European Medicines Agency
Evaluation of Medicines for Human Use

ASSESSMENT REPORT

FOR

Multaq

International Non-proprietary Name: dronedarone

Procedure No. EMEA/H/C/001043

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

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TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Sanofi-aventis submitted on 03 July 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Multaq, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 15 November 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The applicant applied for the following indication: Multaq is indicated in patients with a history of, or current atrial fibrillation or atrial flutter, for the reduction of the risk of cardiovascular hospitalization or death.

Scientific Advice

The applicant did not seek scientific advice or Protocol Assistance at the CHMP.

Licensing status:

A new application was filed and approved in the United States of America, Canada and Switzerland.

The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr. **Pieter de Graeff** Co-Rapporteur: Prof **János Borvendég**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 03 July 2008.
- The procedure started on 23 July 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2008.
- During the meeting on 17 - 20 November 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 November 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 March 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 08 May 2009.
- During the CHMP meeting on 26 – 29 May 2009 the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant. The final consolidated List of Outstanding Issues was sent to the applicant on 29 May 2009.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 03 June 2009.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 11 June 2009.
- During the CHMP meeting on 22 – 25 June 2009 the CHMP agreed on a D196 List of Outstanding Issues to be addressed in writing by the applicant. The final consolidated D196 List of Outstanding Issues was sent to the applicant on 25 June 2009.
- The applicant submitted the responses to the CHMP D196 List of Outstanding Issues on 25 August 2009.
- The Rapporteurs circulated the Final Joint Assessment Report on the applicant's responses to the D196 List of Outstanding Issues to all CHMP members on 07 September 2009.
- During the meeting on 21-24 September 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Multaq on 24 September 2009. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 16 September 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Dronedarone (DRO) is an anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds including amiodarone. DRO demonstrates electrophysiological characteristics belonging to all 4 Vaughan-Williams classes of anti-arrhythmic compounds: (1) To a limited extent it blocks sodium (INa) channels decreasing the slope of the depolarization phase (phase 0) of the action potential (Class I effect); (2) It also has limited non-competitive α and β adrenoceptor antagonist properties (Class II effect); (3) Its primary activity is to block the outward potassium currents involved in cardiac repolarization at both the atrial and the ventricular levels, thus prolonging action potential duration (APD) and the refractory period (Class III effect); (4) Finally, it reduces on a limited basis L-type and T-type inward calcium currents (Class IV effect).

DRO is indicated 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 (see section 5.1).
The recommended dose is 400 mg twice daily in adults. It should be taken as one tablet with the morning meal and one tablet with the evening meal. If a dose is missed, patients should take the next dose at the regular scheduled time and should not double the dose. Treatment with Class I or III antiarrhythmics (such as flecainide, propafenone, quinidine, disopyramide, dofetilide, sotalol, amiodarone) must be stopped before starting DRO. Treatment with DRO can be initiated in an outpatient setting.

AF is the most frequent sustained arrhythmia, affecting 6% of people older than 65 year. The overall incidence rises with each decade; it is estimated that there are 2.2 million AF patients in the United States and several million in Europe. The number of patients with AF is expected to increase 2.5-fold over the next 50 years due in part to the growing proportion of elderly patients. Treatment strategies for patients with AF include rhythm control and rate control. This epidemic of AF has important consequences, given the increased mortality and morbidity associated with this arrhythmia particularly due to hemodynamic and thromboembolic complications. AF is associated with significant morbidity causing symptoms that include palpitations, chest pain, dyspnea and fatigue. AF may cause tachycardia-induced cardiomyopathy resulting ultimately in heart failure. AF is also a major cause of embolic complications. AF is the most frequent arrhythmic cause of hospitalization. A recently published study showed that 36.9% of the enrolled AF patients were hospitalized for cardiovascular (CV) reasons during the 1-year follow-up period. CV hospitalizations integrate information from several outcome domains (e.g. hospitalization for cardioversion or further AF ablation after AF recurrence), heart failure (e.g. hospitalization for acute heart failure), thromboembolic complications (e.g. hospitalization for acute stroke), adverse events (e.g. hospitalization due to symptomatic bradycardia), and health economics. AF is also associated with increased and premature mortality. There are several causes of death. It can be due to the arrhythmia, but AF can also be a 'marker' rather than a cause of death, treatment can cause death, and last but not least death will at times be un-related to AF. In conclusion, patients with AF or AFL are exposed to an increased CV morbidity that translates to an increased risk of CV hospitalization and CV mortality. Therefore, the therapeutic management of these patients should go above and beyond the treatment of their rhythm disorder and should ultimately aim to not only alleviate their symptoms, but also improve outcome. None of the available pharmacological therapies aiming at rhythm or rate control has shown a clear benefit beyond electrocardiogram (ECG) endpoints.

An initial application was submitted in June 2005 (EMEA/H/C/000676). This application was withdrawn in September 2006 at Day 181 of the procedure. During the assessment, the efficacy of DRO 400 mg BID was shown as anti-arrhythmic in the rate and rhythm control in patients with AF, though the lack of actively controlled studies precluded final assessment of its antiarrhythmic properties. The main concerns of the CHMP were related to drug-interaction profile, the lack of actively-controlled studies, overall safety profile. Comparative data are important for an appropriate assessment of benefit and risk and will allow better assessment on the clinical relevance of the effects on rhythm and rate control and also on various safety aspects, in particular ECG effects. Placebo or actively controlled safety data are necessary to allow a final assessment on the effect on morbidity and mortality. One survival study (ANDROMEDA) was carried out in patients with a recent

hospitalization for a severe symptomatic episode of CHF (NYHA class III or IV) and with LVEF ≤35%II-IV with a negative effect on mortality. The benefit/risk of DRO was also considered unfavourable by the Food and Drug Administration in 2006. In support of this new application, the applicant submitted two new clinical studies: EFC5555/ATHENA (to investigate the assumption that the management of AF/AFL patients with DRO versus placebo can lead to reduction of CV hospitalization and death) and DIONYSOS, which is an actively-controlled study, to evaluate the efficacy and safety of DRO versus amiodarone for at least 6 months for the maintenance of sinus rhythm in patients with AF. The indications the company applied for were following: DRO is indicated in patients with a history of, or current AF or atrial flutter (AFL), for the reduction of the risk of cardiovascular hospitalization or death. Clinical trials have been carried out according to general CHMP guidance documents.
In particular, relevant for the current indication is the *EMEA/CHMP Note for Guidance on Antiarrhythmics (CHMP/EWP/237/95).*

2.2 Quality aspects

Introduction

Multaq is presented as film-coated tablets containing 400 mg of dronedarone hydrochloride (expressed as base) as active substance.
The other ingredients include hypromellose, maize starch, crospovidone, poloxamer 407, lactose monohydrate, colloidal anhydrous silica, magnesium stearate and purified water. The film consists of hypromellose, titanium dioxide, macrogol 6000, purified water and carnauba wax.
The film-coated tablets are marketed in PVC/aluminium blister packs.

Active Substance

The drug substance is dronedarone as the hydrochloride salt and its chemical name is *N*-{2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl} methanesulfonamide, hydrochloride according to the IUPAC. This active substance is a new active substance, not yet described in any Pharmacopoeia.
Dronedarone hydrochloride is a white to practically white, non-hygroscopic fine powder. It is practically insoluble in water, slightly soluble in acetonitrile, soluble in ethanol and freely soluble in methanol, in methylene chloride as well as in dimethyl sulfoxide.
Only one crystalline form is known and it shows no isomerism. This active substance has none chiral centre.

- **Manufacture**

The chemical synthesis of this new active substance takes place in three steps followed by purification (crystallisation) and milling.
The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included.
Specifications for starting materials, reagents, catalysts and solvents have been provided. Adequate control of critical steps and intermediates has been presented. The active substance is purified by crystallisation and the crystallised active substance is finally milled in order to reach the desired particle size.
Structure elucidation has been performed by infrared spectroscopy, ultraviolet spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy and mass spectrometry. The results of the elemental analysis are consistent with the proposed molecular formula. Definite proof of structure was provided by X-ray crystallography.

- **Specification**

The active substance specifications include test for appearance (white to practically white fine powder), identity (IR, LC and chloride reaction), appearance of the solution (clarity and colour - Ph.Eur.), particle size (laser diffraction), impurities (LC), residual solvents (GC), water content (Ph.Eur.), heavy metals (Ph.Eur.), sulphated ash (Ph.Eur.), and assay by HPLC.
The specifications reflect all relevant quality attributes of the active substance. Furthermore, the analytical methods which were used in the routine controls were described and their validations are in accordance with the ICH Guidelines.
Impurities have been extensively described, classified as process related impurities and possible degradation products, and qualified with reference to toxicological studies. Residual solvents have been satisfactorily controlled in the active substance and their limits are in accordance with ICH requirements.
Certificates of analyses for the active substances issued by the finished product manufacturer were provided and all batch analysis confirms satisfactory compliance and uniformity with the proposed specifications from batch to batch.

- **Stability**

The stability results from long-term (30°C/65%RH) and accelerated studies (40°C/75%RH) were completed according to ICH guidelines demonstrated adequate stability of the active substance.
It was confirmed that the active substance is very stable when exposed to a variety of stressed conditions such as heat, humidity, oxidative conditions and light exposure. Based on the stability data, it can be concluded that the active substance is stable when stored in the original packing material. The results support the agreed re-test period without specific storage conditions.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the drug substance and the excipients are sufficiently justified.
The particle size of the active substance is relevant for the finished product. Therefore, a specification for particle size has been set based on development work and the particle size distribution of bioequivalence and clinical batches.
Two dosage forms were mainly developed for oral use: hard gelatin capsules (used for Phase 1 and 2A studies), tablet dosage form (used for Phase 2B and 3 studies) and tablet dosage form proposed for commercialisation at 400 mg strength.
The bioavailability between the film-coated tablets used for Phase 2 B and the film-coated tablets used for Phase 3 studies were established.
It was observed a high food effect during Phase 1 with the capsules; therefore, studies were performed to increase the absorption of dronedarone in fasted conditions.
A wet granulation process was selected for the development of the tablet for industrial reasons, properties of dronedarone and because high dronedarone strengths were requested.

Studies were performed to select a suitable solubilising agent in order to enhance potential for in vivo absorption in fasted conditions. Poloxamer 407 was the most effective among the surfactants tested and was selected for the tablet formulation. After several studies it was concluded that the formulation with poloxamer407 had the highest bioavailability in fasted conditions and reduced the food effect the most. Therefore, tablets containing poloxamer were developed and optimized for Phase 2 and 3.

- **Adventitious Agents**

Lactose monohydrate is manufactured from bovine milk. The supplier confirms that the milk used in the manufacture of the lactose is sourced from healthy animals under the same conditions as for human consumption. No other excipients of human or animal origin are used for manufacture of the finished product.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing process such as mixing, wet granulation, drying, sizing, compression and film-coating unit operations. Furthermore the equipment used is commonly available in the pharmaceutical industry. Critical process parameters have been studied for the following steps: granulation, compression and film coating.
The manufacturing process has been validated by several studies at pilot and industrial scale for the major steps of the manufacturing process (granulation and drying end-point, compressibility and coating suspension) and is satisfactory.
Accordingly the batch analysis data the medicinal product can be manufactured reproducibly according to the agreed finished product specifications.

- **Product Specification**

The finished product specifications were established according the ICH guidelines and include the following tests: appearance, identification (LC, UV and titanium dioxide in tablet film-coating), uniformity of mass (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution profile, degradation products (LC), microbial limits (Ph. Eur.) and assay.
All analytical procedures which were used for testing the finished product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the CHMP and ICH guidelines.
The batch analysis data obtained from the analysis of seventeen clinical batches, five stability batches and one production batch confirm that the film-coated tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of the finished product.

- **Stability of the Product**

The stability studies were conducted according to the ICH guideline. Three production scale batches have been stored at long term (30°C/65%RH) and accelerated (40°C/75%RH) conditions in the proposed market packaging.
The following parameters were controlled: appearance, dissolution, assay, and microbiological contamination and degradation products.

One production batch was stored under ICH photostability conditions and no significant changes were observed. It can be concluded that the finished product is not affected by the exposure to the light.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, it can be concluded that the quality characteristics of the finished product are adequate and should have a satisfactory and uniform performance in the clinic. There are no unresolved quality issues which may affect the Benefit/Risk balance.

2.3 Non-clinical aspects

Introduction

Antiarrhythmic agents with class III effects (including DRO and amiodarone) are considered to be effective against re-entrant arrhythmias, due to their ability to prolong the action potential (AP). Unfortunately, class III agents in general share two unwanted properties, "reverse-use-dependency" and the ability to cause early afterdepolarizations (EAD) that may induce Torsades de pointes (TdP). Reverse-use-dependency (action potential prolongation only at slow heart rates and not at short cycle lengths) would reduce effectiveness against re-entrant tachyarrhythmias and increase the likelihood for the emergence of EAD at slow rates. Also, amiodarone induces phospholipid accumulation in lungs and has effects on thyroid hormones levels. The anti-arrhythmic and haemodynamic effects of DRO were assessed by a wide range of models, using different animal species, including basic pharmacological characterization (binding), *in vitro* and *in vivo* electrophysiology (effect on action potential), haemodynamic effects, potential anti-adrenergic effects, anti-arrhythmic effects (many models), pharmacology of main metabolites (SR35021 and SR90154) and safety pharmacology studies.

Pharmacology

- Primary pharmacodynamics

DRO has been found to possess antiarrhythmic properties in AF and in ventricular arrhythmias in several species, in a wide range of experimental models. DRO is a multi-channel blocker with β anti-adrenergic activities which confers to this new drug all characteristics of all four Vaughan-Williams classes of antiarrhythmics: it blocks sodium channels (class I drugs), shows a non-competitive anti-adrenergic action (class II drugs), prolongs the cardiac action potential and refractory period (class III drugs) and possesses calcium antagonistic property (class IV drugs). Nevertheless, based on the low affinity constant of DRO at adrenergic receptors, the mechanisms underlying these effects remain incompletely understood and seem to involve different mechanisms (i.e., beta-adrenergic receptors, but also glucagon and secretin receptors).

In vitro electrophysiology showed that the rate of rapid ascending phase of AP was decreased in ventricular conducting (Purkinje fibres) and contractile (ventricle) tissues. This effect was due to an inhibition of rapid sodium channel demonstrated in human atrial myocytes. The depression of dV/dtmax was frequency-dependent (becomes larger at shorter cycle lengths of stimulation) and was use-dependent with rapid onset and offset of block comparable to those characteristics of class IB agents like lidocaine and amiodarone. The class I property, which would be more pronounced during tachycardia, was relatively modest since, in the several in vivo studies carried out, QRS interval was not significantly changed.

In vitro effects on action potential duration (APD) with acute in vitro exposures of DRO, as well as amiodarone, depended on the tissue and the animal species. These differences between each cell types, which had different composition of inward and outward currents, suggested that the AP lengthening effect, due to outward current block by DRO (IKr, IKs, Isus) counteracted the AP shortening effect due to inward current (mainly L-type Ca2+ current) blocked by DRO: the outcome was different according to the cell type.

The multi-channel blocking properties of DRO, namely inhibition of inward and outward currents, produced opposing effects which might explain (i) the homogenization of repolarisation, and (ii) the prevention or the reduction of EADs and delayed afterdepolarisations (DADs) observed after acute action of DRO in the following experiments. In vitro, DRO diminished the transmural dispersion of repolarisation in dogs; principally by shortening the M cell APD and slightly prolonging the APDs of endocardial and epicardial cells. Ex vivo or in vivo, it eliminated EADs and EAD- or DAD-induced triggered activity elicited by almokalant, dofetilide or strophantidine in canine ventricle and did not change or slightly lengthened QTc in dog and pig hearts. If APD was not always prolonged by DRO and amiodarone, and although, effective refractory period (ERP) mainly depended on APD, ERP was always and clearly lengthened in atrium and weakly increased in ventricle. All these effects demonstrated class III antiarrhythmic property.

DRO blocked the L-type calcium current use-dependently and produced a hyperpolarizing shift in the inactivation curve of ICa-L. These results suggested that DRO had affinity for Ca2+ channels in the

inactivated or depolarized state. DRO thus displayed Ca2+ channel antagonist or class IV antiarrhythmic properties like amiodarone. The inhibition of ICa-L induced a reduction in calcium transient and therefore decreased shortening of isolated ventricular cells, a potential explanation for the decrease in peak tension of isolated papillary muscles by DRO. The calcium antagonistic property of the drug might also explain the slowing down of the atrio-ventricular node conduction in dogs and consequent increases in PQ and AH intervals and prolongation of Wenckebach's cycle length. However the increase in PQ and AH intervals could also be attributed in part to the decrease in heart rate (HR).*In vivo* electrophysiological effects of DRO were evaluated in anesthetized rats and dogs after acute intravenous infusions and after acute as well as chronic oral treatments. In vivo electrophysiological studies showed that DRO had more pronounced effects on atrial and nodal parameters (HR, PR and AH intervals, AERP and AVNERP) and at lower concentrations than on ventricular parameters (HV and QRS intervals, VERP). These observations suggested that DRO was more effective at supraventricular than at ventricular levels. Like amiodarone, DRO possessed non-competitive α and β adrenoceptor antagonist properties. DRO showed only weak direct α and β adrenoceptor interactions, but partially blocked isoprenaline-induced tachycardia and adrenaline-induced hypertension. The basis for these anti-adrenergic actions is poorly understood even though calcium antagonist activity after acute and chronic treatments and down regulation in β-adrenoceptor number and reduction in noradrenaline plasma concentration after chronic treatment may be counted. The antagonism of isoprenaline-evoked responses indicated that DRO possessed class II antiarrhythmic properties, and thus the reduction in HR and in atrio-ventricular node (AVN) conduction velocity described above (AH, PQ intervals and Wenckebach's cycle length increases), might be related to this property in addition to the class IV property. DRO reduced L-type and T-type calcium currents and pacemaker current (If) of sino-atrial node (physiological pacemaker); these effects induced diminution of the slope of slow diastolic depolarization and thus reduction in spontaneous sinus rate (SR) of isolated atrium. DRO also reduced the delayed rectifier potassium of pacemaker cells leading to increase in APD and, thus, sinus cycle length. The decrease of SR or HR was observed in isolated atria or hearts in all experiments and in the majority of cases in in vivo studies. In some canine models, DRO induced an increase in HR (not observed with amiodarone) just after intravenous or oral administrations. As the HR was the result of the decrease in the spontaneous sino-atrial rate, the sympathetic tone (decrease in HR by anti β-adrenergic action) and the vagal tone (increase in HR by IK(Ach) inhibition), predominance of anti-vagal tone was suggested but exploratory studies did not confirm this hypothesis.

