

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

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Bogotá, D.C.,

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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".

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 Dronedarona 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 Dronedarona 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 Dronedarona tiene dominio cardiovascular como agente anti arritmico, por tal razón es útil para suprimir o prevenir las alteraciones del ritmo cardiaco como la fibrilación auricular. D1 refiere a una sal farmacéuticamente de Dronedarona 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 Dronedarona 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 Dronedarona 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.

Item	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 ELECTROPHYSIOLOG Y 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 (FI. 106). La Dronedarona es estructuralmente similar a Amiodarona y presenta características electrofisiológicas in vitro de cuatro clases de acción anti arritmica (FI. 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. (FI. 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

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SYNOPSIS
Standardized agents,
Actual Herbicides,
Carbamates

plans. Doxodessone, a benzofuran derivative without iodine substituents, shows the electrohydrolytic properties of actinodione. This study was designed to determine the most appropriate dose of doxodessone for prevention of atrial fibrillation (AF) after cardioversion.

methods and results Patients with persistent AF were randomly allocated to 800, 1600, or 3200 mg daily doses of amiodarone or placebo. The main analysis was conducted on 191/220 patients, who entered the maintenance phase following the pharmacological cardioversion or, if unsuccessful, DC cardioversion. Within 6 months of follow-up, the time to AF relapse increased in the amiodarone group, with a median of 1640 days vs 5.3 days in the placebo group (relative risk reduction 55% [95% CI, 28 to 72%]). No additional effect was seen at higher doses. Spontaneous conversions to sinus rhythm on amiodarone occurred in 3.8 to 14.5% of patients (p=0.024). There were no proarrhythmic reactions. Drug-induced QT prolongation was only noticed in patients taking the 1600 mg group. Premature drug discontinuations affected 52.5% of subjects taking 800 mg amiodarone versus 1.5% on 1600 mg and 19% on 3200 mg. No pronounced side effects. No evidence of thyroid, ocular or pulmonary toxicity were found.

Concathion Dexamethasone, at a 200 mg daily dose, appears to be effective and safe for the prevention of H^+ releases after lard oxidation. The absence of steroid side effects and of glycaemic changes are important features of the drug. Further studies are needed to better delineate the pharmacodynamic profile of the drug.

and mortality as highlighted by an estimated incidence of over 75,000 AF-related strokes per year in the U.S.

Atrial fibrillation (AF) is the most commonly encountered cardiac rhythm disturbance accounting for 24.5% of arrhythmia-related hospital admissions in a recent US survey.¹ AF is associated with increased mortality

by patients with persistent AF, electrical cardioversion is usually performed. Despite high initial success rates, this strategy is limited by the incidence of AF recurrence

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their use is as high as 70 to 80% after 12 months if no symptomatic arrhythmias occur. The efficacy of antiarrhythmic therapy is administered in a stepwise fashion. Class I and II antiarrhythmic drugs have been studied in controlled trials to evaluate their efficacy in maintaining sinus rhythm.⁸ Overall, approximately 50% of patients on active drug therapy remain in sinus rhythm.

1995-680701/\$ - see front matter © 2003 Published by Elsevier Ltd on behalf of The European Society of Cardiology.

Amiloride is a benzoxazin derivative structurally similar to amiloride, which is being developed as an antiarrhythmic agent. The absence of sodium channels and a less lipophilic character should be associated with a lower antiarrhythmic activity. In fact, amiloride possesses antiarrhythmic activity, but it is much less than that of amiloride. Specifically, it does not alter the electrophysiologic characteristics of all major classes of antiarrhythmic action.¹⁰⁻¹² Specifically, it does not alter the sodium channels at rapid pacing rates, prolongs the action potential duration, and does not alter the action potential upstroke potentials and refractoriness, and produces a small negative inotropic effect. In addition, amiloride shows a noncompetitive antiadrenergic action.

The Dose-dense Adult Flu/Mucosal study after Inter-
mittent Cardioversion (DAFIC) was a double-blind, random-
ized, placebo-controlled trial designed to select the
most appropriate dose of procainamide for prevention of
recurrent AF after successful cardioversion.

