Tables 345.12a. - 345.12d. provide information on the number of patients who relapsed within 12 months and the proportion who remained in NSR at 12 months for the Maintenance Population and the Intent-to-Treat Population. No formal statistical analyses were performed on these subgroups.

Table 345.12a. Number (%) of Patients Who Relapsed by Subgroups (Maintenance Population)

	125 mcg (N=103)	250 mcg (N=118)	500 mcg (N=100)	Sotalol 80 mg (N=108)	Placebo (N=106)
Male	42/72 (58%)	33/75 (44%)	19/67 (28%)	38/54 (45%)	62/79 (78%)
Female	18/31 (58%)	22/43 (51%)	13/33 (39%)	11/24 (46%)	19/27 (70%)
White	60/103 (58%)	55/118 (47%)	32/100 (32%)	49/108 (45%)	80/105 (76%)
Other					1/1
< 65 years of age	33/49 (67%)	16/41 (39%)	12/42 (29%)	26/55 (47%)	46/59 (78%)
≥ 65 years of age	27/54 (50%)	39/77 (51%)	20/58 (34%)	23/53 (43%)	35/47 (74%)

Reviewer's analysis

Table 345.12b. Number (%) of Patients Who Relapsed by Subgroups (Intent-to-Treat Population)

	Dofetilide				
	125 mcg (N=135)	250 mcg (N=133)	500 mcg (N=129)	Sotalol 80mg (N=137)	Placebo (N=137)
Male	64/94 (68%)	43/85 (51%)	39/87 (45%)	56/102 (55%)	86/103 (84%)
Female	28/41 (68%)	27/48 (56%)	22/42 (52%)	22/35 (63%)	26/34 (76%)
White	92/135 (68%)	70/133 (53%)	61/129 (47%)	77/136 (57%)	111/136(82%)
Other				1/1	1/1
< 65 years of age	47/63 (75%)	22/47 (47%)	30/60 (50%)	37/66 (56%)	65/78 (83%)
≥ 65 years of age	45/72 (63%)	48/86 (56%)	31/69 (45%)	41/71 (58%)	47/59 (80%)

Reviewer's analysis

Table 345.12c. Probability of Remaining in NSR at 12 Months by Subgroup. (Maintenance Population)

	Dofetilide									
	125 mcg		250 mcg		500 mcg		Sotalol		Placebo	
	N	Prob.	N	Prob.	N	Prob.	N	Prob.	N	Prob.
Males	72	.39	75	.53	67	.72	84	.51	79	.21
Females	31	.37	43	.48	33	.52	24	.42	27	.19
< 65 years	49	.29	41	.58	42	.68	55	.46	59	.20
≥ 65 years	54	.48	77	.48	58	.64	53	.52	47	.22

Reviewer's analysis

Table 345.12d. Probability of Remaining in NSR at 12 Months by Subgroup. (Intent-to-Treat Population)

	Dofetilide									
	125 mcg		250 mcg		500 mcg		Sotalol		Placebo	
	N	Prob.	N	Prob.	N	Prob.	N	Prob.	N	Prob.
Males	94	.31	85	.47	87	.55	102	.42	103	.16
Females	41	.28	48	.43	42	.41	35	.29	34	.15
< 65 years	63	.23	47	.50	60	.47	66	.38	78	.15
≥ 65 years	72	.36	86	.43	69	.54	71	..39	59	.18

Results Confirmed by Reviewer's Analysis

Pharmacologic Conversions

Table 345.13 lists the number of patients who were pharmacologically converted from AF/AFL to NSR after initiating treatment. Only 1.2% of the placebo patients converted while 29.9% of the 500 mcg group converted with randomized therapy ($p = .001$). The other dofetilide dose groups were less impressive with only 6% of the 125 mcg bid group and 11% of the 250 mcg bid group being successfully converted pharmacologically.

Table 345.13. Number of Patients Pharmacologically Converting to NSR*

	Dofetilide			Sotalol	Placebo
	125 mcg bid	250 mcg bid	500 mcg bid		
Number of Subjects	135	133	129	137	137
Subjects Converting to NSR Pharmacologically	8 (6 %)	14 (11%)	38 (29%)	7 (5%)	2 (1 %)
Difference From Placebo (%)	5	10	28	5	
95% Confidence Interval	0.5 to 9.5	4.4 to 15.6	19.9 to 36.1	-0.2 to 8.2	
P- Value *	0.037	0.001	0.001	0.085	

* Results confirmed by Reviewer's analysis

Symptoms

The number of subjects in each treatment group who reported symptoms on their Hertcard in association with their first attack of AF was similar and the pattern of symptoms reported was also similar in all treatment groups.

Quality of Life

Quality of life was available at baseline and during treatment for 559 of 671 subjects who entered the study. According to the sponsor's results (Sponsor's Tables 15 and 16 of Appendix I), the change in quality of life observed between the responders in the dofetilide treated groups and responders in the sotalol or placebo groups was not different.

Study 311. Double-Blind, Placebo Controlled, Dose-Ranging Pilot Study (311) and Continuation Study (311a) to Assess the Safety, Toleration and Efficacy of Oral Dofetilide in the Prevention of Recurrence of Atrial Fibrillation/Atrial Flutter
Study Dates: 4/91 - 1/93

Protocol

This was a randomized, double-blind, placebo controlled, parallel dose, pilot study in patients with documented chronic AF/AFl (2 weeks to 5 years duration). The primary objective was to assess efficacy and safety of three dose groups of dofetilide. Patients were eligible if they were 18 - 70 years of age, had chronic AF/AFl and were undergoing routine cardioversion either by intravenous dofetilide or electrical cardioversion. Major exclusion criteria included NYHA Class III - IV functional heart failure, recent myocardial infarction, other antiarrhythmic therapy, use of drugs that prolong the QTc interval, DBP > 110 mmHg, QTc interval > 440 msec, second or third degree AV block and other significant medical conditions likely to interfere with the conduct of the study. The trial consisted of a baseline period where patients underwent cardioversion. After restoration of NSR, patients were observed for 1 - 3 hours[32] before being randomized to dofetilide 250 mcg, 500 mcg, 750 mcg or placebo administered as a bid dose for 3 months. Patients remained hospitalized for up to 60 hours after randomization. If patients developed symptoms consistent with their arrhythmia, they were asked to record attacks in a diary and transmit a transtelephonic ECG recording. Therapy could be prematurely discontinued if patients developed proarrhythmic activity, hemodynamic impairment, unacceptable side effects or a QTc interval greater than 550 msec.

No formal sample size estimation was performed. No formal statistical analysis was proposed in the protocol because of the small sample size. The "major" endpoint is "safety and toleration" . The "minor endpoints" included the number in each group remaining in NSR at the end of 3 months, time to first attack of AF/AFl and the number of patients with attacks of pAF/AFl. Interim analysis were performed for planning of future studies and could not be used to stop the study. An optional double-blind continuation period (9 months) was added (protocol 311A) for those patients who remained on randomized, double-blind therapy after 3 months.

Results

Patient Disposition

The study was conducted at eight centers in the Netherlands. The study randomized eighty-three patients from ninety-seven screened. Table 311.1 shows the patient disposition in the study. The number of patients randomized to each group was either 20 or 21. The number completing 3 months of therapy ranged from 12 to 16 per group. There were a similar number of premature withdrawals from each treatment group although they differed in the reasons for withdrawal. Dofetilide subjects were more likely to withdraw because of ventricular arrhythmias compared to placebo patients.

Table 311.1. Patient Disposition

	Dofetilide			
	250 mcg bid	500 mcg bid	750 mcg bid	Placebo
Randomized	21	21	21	20
Completed [A] Study 311	14	16	12	15
Discontinued Prematurely during Study 311	7	5	9	5
Entered Study 311A	6	5	6	6
Discontinued Prematurely during Study 311A [B]	0	2	0	3
Reasons Discontinued				
Lack of Efficacy	4	5	5	6
Adverse Event	0	2	0	1
Lost to Follow-up	0	0	0	1
QTc prolongation	0	0	1	0
Ventricular Arrhythmia	3	0	3	0

[A] = 3 months; [B] = did not complete 9 additional months

[32] If DC cardioversion, patients were observed for 1 hour. If dofetilide cardioversion, patients were observed for 3 hour.

Table 311.1a. (see in appendix of this review) lists the reasons patients did not complete the study.

Table 311.2 shows the demographic characteristics of the patients. The patients were 99% Caucasian and predominately men with a mean age greater than 60 years. Eighty-eight percent had AF. Ninety-five percent were on anti-coagulants.

Table 311.2. Demographics

	Dofetilide			
	250 mcg bid	500 mcg bid	750 mcg bid	Placebo
Randomized	21	21	21	20
Mean Age (yrs.)	62	62	65	60
Females	29%	33%	53%	45%
Mean Weight (kg.)	82	79	78	80

Efficacy

The study was not sufficiently powered to show a difference between treatments. For this reason no statistical analysis will be described. Table 311. 3 shows the number of patients remaining in NSR after 3 months of therapy. So few patients were included in the extension portion of the trial that efficacy data is not contributory.

Table 311.3. Number of Patients Remaining in NSR at 3 months

	Dofetilide			
	250 mcg bid	500 mcg bid	750 mcg bid	Placebo
Randomized	21	21	21	20
# in NSR at 3 Months	10 (48%)	13 (62%)	12 (57%)	7 (35%)

Study 320. A Double-Blind, Placebo Controlled, Dose-Ranging Study (320) and Continuation Study (320a) to Assess the Safety, Toleration and Efficacy of Oral Dofetilide in the Prevention of Recurrence of Atrial Fibrillation / Atrial Flutter

Study Dates: 6/15/92 - 5/3/93

Protocol

This was a randomized, double-blind, placebo controlled trial in patients with chronic AF/AFl (2 weeks - 2 years duration) whose major objective was to determine the ability of dofetilide to prevent the recurrence of AF/AFl after conversion to NSR (by intravenous dofetilide or DC conversion). The trial consisted of an in-patient conversion phase during which the patient received open label dofetilide (8 mcg/kg over 15 minutes intravenously) or DC cardioversion at the discretion of the investigator. After conversion to NSR (maintained for a minimum of 1 hour), the patients were randomized to dofetilide 750 mcg bid, 500 mcg bid or placebo. After initiation of randomized therapy, the patients were observed for approximately 60 hours to detect excessive QTc prolongation. If excessive QTc prolongation occurred, the patient was discontinued from therapy. If patients tolerated therapy, they were discharged and followed as out-patients for three months. Periodically, the patient would transmit transtelephonic ECG recordings for the detection of recurrence of AF and returned for clinic visits at 2, 4, 8 and 12 weeks. There was an optional additional 9 month follow-up period (study 320A).

The trial proposed to randomize 120 patients to treatment. Forty-four patients at eight centers in the United Kingdom were enrolled for cardioversion but only 35 patients were randomized to treatment. The trial was discontinued prematurely due to concerns of a proarrhythmic effect with the 750 mcg bid dose observed in another trial. As a consequence, there is limited efficacy data obtained from this trial. Table 320.1 shows the patient disposition during the study. All subjects were Caucasian and 77% were male. The mean age ranged from 61 - 65 years of age. Seventy-seven percent had AF and the remainder had AFl. Because of limited enrollment, there is an insufficient amount of information to make any statement regarding efficacy. Table 320.2 lists the patients who discontinued from the trial and the reason for discontinuation. Two patients in the dofetilide 750 mcg bid group continued into study 320A.

Table 320.1. Disposition

	Dofetilide 750 mcg	Dofetilide 500 mcg	Placebo
Randomized	12	12	11
Entered the Out-patient period	10	9	9
Recurrent AF/AFl within 3 months	1	2	6
Discontinued Therapy	7	7	6
Continued into Extension	2	0	0

Table 320.2. Patients Discontinued from Therapy

Patient #	Sex	Dose	Day	Reason Discontinued
430037	Male	500 mcg	1	Torsades de Pointes VT
540003	Female	500 mcg	2	Torsades de Pointes
540004	Male	500 mcg	2	Discontinued due to lack of efficacy of drug.
430034	Male	500 mcg	4	Lab abnormality. (Significant increase in ALP and liver enzymes. Renal and hepatic dysfunction.)
550064	Male	500 mcg	4	QT prolongation (episode of non- sustained VT)
530068	Male	500 mcg	8	Discontinued due to lack of efficacy of drug.
560012	Male	500 mcg	20	Discontinued due to lack of efficacy of drug.
430040	Female	750 mcg	2	Torsades de Pointes
530067	Male	750 mcg	9	QT/ QTc prolongation. (Long QTc on Holter intermittently > 620ms)
560055	Male	750 mcg	22	Discontinued due to lack of efficacy of drug. (Back in Atrial flutter)
560011	Male	750 mcg	42	Discontinued due to lack of efficacy of drug.
430038	Male	750 mcg	62	QT prolongation
640049	Male	750 mcg	94	Study terminated by Pfizer.
540002	Male	750 mcg	179	Study terminated by Pfizer.
560007	Male	Placebo	2	Discontinued due to lack of efficacy of drug.
540001	Male	Placebo	8	Adverse experience. (Vasovagal syncope)
530070	Male	Placebo	15	Discontinued due to lack of efficacy of drug.
560010	Male	Placebo	17	Discontinued due to lack of efficacy of drug.
430036	Male	Placebo	18	Adverse experience. (Rapid atrial fibrillation needing cardioversion)
430039	Female	Placebo	23	Discontinued due to lack of efficacy of drug.
550065	Female	Placebo	29	Discontinued due to lack of efficacy of drug.
530069	Male	Placebo	71	Study terminated by Pfizer.

Studies in Patients with Paroxysmal Atrial Fibrillation or Atrial Flutter

Study #	Description	Treatments	N	Primary Endpoint(s)	Page
114	• r, db, pc, p, mc, 14 week Rx period • 4/13/92 - 6/6/93 • USA	placebo dofetilide 750 mcg bid dofetilide 500 mcg bid dofetilide 250 mcg bid total	5 5 6 4 20	• time to recurrence of symptomatic pAF/AFl	51
114A	• r, db, pc, optional extension (up to one year) of study 114	placebo dofetilide 750 mcg bid dofetilide 500 mcg bid dofetilide 250 mcg bid total	0 0 0 1 1	• time to recurrence of symptomatic pAF/AFl	51
114C	• r, 1 year open label F/U in subjects with events from study 114 and 114A	dofetilide 500 mcg bid digoxin .125 or .25 mg total	3 2 5	• none	51
119	• r, db, pc, p, mc, 6 month Rx period • pAF/AFl and pSVT patients • optional db 6 month extension period • 6/20/94 - 10/15/96 • USA	placebo dofetilide 375 mcg bid dofetilide 250 mcg bid total	111 105 100 316	• time to recurrence of symptomatic pAF/AFl	52
128	• r, db, pc, minimum 12 week Rx period • USA • 2/12/96 - 2/5/97	placebo dofetilide 500 mcg bid total	129 132 261	• time to recurrence of symptomatic pAF/AFl	59
363	• r, db, pc, ac, 24 week Rx period • France, Poland • 7/22/94 - 6/21/96	placebo dofetilide 250 mcg bid quinidine 300 mg bid total	50 48 57 155	• time to recurrence of symptomatic pAF/AFl • incidence of adverse events	64
365	• r, db, pc, 12 - 24 week Rx period • Europe • 2/1/96 - 12/19/96	placebo dofetilide 500 mcg bid total	89 181 270	• time to recurrence of symptomatic pAF/AFl	69

r = randomized, db = double-blind, p = parallel, pc = placebo controlled, mc = multi-center, Hx = history, Rx = treatment, F/U = follow-up

Study 114. Randomized, Double-Blind, Parallel, Placebo-Controlled Evaluation of Orally Administered Dofetilide in Patients with Paroxysmal Atrial Fibrillation or Flutter (pAF/AFl)
Study Dates: 4/13/92 - 6/6/93

Protocol

This study was a randomized, double-blind, multi-center, placebo controlled, parallel dose trial in patients with paroxysmal AF or AFl. The study proposed to enroll 100 male and female subjects, 18 - 75 years of age with a history of symptomatic pAF documented by ECG. The trial consisted of a screening visit, baseline period, an in-hospital double-blind treatment initiation period and out-patient treatment period (week 1, 2, 4, 6, 10 and 14 weeks visits). At baseline, the occurrence of 1 attack of symptomatic pAF during 6 weeks or less was to be documented by transtelephonic ECG monitoring. Qualifying patients were to be randomly allocated to one of the following double-blind oral treatments for 14 weeks: placebo, dofetilide 0.25 mg bid, dofetilide 0.5 mg bid and dofetilide 0.75 mg bid. Treatment with double-blind medication was initiated in the hospital. The patients were discharged after 3 days of double-blind dosing only if there are no limiting side effects and the QTc interval is not greater than 550 msec when

measured at any time during the dosing interval. Patients were instructed to transmit transtelephonic ECGs during symptomatic attacks in the double blind treatment period.