The multifactorial mechanisms of action of DRO contributed to its hemodynamic effects. DRO had significant α1-, β1- and β2-adrenoceptor blocking effects and calcium antagonist properties that might contribute to the vasodilating and, possibly, to the negative inotropic effects. However, as stated before, the apparent discrepancy between affinity and efficacy was not explained. Also, DRO transiently increased coronary blood flow in dogs and showed in vitro vasodilatory properties in coronary arteries of the isolated heart; this effect was likely related to the activation of nitric oxide pathway. Main haemodynamic effects of DRO were the decrease in contractility and the increase in LV end diastolic pressure observed at relatively high concentration and mainly after intravenous administration. At higher iv doses, DRO exerted a negative inotropic effect, which might be offset by a reduction in afterload that also occurred, and cardiac output was maintained or increased in anesthetized dogs or pigs. The left ventricular ejection fraction and fractional shortening (ECG measurements) of post myocardial infarction (PMI) (healed) conscious dogs were not modified after chronic oral treatment. The antiarrhythmic activity of DRO has been established in a wide variety of experimental models including auricular and ventricular arrhythmias. DRO was studied in *in vitro* and *in vivo* models of AF induced by a hypokalemic media in isolated hearts (guinea pigs), or by electric burst in dilated atria (rabbits), during acetylcholine infusion (dogs) and in the presence of bilateral vagal stimulation (dogs). Experimental models at ventricular level were more numerous than those in AF models because initially the research of a new amiodarone-like compound, with a better safety profile, was focus on ventricular arrhythmias. In in vitro studies, DRO, after an ex vivo iv treatment, prevented spontaneous AF induced by hypokalemic media. In AF model induced by electrical burst in the dilated atrium, the drug at 0.1 μM restored 100% of hearts to sinus rhythm. In anesthetized dogs AF was induced by acetylcholine infusion or by vagal stimulation, DRO restored sinus rhythm with effective iv doses about 3 times lower than amiodarone. Like amiodarone, DRO with a multifactorial mechanism of action, is effective in several ventricular arrhythmias. After iv and acute or chronic po administrations, DRO was a potent antiarrhythmic agent in ischemia- or reperfusion-induced

arrhythmias (ventricular fibrillation [VF], ventricular tachycardia [VT] and premature ventricular beats [PVBs]) in rats as well as pigs. In canine models, repeated infusion of DRO restored sinus in ouabain-induced VT or prevented sudden death (VF) following an ischemic insult developed in a region remote from an infarct; in this model, chronic oral treatment of DRO was ineffective. But in other canine model where VF was provoked by a sympathetic hyperactivity with a healed myocardial infarction, chronic oral administration of DRO, like amiodarone, prevented VF. This antifibrillatory effect, greater than that observed with a pure anti-adrenergic intervention, was likely to depend upon multiple actions on vulnerable parameters involved in the genesis of lethal arrhythmias of ischemic origin. During pharmacology studies, pro-arrhythmic effects caused by DRO were not observed much. In in vitro experiments DRO had never brought on pro-arrhythmias, on the contrary it suppressed EAD and DAD induced by pure class III antiarrhythmic agent, dofetilide, or by Na-K pump inhibitor, strophantidine in canine Purkinje fibres. In in vivo experiments, DRO (as well as its metabolite SR35021) induced some case of A-V blocks at 10 mg/kg iv in anesthetized rats and extra-systoles in anesthetized dogs. These effects were not observed with amiodarone. DRO appeared to promote the induction of VT during programmed electrical stimulation after 3 x 3 mg/kg iv in conscious post infarction dogs. In one anesthetized dog treated with 40 mg/kg od, VF was induced during ventricular pacing at day 7. In a model of compensated biventricular hypertrophy by chronic complete A-V block, after chronic oral treatment by DRO (20 mg/kg bid), TdP occurred in 4 of 8 animals versus 1 of 6 in vehicle group in anesthetized dogs; whereas amiodarone (40 mg/kg od) did not induce TdP in 7 dogs. This discrepancy between both drugs may be due to dissimilar electrophysiological and haemodynamic baseline values (before treatment), which were less altered in the amiodarone group than the control and DRO groups. In this experiment, plasma levels (1.3 µg/mL) of DRO were clearly higher than that usually observed in dog and man (0.08 to 0,15 µg/mL), whereas plasma levels of amiodarone (3.5 µg/mL) were slightly greater than that measured in patients (1.5 to 2.5 µg/mL). Most of these arrhythmic effects have been obtained with the highest intravenous doses or at high plasma concentrations and tissue level after chronic oral treatment.
The pharmacology studies have shown that DRO was 3 to 20 times more potent than amiodarone in in vitro experiments; haemodynamic, electrophysiological and antiarrhythmic effective doses of DRO were about 3 times lower than those of amiodarone after acute iv and po administration in rats, dogs or pigs. But after chronic oral treatment, effective doses of DRO were similar or upper to those of amiodarone; measurements of plasma and cardiac tissue concentration showed that DRO and SR35021 values were clearly inferior to those of amiodarone and deethylamiodarone (metabolite of amiodarone), respectively. Thus, DRO was intrinsically a more potent antiarrhythmic agent with a higher metabolic clearance and less accumulation than amiodarone. Two metabolites have been studied. SR35021A displayed antiarrhythmic, electrophysiological and haemodynamic activities similar to those of DRO but was less potent (approximately 3 to 10 times) than its parent compound. SR90154 has very little or no activity. Plasma levels of SR35021A were about 10 times lower than those of DRO

- Secondary pharmacodynamics

DRO has been evaluated in a wide variety of experimental models of arrhythmia, including models related to AF and ventricular arrhythmia. These studies are described under the section Primary pharmacodynamics. No other pharmacological activities have been observed in the course of DRO's development and therefore no further studies are described in the context of secondary pharmacodynamics.

- Safety pharmacology programme

Central and autonomic nervous system
The following parameters were assessed in a single experiment in mice following oral and intravenous administration of DRO: behaviour, temperature, muscle tone, motor coordination and body weight follow-up (over 6 days). In mice, the only observed effect on the central nervous system was a decrease in spontaneous activity from the dose of 200 mg/kg and above after oral administration.
Cardiovascular function
In anesthetized dog, administered by the intraduodenal route, DRO induced at 12.5 and 25 mg/kg a dose-dependent decrease in mean arterial blood pressure associated with a vasodilator effect, an

increase in stroke volume and cardiac output associated with a decrease in total peripheral resistances. No ECG changes were observed. Single doses of dronedarone (1 and 5 mg/kg) were administered by intravenous infusion in pentobarbital-anesthetized mongrel dogs of either sex. At 5 mg/kg the main effects consisted of a biphasic decrease in blood pressure, limb peripheral resistances and left ventricular pressure, a negative chronotropic effect (-22%), a decrease in total peripheral resistances (-43%) and moderate increase (39%) in cardiac output associated with a marked increase (54%) in stroke volume.

Respiratory function

The respiratory function was assessed both in conscious guinea-pigs and in anesthetized dogs. In the guinea pig, DRO administered orally did not affect respiratory function up to and including the dose of 100 mg/kg. Single doses of 12.5 or 25 mg/kg dronedarone were administered by intraduodenal administration to groups of 5 anesthetized dogs of either sex. An increase in the respiratory frequency and flow was observed after the administration of the dose of 25 mg/kg.

Gastrointestinal system

On the gastrointestinal tract, DRO in mice and rats had no effects up to the dose of 100 mg/kg.

Renal system

On the hydroelectrolytic balance, the only observed effects in the rat were a decrease in endogenous creatinine clearance (from 30 mg/kg in females and at 100 mg/kg in males), a decrease in urinary volume associated with slight changes in excreted quantities of electrolytes (100 mg/kg only in both sexes). Repeated DRO administration (up to 30 mg/kg/day orally in male rats) over 2 weeks was devoid of effects on renal blood flow, urine production and creatinine clearance.

Lung and liver phospholipid contents

After 14-day repeated administration, DRO unlike amiodarone induced no phospholipid accumulation in lung (up to 150 mg/kg/day) and phospholipid accumulation in liver at 100 mg/kg only. 150 mg/kg produced a slight and non dose-dependent increase in liver phospholipids.

Thyroid hormones plasma levels

The effect of dronedarone of thyroid hormone plasma levels was only minimal. Dronedarone (150 mg/kg/day) only decreased T4 and the T4/T3 ratio, while amiodarone increased rT3, T4/T3 ratio and decreased T3.

- Pharmacodynamic drug interactions

DRO has been evaluated in a wide variety of in vitro and in vivo studies. They showed that DRO, with its multifactorial mechanism of action, induced multiple effects on CV parameters as described under Primary pharmacodynamics. There are a number of drugs which could potentially interact with this kind of antiarrhythmic agent and their impact has been investigated in the clinical program, rather than in the non-clinical program.

Pharmacokinetics

The ADME studies described in mice, rats, rabbits, dogs and macaques provide a view of the disposition of DRO and its active metabolite in animal species. Single and repeat-dose studies have been conducted at dose levels within the range of dosages tested for the safety evaluation program. Data indicates that oral doses of DRO were well absorbed. The time of maximum plasma concentration after oral administration is between 1 to 4 hours whatever the species. Once absorbed, DRO undergoes an extensive first pass extraction resulting in low absolute oral bioavailability in the species tested. The apparent terminal half-life values of DRO after oral administration were between 2 and 7 hours in mice, rats and dogs. However, these data are questionable. According to the assessor, elimination half life in rat and dog is probably longer because in repeated dose studies accumulation of DRO is observed. In all animal species the exposure increased more than dose proportional and some drug accumulation was observed (up to 4-5 fold increase in AUC in dogs as compared to single dose studies). DRO and its active metabolite are both highly bound to plasma proteins in all species including human and not saturable up to 10000 ng/mL. In human plasma it appeared to be difficult to assess the fraction unbound. In a study using equilibrium analysis plasma binding was 99.84 – 100%, whereas a study using ultrafiltration pointed at a binding percentage of 99.14%. DRO does not distribute extensively into red blood cells. The pharmacokinetics of DRO following intravenous administration in rats and dogs are characterized by a large volume of distribution (around 12 and 39-

66 L/kg in dogs and rats, respectively) and a high clearance (about 2-4 L/h/kg). DRO is widely distributed in tissues. The tissues with the greatest radioactive levels are liver > kidney = lung = adrenals = pancreas = spleen = pituitary gland > thyroid = salivary glands = brown fat > Harder's glands = pineal body > heart. In pigmented animals, additional specific binding to melanin-containing structures, such as skin and eyes, was also observed. DRO and/or its metabolites cross the blood-brain barrier, the placenta and is excreted into milk. DRO undergoes extensive metabolism. The main metabolites of DRO observed in humans are also observed in the animal species tested. DRO is an inducer of CYP3A in mice and exhibits no biologically significant inducing effect on CYP-dependent reactions in rats and dogs. This effect seems to be limited to mice since it was not observed in rats, dogs and humans. DRO is rapidly eliminated by metabolic clearance with no excretion of unchanged DRO in bile (rat) and in urine (mice, rat, dog, and macaque). The major route of excretion of the total radioactivity is the feces via the bile with less than 9% of the dose in urine.

Toxicology

- Single dose toxicity

Single-dose toxicity studies with oral (1500 and 2000 mg/kg) administration were performed in mice and rats of both sexes (5 animals/sex/group). The maximum nonlethal dose in the mouse and the rat was 2000 mg/kg. A single oral administration of 2000 mg/kg of DRO caused some clinical signs in rats (prostration, piloerection, ptyalism, and soiled urogenital areas), and a decrease in body weight gain in both species.

- Repeat dose toxicity (with toxicokinetics)

Overview of the repeat dose toxicity studies:

Study type and duration	Route	Species	M/F[a]	Dose levels (mg/kg)	Batch No.	Study reference
Repeat-dose toxicity						
8 days	po	rat	3/3	0, 100, 250, 600	DJ.07.51.5	DDO0497
2 weeks	po	rat	10/10	0, 30, 70, 160	92-01	TSA0879
3 months	po	rat	15/15	0, 5, 17.5, 60	92-01	TXC0887
6 months	po	rat	30/30[b], 20/20[b]	0, 2, 10, 50	5SNP505	TXC0986
4 days	iv	rat	3/3	0, 3, 6, 12	DJ.07.51.5	DDO0499
7 days	iv	rat	3/3	0, 5, 10, 20	92-01	DDO0548
4 weeks	iv	rat	10/10	0, 2, 4, 8	92-01	TSA0963
2 weeks	po	dog	3/3	0, 25, 60, 140	92-01	TSA0883
3 months	po	dog	4/4	0, 5, 17.5, 60	92-01	TXC0886
1 year	po	dog	5/5	0, 5, 15, 45	92-01	TXC0970
2 weeks	iv	dog	1/1	0, 5, 10, 20	92-01	DDO0549
2 weeks	iv	dog	3/3	0, 1, 2.5, 6	92-01	TSA0885
4 weeks	iv	dog	3/3	0, 1, 2, 4	92-01	TSA0962
4 days	iv	macaque	1/1	0, 2, 4, 8, 16	DJ.07.51.5	DDO0503
2 weeks	iv	macaque	3/3	0, 1, 2.5, 6	92-01	TSA0884

po = orally by gavage or capsule (in case of dog); iv = intravenous

[a]: Number of animals by treatment group

[b]: Group vehicle and group 50 mg/mL for toxicology study: 30M/30F, with 10M/10F for recovery ; group 2 and 10 mg/mL: 20M/20F

Consistent with the pharmacological properties of the compound, electrocardiographic changes were noted from the lowest tested oral dose in rats (5 mg/kg/day; i.e. at non-detectable exposure levels) and from 25 mg/kg/day in dogs (i.e. at 5-8 human anticipated clinical exposure). The long-term effects of DRO on cardiac channel density and on channel trafficking has not been studied. It can not be excluded that the reduction of membrane channel density contributes to the long term effects of DRO.

The metabolite SR35021 was detected in all toxicological species. The SR35021 content in plasma was monitored during the long-term carcinogenicity studies and exposure levels relevant to what is observed in the clinic were obtained. Hence this major metabolite is considered qualified with respect to carcinogenicity. Moreover, adequate SR35021 exposure was observed in the separate TK study performed in pregnant rabbits. In principle, the rat S9 fraction used in the in vitro genotoxicity studies should produce SR35021 hence the metabolite is qualified.

SR90154 is the main metabolite in human. This metabolite is a more abundant metabolite than SR35021 in rat, rabbit and dog, and is present at similar levels as SR35021 in mouse. SR90154 exposure was generally higher than exposure to DRO in these animal species (3 to 10 fold for C_{max} and 0.9 to 9 fold for AUC). In addition, these ratios did not significantly change with treatment duration, sex and dose. In the repeated-dose toxicity studies, the estimated animal/human exposure ratio for SR90154 was close to or slightly below 1 at the NOEL values in rats and dogs. However, an adequate exposure (exposure ratio equal or higher than 1) was obtained in the carcinogenicity studies in rats and mice. As such, the preclinical safety of SR90154 has been sufficiently qualified.

Decreased bodyweight gain and food intake appeared in several studies; actually, these were the most frequently observed alterations in animals. The applicant does not discuss in this respect whether the gastrointestinal alterations seen in these repeated dose toxicity studies are the real cause of the general toxicity findings. Effects on the gastrointestinal tract were noted both in dogs and rats without adequate safety margin compared to clinically anticipated exposures. Gastrointestinal side effects are also identified as a clinical issue. For these reasons, the clinical request for measures to minimise the risk of nausea and diarrhoea which are reported as common adverse events in the clinical studies is supported.

In rats, there was no clear correlation between transaminase elevations and the occurrence of minimal foci of liver necrosis. As a result of dose reduction the macro- and microscopic gastrointestinal changes observed in the 2-week studies in rats (i.e. liver) and dogs (i.e. biliary system) were not confirmed in the longer term studies in these species. As these effects occurred at exposures well beyond the clinical anticipated levels, they were not relevant.

Phospholipidosis, as evidenced by foamy macrophages in several tissues, is an important unwanted effect of amiodarone. The applicant modified the molecule of DRO such that phospholipidosis was unlikely to occur. Compared to amiodarone, DRO is less lipophilic, has a higher metabolic clearance and a shorter half life. All these characteristics might lead to lower tissue accumulation of DRO. A comparative safety pharmacology study pointed to the lower potential of DRO to induce phospholipidosis. In the 3 month rat study, foamy macrophages were observed in the lungs and lymph nodes of rats. The effects in the lymph nodes occurred at an exposure levels without an exposure based safety margin. Phospholipidosis was not aggravated after a longer treatment (6 months) employing similar dose levels in rats. In this study a (reversible) increase in perivascular lymphoid hyperplasia was observed. In the rat carcinogenicity study, macrophage infiltration was observed in lungs, and to a lesser extent in mesenteric lymph nodes, at the high dose only (3-6 times clinical exposure levels). Macrophage infiltration of mesenteric lymph nodes occurred in dogs only at supra therapeutic exposure levels (> 20 times human exposure). In the studies conducted by the intravenous route in both rats and dogs, although the exposure was much higher compared to the oral route no macrophage infiltration was noted.

