

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogada **LUZ CLEMENCIA DE PÁEZ**
clientes@cavelier.com
cavelier@cavelier.com

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-154617- -00004-0000

Fecha: 2012-10-10 16:11:09 Dep. 2020 DIR.NUEVASC
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 519 TRASLADOINFORME Folios: 12

ASUNTO	Radicación	10-154617
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	- - - 18352
	Folios	012

Patente de Invención

Vía Nacional

Vía PCT (Fase Nacional)

Patente de Modelo de Utilidad

Cap.I

Cap. II

No. Solicitud Internacional PCT/IB2009/006106

Fecha de Presentación Internacional 08 de Junio de 2009

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 37 a 47	09/Diciembre/2010
Reivindicaciones:	Folios 48 a 49	09/Diciembre/2010
Oposiciones:	Folios 59 a 98	Laboratorios Synthesis 19/Agosto/2011
Prioridad:	EP 08290531.6	10/Junio/2008
	US 60060.263	10/Junio/2008

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486), y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Dronedarona para la prevención de la fibrilación auricular permanente".

Expediente 10 157 617 1er Art 45

El problema planteado en esta solicitud consiste en la necesidad de reducir la probabilidad de permanecer en/ desarrollar fibrilación auricular permanente y evitar que los pacientes padezcan fibrilación/aleteo auricular permanente.

Para resolver este problema técnico la solicitud en estudio proporciona el uso de Dronedaron o una de sus sales farmacéuticamente aceptables para la preparación de un medicamento para uso en la prevención de la fibrilación/aleteo auricular permanente en pacientes con historial de fibrilación auricular o aleteo auricular.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 031/343.

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 1 - 5 no es patentable, de acuerdo con el Art 14.

5. Análisis de las Oposiciones

Argumentaciones de Synthesis

Argumenta al doctora Eliana Isaura Moreno Bohórquez en calidad de apoderada de la sociedad Synthesis, que la presente solicitud no cumple con los requisitos de patentabilidad, ya que las reivindicaciones de uso y método de tratamiento no son patentables según la legislación, Decisión 486 de la Comunidad Andina de Naciones, Artículo 14. El documento D1: MXPA03005221 afecta la patentabilidad de la presente solicitud, el documento D1 revela formulaciones farmacéuticas de administración parenteral, caracterizada porque comprende Dronedaron o una de sus sales farmacéuticamente aceptables como principio activo, una solución tampón aceptable capaz de mantener el pH de la composición entre 3 – 5, un derivado hidrosoluble de Y-ciclodextrina fisiológicamente aceptable. (Pág. 1, Línea 16 y 17). La Dronedaron tiene dominio cardiovascular como agente anti arritmico, por tal razón es útil para suprimir o prevenir las alteraciones del ritmo cardíaco como la fibrilación auricular. D1 refiere a una sal farmacéuticamente de Dronedaron tal como clorhidrato presente en las composiciones reveladas de 0.01% a 4 %, por ejemplo 0.1% a 0.8%. Por lo tanto, la presente solicitud carece de novedad de acuerdo a lo revelado en el documento D1, carece de aplicación industrial ya que algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente.

Respuesta del Examinador Técnico

Los documentos presentados por la doctora Eliana Isaura Moreno Bohórquez en calidad de apoderada de la sociedad Synthesis corresponden los documentos D1 MXPA03005221, en donde D1 revela una composición farmacéutica de Dronedaron o una de sus sales farmacéuticamente estables preferiblemente de administración parenteral, empleado como agente anti arritmico. Sin embargo, la presente solicitud en su capítulo reivindicatorio reclama un uso de Dronedaron en la prevención de la fibrilación/aleteo auricular permanente incluyendo factores de riesgo en los pacientes

en que es administrado, lo cual no es materia patentable según los Artículos 14 y 21 de la Decisión 486.

Se aclara al solicitante que a pesar de que la materia reivindicada en las clausulas 1 a 5 no es patentable, en el estado de la técnica se divulgan en los documento D1 y D2, el uso de Dronedarona en el tratamiento de arritmias cardiacas.

Ítem	Documento	Título	Fecha de Publicación*
D1	Dronedarone for prevention of atrial fibrillation: A dose-ranging study	EUROPEAN HEART JOURNAL AUG 2003, vol. 24, no. 16, August 2003	Agosto/2003
D2	Rationale and design of ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter.	JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY JAN 2008, vol. 19, no. 1, January 2008	Enero/2008

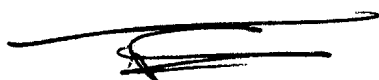
D1 <http://eurheartj.oxfordjournals.org/content/24/16/1481>
Divulga un estudio que revela de la Dronedarona fue desarrollado con un compuesto útil en el tratamiento de arritmias cardiacas, de igual manera de Amiodarona, pero con un perfil de seguridad mejorado respecto a Amiodarona, como efectos adversos relacionados con la tiroides (Fl. 106). La Dronedarona es estructuralmente similar a Amiodarona y presenta características electrofisiológicas in vitro de cuatro clases de acción anti arrítmica (Fl. 104). Adicionalmente da a conocer que Dronedarona tiene actividad en la prevención de fibrilación auricular recurrente en pacientes con antecedentes de fibrilación auricular. El estudio se realizo a pacientes donde se administraron dosis de 800, 1200, 1600 mg de Dronedarona o placebo. El estudio demostró que en pacientes con fibrosis auricular la Dronedaron administrada diariamente una dosis de 800mg mantiene el ritmo sinusal después de la cardioversión de la fibrilación auricular. (Fl. 104).

D2 <http://onlinelibrary.wiley.com/doi/10.1111/j.1540-8167.2007.01016.x/pdf>
Da a conocer métodos para disminuir la probabilidad de fibrilación/aleteo ventricular en un paciente que comprende la administración de Dronedarona. Por ejemplo en el ensayo DAFNE, seis meses de seguimiento demostraron que el tratamiento con Dronedarona 800mg, dosis diaria, prolongó significativamente el tiempo de recurrencia de la fibrilación auricular en pacientes con fibrilación auricular persistente. Adicionalmente, el documento D2 da a conocer los ensayos clínicos ATHENEA en donde los pacientes de alto riesgo presentaban historial de paroxística o persistente de fibrilación auricular y fueron tratados con 800 mg/día de Dronedarona y seguimiento de 12 – 30 meses, se incluyeron riesgo adicionales como la edad, paciente mayor, hipertensión, diabetes mellitus, ataque isquémico, embolismo sistémico entre otras.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 16 OCT. 2012

Elaborado por: Paola Duarte

Revisado por: Consuelo Leguizamón Leguizamón 

Aprobado por: José Luis Salazar López



Dronedronone for prevention of atrial fibrillation: A dose-ranging study

Paul Touboul^a, Josep Brugada^b, Alessandro Capucci^c, Harry J.G.M. Crijns^d, Nils Edvardsson^e, Stefan H. Hohnloser^f

^aDivision of Cardiology, Hôpital Cardiologique, Lyon, France

^bArrhythmic Unit, Cardiovascular Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain

^cDivision of Cardiology, Ospedale Civile Pizzardi, Bologna, Italy

^dDepartment of Cardiology, Academic Hospital Maastricht & Cardiovascular Research Institute, Maastricht, Netherlands

^eDivision of Cardiology, Sahlgrenska University Hospital, 413 45, Göteborg, Sweden

^fJ.W. Goethe University, Department of Cardiology, Frankfurt am Main, Germany

Received 21 January 2002; received in revised form 5 May 2003; accepted 12 June 2003

KEYWORDS

Antiarrhythmic agents;
Atrial fibrillation;
Cardioversion

Aims Dronedronone, a benzofuran derivative without iodine substituents, shows the electrophysiologic properties of amiodarone. This study was designed to determine the most appropriate dose of dronedronone for prevention of atrial fibrillation (AF) after cardioversion.

Methods and results Patients with persistent AF were randomly allocated to 800, 1200, 1600 mg daily doses of dronedronone or placebo. The main analysis was conducted on 199/270 patients, who entered the maintenance phase following pharmacological cardioversion or, if unsuccessful, DC cardioversion. Within 6 months follow-up, the time to AF relapse increased on dronedronone 800 mg, with a median of 50 days vs 5.3 days in the placebo group (relative risk reduction 55% [95% CI, 28 to 72%], $P=0.001$). No significant effect was seen at higher doses. Spontaneous conversion to sinus rhythm on dronedronone occurred in 5.8 to 14.8% of patients ($P=0.026$). There were no proarrhythmic reactions. Drug-induced QT prolongation was only noticed in the 1600 mg group. Premature drug discontinuation affected 22.8% of subjects given 1600 mg dronedronone versus 1.7% on 800 mg and were mainly due to gastrointestinal side effects. No evidence of thyroid, ocular or pulmonary toxicity was found. Dronedronone 800 mg, at a 800 mg daily dose, appears to be effective and safe for the prevention of AF relapses after cardioversion. The absence of thyroid side effects and of proarrhythmia are important features of the drug. Further studies are needed to better delineate the antiarrhythmic profile of the drug.

© 2003 Published by Elsevier Ltd on behalf of The European Society of Cardiology.

Introduction

Atrial fibrillation (AF) is the most commonly encountered cardiac rhythm disturbance accounting for 34.5% of arrhythmia-related hospital admissions in a recent US survey.¹ AF is associated with increased mortality

and morbidity as highlighted by an estimated incidence of over 75,000 AF-related strokes per year in the US.^{2,3}

In patients with persistent AF, electrophysiologic cardioversion is usually performed. Despite high initial success rates, this therapy is limited by the incidence of AF relapses that is as high as 70 to 90% after 12 months if no prophylactic antiarrhythmic therapy is administered.^{4,5} Various class I and II antiarrhythmic drugs have been studied in controlled trials to evaluate their efficacy in maintaining sinus rhythm.⁶ Overall, approximately 50% of patients on active drug therapy remained free of

recurrent AF over the first year after cardioversion. Daily amiodarone showed a higher rate of efficacy as a maintenance therapy.^{7,8} However, amiodarone had to be discontinued due to side effects in up to 13% of patients over the course of 3–2 years according to a recent meta-analysis.⁹

Dronedronone is a benzofuran derivative structurally similar to amiodarone, which is being developed as an antiarrhythmic agent. The absence of iodine substituents and a less lipophilic character should be associated with a better tolerability. Like amiodarone, dronedronone possesses *in vitro* electrophysiologic characteristics of all four classes of antiarrhythmic agents:^{10–12} specifically, it blocks sodium channels at rapid pacing rates, prolongs cardiac action potentials and refractoriness, and possesses Ca^{2+} antagonistic properties. In addition, dronedronone shows a non-competitive antiadrenergic action. The Dronedronone Atrial Fibrillation study after Electrical Cardioversion (DOPPE) was a double-blind, controlled, placebo-controlled trial designed to select the most appropriate dose of dronedronone for prevention of recurrent AF after successful cardioversion.

Methods

Patients with persistent AF scheduled for elective cardioversion were eligible. Effective anticoagulation had to be performed for at least 3 weeks prior to randomization. After signing informed consent, patients were allocated to one of three doses of dronedronone: 800, 1200, 1600 mg daily (800, 600, 800 mg BID) or placebo. This dose range was selected based on pharmacodynamic data assessing ECG-derived parameters as surrogate endpoints for antiarrhythmic activity (heart rate, PQ , and QTc interval). They were continuously monitored by telemetry for at least 12 h from the beginning of treatment. If after drug exposure for 3–7 days sinus rhythm was not restored, electrical cardioversion was performed. In successfully cardioverted patients' treatment was continued for 6 months. Anticoagulation was maintained for at least 4 weeks after conversion.

Study visits in the outpatient clinic were scheduled on day 5–6, 14, 20, 60, 90, 120, 150, and 180 after randomization or at any time in case of recurrent AF or other medical problems. Transcatheter electrocardiogram monitoring was used every day for 5 days following cardioversion, then every two weeks until day 45, and once a month up to the end of the study. Patients were also instructed to transmit their ECG in case of recurrent symptoms at any time. At each study visit, plasma samples were taken for determination of dronedronone trough levels. Five thyroid hormone measurements were planned during the follow-up.

Inclusion criteria

Patients of either sex, aged 20–65 years, with persistent AF (between 72 h and 11 months duration) for whom cardioversion and antiarrhythmic treatment was warranted were included. AF could be lone or associated with ischemic or hypertensive heart disease or dilated cardiomyopathy. Concomitant valvular aetiology did not preclude inclusion except for those patients with hemodynamically significant dysfunction or aortic stenosis.

Exclusion criteria

Patients with one or more of the following criteria were excluded from the study: more than two cardioversions in the

last six months; acute reversible causes; atrial flutter as the prevailing arrhythmia; ventricular pre-excitation or recent myocardial infarction; QT interval <350 msec; or history of bradycardia; severe bradycardia; advanced atrioventricular block; treatment with other antiarrhythmic drugs; congenital heart failure class II or III; left ventricular ejection fraction <35%; 90/90–100/100 mmHg systolic blood pressure; peripheral cardiovascular dysfunction.

Other criteria included profound sinus bradycardia; congenital long QT syndrome; evidence of clinically relevant non-coronary disease; contraindication to oral anticoagulation.

Statistical analysis

The primary outcome was time to first documented AF recurrence. AF recurrence was defined as an episode lasting for at least 30 min and documented by two distinct ECGs separated by the same time duration. Secondary study endpoints were spontaneous conversion of AF following cardioversion, heart rate in case of AF recurrence and the incidence of side effects.

Sample size calculation was based on the hypothesis that an AF recurrence rate of 67% on placebo at 6 months and 37% on at least one dose of dronedronone, a drop-out rate of 15%, a log-rank test equality of survival curves with a 5% two-sided significance level and a 80% power. This resulted in an estimated significance of 48 patients per group.

The main analysis was conducted on the patients entering the maintenance phase after successful cardioversion. An additional analysis also performed the extension to both first and second randomization groups. A Cox's model was used taking into account the dose groups and two additional baseline covariates: presence of documented heart disease and duration of the preceding AF episode.¹³ The same approach was applied to each dronedronone group for calculating the risk ratio with 95% confidence interval. Regarding the secondary endpoints, the trend among treatment groups was compared using a Cochran-Armitage test for qualitative parameters, a Jonckheere-Kaplan test for ordinal parameters, an analysis of variance for continuous parameters.^{14–16} Dronedronone and its main metabolites, the 4-hydroxy derivative, plasma concentrations were summarized by descriptive statistics.

Results

Patient characteristics

Two hundred and seventy patients were randomized in 30 centers and 11 countries. One hundred and ninety-nine patients, in whom sinus rhythm was restored, were included in the primary analysis. Patients randomized to the four groups had similar baseline characteristics as shown in Table 1.