The sample size estimation was based on detecting a doubling of the median time[33] to recurrence with 90% power and $\alpha = 0.05$. The primary endpoint was time to recurrence of symptomatic pAF. Other endpoints included the proportion of patients remaining free of symptomatic pAF at 3 months and the ventricular rate during symptomatic attacks.

Study 114A is a double blind extension of study 114 for those patients who did not experience an attack of symptomatic pAF. There were no formal endpoints identified prospectively for this extension phase.

Study 114C is an open label extension of study 114 and 114A. The eligibility to receive open-label long-term treatment were determined by the following rules: 1) double-blind treatment allocation in study 115-114 was not be disclosed, and 2) no significant side effects or laboratory abnormalities, or QTc interval prolongation (i.e. QTc >550 msec), should have occurred during double-blind treatment. Eligible patients were to be randomized in a 2:1 ratio to receive oral treatment with dofetilide or digoxin as described below. Treatment with dofetilide was to be initiated in the hospital at a dosage of 0.5 mg bid. Treatment with digoxin 0.125 mg or 0.25 mg od was initiated on an outpatient basis, and the dosage was selected by the investigator. Those patients who are discharged from the hospital on dofetilide treatment, or who receive treatment with digoxin, visited the clinic at 1, 2, 4, 8, 12, 20, 28, 36, 44, and 52 weeks of follow-up. The patients were instructed to make a telephone transmission of the ECG at the time of symptoms possibly related to a cardiac arrhythmia and at regularly scheduled intervals. The primary objective of the open-label study was to collect safety data associated with the long-term administration of dofetilide to patients with symptomatic pAF, and to compare the dofetilide safety profile with that of a cohort treated with digoxin.

Results

Twenty-two centers were involved in the conduct of this study. Because of concerns that treatment with 750 mcg dofetilide bid was associated with an increased risk of proarrhythmia (2 subjects developed Torsades de Pointes), enrollment was suspended in these studies before the required sample size was obtained and no efficacy analyses were performed. Twenty patients were randomized (4, 6, 5 and 5 to 250 mcg, 500 mcg, 750 mcg and placebo) into the study and only one completed 14 weeks of treatment. Ten subjects had a recurrence of pAF prior to stopping the study. This study provides an insufficient amount of efficacy information and does not contribute to the determination of efficacy in the population studied.

Study 115-119. A Randomized, Double-Blind, Parallel, Placebo-Controlled Evaluation of Orally Administered Dofetilide in Patients with Symptomatic Paroxysmal Atrial Fibrillation/Flutter (pAF, pAFl) or Paroxysmal Supraventricular Tachycardia (pSVT)

Study Dates: 6/20/94 - 10/15/96

Protocol

Design

This is a randomized, double-blind, placebo-controlled, multi-center trial in patients with a history of paroxysmal AF/AFl. The trial consisted of an in-hospital phase during which subjects were randomized to one of two dofetilide doses or placebo. During the hospitalization, heart rhythm and QT interval were monitored. Patients received up to 5 doses of randomized therapy while hospitalized. If therapy was tolerated, the patients were discharged from the hospital and received double-blind treatment for 6 months. There was an optional 6 month double-blind follow-up period.

Inclusion/Exclusion

Patients were eligible for randomization if they :

- had a documented (Holter, ECG, transtelephonic) episode of symptomatic paroxysmal AF/AFl or paroxysmal SVT during the preceding 6 months;
- were 18 - 85 years of age;
- are male or females of non-childbearing potential.

Exclusion criteria included:

- uncompensated CHF;

[33] Median time to recurrence for placebo was estimated to be 10 days.

- chronic AF/AFl;
- MI, unstable angina or survival from sudden death within the past month;
- QT/QTc > 440 msec;
- SBP < 90 mmHg or DBP > 110 mmHg or heart rate < 60 bpm;
- concomitant therapy with other antiarrhythmic agents, diuretics, antidepressants, anticonvulsants, phenothiazines, amiodarone (within the past month) or cimetidine;
- history of polymorphic VT associated with drugs that prolong the QT interval;
- serum potassium < 4.0 mmol/L or magnesium < 1.5 mmol/L;
- major hematologic, renal or hepatic disease.

Dose Groups

Patients were randomized to one of three dose groups: dofetilide 375 mcg bid, 250 mcg bid or placebo. The actual initial dose depended on the calculated creatinine clearance[34]. Table 119.1 shows the actual initial dose received based on the calculated creatinine clearance.

Table 119.1. Initial Dose Adjustment Based on Calculated Creatinine Clearance

Treatment Group	Dofetilide 375 mcg bid	Dofetilide 250 mcg bid
> 60 ml/min	Dofetilide 375 mcg bid	Dofetilide 250 mcg bid
40 - 60 ml/min	Dofetilide 250 mcg bid	Dofetilide125 mcg bid
20 - 39 mil/min.	Dofetilide 250 mcg once/day	Dofetilide125 mcg once/day

If at the initial dose level the QT or QTc interval increased in excess of 15% or 500 msec at any time during the trial, the dose was down titrated. If after down titration, the QT interval exceeded 500 msec or increased by 20% compared to baseline, the drug would be stopped.

Procedures

After discharge from the hospital, patients returned for follow-up visits at 2, 4, 6, 10, 14, 18, 22 and 26 weeks. Patients were instructed to transmit transtelephonic ECGs between clinic visits and at times of symptoms that they felt were related to cardiac arrhythmia. Table 119.2 lists the procedures performed during the study.

Table 119.2. List of Procedures Performed During the Study (first 26 weeks).

Procedure																		
				Week of Study														
Visits	S[b]	B[c]	H[d]	2	3	4	5	6	8	10	12	14	16	18	20	22	24	26
Medical History	x																	
Physical Exam	x																	
Echocardiogram	x																	
Clinic visit	x			x		x		x		x		x		x		x		x
Cardiopulmonary Exam	x	x	x	x		x		x		x		x		x		x		x
ECG																		
12 lead	x	x	x	x		x		x		x		x		x		x		x
transtelephonic [a]		x	x		x		x		x		x		x		x		x	
Holter	x																	
Lab Tests	x	x	x	x		x		x		x		x		x		x		x
Calc. Creat. Clearance	x																	
Plasma Samples			x	x		x		x		x		x		x		x		x
Adverse Reaction	x	x	x	x		x		x		x		x		x		x		x
Dispense Study Medication			x	x		x		x		x		x		x		x		x
QOL				x								x						x

[a] = also at times of symptoms related to cardiac arrhythmia; b = screening; c = baseline; d = in-hospital

[34] Based on Cockcroft-Gault equation

Table 119.2a. List of Procedures Performed During Study 119 (optional week 26 - 52).

Procedures									
	Week of Study								
	28	30	33	36	39	42	45	48	52
Clinic visit		x		x		x			x
Cardiopulmonary Exam		x		x		x			x
ECG									
12 lead		x		x		x			x
transtelephonic [a]	x		x		x		x	x	
Lab Tests		x		x		x			x
Plasma Samples		x		x		x			x
Adverse Reaction		x		x		x			x
Dispense Study Medication		x		x		x			x
QOL		x		x		x			x

[a] = also at times of symptoms related to cardiac arrhythmia

If transtelephonic transmissions were sent in response to symptoms, a standardized questionnaire was completed over the phone by the central lab receiving the transmission.

Endpoints

The primary endpoint of the study was the time to recurrence of symptomatic pAF/AFl or pSVT documented by ECG (transtelephonic or recorded). Other outcome variables included:

1. proportion of patients remaining free of symptomatic pAF/AFl or pSVT at the end of week 14 and 26;
2. frequency of symptomatic pAF/AFl or pSVT;
3. ventricular rate during pAF/AFl or pSVT;
4. symptomatology of events;
5. health related QOL;
6. nature of health care resources utilization.

The "main" endpoint during the 26 - 52 week follow-up period was the proportion of patients remaining free of symptomatic pAF/AFl or pSVT at week 39 and 52.

Statistics

The study proposed to randomize (stratified by underlying arrhythmia) 100 patients per treatment group. This was based on a placebo recurrence rate of 84% at 6 months, ā dofetilide recurrence rate less than or equal to 64% at 6 months, 80% power and $\alpha = .05$.

Table 119.3 lists the statistical analysis pre-specified in the protocol.

Table 119.3. Statistical Analysis Specified in the Protocol

Endpoint	Statistical Analysis
Time to symptomatic recurrence at 6 months	• Survival distribution using Kaplan-Meier life table method • Log-rank test (intent to treat starting after 5th dose) • Combine centers with fewer than 2 patients • Variables considered for inclusion in the analysis: type of arrhythmia at entry, primary cardiomyopathy, sex, age, +/- LV dysfunction, duration and severity of disease, dose level, calculated creatinine clearance • Patients withdrawn prior to recurrence will be censored at time of withdrawal • Supplemental analysis comparing individual treatment groups will be performed if the initial log-rank test (comparing all groups) is significant
Secondary Endpoints	• Difference among treatment groups using statistical estimation theory
QOL	• difference between treatments at 6 months by analysis of covariance • using QOL battery as dependent variables and baseline variables as covariates

An interim analysis was pre-specified in the protocol after 50% of patients completed 6 months of follow-up

for management purposes and not to stop or modify the trial. No statistical adjustment is necessary.

Results

Disposition

Three hundred and sixty-two (362) subjects were screened for this study at 45 centers in the USA. Forty-six patients did not fulfill the inclusion/exclusion criteria. Three hundred and sixteen patients were randomized to one of the three treatment groups and received one or more doses of study drug. The number of patients randomized per center ranged from 0 to 28. Table 119.4 lists the patient disposition for the study. The sponsor's presentation of the patients who discontinued from the study is somewhat confusing because they do not distinguish between those who discontinued during the in-hospital period from those who discontinued after being counted as an event or being censored.

Table 119.4. Disposition of Patients in Study 119.

	Dofetilide 375 mcg	Dofetilide 250 mcg	Placebo
Randomized	**105**	**100**	**111**
Number Not Included in Intent to Treat. Not Discharged on Randomized Therapy	15	9	18
Ventricular Tachycardia	0	1	1
Not in NSR	12	7	14
QTc prolongation	3	0	0
Adverse Event	0	1	1
Asked to be Withdrawn	0	0	2
Number Included in the Intent to treat Population [A]	**90**	**91**	**93**
Premature Discontinuation (Censored in Analysis)	**8**	9	11
Reason for Discontinuation			
Adverse event	4	2	5
Lab Abnormality	0	1	0
QT prolongation	3	2	0
Lack of Efficacy	0	0	1
Protocol Violation	1	0	1
Patient Requested Withdrawal	0	3	3
Not Known	0	1	1

[A] = patients were included in intent to treat population if they tolerated 5th dose of study medication and fulfilled inclusion/exclusion criteria

Table 119.5 (see in appendix of this review) lists the patients who were not discharged from the hospital on randomized therapy.

Table 119.5a lists the patients who were prematurely discontinued from randomized therapy and are censored in the 180 day analysis.

Table 119.5a. List of Patients Prematurely Discontinued from Double blind Therapy

Patient ID	Sex	Randomized Dose	Age	Actual Dose	Day WD	Reason
5210323	Male	250 mcg	46	250 mcg	8	Asked to be withdrawn from the study.
5420018	Male	250 mcg	80	250 mcg	41	Asked to be withdrawn from the study.
5860327	Female	250 mcg	74	250 mcg	5	Laboratory abnormality. [elevated GGT]
6250042	Male	250 mcg	74	125 mcg	20	QT/ QTc prolongation. [16%]
6250301	Female	250 mcg	84	125 mcg	71	Adverse event. [increasing fatigue]
6270102	Male	250 mcg	28	250 mcg	35	Adverse event. [inability to concentrate, severe fatigue]
6390026	Male	250 mcg	64	125 mcg	4	QT/ QTc prolongation. [21%]
6610118	Female	250 mcg	79	125 mcg	164	Asked to be withdrawn from the study.

Table 119.5a. List of Patients Prematurely Discontinued from Double blind Therapy

Patient ID	Sex	Randomized Dose	Age	Actual Dose	Day WD	Reason
6350644	Male	250 mcg	71	250 mcg	161	No explanation provided.
5860874	Male	Placebo	74	Placebo	181	Adverse event. [acute inferior wall myocardial infarction]
5360056	Male	Placebo	54	Placebo	24	Adverse event. [headaches]
6350047	Male	Placebo	53	Placebo	18	Adverse event. [Hepatitis B]
6850829	Female	Placebo	70	Placebo	3	Adverse event. [prolonged sinus pauses]
6610717	Female	Placebo	53	Placebo	13	Adverse Event. [very frequent palpitations]
5420618	Male	Placebo	74	Placebo	50	Asked to be withdrawn from the study.
6790186	Female	Placebo	68	Placebo	132	Asked to be withdrawn from the study.
6980848	Female	Placebo	70	Placebo	34	Asked to be withdrawn from the study.
5060110	Male	Placebo	59	Placebo	25	Lack of Efficacy .
5860328	Male	Placebo	84	Placebo	155	No explanation in CRF for early discontinuation.
6170050	Male	Placebo	63	Placebo	32	Protocol Violation. Not in NSR at discharge.
5360060	Female	375 mg	59	250 mcg	141	Adverse event. [chest pain]
5800091	Male	375 mg	61	375 mcg	4	Protocol Violation. [not in NSR at discharge]
6050313	Female	375 mg	61	250 mcg	4	Adverse event. [urinary tract infection]
6050859	Female	375 mg	53	375 mcg	55	Adverse event. [nausea]
6250038	Female	375 mg	44	375 mcg	56	Adverse event. [nausea]
6350219	Female	375 mg	79	250 mcg	4	QT/ QTc prolongation. [22%]
6910250	Male	375 mg	62	250 mcg	3	QT/ QTc prolongation. [24%]
7060909	Male	375 mg	51	250 mcg	67	QT/ QTc prolongation. [25%]

During the outpatient therapy, patients could remain on therapy even though they may have reached an endpoint event. Table 119.6 lists the number of patients who discontinued therapy after experiencing an event. Table 119.6a (see in appendix of this review) lists the patients and the reason discontinued from therapy after an event.

Table 119.6. Number of Patients Discontinued from Double blind Therapy after an Event

	Dofetilide 375 mcg	Dofetilide 250 mcg	Placebo
Discontinued at Some Timepoint after an Event	12	6	6
Reason for Discontinuation			
Adverse event	3	2	1
Lab Abnormality	1	0	1
QT prolongation	1	0	0
Lack of Efficacy	3	1	2
Death	0	1	0
Protocol Violation	0	0	2
Other	1	1	0
Patient Requested Withdrawal	3	1	0

Demographics

Table 119.7 lists the demographic characteristics for each treatment group. The study enrolled predominately male subjects with pAF. Approximately 95% of subjects were Caucasian.

Table 119.7. Demographics for Study 119.

	Dofetilide 250 mcg	Dofetilide 375 mcg	Placebo
Randomized	100	105	111

Table 119.7. Demographics for Study 119.

	Dofetilide 250 mcg	Dofetilide 375 mcg	Placebo
Male/Female	65/35	66/39	61/50
Race			
Caucasian	96	97	96
Black	4	5	9
Oriental	0	3	3
Other	0	0	3
Mean Age (yrs.)	64	64	63
Arrhythmia			
pAF	77	81	80
pAFl	3	9	9
pSVT	20	15	22

Results Confirmed by Reviewer's Analysis

Efficacy

Table 119.8 lists the probability of relapse at 4, 12 and 26 weeks. At 26 weeks, the Kaplan-Meier estimate of the probability of relapse is 58%, 72% and 70 % for dofetilide 375 mcg, 250 mcg and placebo respectively. For the overall treatment group comparison, the logrank test was not significant (p = .20). Neither treatment group was significantly different from placebo.

Table 119.8. Number of Patients with Paroxysmal AF, AFl or SVT at 6 Months (180days).

	Dofetilide		
	375 mcg	250 mcg	Placebo
Randomized	105	100	111
Included in Intent to Treat Analysis by Sponsor	90	91	93
Number With Symptomatic pAF/AFl or pSVT at 6 mths.	49 (54%)	62 (68%)	61 (66%)
Number Censored Before 6 months	8 (9%)	9 (10%)	11 (12%)
Number Censored at 6 months	33	20	21
Probability of Event Based on Kaplan-Meier Estimates			
Probability of relapsing at 4 weeks	0.41	0.47	0.46
Probability of relapsing at 12 weeks	0.51	0.57	0.60
Probability of relapsing at 26 weeks	0.58	0.73	0.70
Probability of Difference from Placebo (Logrank)	p = 0.211	p = 0.544	

Results Confirmed by Reviewer's Analysis

Table 119.8 only includes patients who had both symptoms + arrhythmia. Some patients had symptoms but no arrhythmia. The numbers of patients with symptoms who made transtelephonic ECG transmissions that were not associated with arrhythmia attacks are 56, 61 and 65 for dofetilide 250, dofetilide 375 and placebo respectively.

Table 119.9 lists the actual dose received by patients at the start of the maintenance period (at hospital discharge). In both active treatment groups, approximately half of the dofetilide patients received a dose lower than the randomized dose. In the placebo group, approximately a quarter received a lower dose.

Table 119.9. Actual Dose of Double Blind Treatment at Time of Discharge from Hospital.

Actual Dose at Discharge	Randomized Dose		
⇩	Dofetilide 375 mcg	Dofetilide 250 mcg	Placebo
Randomized	105	100	111
# on Therapy at Discharge [A]	97	98	98
375 mcg bid	48 (46%)		
375 mcg OD	10 (10%)		
250 mcg bid	22 (21%)	50 (50%)	
250 mcg OD	18 (17%)	7 (7%)	

Table 119.9. (con't) Actual Dose of Double Blind Treatment at Time of Discharge from Hospital.

Actual Dose at Discharge	Randomized Dose		
⇩	Dofetilide 375 mcg	Dofetilide 250 mcg	Placebo
125 mcg bid		31 (31%)	
125 mcg OD		9 (9%)	
Reduced Dose Placebo			27 (25%)
Full Dose Placebo			78 (66%)

^ Includes all patients still on therapy at time of discharge. Some patients were not in NSR and did not continue therapy in the outpatient period. (data from sponsor's table 3.3). Percentages are based on the number randomized.

Table 119.10 shows the probability of relapsing at 26 weeks as a function of actual dose at hospital discharge. There is no difference between the dofetilide and placebo groups.

Table 119.10. Probability of Relapse at 26 Weeks Based on Actual Dose at Discharge.

	Number Entering Steady State	Number Relapsing	Probability of Relapsing at 26 Weeks
375 mcg bid	48	29	.62
375 mcg OD	5	1	.25
250 mcg bid	72	41	.61
250 mcg OD	18	10	.63
125 mcg bid	31	19	.65
125 mcg OD	6	4	.75
Placebo	92	58	.68

Table 119.11 shows the probability of relapsing at 26 weeks as a function of dose and underlying arrhythmia (pSVT vs. PAF/AFl). There is no difference between treatment groups or underlying arrhythmia.

Table 119.11. Probability of Relapse at 26 Weeks Based on Underlying Arrhythmia.

	Number Entering Steady State	Number Relapsing	Probability of Relapsing at 26 Weeks
375 mcg pSVT	14	8	.60
375 mcg pAF/AFl	76	41	.57
250 mcg pSVT	19	10	.54
250 mcg pAF/AFl	72	52	.78
Placebo pSVT	19	11	.67
Placebo pAF/AFl	74	50	.71

Table 119.12 shows the probability of relapsing at 26 weeks as a function of gender. There is no difference between treatment groups.

Table 119.12. Probability of Relapse at 26 Weeks Based on Gender.

	Males			Females		
	375	250	placebo	375	250	placebo
Number Entering Steady State	54	56	50	36	35	43
Number Relapsing	28	37	32	21	25	29
Probability of Relapsing at 26 Weeks	.54	.71	.69	.64	.75	.72

Table 119.13 lists the number of patients who experienced an event by subgroup. There were too few non-Caucasians to make any assessment. The results are similar regardless of age and sex.

Table 119.13. Number (%) of Patients Who Had a Paroxysmal AF, AFl or SVT by Subgroup

	Dofetilide 375 mcg	Dofetilide 250 mcg	Placebo
Randomized	105	100	111
Male	40/66 (61%)	46/65 (71%)	43/61 (70%)
Female	24/39 (62%)	24/35 (69%)	36/50 (72%)
Caucasian	60/97 (62%)	68/96 (71%)	70/96 (73%)
Black	2/5 (40%)	2/4 (50%)	6/9 (67%)
Asian	0/0	0/0	1/3 (33%)
Other	2/3 (67%)	0/0	2/3 (67%)
< 65 years	32/52 (62%)	34/47 (72%)	39/54 (72%)
>= 65 years	32/53 (60%)	36/53 (68%)	40/57 (70%)

Study 128. A Randomized, Double-Blind, Parallel, Placebo-Controlled Evaluation of Orally Administered Dofetilide in Subjects with Symptomatic Paroxysmal Atrial Fibrillation or Flutter (pAF or pAFl)
Study Dates: 2/12/96 - 2/5/87

Protocol

Design

This was a multi-center, randomized, double-blind, parallel, placebo-controlled evaluation of orally administered dofetilide in subjects with a history of symptomatic attacks of pAF/AFl. The trial consisted of a screening period, an in-hospital dose initiation period and a double-blind treatment period. During the screening period, eligible patients discontinued anti-arrhythmic therapy and arrangements were made for the in-hospital period. During the in-hospital period, eligible subjects were randomized to receive either 500 mcg dofetilide bid or placebo. The initial dose of therapy was adjusted based on calculated creatinine clearance. Once dosing was initiated, further adjustments in dose were permitted based on prolongation of the QTc interval. Subjects in normal sinus rhythm (NSR) on the fourth day of treatment were eligible to continue in the study and were discharged from the hospital. In order to enter the efficacy evaluation period of the study, subjects must have an electrocardiogram, obtained on the morning of the fourth day of therapy with study medication, documenting that they were in sinus rhythm (steady state). This electrocardiogram was referred to as the INDEX ECG. If the electrocardiogram obtained on the morning of the fourth day of therapy with study medication did not show the subject to be in sinus rhythm, study drug was stopped.

For subjects who entered the efficacy evaluation period of the study, the efficacy evaluation began at the time that the INDEX ECG was obtained[35]. Those subjects who were not in NSR at this time were discontinued from the study and followed for safety for a short time. Patients in NSR were discharged from the hospital and followed for 48 weeks or until the termination of the study, whichever came first. The minimum duration of follow-up was 12 weeks unless the patient discontinued double-blind therapy prematurely. Subjects who experienced a study efficacy end-point could remain in the study on double-blind study medication as long as the frequency of attacks of arrhythmia was not greater than that considered clinically acceptable to the investigator and/or the subject.

Inclusion Criteria

- Subjects with a history of symptomatic attacks of pAF/AFl (defined as attacks of AF/AFl lasting up to and including 5 days). Subjects must have at least one symptomatic attack of pAF/AFl during the six months preceding inclusion into the study, which must be documented electrocardiographically.
- Subjects aged 18 years or older.
- Subjects capable of giving written informed consent.

Exclusion Criteria

The protocol excluded subjects with the following characteristics:

- Female subjects of child-bearing potential (i.e., less than 2 years post menopausal or not surgically sterilized);
- Subjects with uncompensated heart failure;

[35] (In other words, the start point for the time-to-event efficacy evaluation will be the date and time of the INDEX ECG.)

- myocardial infarction or unstable angina pectoris or cardiac surgery or survival from sudden cardiac death within the preceding 3 weeks;
- a resting heart (ventricular) rate during sinus rhythm less than 60 beats per minute in the drug-free state, when the subject was awake, or an RR interval greater than 3.5 sec, unless treated with a pacemaker;
- a QT or a QTc interval at baseline, in the absence of the pre-excitation syndrome and bundle branch block, exceeding 440 msec, or exceeding 500 msec in the presence of either of these two;
- known symptomatic abnormalities of the sinus node, unless treated with a pacemaker;
- AV block during SR greater than first degree, unless treated with a pacemaker;
- a history of polymorphic VT secondary to treatment with antiarrhythmic drugs or with other classes of drugs known to prolong the QT interval;
- a systolic blood pressure less than 80 mmHg, or diastolic blood pressure greater than 110 mmHg;
- major hematologic disease (e.g. aplastic anemia or agranulocytosis) or hepatic diseases likely to interfere with the safety/efficacy evaluation of the compound;
- a serum potassium less than 4.0 mEq/L or greater than 5.5 mEq/L at screening or at baseline, or a serum magnesium less than 1.2 mEq/L or greater than 2.5 mEq/L at screening;
- receiving concomitant therapy with Class I, III or IV antiarrhythmic agents, tricyclic antidepressants, anticonvulsants, phenothiazines or other drugs known to prolong the QT interval or receiving such treatment in the period of time corresponding to five times the relevant half life prior to receiving study treatment. Background stabilizing treatment with digoxin, oral anticoagulants, beta-blocking agents and/or diltiazem was permitted. (Sotalol is not to be understood as a beta blocker in this context, and was not permitted.);
- who have received treatment with oral amiodarone within one year prior to study entry;
- thyrotoxicosis, or pAF/AFl resulting from reversible non-cardiac diseases;
- a recent history of severe substance abuse/dependency (e.g. alcohol, controlled drugs or solvents);
- who have received any experimental drug within the past 1 month;
- previously randomized into this or any other studies with dofetilide;
- a creatinine clearance, as calculated by Cockcroft's formula, of less than 20 ml/min;
- receiving cimetidine who cannot be switched to alternative anti-ulcer therapy;
- clinical evidence of digitalis intoxication.

Procedures

Table 128.1 lists the flowchart of procedures performed during the study.

Table 128.1. Procedures Performed in Study 128.

Procedures	Screen	In-Hospital Days				Out-Patient Weeks				
		1	2	3	4	4	12	24	36	48
Medical H + P	x									
Transtelephonic Monitoring	x					T ⇐----------⇒				
Symptomatology						S ⇐----------⇒				
Hospitalization		x	x	x	x					
Lab	x				x		x [b]			x
Potassium Level		x								
ECG	x	x [a]	x [a]	x [a]	x [a]	x	x	x	x	x
Physician Assessment						x	x	x	x	x
Blood Pressure	x									
Echocardiography	x									
PK Sample					x		x [b]			x

(a) Prior to and 2-3 hours after the first dose on Day 1, 2, and 3

(b) Or at earlier date if discontinued the study

(T) Training and familiarization with TTM methodology. (Subjects will transmit an ECG rhythm strip at 2-week intervals and at the time of symptoms related to a cardiac arrhythmia.)

(S) Assessment of symptomatology was performed at baseline, at each clinic visit and at 2-week intervals by telephone between clinic visits.

Treatment Groups

The patients were randomized to either dofetilide 500 mcg bid or placebo. The initial dose was adjusted based

on calculated creatinine clearance as illustrated in table 128.2. If QTc increased after the initial doses or at any time during the study, the dose was reduced.

Table 128.2. Dose Adjustments Based on Creatinine Clearance

	Calculated Creatinine Clearance		
	> 60 ml/min.	40 - 60 ml/min.	20 - 39 ml/min.
Dofetilide	500 mcg bid	250 mcg bid	250 mcg od
Placebo	500 mcg bid	250 mcg bid	250 mcg od

Endpoints

The primary endpoint was time to first recurrence of symptomatic pAF or pAFl (documented electrocardiographically). Secondary endpoints included:

- the frequency of symptomatic recurrences of pAF or pAFl (documented electrocardiographically);
- symptoms associated with pAF or pAFl; and
- the relationship between plasma levels of dofetilide and its efficacy and safety, as assessed by population pharmacokinetic methods and frequency of symptomatic recurrences of pAF or pAFl (documented electrocardiographically).

Statistical Plan

A sample size of 76 subjects per group was sufficient to detect (2-sided level of significance of 5% with 90% power) a 24 week recurrence-free rate of 50% in the dofetilide group (placebo rate 25%). The projected sample size for each group was increased to 100 to account for dropouts during the in-hospital period and out-patient treatment period. Table 128.2 lists the proposed statistical plan for the study.

Study 128.2. Proposed Statistical Analysis

Endpoint	Analysis
Time to first symptomatic recurrence of pAF or pAFl documented by ECG.	• estimated using the product-limit method (Kaplan-Meier) • log rank test was used to compare the time-to-recurrence distributions • subjects discontinuing prior to recurrence will be treated as censored on the date of withdrawal • the primary analysis will be confirmed using the Cox proportional hazard model • supplementary analyses will be conducted on the primary endpoints with subjects grouped by the treatment actually received and excluding subjects with clinically significant protocol violations
Frequency of symptomatic recurrences per time on treatment and for arrhythmia-associated symptoms tabulated by treatment group	• summary statistics will be compared by appropriate statistical methods
Baseline characteristics, adverse events, laboratory and other safety data	• descriptive statistics

Results

Disposition

The study was conducted at 75 centers in the United States. Of 318 patients screened, 261 were randomized. The number of patients randomized per center ranged from 0 to 13. Eleven centers did not enroll any patients. Table 128.3 lists the patient disposition in the trial. The number of patients who were in NSR and remained on therapy at steady state in-hospital were 108 and 98 for the dofetilide and placebo groups respectively. These are the patients that are included in the primary efficacy analysis. The total number of patients discontinued from the study according to the sponsor is 58 and 82 for dofetilide and placebo respectively. These discontinuations include patients discontinued during the hospital period, patients discontinued prior to an event in the double-blind treatment period (i.e.. censored at the time of discontinuation) and patients discontinued at or after an event (e.g.. some patients remained on therapy after

qualifying as an event). During the in-hospital period, 24 and 31 patients were discontinued from the dofetilide and placebo groups respectively. The most common reason for not continuing was failure to remain in NSR. In the dofetilide group, five patients discontinued because of QTc prolongation. None of the placebo patients discontinued for this reason. After entering the steady state period, 34 dofetilide and 51 placebo patients were discontinued from therapy. Of these patients, 8 dofetilide and 20 placebo were discontinued prior to an event and were censored in the primary analysis. The remaining discontinued patients, 26 dofetilide and 31 placebo, had events and were counted as such in the analysis.

Table 128.3. Patient Disposition

	Dofetilide 500 mcg	Placebo
Randomized	132	129
Patients Discontinued in the in-hospital period and Not Included the Primary Analysis.	24	31
Ventricular Tachycardia	1	2
Not in NSR	16	27
QTc prolongation	5	0
Adverse Event	2	0
Did Not Fulfill Exclusion Criteria	0	1
Asked to be Withdrawn	0	1
Number Included in the Intent to treat Population [A]	108	98
Patients Discontinued From Treatment After Discharge from Hospital	34	51
Event Prior to Discontinuation [B]	26	31
Censored Prior to Discontinuation	8	20
Reason for Discontinuation for Censored Patients		
Adverse event	0	4
Lab Abnormality	0	0
QT prolongation	2	0
Lack of Efficacy	3	12
Death	0	0
Protocol Violation	0	1
Other	1	0
Asked to be Withdrawn	0	2
Ventricular Tachycardia	0	1
Lost to Follow-up	2 [C]	0

[A] = patients were included in intent to treat population if they tolerated 5th dose of study medication and fulfilled inclusion/exclusion criteria
[B] = patients discontinued at or after an event (e.g.. some patients remained on therapy after qualifying as an event)
[C] - 12/2/98 fax notified agency that patients are alive as of October 1998

Table 128.4 (see Table in appendix of this review) lists the patients who discontinued prior to the reaching steady state and are not included in the primary analysis.

Table 128.5 lists the patients discontinued from the study prematurely and the reason for discontinuation. All of these patients were censored in the primary analysis. In response to an inquiry, the sponsor clarified why some patients who were discontinued due to lack of efficacy are censored rather than being counted as an event. The sponsor reviewed their database again and determined that some of these patients should have counted as events. Two patients, both receiving dofetilide, were lost to follow-up. The sponsor recently located both patients.