As described in the safety pharmacology section, a comparative study on the effects of DRO and amiodarone on the thyroid showed that DRO only slightly modified circulating thyroid hormone level, whereas with amiodarone, rT3 was increased (2- to 4-fold) and so was T4/T3 (14 to 29%).

Hormone levels were investigated during the chronic studies in rats and dogs. Changes observed with DRO were minor and differ from those induced by amiodarone: decrease in T3 mainly (i.e. -15 to -25% in rats at 1-2 times human exposure levels, and -15 to -50% at 1-2 times human exposure levels in dogs), without any change in TSH, and in the rat only increased incidence of high follicular epithelium. The modifications caused by amiodarone were marked (historical comparison): T4 increased 1.5- to 4- fold and TSH increased 2- to 3-fold in rats, T4 increased 2- to 4- fold in dogs and histological changes consistent with increased thyroid activity were observed at microscopic examination, carcinogenicity studies included adenoma and adenocarcinoma in the latter. No changes in the thyroid were observed in the carcinogenicity studies conducted with DRO.

Slight renal functional alterations were noted in the toxicity studies and appeared as minor plasma and/or urinary biochemistry changes. There were no microscopic changes in the kidney in any of the studies. Nevertheless, effects on plasma creatinine occurred at ≥ 0.5 times the human exposure levels

in the 3-month and 6-month chronic studies. A dose effect relationship could not be established. No creatinine increase was observed in dogs. Protein was detected in the urine of macaques. The effects on creatinine were mentioned in this summary due to the systematic increase in the creatinine plasma levels observed during clinical development both in healthy volunteers and in patients. An effect of the compound on renal function cannot be excluded."

- Genotoxicity

A battery of genotoxic studies was done. All tests were negative and only the HPRT test yielded equivocal results. Two other in vitro genotoxicity assays were negative.

- Carcinogenicity

In the carcinogenicity studies, DRO produced a treatment-related increase in mortality in male mice and resulted in an increase in proliferative changes in the haemolymphoreticular system in male and female mice (histiocytic sarcoma), in mammary glands in female mice (adenocarcinoma) and in the mesenteric lymph nodes *in rats and mice* (angiomatous hyperplasia and hemangioma in both species, hemangiosarcoma in female mice only). All these effects occurred at the highest dose tested leading to exposure level which is 10 fold the clinically anticipated levels. Based on the provided information, the increased incidence of histiocytic sarcomas in mice most likely does not represent a risk for humans. The risk for development of haemangiosarcomas following DRO treatment is low. However, there are no data at this stage and the monitoring for haemangiomas needs to be included in the risk-management plan. In repeat dose and carcinogenicity studies, dark discolouration of mesenteric lymph nodes was observed being the result of blood stasis. The clinical relevance of these effects is unknown. The increased incidence of mammary gland adenocarcinomas in high-dose female mice were considered to be due to a subtle interference with prolactin homeostasis. Indirect evidence for a hormonally driven effect comes from increased incidences of Harderian gland adenomas and uterine changes in treated mice; effects which may be ascribed to an increase in prolactin. This view is supported by the finding that DRO induced a slight but significant increase in prolactin levels in female mice after a single or 28-day administration. This increase was of low magnitude in comparison with the large increases seen with known D2 receptor agonists, and would explain the weak response of mammary tumors observed. In addition, a receptor screening assay showed that DRO, as well as amiodarone has affinities for D3 and D4.2 receptors in the 1 to 5 μM range and are less potent on D1 and D2L receptors. This weak activity on D2 receptors would be consistent with a slight effect on prolactin homeostasis mediated through dopamine. The prolactin-induced mammary carcinogenesis in rodents is not relevant for humans.

- Reproduction Toxicity

In fertility studies, DRO was administered up to 100 mg/kg/day in rats. The NOEL for male (paternal) and female (maternal) animals was 30 mg/kg/day. Based on reproductive effects at 100 mg/kg/day, the NOEL for female fertility and early embryonic development was considered to be 30 mg/kg/day. These effects are probably the result of maternal toxicity. During embryo-fetal development studies performed in rats, DRO was found to be teratogenic in the rat at 100 mg/kg/day. Despite maternal toxicity noted at this dose level (decreased body weight gain associated with decreased food consumption), this was considered to be a direct teratogenic effect. At lower doses, DRO had no adverse effects on the dams or their litters. In the pre- and post- natal development study from GD6 to LD20, the dose of 50 mg/kg/day was shown not to induce any adverse effect on the F1 pups (other than a minor decrease in body weight gain from day 1 to day 4 post-partum imputed to slight maternal toxicity characterized by a moderate decrease in body weight gain), or on the F2 pups. No other effects on reproductive parameters were noted in this study. DRO induced maternal deaths, abortion and marked weight loss at 200 mg/kg/day in an embryofetal study in rabbits. Because of this, high dose litters could not be reliably evaluated as their number was too low to draw meaningful conclusions. At the dose of 60 mg/kg/day, no teratogenic effect was found. There was a reduction in bodyweight gain; the NOEL for dams was determined to be 20 mg/kg/day.

- Local tolerance

There were 3 local tolerance studies performed: (1) Local Tolerance of Two Injectable Formulations by the Intravenous Administration in New Zealand hybrid rabbits (TOL0921) - both formulations and their respective placebos were well-tolerated in this study, (2) Local Tolerance by the Perivenous and

Intra-arterial Administrations (TOL0922) in New Zealand hybrid rabbits - evidence of moderate local intolerance was seen at sites injected with DRO by either route, but not at vehicle and saline control sites. Loss of motility was noted in all rabbits after administration of DRO intra-arterially. One of these was found dead 24 hours after injection. The lesions observed in this animal at necropsy suggested CV collapse, (3) Local Tolerance of 3 formulations of DRO and placebo by the intravenous route in the rabbit (TOL1007) No behavioural changes or cases of mortality were noted during the study. Examination of the local parameters (erythema, edema, hematoma), macroscopic and microscopic examination lead to the conclusion that the tolerability of DRO is good when it is administered by the intravenous route at the concentrations of 1 and 2 mg/mL.

- Other toxicity studies

Phototoxicity was only observed at high dose levels, and no storage was observed in the skin. In addition, DRO did not induce photo allergy. Photosensitivity was observed in patients, although at a low incidence. Potential genotoxic impurities were evaluated.

Ecotoxicity/environmental risk assessment

With respect to the environmental risk assessment, the following conclusions have been drawn: DRO is neither PBT nor vPvB, risk to the microorganisms in a sewage treatment plants, risk to the aquatic compartment, the groundwater compartment and the terrestrial is considered to be negligible. In order to complete the environmental risk assessment, it has been agreed that further studies, i.e. OECD 307 and OECD 308 will be performed as well as recalculation of the kinetic BCF OECD 305 fish BCF study. It has been agreed that these data will provided as a follow-up measures (FUM1 – 3).

2.4 Clinical aspects

Introduction

Six controlled studies are currently submitted. Of these, five are placebo-controlled; 4 of which were already submitted in the previous application to document the efficacy of DRO 400 mg BID in maintaining sinus rhythm or controlling ventricular rate in patients with AF/AFL (EURIDIS/ADONIS and ERATO studies respectively). The new Study ATHENA investigated the efficacy of DRO 400 mg BID on the reduction of the risk of CV hospitalization or death. Additionally, one actively-controlled study (DIONYSOS) is currently submitted with responses to the Day 120 List of Questions. The dose selection in all the studies is based on the dose finding study DAFNE. All studies were multinational, multicenter, double-blind, placebo-controlled, of parallel design and comparable demographics, except DIONYSOS which was actively-controlled. Elderly (>30%) and female patients (43.6%) were well represented and in line with the clinical AF population. Most of the patients were Caucasians; other races contributed with 10%. Included patients had medical histories generally representing clinical practice: structural heart disease, ischemic heart disease and systemic hypertension. However, patients with NYHA class III or LVEF <35% were not adequately represented (less than 4%); NYHA class IV were contraindicated. Medications that are commonly prescribed in AF patients (beta-blockers, digoxin and calcium channel blockers) were co-administered in these trials allowing assessment of the effect of their co-administration. Class I and III antiarrhythmics were contraindicated.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. All clinical studies in the DRO clinical program were sponsored by the Applicant. Audits of study sites were conducted on a routine basis by the Sponsor's Clinical Quality and Compliance personnel to verify the quality of data collection. In 2 cases during the development program, involving 1 site in both the ERATO and ANDROMEDA studies and 1 site in the ATHENA study, routine monitoring revealed evidence of Good Clinical Practice misconduct leading to "for cause" audits. Subsequently the study centre and files were audited to evaluate the extent and consequences of the violation. The data specific to the violating centre were excluded from the main statistical analysis. Additional audits of investigator sites performed in 4 other centres and countries did not identify any further deviations or raise any concerns for other centres involved in the studies. The sponsor concluded that the deviation was investigator- and centre-specific. The applicant has provided a statement to the effect that clinical

trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

- Absorption

DRO is well-absorbed after oral administration (70 to 94%) in fed conditions. Absolute bioavailability due to presystemic first pass metabolism is under fed conditions only 15%. As mentioned before, food increases DRO's absorption. Of note, DRO tablets contain poloxamer as an excipient (surfactant) which has been shown to significantly increase bioavailability under fasting conditions. The applicant states that the strong increase in bioavailability of DRO by poloxamer is due to increased solubility. However, literature data suggest that poloxamer's inhibitory effect on P-gp might be an additional contributing factor.

- Distribution

DRO and its main metabolite SR35021 exhibit high levels of in vitro plasma protein binding (>98%), mainly to albumin. Binding to α1-acid glycoprotein (AAG) under normal conditions has no relevance but may gain importance when AAG concentrations are increased, such as during infectious diseases. After IV administration a large volume of distribution at steady-state (Vss) ranging from 1200 to 1400 L is observed. The large range being can be attributed to the common problem of extrapolation of non-compartmental pharmacokinetics data; i.e. plasma concentrations below the LOQ near the end of the time versus concentration profiles. The ratio of red blood cells/plasma DRO concentrations was approximately 1. DRO has been shown in animal studies to cross the blood brain barrier and the placenta and is excreted into breast milk.

- Elimination

DRO is extensively metabolised mainly (>84%) by CYP3A4. The major metabolic pathways included a) N-debutylation to form SR35021 followed by oxidation (~24%), b) oxidative N-deamination to form the propanoic acid metabolite (SR90154) followed by oxidation (~26%), and c) direct oxidation (~12%). SR35021 is metabolised itself only in part (~50%) by CYP3A4. A higher proportion of metabolites are found after oral than after IV administration indicating a relevant first pass effect. Although there is some evidence that CYP3A4 allelic distribution may differ among populations, there is limited evidence that the resulting protein variants have a substantial effect on enzyme function in vivo. However, CYP3A5, a closely related enzyme with overlapping substrate specificity and a prominent role in intestinal drug metabolism, exhibits functionally important polymorphisms. DRO itself did not appear to be a substrate for CYP2D6, but was shown to inhibit CYP3A4 and CYP2D6. Interestingly, comparison of the results of in-vitro enzyme inhibition studies with the results of the clinical studies shows that in-vivo inhibition of CYP3A4 is stronger than expected. The applicant attributes this difference to "mechanism-based inhibition" which usually means irreversible inhibition, however without presenting relevant experimental results to support this important observation. DRO did not induce CYP1A1, CYP1A2, CYP2A and CYP3A nor inhibit CYP1A2, CYP2C9, CYP2C19, CYP2C8, CYP2B6 and CYP2E1 isoenzymes. The main metabolite SR35021 was shown to inhibit in vitro all CYP isoenzymes tested (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4). On the basis of the in vitro interaction potential of DRO and SR35021 with CYP2C8 and CYP2B6, an interaction with CYP2C8 and CYP2B6 enzymes is considered unlikely in vivo. The clinical development program of DRO has therefore been set up to address potential interactions with CYP3A4, CYP2D6, CYP2C9 and CYP1A2 isoenzymes. The N-debutyl metabolite SR35021 exhibits pharmacodynamic activity but is 3 to 10-times less potent than DRO. After oral administration similar plasma levels of SR35021 compared to DRO are observed and SR35021 contributes only to a limited extent to the pharmacological activity of DRO. However, since its free concentration is substantially higher, it is plausible that SR35021 has a pharmacodynamic activity comparable to DRO. The pharmacokinetics of SR35021 is currently poorly understood. For the time being, however, the pharmacokinetic assessment focuses primarily on DRO. SR35021 pharmacokinetics, especially metabolism will be explored further post-approval (FUM 7 and 8).

Following oral administration 84% and 6% of the DRO dose is excreted mainly as metabolites in feces and urine respectively. After iv administration the plasma clearance of DRO ranges from 130 to 150 L/h and is independent of the dose. Plasma elimination has a bi-phasic profile and steady state

terminal half-lifes ($t_{1/2z}$) of DRO ranges from 27 to 31 h and that of SR35021 ranges from 20 to 24 h. After a 14-day washout period DRO and its metabolite are not detectable in plasma anymore. Due to the biphasic elimination profile the second phase of the concentration time curve does not contribute much to the total extent of DRO extent of exposure. Therefore, despite 30 hours $t_{½z}$ plasma concentration time profiles seem more constant after 400 mg BID instead of 800 mg OD DRO administration. Thus, from a pharmacokinetic point of view a twice daily dosing regimen is defendable. This is supported by the pharmacodynamic data.

- Dose proportionality and time dependencies

DRO exposure increases supraproportional. After a two-fold dose increase plasma levels of DRO and its main metabolite increase 2.4- to 3-fold. Steady state at the clinically relevant dose of 400 mg BID is reached after 4 - 8 days. Based on C_{trough} values in the higher dose range > 800 mg BID it may take longer before steady state is reached than in the therapeutic dose range. An accumulation rate of 2.6 to 4.5 seems independent of the dose in the range of 200 mg to 800 mg DRO administered BID. A larger than expected accumulation rate based on single dose data was observed probably due to a saturated first pass metabolism. Accumulation rates at higher than therapeutic doses are somewhat larger in the range of 3 to 7. After repeated dosing of 400 mg DRO BID in fed conditions, mean $C_{max,ss}$ ranges from 84 to 167 ng/mL for DRO and from 66 to 119 ng/mL for SR35021. The extent of exposure (AUC_{0-12}) ranges from 650 – 1030 ng*h/mL for DRO and from 534 – 930 ng*h/mL for SR35021. Under fasted conditions intra-individual PK variability of DRO pharmacokinetics is considerable (C_{max} ~34%; AUC ~18%), but under fed conditions intra-individual PK variability is moderate (C_{max} 18 – 26%; AUC_{0-12} 10 – 18%) and similar in a patient and healthy volunteer population. Intra-individual variability is estimated from residual coefficients of variance as no replicate-design studies were performed. Interindividual variability is in the range of 30% to 37% under fed conditions. DRO can be considered as a drug with only a limited PK variability under, clinically relevant, fed conditions.

- Special populations

A limited clinical pharmacology program in special populations was performed with DRO.

Hepatic impairment

In patients with moderate hepatic impairment, DRO exposures are on average increased by 1.3-fold and the unbound exposures are increased by 1.9-fold. The total and unbound exposures of the active metabolite are decreased by 1.6 to 1.9-fold. In view of the extensive hepatic metabolism of DRO these changes are considered moderate. Nevertheless, since the unbound fractions of DRO and metabolite are nearly 2-fold changed in opposite directions, the applicant should discuss if a dose reduction to 400 mg qd should be recommended in subjects with hepatic impairment. Furthermore, the influence of moderate hepatic impairment on DRO pharmacokinetics may be underestimated as the subjects studied may not well represent subjects with impaired metabolic capacity. The Applicant adequately justified the current dose recommendation in their response to CHMP.The scores in the moderate hepatic impairment group were mainly related to ascites and encephalopathy and only few patients with affected albumin or PT were included, as with all patients at risk of increased plasma exposure the lack of alternative dose formulations reduces the clinical potential of DRO. Patients are exposed a priori to unnecessary high doses. Due to a lack of information a contra-indication for patients with severe hepatic impairment is indeed warranted.

Renal impairment

The lack of a study in patients with renal impairment is acceptable as DRO undergoes limited renal excretion only, approximately 6%. The lack of impact on DRO PK in patients with renal impairment is supported by population pharmacokinetics analyses.

Elderly

In elderly (>65 years) men DRO rate and extent of exposure are increased by approximately 23% to 33% when compared to young men. Therefore, age by itself does not have a clinically relevant impact on DRO pharmacokinetics. However, a 1.5-fold increase in exposure was observed in elderly female compared to elderly male. Body weight may explain part of these observed differences. This impact of weight is not investigated in a separate clinical pharmacology study but addressed in the population PK assessment only. Elderly women may therefore have a clinically relevant increase in exposure as compared to younger male patients. A single study was performed in Japanese subjects, which did not

point to important differences in pharmacokinetics characteristics as compared with Caucasian subjects. In the clinical efficacy/safety trials only a limited number of non-Caucasian subjects (~10% of total trial population) were investigated.

Children
No clinical pharmacology studies were performed in children. This is considered acceptable in view of the proposed indication of AF/AFL, which is uncommon in children.

