patients for very serious adverse reactions, is of the opinion that initiation and monitoring of treatment should be done under specialist supervision, and that Multaq should therefore be subject to restricted medical prescription in accordance with Article 71(3) of Directive 2001/83/EC, as amended.

Taking into account all the available information on safety and efficacy of dronedarone, the Committee agreed on the positive benefit-risk balance of the following revised indication for Multaq:

maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF). Due to its safety profile (see sections 4.3 and 4.4), Multaq should only be prescribed after alternative treatment options have been considered. MULTAQ should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.

Divergent positions are presented in Appendix 1.

The CHMP also recommended that the MAH conducts further studies to assess the comparative efficacy and safety of the different anti-arrhythmic agents, so that in the future data exists to confirm the exact patient population which is likely to derive greater benefit from dronedarone use. A draft protocol for a study program should be discussed with the Rapporteurs.

4. Overall conclusion

Having reviewed all the available data on hepatic and pulmonary toxicity, as well as the data from the PALLAS study, the Committee recommended the restriction of the therapeutic indication of dronedarone and a number of changes to the Summary of Product Characteristics.

The Committee also agreed on additional pharmacovigilance activities to further clarify the risk of hepatic and pulmonary toxicity. The Committee endorsed additional risk minimisation activities such as the sending out of a DHPC to communicate the outcome of the present review, the revision of the educational material for prescribers. A drug utilisation program will also be put in place to assess the effectiveness of the risk minimisation measures adopted. The Risk Management Plan has been updated to include all of these aspects.

The Committee, in view of the above mentioned restrictions and need for monitoring for very serious adverse reactions, is of the opinion that initiation and monitoring of treatment should be done under specialist supervision, and that Multaq should therefore be subject to restricted medical prescription in accordance with Article 71(3) of Directive 2001/83/EC, as amended.

The Committee, taking into account the restrictions, warnings and risk minimisation measures agreed, concluded that the benefit-risk balance of Multaq is positive for the following revised indication:

maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation. Due to its safety profile, Multaq should only be prescribed after alternative treatment options have been considered.
MULTAQ should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.

5. Action plan

As part of this procedure, the MAH and the CHMP agreed the wording of a 'Dear Healthcare Professional Communication' designed to inform prescribers of Multaq of the key conclusions of this review, to be to be sent from 3 October 2011 to relevant health care professionals.

6. Conclusion and grounds for the recommendation

The Committee reviewed the available data on hepatic and pulmonary toxicity, as well as the data from the PALLAS study.

The Committee considered that the PALLAS study is indicative of a negative effect of dronedarone in patients with permanent atrial fibrillation, left ventricular systolic dysfunction and/or current or previous episodes or heart failure and that dronedarone use should be restricted accordingly.

The Committee considered that there are significant risks associated to dronedarone use, including hepatic and pulmonary adverse reactions, but that these risks are manageable in clinical practice with appropriate contraindications, warnings and additional risk minimisation measures.

The Committee, in view of the above mentioned restrictions and need for monitoring for very serious adverse reactions, is of the opinion that initiation and monitoring of treatment should be done under specialist supervision, and that Multaq should therefore be subject to restricted medical prescription in accordance with Article 71(3) of Directive 2001/83/EC, as amended.

The Committee considered that, in view of the risk profile of alternative therapies for atrial fibrillation, there are still patients likely to derive significant benefit from dronedarone use, provided that the risks are adequately minimised through the measures described.

The Committee, as a consequence, concluded that the benefit-risk balance of Multaq for

maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation (AF). Due to its safety profile, Multaq should only be prescribed after alternative treatment options have been considered. Multaq should not be given to patients with left ventricular systolic dysfunction or to patients with current or previous episodes of heart failure.

is positive under normal conditions of use.

The CHMP has therefore recommended the variation of the marketing authorisation for Multaq and the amendment of the Product Information as set out in annexes I, II and IIIB and update of the Annex related to Article 127a.

The scientific conclusions and the grounds for the amendment of the SPC, Annex II, and package leaflet are set out in Annex IV of the opinion.

The revised conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States according to Art. 127a of Directive 2001/83/EC are set out in the Annex related to article 127a of the opinion.

Appendix 1

Divergent positions

Divergent positions

Procedure No: EMEA/H/C/1043/A20/005

The undersigned members of CHMP did not agree with the Committee's opinion recommending the variation of the marketing authorisation of Multaq. The reasons for divergent opinion were the following:

Dronedarone (Multaq) is an anti-arrhythmic compound, centrally authorized in EU since 2009 for the indication '*adult clinically stable patients with a history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate*'. The current referral procedure is triggered by the reported hepatotoxic potential of dronedarone and the recently reported premature discontinuation of PALLAS study, which showed a higher risk of mortality and morbidity in patients with permanent AF receiving dronedarone.

Data provided suggest that many of the identified risks (increased risk for cardiovascular death, in particular in patients on digoxin and/or heart failure, increased risk for stroke, liver toxicity, pulmonary interstitial disease, renal impairment, and a number of interactions with drugs commonly used in patients with AF) will either not be preventable or can hardly be minimised with the proposed measures in real world practice.

In addition, there are effective and safer alternatives to the drug. Dronedarone is less efficacious than amiodarone and, in light of the adverse reactions reported, it may not be a safer alternative to amiodarone. In addition, it cannot be used in patients with permanent AF or heart failure and there are no robust data on left ventricular hypertrophy or hypertrophic cardiomyopathy. Therefore, dronedarone is not an alternative to amiodarone. The only possibility will be to limit the use of dronedarone to patients with no or minimal myocardial disease. However, many treatment alternatives already exist for these patients (pharmacological, such as flecainide, sotalol or propafenone, and non-pharmacological (ablation)) which do not share the risks for liver toxicity, interstitial lung disease or significant interaction with digoxin and other commonly used drugs identified with dronedarone. Furthermore, the evidence to support the benefit of dronedarone when other antiarrhythmics are ineffective or not tolerated, is very limited.

Therefore, we consider that dronedarone has a negative benefit-risk balance and should be withdrawn from the market.

Concepcion Prieto Yerro	21 September 2011	Signature:
Alar Irs	21 September 2011	Signature:
Tomas Salmonson	21 September 2011	Signature:
Milena Stain	21 September 2011	Signature: