CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20931

MEDICAL REVIEW(S)

D. Rose dec

FEB 3 1999

Medical/Statistical Review: Efficacy Data

NDA #: 20-931
Drug Name: Dofetilide (Tikosyn™)
Type of Document: New NDA
Date Completed: 12/11/98

Sponsor: Pfizer
Date Received: 3/9/98
Medical Reviewer: Charles J. Ganley, M.D.
Statistical Reviewer: James Hung, Ph.D.

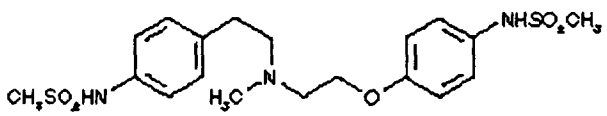
General Information

Name of Drug

Generic: Dofetilide

Trade: Tikosyn™

Chemical: N-[4-(2-{2-[4-(methanesulphonamido)phenoxy]- N-methylethylamino}ethyl) phenyl]methanesulphonamide.



M.W. = 441.6

Pharmacologic Category: TIKOSYN demonstrates Vaughan Williams Class III antiarrhythmic activity, a block of re-entry by prolonging the effective refractory period, through highly selective blockade of a single type of cardiac potassium channel (I_{Kr}).

Proposed Indication:

- Maintenance of normal sinus rhythm with associated symptom relief in patients with supraventricular arrhythmias such as atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardias.
- Conversion of atrial fibrillation and atrial flutter to normal sinus rhythm.

Dosage Form: 125, 250 and 500 mcg capsules

Route of Administration: oral

Approved for Indication in the Following Countries: Dofetilide is not marketed in any country.

Date Efficacy Data Closed: 5/14/97

Resume

The sponsor conducted studies in patients with chronic atrial fibrillation and atrial flutter, paroxysmal atrial fibrillation and flutter, paroxysmal supraventricular tachycardia and ventricular tachycardia. From these studies, the following statements can be made.

- Two studies (study 345 and 120) in patients with chronic atrial fibrillation/flutter showed that dofetilide was effective in converting patients from atrial fibrillation/flutter to normal sinus rhythm (NSR) and preventing the recurrence of atrial fibrillation/flutter over a one year follow-up period.
- One study (study 372) in patients with paroxysmal supraventricular tachycardia (pSVT) showed that dofetilide lengthened the time to recurrence of symptomatic pSVT. There was, however, no effect on the time to recurrence of symptoms (irrespective of the accompanying rhythm) so it is unclear what clinical benefit is derived from this therapy in this population.
- Four (studies 119, 128, 363 and 364) studies in patients with paroxysmal atrial fibrillation/flutter (pAF/AFl) did not show a significant effect on the time to recurrence of pAF/AFl.
- In the studies of ventricular tachycardia/fibrillation, the data does not support the use of dofetilide in patients with a history of sustained ventricular tachycardia or ventricular fibrillation.

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Submissions

Date	Information
	Original NDA
6/5/98 (fax)	Study 128: patients with AF less than 24 hours
6/24/98	Study 120: ECGs
7/1/98	Study 120 and 345: ECGs
7/24/98	Study 345: Disposition of Patients
9/10/98 (Fax), 9/28/98	Study 345: Patients Randomized / Center
9/22/98 (Fax)	Study 311: Protocol
10/6/98 (Fax)	Study 119: Analysis Based on Actual Dose; patients / center
10/16/98	Study 372 information
10/30/98 (Fax)	Study 363 information
11/17/98 (fax)	Study 365: Status of patient 4190209
11/17/98	Study 128 information
11/20/98	Information for studies 119, 363, 365
12/2/98 (fax)	Study 128: status of 2 dofetilide patients
12/7/98 (fax)	Study 365: range of attacks

Abbreviations

AF = Atrial Fibrillation
AFl = Atrial Flutter
pAF/AFl = paroxysmal AF/AFl
SVT = supraventricular tachycardia
pSVT = paroxysmal supraventricular tachycardia
VT = ventricular tachycardia
VF = ventricular fibrillation
NSR = normal sinus rhythm
LV = left ventricle
bid = twice a day dosing
tid = three times a day dosing
od = once a day
CRF = case report form
ICD = implantable cardioverter defibrillator
PES = programmed electrical stimulation

Introduction

Dofetilide is an achiral molecule and has no isomeric forms. It selectively delays cardiac repolarization by inhibition of cardiac ion channels carrying the potassium current I_{kr}. By delaying repolarization, dofetilide exhibits antiarrhythmic actions (Vaughan Williams Class III) on reentrant tachyarrhythmias.

In assessing efficacy, the sponsor conducted studies in patients with chronic atrial fibrillation or flutter, paroxysmal atrial fibrillation or flutter, paroxysmal supraventricular tachycardia and ventricular tachycardia. The results from all efficacy studies in the various patient populations will be summarized. Table 1 lists the efficacy studies included in the submission sorted by the populations enrolled.

Table 1. Listing of Studies by Population Enrolled

Chronic AF/AFl	Paroxysmal AF/AFl	Paroxysmal SVT	Ventricular Tachycardia
Study 120	Study 114	Study 119*	Study 104
Study 311	Study 119*	Study 372	Study 109
Study 320	Study 128		Study 113
Study 345	Study 363		Study 308
	Study 365		Study 330
			Study 331
			Study 333
			Study 334
			Study 335
			Study 336

* patients with pSVT and/or pAF/AFl were eligible for enrollment

Studies were numbered according the phase and country in which it was performed as illustrated in Table 2. There were two exceptions to this rule. Study 127 was conducted in Belgium and some centers in Study 123 were located in Sweden.

Table 2. Study Number Descriptor

Study Number	Study Type And Location
0xx	Phase I study conducted in North America
1xx	Phase II/III study conducted in North America
2xx	Phase I study conducted in Europe
3xx	Phase II/III study conducted in Europe or Australia
400	Phase III mortality studies conducted in Denmark (DIAMOND)

During early 1994, clinical observation and pharmacokinetic study results demonstrated that renal function influenced exposure to dofetilide. An exploratory risk factor analysis suggested that body weight, gender and renal function influenced the risk of Torsades de Pointes. These findings led to introduction of a generic change in dosing regimen (in the form of protocol amendments for ongoing studies) adjusting the dofetilide dose regimen based on

creatinine clearance estimated from serum creatinine using the Cockroft Gault formula[1]. The intent of the adjustment was to normalize individual exposure to dofetilide. (A detailed discussion of the effect of renal impairment on the pharmacokinetics of dofetilide is presented in NDA Section 2.F)

The creatinine clearance amendment took effect in the first half of 1994, although the effective date of the amendment varied among the studies in progress at that time due to administrative reasons. The desired dose adjustment was to one-half of the randomized dose for subjects with estimated creatinine clearance (CLcr) of 40 to <60mL/min, and to one-quarter of the randomized dose for subjects with estimated CLcr of 20 to <40mL/min. In some ongoing studies, however, it was not possible to achieve this for all dose groups, either because the adjusted doses were less than the lowest potency dofetilide capsules available, or because the change in dose regimen would have also reduced the dose of an active comparator in a double-blind study. Table 3 gives the details of the implementation of the creatinine clearance amendment. If a subject whose dose had been adjusted because of reduced CLcr also had a change in QTc interval that required a dose adjustment, that adjustment was made from the CLcr-adjusted dose.

