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Safety and Efficacy of Intravenously Administered Tedisamil for Rapid Conversion of Recent-Onset Atrial Fibrillation or Atrial Flutter

Stefan H. Hohnloser, MD,* Paul Dorian, MD,† Matthias Straub, MD,‡ Katrin Beckmann,‡ Peter Kowey, MD§

Frankfurt and Hannover, Germany; Toronto, Canada; and Wynnewood, Pennsylvania

OBJECTIVES The goal of the present study was to assess the efficacy and safety of intravenous tedisamil, a new antiarrhythmic compound, for conversion of recent-onset atrial fibrillation (AF) or atrial flutter (AFL) to normal sinus rhythm (NSR).

BACKGROUND Tedisamil is a novel antiarrhythmic drug with predominantly class III activity. Its efficacy and safety for conversion of recent onset AF or AFL to NSR is not known.

METHODS This was a multicenter, double-blind, randomized, placebo-controlled, sequential ascending dose-group trial. A total of 201 patients with symptomatic AF or AFL of 3 to 48 h duration were enrolled in a two-stage study. During stage 1, patients were randomized to receive tedisamil at 0.4 mg/kg body weight or matching placebo; during stage 2, patients received tedisamil at 0.6 mg/kg body weight or matching placebo. Treatments were given as single intravenous infusions. The primary study end point consisted of the percentage of patients converting to NSR for at least 60 s within 2.5 h.

RESULTS Of 175 patients representing the intention-to-treat sample, conversion to NSR was observed in 41% (25/61) of the tedisamil 0.4 mg/kg group, 51% (27 of 53) of the tedisamil 0.6 mg/kg group, and 7% (4/59) of the placebo group ($p < 0.001$ for both tedisamil groups vs. placebo). Average time to conversion was 35 min in patients receiving tedisamil. There were two instances of self-terminating ventricular tachycardia: one episode of torsade de pointes and one of monomorphic ventricular tachycardia, both in patients receiving 0.6 mg/kg tedisamil.

CONCLUSIONS Tedisamil at dosages of 0.4 and 0.6 mg/kg was superior to placebo in converting AF or AFL. Tedisamil has a rapid onset of action leading to conversion within 30 to 40 min in the majority of responders. (J Am Coll Cardiol 2004;44:99–104) © 2004 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common sustained arrhythmia requiring hospitalization, and affects millions of people worldwide (1). The prevalence of AF increases with age and in the presence of structural heart disease (2). Atrial fibrillation is associated with significant mortality and morbidity and impacts significantly on quality of life. Restoration of normal sinus rhythm (NSR) in patients with these arrhythmias may improve their hemodynamic condition, relieve symptoms, and probably reduce embolic risk. Although this may be achieved using direct current cardioversion, the technique has limitations such as the need for general anesthesia and hospitalization. Accordingly, pharmacologic conversion has been proposed as an alternative; a variety of antiarrhythmic drugs have been tested for this purpose (3). However, many of these agents have important side effects such as the potential for proarrhythmia, impairment of left ventricular function, or extracardiac unwanted effects. Consequently, there is a need to develop new antiarrhythmic drugs not only with good clinical efficacy but also with a favorable safety profile.

Tedisamil is a novel class III antiarrhythmic agent that blocks multiple potassium-channels and slows sinus rate. It prolongs both atrial and ventricular action potential duration by blocking the transient outward I_{to} (4), the adenosine triphosphate-dependent $I_{K\text{-}ATP}$ (5), and the delayed rectifier potassium currents I_{Kr}, I_{Ks}, and I_{Kur} (6–8). Tedisamil prolongs action potential duration more strongly in the atria than the ventricles. The drug is not metabolized, is excreted via the kidney, and has a half-life of 8 to 13 h. Tedisamil also possesses significant antianginal and anti-ischemic properties (9). The present prospective, randomized, controlled trial evaluated the efficacy and safety of tedisamil for rapid conversion of recent-onset AF or atrial flutter (AFL).