Patients with previous MI obtained an electrocardiogram (ECG) and echocardiogram within 2 weeks after the myocardial infarction. Effective left ventricular ejection fraction (EF) was determined at least 2 months prior to randomization. All patients included in the study were allocated to one of two groups of treatment: 1) treatment with the combination of aspirin, clopidogrel, and statins (ASA-CLO-STAT) or 2) treatment with aspirin, clopidogrel, and statins plus a second statin (ASA-CLO-STAT-2). The first group was selected based on observational data suggesting that treatment with a statin alone may be sufficient to reduce the risk of cardiovascular morbidity and mortality in patients with previous MI. The second group was selected based on observational data suggesting that treatment with a statin plus a second statin may be more effective in reducing the risk of cardiovascular morbidity and mortality in patients with previous MI. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the local ethics committee. All patients gave written informed consent before entering the study.

Study sites in the captopril clinic were scheduled on the days 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, and 60 after randomization at entry time in case of treatment A or after medical publication in case of treatment B. The captopril clinic was mostly open for 5 days following randomization, three every two weeks. Patients were scheduled to come to the clinic on the study days 48, and were informed up to the end of the study. Patients were also instructed to bookmark their AEC in case of recurrent symptoms at any time. At each study visit, plasma captopril levels were taken for determination of dose-toxicity through the use of the World Pharmacokinetics Assays during the last visit.

patients with a history of stroke, and 10 patients with a history of stroke and a history of stroke.

Conclusion: *Shigella* spp. and *Shigella* spp. are the most common causes of bacterial dysentery in children in the United States.

completes with one or more of the following criteria met and added from the reader's note (but two must be met):

[illegible]

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 ambulatory ECG monitoring at the same time interval. Secondary study endpoints were spontaneous conversion of AF following consolidation, heart rate in case of recurrence and the incidence of side effects.

the 1990s, the U.S. economy has been in a period of relative stagnation. The unemployment rate has risen from 5.6% in 1989 to 7.6% in 1995. The economy has been plagued by a series of recessions, and the federal government has been forced to raise taxes and cut spending to reduce the budget deficit. The economy has been hit hard by the Asian crisis, and the U.S. economy is expected to continue to struggle in the near future.

The study patients were categorized in the patients according to the anatomic site of the tumor. The patients were divided into three groups: the patients with the tumor in the oral cavity, the patients with the tumor in the nasopharynx, and the patients with the tumor in the larynx. The patients with the tumor in the oral cavity were divided into two groups: the patients with the tumor in the tongue and the patients with the tumor in the pharynx. The patients with the tumor in the nasopharynx were divided into two groups: the patients with the tumor in the nasopharynx and the patients with the tumor in the oropharynx. The patients with the tumor in the larynx were divided into two groups: the patients with the tumor in the larynx and the patients with the tumor in the trachea.

Patient Characteristics

Fifty-headed and seventy patients were randomized in 10 centers and 11 countries. One hundred and ninety-nine patients, in whom abuse of force was restored, were included in the primary analysis. Patients randomized to the four groups had similar baseline characteristics as shown in Table 1.

Angiotensin-converting enzyme for the primary cultures are shown in Fig. 1. These values are increased here to 44% compared with the control. This effect is being less apparent at the concentration 800 mg. The difference compared with higher doses. Only with 800 mg. the difference compared with placebo was statistically significant. The median time to first attack recurrence was 121 days in the placebo group, and 109 days in the dexamethasone 800 mg group (relative reduction of recurrence, 55% [32-72, $p=0.20$]). In the two other reductions, 55% [32-72, $p=0.20$]. In the two other reductions, no significant difference was noticed here.

Table 1 Neurographic and invasive characteristics of patients

	Placebo n=41	100 mg n=54	300 mg n=54	1000 mg n=13
Age (years)	65	64	63	62
Male sex (%)	79	59	70	87
Heart failure (%)	26	31	20	44
CAD (%)	37	26	38	30
Ventricular fibrillation (%)	29	25	31	17
Heart failure (%)	22	24	24	48
AF duration (days)	22	22	24	48
Recurrence AF (%)	65	59	54	74
24-h size (mm)	46	44	45	45
LVESV (%)	36	33	53	34

*CAD, coronary artery disease.

*AF, atrial fibrillation.

*LVESV, left ventricular end-systolic volume.

*LVESV, left ventricular end-systolic volume.