Table 3. Adjustments to Randomized Doses for Subjects with Reduced Creatinine Clearance as Specified by Study Protocol or Protocol Amendments (Relevant Phase II/III Studies)[a] [from H.2 Overview Of Clinical Studies]

		Adjustment (Randomized Dose → Adjusted Dose) for Subjects with Estimated Creatinine Clearance [b] of		
Study Number(s) Amendment Date	Randomized Dose Groups	40-< 60 ml/ min	20-< 40 ml/ min	<20 ml/ min
115- 120 5 April 1994 [c]	500 mcg bid 250mcg bid 125mcg bid	**Dose reduced to ½** 500mcg bid→250mcg bid 250mcg bid→125mcg bid 125mcg bid→62.5mcg bid	**Dose reduced to ¼** 500mcg bid→250mcg od 250mcg bid→125mcg od 125mcg bid→62.5mcg od	**Excluded from Study**
115- 363 18 May 1994	250mcg bid	**No adjustment**	**Excluded from Study**	**Excluded from Study**
115- 372 5 May 1994	500mcg bid	**Excluded from Study**	**Excluded from Study**	**Excluded from Study**
115- 113 5 April 1994	500mcg bid	**Dose reduced to ½** 500mcg bid→250mcg bid	**Dose reduced to ¼** 500mcg bid→250mcg od	**Excluded from Study**
115- 330 1 July 1994 115- 331 2 June 1994	500 mcg bid 250mcg bid	**Dose reduced to ½** 500mcg bid→500mcg od 250mcg bid→250mcg od	**Excluded from Study**	**Excluded from Study**
115- 335/ 336 1 July 1994	500mcg bid	**Excluded from Study**	**Excluded from Study**	**Excluded from Study**
115- 333 [d] 15 June 1994 115- 334 [d] 2 June 1994	500mcg bid	**Dose reduced to ½** 500mcg bid→500mcg od	**Excluded from Study**	**Excluded from Study**
115- 345 [c] 29 April 1994	500mcg bid 250mcg bid 125mcg bid	**Dose reduced to ½** 500mcg bid→500 mcg od 250mcg bid→250mcg od 125mcg bid→125mcg od	**Excluded from study**	**Excluded from study**
115- 400CHF, 115- 400MI [e] 1 May 1994	500mcg bid 250mcg bid (for AF)	**Dose reduced** 250mcg bid No adjustment	**Dose reduced** 250mcg od 250mcg od	**Excluded from study**

[1] Male Creatinine clearance = (140 - Age) x (weight in kg) / (72) x (serum creatinine in mg/ml).
Female Creatinine Clearance = Male Creatinine Clearance x (.85)

Table 3. (con't) Adjustments to Randomized Doses for Subjects with Reduced Creatinine Clearance as Specified by Study Protocol or Protocol Amendments (Relevant Phase II/IIII Studies)[a] [from H.2 Overview Of Clinical Studies]

		Adjustment (Randomized Dose → Adjusted Dose) for Subjects with Estimated Creatinine Clearance [b] of		
Study Number(s) Amendment Date	Randomized Dose Groups	40-< 60 ml/ min	20-< 40 ml/ min	<20 ml/ min
Studies initiated after 1Q94 (Dose adjustments included in original protocol)				
115- 119	375mcg bid 250mcg bid	**Dose reduced** 375mcg bid→250mcg bid 25mcg bid→125mcg bid	**Dose reduced** 375mcg →250mcg bid 250mcg →125mcg bid	**Excluded from study**
115- 128	500mcg bid	**Dose reduced to ½** 250mcg bid	**Dose reduced to ¼** 250mcg od	**Excluded from study**
115- 365	500mcg bid	**Dose reduced to ½** 500mcg bid→250mcg bid	**Dose reduced to ¼** 500mcg bid→250mcg od	**Excluded from Study**

a: Dose reductions required by the protocol for subjects with specified increases of QTc from baseline were made from the randomized dose adjusted for creatinine clearance.
b: Creatinine clearance was estimated using the Cockroft- Gault formula.
c: Amendment effective as of the amendment date, except for studies 120 (12 Apr 94), and 330 and 331 (1 Jul 97).
d: All subjects in Studies 333 and 345 were enrolled after the protocol was amended.
e: 115- 400CHF and 115- 400MI are not included in the combined database for the safety summary (NDA Section 2. H. 6).
f: AF = subjects with atrial fibrillation at baseline

This review will provide a brief summary of the clinical efficacy studies (Efficacy Summary) followed by reviews for each individual trial. Tables and figures in this review are numbered according to the study number for which they pertain (e.g., tables pertaining to study 120 will be numbered starting with Table 120.1). Clinical pharmacology studies (pharmacodynamic or pharmacokinetic) involving intravenous or oral dosing and the safety review of the clinical trials are summarized in a separate review. In the description of the clinical trials, it is important to note that various populations of patients are included in the statistical analyses. For the purpose of this review, an intent to treat analysis includes all patients randomized to treatment. It does not suggest that subjects were followed for the entire follow-up period if they discontinued therapy for reasons other than reaching a study endpoint. In fact, none of the studies continued to collect endpoint data for patients who discontinued prematurely. Patients who discontinue therapy prematurely for any reason other than achieving a study endpoint are censored in the analysis at the time of premature discontinuation[2]. This deviates somewhat from what typically occurs in the intent to treat analysis of clinical trials that include mortality as an endpoint[3]. All of the studies included an initial hospitalization period during which study drugs were initiated. This permitted close observation of the patients for evidence of QTc prolongation or evidence of a proarrhythmic effect. In the studies that had a chronic therapy phase, patients were discharged from the hospital and followed as outpatients. The primary analyses in some of these trials included only the patients who completed the in-hospital phase. In this review, this population is referred to as the Maintenance therapy population or, in some cases, the steady state population.

It is also important to note that in some of the trials, patients were given a Hertcard recording device to wear during double-blind treatment as outpatients. This device allows patients to record an ECG during symptoms which they believe are consistent with their underlying arrhythmia. This recording can be analyzed to determine whether a patient experienced a recurrence of their underlying abnormal rhythm.

[2] This is consistent with the types of analysis performed in the past for trials evaluating supraventricular arrhythmias.
[3] In trials with mortality as an endpoint, patients withdrawn prematurely from randomized therapy are followed until the trial is completed or pre-specified period of follow-up is completed. They are not censored at the time of premature discontinuation.

Efficacy Summary

The sponsor has conducted studies in populations with supraventricular or ventricular arrhythmias. In the studies of chronic atrial fibrillation/atrial flutter, the primary focus was on the documentation (by ECG recording) of recurrence of atrial fibrillation or flutter after conversion to NSR without documentation of symptomatic improvement attributable to a particular therapy. In the studies of paroxysmal AF/AFl or paroxysmal SVT, the goal of therapy was to delay or increase the time to symptomatic recurrence (symptoms + ECG documentation). In the studies of ventricular arrhythmia, the goal was to prevent the induction of VT by PES or to delay the time to recurrence of VT requiring cardioversion by a ICD.

Chronic Atrial Fibrillation or Atrial Flutter

The sponsor conducted four studies that enrolled patients with chronic atrial fibrillation. Two studies (study 311 and 320) randomized fewer than 100 patients and neither was designed to provide a significant contribution to the determination of efficacy in this population. Both studies did, however, contribute to the knowledge that the dofetilide 750 mcg bid dose had an unacceptable risk for proarrhythmia. Although not sufficiently powered to provide efficacy data, the results from study 311 did suggest that dofetilide might prevent relapse of chronic AF/AFl. The remaining two studies (study 120 and 345) are the principle studies designed to document efficacy in patients with chronic atrial fibrillation.

Table ES.1 compares the design features of study 120 and study 345. The studies were similar in design. They were randomized, double blind, placebo controlled and each included a conversion phase and a maintenance phase. Study 120 was conducted in the U.S. and Canada. Study 345 was conducted in Europe. During the conversion phase, subjects were hospitalized and randomized to therapy. If after 5 doses of therapy they had not converted to NSR, they underwent DC cardioversion. Subjects who failed to convert to NSR[4] did not enter the maintenance phase. The definition for successful conversion differed between the two studies. To enter the maintenance phase, subjects had to remain in NSR for 24 hours in study 120 but only one hour in study 345. Both studies randomized subjects to the same dofetilide dosage regimens and a placebo group. Study 345 also included a sotalol 80 mg bid dose group. In both studies, dose was adjusted based on calculated creatinine clearance. The primary endpoint for both studies involved the proportion of patients remaining in NSR at various timepoints during the maintenance phase. Both studies utilized a Kaplan-Meier plot for estimation of the proportion and a Logrank analysis. A relapse required documentation of AF/AFl for 24 hours.

Table ES.1. Comparison of the Designs for Studies 120 and 345.

	Study 120	Study 345
Study Dates	2/16/93 - 10/24/96	5/3/94 - 1/15/97
Location	U.S. and Canada	Europe
Design	• r, db, pc, p, mc • In-patient conversion phase and out-patient maintenance phase.	• r, db, pc, p, mc • In-patient conversion phase and out-patient maintenance phase.
Treatment Groups	• Dofetilide 125 mcg bid • Dofetilide 250 mcg bid • Dofetilide 500 mcg bid • Placebo Dose Adjustment based on calculated creatinine clearance.	• Dofetilide 125 mcg bid • Dofetilide 250 mcg bid • Dofetilide 500 mcg bid • Sotalol 80 mg bid • Placebo Dose Adjustment based on calculated creatinine clearance.
Total Randomized	325	671
Maintenance Phase Duration	1 year	1 year [B]
Inclusion Criteria	Chronic atrial fibrillation of 2 weeks to 6 months duration.	Chronic atrial fibrillation of 1 week to 2 years duration
Criteria for Entering Maintenance Phase	Maintain NSR for 24 hours.	Maintain NSR for 1 hour.

[4] Conversion by pharmacologic therapy or DC conversion

Table ES.1. Comparison of the Designs for Studies 120 and 345.

	Study 120	Study 345
Determination of Endpoint	Detection AF/AFl by ECG at scheduled or unscheduled visit	Detection AF/AFl by ECG at scheduled or unscheduled visit
Primary Endpoint	• Proportion of patients in NSR at 6, 9 and 12 months [A] • Frequency and severity of symptoms	• Proportion of patients in NSR at 3, 6, 9 and 12 months [C]
Definition of AF/AFl Recurrence	Required documentation of AF/AFl for at least 24 hours.	Required documentation of AF/AFl for at least 24 hours. (see p. 36 for all criteria)
Primary Analysis	• Included all randomized patients	• Included only patients entering maintenance phase
Secondary Endpoints	• Exercise Substudy • Time to recurrence of AF/AFl • Proportion patients converting to NSR on Rx • Number and energy of shocks for conversion to NSR	• Ten secondary endpoints specified

[A] = the study was powered based on the 6 month analysis
[B] = optional 15 month follow-up permitted
[C] = the study was powered based on the 12 month analysis

Both studies enrolled similar populations with regard to age, sex and race. Racial groups other than Caucasians were grossly underrepresented in both studies. Males accounted for the majority of subjects in both trials. Table ES.2 shows the demographic characteristics for studies 120 and 345.

Table ES.2. Demographics for Study 120 and Study 345.

	Study 120	Study 345
Mean Age	67 years	64 years
Caucasians	92%	99.7%
Males	84%	70%
Structural Heart Disease [A]	67%	50%
AF	85%	89%

[A] A subject was defined as having structural heart disease if any of the following were recorded on the medical history section as being 'present now' or 'once present, now inactive': congestive heart failure, myocardial infarction (old), ischemic heart disease, valvular heart disease, dilated cardiomyopathy, obstructive cardiomyopathy.(study 345 also included patients with PDA, coarctation of the aorta, myocarditis, pericarditis)

Proportion of Patients Remaining in NSR

Both study protocols proposed to compare the proportion of patients remaining in NSR for each treatment group at several timepoints without specifying any adjustment in the p value to account for multiple comparisons. Any method chosen to make adjustments after the completion of the study would be arbitrary. In both protocols, the study sample sizes were calculated based on the placebo recurrence rates at a single timepoint Because of this, it has been assumed that the primary analysis for each study will focus on the timepoint used to calculate the sample size, 6 months for study 120 and 12 months for study 345.

Table ES.3 compares the primary efficacy analysis for study 120 and 345. For study 345, there was a significant difference between dofetilide and placebo. All dofetilide treatment groups were significantly superior to placebo (p values range from .029 to .0001; see table 345.5). The primary analysis compared the effect of therapy only in the patients entering the maintenance phase. If all randomized patients are analyzed, the results are the same.

The primary analysis for study 120 yielded a p value of 0.12.

Table ES.3. Primary Efficacy Analysis for Study 120 and Study 345

	Study 120				Study 345				
Population in Analysis	All Randomized				Maintenance				
Timepoint	6 months				12 months				
Treatment Groups	Dofetilide			placebo	Dofetilide			sotalol	placebo
Dose Strength	125	250	500		125	250	500	80	
# Randomized	82	82	77	84	135	133	129	137	137
# in Analysis Population	82	82	77	84	103	118	100	108	106
Probability of Remaining in NSR ^ at Timepoint	.32	.37	.50	.30	.30	.46	.51	.39	.16
Logrank p value	.12				.0001				

^ based on Kaplan-Meier estimate

If study 120 is judged solely by the protocol specified primary analysis, it does not achieve statistical significance. This does not preclude further interpretation of the data in study 120 to determine whether the results are different from the observations of study 345. Table ES.4 lists alternative analysis to the primary analysis. The first analysis compares treatments for all randomized patients over a 12 month period and second analysis compares the maintenance population over a 12 month period (this is the same analysis as the primary analysis for study 345). When the duration of follow-up is extended to 12 months, the analysis yields a p value of .035. When the duration of follow-up is extended to 12 months and the analysis population is only those patients entering the maintenance period, the analysis yields a p value of 0.011. An analysis of the maintenance population at 6 months yields an overall p value of .062. These results appear to be supportive of the findings of study 345.

Table ES.4. Alternative Efficacy Analysis for Study 120

	Study 120				Study 120			
Population in Analysis	All Randomized				Maintenance			
Timepoint	12 months				12 months			
Treatment Groups	Dofetilide			Placebo	Dofetilide			Placebo
Dose Strength	125	250	500		125	250	500	
# Randomized	82	82	77	84	82	82	77	84
# in Analysis Population	82	82	77	84	60	61	62	68
Probability of Remaining in NSR ^ at Timepoint	.29	.28	.47	.20	.40	.37	.58	.25
Logrank p value	.035				.011			

^ based on Kaplan-Meier estimate

Because subjects withdrawn prematurely from the study are censored in the analysis, the Kaplan-Meier estimates most likely overstate the actual probability of remaining in NSR at a specified point in time. In the worst case scenario, it could be assumed that all patients prematurely discontinuing therapy relapsed back into atrial fibrillation. If this was the case, then the proportion completing the pre-specified follow-up without relapsing into atrial fibrillation would provide the worst case estimate. Table ES.5 compares the proportion completing 351 days of follow-up in NSR with the Kaplan-Meier estimates. In both studies, the dofetilide 500 mcg group maintained NSR in 44 - 47% of the patients compared to 14 - 21% of placebo patients.

Table ES.5. Comparison of the Proportion Completing the Study in NSR with the Kaplan-Meier Estimates at One Year (Maintenance Population)

	Study 120				Study 345				
Treatment Groups	Dofetilide			placebo	Dofetilide			sotalol	placebo
Dose Strength	125	250	500		125	250	500	80	
# in Analysis Population	60	61	62	68	103	118	100	108	106
Proportion Completing 1 Year of Follow-up in NSR	.28	.21	.44	.21	.24	.43	.47	.30	.14
Probability of Remaining in NSR ^ at 1 year	.40	.37	.58	.25	.30	.46	.51	.39	.16

^ based on Kaplan-Meier estimate

The effectiveness of dofetilide 125 mcg and 250 mcg is less than 500 mcg in both studies. In study 345, the effect of 250 mcg compared favorably with 500 mcg (.46 vs. .51; Kaplan-Meier Estimate of probability of remaining in NSR at 12 months). In study 120, the effect of 250 mcg compared less favorable to 500mcg (.37 vs. .58; Kaplan-Meier Estimate of probability of remaining in NSR at 12 months).

Subgroup Analysis

The studies were homogenous with regard to race in that few non-Caucasians were enrolled. Most subjects were male (84% and 70%). Table ES.6 shows the proportion of patients relapsing into AF/AFL based on sex and age.