Primary study endpoint

Kaplan-Meier curves for the primary outcome are shown in Fig. 1. There was an increased time to AF relapse with dronedronone 800 mg, this effect being less apparent at higher doses. Only with 800 mg, the difference compared to placebo was statistically significant. The median time to first AF recurrence was 5.3 days in the placebo group, and 50 days in the dronedronone 800 mg group (relative risk reduction 55%, 95% CI 27–72%, $P=0.001$). In the two other groups, no significant change was seen indicating a

* Corresponding author. Stefan H. Hohnloser, MD, Department of Medicine, Division of Cardiology, J.W. Goethe University, Theodor Stern-Kai 7, 60590 Frankfurt, Germany. Tel.: +49-69-4301-2731; fax: +49-69-4301-2932.
E-mail address: hohnloser.stefan@klinik.uni-frankfurt.de (S.H. Hohnloser).

Table 1 Demographic and baseline characteristics of patients

	Placebo n=48	DR 800 mg n=54	DR 1200 mg n=54	DR 1600 mg n=53
Age (years)	65	64	63	62
Male sex (%)	79	57	78	67
Hypertension (%)	58	51	70	57
CHD (%)	27	20	36	29
Valve disease (%)	28	35	31	37
Heart failure (%)	22	19	24	18
AP duration (days)	62	62	62	60
Recurrent AF (%)	65	59	64	76
LA* size (mm)	46	44	45	45
LVEF* (%)	56	55	53	54

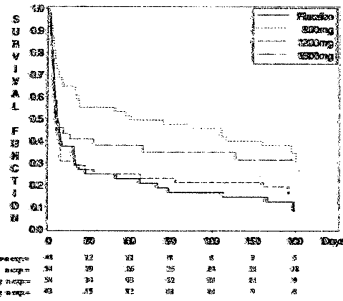
*LA: left atrial size; LVEF: left ventricular ejection fraction.

*CHD: coronary artery disease.

*AF: atrial fibrillation.

*LA: left atrium.

*LVEF: left ventricular ejection fraction.


Fig. 1 Kaplan-Meier analysis of the time to first AF recurrence according to assigned treatment. The difference between the dronedarone 800 mg group and the placebo group was significant ($P=0.001$). n.s.p.: number of censored patients.

lack of dose effect. At 6 months, 35% of the patients treated with 800 mg dronedarone were still in sinus rhythm, as compared to 10% in the placebo group. Attention to time analysis found similar results with time to AF recurrence of 56 days in the dronedarone 800 mg group, versus 5.3 days in the placebo group.

Conversion to sinus rhythm

The incidence of spontaneous conversion to sinus rhythm was associated with a significant dose-effect relationship ($P=0.001$). Patients in the dronedarone 800, 1200, and

1600 mg groups exhibited 5.6%, 8.2%, and 14.8% conversion rates respectively, as 3.1% on placebo. Moreover the incidence of successful electrical cardioversion was not statistically different among groups: 77.3% (800 mg), 87.5% (1200 mg), and 75.6% (1600 mg) compared to 79.3% in the placebo group.

Ventricular rate during recurrence

At the time of first AF recurrence, dronedarone appeared to slow the ventricular response in a dose-dependent

1453-1454, downloaded from www.oxfordjournals.org by [IP: 128.192.252.100] on 14 May 2014

Table 2 Adverse events leading to study drug discontinuation

	Placebo	DR 800 mg	DR 1200 mg	DR 1600 mg	Dronedrone
Adverse event	n=48	n=54	n=54	n=53	n=204
Total	0 (0.0)	0 (0.0)	5 (9.3)	0 (0.0)	0 (0.0)
Gastrointestinal (including diarrhea, vomiting, nausea, gastroenteritis)	0 (0.0)	1 (1.9)	1 (1.9)	1 (1.9)	0 (0.0)
General disorders (including malaise, accidental injury, amphetamine shock, weight decrease)	0 (0.0)	0 (0.0)	1 (1.9)	4 (7.5)	5 (2.5)
Cardiac failure	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)	2 (1.0)
Central nervous system (dizziness)	0 (0.0)	1 (1.9)	0 (0.0)	1 (1.9)	2 (1.0)
Dermatology	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Extrapyramidal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
QT increase	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.5)
Tachycardia supraventricular	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.5)
Thrombosis	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.5)

fashion. Patients receiving 800, 1200, or 1600 mg dronedarone had their ventricular rate reduced by 13.2, 19.2, and 17.8 bpm on average, respectively, compared to those on placebo ($P=0.001$).

Adverse events

One death was reported in this study: this concerned a patient in the 1600 mg dronedarone group who suffered trauma due to accidental injury. Twenty-two (10.8%) dronedarone patients discontinued treatment due to adverse events. In the 800 mg, 1200 mg and 1600 mg dronedarone groups, the discontinuation rates were 3.9%, 7.6% and 22.6%, respectively (Table 2). There were no premature discontinuations in the placebo group. Most frequently, gastro-intestinal side effects (diarrhea, nausea, vomiting) led to drug cessation. No evidence of thyroid, hepatic, neurological, ocular or pulmonary complications was found.

In terms of cardiovascular side effects, no proarrhythmic reactions, including torsades de pointes, were reported. The incidence of cardiac failure was not statistically different in patients receiving dronedarone versus placebo. ECG changes were consistent with the known electrophysiological properties of the drug. On day 5-8, heart rate was decreased by 7.2, 6.9, and 11.1 bpm in the 800, 1200 and 1600 mg groups respectively ($P=0.004$). The PR-interval was lengthened by 13.4, 16.6, and 28.4 ms in the 800, 1200 and 1600 mg groups ($P=0.001$). Conversely there was no clear effect on QRS duration. The QTc-interval was variably affected across visits: on day 14, after steady state was reached a mean prolongation of 39 ms was found in the 1600 mg group compared to placebo ($P=0.003$), consistent with the class III properties of the drug. The proportion of patients with at least 1 QT interval >500 ms was 7.7, 6.6, 9.1, and 16.4% in the placebo, 800 mg, 1200 mg, and 1600 mg groups, respectively. Fig. 2 shows the changes in QT over time.

Pharmacokinetics

According to the trough plasma level determinations, dronedarone steady state was reached on day 14 after randomization and the steady state for the N-debutyl metabolite, on day 5-8. A 2-fold dose increase led to a 2.65- and 2.40-fold increase in dronedarone and N-debutyl metabolite concentrations, respectively. The mean metabolic ratio (N-debutyl metabolite/dronedarone) was around 0.6 whatever the dose.

Discussion

Main study findings

DAFNE is the first prospective randomized trial evaluating the efficacy and safety of dronedarone, a new antiarrhythmic agent, in patients undergoing cardioversion for persistent AF. The results demonstrate that dronedarone at a dose of 800 mg/day significantly increases the average time to first AF recurrence when compared to placebo. Importantly, at this dose, the drug was well tolerated and proved to be safe during short-term exposure. No proarrhythmic reactions were observed.