Other
Although clearance was statistical significantly related to age, gender and weight, the clinical relevance of this finding is less clear. Based on simulated data, females would have 19% higher AUC compared to males. AUC would be 20% higher in patients with relatively low body weight (<59 kg), compared to "average" patient (84 kg in this population PK study). Vice versa, AUC would be 15% lower in overweight patients (BW>95kg). Age has relatively little influence: AUC would be 5% higher for patient > 82 yrs compared to 65 yrs old patients. The exposure would be highest for older female patients, with relatively low bodyweight.

- Pharmacokinetic interaction studies

In vitro DRO is for >84% metabolised through cytochrome P450 3A4 (CYP3A4) isoenzymes and is shown to be itself a moderate inhibitor of CYP3A4 and CYP2D6 isoenzymes. In addition, the main metabolite SR35021 demonstrated a potential for inhibition of CYP2C9, CYP2C19 and CYP1A2 as well.

Co-administered drugs affecting DRO exposure

CYP3A4 inhibitors
Repeated doses of 200 mg ketoconazole daily resulted in a 17-fold increase in DRO exposure. Therefore, concomitant use of ketoconazole as well as other potent CYP 3A4 inhibitors such as itraconazole, voriconazole, pozaconazole, ritonavir, telithromycin, clarithromycin or nefazodone is contraindicated. Calcium antagonists, diltiazem and verapamil, are substrates and/or moderate inhibitors of CYP 3A4. Moreover, due to their heart rate-lowering properties, verapamil and diltiazem have the potential to interact with DRO from a pharmacodynamic point of view. Repeated doses of diltiazem (240 mg twice daily), verapamil (240 mg once daily) and nifedipine (20 mg twice daily) resulted in an increase in DRO exposure of 1.7-, 1.4- and 1.2- fold, respectively. Calcium antagonists also have their exposure increased by DRO (400 mg twice daily) (verapamil by 1.4- fold, and nisoldipine by 1.5- fold). In clinical trials, 13% of patients received calcium antagonists concomitantly with DRO. There was no increased risk of hypotension, bradycardia and heart failure. Overall, due to the pharmacokinetic interaction and possible pharmacodynamic interaction, calcium antagonists with depressant effects on sinus and atrio-ventricular node such as verapamil and diltiazem should be used with caution when associated with DRO. These medicinal products should be initiated at low dose and up-titration should be done only after ECG assessment. In patients already on calcium antagonists at time of DRO initiation, an ECG should be performed and the calcium antagonist dose should be adjusted if needed. Other moderate inhibitors of the CYP3A4 such as erythromycin are also likely to increase DRO exposure. The MAH committed to perform an in vivo pharmacokinetic interaction study to assess the potential of inhibition of erythromycin on dronedarone and to evaluate any potential impact on the SPC (FUM 10).

CYP3A4 inducers
Rifampicin (600 mg once daily) decreased DRO exposure by 80% with no major change on its active metabolite exposure. Therefore, co-administration of rifampicin and other potent CYP 3A4 inducers such as phenobarbital, carbamazepine, phenytoin or St John's Wort is not recommended as they decrease DRO exposure.

CYP3A4 inhibitors and inducers on SR35021 exposure

The impact of CYP3A4 inhibitors and inducers on the active SR35021 metabolite is modest, because of the involvement of CYP3A4 both in its formation and further metabolism. Considering that SR35021 is 3- to 10-fold less pharmacologically potent than DRO with similar plasma concentrations under normal conditions, CYP3A4 mediated drug-drug interactions are not likely to influence DRO's clinical efficacy and safety through changes in SR35021 exposure.

Absorption modification of DRO

Pantoprazole did increase DRO C_{max} by 13%. Therefore alteration of pH does not influence DRO bioavailability to a relevant extent. Food increases DRO bioavailability 2- to 4.5-fold (see section II.1.3). Meals with a high fat content increase DRO exposure 1.2- to 1.5-fold compared to meals with a low fat content. In view of this relatively small impact of the type of meal, DRO can be recommended to be taken with food as was done in the clinical efficacy/safety studies without making specific and unrealistic recommendations regarding type of food-intake.

DRO affecting exposure of co-administered drugs

CYP3A4 substrates

Statins: DRO can increase exposure of statins that are substrates of CYP 3A4 and/or P-gp substrates. DRO (400 mg twice daily) increased simvastatin and simvastatin acid exposure by 4- fold and 2- fold respectively. It is predicted that DRO could also increase the exposures of lovastatin and atorvastatin within the same range as simvastatin acid. Interaction of DRO on statins transported by OATP, such as fluvastatin and rosuvastatin has not been studied. In clinical trials, there was no evidence of safety concerns when DRO was co-administered with statins metabolized by CYP 3A4. As high doses of statins increase the risk of myopathy, concomitant use of statins should be undertaken with caution. Lower starting dose and maintenance doses of statins should be considered according to the statin label recommendations and patients monitored for clinical signs of muscular toxicity. The MAH committed to perform an in vitro study to investigate the potential inhibition of dronedarone, SR35021 and SR90154 on OATP1B1, OATP1B3, OAT3 and OCT and to evaluate any potential impact on the SPC (FUM9).

Calcium antagonists: the interaction of dronedarone on calcium antagonists is described above.

Sirolimus, tacrolimus: DRO could increase plasma concentrations of tacrolimus and sirolimus. Monitoring of their plasma concentrations and appropriate dose adjustment is recommended in case of coadministration with DRO.

Oral contraceptives: no decreases in ethinylestradiol and levonorgestrel were observed in healthy subjects receiving DRO (800 mg twice daily) concomitantly with oral contraceptives.

P-glycoprotein substrates

Digoxin

DRO (400 mg twice daily) increased digoxin exposure by 2.5- fold by inhibiting P-gp transporter. Moreover, digitalis has the potential to interact with DRO from a pharmacodynamic point of view. A synergistic effect on heart rate and atrio-ventricular conduction is possible. In clinical trials, increased levels of digitalis and/or gastrointestinal disorders indicating digitalis toxicity were observed when DRO was co-administered with digitalis. The digoxin dose should be reduced by approximately 50%, serum levels of digoxin should be closely monitored and clinical and ECG monitoring is recommended. The MAH committed to perform an in vitro study in Caco-2 cells in order to specifically assess the potential of inhibition of poloxamer 407 on typical P-gp probe substrate such as digoxin. Based on the results obtained, the need for a further study will be evaluated (FUM 4).

CYP2D6 substrates

Beta blockers Beta blockers that are metabolized by CYP 2D6 can have their exposure increased by DRO. Moreover, beta blockers have the potential to interact with DRO from a pharmacodynamic point of view. DRO 800 mg daily increased metoprolol exposure by 1.6- fold and propranolol exposure by 1.3-fold (i.e. much below the 6- fold differences observed between poor and extensive CYP 2D6 metabolisers). In clinical trials, bradycardia was more frequently observed when DRO was given in combination with beta-blockers. Due to the pharmacokinetic interaction and possible

pharmacodynamic interaction, beta blockers should be used with caution concomitantly with DRO. These medicinal products should be initiated at low dose and up-titration should be done only after ECG assessment. In patients already taking beta blockers at time of DRO initiation, an ECG should be performed and the beta blocker dose should be adjusted if needed.
Antidepressants Since DRO is a weak inhibitor of CYP 2D6 in humans, it is predicted to have limited interaction on antidepressant medicinal products metabolized by CYP 2D6.
CYP2C9 substrates
DRO (600 mg twice daily) increased by 1.2- fold S-warfarin with no change in R warfarin and only a 1.07 increase in International Normalized Ratio (INR). No interaction was observed between DRO and losartan and an interaction between DRO and other Angiotensin II Receptor Antagonists is not expected.
CYP1A2 substrates
DRO does not have a potential to inhibit CYP1A2 to a clinically significant extent.
CYP2C19 substrates
DRO's potential to inhibit CYP2C19 has not been yet established and therefore the applicant is required to address this issue post-approval (FUM 5).

In the opinion of the CHMP the applicant has not been able to substantiate fully its claim of having developed a compound with a clinically relevant improved pharmacokinetic profile over the parent compound amiodarone. DRO's main pharmacokinetic advantage is that, compared to amiodarone, its half-life is shorter due to a smaller distribution volume. These PK characteristics may reduce the long-term pulmonary adverse events observed with amiodarone. However, it was the interaction profile (inhibition potential of CYP3A4, CYP2D6 and Pgp) of DRO that was a major cause for concern in the previous application. At present this pharmacokinetic issue was however largely solved with the submission of the ATHENA study in which generally drug-drug interactions were manageable in a clinical trial setting. In fact, potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone and ritonavir) are rightly contraindicated by the SPC and as such are not expected to pose a major concern. The same applies to grapefruit juice; the SPC instructs the medical care provider to instruct and warn the patients to avoid grapefruit juice beverages while taking DRO. When moderate/weak CYP3A4 inhibitors such as calcium-antagonists (e.g., verapamil and diltiazem) are co-administered with DRO this should be done with caution and with low doses that are only increased under ECG guidance. Potent CYP 3A4 inducers such as phenobarbital, carbamazepine, phenytoin, St John's Wort are not recommended by the SPC as they decrease DRO exposure up to five-fold. Although the impact on statins (CYP3A4 substrates) could hypothetically lead to increased risk of statin dose-related adverse events, especially myopathy, the data from ATHENA and the integrated analyses do not backup this assumption. However, it should be noted that the possible interaction with clopidogrel – an important drug for the targeted patient population – has not been evaluated by the applicant. Since the active metabolite of clopidogrel is formed by CYP3A4 and since clopidogrel is possibly also a P-gp substrate, DRO may decrease the therapeutic effect of clopidogrel. Consequently, it is very difficult to predict what will be the overall effect if DRO is taken together with clopidogrel. A DDI study is going to be performed post-approval (FUM 6).

- Pharmacokinetics using human biomaterials

Pharmacodynamics

- Mechanism of action

DRO is an anti-arrhythmic agent belonging to the benzofurane class of anti-arrhythmic compounds including amiodarone. DRO demonstrates electrophysiological characteristics belonging to all 4 Vaughan-Williams classes of anti-arrhythmic compounds:
1. To a limited extent it blocks sodium (INa) channels decreasing the slope of the depolarization phase (phase 0) of the action potential (Class I effect);
2. It also has limited non-competitive α and β adrenoceptor antagonist properties (Class II effect);
3. Its primary activity is to block the outward potassium currents involved in cardiac repolarization at both the atrial and the ventricular levels, thus prolonging action potential duration (APD) and the refractory period (Class III effect);
4. Finally, it reduces on a limited basis L-type and T-type inward calcium currents (Class IV effect).

- Primary and Secondary pharmacology

Pharmacodynamic studies focused on CV and ECG effects; electrophysiological studies are lacking. DRO decreases heart rate HR at higher than therapeutic doses and to a larger extent during exercise testing. At the clinically significant 400 mg BID dose DRO showed only moderate changes in systolic blood pressure SBP and diastolic blood pressure DBP. PR interval was increased as was QTc (10-20 ms with 400 mg BID dose), the latter increasing with dose. The dose range tested indicates that lower than 400 mg BID doses may not be clinically effective, but possibly if a 300 mg BID dose had been administered instead of 600 mg OD this dose might have shown clinical benefit. However, from these PD data the dose range chosen in the dose finding study DAFNE (see Efficacy) seems defendable, though with hindsight not very fortunate, as a lower daily dose may have had clinical relevance in special patient groups (e.g. female). DRO's antiarrhythmic properties were confirmed in a patient population especially for its heart rate lowering effect with only a limited impact on clinical endpoints e.g. conversion to sinus rhythm or impact on six minute walking distance test. A not very strong PK/PD correlation was observed for QTc and lower than average plasma ranges may have clinical significance for time to recurrence of AF/AFL.
Verapamil shows clinically relevant PK and PD interactions with DRO which may have clinical consequences (see efficacy and safety concerns). A more limited and predictable impact of co-administered beta-blockers was observed.

The results of the PD studies showed that in healthy volunteers the administration of DRO 400 mg BID was associated with a reduction in renal creatinine clearance and an increased creatinemea which returned to normal levels 14 days after drug discontinuation. This was similarly observed in patients with normal renal function or mild to moderate renal insufficiency. These observations substantiate the claim of the Sponsor regarding the possibility that the increased creatinine levels are only due to a pharmacodynamic interaction of DRO at the renal level resulting in inhibition of its clearance by inhibition of organic cation transport. However, patients with severe renal failure were not addressed in these studies. Compared with historical data of cimetidine (another known inhibitor of organic cation transporters) DRO appeared to have an equivalent or slightly lower potential to interact with creatinine secretion than cimetidine. Nevertheless, the issue still remains that an important and easily available clinical parameter for renal function is lost for daily clinical practice. This subject is further discussed under the ATHENA and ANDROMEDA studies.

Clinical efficacy

- Dose response study

Study DRI3550/DAFNE

The selected dose range was chosen on the basis of ECG effects in the phase I studies and included DRO 400 mg BID, 600 mg BID and 800 mg BID. The objective of the DAFNE study was to determine the most effective dose of DRO for the maintenance of sinus rhythm in patients with persistent AF undergoing cardioversion. Following an amendment in the protocol, the primary endpoint focussed on time to first recurrence after successful conversion to normal sinus rhythm. The efficacy results did indicate that DRO 400 mg BID had a significant effect on maintenance of sinus rhythm after conversion of AF.as shown in table below.

Table. Time to first AF recurrence in the PPM population DAFNE

Parameter	Statistics	Placebo N=48	400 mg BID N=54	600 mg BID N=54	800 mg BID N=43	Cox's Model
Duration In sinus Rhythm (days)	Median	5.32	59.92	4.31	5.18	Dose effect P=0.7188 Covariates SHD P==0.0737 AFD P=0.2943

SHD: structural heart disease AFD: AF duration

At 6 months (end of study), the recurrence rate was 65% (DRO 400 mg BID) vs. 90% (placebo) which is considered clinically relevant. This was further supported by outcomes of the secondary endpoints. This study however raises the issue of lack of dose response. No significant effects were seen in the median time to first AF recurrence in the PPM population following the 600 mg BID or 800 mg BID dosages. This difference could be due to the heterogeneity of the groups, but the results contrasted with the effect on non-electrical cardioversion and ventricular rates in case of recurrence where the higher doses showed slightly better results. In the previous assessment, the issue of lack of dose response was discussed by the applicant. As already stated, lower doses were not investigated in the PD studies, which is a weak point of the clinical development program. Further analysis of the subsequent studies EURIDIS/ADONIS data in which patients were administered DRO 400 mg BID showed that patients achieving lower than median plasma concentrations had worse results (albeit significant) than those achieving higher concentrations. This probably denotes that lower DRO doses may not be effective but where the cut-off point lays remains unclear. Still, available PK/PD data show only a minimal correlation of electrophysiological changes with plasma concentration. The unavailability of data on a lower dose and the lack of a drug formulation of e.g. 300 mg to be given BID, is especially unfortunate in view of specific patient groups, e.g. patients with specific interacting co-medications, who are at risk of increased DRO exposure.

- Main studies

Studies EFC3153/EURIDIS and EFC4788/ADONIS

EURIDIS is EURopean trial In AF or flutter patients receiving DRO for the maintenance of Sinus rhythm. It was conducted in 65 active centres in 12 European countries: in the period between: November, 2001 and August, 2003. ADONIS is: American-Australian-African trial with DRO In AF or flutter patients for the maintenance of Sinus rhythm, conducted in 101 active centres in 5 countries: USA, Canada, Australia, South Africa and Argentina in the period between: November, 2001 and September, 2003. Due to the similarities in the study design in both studies, they will be presented together.

METHODS

Study Participants

Patients included in these studies were of either sex aged 21 years or older, in sinus rhythm for at least 1 hour at the time of randomization and with at least one ECG-documented AF/AFL episode in the last 3 months were included. The main exclusion criteria were New York Heart Association (NYHA) class III and IV congestive heart failure (CHF); second degree AV block or higher, or significant sinus node disease (documented pause of 3 seconds or more) without a permanent pacemaker implanted; QT >500 msec; documented AF/AFL episode motivating inclusion in the study starting and not persisting beyond 10 days after an acute condition known to cause AF/AFL (eg, alcohol intake, thyrotoxicosis, infection, myocardial infarction, pericarditis, pulmonary embolism, cardiac surgery); antiarrhythmic therapy (see below), patients in whom amiodarone or 3 or more Class I or III antiarrhythmic drugs prescribed for sinus rhythm maintenance were discontinued for inefficacy.