Table ES.6. Proportion of Patients Relapsing at 1 Year Based on Age and Sex

	Study 120				Study 345				
Treatment Groups	Dofetilide			placebo	Dofetilide			sotalol	placebo
Dose Strength	125	250	500		125	250	500	80	
# in Analysis Population	60	61	62	68	103	118	100	108	106
All Patients	.57	.57	.38	.72	.58	.47	.32	.45	.76
Females	.55	.50	.36	1.00	.58	.51	.39	.46	.70
Males	.57	.59	.38	.67	.58	.47	.32	.45	.78
< 65 yrs.	.58	.67	.50	.67	.67	.39	.29	.47	.78
≥ 65 yrs.	.56	.53	.32	.74	.50	.51	.34	.43	.74

Conversion from AF/AFl to NSR

Both studies show that dofetilide 500 mcg bid was effective in converting patients from chronic atrial fibrillation to NSR. In both studies, the conversion rate was approximately 30%. The dofetilide 250 mcg and 125 mcg groups, although numerically superior to placebo, convert only 10% and 6% of subjects respectively. In both studies, placebo converted fewer than 2% of subjects.

Table ES.7. Percentage of Patients Converting to NSR in Study 120 and 345.

	Study 345	Study 120
placebo	1.5%	1.2%
dofetilide 125 mcg	5.9%	6.1%
dofetilide 250 mcg	10.5%	9.8%
dofetilide 500 mcg	29.5%	29.9%
sotalol 80 mg	5.1%	-

Secondary Endpoints

There are secondary endpoints for the studies that are described in the reviews of the individual studies. There are several, however, that are worth mentioning. In study 120, an exercise substudy was performed (study 120x). Without going into great detail, 56 patients at designated centers performed exercise testing at baseline, after attempted conversion and at 2 months post-conversion. The substudy was not designed to show a difference among treatment groups but to show that maintaining NSR was beneficial compared to the alternative, remaining or relapsing into

AF/AFl. The data shows that the exercise time increased in the patients maintaining NSR at 2 months. An analysis was planned that compared patients remaining or relapsing to AF/AFl with those in NSR at 2 months. Unfortunately, there was a failure to perform exercise tests in the patients who relapsed or remained in AF/AFl so an adequate comparison could not be performed. The analysis does not support an improvement in exercise duration.

Quality of life and symptom score analyses were reported in study 345 and 120 respectively. Neither was able to show a treatment effect. The sponsor conducted analyses (pre-specified) of symptom scores in study 120 that compared the scores of patients remaining in NSR with those who relapsed to AF/AFl. There are several difficulties in the interpretation of the results of this endpoint. First, the majority of patients had either no symptoms or mild symptoms at baseline. As a consequence, it is difficult to improve symptom scores and one can only hope that patients who relapsed worsen their score. Second, the symptom severity was measured by categories (none, very mild, mild, moderate, severe, very severe were given scores or 0 - 5). The sponsor has assigned a numerical value each category and performed analyses based on changes of central tendency (e.g. mean). It can be argued that categorical analyses are more appropriate. Third, the end result is a change in symptom scores of values less than one. These are clinically not interpretable. A categorical analysis[5] yielded nominal p values less than .05 for some of the symptoms (see Table 120.21 on page 32).

Paroxysmal Atrial Fibrillation/Flutter

There were four primary studies performed in patients with paroxysmal atrial fibrillation[6] (Studies 119, 128, 363 and 365). All were randomized, parallel, double-blind, placebo controlled studies in patients with a history of paroxysmal atrial fibrillation/atrial flutter [7]. Study 119 and 128 were conducted in the United States while studies 363 and 365 were conducted in Europe. All had a follow-up period of 24 - 26 weeks except for study 128. In study 128, patients could have follow-up as short as 12 weeks. The primary endpoint was the same for all studies: time to recurrence of symptomatic AF/AFl [8]. Table ES.8 outlines the study designs.

Table ES.8. Summary of Design of Studies in Patients with pAF/AFl.

	119	128	363	365
Study Dates	6/94 - 10/96	2/96 - 2/97	7/94 - 6/96	2/96 - 12/96
Population	pAF/AFl and pSVT	pAF/AFl		
Location	USA	USA	France	Europe
Design	r, db, pc, p	r, db, pc, p	r, db, pc, p	r, db, pc, p
Treatment Groups (N)				
Placebo	111	129	50	89
Dofetilide 500 mcg bid	-	132	-	181
Dofetilide 375 mcg bid	105	-	-	-
Dofetilide 250 mcg bid	100	-	48	-
Quinidine 300 mg bid	-	-	57	-
Total Randomized	316	261	155	270
Maintenance Phase Duration	6 month	12 wks. +	24 weeks	24 weeks
Primary Endpoint	time to recurrence of symptomatic pAF/AFl or pSVT	time to recurrence of symptomatic pAF/AFl		

Table ES.9 shows the probability of remaining attack free based on Kaplan-Meier estimates. There were no significant differences between dofetilide and placebo in any of the studies. The studies do not support the efficacy of dofetilide in the treatment of pAF/AFl.

[5] Chi-Square
[6] study 119 also enrolled patients with paroxysmal supraventricular tachycardia
[7] Study 128 also enrolled patients with pSVT.
[8] Study 128 also enrolled patients with pSVT. In pSVT patients, the recurrence of symptomatic pSVT defined an event.

Table ES.9. Probability of Remaining Attack Free Based on Kaplan-Meier Estimate

	Study 119	Study 128	Study 363	Study 365
Placebo	.30	.42	.34	.28
Dofetilide 500 mcg bid	-	.47	-	.34
Dofetilide 375 mcg bid	.42	-	-	-
Dofetilide 250 mcg bid	.27	-	.44	-
Quinidine 300 mg bid	-	-	.49	-
P value	0.2	0.4	0.73 ^A	0.3

^A for comparison of dofetilide to placebo

Paroxysmal Supraventricular Tachycardia

Two studies randomized patients with a history of pSVT (studies 372 and 119). Study 372 was a randomized, double-blind, placebo controlled, multi-center study conducted in Poland. Patients with pSVT were randomized to dofetilide 500 mcg bid (n = 40), propafenone 150 mg tid (n = 41) or placebo (n = 41). The subjects were predominately female, < 65 years of age (mean age 48) and Caucasian (100%). The primary endpoint was the time to symptomatic pSVT during 6 months of treatment. Table ES.10 shows the probability of remaining attack free at 6 months. There was a significant difference between dofetilide and placebo.

Table ES.10. Probability of Remaining Attack Free at 6 Months.

	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 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.

The primary reason to treat patients with pSVT is the need to reduce symptoms. If just symptoms are assessed (regardless of the underlying rhythm), there is no benefit with dofetilide therapy (see table 372.5 in the review of study 372, page 81).

In study 119, patients with pSVT, along with patients with pAF/AFl, were randomized to dofetilide 375 mcg bid, dofetilide 250 mcg or placebo. Of the 293 patients entering steady state, only 52 had pSVT. Because of the small number of patients with pSVT, study 119 does not provide sufficient support for study 372. In the pSVT patients, the probability of remaining attack free was .60, .54 and .67 for the dofetilide 375 mcg, dofetilide 250 mcg and placebo groups respectively.

Ventricular Tachycardia

Ten studies were conducted in patients with a history of ventricular tachycardia and or inducible sustained ventricular tachycardia by PES. Some of the studies included a phase during which intravenous dofetilide was infused. Eight of the ten enrolled fewer than 100 patients. Studies 113 and 333 were the primary studies. Table ES.11 outlines the designs of the studies 113 and 333.

ES.11. Summary Table for Study 113 and 333.

	Study 113	Study 333
Design	r, db, p, pc, mc, 12 month Rx period	r, db, mc, acute phase co, 12 month Rx in responders in the acute phase
Population	Hx of sustained and/or inducible ventricular tachycardia/fibrillation implanted with a cardioverter defibrillator (ICD)	Hx of ischemic heart disease and inducible sustained ventricular tachycardia
Location	USA	Europe
# Randomized	174	135

ES.11. Summary Table for Study 113 and 333.