Dronedrone antiarrhythmic effect

Dronedrone at a dose of 800 mg/day prolonged the time to first AF recurrence from an average of 5 to 60 days. This was associated with a time rhythm maintenance rate at 6 months of only 35%. However this figure has to be viewed in the light of the unexpectedly high relapse rate in the control group where only 10% of patients remained free from recurrent AF. The AF recurrence rate in the placebo group is much higher than that observed in recent trials evaluating new antiarrhythmic drugs.²⁰⁻²² In these two trials, 19 to 29% of placebo treated patients remained free of recurrent AF at 6 months. Accordingly, our study population appears to be at high risk for AF

1453-1454, downloaded from www.oxfordjournals.org by [IP: 128.192.252.100] on 14 May 2014

1453-1454

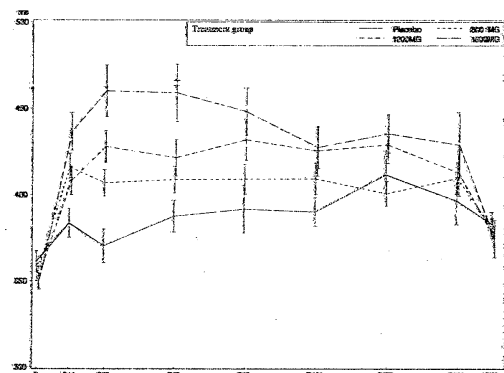


Fig. 2 Plot of QT interval (QTc) over time.

recurrences, although the precise reason for this increased atrial vulnerability remains unknown. An important methodological aspect may also account for the overall high incidence of recurrent AF within our trial. The efficacy analysis was based on transtelephonic monitoring that was symptom-activated and also coded at regular follow-up visits. It can be assumed that early AF recurrences, even transient, were thus more rigorously detected.

A puzzling observation in this study was the lack of a clear-cut dose-response pattern observed with other new class III agents.^{20,21} Even after adjustment using Cox's model for covariates such as baseline characteristics or concomitant therapies, there was still no dose-effect relationship detectable, while the superiority of dronedarone 800 mg over placebo remained significant. This finding could also not be explained by pharmacokinetic parameters. The plasma concentrations of dronedarone and its metabolite measured in this study were in agreement with the drug characteristics as determined in healthy subjects (Clinical Investigator's brochure, unpublished data, 2005). Another hypothesis implies the multifactor mode of action of dronedarone.^{10,11,13} This would result in a bell-shaped response curve, a notion that has never been documented with dronedarone in animal models (Clinical Investigator's Brochure,

Unpublished data, 2005). Finally, an important issue is the higher proportion of patients, occurring in the 1600 and 3200 mg dronedarone groups, possibly due to adverse events resulting in drug discontinuations. This factor may have played a role in the absence of dose-effect relationship. Thus, with dronedarone daily doses exceeding 800 mg, the reduction of the safety margin might impair the clinical benefit of the drug, however this notion has to be regarded with caution due to the limited size of the study groups.

The ability of dronedarone to convert AF to sinus rhythm was demonstrated in this trial. The drug efficacy was modest and increased with dose. The low conversion rate of dronedarone is similar to that of amiodarone or of newly developed drugs such as dofetilide.^{20,22} In this setting, there was a distinct dose-response effect of dronedarone, a behaviour that appeared to be different from that seen during maintenance therapy. The most likely explanation for this discrepancy is the complex action profile of this compound. For dronedarone as for other antiarrhythmic drugs, the ion channels involved in rhythm control might be different from those contributing to pharmacological cardioversion.²³

In case of AF relapses, patients on dronedarone had a lower heart rate as compared to those on placebo. This most reflect a slowing effect on atrioventricular

nodal conduction, a notion in accordance with the drug-induced PR prolongation during sinus rhythm.²⁴ Dronedarone may be a valuable adjunct to the arrhythmia-tarum intended to control ventricular rate in permanent AF, and thus improve arrhythmia tolerance.

Safety

In the present study, there was no evidence for dronedarone-associated proarrhythmic reactions in any patient. In particular, no cases of torsade de pointes were observed notwithstanding the electrophysiological profile of the substance with predominant class III properties. It is noteworthy that the effect of dronedarone on the QT interval remained modest. In this respect dronedarone appears to share the benefits of amiodarone.²⁵ Dronedarone also proved to be hemodynamically well tolerated. However low left ventricular ejection fraction was an exclusion criterion in this trial. This overall safety profile, if confirmed in future studies including a larger and perhaps a sicker patient population, would make dronedarone particularly attractive for therapy of patients with AF in the context of structural heart disease. As expected from the absence of iodine substituents, dronedarone, unlike amiodarone, did not cause any thyroid abnormalities. This notion is of prime importance since the objective, when synthesizing dronedarone, was to get a drug sharing the properties of amiodarone, but devoid of thyroid side effects.

Conclusion

This dose-ranging study demonstrated that, in AF patients, dronedarone given at an 800 mg daily dose was effective for the maintenance of sinus rhythm following cardioversion. However further studies are required to better delineate the antiarrhythmic properties of the drug. The good safety profile associated with the 800 mg dose is an encouraging finding. The absence of thyroid side effect, as shown herein, might well be a key-factor of dronedarone's clinical future.

Acknowledgements

Sanofi-Synthelabo Recherche, France, sponsored the study. We are indebted in particular to B. Radtke, G. Frangin and A.C. Meiss who contributed to the good conduct of the study.

Appendix A

The following Investigators participated in the DAFNE trial: Investigators – I. Blankoff, CHU Saint-Pierre, Brussels, Belgium; J.L. Vanquere, CHU de la Citadelle, Liège, Belgium; R. Tavernier, UZ Gent, Gent, Belgium; P. Brugada, UZ Vrije Ziekenhuis, Aalst, Belgium; K. Penttinen, Kuopio University Hospital, Kuopio, Finland; P. Touboul, Hôpital Louis Pradel, Lyon, France; J. Victor, CHU Angers, France; P. Defaye, Hôpital A.