Treatments
These were two multi-centre, multinational, double-blind, parallel-group, placebo-controlled studies assessing the efficacy of DRO 400 mg BID versus placebo for the maintenance of normal sinus rhythm after conversion of AF/AFL

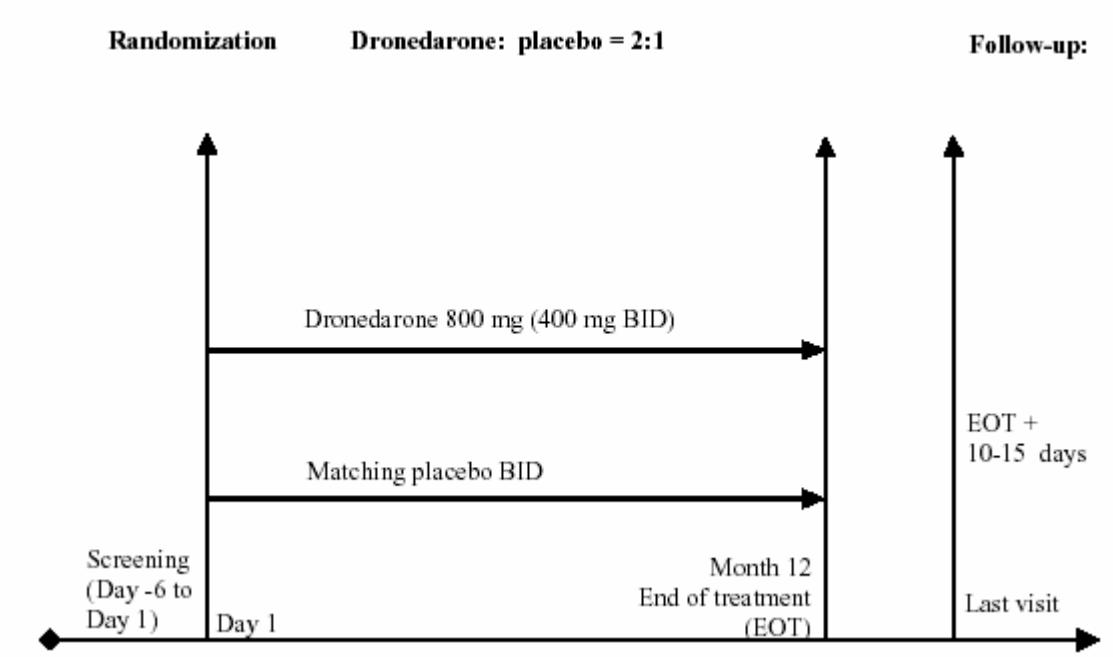


Fig: Overall Design EURIDIS/ADONIS

Objectives
The primary objective of these studies was to assess the efficacy of DRO 400 mg BID versus placebo for the maintenance of normal sinus rhythm after electrical, pharmacological or spontaneous conversion of AF/AFL. The secondary efficacy endpoints were: symptomatic AF/AFL among the adjudicated first AF/AFL recurrence, time elapsed in days between Day 5 midnight (steady state) and the adjudicated first AF/AFL recurrence within 12 months from randomization, ventricular rate assessed at the time of the adjudicated first AF/AFL recurrence.

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

Sample size
A total sample size of 552 patients was planned for each study with a ratio of 2 DRO patients for 1 placebo patient in each study (368 patients in the DRO 400 mg BID group, and 184 in the placebo group) in order to maximize the number of patients on study drug. Sample size determination were computed based on Lachin and Foulkes formulas to detect a relative decrease of at least 25% between DRO and placebo with 90% power using a log-rank test of equality of survival curves with 5% two-sided significance level, assuming 60% of patients on placebo would have a recurrence within 12 months, a common drop out rate of 20% and a recruitment period of 12 months.

Randomisation and blinding
These were a double-blind study. Two parallel groups of patients in each study were allocated according to central randomization

Statistical methods

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

RESULTS

Primary endpoint

The time from randomization to adjudicated first AF/AFL recurrence within 12 months is presented on Figure 1. Overall, DRO 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 median time from randomization to adjudicated first AF/AFL recurrence in the DRO 400 mg BID group was 2.2-fold longer than in the placebo group. The on-treatment analysis in the PP population, confirmed the results of the primary analysis. The time to recurrence was significantly longer in the DRO versus placebo group (Log-rank test, p = 0.0131 for EURIDIS and p=0.0018 for ADONIS). At 12 months, 64.1% of DRO 400 mg BID-treated patients were estimated (Kaplan-Meier) to have experienced a first AF/AFL recurrence, compared to 75.2% of placebo-treated patients.

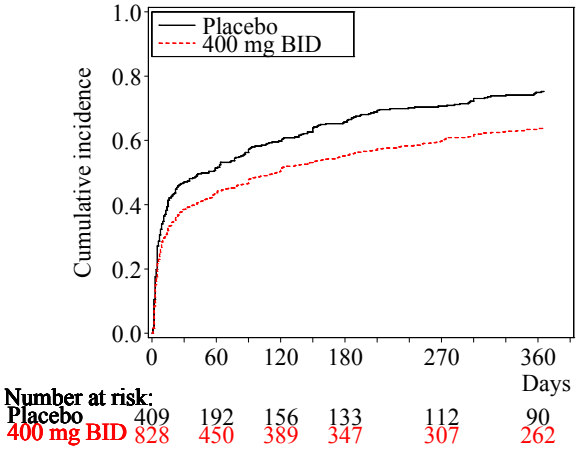


Figure 1 Time to adjudicated first AF/AFL recurrence

However, a median difference of 63 days time from randomization to adjudicated first AF/AFL recurrence within 12 months again raises the issue of clinical relevance, in particular as the difference in recurrence rate after 12 months of approximately 10% is less than seen in the DAFNE study after 6 months. At one year the absolute benefit for the primary endpoint of AF/AFL recurrence is 11.2% and 11.8% in EURIDIS and ADONIS respectively. The NNT to prevent one event is 12 and 9 in EURIDIS and ADONIS respectively. In the SAFE-T study[1] (a three-armed study, comparing the time to AF recurrence between amiodarone, sotalol and placebo), the median time to recurrence of AF seems more clinically relevant compared to the EURIDIS/ADONIS study results. This was a major efficacy objection raised during the first assessment. According to the MAH, in the SAFE-T the counting of AF recurrences started almost one month after the beginning of treatment when blood and tissue levels of the study drugs were at steady-state, effective levels. In EURIDIS/ADONIS patients were randomized while in sinus rhythm, with the counting of AF/AFL recurrences starting at randomization, well before DRO reached effective plasma and tissue levels. According to the CHMP this explanation appeared plausible, although it is not unlikely that differences in study population may have contributed to different outcomes too. These questions could only be definitely answered by a head-to-head comparative study within one study population as recommended by the NfG on antiarrythmics (CPMP/EWP/237/95). Although such studies may need to restrict specific patient populations, they are necessary to clearly define the place of DRO in AF/AFL therapy. The results of the comparative study of DRO DIONYSOS against amiodarone currently submitted helped to solve this issue (see below).

[1] N. Eng J Med 352; 18; 2005

Regarding patients with atrial flutter AFL, further analysis of the data (Day 150 of the previous assessment) showed that a subpopulation of 131 (out of 828) patients with AFL were recruited in the EURIDIS/ADONIS. The efficacy results in maintenance of sinus rhythm in the AFL patients were comparable to those described with AF. Regarding rate control, it did not reach the ESC recommended targets. The extent of rate control for patients with AFL who did not have an AF/AFL recurrence is unknown in the EURIDIS/ADONIS studies. Furthermore, no impact on symptom relief in this patient population is known precluding any conclusions.

Secondary endpoints

Symptomatic AF/AFL recurrence among first recurrence

Overall, the adjudicated first AF/AFL recurrence was associated with symptoms in 58.7% (304/518) of patients in the DRO 400 mg BID group (55.1% in EURIDIS, 62.6% in ADONIS, Sec. 5.3.5.1), versus 61.1% (184/301) in the placebo group (61.3% in EURIDIS, 61.0% ADONIS).

Time between steady state and adjudicated first AF/AFL recurrence

Overall, DRO 400 mg BID significantly lowered by 28%, the risk of first recurrence of AF/AFL from Day 5 midnight compared to placebo. The median time from presumed steady state to adjudicated first AF/AFL recurrence in the DRO 400 mg BID group was 2-fold longer than in the placebo group. At 12 months, 53.8% of DRO 400 mg BID-treated patients were estimated to have experienced a first AF/AFL recurrence, compared to 66.2% of placebo-treated patients.

Effects on ventricular rate in case of recurrence

Heart rate assessed at time of adjudicated first AF/AFL recurrence during study period up to Day 365 is summarized in Table E12. DRO 400 mg BID-treated patients had significantly lower mean heart rates at the time of the first AF/AFL recurrence in both EURIDIS and ADONIS studies (TTEM method, $p<0.0001$, ANOVA and $p=0.0009$, ANOVA, respectively; $p<0.0001$ for the pool of EURIDIS /ADONIS).

Ancillary analyses

The time from randomization to first hospitalization or death within 12 months is summarized in table below. Overall, the risk of first hospitalization or death within the 12-month period was significantly reduced by 27% with DRO 400 mg BID compared to placebo. 22.8% of DRO -treated patients were estimated to have a first hospitalization or death at 12 months, compared to 30.9% of placebo-treated patients.

Table: Unadjusted analysis of time from randomization to first hospitalization or death within 12 months - randomized and treated patients population EURIDIS/ADONIS

	EFC3153/EURIDIS		**EFC4788/ADONIS**		**Pooled**	
	Placebo (N=201)	**Dronedarone 400 mg BID (N=411)**	**Placebo (N=208)**	**Dronedarone 400 mg BID (N=417)**	**Placebo (N=409)**	**Dronedarone 400 mg BID (N=828)**
Number of patients with endpoints	54	76	47	84	101	160
Relative risk with 95% CI[a]	0.659 [0.465;0.934]		0.799 [0.559;1.142]		0.726 [0.566;0.931]	
Log-rank's test result (p-value)	0.01834		0.217		0.01134	

[a] Determined from Cox regression model

Study EFC4508/ERATO

This was a multicentre, multinational, double-blind, randomized, parallel-group, placebo-controlled study. About 160 patients with AF at rest were to be randomized to receive DRO 400 mg BID or placebo. The planned treatment duration for each patient was 6 months to assess the efficacy of DRO for the control of ventricular rate in patients with AF at rest.

METHODS

Study Participants

There were two inclusions criteria: a) Patients of either sex aged 21 years or older, with symptomatic (any AF-related symptoms including palpitations), permanent AF (defined as duration of AF>6 months) for which cardioversion was not considered. b) Resting ventricular rate ≥ 80 bpm at screening measured on a 6-second rhythm strip. The main exclusion criteria were NYHA class III and IV; second degree AV block or higher; antiarrhythmic therapy (see below).

Treatments

This was a multicentre, multinational, double-blind, randomized, parallel-group, placebo-controlled study. About 160 patients with AF at rest were to be randomized to receive DRO 400 mg BID or placebo. The planned treatment duration for each patient was 6 months (Figure E7). The effects of dronedarone administered on top of standard therapy on HR were measured using a 24-hour Holter recording starting after a 2-week administration, and compared to those in the placebo group. Previous studies had shown that at this time PK and pharmacodynamic (PD) steady state were reached. The effects on ventricular rate during exercise and exercise performance were assessed using a symptom-limited exercise test coupled, in a subset of patients, to gas exchange analysis. Long term efficacy was confirmed by a second 24-hour Holter recording after 4 months of treatment. An end-of-study visit was done at 6 months +10 to 15 days

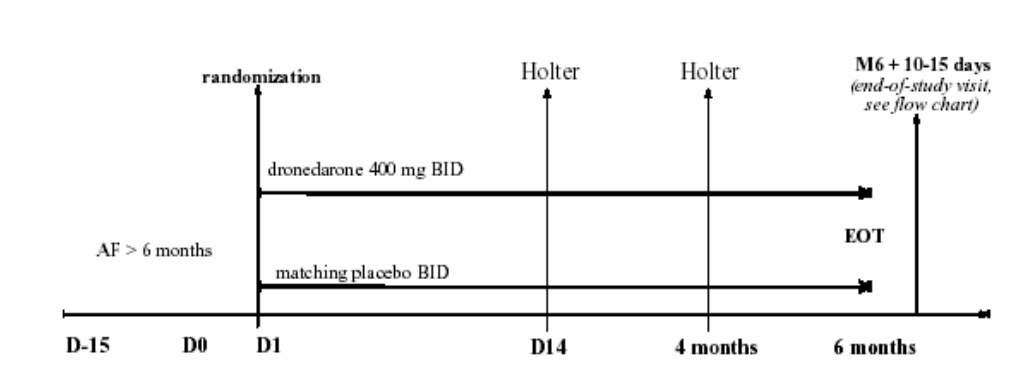


Fig Study Design ERATO

Objectives
To assess the efficacy of DRO for the control of ventricular rate in patients with AF at rest.

Outcomes/endpoints
The primary efficacy variable was the change in mean HR measured by a 24-hour Holter recording at rest on Day 14 (steady state) compared to baseline. The main secondary efficacy variable was the exercise tolerance on Day 14 compared to baseline (maximal exercise duration defined as time elapsed between the start of the exercise test and its stop). The other secondary efficacy variables were: evaluation of exercise performance: difference in HR at sub-maximal and maximal exercise between baseline and Day 14; to document that exercise performance was not diminished by the expected decrease in HR; difference for each gas exchange parameter and for SBP between baseline and Day 14 (at rest, sub- maximal, anaerobic threshold and maximal intensity); difference for anaerobic threshold between baseline and Day 14; difference in heart rate evaluated by the 24-hour Holter recording between baseline and Month 4.

Sample size
174 patients were randomized and treated. Of the 174 randomized patients, 85 received DRO and 89 received placebo. Demographic characteristics in the all randomized patient population were similar in the 2 treatment groups. Demographic characteristics in the PP population were similar to those of the all randomized patient population.

Randomisation and blinding
This was a double-blind study. Treatment was assigned to either DRO or placebo by randomization in a 1:1 proportion.

Statistical methods
Primary Analysis: summaries on changes from baseline were derived from ANCOVA and Rubin's rule: (1) mean change from baseline (adjusted for age, baseline Holter HR value, and baseline intake of beta-blockers, calcium antagonists and digitalis) for each treatment group, as well as standard error and 95% CIs; (2) difference between change from baseline, as well as standard error and 95% CIs.

Secondary analysis of primary endpoint: the same ANCOVA was performed in the all randomized patient population with non-missing primary endpoint evaluation (sensitivity analysis) and in the PP population.

RESULTS
The patient population recruited for this study included permanent AF patients defined as having AF for more than 6 months. No patients with AFL were recruited, precluding any claims. The same dose of 400 mg BID was chosen for this study based on the results of the dose finding study DAFNE and further confirmed in the EURIDIS/ADONIS studies. The studied patients and their concomitant medications can be considered representative of the claimed population, although numbers are small. The primary efficacy variable was the change in mean HR measured by a 24-hour Holter recording at rest on Day 14 (steady state) compared to baseline. Duration of the study is limited to 4 months, which is still considered sufficient to assess maintenance of effect on heart rate. Results showed a significant effect on mean heart rate compared to baseline at rest in the DRO group compared to the placebo group when measured after 14 days of treatment (table below).

Table: 24-hour Holter heart rate (bpm) after 14 days ERATO

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

Comparable reductions were also shown during maximal exercise (–28 vs. –3 bpm). Holter monitoring after 4 months showed maintenance of the effect without interaction with other heart-rate lowering agents (beta blockers, calcium antagonists and digitalis). However, these reductions in heart rate were not accompanied by improvement in exercise testing, or by improvement in gas exchange parameters, anaerobic threshold, nor in symptom scores, limiting the clinical relevance of the findings. Two studies have been performed (AFFIRM, RACE) suggesting that a rate control strategy might be acceptable at least for some patients, but this has not been tested in the ERATO study.

Study EFC5555/ATHENA

In support of the new proposed indication *reduction of CV hospitalization or death from any cause in patients with AF/AFL or a history of AF/AFL*, the applicant submitted the results of one confirmatory study ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of DRO 400 mg bid for the prevention of CV Hospitalization or death from any cause in patiENts with AF/atrial flutter (AF/AFL).

METHODS

Study Participants

Originally, patients ≥70 years in sinus rhythm or in AF/AFL could be included. All patients were to have at least 1 risk factor (including age, hypertension, diabetes, prior cerebro-vascular accident, left atrium (LA) diameter greater than or equal to 50 mm or left ventricular ejection fraction less than 0.40). Available ECG within the previous 6 months documenting that the patient was or is in AF/AFL or sinus rhythm was necessary. To ensure sufficient recruitment, an amendment in the protocol was made to allow recruitment of patients aged 75 years with or without additional risk factors. The main exclusion criteria were: permanent AF; NYHA class IV CHF; second degree AV block or higher, or significant sinus node disease (documented pause of 3 seconds or more) without a permanent pacemaker implanted; bradycardia <50 bpm and/or PR-interval ≥0.28 sec on the last 12-lead ECG; patients in whom concomitant medication with Class I or III antiarrhythmic drugs were necessary; plasma potassium <3.5 mmol/L. Through a protocol amendment, patients with calculated glomerular filtration rate (GFR) at baseline <10 mL/min using the Cockroft Gault formula were also excluded. The identified high risk patients in the previous studies e.g. patients ≥ 75 years and females patients were well represented (41% and 46% respectively). More patients were administered beta-blockers, digoxin and calcium channel blockers than those reported in the previous phase III studies. This could allow identification of any associated risk in this AF/AFL population.

The 2 treatment groups were well-balanced for baseline CV examination and history. Despite the wide inclusion criteria, patients with NYHA III or LVEF<30% formed only 4% of the recruited patients which questions the robustness of any results pertaining to these subgroups. The CV history of the recruited patients shown in table E3 illustrates that hypertension was the predominant associated morbidity.

Baseline creatinine clearance was balanced between the two treatment groups. DRO is primarily metabolized by the liver, but the effect of administration of DRO in patients with severe renal insufficiency is particularly important considering that one of the risk factors associated with mortality in the ANDROMEDA study was baseline creatinine clearance. (see further discussion under Safety)

Treatments
This was a multicenter, multinational, double-blind, randomized, parallel-arm, placebo-controlled study evaluating the effects of DRO 400 mg BID versus placebo over a minimal follow-up period of 12 months in patients with AF/AFL or a history of AF/AFL with additional risk factors.

Patients first entered a screening period for a maximum of 7 days. After randomization, all patients were to be followed until the common study end date, which was to be 1 year after the last patient was randomized. Thus the minimum follow-up time was to be 12 months. Patients could be randomized in the study while in sinus rhythm if conversion had occurred either spontaneously or following a procedure such as electrical cardioversion (or overdrive pacing) or administration of an anti-arrhythmic drug. Patients could also be randomized while in AF/AFL, and in this case they could undergo cardioversion after appropriate anticoagulation.