METHODS

Study population. The study protocol complied with all national and international ethical standards and was approved by the local institutional review board of all participating centers. Each patient gave written informed consent before enrollment. The study was conducted as a multicenter, double-blind, randomized, placebo-controlled, sequential ascending dose-group trial. Patients were entered into the trial from 34 centers applying the following inclusion criteria: age >18 years; documented (60-s rhythm

From the *J. W. Goethe University, Frankfurt, Germany; †St. Michel's Hospital, Toronto, Canada; ‡Solvay Pharmaceuticals GmbH, Hannover, Germany; and §Lankenau Hospital and the Main Line Health System, Wynnewood, Pennsylvania. Sponsored by an unrestricted grant from Solvay Pharmaceuticals. Drs. Hohnloser, Dorain, and Kowey are serving as scientific advisors to Solvay Pharmaceuticals, and Dr. Straub and Mrs. Beckmann are employees of Solvay Pharmaceuticals.

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JACC Vol. 44, No. 1, 2004
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Abbreviations and Acronyms

AF = atrial fibrillation
AFL = atrial flutter
ECG = electrocardiogram/electrocardiographic
NSR = normal sinus rhythm

strip), symptomatic AF or AFL of 3- to 48-h duration (either as a first or a recurrent episode); and a supine blood pressure of >90 mm Hg systolic and <105 mm Hg diastolic. The following exclusion criteria were applied: congestive heart failure New York Heart Association functional class III/IV; acute coronary syndrome at the time of randomization; acute myocardial infarction or percutaneous coronary intervention within the previous 30 days; cardiac surgery within the last 90 days; history of cerebrovascular events within the last six months; known Wolff-Parkinson-White syndrome; history of life-threatening ventricular arrhythmias including torsade de pointes; previous electrocardiogram (ECG)-derived evidence of second or third degree atrioventricular block; congenital long QT syndrome; QT interval >470 ms before randomization; plasma creatinine >1.8 mg/dl; serum potassium <4.0 mEq/l; evidence of digitalis toxicity; concurrent therapy with antiarrhythmic drugs except beta-blockers, diltiazem, or digoxin not discontinued at least five half-lifes before randomization; and treatment with amiodarone within the last three months.

Study protocol. Eligible patients were stratified according to the presence of AF or AFL and randomized to receive intravenous tedisamil or placebo. All patients were treated in hospital under close surveillance. Specifically, continuous ECG monitoring via ECG telemetry and Holter monitoring was performed starting 10 min before start of drug infusion until 24 h later. During stage 1, subjects were randomized to receive a single infusion of tedisamil at a dose of 0.4 mg/kg body weight or matching placebo (2:1 ratio); during stage 2, the dose of tedisamil was increased to 0.6 mg/kg body weight (2:1 vs. placebo). Infusions were administered in 150 ml saline solution over a 30-min period with half of the dose given in the first 10 min and the remainder over the subsequent 20 min. A safety follow-up visit was conducted 28 days after the end of the 24-h study period.

Statistical analysis. The primary objective of this study was to demonstrate superiority of any dose of tedisamil over placebo in the termination of AF or AFL, as measured by the percentage of patients converting to NSR for at least 60 s at any time within 2.5 h after the start of the treatment infusion. Secondary efficacy objectives included determination of the percentage of subjects who converted to NSR within 2.5 h and remained in NSR until 24 h, and the time to first conversion to normal NSR. Efficacy was evaluated according to the intention-to-treat principle. For analysis, placebo patients enrolled in the two study stages were combined. Differences in conversion rates were compared among treatment groups using the Pearson chi-square test. Distribution of times to conversion to NSR was described by the Kaplan-Meier method and compared among treatment groups using a Cox proportional hazards model with factors for treatment group and center. The ECG changes from baseline were compared using two-sample t tests. Statistical significance was assumed at a two-sided p value of 0.05.

RESULTS

Patient population. A total of 201 patients were randomized into the trial. Of these, 21 patients converted to NSR before they received treatment. Thus, the safety patient sample consisted of 180 patients. In five patients, no continuous ECG monitoring during drug infusion was carried out (protocol violation), thus prohibiting acquisition of efficacy data. Accordingly, efficacy results are based on data derived from 175 patients (Table 1).

Primary study end point. Two patients underwent direct cardioversion within the first 2.5 h after start of drug infusion due to hemodynamic instability, which was not felt to be a side effect of the medication according to the local investigator. Of the remaining 173 patients without direct current cardioversion, the percentage conversion to NSR for at least 60 s within the first 2.5 h was 41% in the tedisamil 0.4 mg/kg group (25 of 61 patients), 51% in the tedisamil 0.6 mg/kg group (27 of 53 patients), and 7% (4 of 59 patients) in the placebo group ($p < 0.001$ for both tedisamil groups vs. placebo) (Fig. 1).