Michalon, Grenoble, France; A. Da Costa, Hôpital Nord, Saint Priest en Jarez, France; S. Kacet, CHU Lille, France; E. Quirion, SCUS, ONCO, Schtrighem, France; A. Grand, Centre Hospitalier, Valence, France; P. Djiane, Hôpital Sainte Marguerite, Marseille, France; J. Pousonville, Hôpital Gabriel Montpied, Clermont Ferrand, France; P. Blanc, Hôpital Universitaire Dupuytren, Limoges, France; S. Hohlmeier, Klinikum der J.W. Goethe Universität, Frankfurt, Germany; J. Meunier, Klinik Forschungsgesellschaft, Bad Nauheim, Germany; B. Kallische, Herz-Zentrum, Bad Krozingen, Germany; K. H. Kuck, Allgemeines Krankenhaus St Georg, Hamburg, Germany; W. Block, Augustenwald, München, Germany; M. Eldar, Muehlberg Cardiac Research Inst, Tel Hashomer, Herzl, Z. Veng, Cardiology Institute, Zrifin, Israel; B. Strassberg, Rabin Medical Center, Petach Tikva, Israel; P. Rizzon, Università degli Studi di Bari, Italy; H. Krijns, Academisch Ziekenhuis Groningen, The Netherlands; J.A. Kragten, Adriaan Ziekenhuis, Heerlen, The Netherlands; J.M. Timmermans, Medisch Spectrum Twente, Enschede, The Netherlands; F.A.E. Brucke, Catharina Ziekenhuis, Eindhoven, The Netherlands; A.R. Randal Mission, Isala Kliniek, Zwolle, The Netherlands; J.G. Meeder, St Maartens Gasthuis, Venlo, The Netherlands; D.J. Lok, St Deventer Ziekenhuis, Deventer, The Netherlands; E.M. Van Kempen, Ziekenhuis Velp, The Netherlands; H.A. Oude Luttikhuis, Isala Kliniek, Zwolle, The Netherlands; A.M. Wilde, Academisch Medisch Centrum, Amsterdam, The Netherlands; L.H. Sawicki, Medisch Centrum Haaglanden, Via Dan Haag, The Netherlands; P.A. Törn, Westfries Gasthuis, Hoor, The Netherlands; L. Czerwinski, Klinika Kardiologii, Warszawa, Poland; G. Opolski, Klinika Kardiologii, Warszawa, Poland; W. Trzacz-Guzia, Klinika Kardiologii, Katowice, Poland; L. Wawrzynska, Instytut Gruźlicy i Chorób Płuc, Warszawa, Poland; W. Trzacz, Główny Kliniczny Ośrodek Serca i Kierowni, Kraków, Poland; H. Kozłowska-Pałucha, Klinika Kardiologii, Łódź, Poland; W.J. Marosi, Klinika Kardiologii, Bielski, Poland; C. Moro, Hospital Francisco Gaján, Madrid, Spain; J. Brugada, Hospital Clinic Universitario, Barcelona, Spain; I. Fernandez-Lazaro, Clínica Puerta de Hierro, Madrid, Spain; J. Alameda Rodríguez, Hospital Clínico Universitario, Málaga, Spain; J. Alameda, Hospital Gregorio Marañón, Madrid, Spain; J. Olagüe de Ros, Hospital La Fe, Valencia, Spain; M. Pashan Rebolio, Hospital General de Asturias, Oviedo, Spain; F. Garcia-Criso, Hospital Universitario de Getafe, Madrid, Spain; N. Edvardsson, Sahlgrenska Universitetssjukhuset, Göteborg, Sweden; P. Blomström, Thoraxcenter Akademiska Sjukhuset, Öppsala, Sweden; C. Sylven, Hjärtkliniken, Stockholm, Sweden; S. Jull-Jensen, Universitetssjukhuset Ås, Ås, Sweden; T. Åkesson, Cardiocentro Ticino, Lugano, Switzerland; S. Oswald, Lettenberg Artz Klinologie, Basel, Switzerland; J. Fuhrer, Oberarzt Kardiologie, Bern, Switzerland; G. Meier, Primario Medico Interno, Mendrisio, Switzerland; Data Safety Monitoring Board – A. Lelencowicz (head), J. Camm, G. Schmidt, Steering Committee – P. Touboul (chair), J. Brugada, A. Capucci, N. Grijns, N. Edvardsson, S. H. Hohlmeier, B. Radtke.

References

1. Baily D, Lohmann MH, Schonecker DH et al. Hospitalization for arrhythmia in the United States: importance of atrial fibrillation (abstract). *J Am Coll Cardiol* 1992;19:41A.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. *Arch Intern Med* 1987;147:1561-4.
3. Wolf PA, Strehler DE, Thomas DE et al. Epidemiologic assessment of chronic atrial fibrillation and its risk of stroke: the Framingham study. *Neurology* 1983;33:977-7.
4. Lantieri T, Rydén L. Chronic atrial fibrillation. Long-term results of direct current cardioversion. *Acta Med Scand* 1988;223:53-9.
5. Caponi SP, Antonici L, Bello JG et al. Efficacy and safety of electrical therapy for maintenance of sinus rhythm after cardioversion: a meta-analysis of randomized controlled trials. *Circulation* 1998; 98:1536-46.
6. Levy S, Brilhart G, Campbell RH et al. Atrial fibrillation: current knowledge and recommendations management. Working Group on Arrhythmias of the European Society of Cardiology. *Eur Heart J* 1994; 15:154-62.
7. Chou SE, Sager PT, Sweeney HW et al. Chronic atrial fibrillation. Long-term results of direct current cardioversion. *Acta Med Scand* 1988;223:55-9.
8. Roy D, Tatjic M, Dorian P et al. Acetaminophen to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *Br J Med* 2000;341:13-20.
9. Vergeles W, Monaghan TC, Miller S et al. Adverse effects of low dose acetaminophen: a meta-analysis. *J Am Coll Cardiol* 1997;30:293-9.
10. Francis D, Manning A, Chatterjee P. Effects of a new antiarrhythmic drug, SR 30859, in comparison to sotalolol, D,L-cis-L-cis, and D,L-trans-L-cis, on ischemia-induced ventricular arrhythmias in anesthetized pigs. *J Cardiovasc Pharmacol* 1995;13:1738-4.
11. Manning AG, Brugada J, Brugada J et al. SR 30859, a new antiarrhythmic drug, effects on ischemia- and reperfusion-induced arrhythmias in anesthetized rats. *J Cardiovasc Pharmacol* 1995; 26:473-81.
12. Manning A, Tibboe V, Hodge D et al. SR 30859, a new antiarrhythmic drug, effects on ischemia- and reperfusion-induced arrhythmias in anesthetized rats. *J Cardiovasc Pharmacol* 1995;25:202-13.
13. Sun W, Surawski B, Singh BN. Electrophysiological effects of ibuprofen SR 30859, a nonsteroidal antiinflammatory derivative, in the rabbit heart: comparison with antiarrhythmic. *Circulation* 1999;100:2276-81.
14. Nishigaki T, Heyndrickx SP, Chatterjee P et al. SR 30859, a new antiarrhythmic drug, effects on ischemia- and reperfusion-induced arrhythmias in anesthetized and conscious dogs. *Eur J Pharmacol* 1999; 299:21-31.
15. Converse Pauline S, Glickson R, Hodge D et al. Effects of antiarrhythmic and antiarrhythmic in the prevention of atrial arrhythmias in guinea pigs (abstract). *Arch Med Gen* 2001;104:304.
16. Cox SR. Regression models and data tables. *J R Stat Soc* (B) 1982; 34:187-220.
17. Amisano T. Test for linear trend in proportions and frequencies. *Biometrics* 1955;11:375-86.
18. Pie W. *Nonlinear models for ordered alternatives*. In: Ruz D, Johnson O, editors. *Encyclopedia of statistical sciences*. New York: John Wiley & Sons, Inc; 1983;4:175-8.
19. Steel RDG, Torrie JH. *Principles and procedures of statistics*. 1980. New York: McGraw-Hill Book Co.
20. Singh BN, Zelen M, Wilson L et al. Efficacy and safety of oral ibuprofen in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the asymptomatic atrial fibrillation investigator research on celecoxib (SAFARI) study. *Circulation* 2000;102:2395-96.
21. Probst C, Page R, Connolly SJ et al. Antiarrhythmic effects of sotalolol in atrial fibrillation: efficacy and dose response. Canadian Superiority of Ibuprofen (SR 30859) Investigators. *J Am Coll Cardiol* 2000;35:794-802.
22. Halkinck M, Ruz D, L'Herminier J. Effects of oral celecoxib on atrial fibrillation: pharmacological intervention in Atrial Fibrillation (PAF) a randomized trial. *Coron* 2000;35:1789-94.
23. Koster S, Bouillon G, Talaris A. Ischemic heart mechanisms of antiarrhythmic drug action from experimental models of atrial fibrillation. *J Cardiovasc Electrophysiol* 1997;8:66-80.
24. Halkinck M, Singh BN. Pharmacological effects of antiarrhythmic drugs: definition, electrophysiological mechanisms, incidence, predicting factors and clinical implications. *J Cardiovasc Electrophysiol* 1999;10:33-44.