Concomitant medications like beta-blockers, calcium channel blockers and digoxin were also permitted, with caution as in the previous studies. The prescribed up-titration of initial low dose CCB, beta-blockers and digoxin under ECG guidance is reflected in the proposed SPC. There were three amendments to the protocol of the Athena study, including modification of the inclusion criteria, increase in the sample size and classification of all deaths for descriptive purposes and a substudy of symptoms according to the Bubien and Kay scale. According to the applicant the first 2 amendments were implemented in order to prevent a lowering of the event rate and allowed recruitment of patients with higher CV risk. The Applicant provided detailed analysis of the results obtained before and after the interim analysis. According to the analysis the observations made in both populations for primary and secondary endpoints were consistent validating the pooling of the data before and after the amendments.

Objectives
The primary objective was to assess the efficacy of DRO 400 mg BID in preventing CV hospitalizations or death from any cause in patients with AF/AFL or a history of AF/AFL with additional risk factors.

Outcomes/endpoints
The primary efficacy endpoint of the study was the time from randomization to first CV hospitalization or death from any cause, whatever was earlier, as assessed by the Investigator. Pre-defined main causes for non-planned CV hospitalizations were specified. Death was defined as any death in a participating patient during the study period. The secondary efficacy endpoints were time from randomization to: (1) death from any cause, (2) first CV hospitalization, (3) CV death.

Sample size
This is the largest clinical study submitted in the current application (or in the indication of AF yet) recruiting around 4000 patients, evaluating the effects of DRO 400 mg BID versus placebo (ratio 1:1) over a minimum treatment and follow-up duration of 12 months in patients with paroxysmal or persistent AF/AFL. Patients aged 75 years or older were eligible with or without additional risk factors. Alternatively, patients of at least 70 years of age were eligible if one or more of the following risk factors are present: hypertension, diabetes, prior cerebro-vascular accident, left atrium (LA) diameter ≥50 mm or LVEF< than 0.40. The inclusion criteria allow investigating DRO under realistic circumstances.

Randomisation and blinding
This was a double-blind study. Two parallel groups of patients were allocated to DRO 400 mg BID or placebo according to central randomization. The randomization was performed in a 1:1 ratio, stratified by study centre and by the presence of AF/AFL at randomization time.

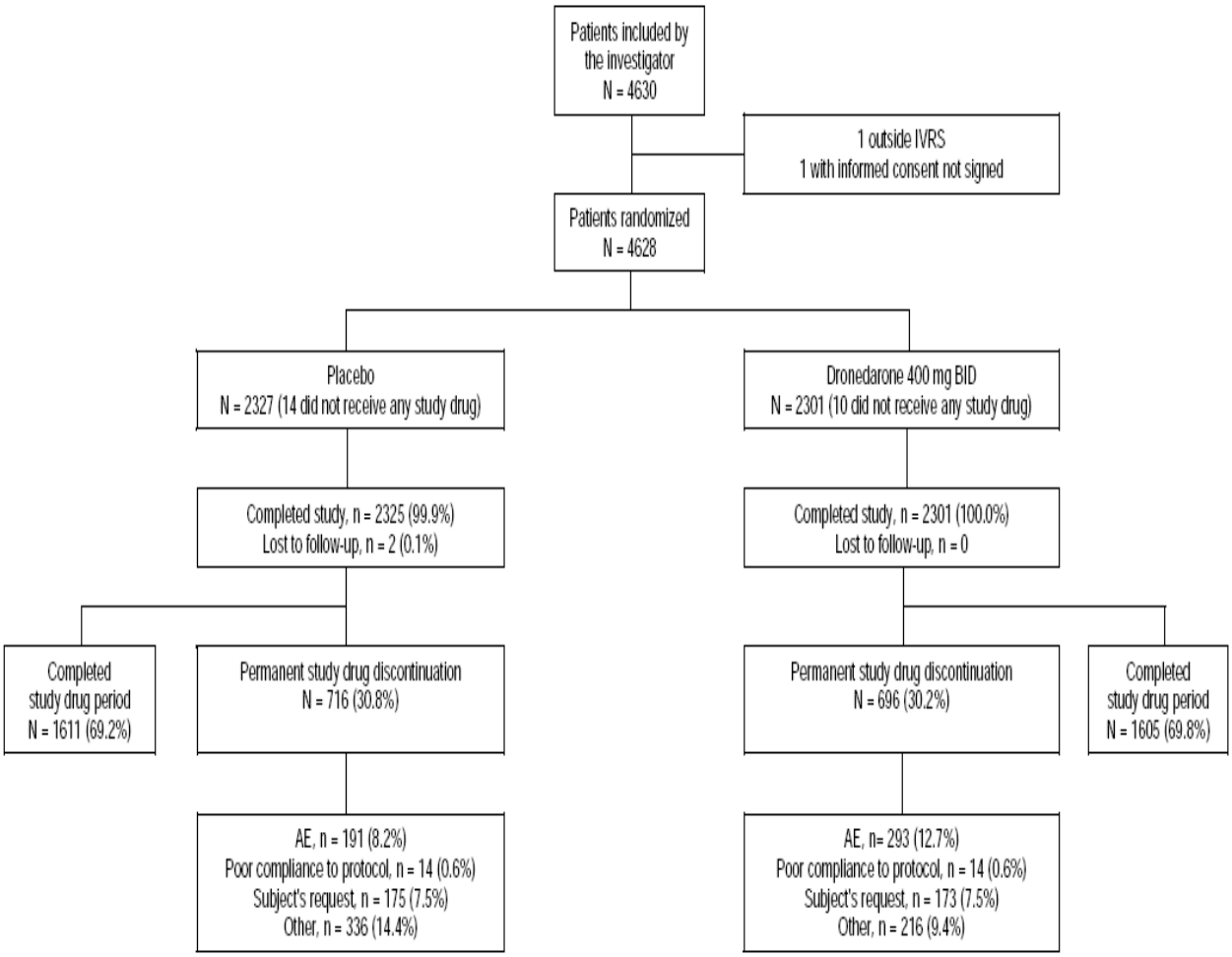
Statistical methods
Primary endpoint: the efficacy analysis considered all assessments from randomization to the end of study date, which was defined as the final follow-up visit/last contact date or the date of death, whatever came first. The primary analysis was the comparison of the time from randomization to the primary endpoint between the 2 treatment groups using a 2-sided log-rank asymptotic test. Cumulative incidence functions in each treatment group were calculated and plotted using non-parametric Kaplan-Meier estimate. The corresponding 95% confidence interval (CI) was computed at each scheduled

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

Secondary endpoints: In order to protect the global type I error of 5%, a hierarchical procedure was to be applied to the secondary efficacy endpoints. "All deaths whatever the cause" was to be tested first, then testing of "CV hospitalization" was to be performed, and then "CV death" was to be tested lastly. The same analysis approach as for the primary endpoint was used for all secondary endpoints.

RESULTS

Participants flow



Patient disposition in ATHENA

N = population size; n = sample size; IVRS = interactive voice response system; BID = twice daily; AE = adverse event. Other reasons included: AF/AFL recurrence, family request, and treatment with prohibited medications.

The primary endpoint of the incidence of CV hospitalization or death from any cause was significantly reduced when using DRO 400 mg BID compared with placebo (table and figure below). At one year the absolute benefit for the primary endpoint (first CV hospitalization or death from any cause) is 7.4%. NNT to prevent one event is 16.

Table : Unadjusted analysis of time from randomization to first CV hospitalization or death from any cause – all randomized patients- ATHENA

	Placebo* (N= 2327)	**DRO 400 mg BID* (N= 2301)**
Number of events, n	917 (39,4%)	734 (31,89%)
Median survival [95% CI](day)	NA	NA
Cumulative incidence of events at 6 months [95% CI]	0.202 [0.185 ; 0.218]	0.147 [0.132 ; 0.161]
Cumulative incidence of events at 1 year [95% CI]	0.302 [0.283 ; 0.320]	0.228 [0.211 ; 0.245]
Cumulative incidence of events at 2 years [95% CI]	0.422 [0.400 ; 0.444]	0.354 [0.332 ; 0.377]
Endpoint's composition:		
Cardiovascular hospitalization	859 (36,9%)	675 (29,3)
Death from any cause	58 (2,49%)	59 (2,56%)
- Cardiovascular death	33 (1,41%)	26 (1,12%)
- Non cardiovascular death	25 (1,07%)	33 (1,43%)
Log-rank test p-value	2E-8	
Relative risk [95% CI][a]	0.758 [0.688; 0.835]	

a Determined from cause-specific Cox regression mode

* - percentage calculated by the assessor using a binomial approach

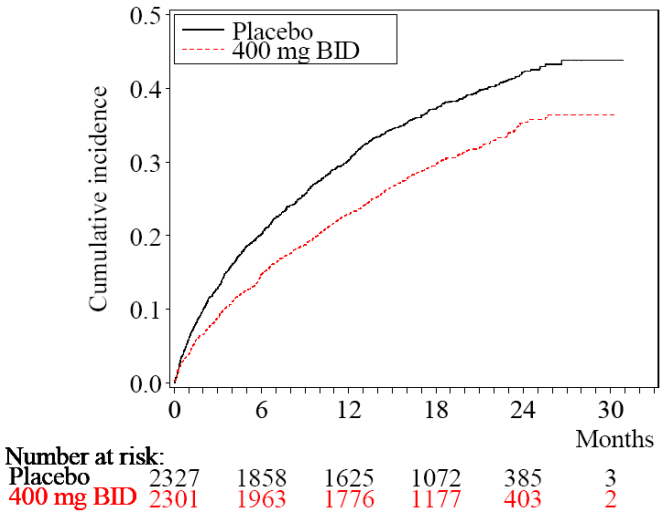


Figure: Kaplan-Meier cumulative incidence curves from randomization to A. first cardiovascular hospitalization or death from any cause –all randomized patients- ATHENA

The results are mainly driven by the number of CV hospitalization; the incidence of death was not significantly different between the two groups [n= 58 (2.49%) and n=59 (2.56%)] precluding any claims on that point. However, in light of the results of the ANDROMEDA study, it is reassuring that no increased overall mortality was seen in the DRO group. This effect was adequately shown till 24 months; thereafter the number of patients at risk is too few to allow any conclusions.

The results of the primary endpoint of ATHENA pointed that DRO decreased the risk of CV hospitalizations [29.3% (675/2301) vs. 36.9% (856/2327) compared to placebo]. That was mainly driven by a reduction in AF-related hospitalizations (12.9% (296/2301 versus 19.6% (457/2327)] i.e. 44% and 53% of all CV hospitalizations in the DRO and placebo groups respectively). Collectively, other reasons for CV hospitalizations account for 16.4% in the DRO group and 17.3% in the Placebo group with a difference of 0.9%. One major objection was posed against the claim of "reduction of CV hospitalizations". The applicant was requested to show a definite reduction in CV-hospitalizations beyond those that could be attributed to the rate and rhythm regulating properties of DRO in the treatment of AF. In their response, the applicant has failed to adequately address this point as such data was not collected at time of hospital admission, a major failing in ATHENA. From the currently submitted admission data, the main reason for admission was still not identified in a large number of cases (7.9% and 5.6% in of the placebo and DRO groups respectively) where no electrical cardioversion or CHF was reported.

A post-hoc analysis from seven countries accounting for 58% of the total number of CV hospitalizations contributing to the primary endpoint of the study (placebo= 246 and DRO=159) was presented. This post-hoc analysis is subject to a possible selection bias. Data show that the main reasons associated with first CV hospitalization adjudicated post-hoc as AF/AFL were related to pharmacological or non-pharmacological treatment related to the arrhythmias (88.2% for placebo versus 81.8% for DRO) and associated symptoms of AF/AFL (72% for placebo versus 74.2% for DRO). A benefit of DRO can be observed in these cases suggesting that its beneficial effect on AF-related hospitalisations is mainly due to its antiarrhythmic properties. Besides, a benefit was seen in the number of hospitalisations due to adjustment of antithrombotic/anticoagulant treatment.

Additional analyses showed that a larger benefit for DRO in the reduction of CV-hospitalizations was shown in patients with permanent AF/AFL throughout the study compared to patients who were in permanent sinus rhythm, but the numbers of this subgroup are too few precluding any conclusions. In patients with non-permanent AF/AFL, a slightly higher percent was recorded with hospitalizations due to myocardial infarction in the DRO group compared to the placebo group, but, again, the numbers are too few to allow robust conclusions. Although some benefit was seen with DRO in patients in sinus rhythm (reported higher frequency of major bleeding in the placebo group [n=12, 1.6% versus n=7, 0.8%] associated with a lower pulmonary embolism/deep venous thrombosis [PE/DVT] compared to the DRO group [n=1,0.1% versus n=5, 0.6%]), this effect is not shown with the general ATHENA cohort group. Otherwise, the results are consistent across the baseline selected characteristics and the geographical regions. No target group could be specifically defined.

At baseline, around 75% of the patients were in sinus rhythm. At time of CV hospitalization, this percentage is reversed in the post-hoc group where most of the patients are with AF/AFL. More patients in the DRO group (38.5%) were in sinus rhythm than in the placebo group (24.8%) at the time of first CV-hospitalisation. Similarly more patients in the DRO group (17.9%) hospitalised with AF-AFL related hospitalisation were in sinus rhythm at the time of first CV-hospitalization than placebo (12.8%). At the time of CV-hospitalization, the recorded heart rate was generally lower in the DRO group compared to the placebo group. This is an expected finding considering the mechanism of action of DRO. The impact of DRO treatment on duration of hospitalization appears to be minimal on the total number of nights (mean nights= 7.8 and 7.5 for placebo and DRO respectively) but with slightly better results on the nights spent in ICU/CCU (mean nights 4.7 and 3.9 respectively). The number of deaths from any cause on study (secondary endpoint) was comparable between the DRO (116/2301) and placebo (139/2327). The incidence of non-CV deaths was numerically higher in the DRO group (51 vs. 45 in the placebo group).

During the on-study period, DRO significantly decreased by 30.2% the incidence of CV death (secondary endpoint) compared with placebo (p=0.0252). The reduction of CV death with DRO 400 mg BID was mainly due to a reduction in sudden cardiac deaths and stroke. The reduction in sudden cardiac death further alleviates the concerns regarding the possible pro-arrhythmic potential of DRO raised following the ANDROMEDA study (described below). Very few numbers of deaths due to heart failure were recorded in both groups (DRO 0.6%; placebo 0.4%) which are reassuring.

Subgroup Analysis

Relative risk analysis (DRO 400 mg BID versus placebo) based on some baseline characteristics/medications did not show any significant interactions for the primary endpoint. Similarly no significant interactions were seen for all death or CV deaths except with diuretics use which was associated with a significant reduction in RR. The exact relation is not established, but according to the applicant, this could either be due to chance or related to different patient profile or related to the pharmacological activity of DRO on potassium homeostasis. On the other hand, there was a trend for higher relative risk in patients below 65 years (n=875; RR: 1.19; 95%CI: 0.58-2.43). Further analysis of the data revealed no specific causes of death for the recorded trend. A causal relationship appears unlikely.

In the subgroup of patients in sinus rhythm at randomization, DRO 400 mg BID significantly delayed the time to first AF/AFL recurrence and significantly lowered the risk of first recurrence of AF/AFL compared to placebo, by 25.1% (RR: 0.749; 95% CI: 0.681-0.824).

Assessment of symptoms according to the Bubien and Kay scale did not show any significant treatment effects of DRO on AF-related symptoms. This substudy was implemented in a protocol amendment and according to the applicant, baseline AF-related symptoms are lacking in ATHENA. This complicates the interpretation of the results.

Another major objection related to patients in atrial flutter (AFL), as no separate analysis was presented for these patients. The recruited patient subgroup with AFL at baseline was small (n= 104; placebo= 55 and DRO= 49) making it difficult to draw robust conclusions in this subgroup based on the ATHENA results therefore no claim on AFL could be made.

According to the applicant in the ATHENA study, fewer patients in the DRO group had a successful electrical cardioversion (n=305) compared to the placebo group (n=430), but the total number of cardioversions was not reported. The timing of this cardioversion to drug intake was not specified by the applicant precluding any conclusion about the reason for the less successful rate of cardioversion in the DRO group. Furthermore, once a cardioversion is performed, no benefit is shown for DRO to prolong the time to recurrence. These data do not support administering DRO as a pre-treatment before electro-conversion.

Generally, it can be concluded that the recorded heart rate in patients in AF in ATHENA is comparable to those in ERATO. On day 14 in ERATO, AF patients (only AF patients were recruited in ERATO) on DRO had a mean heart rate of 76.2±1.4 bpm compared to a mean ± SD of 78.5 ± 18.23 bpm recorded in ATHENA. A benefit was shown regarding CV hospitalisations for patients with persistent AF throughout ATHENA in time to first CV hospitalization, although the numbers are too few for robust conclusions. The submitted data for patients in SR or AF at baseline show that DRO significantly reduced HR throughout ATHENA compared to placebo. The HR at time of AF/AFL at recurrence was not submitted as it was not recorded systematically.
In summary, the majority of the CV hospitalizations are attributed to AF-related causes. The benefit in other non-AF related reasons amounts to 0.9%. The exact reason for AF-related hospitalizations is still not known, but could probably be related to the need for pharmacological interventions for the treatment of the arrhythmias. No benefit was shown in the incidence of time to death.

Study EFC4968/ DIONYSOS

An actively-controlled study was considered essential in order to establish the place of DRO in clinical practice. DIONYSOS was a randomized, double-blind, parallel-arm study to evaluate the efficacy and safety of DRO (400 mg BID) versus amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) for at least 6 months for the maintenance of sinus rhythm in patients with AF.