Table 128.5. Patients Discontinued Prematurely from Study 128 and Censored in the Analysis (from Sponsor's Table 4.2 and Sponsor's Appendix IIIA, table 1.1)

Patient ID	Sex	Age	Dose**	Day*	Reason Discontinued
5360190	female	52	placebo	120	Adverse Event. [patient discontinued medication due to constipation]

Table 128.5. Patients Discontinued Prematurely from Study 128 and Censored in the Analysis (from Sponsor's Table 4.2 and Sponsor's Appendix IIIA, table 1.1)

Patient ID	Sex	Age	Dose**	Day*	Reason Discontinued
5420161	male	77	placebo	186	Adverse event. [increased ventricular ectopic activity, ventricular premature beats increasing]
5860031	female	72	placebo	117	Protocol violation. [medication non-compliance]
5870181	**female**	**64**	**placebo**	**13**	**Discontinued due to lack of efficacy of drug.**
6020185	**male**	**56**	**placebo**	**7**	**Discontinued due to lack of efficacy of drug.**
6340153	**female**	**63**	**placebo**	**12**	**Discontinued due to lack of efficacy of drug.**
6350379	male	81	placebo	31	Discontinued due to lack of efficacy of drug.
6610257	Male	79	placebo	93	Discontinued due to lack of efficacy of drug.
7070009	**male**	**54**	**placebo**	**21**	**Discontinued due to lack of efficacy of drug.**
7070013	**male**	**66**	**placebo**	**10**	**Discontinued due to lack of efficacy of drug.**
7070017	male	37	placebo	22	Discontinued due to lack of efficacy of drug.
7120362	**male**	**54**	**placebo**	**5**	**Discontinued due to lack of efficacy of drug.**
7370279	**male**	**71**	**placebo**	**25**	**Discontinued due to lack of efficacy of drug.**
7400026	male	50	placebo	162	Asked to be withdrawn from the study.
7400195	female	57	placebo	132	Adverse event. [frequent non-sustained VT]
7470310	female	80	placebo	8	Adverse event. [headache]
7510135	female	74	placebo	125	Adverse event. [worsening chronic obstructive pulmonary, worsening heart]
7570236	**female**	**57**	**placebo**	**95**	**Discontinued due to lack of efficacy of drug.**
7650475	Male	71	placebo	81	Discontinued due to lack of efficacy of drug.
50020107	female	58	placebo	49	Asked to be withdrawn from the study.
7060213	male	71	500 mcg	28	Discontinued due to lack of efficacy of drug.
7650485	male	46	1000 mcg	36	Discontinued due to lack of efficacy of drug.
7120441	**male**	**66**	**500 mcg**	**30**	**Discontinued due to lack of efficacy of drug.**
5870184	female	78	1000 mcg	88	QT/QTc prolongation. [44%]
50020106	male	71	500 mcg	259	QT/QTc prolongation. [36%]
7650474	male	63	1000 mcg	116	Other. [referring MD instruction:]
7400193	male	46	1000 mcg	265	Lost to follow up. (alive as of October 1998)
7510136	male	21	1000 mcg	92	Lost to follow up. (alive as of October 1998)

* Day Discontinued; **total daily dose after adjustment for creatinine clearance and/or QTc prolongation.
Highlighted and bolded patients are the patients who should have counted as events in the primary analysis.

Table 128.6 (in appendix of this review) lists the patients who discontinued from double-blind therapy at or after an event (pAF/AFl). The majority were discontinued due to lack of efficacy.

Demographics

Table 128.7. lists the demographic variables for each treatment group. The majority of subjects were male and Caucasian with a history of pAF. For 48% of subjects, the duration of pAF/AFl was not known. Of the patients with known duration of AF/AFl, 59% had pAF/AFl for 6 months or less.

Table 128.7. Demographics

	Dofetilide	Placebo
N	132	129
Male	61%	65%
Caucasian	91%	91%
Black	5%	5%

Table 128.7. Demographics

	Dofetilide	Placebo
Other	4%	3%
Mean Age (yrs.)	64	65
AF	88%	81%
AFl	12%	19%

Efficacy

Table 128.8 shows the proportion of patients remaining free of pAF/AFl at 4, 12 and 24 weeks. During the review, it was noted that nine patients (8 placebo and one dofetilide) were classified as premature discontinuations and censored in the analysis but should have been counted as events. Table 128.8 provides the original analysis and the revised numbers. The proportions at each time point were obtained from the Kaplan-Meier plot. There is no difference between treatment groups at any of the timepoints. The median number of days to attack was 137 days for dofetilide and 102 days for placebo. In the revised analysis, the median number of days to attack was 137 days for dofetilide and 53 for placebo. Median days to attack was not a pre-specified analysis and no statistical testing was done.

Table 128.8. Efficacy Results (Patients Entering Steady State Period)*

	Dofetilide	Placebo
Number Randomized	132	129
Number Entering Steady State [C]	108	98
Number Remaining Attack Free [A]	46 (43%)	31 (32%)
Number with Attacks of pAF/AFl [B]	54 (50%)	47 (48%)
Number with Attacks of pAF/AFl [D]	55 (51%)	55 (55%)
Number Discontinued Prematurely	8 (7%)	20 (20%)
Revised Number Discontinued Prematurely [D]	7 (6%)	12 (12%)
Median Time To Attack (Days)	137	102
Median Time To Attack (Days) [D]	137	53
Probability Of Remaining Attack Free At 4 Weeks	0.66	0.61
Probability Of Remaining Attack Free At 12 Weeks	0.53	0.53
Probability Of Remaining Attack Free At 24 Weeks	0.48	0.47
Hazard Ratio (dofetilide:placebo) and 95% C.I.	0.95 (0.64, 1.4)	
Probability of treatment difference between curves	(logrank test) p =0.78	
Probability Of Remaining Attack Free At 4 Weeks [D]	.66	.57
Probability Of Remaining Attack Free At 12 Weeks [D]	.52	.49
Probability Of Remaining Attack Free At 24 Weeks [D]	.47	.42
Hazard Ratio (dofetilide:placebo) [D] and 95% C.I.	.85 (.58, 1.24)	
Probability of treatment difference between curves [D]	(logrank test) p =0.40	

[A] from Sponsor's Table 6.1.1; [B] from Sponsor's Appendix IIIA, table 1.1;
[C] patients were included in primary analysis population if they tolerated 5th dose of study medication and fulfilled inclusion/exclusion criteria;
[D] revised because some patients listed as discontinued for lack of efficacy should have been counted as events; * Results confirmed by reviewer's analysis.
An event is defined as the first documented, symptomatic pAF/AFl attack from steady state

An analysis that included all patients randomized (1st dose analysis) was no different than the primary analysis.

Study 363. Efficacy and Safety of Dofetilide in The Prevention of Recurrence of Paroxysmal Atrial Fibrillation / Atrial Flutter (pAF/pAFl). A Double-Blind, Randomized Comparison with Quinidine and Placebo
Study Dates: 7/22/94 - 6/21/96

Protocol

This a randomized, double-blind, placebo and active controlled trial to evaluate the efficacy of dofetilide in the prevention of symptomatic pAF/AFl. The trial consisted of a screening visit, an in-patient period of three days for

initiation of randomized therapy and an out-patient period. During the in-hospital period, eligible patients were randomized to either placebo, dofetilide or quinidine. ECGs were obtained at 2 - 4 hours after the morning dose on days 2 and 3 to assess QT prolongation. There was no provision in the protocol for dose reduction if QT/QTc was prolonged. Patients were instructed on the use of the Hertcard recorder and symptom diary as the method for documenting a recurrence of pAF/AFl. After discharge from the hospital, patients had visits at 2, 6, 12 and 24 weeks. At 24 weeks, patients were discontinued from therapy. Table 363.1 lists the procedures performed in study 363.

Table 363.1. Procedures in Study 363.

	Screening	In-hospital (days)			Out-patient (weeks)			
Procedure		1	2	3	2	6	12	24 or WD
H + P	x							
Hertcard		⇐----------⇒						
Symptom Diary		⇐----------⇒						
Hospitalization		⇐----------⇒						
Initiate Therapy		x						
Labs	x	x			x	x	x	x
ECG	x	x			x	x	x	x
QOL	x				x	x	x	x
Health Economics					x	x	x	x
Dofetilide levels		x					x	x

Inclusion Criteria

Patients were required to fulfill the following criteria in order to be enrolled.

- 18 years of age or older;
- in sinus rhythm at the time of randomization; and
- two attacks of symptomatic pAF/AFl lasting ≤ 7 days during the preceding six months (documented electrocardiographically).

Patients who were converted from AF/AFl were eligible for enrollment into the study starting within one hour of DC conversion if they were still in NSR. Patients who were converted with intravenous Class I, III or IV antiarrhythmic agents had to wait at least 24 hours before receiving randomized therapy. Patients who were converted with oral Class I, III or IV antiarrhythmic agents had to wait at least 5 half-lives before receiving randomized therapy.

Exclusion Criteria

Patients were excluded for the following reasons:

- female of child-bearing potential;
- clinically unstable heart failure;
- MI, unstable angina, cardiac surgery or survival from sudden cardiac death within the preceding three weeks;
- heart rate < 50 beats per minute;
- QTc > 440 msec (if pre-excitation syndrome or bundle branch block is present > 500 msec);
- 2nd or 3rd degree AV block;
- a history of polymorphic VT secondary to treatment with antiarrhythmic drugs;
- SBP < 80 mm Hg or DBP > 110 mm Hg;
- concomitant Class I, II or III agents, tricyclic antidepressants, anticonvulsants, phenothiazines or other drugs known to prolong the QT interval;
- thyrotoxicosis;
- amiodarone in the last 3 months or in the last 6 months where amiodarone blood level > 0.3 mcg/ml.;
- potassium < 3.6 or > 5.5 mmol/L or magnesium < 0.6 or > 1.25 mmol/L.

Treatment Groups

Patients were randomized to placebo, dofetilide 250 mcg or quinidine 300 mg bid in a 1:1:1 ratio. There was no dose adjustment proposed in the original protocol based on creatinine clearance or QTc interval prolongation. A protocol amendment dated 5/18/94 allowed for exclusion from the study any subject with a calculated creatinine clearance < 40 ml/min.

Primary Endpoints

The primary endpoints included:

- time to first symptomatic attack of pAF/AFl (document electrocardiographically)
- incidence of adverse events.

Secondary Endpoints

Secondary endpoints included:

- ventricular rate during symptomatic attacks of pAF/AFl;
- proportion of patients remaining free of documented pAF/AFl at 6 months;
- interval between attacks;
- number of patients withdrawn due to therapeutic failure, adverse events or other reasons;
- frequency and severity of symptoms;
- adverse event frequency and severity;
- quality of life (questionnaire);
- healthcare resource utilization data;
- population pharmacokinetics.

Statistical Plan

The sample size was calculated based on α of 0.05, a power of 80%, 20% of placebo patients remaining free from attacks at six months and 55% of dofetilide patients remaining free of attacks at 6 months. Based on these criteria, a sample size of 38 patients per treatment group was needed. The study planned to enroll 50 per group to account for patients lost to follow-up. Table 363.2 lists the analyses planned for the endpoints.

Table 363.2. Statistical Analysis Plan

Endpoint	Proposed Analyses
time to recurrence of pAF/AFl	• survival function for dofetilide versus placebo and quinidine versus placebo
secondary endpoints	• comparisons between treatments blocking on center

No interim analysis was planned for the study.

Results

Disposition

One hundred and sixty-nine subjects were screened and 155 randomized at 48 sites in France and Poland[36]. Forty-eight subjects were randomized to dofetilide, 57 to quinidine, and 50 to placebo. Eight patients discontinued in the in-hospital phase for various reasons. During the outpatient phase, twenty-eight patients discontinued prematurely and were consequently censored in the analysis.

Table 363.3. Patient Disposition (from sponsor's table 1.)

	Dofetilide	Quinidine	Placebo
Randomized	48	57	50
Subjects discontinuing study treatment in hospital phase	6 (12.5)	1 (1.8)	1 (2.0)
Reason Discontinued			
Did not meet selection criteria.	1	0	0
QT/ QTc prolongation	2	0	0
Protocol violation	1	0	1
Discontinued due to lack of efficacy of drug.	1	1	0
Ventricular Tachycardia	1	0	0
Subjects entering outpatient phase	42 (87.5)	56 (98.2)	49 (98.0)

[36] ten sites did not randomize any patients

Table 363.3. (con't) Patient Disposition (from sponsor's table 1.)

	Dofetilide	Quinidine	Placebo
Patients Discontinued Prematurely (Censored)	8	7	13
QT/ QTc prolongation	0	2	0
Discontinued due to lack of efficacy of drug.	6	1	10
Asked to be Withdrawn.	0	1	0
Other	1	0	0
Adverse Event	1	3	3
Subjects completing 24 weeks of treatment	13	23	10
Subjects with Events	21	27	26

Table 363.4 lists the patients discontinued in the in-hospital phase and the reason for discontinuation.

Table 363.4. Patients Discontinued During the In-hospital Phase

Patient ID	Sex	Age	Treatment	Day	Reason discontinued
1520183	male	69	Dofetilide	2	Adverse event. [ventricular arrhythmia]
2540078	female	83	Dofetilide	1	Did not meet selection criteria.
3960215	male	69	Dofetilide	1	Discontinued due to lack of efficacy of drug.
2450001	female	59	Dofetilide	2	Protocol violation.
1290189	male	58	Dofetilide	2	QT/ QTc prolongation.
4000200	male	50	Dofetilide	2	QT/ QTc prolongation.
3800096	male	81	Placebo	3	Protocol violation.
2630088	male	46	Quinidine	3	Discontinued due to lack of efficacy of drug.

Table 363.5 lists the patients discontinued prematurely during outpatient treatment and censored in the analysis. The primary reason for discontinuation was for lack of efficacy. Some patients were categorized as lack of efficacy even though they are not counted as an event (pAF/AFl = ECG documentation + symptoms). This occurred because some patients may have had symptoms but no pAF/AFl on ECG associated with the symptoms.

Table 363.5. Patients Discontinued During the Outpatient Treatment Phase
(Censored in the Analysis)

Patient ID	Sex	Age	Treatment	Day	Reason discontinued
1290192	male	76	Dofetilide	8	Adverse event. [diarrhea, nausea]
2960071	male	57	Dofetilide	5	Discontinued due to lack of efficacy of drug.
2540056	female	73	Dofetilide	18	Discontinued due to lack of efficacy of drug.
1530241	female	58	Dofetilide	20	Discontinued due to lack of efficacy of drug.
3800095	male	75	Dofetilide	42	Discontinued due to lack of efficacy of drug.
3950209	male	64	Dofetilide	49	Discontinued due to lack of efficacy of drug.
2660028	female	68	Dofetilide	69	Discontinued due to lack of efficacy of drug.
4030220	female	61	Dofetilide	9	Other.
4040155	female	64	Placebo	94	Adverse event. [diarrhea]
3440226	female	58	Placebo	61	Adverse event. [hepatitis]
4000157	female	67	Placebo	82	Adverse event. [rash]
3960214	male	57	Placebo	4	Discontinued due to lack of efficacy of drug.
2500118	female	62	Placebo	5	Discontinued due to lack of efficacy of drug.
2450002	female	64	Placebo	6	Discontinued due to lack of efficacy of drug.
4070203	male	81	Placebo	6	Discontinued due to lack of efficacy of drug.
2570080	female	60	Placebo	7	Discontinued due to lack of efficacy of drug.

Table 363.5. Patients Discontinued During the Outpatient Treatment Phase
(Censored in the Analysis)

Patient ID	Sex	Age	Treatment	Day	Reason discontinued
2540055	male	30	Placebo	8	Discontinued due to lack of efficacy of drug.
1550244	female	62	Placebo	9	Discontinued due to lack of efficacy of drug.
1550178	male	69	Placebo	15	Discontinued due to lack of efficacy of drug.
2660029	male	66	Placebo	18	Discontinued due to lack of efficacy of drug.
2540076	female	64	Placebo	28	Discontinued due to lack of efficacy of drug.
4050167	male	65	Quinidine	31	Adverse event. [abdominal pain, diarrhea, dry mouth, petechia, rash, respiratory tract infection]
1280197	female	60	Quinidine	11	Adverse event. [abdominal pain, diarrhea]
2570024	male	52	Quinidine	101	Adverse event. [diarrhea]
3070146	male	62	Quinidine	18	Asked to be withdrawn from the study.
2570093	male	56	Quinidine	44	Discontinued due to lack of efficacy of drug.
2670031	male	66	Quinidine	14	QT/ QTc prolongation.
2960070	male	58	Quinidine	49	QT/ QTc prolongation.

Patients who experienced an event could remain on randomized, double-blind therapy until the completion of the trial. Some of these patients discontinued prior to the completion date of the trial. Table 363.6 lists those patients who discontinued after experiencing an event or after completing 24 weeks of follow-up (for reasons other than lack of efficacy)[37].

Table 363.6. Patients Discontinued at or after an Event

Patient ID	Sex	Age	Treatment	Day	Reason discontinued
2630069	male	75	Dofetilide	12	Adverse event. [atrial fibrillation, coronary occlusion]
2620065	male	73	Dofetilide	92	Adverse event. [bundle branch block]
1530186	female	63	Placebo	40	Laboratory abnormality. [AF, SGPT increased]
3010034	male	63	Quinidine	50	Adverse event. [congestive heart failure, diarrhea, rash, skin disorder]
3940207	male	58	Quinidine	63	Asked to be withdrawn from the study.

Demographics

Table 363.7 lists the demographic characteristics of the population randomized into the trial. All of the subjects were Caucasian except for one Black male in the quinidine group. Approximately 60% of the subjects were male with an average age ranging from 58 to 63 years of age.

Table 363.7. Demographics

	Dofetilide	Quinidine	Placebo
N	48	57	50
Male	58%	60%	54%
Caucasian	100%	98%	100%
Black	0%	2%	0%
> 65 yrs. Of age	35%	32%	44%
Mean Age (yrs.)	60	58	63

Primary Endpoint

Table 362.8 lists the number of patients with events in the double-blind treatment period. More subjects were censored in the placebo group compared to the active treatment groups.