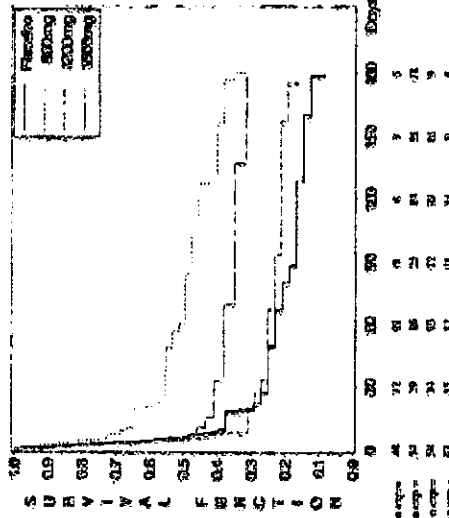


Fig. 1 Kaplan-Meier analysis of time to first AF recurrence. The difference between the 1000 mg group and the placebo group was significant (P=0.001) in favour of the 1000 mg group.

Lack of dose effect. At 6 months, 10% of the patients treated with 1000 mg dronedarone were in sinus rhythm, as compared to 10% in the placebo group. A significant difference was observed between the 1000 mg group and the placebo group (P=0.001). The difference between the 1000 mg group and the placebo group was significant (P=0.001) in favour of the 1000 mg 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 300, 1000, and 1000 mg groups, respectively, showed a dose-dependent response to a dose-dependent

Table 2 Adverse events leading to study drug discontinuation

Adverse event	Placebo n=65	100 mg n=54	300 mg n=54	1000 mg n=13	Discontinuation n=1204
Total	9 (14%)	9 (17%)	14 (26%)	2 (15%)	34 (28%)
Gastrointestinal (including diarrhoea, vomiting, nausea, gastroenteritis)	3 (5%)	3 (6%)	5 (9%)	1 (8%)	10 (8%)
General disorders (including malaise, asthenia, fatigue, weight decrease)	2 (3%)	2 (4%)	3 (6%)	1 (8%)	8 (7%)
Cardiac failure	1 (2%)	1 (2%)	1 (2%)	1 (8%)	4 (3%)
Control nervous system (dizziness)	1 (2%)	1 (2%)	1 (2%)	1 (8%)	4 (3%)
Headache	1 (2%)	1 (2%)	1 (2%)	1 (8%)	4 (3%)
QT interval	1 (2%)	1 (2%)	1 (2%)	1 (8%)	4 (3%)
Tachycardia supraventricular	1 (2%)	1 (2%)	1 (2%)	1 (8%)	4 (3%)
Thrombocytosis	1 (2%)	1 (2%)	1 (2%)	1 (8%)	4 (3%)

tion. Patients receiving 800, 1200, or 1600 mg dronedarone had their ventricular rate reduced by 11.2, 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 from a stroke due to a cerebral embolism. Twenty-two (10.5%) 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 (diarrhoea, 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 parasympathetic reactions, including bradycardia or sinus arrest, 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, 16.9, and 11.1 bpm in the 800, 1200 and 1600 mg groups, respectively (P<0.001). The PR interval was lengthened by 11.4, 16.9, and 23.4 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 verifiably 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<0.001), consistent with the class II properties of the drug. The proportion of patients with at least 1 QT interval >500 ms was 7.3, 6.5, 9.1, and 15.4% 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 2.48-fold increase in dronedarone and N-debutyl metabolite concentrations, respectively. The mean metabolic ratio (N-debutyl metabolite/dronedarone) was around 6.6 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 cardiovascular surgery. The results demonstrate that dronedarone is effective at a dose of 800 mg/day significantly increasing 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.

Dronedarone antiarrhythmic effect

Dronedarone at a dose of 800 mg daily prolonged the time to first AF recurrence from an average of 5 to 60 days. This was associated with a sinus rhythm maintenance rate at 6 months of only 10%. However, this figure has to be viewed in the light of the unexpectedly high efficacy 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 involving new antiarrhythmic drugs. In the recent trials involving new antiarrhythmic drugs, the AF recurrence rate at 6 months was 28% for placebo-treated patients, 28% for dronedarone-treated patients, and 28% for dronedarone-treated patients. Accordingly, our study population appears to be at high risk for AF.