© 1999 Blackwell Science Ltd, *Journal of Clinical Pharmacy and Therapeutics*, 24, 1935-1941

107

111

Rationale and Design of ATHENA: A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg Bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter

STEFAN H. HOHNLOSER, M.D.,* STUART J. CONNOLLY, M.D.,†
HARRY J.G.M. CRIJNS, M.D.,‡ RICHARD L. PAGE, M.D.,¶ WERNER SEIZ, M.D.,§
and CHRISTIAN TORP-PETERSEN, M.D.¶

From the *J. W. Goethe University, Department of Cardiology, Frankfurt, Germany; †McMaster University, Department of Cardiology, Hamilton, Canada; ‡University Hospital Maastricht, Department of Cardiology, Maastricht, the Netherlands; ¶University of Washington, Seattle, Washington, USA; §sanofi-aventis, Clinical Investigations, Frankfurt, Germany; and #Bispebjerg University Hospital, Copenhagen, Denmark

Rationale and Design of ATHENA. *Background:* Atrial fibrillation (AF) is the most commonly encountered clinical arrhythmia, predominantly affecting elderly patients. There is a continued need for new antiarrhythmic drugs to treat the ever-increasing number of patients with this arrhythmia. Dronedarone is a new antiarrhythmic compound currently being developed for treatment of AF.

Methods: The ATHENA trial (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter) is the largest single antiarrhythmic drug trial ever conducted. More than 4,600 patients with a history of AF or atrial flutter (AFL) have been randomized to receive dronedarone 400 mg bid or matching placebo. The primary study endpoint is time to first cardiovascular hospitalization or death from any cause. The study has completed patient enrollment in December 2006 and is expected to end follow-up 1 year later.

Conclusion: ATHENA will be the largest efficacy and safety trial of dronedarone, a multichannel blocker compound with properties from class I, II, III, and IV antiarrhythmic drugs developed to treat patients with AF. (*J Cardiovasc Electrophysiol*, Vol. 19, pp. 69-73, January 2008.)

atrial fibrillation, antiarrhythmic drugs, mortality, cardiovascular hospitalization, dronedarone

Introduction

In the face of a burgeoning older population, the prevalence of atrial fibrillation (AF) is rapidly increasing.¹ AF is associated with increased morbidity and mortality,^{2,3} particularly in patients with structural heart disease impairing systolic or diastolic⁴ LV function. In Western societies, AF

has grown as a major contributing cause of hospitalization and thus, socioeconomic burden.⁵ Accordingly, attempts to restore and maintain sinus rhythm (SR) in patients with AF are currently the preferred treatment modalities in most institutions, despite the results of studies showing similar mortality figures for patients undergoing rhythm or rate control.⁶⁻⁸ Given the epidemic character of the rhythm disorder, non-pharmacological therapy (particularly catheter ablation) is only feasible in selected patient populations, such as younger patients with symptomatic AF but no or only minor structural heart disease. For the great majority of elderly or old patients in whom more or less advanced heart disease constitutes the background of the arrhythmia, pharmacological treatment will remain the mainstay of therapy.

Antiarrhythmic Drug Therapy in AF

A variety of antiarrhythmic drugs is currently used to treat patients with AF, mostly to prevent recurrent AF after successful restoration of SR. As recently demonstrated in a comprehensive meta-analysis, class IA, IC, and III drugs are effective in maintaining SR, but increase adverse effects.⁹ Moreover, at least for the class IA and pure class III (SWORD trial) drugs, it was shown that they increase mortality. This is in agreement with findings of the AFFIRM trial, in which the only predictor of improved outcome was maintenance of SR,

This manuscript was processed by a guest editor.

Dr. Seiz is an employee of sanofi-aventis.

Research support from sanofi-aventis was received by Drs. Hohnloser, Connolly, Crijns, and Torp-Petersen.

Drs. Hohnloser, Connolly, Crijns, Page, and Torp-Petersen received honoraria and/or consulting fees from sanofi-aventis.

Address for correspondence: Stefan H. Hohnloser, M.D., F.A.C.C., F.E.S.C., F.H.R.S., Professor of Medicine and Cardiology, Division of Clinical Electrophysiology, J. W. Goethe University Hospital, Theodor-Stern-Kai 7, D 60590 Frankfurt, Germany. Fax: +49-69-6301-7017; E-mail: Hohnloser@em.uni-frankfurt.de

Manuscript received 24 May 2007; Revised manuscript received 26 July 2007; Accepted for publication 30 July 2007.

doi: 10.1111/j.1540-8167.2007.01016.x

but on the other hand, the use of contemporary antiarrhythmic drugs was found to be associated with adverse prognostic implications.¹⁰ Accordingly, there is a continued need for more effective, safer, and well-tolerated antiarrhythmic drugs for therapy of millions of patients who are not primarily candidates for nonpharmacological therapy of AF.

Development of Dronedaron

Dronedaron is a noniodinated benzofuran derivative with a sulfonamide group on the benzofuran ring. The electrophysiological properties of dronedaron are very similar to those of amiodaron, which is at present the most effective drug to maintain SR in patients with AF. Like amiodaron, dronedaron demonstrates electrophysiological characteristics belonging to all four Vaughan-Williams classes: it blocks sodium channels, shows a noncompetitive antiadrenergic activity, prolongs action potential and refractory periods, and has calcium antagonist properties. Dronedaron is effective in experimental models of AF, ventricular tachycardia, and ventricular fibrillation.¹¹⁻¹⁴

The first clinical study to evaluate the efficacy and safety of dronedaron in maintaining SR in patients with a history of AF was the dose-ranging Dronedaron Atrial Fibrillation Study after Electrical Cardioversion (DAFNE) trial.¹⁵ In DAFNE, patients with persistent AF were randomly assigned to treatment with dronedaron 400 mg, 600 mg, and 800 mg bid or placebo. Analyses were carried out on 199 of 270 patients who entered the maintenance phase following pharmacological conversion or, where unsuccessful, DC conversion, with time to first recurrence as the primary study endpoint. Six-month follow-up showed that treatment with dronedaron 400 mg bid significantly prolonged the time to AF recurrence. The median time to recurrence was 60 days in the dronedaron 400 mg bid, treatment arm compared with 5.3 days in placebo recipients resulting in a relative risk reduction of 55% (95% CI, 28–72%; $P = 0.001$). Spontaneous conversion to SR occurred in 5.8–14.8% of dronedaron-treated patients compared with only 3.1% on placebo ($P = 0.026$). During recurrent AF, a significant slowing of the ventricular rate was also observed during DAFNE.