[37] 32 patients were discontinued for lack of efficacy and are counted as events in the primary analysis

Table 363.8. Number of Patients with Events and Completing the Study

	Dofetilide	Quinidine	Placebo
Subjects entering outpatient phase	42 (87.5)	56* (98.2)	49 (98.0)
Subjects with Events	21 (44%)	27 (48%)	26 (53%)
Subjects Censored	8	7	13
Subjects completing study treatment	13	23	10

* from sponsor's table 1; the sponsor's primary analysis did not exclude patient 2630088 (see table 363.4)

From the Kaplan-Meier plots, the probability of remaining free of attacks at 24 weeks trended in favor of both active treatments but neither was significantly different from placebo. Table 363.9 lists the probability of remaining free of attacks at 4, 12 and 24 weeks (only includes patients in out-patient portion of trial). There was no significant difference from placebo (logrank p = .729 for dofetilide compared to placebo).

Table 363.9. Probabilities of Remaining Attack Free (From steady state)

	Dofetilide	Quinidine	Placebo
Probability of remaining attack free at 4 weeks	0.60	0.70	0.59
Probability of remaining attack free at 12 weeks	0.48	0.58	0.50
Probability of remaining attack free at 24 weeks & 95% CI	0.44 (0.28, 0.61)	0.49 (0.36, 0.63)	0.34 (0.18, 0.49)
Logrank comparison to placebo	p=0.729	p=0.138	

Secondary Endpoints

The ventricular rate during attacks (symptoms + pAF/AFl) is similar between treatment groups (170 bpm for dofetilide, 150 bpm for quinidine, 168 bpm for placebo).

Table 363.10 categorizes patients by the number of attacks experienced over 24 weeks. The median number of attacks was 2 for dofetilide and 4 for placebo. There is no difference in the distribution of patients within each category for the dofetilide/placebo comparison.

Table 363.10. Number Of Documented Attacks

	Dofetilide	Quinidine	Placebo
Withdrawn before 24 weeks - no attacks	13	6	14
No attacks	13	23	10
1- 2 attacks	5	8	6
3- 4 attacks	2	4	3
5- 6 attacks	2	2	2
>6 attacks	13	14	15
Median	2	1	4

Study 365. Efficacy and Safety of Dofetilide in the Prevention of Recurrence of Symptomatic Attacks of Paroxysmal Atrial Fibrillation/Atrial Flutter. A Double-Blind, Randomized, Parallel Comparison with Placebo
Study dates: 2/1/96 - 12/19/96

Protocol

This was a randomized double-blind, placebo-controlled, parallel dose, multi-center study in patients with pAF/AFL. The primary objective of the study was to assess the long term efficacy and safety of dofetilide compared to placebo. The trial consisted of a screening visit, an in-hospital drug initiation phase and an outpatient treatment period of 24 weeks duration[38]. During the initial hospitalization, the patient was instructed on the use of the Hertcard recorder and symptom diary card. During the course of the out-patient follow-up, subjects who experienced symptoms

[38] The original protocol suggested that follow-up would continue for 12 - 48 weeks . A protocol amendment changed the duration of follow-up to 24 weeks for all patients.

consistent with their underlying pAF/AFl were expected to record the event on the Hertcard recorder and in the symptom diary. Patients returned for clinic visits at 4, 12 and 24 weeks. Patients discontinued prematurely were followed for a short time after discontinuation. Table 356.1 lists the procedures performed during the study.

Table 365.1. Flowchart of Procedures Performed during the Study

		Dose Initiation				Steady State Phase		
	Screen	In- Hospital (days)				Outpatient (weeks)		
		1	2	3	4	4	12	24 or withdrawal
Medical History	x							
Body Weight	x						x	
Hertcard		⇐----------						----------⇒
Diary		⇐----------						----------⇒
Initiate Therapy		x						
Labs	x							
ECG	x	x	x	x	x	x	x	x
BP	x							
Echo	x							
PK		x				x	x	x

Inclusion Criteria

Patients were included if they fulfilled the following criteria:

- symptomatic attacks of pAF/AFl defined as attacks of AF/AFl lasting up to and including 5 days:
- the minimum duration of these attacks must be such that a clinical indication exists for pharmacological therapy;
- patients must have at least one attack of pAF/AFl during the six months preceding inclusion into the study, which must be documented electrocardiographically;
- Patients aged 18 years or older.
- Patients capable of giving written informed consent.
- Patients must have been in sinus rhythm at baseline and must be in sinus rhythm at the start of the efficacy period, defined as the post-dose ECG on Study Day 4.

Exclusion Criteria

- Female patients of child-bearing potential (i.e., less than 2 years post-menopausal or not surgically sterilized).
- Patients with uncompensated heart failure.
- Patients with myocardial infarction or unstable angina pectoris or cardiac surgery or survival from sudden cardiac death within the preceding 3 weeks.
- Patients with resting heart (ventricular) rate during sinus rhythm (SR) less than 50 beats per minute in the drug-free state, when the patient is awake or RR interval greater than 3.5 msec unless treated with pacemaker.
- Patients with either QT or QTc intervals during NSR at baseline and in the absence of the pre-excitation syndrome and bundle branch block exceeding 440 msec or in the presence of either of these two exceeding 500 msec.
- Patients with known symptomatic abnormalities of the sinus node, unless treated with a pacemaker.
- Patients with AV block during SR greater than first degree, unless treated with a pacemaker.
- Patients with a history of polymorphic VT secondary to treatment with antiarrhythmic drugs or with other classes of drugs known to prolong the QT interval.
- Patients with a systolic blood pressure less than 80 mmHg, or diastolic blood pressure greater than 110 mmHg.
- Patients with major hematologic disease (i.e. aplastic anemia or agranulocytosis), hepatic disease, likely to interfere with the safety/ efficacy evaluation of the compound.
- Patients with serum potassium < 3.6 mmol/ L or > 5.5 mmol/ L at screen and baseline, or serum magnesium < 0.6 mmol/ L or > 1.25 mmol/ L at screen.
- Patients receiving concomitant therapy with Class I, III or IV antiarrhythmic agents, tricyclic antidepressants. anticonvulsants, phenothiazines or other drugs known to prolong the QT interval or receiving such treatment in the period of time corresponding to five times the relevant half-life prior to receiving study treatment. Background stabilizing treatment with digoxin, oral anticoagulants, beta- blocking agents (with the exception of sotalol) and/ or diltiazem was permitted.

- Patients treated with amiodarone within the last 12 months.
- Patients with thyrotoxicosis, or pAF/AFl resulting from reversible non-cardiac diseases.
- Patients with a recent history of severe substance abuse/dependency (i.e. alcohol, controlled drugs or solvents).
- Patients who have received an experimental drug within the past 1 month.
- Patients previously randomized into this or other studies with dofetilide.
- Patients with a creatinine clearance, calculated by Cockcroft's formula, of less than 20 ml/minute.
- Patients receiving cimetidine, who cannot be switched to alternative anti-ulcer therapy.
- Patients with clinical evidence of digitalis intoxication.

Treatment Groups

Patients were randomized to dofetilide 500 mcg bid or placebo in a 2:1 ratio. The dose of dofetilide for a patient with a creatinine clearance greater then 60 ml/min is 500 mcg/bid, for a patient with a creatinine clearance of between 40 ml/min and 60ml/min the dose is 250 mcg/bid and for a patient with a creatinine clearance of between 20 ml/min and 40 ml/min the dose is 250 mcg/od. If QT/QTc interval increases by more than 15% of the baseline value or 500 msec (550 msec in the presence of bundle branch block) the dose was to be adjusted in a double-blind fashion as outlined in table 365.2.

Table 365.2. Dose Adjustment for Prolonged QT Interval.

Actual Dose at Randomization	Adjusted Dose
500 mcg bid	250 mcg bid
250 mcg bid	250 mcg od
250 mcg od	withdraw from study

The randomization was stratified by center.

Primary Endpoint

The primary endpoint was the Time to first symptomatic attack of pAF/AFl (documented electrocardiographically). Patients are evaluable for efficacy if they are documented to be in sinus rhythm by an ECG recorded after 72 hours of study medication.

Secondary Endpoint

The secondary endpoints included:

- Frequency of symptomatic attacks of pAF/AFl (documented electrocardiographically).
- Frequency of disease related symptoms.
- Population pharmacokinetics.

Statistical Analysis Plan

Power calculations assume proportional hazards between groups and analysis by the logrank test with average subject follow-up of 24 weeks. Assuming that 25% of patients in the placebo group are free from recurrence at 24 weeks (as estimated from an interim analysis of study 119), a sample size of 98 patients in the dofetilide group and 49 patients in the placebo group, is sufficient to detect (2-sided level of significance of 5% with 90% power) a 24 week recurrence-free rate of 50% in the dofetilide group. Assuming a 15% drop out during the efficacy evaluation period before an end point event, it is estimated that 114 patients in the dofetilide group and 57 patients in the placebo group (total of 171 patients), must be randomized.

Patients are evaluable for efficacy if they are documented to be in sinus rhythm by an ECG recorded after 72 hours of study medication. Table 365.3 describes the statistical analysis plan for the study.

Table 365.3. Statistical Analysis Plan

Variable	Statistical Analysis
Time to symptomatic recurrence of pAF/AFl	• The distribution for time to recurrence for each treatment group will be estimated using the product-limit method (Kaplan-Meier) • Logrank test to compare the two distributions • Analysis will include complete data for all patients who have entered the efficacy evaluation period (thus, not a true intent to treat) • Patients discontinuing after entering the period, but prior to recurrence, will be treated as censored on the date of withdrawal. • Secondary analysis include a Cox Regression analysis, an analysis based on actual dose received and excluding patients with significant protocol violations
Baseline Characteristics	Descriptive Statistics
Frequency of symptomatic, documented recurrences	None Specified

An interim analysis was pre-specified for when 50% of the patients completed 12 weeks of therapy or experienced a primary endpoint. The study could not be stopped based on this analysis and consequently no statistical adjustment was warranted.

Results

The results provided by the sponsor include events as determined by the investigator. The report of the endpoints committee were not yet available.

Disposition

The study was conducted in eight countries (Italy, Spain, Israel, Estonia, Finland, Poland, Lithuania, United Kingdom) at 51 centers. Table 365.4 lists the patient disposition in the trial. Two-hundred and seventy patients were randomized to dofetilide (N = 181) or placebo (N = 89). Twenty-two patients did not proceed to the steady state out-patient period. The most common reasons for not continuing into the out-patient phase (steady state) were QT prolongation (dofetilide only), failure to meet selection criteria and lack of efficacy. Table 365.5 lists the patients discontinued prematurely during the in-patient phase.

Table 365.4. Patient Disposition

	Dofetilide 500 mcg bid	Placebo
Randomized	181	89
Number Discontinuing during the In-hospital phase	16 (9%)	6 (7%)
Reason Discontinued		
QT/ QTc prolongation.	5	0
Death	1	0
Ventricular Arrhythmia	1	0
Adverse Event	4	2
Did not meet selection criteria	1	2
Discontinued due to lack of efficacy of drug	3	2
Protocol violation	1	
Number Entering Steady State	165	83
Number Discontinued Prematurely in Steady State Phase	12 (7%)	11 (13%)
Lab Abnormality	1	0
Protocol Violation	1	0
Ventricular Arrhythmia	0	1
Adverse Event	4	1

Table 365.4. Patient Disposition

	Dofetilide 500 mcg bid	Placebo
Discontinued due to lack of efficacy of drug	3	7
Asked to be Withdrawn	3	2
Number Completing Treatment without symptomatic pAF	55 (33%)	21 (25%)
Number with Symptomatic pAF	98 (59%)	51 (61%)

Table 365. 5. Patients Discontinued From Therapy During the In-Hospital Phase
(These patients are not included in the primary analysis.)

Patient #	Treatment	Sex	Age	Day	Reason
3990308	dofetilide	female	69	3	Adverse event. [ECG changes]
1170106	dofetilide	Male	59	3	Adverse event. [hyperglycemia, prolonged QT, vomiting]
4230681	dofetilide	Male	46	1	Adverse event. [non sustained VT, rapid AF]
4180191	dofetilide	female	53	1	Adverse event. [t- wave distortions]
1970609	dofetilide	Male	70	3	Adverse event. [urticarial rash]
3270269	dofetilide	female	59	4	Did not meet selection criteria.
3270241	dofetilide	Male	59	2	Discontinued due to lack of efficacy of drug.
4330343	dofetilide	Male	67	3	Discontinued due to lack of efficacy of drug.
1570367	dofetilide	Male	54	4	Discontinued due to lack of efficacy of drug.
3270273	dofetilide	female	71	1	Patient died.
3280237	dofetilide	Male	60	3	Protocol violation.
2260028	dofetilide	female	70	1	QT/ QTc prolongation.
3280238	dofetilide	Male	55	2	QT/ QTc prolongation.
3280240	dofetilide	female	58	2	QT/ QTc prolongation.
4220631	dofetilide	Male	63	3	QT/ QTc prolongation.
4360356	dofetilide	Male	45	4	QT/ QTc prolongation.
2720644	placebo	Male	62	2	Adverse event. [bradycardia, prominent u- wave]
3990309	placebo	female	83	2	Adverse event. [bradycardia]
430078	placebo	female	50	4	Did not meet selection criteria.
4050383	placebo	female	52	4	Did not meet selection criteria.
1570368	placebo	Male	60	1	Discontinued due to lack of efficacy of drug.
2700623	placebo	female	57	4	Discontinued due to lack of efficacy of drug.

During the out-patient phase, 23 patients discontinued therapy prematurely[39]. The majority were discontinued due to lack of efficacy. As with Study 363, some patients were categorized as lack of efficacy even though they are not counted as an event (pAF/AFl = ECG documentation + symptoms). This occurred because some patients may have had symptoms but no pAF/AFl on ECG associated with the symptoms. Table 365.6 lists the patients discontinued prematurely during the out-patient phase.

Table 365. 6. Patients Prematurely Discontinued From Therapy Prior to an Event (Censored in the analysis)

Patient #	Treatment	Sex	Age	Day	Reason
1350435	dofetilide	female	55	8	Adverse event. [asthenia, headache, dizziness]
4230680	dofetilide	Male	66	78	Adverse event. [fatigue]
4030316	dofetilide	female	71	150	Adverse event. [hyperthyroidism]
4250721	dofetilide	female	68	99	Adverse event. [sinus bradycardia]

[39] That is, they did not experience an event and did not complete the protocol specified time of follow-up.

1290362	dofetilide	female	66	9	Asked to be withdrawn from the study.
4050408	dofetilide	female	69	55	Asked to be withdrawn from the study.
4180226	dofetilide	female	59	65	Asked to be withdrawn from the study.
4190204	dofetilide	female	63	27	Discontinued due to lack of efficacy of drug.
4180176	dofetilide	female	69	42	Discontinued due to lack of efficacy of drug. [the patient cannot tolerate her symptoms]
4180182	dofetilide	female	58	37	Discontinued due to lack of efficacy of drug.[the patient cannot tolerate her symptoms]
4050403	dofetilide	Male	71	94	Laboratory abnormality. [abnormality of liver enzymes tests, nausea, worsening liver function]
1470009	dofetilide	Male	60	92	Protocol violation. [patient not compliant with study drug dose]
4180179	placebo	Male	57	100	Adverse event. [drug allergies, (urticaria)]
4010301	placebo	Male	46	12	Adverse event. [ventricular fibrillation]
4190210	placebo	Male	38	91	Asked to be withdrawn from the study.
4180185	placebo	Male	58	110	Asked to be withdrawn from the study.
3270274	placebo	Male	54	13	Discontinued due to lack of efficacy of drug.
4240670	placebo	Male	61	18	Discontinued due to lack of efficacy of drug.
4190194	placebo	Male	65	66	Discontinued due to lack of efficacy of drug.
4180220	placebo	female	67	94	Discontinued due to lack of efficacy of drug.
3990307	placebo	female	71	106	Discontinued due to lack of efficacy of drug.
4180172	placebo	female	67	51	Discontinued due to lack of efficacy of drug. [asymptomatic relapse of AF]
1470011	placebo	Male	56	159	Discontinued due to lack of efficacy of drug. [asymptomatic relapse of AF.]

Patients who experienced an event could remain on randomized, double-blind therapy until the completion of the trial. Some of these patients discontinued prior to the completion date of the trial. Table 365.7 (see in appendix of this review) lists those patients who discontinued after experiencing an event or after completing 24 weeks of follow-up (for reasons other than lack of efficacy)[40].

Demographics

The average age of randomized subjects was 60 years of age with 42% of patients being ≥ 65 years of age. All were Caucasian and 56% - 63% were male. The majority of subjects had pAF as the underlying baseline rhythm abnormality. Table 365.8 lists the demographic characteristics for each treatment group.