	Study 113	Study 333
Treatments		
Placebo	87	
Dofetilide 500 mcg bid	87	132 [A]
Sotalol 80 mg bid		131 [A]
Primary Endpoint	time to first recurrence of VT or VF requiring ICD cardioversion	Prevention of induction of VT by PES.

[A] crossover study; r = randomized, db = double-blind, p = parallel, pc = placebo controlled, mc = multi-center, co = crossover, Hx = history, Rx = treatment

In study 113, there was no significant difference (p = .99) in the probability of remaining attack free at 12 months between placebo (probability = .32) and dofetilide (probability = .27). In study 333, there was no difference between dofetilide and sotalol in the proportion of patients who had the induction of VT prevented.

Studies In Patients With Chronic Atrial Fibrillation Or Atrial Flutter

Study #	Description	Treatments	N	Primary Endpoints	Page
120	• r, db, pc, p, 1 year Rx • conversion and maintenance phase • USA and Canada • 2/16/93 - 10/24/96	Placebo Dofetilide 500 mcg bid Dofetilide 250 mcg bid Dofetilide 125 mcg bid Total	84 77 82 82 325	• proportion of patients in NSR at 6 months • proportion of patients in NSR at 9 and 12 months • frequency and severity of symptoms	13
120X	• substudy of study 120 • modified Naughton protocol at baseline, post conversion, day 30 and 60	Placebo Dofetilide 500 mcg bid Dofetilide 250 mcg bid Dofetilide 125 mcg bid Total	13 16 14 13 56	• change in exercise time between patients remaining in NSR and those in AF/AFl at 2 months • change from baseline in exercise time	13
345	• r, db, pc, p, 1 year Rx • conversion and maintenance phase • Europe • 5/3/94 - 1/15/97	Placebo Dofetilide 500 mcg bid Dofetilide 250 mcg bid Dofetilide 125 mcg bid Sotalol 80 mg tid Total	137 129 133 135 137 671	• proportion of patients in NSR at 3, 6, 9 and 12 months	34
311	• r, db, pc, p, 3 month Rx, pilot study • Netherlands • optional db continuation (study 311A) • 4/91 - 1/93	Placebo Dofetilide 750 mcg bid Dofetilide 500 mcg bid Dofetilide 250 mcg bid Total	20 21 21 21 83	• safety and toleration	48
320	• r, db, pc, p, 3 month Rx • United Kingdom • 6/15/92 - 5/3/93	Placebo Dofetilide 750 mcg bid Dofetilide 500 mcg bid Total	11 12 12 35	• time to reoccurrence of AF/AFl	49

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

Study 120/120X.
Study Dates: 2/16/93 - 10/24/96

Protocol

The protocol was submitted to the FDA on June 7, 1993 (IND [redacted]). There were three amendments to the protocol in August 1993 (serial #65), March 1994 (serial # 81) and April 1994 (serial #86). The primary protocol is designated Study 120. An exercise substudy is designated Study 120X.

Design

This was a multi-center, double-blind, randomized comparison of three different dose levels of oral dofetilide (125, 250 and 500 mcg bid) and placebo in subjects who had a history of persistent atrial fibrillation/flutter for two weeks to 6 months from the time of the original diagnosis. The study was to recruit 300 subjects and had two main parts: 1. Conversion Phase. Dosing of randomized therapy was initiated in-hospital, and pharmacological conversion was evaluated. Subjects not converting pharmacologically by Day 3 were electrically cardioverted. Those for whom electrical or pharmacological cardioversion was not achieved were discontinued. 2. Maintenance Phase. Those who achieved stable sinus rhythm for 24 hours were discharged from the hospital on double-blind therapy and entered into the Maintenance Phase. The maintenance of normal sinus rhythm (NSR) was monitored for up to one year.

The study was preceded by a run-in period, during which subjects received anticoagulation therapy[9]. A subset of 48 subjects were to participate in Study 120X and have exercise tolerance testing performed.

[9] Warfarin at a dose adjusted to prolong the prothrombin time to create an international normalized ratio (INR) of 2.0-4.5 (prothrombin time ratio 1.3-1.8 x control using conventional rabbit brain thromboplastin reagent) for a minimum of two weeks. A protocol amendment in July 1993 allowed the ratio to be adjusted according to local practice. Anticoagulation therapy was to be continued for a minimum of 3-4 weeks after sinus rhythm was established, but could be continued throughout the trial, according to local practice. Subjects with lone atrial flutter were not required to have anticoagulation therapy.

During the Conversion Phase, subjects were to remain hospitalized and on a cardiac monitor for the entire in-hospital period which was to last a minimum of three days to ensure that subjects had received at least five doses of double-blind study drug. Subjects who had not converted to NSR by Day 3, and who had received a minimum of 5 doses of study drug, were to be electrically cardioverted. If neither pharmacological nor electrical cardioversion was achieved in a subject, the subject was to be discontinued. Subjects who converted to NSR on double-blind study drug or by cardioversion were to have an echocardiogram on the day of conversion. They were to remain hospitalized for an additional 24 hours after sinus rhythm had been established before being discharged from the hospital on Day 4.

In order to continue into the Maintenance Phase, patients had to maintain a NSR for at least 24 hours. During the Maintenance Phase, subjects were scheduled to return to the clinic at Days 14, 30, 60, and 90, and at 90 day intervals thereafter until planned completion of one year of study drug therapy. Patients could be seen at other times based on symptoms suggestive of an arrhythmia or because of adverse events. At these visits, subjects were to have a cardiopulmonary exam and the rhythm status was to be determined and documented by an electrocardiogram. Safety assessments[10] were to be made and plasma samples drawn for measurement of dofetilide plasma concentrations. In addition, an echocardiogram was to be recorded after 60 days of double-blind therapy. Subjects who relapsed to AF/AFl for at least 24 hours, as documented by ECG, were considered to have reached their clinical endpoint. These subjects were to be given their termination visit evaluations and recorded as having completed the study.

By an amendment to the protocol in July 1993, subjects were also to be asked, at all visits, to complete a questionnaire on symptoms likely to be associated with AF/AFl. Between visits, subjects were to be asked to complete the same questionnaire at two week intervals and mail the questionnaire back to the site. (The investigator/study coordinator was to make every effort to follow-up with phone calls on subjects who did not mail in their questionnaires.)

For subjects participating in the exercise substudy (120X), treadmill exercise testing was to be performed at screening (training only), baseline (in AF/AFl), 1-3 days post cardioversion (in NSR), Day 30 (in NSR), Day 60 (in NSR), and at the termination visit (in NSR or AF/AFl). The exercise protocol was to be a Naughton Protocol modified to include one additional increment between stages II and III of the standard protocol.

The following flowchart illustrates the procedures performed during the study (Table 120.1).

Table 120.1. Flowchart of Procedures Performed in Study 120.

	Run-in		In-hospital Phase (days)				Maintenance Phase (days)							
	-14	-7	0	2	3	4	14	30	60	90	180	270	360[A]	Unpd.
Medical History	x													
Physical Exam	x		x[B]										x	
Cardiac Exam	x		x[B]	x	x	x	x	x	x	x	x	x	x	x
ECG	x		x[B,C]	x	x	x	x	x	x	x	x	x	x	x
Cardioversion					x									
Warfarin Dosing	x	x	x	x	x	x	x[D]	x[D]	x	x	x	x	x	x
Dosing			x	x	x	x	x	x	x	x	x	x	x	
Echocardiogram		x			x[E]									
Laboratory Tests	x	x[F]	x[B]				x	x	x	x	x	x	x	x
Questionnaire [G]							x	x	x	x	x	x	x	x
Investigator Symptom Assessment							x	x	x	x	x	x	x	x
Plasma Sample			x[C]	x	x		x	x	x	x	x	x	x	x
Adverse Reaction			x	x	x	x	x	x	x	x	x	x	x	x

[A] 360 days or at discontinuation. [B] Pre-dose. [C] 2 - 3 hours after the first dose. [D] Warfarin dosing should be continued at least 3 or 4 weeks, or throughout the trial according to local practice. [E] after sinus rhythm established. [F] only potassium .