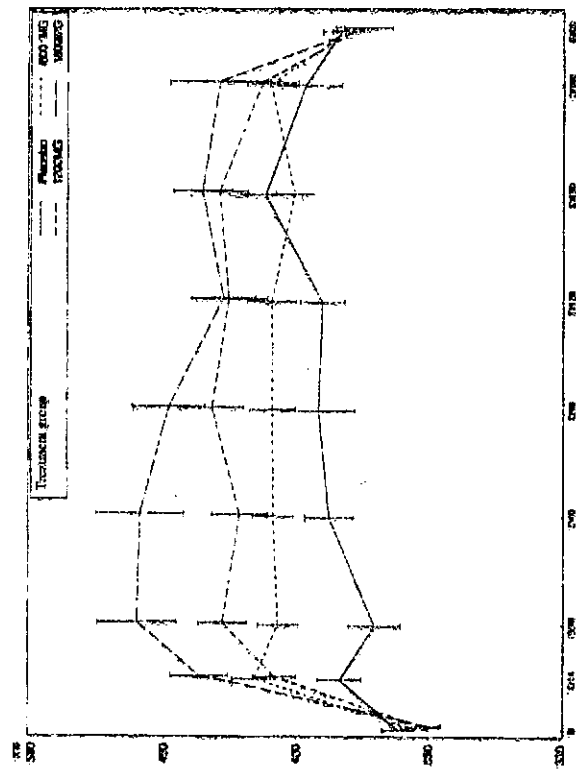


Fig. 2. Rate of AF (per 1000 h) over time.

recurrences, although the precise reason for this increased arrhythmia 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 trans-telephonic monitoring that was symptom-activated and also used 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 dronedone 400 mg over placebo remained significant. This finding could also not be explained by pharmacokinetic parameters. The plasma concentrations of dronedone 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, 2001). Another hypothesis implies the multifactorial mode of action of dronedone, mainly this would result in a bell-shaped response curve, a notion that has never been documented with dronedone. In animal models (Clinical Investigator's Brochure,

unpublished data, 2001). Finally, an important issue is the higher proportion of patients occurring in the 1000 and 1400 mg dronedone groups, mainly due to adverse events resulting in drug discontinuations. This factor may have played a role in the absence of dose-effect relationship. Thus, with dronedone 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 dronedone 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 dronedone is similar to that of amiodarone or other antiarrhythmic drugs such as sotalolol.^{22,23} In this setting, there was a distinct dose-response effect of dronedone, 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 dronedone as for other antiarrhythmic drugs, the low channels involved in rhythm control might be different from those contributing to pharmacological cardioversion.²⁴

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

nodal conduction, a notion in accordance with the drug-induced PR prolongation during sinus rhythm.²⁵ Dronedone may be a valuable adjunct to the amiodarone intended to control ventricular rate in permanent AF, and thus improve arrhythmia tolerance.

Safety

In the present study, there was no evidence for dronedone-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 dronedone on the QT interval remained modest. In this respect dronedone appears to share the benefits of amiodarone.²⁶ Dronedone 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 dronedone particularly attractive for therapy of patients with AF in the context of structural heart disease. As expected from the absence of iodine substituents, dronedone, unlike amiodarone, did not cause any thyroid abnormalities. This notion is of prime importance since the objective, when synthesizing amiodarone, 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, dronedone 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 dronedone's clinical future.

Acknowledgements

Sandoz-Synthelabo Recherche, France, sponsored the study. We are indebted in particular to D. Fachin, G. Fraigne and A.C. Delis who contributed to the good conduct of the study.

Appendix A

The following investigators participated in the DUNE trial: Investigators - J. Guasch, CHU Saint-Pierre, Brussels, Belgium; J.L. Wainque, CHU de la Citadelle, Liège, Belgium; R. Taverier, UZ Gent, Gent, Belgium; P. Brugada, CHU Vrije Ziekenhuis, Leiden, The Netherlands; Kuopio University Hospital, Kuopio, Finland; P. Touboul, Hôpital Louis Pradel, Lyon, France; J. Victor, CHRU Angers, France; P. Delays, Hôpital A.

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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

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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,

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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 DescreAse) 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.

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 < 10 mL/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 Dronedaron 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 dronedaron. 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 dronedaron'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, amiodaron 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. Dronedaron has similar electrophysiological properties as amiodaron in various experimental settings.¹¹ In two large pivotal efficacy trials involving 1,237 patients with AF, dronedaron was demonstrated to reduce the risk of recurrent AF by 20–30%.¹⁶ In

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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 con-

trolling 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.

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