Analysis of efficacy according to the underlying arrhythmia (i.e., AF vs. AFL) revealed the following results: of the 142 patients presenting with AF, 4 of 46 placebo patients (9%) converted to NSR. The respective numbers were 24 of 52 patients in the tedisamil 0.4 mg/kg group (46%) and 24 of 42 patients in the tedisamil 0.6 mg/kg group (57%) ($p < 0.001$ for both tedisamil groups vs. placebo). Of the 33 patients presenting with AFL, the percentage conversion to NSR was 11% in the tedisamil 0.4 mg/kg group (1 of 9 patients), 27% in the tedisamil 0.6 mg/kg group (3 of 11 patients), and 0% in the 13 placebo patients (Fig. 1). The difference between the 0.6 mg/kg group and placebo reached statistical significance ($p = 0.044$).

Between 2.5 and 24 h after start of drug infusion, two additional patients on tedisamil 0.4 mg/kg, two on 0.6 mg/kg, and nine patients on placebo converted to NSR.

Secondary end points. Comparison of secondary efficacy objectives in patients with AF showed superiority of tedisamil 0.4 and 0.6 mg/kg over placebo for the percentage of subjects who converted to NSR within 2.5 h and remained in NSR until 24 h, and the time to first conversion to NSR. The respective numbers were 22 of 52 patients in the tedisamil 0.4 mg/kg group (42%) and 22 of 42 patients in the tedisamil 0.6 mg/kg group (52%) ($p < 0.001$ for both tedisamil groups vs. placebo). The percent of converted patients versus time is displayed in Figure 2. The estimation

Table 1. Patient Characteristics at Baseline

	Treatment Group, n (%)			
	Tedisamil 0.4 mg/kg	Tedisamil 0.6 mg/kg	Placebo	Total
Gender				
Male	43 (68%)	31 (58%)	34 (58%)	108 (62%)
Female	20 (32%)	22 (42%)	25 (42%)	67 (38%)
Age (yrs)	62.1 ± 13.0	63.7 ± 14.7	65.0 ± 13.6	63.6 ± 13.7
Concomitant therapy*				
Beta-blocking agents	51 (78%)	33 (61%)	39 (64%)	123 (68%)
Digitalis glycosides	10 (15%)	16 (30%)	18 (30%)	44 (24%)
Agents acting on the renin-angiotensin system	26 (40%)	31 (57%)	28 (46%)	85 (47%)
Diuretics	22 (34%)	14 (26%)	18 (30%)	54 (30%)
Calcium channel blockers	16 (25%)	15 (28%)	21 (34%)	52 (29%)
Heart rhythm				
Atrial fibrillation	54 (86%)	42 (79%)	46 (78%)	142 (81%)
Atrial flutter	9 (14%)	11 (21%)	13 (22%)	33 (19%)
CHF NYHA functional class				
I	46 (73%)	30 (57%)	35 (59%)	111 (63%)
II	14 (22%)	21 (40%)	24 (41%)	59 (34%)
Duration (h) of current arrhythmia episode				
Mean (SD)	21.98 (13.12)	25.02 (12.01)	25.65 (12.83)	24.11 (12.73)
Median	18.8	24.7	24.7	23.5
Min-max	1.7–48.3	4.9–47.8	4.8–53.0	1.7–53.0

*Concomitant medication was defined as medication taken during the double-blind period or the 28-day follow-up period including medications started before randomization and medications started during the study.
CHF = congestive heart failure; NYHA = New York Heart Association; SD = standard deviation.

of the hazard ratios to convert to NSR showed statistically significant results in favor of both tedisamil groups (hazard ratios: 2.46 [95% confidence intervals: 1.26 to 4.79] and 3.32 [1.70 to 6.48], respectively; $p < 0.01$ for both groups vs. placebo). The mean (SD) time to NSR conversion was 35 ± 27 min and 34 ± 21 min for tedisamil 0.4 mg/kg and 0.6 mg/kg, respectively.