[G] At all visits, patients will be asked to complete a questionnaire on symptoms likely to be associated with atrial fibrillation or flutter. Between visits, patients are asked to complete the same questionnaire at two week intervals and mail the questionnaire back to the site. The investigator/study coordinator will make every effort to follow-up with telephone calls on patients who do not mail in their questionnaire at the specified time point between the visits (see flow chart II). If patients experience a substantial change in the severity and/or frequency of symptoms, they will be instructed to come to the clinic for an unplanned visit to evaluate their main rhythm and a possible relationship between the rhythm and the symptoms.

Unpd. = unplanned

[10] adverse reactions recorded and laboratory safety tests

Inclusion Criteria

- Males, and females of non-childbearing potential (at least 2 years post-menopausal or surgically sterilized).
- Age 18 to 85 years.
- Written informed consent.
- History of chronic, persistent atrial fibrillation/flutter documented by ECG for a minimum of two weeks up to 6 months from the time of the original diagnosis, excluding transient, self-limited atrial fibrillation/flutter (e.g. post traumatic).
- Documentation of atrial fibrillation/flutter (by ECG) at baseline prior to electrical or pharmacological conversion to sinus rhythm.

Exclusion Criteria

- Pregnant women and women of childbearing potential.
- Inability to tolerate withdrawal from current anti-arrhythmic therapy.
- History of undiagnosed cause of syncope in the six months preceding the study.
- Active thyrotoxicosis or atrial fibrillation/flutter resulting from other reversible non-cardiac diseases (e.g. pericarditis or alcohol intoxication).
- Uncompensated or rapidly progressive congestive heart failure.
- Myocardial infarction or unstable angina pectoris within the preceding 1 month or PTCA within the preceding 3 months.
- Cardiac surgery within the preceding 2 months.
- Significant abnormalities of the sinus node (including sick sinus syndrome) or atrio-ventricular block greater than first degree, unless treated with a proper functioning pacemaker.
- ECG intervals exceeding the following limits in the drug-free state and in the absence of pre-excitation syndrome and BBB: QRS >180 msec, QT or QTc > 440 msec. In the case of BBB, QT or QTc was not to exceed 500 msec (Note: For QT or QTc measurements, whichever was greater had to be used). RR interval greater than 3.5 seconds, ventricular rate of less than 50 beats/minute (12 lead ECG). Systolic blood pressure < 90 mm Hg, or diastolic blood pressure >110 mm Hg (or > 105 mm Hg for Canadian Centers after January 1994 protocol amendment).
- Major hematologic, pulmonary, hepatic, or renal disease (serum creatinine > 2.5 mg/dl or, after April 1994 protocol amendment, calculated creatinine clearance < 20 ml/min).
- Serum potassium < 4.0 mEq/L or > 5.5 mEq/L, or serum magnesium <1.5 mEq/L or > 2.5 mEq/L. Serum potassium was to be determined three times prior to entry into the study (at screening, 1 week prior to entry, and immediately prior to entry into the study).
- Concomitant therapy with: other anti-arrhythmic agents, verapamil, diltiazem, diuretics (unless serum potassium was within the limits specified above), antihistamines, tri-cyclic antidepressants, anticonvulsants, or phenothiazines. Therapy with digoxin was allowed provided the dosage was kept constant throughout the study.
- After the April 5, 1994 protocol amendment, subjects on cimetidine were also excluded. However, low doses of other H_2 blockers were permitted.
- Amiodarone blood level > 0.3 mcg/ml.
- History of polymorphic ventricular tachycardia associated with the use of antiarrhythmic drugs or with other classes of drugs known to prolong the QT or QTc interval.
- Patients with known substance abuse/dependency (i.e. alcohol, controlled drugs, etc.), or inability to give informed consent.
- Therapy with another investigational drug within one month prior to entry or concomitantly with this study.
- Participation in a previous dofetilide study.

For subjects participating in the exercise substudy (120X), the following two exclusion criteria were additionally applied:

- Any clinical conditions which, in the investigator's opinion, significantly interfered with the subject's ability to exercise on a treadmill (neurologic, muscular, orthopedic, vascular or pulmonary disorder) and could prevent the detection of changes secondary to an improvement in cardiac function.
- Patients with exercise duration of less than 2 minutes or greater than 90% of the normal exercise capacity of an age matched active population of males at baseline.

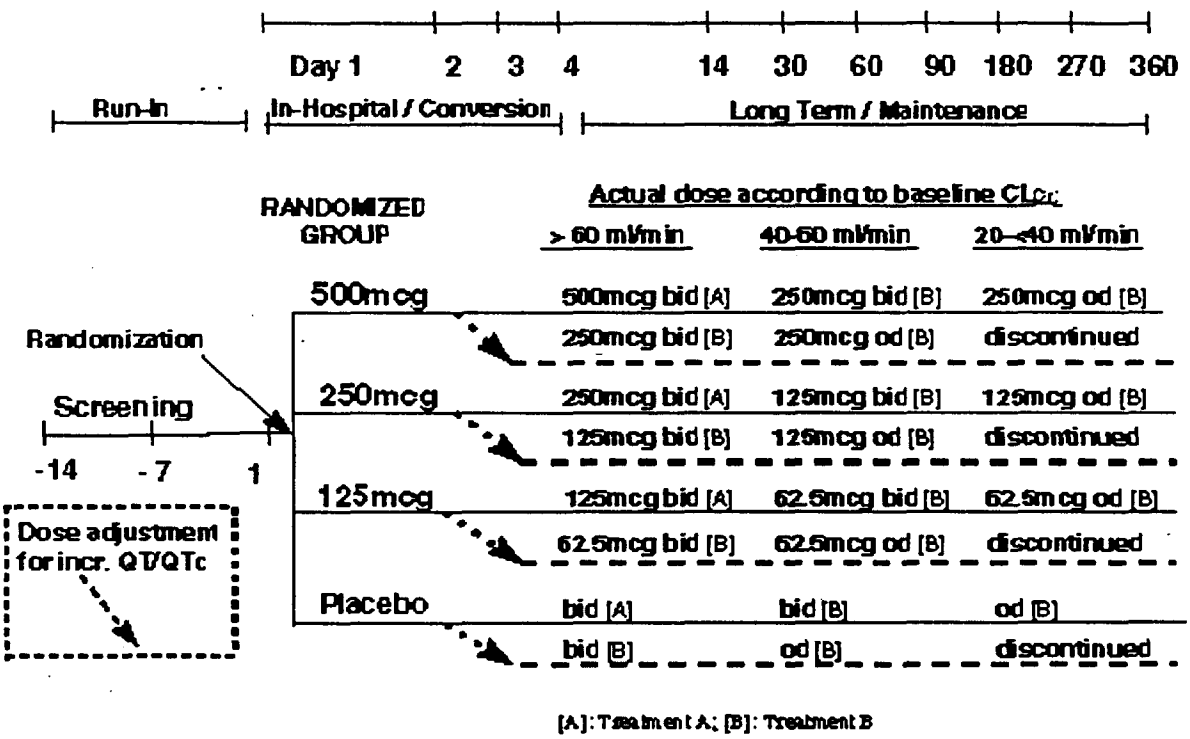
Dose Groups

Subjects were to be randomized to one of four groups: dofetilide 500 mcg bid, dofetilide 250 mcg bid, dofetilide 125 mcg bid, or placebo. Two to three hours after the first dose of double-blind medication, an ECG was to be recorded and a plasma sample taken. The QT/QTc interval was to be calculated (averaged over 10-15 beats for subjects in AF/AFl), and compared to the baseline QT/QTc. If there was an increase in the QT/QTc in excess of 15%, the subject's dose was to be adjusted to the next lower dose level. The QT/QTc was to be measured after subsequent dosing, but no further dose adjustments were to be made. If, at any time during the study, the QT/QTc was > 550msec or > 25% greater than baseline, the subject was to be discontinued from the study.