Table 365. 8. Demographics

	Dofetilide	Placebo
Randomized	181	89
Mean Age (yrs.)	61	60
≥ 65 years of age	42%	42%
Caucasian	100%	100%
Male	56%	63%
pAF	91%	92%
Median # Attacks in previous 6 months	4	4

[40] 55 patients were discontinued for lack of efficacy and are counted as events in the primary analysis

Primary Endpoint

The primary endpoint of the study was the Time to first symptomatic attack of pAF/AFl (documented electrocardiographically). Table 365.9 lists the probability of remaining attack free at 4, 12 and 24 weeks. There was no significant difference between dofetilide and placebo (logrank p = .766). At 12 weeks, the probability of remaining attack free (calculated from the Kaplan-Meier plot) was .47 for dofetilide and .44 for placebo.

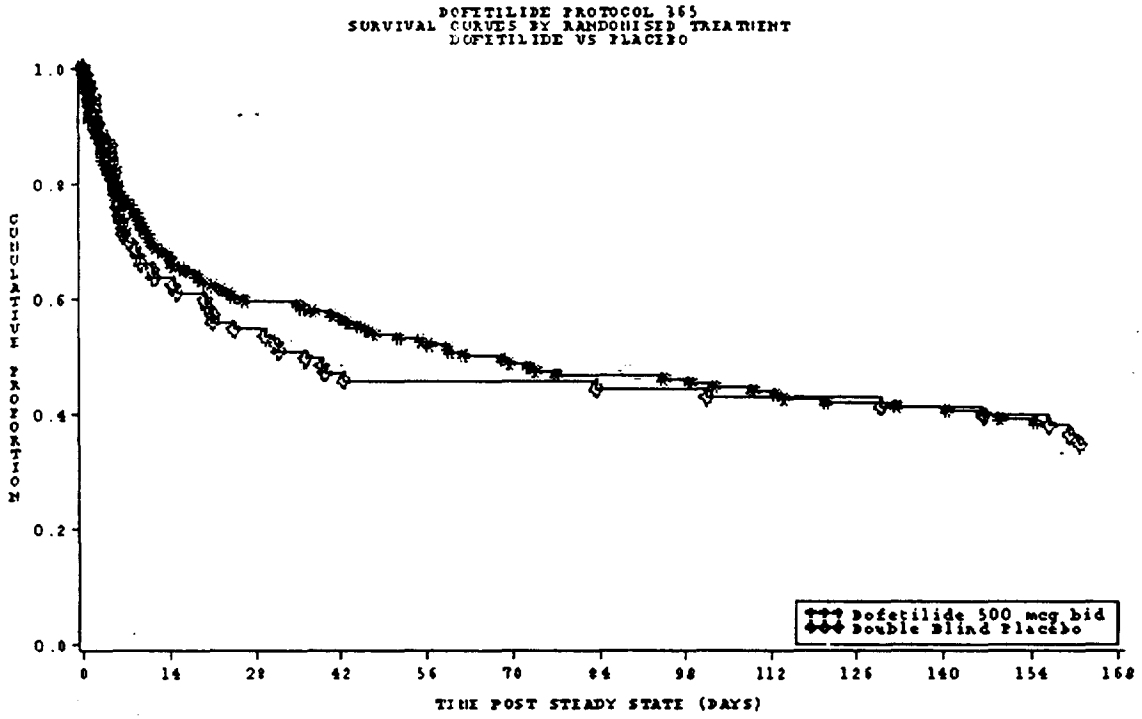
Table 365.9. Probability of Remaining Attack Free

	Dofetilide	Placebo
Entered Steady State Outpatient Phase	165	83
Number with Symptomatic pAF	98 (59%)	51 (61%)
Probability of remaining attack free at 4 weeks	0.60	0.55
Probability of remaining attack free at 12 weeks	0.47	0.44
Probability of remaining attack free at 24 weeks	0.39	0.35

Hazard ratio (dofetilide:placebo) and 95% CI = 0.95(0.67, 1.34); logrank p = .77 for overall analysis

Figure 365.1 shows the Kaplan-Meier plot of the proportion of patients remaining event free. In the first 14 days, 34% of dofetilide patients and 37% of placebo patients experienced events. The failure of dofetilide to have a greater effect on the prevention of early events contributed to the failure to show an overall treatment effect.

Figure 365.1 Kaplan-Meier Plot of Cumulative Proportion of Patients Remaining Event Free.
(from figure 1 of sponsor's report)



The sponsor also performed an analysis for time to first symptoms with or without documented pAF. There was no significant difference between treatment groups when only symptoms are analyzed (Logrank p = .30). Table 365.10 shows the probability of remaining symptom free at 4 and 12 weeks.

Table 365.10. Probability of Remaining Symptom Free (Associated with Any Rhythm)

	Dofetilide	Placebo
Entered Steady State Outpatient Phase	165	83
Number with Symptoms [A]	106 (64%)	58 (61%)
Probability of remaining symptom free at 4 weeks	0.55	0.50
Probability of remaining symptom free at 12 weeks	0.43	0.37
Probability of remaining symptom free at 24 weeks	0.34	0.28

[A] The number of attacks ranged from 1 - 900 for dofetilide and 1 - 500 for placebo (fax 12/7/98)
Hazard ratio (dofetilide:placebo) and 95% CI = 0.85 (0.61, 1.17); logrank p = .30 for overall analysis

Secondary Endpoints

There were three secondary endpoint: frequency of symptomatic attacks of pAF/pAFl (documented electrocardiographically), frequency of disease related symptoms and population pharmacokinetics. Table 365.11 categorizes patients by the number of attacks experienced in the first 12 weeks of treatment. The median number of attacks was 1 for dofetilide and 2.5 for placebo.

Table 365.11. Number Of Documented Attacks In First 12 Weeks
(all randomized patients)

	Dofetilide	Placebo
Randomized	181	89
Withdrawn early - no attacks	18%	22%
No attacks	35%	28%
1- 2 attacks	15%	10%
3- 4 attacks	9%	7%
5- 6 attacks	4%	9%
>6 attacks	20%	24%

The endpoint of frequency of disease related symptoms is not defined in the protocol and appears to be indistinguishable from the frequency of symptomatic attacks. The population pharmacokinetics will be discussed in the Biopharm review.

Studies In Patients With Paroxysmal Supraventricular Tachycardia

Study #	Description	Treatments	N	Primary Endpoints	Page
372	• r, db, pc, ac, p, 6 month Rx, • patients with pSVT during placebo baseline	Dofetilide 500 mcg bid Propafenone 150 mg tid Placebo Total	40 41 41 122	• recurrence of SVT during db Rx • adverse events • discontinuations due to severity and frequency of attacks of pSVT	77
119	• r, db, pc, p, mc, 6 month Rx period • pAF/AFl and pSVT (18%) randomized • optional db 6 month extension period • 6/20/94 - 10/15/96 • USA	placebo dofetilide 375 mcg bid dofetilide 250 mcg bid total	111 105 100 316	• time to recurrence of symptomatic pAF/AFl	52

r = randomized, db = double-blind, p = parallel, pc = placebo controlled, mc = multi-center, Hx = history, Rx = treatment

Study 372. Efficacy and Safety of Dofetilide in the Prevention of Symptomatic Attacks of Paroxysmal Supraventricular Tachycardia - A Six Month, Double Blind Comparison with Placebo and Propafenone
Study Dates: 11/29/93 - 4/2/96

Protocol

This was a randomized, double-blind, placebo-controlled, parallel group trial in patients with paroxysmal supraventricular tachycardia. The objective was to compare the efficacy and safety of dofetilide compared to placebo and propafenone. The trial consisted of a six week placebo period during which patients with a history of recurrent paroxysmal supraventriculat tachycardia were monitored with a Hertcard recorder. Major exclusion criteria to the study included: uncompensated CHF, MI or unstable angina within 3 months, QTc > 440 msec, pre-excitation syndromes and amiodarone therapy with the past three months. To enter the double-blind period, patients had to have a episode of supraventricular tachycardia documented during the placebo period. Patients fulfilling these criteria were hospitalized and randomized to placebo, dofetilide 500 mcg bid or propafenone 150 mg tid. Subjects were to remain hospitalized for the first two days of the double blind treatment period. A recording of the QTc interval was to be made after the sixth dose of study treatment (Day 2 or 3 depending on what time of day the first dose was administered). Subjects whose Day 2/3 QTc interval did not exceed 550msec and/or had not increased by more than 20% from baseline were to be followed on an outpatient basis for the rest of the treatment period. Subjects whose QTc interval exceeded these limits were to be withdrawn from the study. Patients were continued on double-blind therapy for up to six months unless terminated prematurely due to recurrent episodes of pSVT or adverse events. Patients who experienced a QTc interval > 550 msec or a 20% increase in QTc interval were discontinued prematurely from the study.

The projected sample size was 32 patients per group to detect a 30% increase in the proportion of patients remaining in NSR at 6 months (α = .05, power = 80%).

The study endpoints included: occurrence of symptomatic attacks of pSVT during the DB therapy, discontinuations due to frequency and/or severity of attacks of pSVT and adverse events during double blind therapy. None of the endpoints was specifically listed as a primary or secondary. Sample size justification was based on the recurrence of SVT and incidence of adverse events. Episodes of symptomatic supraventricular tachycardia were documented on the Hertcard recorder and a patient diary. An event required documentation of SVT in conjunction with symptoms. The procedures performed during the study are listed in Table 372.1.

Table 372.1. Procedures Performed in Study 372.

Procedures	Scr.	Run-in	Bsl.	1	2	1	2	4	8	12	18	26
Clinical Examination	x		x	x	x	x	x	x	x	x	x	x
Documented pSVT attack	x											
Symptom Diary	x					x	x	x	x	x	x	x
Event Monitoring	x	x	x	x	x	x	x	x	x	x	x	x
Lab Tests			x			x				x		x
Population pharmacokinetics				x	x	x				x		x
12 lead ECG	x		x	x	x	x	x	x	x	x	x	x
Demography	x											
Concomitant therapy	x		x	x	x	x	x	x	x	x	x	x
Medical History	x											
Adverse Event		x	x	x	x	x	x	x	x	x	x	x
Pregnancy test			x									x

Scr. = screening; Bsl. = baseline

Table 372.1a lists the protocol specified statistical analysis. The primary efficacy analysis is the time to recurrence of pSVT during the 6 month treatment period based on a survival function.

Table 372.1a. Statistical Analysis Plan

Endpoint	Statistical Analysis
time to recurrence of pSVT	• principle comparison is dofetilide vs. placebo • survival function (blocking on center) will be estimated over 6 month period • Secondary Analysis include: proportion of patients remaining event free at 6 months, interattack interval and total number of attacks during the 6 month interval
Lab and safety data	• incidence of treatment related adverse events in the dofetilide treated group will be compared with the incidence in the propafenone treated group.

Results

Before discussing the results, it is important to note the following. The primary efficacy analysis was time to the first documented symptomatic attack of pSVT during the 6 month treatment period. A documented symptomatic attack was defined as one which was recorded on the Hertcard and could be linked to symptoms recorded on the patient diary card that occurred within one hour before or after onset of the attack. Therefore, attacks of pSVT recorded by any method other than the Hertcard were not included in this analysis. Furthermore, attacks recorded on the Hertcard with no link to symptoms on the patient diary or vice versa were not included in these analyses. In addition, the efficacy period did not start until 72 hours after the start of the dosing.

Disposition

The study was conducted at 13 centers in Poland. Of the 253 subjects screened, 131 did not have an attack of pSVT during the run-in period and therefore were withdrawn prior to randomization. The remaining 122 subjects were randomized to receive treatment. Subjects were randomized equally into the three treatment groups: 40 received dofetilide, 41 received propafenone and 41 received placebo. Table 372.2 lists the patient disposition during the study. Tables 372.2a,372.2b. and 372.2c. list the patients discontinued during the study.

Table 372.2. Patient Disposition

	Dofetilide	Propafenone	Placebo
Randomized	40	41	41
Discontinued Prior to Outpatient Period	2	1	2
Entered Outpatient Period	38	40	39
Premature Withdrawals	9	10	2
Reason Withdrawn*			
Adverse Event	3	5	2
Unknown	1	2	0
Withdrew Consent	0	2	0
Lab Abnormality	2	0	0
Lost-to-follow-up	1	0	0
Other	1	0	0
QT Prolongation	1	0	0
Protocol Violation	0	1	0

* (from Table 4.2 of sponsor's summary report)

Table 372.2a. Listing of Patients Discontinued from Study 372 During In-hospital Period

Patient ID	Sex	Age	Treatment	Day	Reason
1540117	male	71	Placebo	1	Adverse event. [atrial arrhythmia]
1590062	female	47	Placebo	1	Adverse event. [pericarditis]
1280089	female	66	Dofetilide	2	QT/ QTc prolongation.
1530015	female	58	Dofetilide	1	Adverse event. [strong metallic taste]
1540023	female	72	Propafenone	2	Adverse event. [bundle branch block, lung edema, supraventricular tachycardia]

Table 372.2b. Listing of Patients Discontinued Prematurely from Study 372 During Outpatient Period

Patient ID	Sex	Age	Treatment	Day	Reason
1540020	female	65	Placebo	4	Adverse event. [arrhythmia, bundle branch block, electrocardiogram abnormal]
1540024	male	56	Placebo	28	Adverse event. [asthenia]
1290038	female	36	Dofetilide	49	Adverse event. [nausea]
1520008	male	16	Dofetilide	29	Lost to follow up.
1520105	female	73	Dofetilide	32	Laboratory abnormality. [creatinine clearance decreased]
1530098	female	21	Dofetilide	50	QT/ QTc prolongation.
1530099	female	50	Dofetilide	7	Adverse event. [gastrointestinal troubles nausea, vomiting, abdominal pain]
1540022	female	74	Dofetilide	27	Laboratory abnormality. [creatinine clearance decreased]
1560034	female	31	Dofetilide	35	Other. [patient was randomized after end of recruitment to this study]
1580082	female	60	Dofetilide	26	Adverse event. [diarrhea]
1600069					
1520107	male	38	Propafenone	56	Asked to be withdrawn from the study.
1530018	female	35	Propafenone	99	Asked to be withdrawn from the study. [going abroad for 6 weeks]
1550025	male	48	Propafenone	127	Adverse event. [ventricular premature beats]
1550026	female	52	Propafenone	128	Adverse event. [AV block second degree]
1550133	female	47	Propafenone	84	Adverse event. [worsening heart failure]
1550137	female	53	Propafenone	7	Adverse event. [tachycardia causing discomfort, requiring administration of drug not allowed in study]
1570122	female	64	Propafenone	29	Adverse event. [dyspnea]
1570124	female	68	Propafenone	10	Protocol violation. [creatinine clearance < 60 ml/ min]
1580057					
1580083					

Table 372.2c. Listing of Patients Discontinued from Study 372 During Outpatient Period after Event

Patient ID	Sex	Age	Treatment	Day	Reason
1590061	female	55	Dofetilide	153	Adverse event. [bronchitis, pharyngitis]
1280054	female	63	Placebo	29	Adverse event. [hypotonia]
1290041	male	35	Placebo	162	Adverse event. [supraventricular tachycardia]
1520009	female	56	Placebo	32	Asked to be withdrawn from the study.
1520106	female	74	Placebo	125	Asked to be withdrawn from the study.
1530017	female	65	Placebo	85	Adverse event. [supraventricular tachycardia]
1550027	female	44	Placebo	9	Discontinued due to lack of efficacy of drug.
1550138	female	56	Placebo	125	Discontinued due to lack of efficacy of drug.
1560033	female	44	Placebo	162	Patient died.
1570047	male	40	Placebo	63	Discontinued due to lack of efficacy of drug.
1570123	male	41	Placebo	58	Discontinued due to lack of efficacy of drug.
1570073	male	54	Propafenone	25	Laboratory abnormality. [bilirubinemia, SGOT increased, SGPT increased]

Demographics

Table 372.3 lists the demographic characteristics of the patients randomized. The majority of subjects were female and less than 65 years of age. Of note, all subjects were Caucasian which is not surprising in view of the location of the investigative sites.

Table 372.3. Demographic Characteristics

	Dofetilide	Propafenone	Placebo
Randomized	40	41	41
Females	73%	66%	68%
Caucasian	100%	100%	100%
>= 65 years	15%	12%	17%
Mean Age	50	47	48

Time to First pSVT Attack

The sponsor performed survival analysis which start at steady state or after the first dose. Table 372.4a and 372.4b show the probability of remaining attack free at 4, 12 and 26 weeks. Regardless of the population analyzed (all randomized vs. steady state), there is a significant treatment difference (logrank $p < 0.001$).