These promising features have been extensively evaluated in two pivotal trials, EURIDIS (EUROPEAN Trial In Atrial Fibrillation Or Flutter Patients Receiving Dronedaron for the Maintenance of Sinus Rhythm) and ADONIS (AMERICAN-AUSTRALIAN-AFRICAN Trial With Dronedaron In Atrial Fibrillation/flutter Patients For The Maintenance of Sinus Rhythm).¹⁶ EURIDIS was performed at 65 centers in 12 European countries and ADONIS at 101 centers in the United States, Canada, Australia, South Africa, and Argentina. Both placebo-controlled, multi-center, multinational, double-blind, parallel-group trials utilized identical protocols to determine the effectiveness of dronedaron in maintaining SR in patients with AF. Patients with at least one documented episode of AF during the previous 3 months and SR for at least 1 hour were randomized to dronedaron 400 mg bid or placebo. Analyses were performed on the intent-to-treat populations (612 and 625 patients in the EURIDIS and ADONIS trials, respectively) to determine the time to AF recurrence over 12 months—the primary study endpoint. When analyzed separately or in combination, dronedaron proved to be superior in maintaining SR with an excellent safety and tolerability profile.¹⁶

The ANDROMEDA (Antiarrhythmic trial with Dronedaron in Moderate to severe CHF Evaluating morbidity Decrease) was a placebo-controlled outcome study of dronedaron in patients with a recent episode of decompensated heart failure and a left ventricular ejection fraction (LVEF) < 0.35 . A history or the presence of AF was not an inclusion criterion for this study. This trial was stopped by the Data Safety Monitoring Board (DSMB) after recruitment of 627 patients because of excess mortality in the treatment group, compared with the placebo group. Detailed results of this study are yet to be reported and data analysis and interpretation is ongoing at the present time (personal communication: Christian Torp-Petersen).

Design of ATHENA

The ATHENA trial (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedaron 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter) is a large outcomes trial to further examine the efficacy and safety of dronedaron in the treatment of AF or atrial flutter (AFL). This study will be of paramount importance for the future of dronedaron. It is a prospective, randomized, placebo-controlled, double-blind, multi-national, multi-center, parallel-group trial evaluating the effects of dronedaron 400mg 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. The trial is registered under ClinicalTrials.gov #NCT 00174785.

The Steering Committee gives advice on the scientific and clinical aspects of the study protocol and related documents and carries the overall responsibility for the execution and scientific reporting of the study. The three amendments to the protocol were based upon recommendations by the Steering Committee and were taken in mutual agreement with the sponsor.

Patient Selection

High-risk patients with a history of paroxysmal or persistent AF/AFL were eligible for participation in ATHENA if they meet the following inclusion criteria: 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: arterial hypertension (ongoing therapy with at least two antihypertensive drugs of different classes); diabetes mellitus; prior stroke or transient ischemic attack or systemic embolism; left atrium diameter greater than or equal to 50 mm by M-mode echocardiography; left ventricular ejection fraction less than 0.40 by 2D-echocardiography. In addition, for each patient one 12-lead ECG within the last 6 months had to be available, showing that the patient had been or was in AF/AFL, and a second 12-lead ECG within the last 6 months, showing that the patient had been or was in SR. Originally, the protocol had allowed patients of younger age with additional risk factors into the study. However, due to the lower than expected mortality figures, the steering committee had recommended to change the inclusion criteria to enrich the risk profile of the overall study population. This protocol amendment was implemented on March 25, 2006.

143
114

Exclusion Criteria

Patients were ineligible for participation in ATHENA if they had one of the following cardiac conditions: Permanent AF, unstable hemodynamic situation (i.e., recently decompensated heart failure); congestive heart failure NYHA class IV; planned major noncardiac or cardiac surgery; acute myocarditis; bradycardia < 50 bpm and/or a PR interval > 0.28 seconds; significant sinus node disease in the past, if not treated with a pacemaker. The following general exclusion criteria were applied: refusal or inability to give informed consent; any noncardiac severe illness limiting life expectancy; pregnancy and breastfeeding; women of child-bearing potential without adequate birth control; participation in another clinical trial; patients with a calculated GFR at baseline < 10mL/min using the Cockcroft Gault formula; potassium level < 3.5 mmol/L if not corrected. Finally, patients needing concomitant medication which is prohibited within ATHENA (i.e., other antiarrhythmic drugs of Vaughan-Williams class I or III) were excluded.

Study Design

Patients could be included in the study while in SR if conversion has occurred either spontaneously or following electrical or pharmacological cardioversion. Patients also could be included while in AF/AFL, and in this case they could undergo cardioversion after appropriate anticoagulation. Randomization was stratified by center and by the presence or absence of AF/AFL at the time of randomization. After randomization, all patients will be followed until the common study end date; the last patient included in the study will be followed for 1 year. The study will be completed for all patients at this common study end date. Therefore, patients will be followed up for a minimum of 12 months, depending on their time of recruitment into the study. The range of duration of follow-up is anticipated to be 12–30 months.

Study Endpoints

The primary study outcome is the first occurrence of cardiovascular hospitalization or death from any cause during the study period. Any unplanned hospitalization (i.e., admission with an overnight stay in hospital—covering at least 2 consecutive dates) will be categorized depending on the cause and divided into cardiovascular and noncardiovascular. The prespecified main causes for cardiovascular hospitalization are detailed in Table 1.

Deaths will be categorized by a blinded adjudication committee according to a modified Hinkle and Thaler classification¹⁷ into four categories: cardiac death, arrhythmic; cardiac death, nonarrhythmic; vascular death, noncardiac; and noncardiovascular death. This classification scheme has been previously validated in several large trials.^{18–20}

Secondary study endpoints are death from any cause; cardiovascular deaths; and hospitalization for cardiovascular reasons.

Sample Size and Statistical Analysis

According to the pooled results of ADONIS and EURIDIS, the 1-year placebo-group cardiovascular hospitalization rate is anticipated to be 20%, a figure that was also ob-

TABLE 1	
Main Causes for Cardiovascular Hospitalizations	
●	Atherosclerosis related (if not otherwise specified)
●	Myocardial infarction or unstable angina
●	Stable angina pectoris or atypical chest pain
●	Syncope
●	Transient ischemic attack or stroke (except intracranial hemorrhage)
●	Atrial fibrillation and other supraventricular rhythm disorders
●	Nonfatal cardiac arrest
●	Ventricular arrhythmia
●	Cardiovascular surgery except cardiac transplantation
●	Cardiac transplantation
●	Implantation of a pacemaker, ICD, or any other cardiac device
●	Transcatheter coronary, cerebrovascular, or peripheral procedure
●	Blood pressure-related (hypotension, hypertension; except syncope)
●	Cardiovascular infection
●	Major bleeding (requiring two or more units
●	of blood or any intracranial hemorrhage)
●	Pulmonary embolism or deep vein thrombosis
●	Worsening congestive heart failure, including pulmonary
●	edema or dyspnea of cardiac origin

served in the AFFIRM study.⁷ Dronedarone reduced the risk of rehospitalization by approximately 20% in the two pivotal efficacy trials. Cardiovascular hospitalization is anticipated to precede the majority of cardiovascular deaths. The remaining deaths, by default deaths not preceded by cardiovascular hospitalization, are unlikely to be influenced by dronedarone. Thus, the overall decrease of risk for the primary endpoint in ATHENA is assumed to be 15% at 1 year. Nine hundred seventy patients reaching the primary endpoint will give 80% power to the trial for testing dronedarone's superiority over placebo at a two-sided 5% alpha-level.

In order to observe about 260 deaths, which will allow to estimate the relative risk of death with a precision of ±0.13, within an inclusion period of 1.5 years, a minimum follow-up of 1 year and a maximum follow-up of 2.5 years (mean follow-up of 1.7 years), enrollment of 2,150 patients per group (4,300 in total) is anticipated to be necessary. All analyses will be done according to the intent-to-treat principle.

Study Progress

Patient enrollment commenced in June 2005. Enrollment of 4,628 patients was completed on December 30, 2006, with planned follow-up expected to end by December 30, 2007. Key baseline demographics of enrolled patients are depicted in Table 2.