Safety. Two patients randomized to placebo died during the study period. One patient died before the start of the infusion from recurrent pulmonary embolism caused by postoperative immobility. The other patient died from pancreatic carcinoma leading to respiratory failure 18 days after start of infusion. The incidence of patients with at least one treatment-emergent adverse event was dose-dependent and occurred in 38 patients (58%) in the tedisamil 0.4 mg/kg group, in 42 patients (78%) in the tedisamil 0.6 mg/kg group, and in 35 patients (57%) in the placebo group (safety sample). Only the difference between the tedisamil 0.6 mg/kg group and the placebo group was statistically significant ($p = 0.02$). Most frequently reported tedisamil

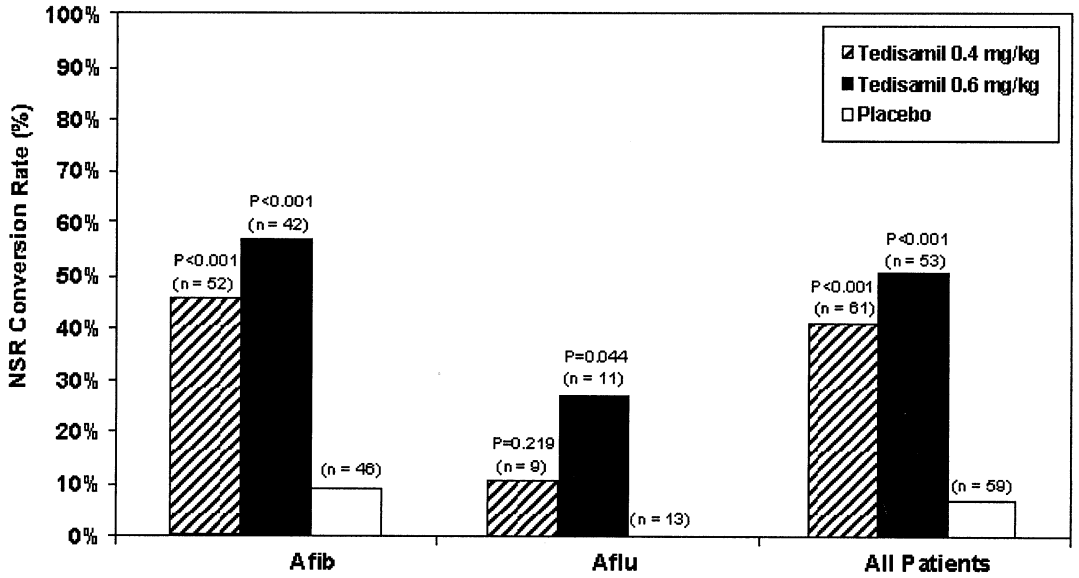

Figure 1. Cumulative incidence of drug-associated conversion to normal sinus rhythm (NSR) within the first 2.5 h after drug administration in patients with atrial fibrillation (Afib) or atrial flutter (Aflu) and in the entire patient population. **Numbers in parentheses** indicate patients treated.

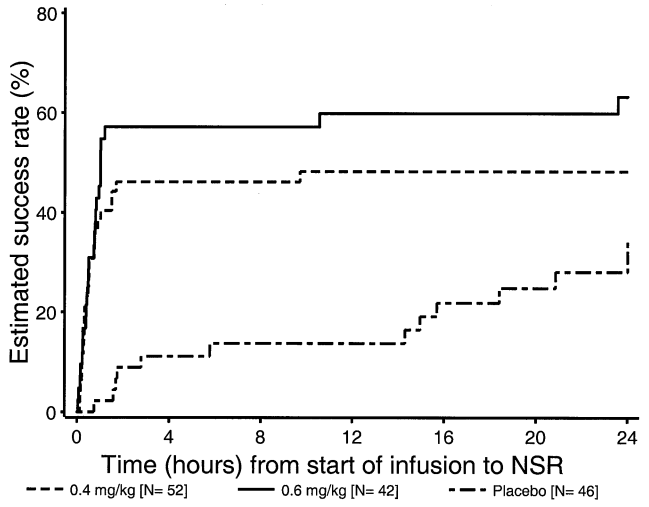

Figure 2. Kaplan-Meier estimates for time to first conversion to normal sinus rhythm (NSR) in patients presenting with atrial fibrillation.