Table 372.4a. Survival Analysis from Steady State *

	Dofetilide	propafenone	Placebo
Number at Baseline	40	41	41
Number entering steady state	38	40	39
Premature Withdrawals	9	10	2
Number with Attacks	15	16	34
Number remaining attack free for 26 weeks	14	14	3
Probability of remaining attack free at 4 weeks	0.76	0.76	0.40
Probability of remaining attack free at 12 weeks	0.66	0.61	0.20
Probability of remaining attack free at 26 weeks	0.55	0.53	0.085

Hazard Ratio (dofetilide:placebo) and 95% CI = 0.28 (0.14, 0.54)
Probability of treatment difference (logrank test) p = .0001; * Results confirmed by reviewer's analysis

Table 372.4b. Survival Analysis from First Dose *

	Dofetilide	propafenone	Placebo
Number at baseline	40	41	41
Premature Withdrawals	10	11	4
Number with Attacks	17	16	35
Number remaining attack free for 26 weeks	13	14	2
Probability of remaining attack free at 4 weeks	0.71	0.74	0.37
Probability of remaining attack free at 12 weeks	0.61	0.62	0.17
Probability of remaining attack free at 26 weeks	0.50	0.54	0.057

Hazard Ratio (dofetilide:placebo) and 95% CI = 0.330 (0.18, 0.61)
Probability of treatment difference (logrank test) p = .0001; * Results confirmed by reviewer's analysis

Because the survival analysis censors patients who withdrew prematurely, the probabilities of remaining attack free are likely overestimated especially in the dofetilide treatment group. Table 372.4a. lists the 6 month probability of remaining attack free for Dofetilide patients as 55%. If patients would have been followed for documentation of pSVT after they prematurely discontinued treatment, the probability of remaining attack free would lie somewhere between 55% and 37% (# remaining attack free at 26 weeks / # in steady state). Because only two patients in the placebo group were censored for premature withdrawal, the impact on the placebo group probability is much less (8.5%→ 7.7%). For the propafenone group, the probability lies somewhere between 53% and 35%. There is no difference between dofetilide and propafenone in the incidence of pSVT.[41]

One of the purposes of therapy is to decrease the recurrence of symptoms. Table 372.5 lists the number of subjects who had symptoms but the rhythm noted at the time of symptoms was not pSVT. The number of patients who experienced symptoms is not significantly different between treatment groups. If the purpose of drug therapy is to reduce the incidence of symptoms, both active therapies did not achieve this goal.

[41] This does not imply that they are equally efficacious.

Table 372.5. Incidence of Non-pSVT Attacks.

	Dofetilide	Propafenone	Placebo
Withdrawn early - no attacks of any kind	3	5	4
No. of subjects with non- pSVT attacks	32	26	30
No. of subjects in SR throughout study	7	7	1
No. of subjects with other rhythm	27	23	25
No. of non- pSVT attacks throughout study	134	122	101
No. of non- pSVT attacks but no symptoms	36	67	29

The total number of pSVT attacks is 204, 143 and 156 [42]for placebo, dofetilide and propafenone respectively. The total number of pSVT and non-pSVT episodes is influenced by the duration of follow-up of each patient.

Table 372.6 lists the incidence of pSVT attacks by subgroup. An analysis by age or race is not reasonable because the study enrolled predominately Caucasians less than 65 years of age. The analysis by gender shows that all of the treatment effect is provided by the effect in female patients but the small percentage of males enrolled in the study makes is difficult to make definitive conclusions.

Table 372.6 Number (%) of Patients Experiencing a pSVT Attack (All Randomized Patients)

	Dofetilide	Propafenone	Placebo
	(N=40)	(N=41)	(N=41)
Male	8/11 (73%)	7/14 (50%)	9/13 (69%)
Female	9/29 (31%)	9/27 (33%)	26/28 (93%)
Caucasian	17/40 (43%)	16/41 (39%)	35/41 (85%)
< 65 years	16/34 (47%)	13/36 (36%)	31/34 (91%)
>= 65 years	1/6 (17%)	3/5 (60%)	4/7 (57%)

Reviewer's Analysis

Studies In Patients With Ventricular Tachycardia

Study #	Description	Treatments	N	Primary Endpoints	Page
113	• r, db, p, mc, pc, 12 month Rx period • patients with ICD • USA • 11/19/92 - 12/3/96	Dofetilide 500 mcg bid Placebo Total	87 87 174	• Time to first recurrence of documented sustained ventricular tachycardia or ventricular fibrillation resulting in ICD cardioversion or defibrillation therapy	82
333	• r, db, acute phase co, mc, 1 yr. Rx in responders • patients with IHD and inducible sustained VT • Europe • 11/3/94 - 2/13/97	dofetilide 500 mcg bid sotalol 80 mg bid total	132 131 135	• no primary specified • Prevention of induction of sustained monomorphic ventricular tachycardia by PES	88
334	• r, db, acute phase co, mc, 6 month Rx in responders • patients with IHD and inducible sustained VT • Europe • 11/9/93 - 1/29/97	dofetilide 500 mcg bid sotalol 80 mg bid total	30 33 40	• prevention of induction of ventricular tachycardia by PES	92

[42] from appendix IV, Table 3.

Studies In Patients With Ventricular Tachycardia

Study #	Description	Treatments	N	Primary Endpoints	Page
109	• ol, multi-phase, sc, 12 month Rx in responders • patients with hypertrophic cardiomyopathy and inducible VT • USA • 1/7/91 - 10/26/93	dofetilide iv dofetilide 250 mcg tid dofetilide 375 mcg tid procainamide 1000 mg tid	17	• prevention of induction of ventricular tachycardia by PES	103
308	• ol, mc, sequential dose design, patients with Hx sustained VT inducible by PES • patients • Europe • 12/90 - 4/93	dofetilide 250 mcg bid dofetilide 500 mcg bid dofetilide 750 mcg bid dofetilide 1000 mcg bid total	8 10 10 7 35	• prevent the induction of sustained VT	95
330	• ol, mc, study in patients with inducible VT • iv phase, acute oral and 1 year chronic oral phase • Europe • 7/5/93 - 8/9/95	dofetilide 500 mcg bid	19	• prevent the induction of sustained VT	104
331	• ol, mc, study in patients with inducible VT • iv phase, acute oral and 1 year chronic oral phase • Europe, 8/5/93 - 10/4/95	dofetilide 500 mcg bid dofetilide 250 mcg bid	27	• prevent the induction of sustained VT	105
104	• ol, mc, co, titration • 1 yr. Rx in responders • patients with Hx sustained VT inducible by PES • USA, 4/24/91 - 8/18/93	dofetilide 250 mcg tid titrated to 750 mcg tid	61	• prevent the induction of sustained VT	94
335	• db, mc, p, patients with dilated cardiomyopathy and Hx of PVCs + VT • Europe • 11/10/93 - 5/6/96	dofetilide 500 mcg bid amiodarone 300 mg/day total	38 37 75	• Incidence of documented ventricular arrhythmias	97
336	• same as study 335 except patients had hypertrophic cardiomyopathy	dofetilide 500 mcg bid amiodarone 300 mg/day total	18 17 35	• Incidence of documented ventricular arrhythmias	97

r = randomized, db = double-blind, p = parallel, pc = placebo controlled, mc = multi-center, Hx = history, Rx = treatment, sc = single center

Protocol 113. A Randomized, Double-Blind Study of Orally Administered Dofetilide and Placebo in Patients with an Implanted Arrhythmia Control Device
Study Dates: 11/19/92 - 12/3/96

Protocol
Design

This was a randomized, double-blind, parallel group, multi-center study in patients with a history of sustained or inducible ventricular tachycardia/fibrillation who are implanted with a cardioverter defibrillator. The primary objective was to determine whether dofetilide was able to prevent the recurrence of ventricular tachycardia or fibrillation compared to placebo. The study proposed to randomize 150 patients. The first thirty patients would be part

of a pilot phase where is was determined whether the study design was feasible. The trial consisted of an acute in-hospital phase (5 days) and a chronic outpatient treatment phase (up to 12 months). The procedures performed during the study in the acute and chronic phases are listed in tables 113.1a - 113.1b. Table 113.1c lists the procedures performed after hospital discharge.

Table 113. 1a. Procedure Flowchart.
(patients who received ICD device during the course of the study)

	Screening Days		In-patient Days					
	-2	-1	0@	1	2	3	4	5
Medical History	x							
Physical Exam	x		x			x#		x
CV Physical Exam	x		x	x	x	x	x	x
12- Lead ECG	x		x	x	x	x	x	x
24- h Holter	x***		x			x#		x
Implantation		x						
Dosing with Study			x	x	x	x	x	x
Medication								
Electrophysiologic Evaluation (PES)	x					x**#		x
Anti- tachycardia Device Interrogation		x				x#		x
Laboratory Tests	x		x			x#		x
Plasma Samples						x#		x
Adverse Reaction Assessment			x	x	x	x	x	x

@ Note: Day 0 assessments are made prior to administration of study drug and constitute the baseline assessments.
** Non-invasive
*** Holter should be done after washout of previous AA therapy
# Omit day 3 EP and other related tests, only for patients on QD dosing, they will be done on day 5

Table 113. 1b. Procedure Flowchart. (patients already implanted with ICD device)

	Screening	In-hospital Days					
	Day -2	0@	1	2	3	4	5
Medical History	x						
Physical Exam	x				x#		x
CV Physical Exam	x	x	x	x	x	x	x
12- Lead ECG	x	x	x	x	x	x	x
24- h Holter	x***				x#		x
Dosing with Study		x	x	x	x	x	x
Medication							
PES	x*				x**#		x
Anti- tachycardia Device Interrogation					x#		x
Laboratory Tests	x	x			x#		x
Plasma Samples					x#		x
Adverse Reaction Assessment		x	x	x	x	x	x

@ Note: Day 0 assessments are made prior to administration of study drug and constitute the baseline assessments.
* PES data prior to device implantation will be used for patients who received the ICD device prior to enrollment into the study
** Non-invasive
*** Holter should be done after washout of previous AA therapy
# Omit day 3 EP and other related tests, only for patients on QD dosing, they will be done on day 5

Table 113.1c. Study Flowchart (chronic phase)

	Months								
	0.5	1	2	4	6	8	10	12	Unplanned
CV Physical Exam	x	x	x	x	x	x	x	x	x
12- Lead ECG	x	x	x	x	x	x	x	x	x
24- hour Holter	x		x					x	x
Dosing with Study Medication	x	x	x	x	x	x	x	x	
Anti- tachycardia Device Interrogation	x	x	x	x	x	x	x	x	x
Non- Invasive PES		x						x	
Laboratory Tests	x		x	x		x		x	x
Plasma Samples	x		x	x		x		x	x
Adverse Reaction Assessment	x	x	x	x	x	x	x	x	x

Inclusion Criteria

- Males, and females of non-childbearing potential (at least 2 years post- menopausal or surgically sterilized).
- Age 18 to 75 years.
- Medical history, physical examination, laboratory safety evaluation, and 12-lead ECG prior to entry into the study.
- Written informed consent.
- History of documented spontaneous and/or inducible sustained ventricular tachycardia/ventricular fibrillation not associated with acute myocardial infarction (The frequency of spontaneous ventricular tachycardia episodes for up to one year preceding entry into the study as well as the duration and rate of the longest VT episode will be recorded). Ventricular tachycardia was defined as sustained if it lasted longer than 30 seconds at a rate of > 110 beats/min or if it requires cardioversion because of hemodynamic symptoms prior to 30 seconds.
- Patients who will be implanted with an anti-tachycardia pacemaker cardioverter-defibrillator with the capacity for storage of intracardiac electrograms and events or those patients who already have the cardioverter-defibrillator implanted.

Exclusion Criteria

- Pregnant women and women of childbearing potential.
- Clinically evident acute heart failure.
- Myocardial infarction or unstable angina pectoris within the past 1 month.
- Clinically evident hypertrophic obstructive cardiomyopathy.
- Major hematologic, pulmonary, hepatic, or renal disease (serum creatinine > 2.0 mg/dl) or calculated creatinine clearance < 20 ml/min.
- Systolic blood pressure < 90 mm Hg or diastolic blood pressure > 110 mm Hg (> 105 mm Hg for Canadian centers).
- Serum potassium < 4 mEq/L or > 5.5 mEq/L or serum magnesium < 1.5 mEq/L or > 2.5 mEq/L.
- ECG intervals exceeding the following limits in the drug-free state and in the absence of the pre-excitation syndrome: QRS > 180 msec, and QT> 440 c msec. In case of BBB, QT must not exceed 500 msec.
- History of polymorphic ventricular tachycardia secondary to treatment with antiarrhythmic or other classes of drugs known to prolong the QT interval.
- Concomitant therapy with other antiarrhythmic agents, tricyclic antidepressants, anticonvulsants, or phenothiazines. Patients on cimetidine were excluded. However, low doses of other H_2 blockers were permitted.
- Treatment with oral amiodarone within the preceding 3 months. Plasma samples were taken to insure that amiodarone blood levels are < 0.3 mcg/l.
- Abuse of alcohol or drugs, or inability to give informed consent.

Treatment Groups

Patients were randomized to dofetilide 500 mcg bid or placebo. The initial dose was adjusted based on calculated creatinine clearance. Patients with calculated creatinine clearance > 60 ml/min received 500 mcg bid. Those with a creatinine clearance between 40 - 60 ml/min. received 250 mcg bid. Those with creatinine clearance between 20

- 39 ml/min received 250 mcg od. [43] If at any time during hospitalization or outpatient treatment, the QT/QTc increases by more than 15%, the dose was down-titrated as follows: dofetilide 500 mcg bid ⇒ dofetilide 250 bid, dofetilide 250 mcg bid ⇒ dofetilide 250 od and dofetilide 250 mcg od ⇒ discontinue. If the QT/QTc increases more than 25% over baseline or 550 msec (whichever applies) on lower dose, the patient will be discontinued from the study.

Patients were stratified for sustained ventricular tachycardia or ventricular fibrillation (e.g. aborted sudden death) as their primary diagnosis.

Primary Endpoints

- Time to first recurrence of documented sustained ventricular tachycardia or ventricular fibrillation resulting in ICD cardioversion or defibrillation therapy. (Events will be defined as device discharge due to sustained ventricular tachycardia or ventricular fibrillation.) Device discharges during the time immediately after device implantation to the end of the hospital discharge (usually day 3) are not relevant to the efficacy evaluation of the study drug. This time period is typically characterized by frequent adjustments to the programming of the device and is also used to dose patients to steady state with study drug. Therefore, the efficacy evaluation begins after hospital discharge.
- Rate of device intervention due to recurrence of VT/VF. The time interval between further recurrences of VT or VF.

Secondary Endpoints

- Number of patients free of spontaneous VT/VF resulting in ICD therapy at 2, 6, 8, and 12 months of follow-up.
- Number and type of device therapies for supraventricular tachycardia.
- Time to and frequency of the occurrence of symptomatic arrhythmias not requiring ICD therapy.
- Correlation between plasma levels of dofetilide and its activity to prevent recurrence of ventricular arrhythmias.

Statistical Analysis Plan

A sample size of 75 patients per treatment group has been proposed and will have an 80% power of detecting treatment group differences at the 0.05 level in the following circumstances:

Table 113.2.

Placebo Event Rate (%/ year)	Risk Reduction for Dofetilide (%)	Dofetilide Event Rate (%/ year)
50	45	27
55	40	33
65	35	42
75	30	52

A formal hypothesis test will be run comparing the time to event between treatments. Events will be defined as device discharge due to sustained ventricular tachycardia or ventricular fibrillation. The documentation of these events and the definition of censoring events will be decided upon after blinded evaluation of the data from the first 30 patients, and an amendment will be filed to this protocol, describing the methods that will be used, prior to any unblinded analysis of data. The null hypothesis being tested is that the time to event has the same distribution for both treatment groups. The comparison will take into account any covariates (primary diagnosis, ejection faction, NYHA functional class) that appear to be important in the unblinded analysis of the first 30 patients' data, and the method of analysis will depend upon patterns of events seen in the first 30 patients.

When half the intended number of patients have been enrolled and followed for at least 6 months, the blind will be broken and data examined to aid in the planning of other studies in this program. This study will not be stopped because it shows dofetilide efficacious, regardless of the outcome of this analysis. The analysis only purpose will be to plan other studies in this program.

[43] The amendment for the adjustment of dose based on calculated creatinine clearance was implemented on 4/5/94.

Results

Disposition

The study was conducted at 53 centers in the United States [44]. One hundred and seventy-four subjects were randomized to dofetilide (N= 87) or placebo (N = 87). The disposition of patients by treatment group is listed in Table 113.3. Fourteen patients discontinued during the in-hospital period and did not proceed to chronic therapy (Table 113.4a). The primary reason for not proceeding into the chronic phase was the occurrence of Torsades de Pointes or ventricular tachycardia, specifically in the dofetilide group. Only two placebo patients did not proceed to the chronic phase. During the chronic treatment period, 28 patients discontinued prematurely. Table 113.4b (see in appendix of this review) lists the patients who discontinued prematurely during the chronic treatment phase.