Discussion

Antiarrhythmic Drug Therapy in AF

The increasing prevalence of AF due to the aging populations requires development of new effective and safe pharmacological therapies for wide-spread use. At present, amiodarone is the most effective drug for maintaining SR in patients with structural heart disease, but its noncardiac side effects require drug discontinuation in a significant proportion of patients. Dronedarone has similar electrophysiological properties as amiodarone in various experimental settings.¹¹ In two large pivotal efficacy trials involving 1,237 patients with AF, dronedarone was demonstrated to reduce the risk of recurrent AF by 20–30%.¹⁶ In

115

TABLE 2
Patient Baseline Data (n = 4,628 Patients)

Baseline Characteristics	Incidence / Mean Value
Patient age	
<65 years	19%
65–74 years	40%
≥75 years	42%
Female gender	47%
Hypertension	86%
Mean systolic blood pressure	134 mmHg
AF at baseline*	25%
History of cardioversion	34%
Structural heart disease**	60%
–History of coronary artery disease	30%
–Ischemic dilated cardiomyopathy	5%
–Nonischemic dilated cardiomyopathy	4%
–Rheumatic valve disease	2%
–Nonrheumatic valve disease	15%
–Hypertrophic cardiomyopathy	2%
–History of congestive heart failure	29%
–LVEF < 0.45	12%
Lone atrial fibrillation***	6%

*AF at baseline: according to the stratification factor at randomization.
**Structural heart disease: coronary heart disease and/or ischemic dilated cardiomyopathy and/or nonischemic dilated cardiomyopathy and/or rheumatic valvular heart disease and/or nonrheumatic valvular heart disease and/or hypertrophic cardiomyopathy and/or history of congestive heart failure and/or left ventricular ejection fraction (LVEF) < 45%.
***Lone atrial fibrillation: patients without hypertension and without structural heart disease.

addition, the drug has marked rate-controlling potency in cases of relapses of AF. Importantly, dronedarone had a very good safety and tolerability profile. Specifically, there was no case of torsade de pointes proarrhythmia reported in the entire clinical development program up to the start of this study. Thus, dronedarone appears to be a promising new antiarrhythmic compound for treatment of AF. Despite the lack of apparent proarrhythmic effects, dronedarone was associated with increased mortality in patients with a recent history of decompensated heart failure (ANDROMEDA). Of note, ANDROMEDA was not an AF study. Although the precise cause for this unexpected observation is at present still unclear, the finding reemphasizes the need for a large dronedarone outcomes study in a typical population of elderly AF patients.

Unique Features of ATHENA

ATHENA is the pivotal outcome study for the development of dronedarone. Several features of this trial deserve further comments. ATHENA is the first large AF trial which does not use any “conventional” endpoint directly related to AF such as prevention of recurrent AF, time to first AF recurrence, AF burden or others.²¹ This randomized clinical trial uses for the first time exclusively the combined endpoint of all-cause mortality and rehospitalization for cardiovascular causes. The reason to choose this endpoint is due to the fact that AF represents an increasing socioeconomic burden to Western societies, particularly as a consequence of repeated requirement of arrhythmia-related hospitalizations. Moreover, rehospitalization is one of the major reasons for a significant impairment in quality of life in these patients. Since it was shown that dronedarone is not only capable of maintaining SR in many patients, but also of controlling

heart rate in case of AF relapses, it is expected that treatment with this compound will result in a significant reduction in the need of rehospitalizations for cardiovascular reasons.

ATHENA is the largest study ever conducted to evaluate the efficacy and safety of a single antiarrhythmic compound in a typical AF population. More than 4,600 patients have been enrolled in more than 700 investigational sites around the globe. A history of hypertension was the most prevalent underlying cardiovascular disease, 30% of patients had a history of coronary disease, and 29% presented with a previous history of heart failure. The median age of patients enrolled in the study is 73 years. Therefore, the patients enrolled in ATHENA represent the largest group of individuals seeking medical attention for treatment of AF.

In summary, ATHENA will be the largest antiarrhythmic drug trial conducted in AF. The trial is well powered to establish the efficacy and safety of dronedarone, a new antiarrhythmic compound, for the treatment of AF.

References

- Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE: Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA* 2001;285:2370-2375.
- Benjamin EJ, Wolf PA, D’Agostino RB, Silbershatz H, Kannel WB, Levy D: Impact of atrial fibrillation on the risk of death: The Framingham heart study. *Circulation* 1998;98:946-952.
- Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D’Agostino RB, Murabito JM, Kannel WB, Benjamin EJ: Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham heart study. *Circulation* 2003;107:2920-2925.
- Tsang TS, Gersh BJ, Appleton CP, Tajik AJ, Barnes ME, Bailey KR, Oh JK, Leibson C, Montgomery SC, Seward JB: Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. *J Am Coll Cardiol* 2002;40:1636-1644.
- Wattigney WA, Mensah GA, Croft JB: Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: Implications for primary prevention. *Circulation* 2003;108:711-716.
- Hohnloser SH, Kuck KH, Lilienthal J, for the PLAF Investigators: Rhythm versus rate control in atrial fibrillation—Pharmacological intervention in atrial fibrillation (PIAF): A randomised trial. *Lancet* 2000;356:1789-1794.
- The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators: A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-1833.
- Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ, Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group: A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;347:1834-1840.
- Lafuente-Lafuente C, Mouly S, Longas-Tejeor MA, Mahe I, Bergmann JF: Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation. A systematic review of randomized controlled trials. *Arch Intern Med* 2006;166:719-728.
- The AFFIRM Investigators: Relationship between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Circulation* 2004;109:1509-1513.
- Wegener F, Ehrlich J, Hohnloser SH: Dronedarone: An emerging agent with rhythm- and rate- controlling effects. *J Cardiovasc Electrophysiol* 2006;17 (Suppl 2):S17-S20.
- Sun W, Sarma JS, Singh BN: Electrophysiological effects of dronedarone (SR33589), a noniodinated benzofuran derivative, in the rabbit heart: Comparison with amiodarone. *Circulation* 1999;100:2276-2281.

13. Gautier P, Guillemare E, Marion A, Bertrand JP, Tourneur Y, Nisato D: Electrophysiologic characterization of dronedarone in guinea pig ventricular cells. *J Cardiovasc Pharmacol* 2003;41:191-202.
14. Lalevee N, Nargeot J, Barrere-Lemaire S, Gautier P, Richard S: Effects of amiodarone and dronedarone on voltage-dependent sodium current in human cardiomyocytes. *J Cardiovasc Electrophysiol* 2003;14:885-890.
15. Touboul P, Brugada J, Capucci A, Crijns HJ, Edvardsson N, Hohnloser SH: Dronedarone for prevention of atrial fibrillation: A dose-ranging study. *Eur Heart J* 2003;24:1481-1487.
16. Singh BN, Connolly SJ, Crijns HGJM, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EA, Hohnloser SH (Members of the Steering Committee), for the EURIDIS and ADONIS Investigators: Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;357:987-99.
17. Hinkle LE Jr, Thaler HT: Clinical classification of cardiac deaths. *Circulation* 1982;65:457-464.
18. Cairns JA, Connolly SJ, Roberts R, Gent M: Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial). *Lancet* 1997;349:675-682.
19. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B: Canadian Implantable Defibrillator Study (CIDS): A randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;101:1297-1302.
20. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ: Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481-2488.
21. Wyse DG, Gersh BJ: Atrial fibrillation: A perspective. *Circulation* 2004;109:3089-3095.