adverse events were (recurrent) AF (8% in the 0.4 mg tedisamil group, 9% in the 0.6 mg tedisamil group, and 2% in the placebo group), bradycardia (2% in the 0.4 mg tedisamil group, 15% in the 0.6 mg tedisamil group, and 9% in the placebo group), injection site burning/pain (9% in the 0.4 mg tedisamil group, 8% in the 0.6 mg tedisamil group, and 0% in the placebo group), first degree atrioventricular block (0% in the 0.4 mg tedisamil group, 9% in the 0.6 mg tedisamil group, and 5% in the placebo group), and ventricular tachycardia (3% in the 0.4 mg tedisamil group, 7% in the 0.6 mg tedisamil group, and 2% in the placebo group). Two of these ventricular tachycardias were considered to represent relevant proarrhythmic events by an independent safety and monitoring committee. Both occurred in the tedisamil 0.6 mg/kg group in AF patients and consisted of one episode of a nonsustained polymorphic ventricular tachycardia of the torsade de pointes type and of one episode of sustained monomorphic ventricular tachycardia. The torsade de pointes occurred 44 min after start of drug infusion in an 87-year-old female with a baseline QTc of 447 ms and a serum K^+ concentration of 4.4 mEq/l. The episode of nonsustained monomorphic ventricular tachycardia occurred in a 55-year-old female with a baseline QTc of 500 ms and a serum K^+ concentration of 4.3 mEq/l. Neither of the two events required cardioversion.

ECG data. Mean RR and QT intervals increased in a dose-dependent manner (Tables 2 and 3) and returned to baseline within approximately 4 h. Twenty-eight percent of placebo patients, 25% of those receiving 0.4 mg/kg, and 56% of those receiving 0.6 mg/kg tedisamil showed at least once during the 24-h observation period a QTc value of ≥500 ms. An increase from baseline of ≥60 ms in QTc was observed in 22%, 27%, and 41% of patients, respectively. Eight patients showed QT interval prolongation of ≥550 ms: two (3%) from the tedisamil 0.4 mg/kg group and six (11%) from the tedisamil 0.6 mg/kg group.

DISCUSSION

The results of this randomized placebo-controlled study demonstrate that intravenously administered tedisamil is effective in the acute conversion of patients with AF or AFL of up to 48 h duration. There was a conversion rate of 46%

Table 2. Electrocardiographic Data

	Treatment					
	Tedisamil 0.4 mg/kg		Tedisamil 0.6 mg/kg		Placebo	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Heart rate (beats/min)						
Baseline	61	103 (25)	51	103 (26)	57	102 (26)
Change from baseline	60	−17 (23)	51	−25 (28)	56	0 (13)
p value (compared to placebo)		<0.001		<0.001		
RR (ms)						
Baseline	61	622.9 (175.0)	51	628.5 (185.0)	57	624.5 (157.1)
Change from baseline	60	165.1 (215.8)	51	230.1 (269.9)	56	0.8 (78.8)
p value (compared to placebo)		<0.001		<0.001		
QRS (ms)						
Baseline	63	88.9 (21.3)	52	94.5 (17.9)	58	88.7 (19.0)
Change from baseline	61	1.4 (8.8)	51	2.5 (11.8)	57	−0.1 (7.0)
p value (compared to placebo)		0.322		0.161		
QT (ms)						
Baseline	63	337.9 (36.1)	52	347.8 (52.4)	58	347.3 (47.1)
Change from baseline	61	48.2 (53.7)	51	74.7 (70.6)	57	1.6 (23.7)
p value (compared to placebo)		<0.001		<0.001		
QTc (Bazett) (ms)						
Baseline	61	435.7 (39.2)	51	443.1 (40.5)	57	443.4 (39.8)
Change from baseline	60	10.8 (45.9)	50	16.9 (45.2)	56	1.5 (28.8)
p value (compared to placebo)		0.197		0.037		

SD = standard deviation.

Table 3. Heart Rate Changes During Tedisamil Administration

	Treatment					
	Tedisamil 0.4 mg/kg		Tedisamil 0.6 mg/kg		Placebo	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	61	103 (25)	51	103 (26)	57	102 (26)
All patients (data obtained at 30 min)						
Change from baseline	60	−17 (23)	51	−25 (28)	56	0 (13)
All patients (data obtained before conversion for converters to NSR within 30 min)						
Change from baseline	60	−10 (20)	51	−16 (26)	56	0 (13)
Nonconverters (data obtained at 30 min)						
Change from baseline	47	−12 (21)	38	−20 (28)	56	0 (13)

NSR = normal sinus rhythm; SD = standard deviation.

observed with 0.4 mg/kg tedisamil and of 57% at a dose of 0.6 mg/kg. There was a rapid onset of action with an average time to cardioversion of 35 min after start of tedisamil administration.