Table 113.3. Patient Disposition

	Dofetilide 500 mcg	Placebo
Randomized	87	87
Number Discontinuing in the in-hospital phase	12	2
Reason Discontinued		
Torsades de Pointes	5	0
Adverse Event	1	0
QT prolongation	1	0
Ventricular Tachycardia	4	0
Non-compliance	0	1
Lack of Efficacy	0	1
Unaccounted	1	0
Number Entering the Chronic Phase	75	85
Number Experiencing an Event	49	50
Number Completing One Year of Follow-up Without an Event	16	17
Number Discontinued Prematurely Without an Event	10	18

Table 113.4a. Patients* Discontinued in the Acute Phase (Did not Enter the Chronic Phase)

Patient ID	Sex	Age	Treatment	Day	Reason discontinued
6531082	male	52	dofetilide	1	Adverse experience related to concurrent illness. [abdominal ileus]
5800107	male	47	dofetilide	2	Adverse experience related to disease under study. [polymorphic ventricular tachycardia]
5880095	female	67	dofetilide	1	Did not meet selection criteria. [QT/ QTc prolonged]
5161107	male	60	dofetilide	1	Side effect probably related to study drug. [increased frequency of ventricular tachycardia - resistant to cardioversion]
5900297	female	54	dofetilide	1	Side effect probably related to study drug. [polymorphic ventricular tachycardia]
6190145	male	70	dofetilide	2	Side effect probably related to study drug. [sustained polymorphic to Monomorphic ventricular tachycardia requiring frequent shocks].
5061289	male	66	dofetilide	1	Side effect probably related to study drug. [Torsades de Pointes]
5160038	male	58	dofetilide	1	Side effect probably related to study drug. [Torsades de Pointes]
5660286	female	68	dofetilide	1	Side effect probably related to study drug. [Torsades de Pointes]
6021118	male	56	dofetilide	1	Side effect probably related to study drug. [Torsades de Pointes]
5160033	male	72	dofetilide	3	Side effect probably related to study drug. [Torsades de Pointes]
5871037	male	73	Placebo	1	Discontinued due to lack of efficacy of drug.
6050129	male	80	Placebo	4	Noncompliance - irregular dosing.

Two patients in the dofetilide group were not accounted for in the listing of discontinued patients.

[44] 16 centers did not enroll any subjects

Demographics

The study randomized predominately Caucasian males with an average age of 64 years. The majority of subjects had a history of sustained ventricular tachycardia. Table 113.5 lists the demographic characteristics for each treatment group.

Table 113.5. Demographics

	Dofetilide	Placebo
Randomized	87	87
Mean Age (years)	64	64
>= 65 years	46%	56%
Females	13%	8%
Caucasians	92%	94%
Sustained Ventricular Tachycardia	78%	79%
Ventricular Fibrillation	22%	21%

Primary Endpoint

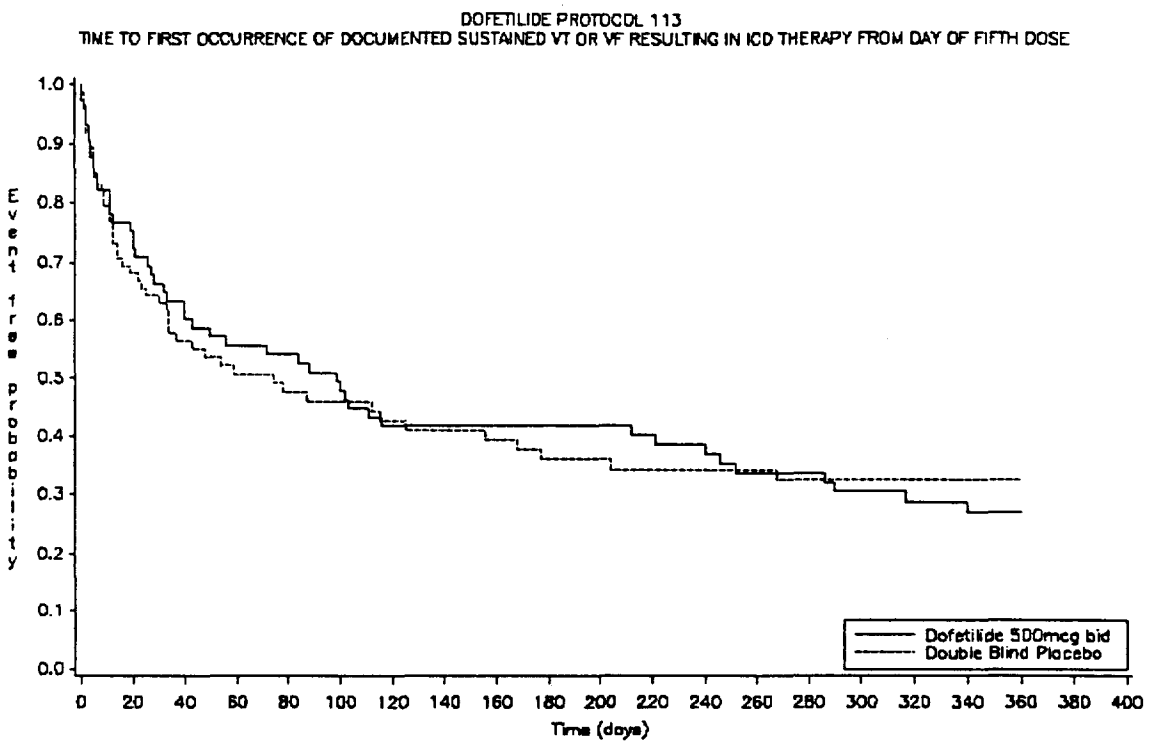
The primary measure of efficacy was the Time to first recurrence of documented sustained ventricular tachycardia or ventricular fibrillation resulting in ICD cardioversion or defibrillation therapy. Table 113.6 shows the probability of remaining attack free during the course of follow-up. There is no difference in time to first occurrence of VT or VF requiring ICD cardioversion. Figure 113.1 shows the Kaplan-Meier plot of time to first occurrence.

Table 113.6. Probability of Remaining Attack Free

	Dofetilide	Placebo
Probability of remaining attack free at 60 days	0.5569	0.5077
Probability of remaining attack free at 180 days	0.4177	0.3614
Probability of remaining attack free at 240 days	0.3695	0.3433
Probability of remaining attack free at 360 days	0.2713	0.3243

Hazard Ratio (dofetilide:placebo) = 1.003 (0.6704 , 1.4993); logrank p = .99

Figure 113.1. Time to First Occurrence of VT or VF Requiring ICD Cardioversion



Study 333. A Multi-center, Double Blind, Crossover Comparative Study of the Efficacy and Safety of Dofetilide Versus Sotalol, in the Management of Sustained Ventricular Tachycardia Secondary to Coronary Heart Diseases.

Study Dates: 11/3/94 - 2/13/97

Protocol

This was a randomized, double-blind, crossover study that planned to enroll 130 patients with a history of ischemic heart disease[45] and inducible sustained ventricular tachycardia[46]. The primary objective was to show that the ability of dofetilide to prevent the induction of sustained ventricular tachycardia was similar to sotalol. The study consisted of two acute treatment phases that were separated by a washout period. During the first acute treatment phase, patients received 3 - 5 days of sotalol 80 mg bid [47] or dofetilide 500 mg bid[48] before undergoing programmed electrical stimulation (PES) in an attempt to induce sustained ventricular tachycardia. After completion of the 1st PES study, therapy was discontinued and a short washout phase was performed. During the second acute treatment phase, patients received the opposite therapy and a 2nd PES study was performed. The final phase was a chronic therapy phase during which patients received either therapy depending on which therapy successfully prevented the induction of sustained ventricular tachycardia. If both therapies successfully prevented induction, the second therapy was given chronically for up to one year. The study design is depicted in figure 333.1.

[45] abnormal exercise test or Thallium study, and/or abnormal coronary angiography

[46] Documented during screening PES

[47] patients received sotalol 80 mg bid on day 1 and sotalol 160 mg bid on subsequent days

[48] During the study, an amendment to the protocol allowed for decreasing the dose by half if the calculated creatinine clearance was between 40 - 60 ml/minute. If the calculated creatinine clearance was less than 40 ml/min., the patient was withdrawn.

Figure 333.1. Study Phases

Washout	1st Therapy	PES [A]	Washout	2nd Therapy [B]	PES	Chronic Therapy
	3 - 5 days	1 day	2 - 3 days	3 - 5 days	1 day	up to one year

[A] If patient did not tolerate therapy due to side effects, PES was not performed and they proceeded to the next phase.
[B] Patient is crossed over to the other therapy not received as 1st therapy.

The study endpoints[49] included:

- Prevention of induction of sustained monomorphic ventricular tachycardia with oral dofetilide versus oral sotalol.
- Incidence of adverse events and withdrawal.
- Clinical long term benefit (prevention or reduction of VT/VF attacks) with oral dofetilide versus oral sotalol.

No primary endpoint was specified.

It was expected that 40% of patients would be responders (VT non-inducible) on both dofetilide and sotalol. The sample size of 130 patients was based on a response rate of 40% for dofetilide and was sufficient to detect an increase or decrease of 20 percentage points on Sotalol as statistically significantly different at the 5% level with 80% power. The sample size calculation was based on an approximate formula for pair-matched studies with binary outcomes [50]. The sample size of 130 patients was also sufficient to detect at the 5% level of significance with 80% power an increase from 10% to 25% in the percentage number of patients reporting adverse events in the acute part of the study. This calculation was again based on the formula by Royston.[51] It was expected that approximately 52 patients (26 patients on each treatment) will enter the chronic phase of the study. This sample size was sufficient to detect at the 5% level of significance and with 80% power a difference in withdrawal rates (due to adverse events or lack of efficacy) of 61% on dofetilide compared to 42% on sotalol. This calculation was based on a formula for two independent proportions (Biometrics, 36, 347-351. 1980).

Table 333.1 lists the statistical analysis proposed by the protocol. Some of the variables listed in the table are not listed as endpoints by the protocol.

Table 333.1. Statistical Analysis Plan

Variables	Statistical Analyses
Number of responders to dofetilide and sotalol	• compared between treatments using Prescott's test (Applied Statistics, 30,9-15. 1981); • The actual test will be part of a formal statistical model proposed by Kenward and Jones (Applied statistics, 36, 192-204. 1987) where effects are represented in terms of logarithms of odd ratios;
Number of patients reporting treatment related adverse events on dofetilide and sotalol during the acute oral phase	• same as above
Responders at the end of 1 year long term therapy.	• chi-squared test
Time to withdrawal from therapy	• log rank test
Number of patients who are readmitted to hospital because of ventricular tachycardia or syncope	• chi-squared test

[49] A primary endpoint was not specified.
[50] Royston J.P. Exact conditional and unconditional sample size for pair-matched studies with binary outcome: a practical guide. Statistics in medicine (in press).
[51] Royston J.P. Exact conditional and unconditional sample size for pair-matched studies with binary outcome: a practical guide. Statistics in medicine (in press).

Table 333.1. (con't) Statistical Analysis Plan

Variables	Statistical Analyses
Number of patients who report treatment related adverse events will also be compared between treatments	• chi-squared test
Frequency of symptoms/month will be compared between patients	• non-parametric test

Results

Disposition

The study was conducted at 50 centers in Europe (Belgium, Germany, Hungary, Czech Republic, Denmark, Italy, Netherlands, Poland, Norway) [52]. One hundred and thirty-five patients were randomized to therapy. Table 333.2a shows the patient disposition in the study. Patients discontinued during the acute phase on one therapy could still receive the other therapy. Fifteen subjects discontinued therapy in the acute phase (Table 333.2b.). Forty-two patients entered the chronic phase on dofetilide. Twenty-seven patients entered the chronic phase on sotalol. Ten patients withdrew from each group during the chronic phase (Table 333.2c.).

Table 333.2a. Patient Disposition

	Dofetilide	Sotalol
Number Screened	138	
Number Randomized	135	
Number Receiving Therapy in Acute Phase	132	131
Number Discontinued in the Acute Phase [A]	8	7
Number Entering the Chronic Phase	42	27
Number Discontinuing Prematurely in the Chronic Phase	10	10

[A] Patients could be discontinued from one therapy but still crossover to the other therapy.

Table 333.2b. Patients Discontinued in the Acute Phase

Patient #	Sex	Age	Treatment	Day	Reason Discontinued
110168	male	60	dofetilide	12	Discontinued due to lack of efficacy of drug.
3070012	female	67	dofetilide	2	Adverse event. [Monomorphic sustained VT, Torsades de Pointes]
2260047	female	55	dofetilide	1	Adverse event. [Torsades de Pointes]
2900219	male	58	dofetilide	8	Adverse event. [Torsades de Pointes]
2810027	male	73	dofetilide	1	Asked to be withdrawn from the study.
3430051	male	78	dofetilide	9	Asked to be withdrawn from the study.
1450084	male	48	dofetilide	1	Other. [CABG]
1450083	male	65	dofetilide	9	Other. [clinical decision for ICD implantation]
3320131	male	71	sotalol	7	Adverse event. [ASTHMA CARDIALE, Leg edema]
2820021	male	70	sotalol	9	Adverse event. [Lipothymia]
3120149	male	60	sotalol	1	Adverse event. [SYNCOPE]
320082	male	51	sotalol	7	Discontinued due to lack of efficacy of drug.
2260258	male	65	sotalol	10	Laboratory abnormality. [Elevated GGT, Elevated SGOT, Elevated SGPT, Hepatitis]
3410039	male	74	sotalol	2	Patient died.
3520231	female	71	sotalol	5	Patient died.

[52] Only 35 centers randomized patients

Table 333.2c. Patients Discontinued During the Chronic Treatment Phase

Patient #	Sex	Age	Treatment	Day	Reason Discontinued
110166	Female	37	dofetilide	15	Discontinued due to lack of efficacy of drug
270178	Male	63	dofetilide	11	Protocol violation. [Non-responder in acute phase]
310087	Male	57	dofetilide	93	Discontinued due to lack of efficacy of drug
760148	Female	63	dofetilide	279	Adverse event. [angina of effort, congestive pulmonary edema, myocardial infarction]
2260251	Male	71	dofetilide	148	Adverse event. [decompensated heart failure, elevated LFTs, inappropriate ICD discharges, pulmonary edema
2900218	Male	70	dofetilide	226	Adverse event. [sustained ventricular tachycardia]
3030061	Male	64	dofetilide	475	Discontinued due to lack of efficacy of drug
3030062	Male	71	dofetilide	99	Adverse event. [diarrhea, syncope, vomiting, nausea]
3300140	Male	66	dofetilide	403	Discontinued due to lack of efficacy of drug
3410035	Male	48	dofetilide	48	Asked to be withdrawn from the study.
3410040	Male	57	dofetilide	378	Asked to be withdrawn from the study.
3430026	Male	66	dofetilide	204	Other. [Patient will undergo CABG by the end of the month.]
110169	Male	59	sotalol	19	Adverse event. [sustained VT, VF]
270177	Male	65	sotalol	302	Laboratory abnormality. [bronchitis, impaired renal function]
310054	Male	60	sotalol	88	Discontinued due to lack of efficacy of drug
2820022	Male	52	sotalol	374	Asked to be withdrawn from the study.
2820253	Male	51	sotalol	378	Asked to be withdrawn from the study.
2900008	Male	75	sotalol	95	Asked to be withdrawn from the study.
3130031	Male	65	sotalol	303	Asked to be withdrawn from the study.
3510233	Male	58	sotalol	11	Discontinued due to lack of efficacy of drug
3520230	Female	69	sotalol	14	Patient died.
3520235	Male	64	sotalol	103	Discontinued due to lack of efficacy of drug

Demographics

All of the patients were Caucasian. Eighty-nine percent were male. The average age of patients was 63 years of age. Ninety-four percent had a prior history of myocardial infarction. Ninety-five percent of patients were categorized as NYHA Class I or II.

Primary Endpoint

The study was designed to be able to detect a difference of +/- 20 percentage points in the proportion of patients who would not have their arrhythmia induced by PES. The projected response rate was 40% for dofetilide and sotalol. The study was powered to detect an absolute difference if one of the therapies had a response rate of < 20% or > 60 percent while the other therapy had a response rate of 40%. So, the study was powered to detect a relative increase or decrease in response of 50%. The interpretation of the study results depends on what one believes is a clinically meaningful difference. The implication here is that a failure to find a significant difference in the response rate between treatment groups can be construed as indicating that they are equally effective[53]. This , however, is only true if the study is adequately powered to detect a difference that is believed to be clinically meaningful. If a relative difference in response of 25% is deemed clinically relevant then the study is not adequately powered to conclude anything.

[53] Sotalol is an effective treatment for life threatening ventricular arrhythmias. If it is shown that dofetilide is not different from sotalol then it might be concluded that dofetilide is effective treatment for life threatening ventricular arrhythmias.