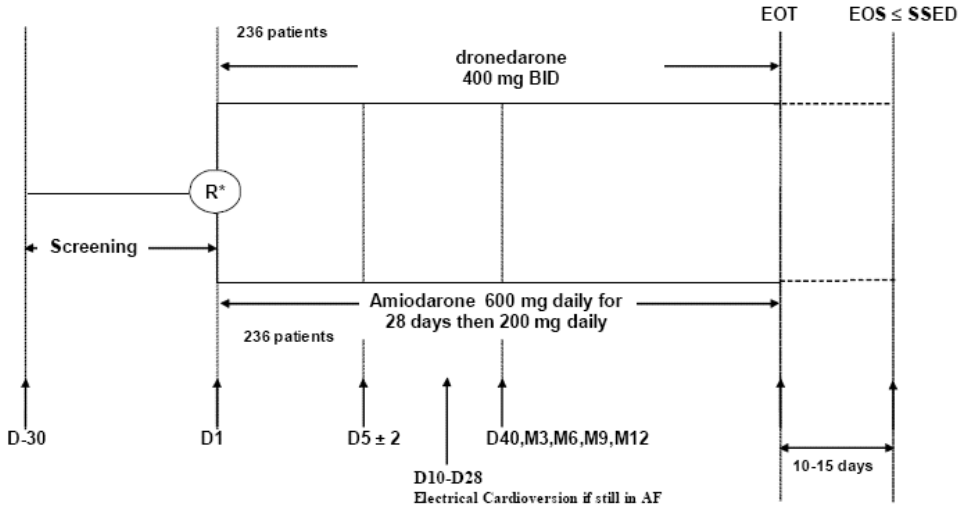
METHODS

Study Participants

Patients with a documented AF for more than 72 hours, for whom cardioversion and antiarrhythmic treatment were indicated in the opinion of the Investigators, and who were receiving anticoagulants. Patients with clinically overt CHF, NYHA III and NYHA IV were excluded in this study. This exclusion takes into account the uncertain safety profile of DRO in this patient population.

Treatments

Patients with a documented AF for more than 72 hours, for whom cardioversion and antiarrhythmic treatment were indicated in the opinion of the Investigators, and who were receiving anticoagulants were to be randomized in a ratio of 1:1 to DRO or amiodarone as shown in figure below.



*R : Randomization
SSED: Scheduled Study End Date = Last patient randomization date + 190 days (6 months on treatment + 10 days)

Figure: Design of DIONYSOS.

The choice of the loading dose of amiodarone (600 mg for 4 weeks) is higher than that used in many EU countries, though is admittedly still lower than that used in the SAFE-T study.

Objectives
The objective of the study was to demonstrate that DRO is superior to amiodarone and to evaluate the safety of DRO compared to amiodarone.

Outcomes/endpoints
The primary endpoint was a combined endpoint of first occurrence of either recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy. A combination of efficacy and safety is not a preferred endpoint considering the difficulty in interpretation of data. In this case, it was probably anticipated by the applicant that DRO may not demonstrate higher efficacy, but is probably better tolerated than amiodarone and accordingly the combined endpoint.

Sample size
A total of 618 patients were screened for the study. Five-hundred and four (504) patients were randomized and treated, 249 patients in the DRO group and 255 in the amiodarone group. No patients were lost to follow-up.

Randomisation and blinding
Patients were randomised in a ratio 1 :1 to DRO or amiodarone.

RESULTS
There was more premature permanent discontinuation of the study drug reported with DRO (38.6%) than amiodarone (27.1%), based mainly on lack of efficacy (21.3% for DRO versus 5.5% for amiodarone). On the other hand, less discontinuation was reported with DRO due to adverse events (12.9% versus 17.6% for amiodarone). More patients in the DRO group underwent electrical cardioversion less than 9 days after the first drug intake than in the amiodarone group, which could reflect an advantage for amiodarone. Still, conversion to sinus rhythm is not a claimed indication for DRO. The incidence of the primary efficacy endpoint was 75.1% and 58.8% in the DRO and the amiodarone groups respectively after 12 months of treatment (hazard ratio=1.59, log-rank p-value <0.0001).

The efficacy results are especially disappointing for DRO where AF recurrence was shown to be at a rate of 63.5% versus 42% for amiodarone. On the other hand, driven mainly by intolerance, there is a slight advantage of DRO over amiodarone in reduction of premature study drug discontinuation (10.4% versus 13.3% respectively).

Safety results

The applicant selected a main safety endpoint (MSE) capturing most of the expected AEs of amiodarone **(***occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye AEs)* in addition to diarrhoea, a frequently reported AE with DRO, and premature study drug discontinuation following any AE. A non-significant relative risk reduction of 19.8% (p=0.129) in the incidence of the main safety endpoint was observed with DRO (table below).

Table: Composition of the main safety endpoint - All randomized and treated patients

First main safety endpoint	Dronedarone 400 mg BID (N=249)	Amiodarone 600 mg/200 mg OD (N=255)
Number of patients with endpoint	83 (33.3%)	107 (42.0%)
Thyroid events	2 (0.8%)	15 (5.9%)
Hypothyroidism	2 (0.8%)	7 (2.7%)
Hyperthyroidism	0	3 (1.2%)
Thyroid function test abnormal (requiring medical intervention)	0	5 (2.0%)
Hepatic events	30 (12.0%)	27 (10.6%)
Liver enzymes (AST/ALT) increased	30 (12.0%)	27 (10.6%)
Neurological events	3 (1.2%)	17 (6.7%)
Tremor	0	5 (2.0%)
Sleep disorder	3 (1.2%)	12 (4.7%)
Skin events	2 (0.8%)	4 (1.6%)
Photosensitivity reaction (skin)	2 (0.8%)	4 (1.6%)
Eye events	1 (0.4%)	3 (1.2%)
Photophobia	0	2 (0.8%)
Vision blurred	1 (0.4%)	1 (0.4%)
Gastrointestinal events	32 (12.9%)	13 (5.1%)
Diarrhea	20 (8.0%)	5 (2.0%)
Nausea	10 (4.0%)	6 (2.4%)
Vomiting	2 (0.8%)	2 (0.8%)
Premature study drug discontinuation due to any AE	13 (5.2%)	28 (11.0%)

The advantage of DRO was driven by the occurrence of significantly fewer thyroid and neurological events and a trend for less skin or ocular events, and fewer premature study drug discontinuations compared to the amiodarone group. More gastrointestinal AEs, mainly diarrhoea, were observed in the DRO group. No pulmonary specific events were reported which could have been expected because of the short study duration. Seven cases of deaths (2 in the DRO group and 5 in the amiodarone group) occurred during the on-treatment period, and 4 additional deaths (2 patients in each treatment group) occurred after the end of the on-treatment period. The reported deaths appear in line with what is expected in this patient population. The reported incidence of SAEs also appears balanced between the DRO and the amiodarone treatment groups. Adverse events leading to withdrawal from study treatment were reported less frequently with DRO (12.9%) than amiodarone group (17.6%). In order to further improve the tolerability of DRO the applicant should discuss possible methods to minimize diarrhoea (and nausea) which are the most frequent causes of DRO discontinuation.This aspect is addressed in the SPC.

Generally, the CV safety profile of DRO appears comparable if not better to that of amiodarone, especially regarding bradyarrhythmia and effect on QT-interval. The higher incidence of treatment emergent adverse events (TEAEs) of the "Respiratory, thoracic and mediastinal disorders" system organ class reported with DRO (10.0%) compared to 8.2% in the amiodarone group was not expected. DIONYSOS is a short study and these TEAEs are probably more related to the general disorder (dyspnoea, acute pulmonary oedema), than to pulmonary toxicity reported with amiodarone. However, these TEAEs will be followed up in the RMP.

Based on the results of DIONYSOS, DRO appears to be less efficacious than amiodarone in maintaining sinus rhythm in patients with a history of AF, but safer in terms of thyroid or neurological safety issues, albeit with a higher occurrence of diarrhoea. For other adverse events encountered with

amiodarone e.g. skin/ocular adverse events, the advantage of DRO is less clear, but this will need a larger cohort of patients studied for a longer period of time.

- Analysis performed across trials (pooled analyses and meta-analysis)

Due to the similarities in the study design in EURIDIS and ADONIS both studies were presented together.

- Clinical studies in special populations

Study EFC4966/ANDROMEDA
See section: safety in special populations

Clinical safety

- Patient exposure

The safety evaluation in the targeted AF/AFL patient population pooled across all patients with AF/AFL (DAFNE, EURIDIS, ADONIS, ERATO and finally ATHENA, excluding DIONYSOS) included 6285 patients of whom 3410 patients were treated with DRO and 2875 patients treated with placebo. Of the patients administered DRO, 96.2% were administered the proposed dose 400 mg BID with 60.8%, 34.9% and 12.9 % exposed for a duration of 1 year, 1.5 years and up to 2 years respectively which allows adequate assessment of long term safety. The medical history and the concomitant medications of the patients are in line with clinical practice. Patients with NYHA class III or LVEF <35% are under-represented (less than 4%). Instead, these patients were studied in study EFC4966/ANDROMEDA consisting of 627 patients with CHF II-IV and study DR13151/LTS3841 in 116 patients with ventricular arrhythmias in whom an ICD was implanted.

- Adverse events

Over 60% of all patients reported an adverse event in the AF/AFL population. The most frequent adverse reactions observed with DRO 400 mg twice daily in the 5 studies were diarrhoea, nausea and vomiting, fatigue and asthenia. No dose response can be observed for patients with any TEAEs (70.4%; 63.6% and 72.65%) or serious TEAEs (18%; 6.1% and 12.9%) for the DRO 400, 600 and 800 mg BID respectively. However, more permanent discontinuations due to adverse events were observed with the DRO 400 mg BID and 800 mg BID (11.8% vs. 22.6%) as compared to placebo (7.7%). A dose response in the GI disorders (diarrhoea), investigations (QT-prolonged and increased blood urea) and cardiac disorders (bradycardia, palpitations and atrial tachycardia) SOCs is observed. With respect to the TEAE reported with the recommended dose of 400 mg BID, the highest relative risk incidence occurred with increased blood creatinine, “ECG investigations” (mainly prolonged QT interval), “Rate and rhythm disorders” (mainly bradycardia), “Rashes, eruptions and exanthems”, “Nausea and vomiting symptoms”, “Diarrhoea (excl infective)”, and “Asthenic conditions” (mainly fatigue).

The extra-cardiac safety problems reported with amiodarone, in particular respiratory, thoracic and mediastinal disorders; nervous system disorders; endocrine disorders and eye disorders were reported in comparable frequencies with DRO and placebo. This supports a better extra-cardiac safety profile for DRO than amiodarone. There was a comparable incidence of haemorrhages recorded in patients on at least one anti-coagulant in the DRO group compared to placebo group alleviating previous concerns. One case of toxic hepatitis was reported which is unlikely to be related to the use of DRO.

- Serious adverse event/deaths/other significant events

SAE occurred to a similar extent in placebo (19.7%) and the DRO 400 mg BID (18.0%) groups. Comparable incidences of serious events were also observed for the Primary System Organ Class: cardiac disorders (1.4% vs. 1.8% for the placebo and DRO 400 mg BID respectively). However within that group, cases of heart failures [HLGT] were more commonly reported in the DRO 400 mg BID group than placebo (0.5% vs. 0.2%). The highest incidence of SAE observed during the ongoing study DIONYSOS occurred with cardiac disorders, with cardiac failure as the leading cause (1%). In the AF/AFL population, the incidences of all deaths and CV deaths were numerically lower in the DRO 400 mg BID than the placebo groups.

Regarding the pro-arrhythmic potential, the current data show that the RR of ventricular arrhythmia and cardiac arrest is 1.61 (CI: 0.78-3.3), however, the incidence of serious adverse events pertaining to these events is not worrisome. One case of TdP was reported with DRO 400 mg BID, with risk factors for TdP: female, prolonged QTcB (522 ms at baseline). Considering that preclinical studies showed that the TdP potential of DRO is probably higher than that of amiodarone, it would be realistic to predict the incidence of TdP for DRO in clinical practice to be comparable to that of amiodarone (<1%) if not higher. The pharmacological action of DRO may induce a moderate QTc Bazett prolongation (about 10 msec), related to prolonged repolarisation. These changes are linked to the therapeutic effect of DRO and do not reflect toxicity. Follow up, including ECG, is recommended during treatment. If QTc Bazett interval is ≥500 milliseconds, dronedarone should be stopped.

The ECG data show that DRO decreases heart rate, prolongs PR and QTcB which are in line with its pharmacodynamic properties. The SPC clearly identifies patients at possible risk and they are consequently contraindicated e.g. patients with second or third degree heart block, bradycardia <50 bpm and QTcB interval ≥500 msec.

- Laboratory findings

The increased creatininemia observed with DRO is another concern. Serum creatinine levels were significantly but reversibly increased in a large proportion of patients treated with DRO. This was not associated with a parallel increase in blood urea. It is recommended to measure plasma creatinine values 7 days after initiation of DRO. An increase in plasma creatinine has been observed with DRO 400 mg twice daily in healthy subjects and in patients. This increase occurs early after treatment initiation and reaches a plateau after 7 days. If an increase in creatininemia is observed, this value should be used as the new reference baseline taking into account that this may be expected with DRO.
An increase in creatininemia should not necessarily lead to the discontinuation of treatment with ACE-inhibitors or Angiotensin II Receptors Antagonists (AIIRAs). The increased creatininemia observed with DRO is addressed in the RMP.

- Safety in special populations

Patients with congestive heart failure
Study EFC4966/ANDROMEDA
This study specifically investigated the potential clinical benefit of DRO 400 mg BID treatment versus placebo for reducing death or hospitalization for worsening heart failure in patients with symptomatic CHF when added on-top of treatments for CHF NYHA II-IV. The study was discontinued after seven months due to the reported higher mortality in the DRO group (n=25) compared to the placebo group (n=12) [RR: 2.13 (95%CI: 1.07-4.25)]. The applicant postulated that this increased mortality might have been related to the observed increase in serum creatinine levels with DRO, which may have led investigators to discontinue ongoing treatment with ACE inhibitors/AII receptor antagonists or not to initiate these treatments. A pro-arrhythmic cause of death was excluded, as there were no cases of torsades de pointes. After an additional 6 months follow-up of study termination, when off DRO, the death rate had equalled between the treatment groups. This implies the absence of long term detrimental effects for DRO.
A requested analysis concerning ACE-inhibitors /ARBs use in the AF/AFL population (excluding the ATHENA study) showed that in contrast to the findings in ANDROMEDA, these drugs were not discontinued more frequently in patients receiving DRO than placebo. This finding is likely to be explained by smaller increases of creatinine levels in the AF/AFL patients than in the ANDROMEDA population (mean 10 μM vs. 19 μM), which again is in agreement with the reduced renal function in patients with symptomatic CHF. Additionally one of the significant prognostic factors for the primary endpoints in ANDROMEDA was a decreased baseline creatinine clearance <50 ml/min. There are remaining concerns regarding administration of DRO in patients with severe renal insufficiency. Patients with Cr Cl<10 m/.min were excluded in ATHENA, and patients with CrCl ≤30 ml/min represented less than 3 % of the patients. The excess of mortality observed in ANDROMEDA can not be explained but an effect of baseline creatinine clearance can not be ruled out. Accordingly, patients with severe renal impairment CrCl ≤30 ml/min are still recommended to be contraindicated.

One of the main differences in the recruited patients in ATHENA and ANDROMEDA is the patient hemodynamic status. ANDROMEDA recruited patients who were hospitalized with new or worsening heart failure and who had had at least one episode of shortness of breath on minimal

exertion or at rest ([NYHA functional class III or IV) or paroxysmal nocturnal dyspnoea within the month before admission. This indicates patients suffering from recurrent attacks of CHF. On the other hand, ATHENA excluded any patient with hemodynamic instability, such as NYHA IV within the past 4 weeks. The possible influence on these recruitment criteria on the respective results of the studies can not be ignored. Accordingly, patients in unstable hemodynamic conditions are contraindicated. Although ATHENA still recruited patients in NYHA III, these patients were minimally represented 4% (91/2301) and 4.7% (109/2327) of the recruited DRO and placebo groups in ATHENA at baseline respectively). Likewise, patients with LVEF <35% were minimally represented: 4% (92/ 2301) and 3.7 % (87/2327) of the recruited DRO and placebo groups in ATHENA at baseline respectively. The results of these subgroups are in line with the general ATHENA population, but due to their minimal representation, and to be on the cautious side, necessitate a warning in section 4.4 of the SPC against the use of DRO in these patients.
Currently dronaderone is contraindicated in patients with unstable hemodynamic status i.e. NYHA IV and unstable NYHA III. Because of limited experience in stable patients with NYHA class III heart failure or with LVEF <35%, the use of DRO is not recommended.

The major safety objections raised during the previous application, mainly due to the higher mortality observed in the ANDROMEDA study are largely solved with the submission of the results of the ATHENA study.

Heart failure had a relative risk of 1.17 (CI: 0.84-1.62) which is reassuring. Still, a dose response can be observed in the incidence of heart failure raising concerns in patients who are at risk of higher exposure. Serious adverse events of heart failure were more commonly reported in the DRO 400 mg BID group than placebo (0.5% vs. 0.2%). It is difficult to draw a firm conclusion considering the scarcity of the recorded cases: 15 vs. 7 cases respectively.

Women
Investigating the influence of some intrinsic factors on the incidence of TEAEs, females appear to be at higher risk for the development of any TEAE or serious TEAE. This corresponds with the observed higher DRO plasma exposure in female patients in the pharmacokinetics studies. As only one dose scheme is proposed i.e. 400 mg BID, the management of the female population using DRO is expected to be problematic in clinical practice. This is reflected in the SPC section 5.2. The MAH should present data per gender in the upcoming PSURs.