After the April 1994 protocol amendment, the actual starting dose of study drug was to be adjusted according to the subject's calculated creatinine clearance. By providing study drug as treatment A (500, 250, 125mcg) and treatment B (250, 125, 62.5mcg) it was possible to make adjustments in a double-blinded manner. Figure 120.1 shows the dosing algorithm for each treatment group based on creatinine clearance and adjusted for QT/QTc prolongation after dosing. Within a treatment group, there could several different dose regimens to which a patient was randomized. For example, in the Dofetilide 500 mcg bid treatment group the total daily dose could range from 1000 mg (500 mg bid) to 250 mg (250 mg OD).

In addition to the randomized therapy, patients received warfarin at a dose adjusted to maintain an international normalized ratio (INR) between 2.0 and 4.5 for at least 2 weeks prior to attempted cardioversion. After conversion, anticoagulation was continued based on local practices but at a minimum of 3 - 4 weeks.

Figure 120.1. Flow Diagram of Dose Adjustments During the Conversion Phase



Endpoints

The primary endpoints included:

- Proportion of patients in sinus rhythm at 6 months of double-blind therapy for all treatment groups (based on Kaplan-Meier survival function).

- Proportion of patients in sinus rhythm at 9 and 12 months of double-blind therapy for all treatment groups (based on Kaplan-Meier survival function).
- Frequency and severity of symptoms.[added with the July 1993 protocol amendment]

The secondary endpoints included:

- Time to recurrence of chronic atrial fibrillation/flutter for all treatment groups.
- Proportion of patients converting to sinus rhythm due to double-blind treatment.
- Number and energy of shocks for conversion to sinus rhythm at baseline.
- Non-invasive hemodynamic parameters using echocardiography and atrial dimensions and other functional parameters day -7, day 0 and after 2 months.

The endpoints for the exercise substudy include:

- (Primary Endpoint) Change in exercise duration, when compared to baseline while in AF, after 2 months of NSR.
- (Primary Endpoint) Comparison of the change in exercise duration after 2 months in NSR with the change in exercise duration in patients failing to convert or relapsing earlier than 2 months.
- Time-dependent effects on the change in exercise duration after conversion to NSR and correlation with changes in echocardiographic indices of cardiac function.
- Impact of relapse in AF on exercise duration in patients who remained in NSR at least 2 months.
- Health-related quality of life in NSR or in AF.
- On an intention to treat basis, and carrying forward the last value of exercise duration assessed, the difference in exercise duration at 2 months and at 12 months among the dofetilide and placebo groups.

Statistical Analysis

The sample size was projected to be 75 per treatment group. This was calculated based on a power of 80%, α = .05, 30% of the placebo patients remaining in sinus rhythm and 55% of the dofetilide patients remaining in sinus rhythm after 6 months of treatment.

The primary hypothesis tested is that the proportion of patients remaining in sinus rhythm at six months is different among the four treatment groups. The survival distributions were to be estimated using the Kaplan-Meier method. A log rank test was to be used to test the null hypothesis that the survival probabilities of the treatment groups up to six months are equivalent.

An unblinded interim analysis was permitted when 150 subjects had been followed for 6 months. The trial could not be stopped for efficacy at this interim analysis.

Efficacy Results

Before providing the results from the study, it would be worthwhile to discuss various facets of the protocol design that will have an impact on the conclusions that may be drawn from this study. First, the primary measure of efficacy is the number of patients who remained in NSR after 6 months of therapy. As defined by the protocol, patients who could not be converted to NSR by either pharmacological or electrical means are counted as treatment failures. The consequence of this can be quite staggering if the number of patients who could not be converted to NSR is a significant proportion of the number randomized. By choosing this analysis, the sponsor could dilute any treatment effect (if present) by adding events to all treatment groups.

Second, the protocol lists three primary endpoints but makes no adjustment to the p value to account for the multiple analysis. As a consequence, it difficult to define the nominal p value for any of the primary endpoints. In the statistical section of the protocol , the primary hypothesis tested is that the proportion of patients remaining in sinus rhythm at six months is different among the four treatment groups. The importance of this endpoint is supported by the fact that the study sample size was calculated based on the treatment effect at six months for this endpoint. This contradicts the sponsor's summary report which states that the primary comparison for all analyses was between the dofetilide 500 mcg group and placebo. The 500 mcg vs. Placebo comparison is not the primary pre-specified analysis.

Third, the randomized dose regimen may not be the actual dose received by the patient from Day 1 of the study[11]. If the proportion of patients receiving lessor doses of therapy is not significantly different among treatment groups, this may not be problematic. If there is a difference between treatments, the determination of an effective dose requires an analysis by the actual dose received by the patient.

[11] This is especially true for those patients randomized after the initial dose was adjusted based on the calculated creatinine clearance.

Fourth, patients who discontinue for reasons other than recurrence of AF/AFl are censored at the time of discontinuation. In this case, a patient who relapses into AF/AFl after discontinuing therapy is not counted as an event. If there is a disproportionate number of premature discontinuations in one group compared to placebo, this could influence the determination of a overall clinical benefit. [12] If dofetilide effectively prevents recurrence but patients cannot tolerate the medication for various reasons resulting in premature discontinuation, the patients will be likely to revert back to AF/AFl after discontinuation. Although it may be possible to show a treatment effect with therapy, the overall clinical benefit to the patient may be questioned because they were not followed after discontinuation.

Demographics

The study randomized 325 subjects at 37 centers in the United States (33 centers) and Canada (4 centers). The number of patients randomized per center ranged from 1 to 49. Center 5002 and 0512 enrolled 15% and 10% of the patients respectively. The number of patients randomized to each treatment group ranged from 77 to 84. A subset of 56 subjects (13, 14, 16 and 13 for dofetilide 125, 25, 500 and placebo respectively), at 9 sites, participated in exercise substudy 120X. The majority of subjects were male, ≥ 65 years and Caucasian (see Table 120.2).

Table 120.2. Demographic characteristics for patients randomized into study 120.

	Dofetilide									Placebo		
	125 mcg bid			250 mcg bid			500 Mcg bid					
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number Of Subjects	68	14	82	69	13	82	63	14	77	73	11	84
Age (Years)												
< 18	0	0	0	0	0	0	0	0	0	0	0	0
18 - 44	2	1	3	1	0	1	3	0	3	2	0	2
45 - 64	27	3	30	20	2	22	22	3	25	21	2	23
>= 65	39	10	49	48	11	59	38	11	49	50	9	59
Age Range (Years)												
FROM :	30	43	30	39	55	39	33	52	33	37	51	37
TO :	88	80	88	86	78	86	85	87	87	85	79	85
Mean Age (Years) :	66	67	66	68	69	68	66	71	67	67	68	67
Race:												
White	62	14	76	63	12	75	57	13	70	66	11	77
Black	3	0	3	4	1	5	5	1	6	4	0	4
Asian	1	0	1	0	0	0	0	0	0	3	0	3
Other	2	0	2	2	0	2	1	0	1	0	0	0

Results Confirmed by the Reviewer's Analysis

Approximately 60% - 70% had no symptoms at baseline while less than 10% had symptoms characterized as moderate or severe. The percentage with structural heart disease ranged from 57% - 77% between the treatment groups[13]. Approximately 60% of patients did not receive any anti-arrhythmic therapy in the previous 6 months (see Table 120.2a.). The majority of subjects had AF/AFl for 1 - 13 weeks. Eighty to ninety percent of patients were receiving digoxin or anti-coagulants at baseline. Over 90% of patients received warfarin after randomization.

[12] A drug that causes a high proportion of patients to discontinue due to adverse events (e.g., prolong QT interval) may show a treatment effect but not provide a clinical benefit. Patients who go off of therapy may relapse into AF/AFl after discontinuation but this would not be counted as an event.