Previous studies. Most antiarrhythmic drugs have only limited efficacy for rapid pharmacologic conversion of AF or AFL, particularly when given orally. An exception to this rule are class IC drugs such as flecainide or propafenone (10–13). Cumulative conversion rates of up to approximately 75% within 8 to 12 h after oral drug administration have been reported. After intravenous administration, conversion rates within the first 2 h ranged between 39% and 60% (10–13). However, there are some important limitations to these agents. The intravenous formulations of these drugs are not available in many countries (such as the U.S.). Moreover, class IC drugs have negative inotropic and significant proarrhythmic side effects that limit their use in patients with structural heart disease (14).

A number of class III antiarrhythmic agents have also been tested for acute termination of AF or AFL. For instance, amiodarone has been the subject of several smaller studies (13). However, due to its complex pharmacodynamic and pharmacokinetic properties, no single dosing recommendation has gained widespread acceptance. Even when given in relatively large doses intravenously, the onset of action of amiodarone in converting AF is often delayed, and it usually takes >24 h to achieve a significant effect (13). Conversion rates ranged between 6% and 20% for the first 2 h of drug administration (13). Amiodarone is not approved for conversion of AF in the U.S.

Ibutilide is another class III antiarrhythmic drug that delays repolarization predominantly by activating a slow inward sodium current (15). After having been tested in several controlled randomized studies (16–19), intravenous ibutilide has recently been approved for the acute conversion of AF and AFL. In an initial dose-ranging study, ibutilide showed a conversion efficacy between 12% and 46% (16). In a comparative study, ibutilide converted 58% of patients with AF compared with 18% when intravenous procainamide was given (18). The drug carries a definite proarrhythmic risk of torsade de pointes that ranges between 2% and 5% and has led to important restriction regarding its use (15).

The efficacy rates observed for tedisamil in the present study compare favorably to these agents, particularly in patients presenting with AF. Importantly, the spontaneous conversion rate in patients randomized to placebo was only 9% in the first 2.5 h after start of the infusion. In patients with AFL, only the higher tedisamil dose achieved a statistically significant conversion effect. This is in contrast with other class III agents such as ibutilide, which seems to have better efficacy rates in AFL. However, the present study included only a relatively small number of patients with AFL. Therefore, more data are needed to clarify tedisamil's efficacy in converting this arrhythmia.

Safety aspects. Tedisamil was well-tolerated in the majority of patients. The most frequently encountered side effect was pain or burning sensations at the site of drug infusion. There were two instances of serious ventricular tachyarrhythmic events: one episode of monomorphic spontaneously terminating ventricular tachycardia and one episode of nonsustained torsade de pointes. Particularly, the latter may represent a drug-associated proarrhythmic effect, which emphasizes the need for close surveillance of patients when attempting acute pharmacologic cardioversion by means of administration of class III antiarrhythmic compounds. The overall incidence of potential proarrhythmic reactions was thus 1.8% (2 of 114 patients), a number that compares favorably with the incidence of proarrhythmia associated with the use of ibutilide (15–19). It is important to note in this regard that tedisamil caused a significant increase in the RR interval (Table 2). As a consequence from the observations of this study it is recommended that close surveillance including ECG monitoring for approximately 8 h after drug administration be performed.

Clinical summary. This is the first clinical evaluation of the cardioversion efficacy and safety of intravenously administered tedisamil, a new class III antiarrhythmic agent. The results of this prospective dose-finding study demonstrate that this compound may represent a valuable addition to the armamentarium of antiarrhythmic drugs used to treat this arrhythmia. Further data are warranted, including on lower

JACC Vol. 44, No. 1, 2004
July 7, 2004:99–104

tedisamil dosages (potentially resulting in enhanced safety) and higher dosages (potentially enhanced efficacy).

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Reprint requests and correspondence: Dr. Stefan H. Hohnloser, J. W. Goethe University, Department of Cardiology, Division of Electrophysiology, Theodor-Stern-Kai 7, 60596 Frankfurt/Main, Germany. E-mail: hohnloser@em.uni-frankfurt.de.

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APPENDIX

For a list of the participating study centers, please see the July 7, 2004, issue of *JACC* at http://www.cardiosource.com/jacc.html.