Paediatric Population
There is no experience in children and adolescents below 18 years of age. Therefore, DRO is not recommended in this population.

Elderly
Efficacy and safety were comparable in both elderly and younger patients. Although plasma exposure in elderly females was increased in a pharmacokinetic study conducted in healthy subjects, dose adjustments are not considered necessary.

Hepatic impairment
DRO is contraindicated in patients with severe hepatic impairment because of the absence of data. No dose adjustment is required in patients with mild or moderate hepatic impairment.

Renal impairment
DRO is contraindicated in patients severe renal impairment (creatinine clearance (CrCl) <30 ml/min). No dose adjustment is required in other patients with renal impairment.

- Safety related to drug-drug interactions and other interactions

DRO is primarily metabolized by CYP3A4 and has a moderate potential to inhibit CYP3A4 and CYP2D6, making it a potential candidate for important drug interactions. The relative risk of digitalis intoxication with co-administration with DRO is almost 4 fold in the AF/AFL population. No significant interactions were observed between DRO and oral anticoagulants in the submitted main studies which is reassuring considering their frequent co-administration in the AF population. The encountered adverse events when beta-blockers or calcium antagonists are concomitantly administered with DRO are expected from their pharmacodynamic properties and the impact on TEAEs appears

limited. Overall drug-drug interactions were manageable in the main clinical trials and did not influence safety or efficacy to a significant extent. However, specific measures were taken to manage anticipated problems in a clinical trial setting. Beta-blockers, Ca-antagonists (diltiazem and verapamil) and digoxin had to be co-prescribed at low dose and could only be up-titrated under ECG guidance. These precautions are currently reflected in the SPC.

- Discontinuation due to adverse events

In clinical trials, premature discontinuation due to adverse reactions occurred in 11.8% of the DRO-treated patients and in 7.7% in the placebo-treated group. The most common reasons for discontinuation of therapy with Multaq were gastrointestinal disorders (3.2% of patients versus 1.8% in the placebo group).

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considers that the Pharmacovigilance System as described by the applicant fulfils the legislative requirements and provides evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for notification of any adverse reaction suspected of occurring either in the community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Important identified risks		
Inappropriate management of the signal of serum creatinine increase	Prescription surveys to evaluate prescribers understanding of labeling recommendations THIN and LabRx® repeated cross-sectional studies of the proportion of dronedarone users having a serum creatinine tested after treatment initiation.	Labeling: [Section 4.4] of the SPC recommends "to measure plasma creatinine values 7 days after initiation of dronedarone. An increase in plasma creatinine has been observed with dronedarone 400 mg twice daily in healthy subjects and in patients. This increase occurs early after treatment initiation and reaches a plateau after 7 days. If an increase in creatininemia is observed, this value should be used as the new reference baseline taking into account that this may be expected with dronedarone. An increase in creatininemia should not necessarily lead to the discontinuation of treatment with ACE-inhibitors or Angiotensin II Receptors Antagonists (AIIRAs)." [Section 4.8] of the SPC lists "Blood creatinine increased" as a very common ADR. Communication process on appropriate usage of MULTAQ®: An educational program with a goal to alert the prescriber on the appropriate utilization of serum creatinine testing in patients treated with dronedarone will be implemented. In each country, educational vehicles will be developed, seeking the collaboration of scientific societies, targeting physicians likely to initiate the treatment with

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		MULTAQ®.
Drug-Drug Interactions with potent CYP3A4 inhibitors	Routine pharmacovigilance. Prescription surveys to evaluate prescribers understanding of labeling recommendations. THIN and LabRx® repeated cross-sectional studies of the concomitant prescribing of interacting medications in dronedarone users.	Labeling: Coadministration with strong CYP3A4 inhibitors such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone, and ritonavir is contraindicated in [Section 4.3] of the SPC. [Section 4.5] of the SPC provides the pharmacokinetic information about this interaction. For grapefruit juice (CYP3A4 inhibitor): [Section 4.2] ,[Section 4.4] and [Section 4.5] of the SPC indicate that "patients should be warned to avoid grapefruit juice beverages while taking dronedarone" Communication process on appropriate usage of MULTAQ®: An educational program with a goal to prevent the concomitant use with dronedarone of potent CYP3A inhibitors will be implemented. In each country, educational vehicles will be developed, seeking the collaboration of scientific societies, targeting physicians likely to initiate the treatment with MULTAQ®. The educational material will include a drug interaction check card to be used in all EU countries that will be communicated to the Health care professionals (ie, doctors and pharmacists) for preventing these drug-drug interactions (see Annex II of the Marketing Authorisation).
Important potential risks		
Use in unstable hemodynamic condition including patients with symptoms of heart failure at rest or with minimal exertion (corresponding with NYA class IV and unstable class III patients).	Routine pharmacovigilance. Prescription surveys to evaluate prescribers understanding of labeling recommendations. THIN and LabRx® repeated cross-sectional studies of the proportion of dronedarone users having unstable hemodynamic condition at time of treatment initiation.	Labeling: contraindication to use in these patients in [Section 4.3] of the SPC. In addition, [Section 4.4] of the SPC states that the use of dronedarone is not recommended in stable patients with recent (1 to 3 months) NYHA class III heart failure or with LVEF <35%, because of limited experience in these patients. Communication process on appropriate usage of MULTAQ®: An educational program will be implemented, with the goals to prevent the use of dronedarone in patients in unstable hemodynamic conditions including patients with symptoms of heart failure at rest or with minimal exertion (corresponding with NYHA class IV and unstable class III patients), and to limit use in stable patients with recent (1 to 3 months) NYHA class III heart failure or with LVEF <35%. In each country, educational vehicles will be developed, seeking the collaboration of scientific societies, targeting physicians likely to initiate the treatment with MULTAQ®.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Drug-Drug Interactions with digitalis, calcium antagonists with heart rate lowering properties, beta-blockers, statins, tacrolimus and sirolimus, potent CYP3A4 inducers.	Routine pharmacovigilance. Prescription surveys to evaluate prescribers understanding of labelling recommendations. THIN and LabRx® repeated cross-sectional studies of the concomitant prescribing of interacting medications in dronedarone users. Study of interaction with statins and digoxin in the THIN and LabRx® databases.	Labelling: - For digitalis: [Section 4.4] and [Section 4.5] of the SPC indicate that the digoxin dose should be reduced by approximately 50%, serum levels of digoxin should be closely monitored and clinical and ECG monitoring is recommended. A synergistic effect on heart rate and atrioventricular conduction is also possible. - For calcium antagonists: [Section 4.4] and [Section 4.5] of the SPC indicate that the coadministration of calcium antagonists with depressant effect on sinus and atrio-ventricular node should be undertaken with caution. These drugs should be initiated at low dose and up-titration should be done only after ECG assessment. In patients already on calcium antagonists at time of dronedarone initiation, an ECG should be performed and the dose should be adjusted if needed. - For beta-blockers: [Section 4.4] and [Section 4.5] of the SPC indicate that the coadministration of beta-blockers with depressant effect on sinus and atrio-ventricular node such as verapamil and diltiazem should be undertaken with caution. These medicinal products should be initiated at low dose and up-titration should be done only after ECG assessment. In patients already on beta blockers at time of dronedarone initiation, an ECG should be performed and the dose should be adjusted if needed. - For statins: o [Section 4.4] of the SPC indicates that statins should be used with caution. Lower starting dose and maintenance doses of statins should be considered according to the statin label recommendations and patients monitored for clinical signs of muscular toxicity. o [Section 4.5] of the SPC indicates that "As high doses of statins increase the risk of myopathy, concomitant use of statins should be undertaken with caution. Lower starting dose and maintenance doses of statins should be considered according to the statin label recommendations and patients monitored for clinical signs of muscular toxicity."

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		- For tacrolimus and sirolimus, [Section 4.5] of the SPC indicates that dronedarone could increase plasma concentrations of tacrolimus and sirolimus, so monitoring of their plasma concentrations and appropriate dose adjustment is recommended in case of coadministration with dronedarone. - For potent CYP3A4 inducers, [Section 4.4] and [Section 4.5] indicate that "co-administration of rifampicin and other potent CYP3A4 inducers such as phenobarbital, carbamazepine, phenytoin, St John's Wort is not recommended as they decrease dronedarone exposure.
Amiodarone-like effects: Interstitial lung Disease, Severe Skin disorders (including photosensitivity), Neuropathy (including Optic Neuropathy), hepatic injury	Routine pharmacovigilance. Use of specific report forms to document spontaneous reports of interstitial lung disease and potential hepatic injury. Background frequencies in the RecordAF disease registry (AF/AFL population). THIN and LabRx® retrospective cohort studies of the safety outcome of interest.	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 Use of specific report forms for spontaneous reports to better document the reported cases	Labelling: Use in pregnancy is not recommended per [Section 4.6] of the SPC. Information about the existence of findings in animals is provided in [Section 5.3] of the SPC.
Effect in lactation	Routine pharmacovigilance	Labelling: [Section 4.6] of the SPC indicates that a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with MULTAQ® should be made taking into account the benefit of breast-feeding to the child and the benefit of MULTAQ® to the woman. Information about excretion of dronedarone and its metabolites in breast milk in animals is provided.
Effect in severe hepatic impairment	Routine pharmacovigilance	Labelling: Use in severe hepatic impairment is contraindicated in [Section 4.3] of the SPC. Information about the lack of data in this sub-population is provided in [Section 4.2] of the

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		SPC
Effect in children (potential off-label use)	Routine pharmacovigilance THIN and LabRx® repeated cross-sectional studies of the proportion of paediatric patients prescribed dronedarone.	Labelling: [Section 4.2] of the SPC states that, as there is no experience in children and adolescents, therefore, MULTAQ® is not recommended.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
There are no unresolved quality issues which may affect the Benefit/Risk balance.

Non-clinical pharmacology and toxicology

Pharmacology studies in animal models demonstrated that DRO reduces the heart rate, prolongs Wenckebach cycle length and AH-, PQ-, QT- intervals; with no marked effect or weak increase on QTc-intervals, and with no change in HV- and QRS- intervals. It increases effective refractory periods of the atrium, atrio-ventricular node, and ventricles. DRO decreases arterial BP and myocardial contractility with no change in left ventricular ejection fraction and reduces myocardial oxygen consumption. It has coronary and peripheral arteries vasodilatory properties related to the activation of the nitric oxide pathway. DRO displays indirect antiadrenergic effects and partial antagonism to adrenergic stimulation. In non-clinical toxicology studies DRO had no genotoxic effects, based on one in vivo micronucleus test in mice and four in vitro tests. In 2-year oral carcinogenicity studies, the highest DRO dose administered for 24 months was 70 mg/kg/day in rats and 300 mg/kg/day in mice. Observations were increased incidence of mammary gland tumors in female mice, histiocytic sarcomas in mice and hemangiomas at the mesenteric lymph node level in rats, all at the highest tested dose only, corresponding to an exposure of 5 to 10 times that of the human therapeutic dose. Hemangiomas are not precancerous changes and do not transform into malignant hemangiosarcomas in either animals or man. None of these observations was considered relevant for humans. In chronic toxicity studies, slight and reversible phospholipidosis was observed in mesenteric lymph nodes mainly in the rat. This effect is considered specific to this species and not relevant to humans. DRO caused marked effects on embryo-foetal development at high doses in rats, such as increased post-implantation losses, reduced foetal and placental weights, and external, visceral and skeletal malformations.

Efficacy

The current submission is based on five placebo-controlled studies and one actively-controlled study. The rhythm and rate -control properties of DRO were demonstrated in DAFNE, EURYDIS/ADONIS and ERATO studies. In EURIDIS/ADONIS DRO 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 DRO group compared to the placebo group when measured after 14 days of treatment. In the previous application, the assessment of DAFNE, EURIDIS/ADONIS and ERATO studies, ended however in a negative benefit/risk profile for DRO in the indication: maintenance of sinus rhythm or decrease of ventricular rate in AF/AFL patients. The main objections posed were against the drug-interaction profile, the lack of actively-controlled studies and the overall safety profile. The submission of ATHENA and

DIONYSOS studies was awaited to clarify many of these issues. The claimed indication was: *patients with either a recent history of, or current non-permanent atrial fibrillation. Multaq has been shown to decrease the risk of AF-related hospitalisation.* This would therefore be the first anti-arrhythmic agent for AF to claim an improvement in a clinical outcome instead of the standard claim of anti-arrhythmic properties. Further analysis indicates some clinical benefit in patients in AFL though the recruited numbers in ATHENA of this subgroup are too few to allow robust conclusions. ATHENA was a large study recruiting around 4000 haemodynamically stable patients to investigate the clinical outcome of the time from randomization to first cardiovascular hospitalization or death from any cause in patients with AF/AFL or history thereof. The achieved statistical significance of the primary endpoint was driven by reduction in the incidence of time to first cardiovascular hospitalization. No significant effect on time to death was shown precluding any claims on that endpoint. Around half of these CV hospitalizations were due to AF-related reasons. The exact reason for these AF- hospitalizations was not given, because they were not collected at hospital admission. Available data indicate that these AF-hospitalizations may not only be related to electrical cardioversion, but also to the need for pharmacological management of the arrhythmias. The results thus positively verify the efficacy of DRO as an anti-arrhythmic, with a consequent reduction of AF-related hospitalizations. The applicant showed that the reduction in AF-related hospitalisations by DRO is a clinically relevant finding that may be accompanied with a reduction of potentially life-threatening conditions. However, the number of events such as TIA/stroke and heart failure was small and the absolute difference to placebo small. It cannot be established on the basis of ATHENA whether CV hospitalization can be used as surrogate for outcome, nor whether other effects than its antiarrhythmic properties are co-responsible for this effect of DRO. Also, it cannot be automatically assumed that other effective antiarrhythmics will result in similar reduction in hospitalization as this has not been studied systematically. The CHMP considered therefore that the results do not justify the inclusion of this finding in the indication as it may be a direct consequence of its antiarrhythmic effects that can mentioned in section 5.1. Moreover the CHMP considered the inclusion of clinical endpoints in the indication is not in line with the SPC guideline. During the on-study period, DRO significantly decreased the incidence of cardiovascular death that was studied as a secondary endpoint, compared with placebo (2.8% vs. 4.0%). The reduction of cardiovascular death with DRO 400 mg BID was mainly due to a reduction in the incidence sudden cardiac death and stroke, but incidences were low and differences were small and warrant further study. The reduction in sudden cardiac death further alleviates the concerns regarding the possible pro-arrhythmic potential of DRO raised following the ANDROMEDA study. The results of the study DIONYSOS comparing the efficacy and safety of DRO versus amiodarone for the maintenance of sinus rhythm in patients with AF showed that DRO is less effective than amiodarone as an anti-arrhythmic. However, a direct comparison between amiodarone and DRO regarding the risk of AF-related hospitalizations is not submitted. The results complicate the interpretation of the place of DRO in the treatment of atrial fibrillation.

Safety

The numbers and the duration of exposure of patients in the targeted AF/AFL population were adequate to properly estimate the associated risks of using DRO 400 mg BID. From the safety database all the adverse reactions reported in clinical trials have been included in the SPC. As expected, the extra-cardiac safety profile of DRO appears to be better than that described with amiodarone, as shown by the DIONYSOS study for thyroid and neurological events. The increased mortality reported in the ANDROMEDA study is not confirmed by the results of the ATHENA study, but this latter study excluded haemodynamically unstable patients. Therefore, these patients should be contraindicated and the indication should specifically mention that DRO should only be used in clinically stable patients. Death from all causes was comparable in DRO and placebo groups or amiodarone in the AF/AFL population. The results of stable patients with NYHA III and patients with an LVEF < 35% were comparable to those of the general recruited cohort, but numbers were small and the use of DRO is these patients can still not be recommended. No increased risk of heart failure or pro-arrhythmic potential was observed. DRO has an even more complex interaction potential than amiodarone, being both a substrate and an inhibitor of CYP P450 enzymes, in addition to P-gp that can potentially lead to major problems in daily clinical practice. SPC addresses specifically safe use of the combination of DRO and digitalis, beta-blockers or calcium channel blockers. The lack of lower dose recommendations is a disadvantage considering the possible interactions (e.g. verapamil), and higher exposure in female patients and will be followed up in upcoming PSURs. The increased

creatininemia observed with DRO remains a concern, though is currently appropriately addressed in the RMP.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these concerns.

- **User consultation**

The Applicant performed a user consultation testing on the package leaflet. The design of the test formed the basis of an adequate and competent testing of the PIL in regard to finding, diagnosing and amending possible weaknesses. The present readability test was well designed to meet its main objectives. The results of the user testing described in the user testing report support the changes made to the PIL.

Risk-benefit assessment

DRO demonstrates electro-physiological characteristics belonging to all 4 Vaughan-Williams classes of anti-arrhythmic compounds. These characteristics are in line with those of amiodarone, which has been shown to be an effective drug in the management of AF, but also one associated with many extra-cardiac adverse events. A safer alternative for amiodarone would be an advantage. The presented data demonstrate the efficacy of DRO 400 mg BID as an anti-arrhythmic in patients in AF both in terms of rhythm and rate control. It has been shown to decrease the risk of AF related hospitalisations. The effects of dronedarone beyond its antiarrhythmic properties have not been clearly demonstrated. There is only one comparative study with amiodarone. In this efficacy/safety study, dronedarone appears less effective than amiodarone in the maintenance of sinus rhythm. In terms of safety it may be advantageous compared to amiodarone, but patients with severe and/or unstable heart failure should be contraindicated and its use in stable patients with NYHA class III heart failure or with LVEF <35% cannot be recommended.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- The following additional risk minimisation activities were required: see as detailed in section 2.3

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Multaq in the treatment stable patients with either a recent history of, or current non-permanent atrial fibrillation is favourable and therefore recommended the granting of the marketing authorisation.