[13] A subject was defined as having structural heart disease if any of the following were recorded on the medical history section as being 'present now' or 'once present, now inactive': congestive heart failure, myocardial infarction (old), ischemic heart disease, valvular heart disease, dilated cardiomyopathy, obstructive cardiomyopathy.

Table 120.2a. Demographic characteristics for patients randomized into study 120.

	Dofetilide			Placebo
	125 mcg	250 mcg	500 mcg	
Number of Subjects	82	82	77	84
Underlying Heart Disease				
Structural Heart Disease	47 (57%)	55 (67%)	59 (77%)	58 (69%)
Hypertension	45	42	52	47
History Of CHF	27	33	32	37
Previous MI	20	22	22	25
NYHA Classification				
Missing Data	2	0	0	0
Class I	22	24	21	22
Class II	51	48	52	58
Class III	7	10	4	4
Mean number of previous anti-arrhythmic therapies in past 6 months				
None	60	56	53	58
1	20	21	19	20
2	2	4	5	3
>= 3	0	1	0	3

Note: Previous anti-arrhythmic therapies include only antiarrhythmic drugs (cardiac glycosides, calcium channel blockers, beta blockers and anticoagulants are not included)

Forty-eight (15%) subjects had atrial flutter while 277 (85%) had atrial fibrillation at enrollment (see Table 120.3).

Table 120.3. Distribution of Patients Based on the Underlying Rhythm

	Dofetilide			Placebo	Total
	125	250	500		
Atrial Fibrillation	70	75	65	67	277
Atrial Flutter	12	7	12	17	48

Table 120.4 lists echocardiographic data at baseline for the treatment groups. The groups are similar with regard to these attributes. Approximately 20% in each group were characterized as having structurally normal hearts.

Table 120.4. Baseline Echo Data and Etiology of AF/AFl.

	Dofetilide			**Placebo**
Baseline Echocardiographic Data	**125mcg**	**250mcg**	**500mcg**	
Mean cardiac index (L/ min/ m) ^{2}	2.54	2.43	2.66	2.73
Mean stroke volume index (ml/ min) ^{2}	30.53	30.73	32.42	31.59
% Subjects with Ejection Fraction <35%	13%	9%	12%	12%
LV dilation	23%	21%	21%	25%
LV regional wall motion abn.	26%	33%	27%	32%
LV hypertrophy	12%	12%	14%	17%
RV dilation	15%	26%	18%	18%
valve lesions	68%	81%	81%	75%
LAD >4.0cm	56%	67%	68%	70%
Presumptive etiology of AF:				
% Subjects with LV dysfunction	27%	40%	29%	31%

valvular disease	18%	15%	20%	16%
structurally normal heart	20%	17%	21%	20%

The groups were similar with respect to other cardiovascular and non-cardiovascular disease (Table 120.5).

Table 120.5. Previous Medical History

	Dofetilide			Placebo
Medical History	**125mcg**	**250mcg**	**500mcg**	
Cardiovascular Diseases in Past				
% subjects with:				
ischemic heart disease	31%	34%	38%	37%
congestive heart failure	12%	17%	22%	20%
operations of the cardiovascular system	18%	23%	17%	29%
Cardiovascular Diseases at Entry				
% subjects with:				
hypertensive disease	45%	38%	60%	46%
congestive heart failure	21%	23%	20%	24%
chronic rheumatic heart disease	9.8%	7.3%	6.5%	1.2%
Non- Cardiovascular Diseases at Entry				
% subjects with:				
arthropathies and related disorders	27%	38%	35%	30%
hyperlipidemia	26%	23%	23%	17%
chronic obstructive pulmonary disease	15%	21%	13%	19%
Source: Sponsor's Appendix 1, Tables 2.1, 2.2				

Disposition

Table 120.6 shows the disposition of patients in the trial. Approximately 20 - 25% of the patients in each treatment group did not enter the Maintenance period for a variety of reasons. The most common reason patients failed to enter the Maintenance period involved the failure to convert to NSR for > 24 hours. QT prolongation or ventricular tachycardia were the next most common reason for failing to enter the Maintenance period. The number of patients entering the Maintenance period ranged from 60 - 68 per treatment group.

Table 120.6. Disposition Prior to Maintenance Phase

Randomized Dose [A]	Dofetilide			Placebo
	125 mcg bid	250 mcg bid	500 mcg bid	
Number Randomized	82	82	77	84
Number Not Entering the Maintenance Phase	22 (26.8%)	21 (25.6%)	15 (19.5%)	16 (19.0%)
Failure to Convert to NSR	15	13	6	13
Adverse Event	1	1	0	1
NSR < 24 hours	2	4	3	1
QT/QTc prolong	1	2	3	0
Vent. Tachycardia	2	1	2	1
Withdrew Consent	0	0	1	0
Death	1	0	0	0
Number Converting to NSR and Entered Maintenance	60 (73.1%)	61 (74.4%)	62 (80.5%)	68 (81.0%)
Successful Pharmacologic	5 (6.1%)	8 (9.8%)	23 (29.9%)	1 (1.2%)
Successful Electrical	55 (67.0%)	53 (64.6%)	39 (50.6%)	67 (79.8%)
Attempted Electrical	72	68	48	81
Not Attempted Electrical	4	6	6	2

[A] Does not represent the actual dose received.; NSR = Normal Sinus Rhythm

Table 120.7 (in the appendix of this review) lists the patients not continuing into the Maintenance period and the reason the patient did not continue.

Table 120.8 shows the disposition of patients after entering the maintenance period. Patients were to be followed for at least one year unless they had a relapse or prematurely discontinued from the study. Patients who experienced a relapse of AF/AFl were discontinued from randomized treatment and were no longer followed after the relapse. Premature withdrawals from therapy were censored in the analysis at the time of discontinuation. Patients who did not have a relapse of AF/AFl and remained on randomized therapy were considered to have completed the trial.[14] The number of premature withdrawals ranged from 5 to 12 between treatment groups. Four patients did not have one year of follow-up but were counted as completed by the sponsor. These patients were followed for less than 351 days because of errors in the scheduling of appointments.

Table 120.8. Disposition of Patients by Randomized Dose (Only Patients Entering Maintenance Phase)

Randomized Dose [A]	Dofetilide			Placebo
	125 mcg bid	250 mcg bid	500 mcg bid	
Number Randomized	82	82	77	84
Number Converting to NSR and Entering Maintenance	60 (73.1%)	61 (74.4%)	62 (80.5%)	68 (81.0%)
Outcome in Maintenance Phase @ 12 months (351 days)				
AF/AFl Recurrence	35*	35*	23	49
Complete 12 months	18 (28%)	13 (21%)	27 (44%)	14 (21%)
Premature Withdrawal	6	10	12	5
< 351 days of follow-up and not Premature Withdrawal	1 [B]	3 [C]	0	0

[A] Does not represent the actual dose received.; NSR = Normal Sinus Rhythm; DC = Discontinuation
[B] Patient 05940236; [C] Patient 05680484, 05420146 and 05920178. * Counts 2 relapses after day 351;

Table 120.9 lists the reasons patients prematurely discontinued therapy in the Maintenance period. Four patients, all on dofetilide, died during the Maintenance period.

Table 120.9. Reasons Patients were Withdrawn in the Maintenance Period.

Reason Withdrawn	Placebo	Dofetilide		
		125 mcg bid	250 mcg bid	500 mcg bid
Adverse Event	3	2	6	2
QT/QTc prolongation	1	1	0	2
Lack of Efficacy	1	0	0	0
Death	0	1	1	2
Other	0	2	1	1
Non-compliance	0	0	0	3
Requested Withdrawal	0	0	2	2

Table 120.10 lists the patients who discontinued prematurely during the maintenance period and the reason for discontinuation.

Table 120.10. Patients Prematurely Discontinued During the Maintenance Period in Study 120.

Patient #	Treatment	Sex	Age	Day	Reason
05760138	Placebo	Male	59	3	Adverse Event: Second Degree AV Block
05860230	Placebo	Male	70	4	Adverse Event: Bursts Of Non-sustained Ventricular Tachycardia

[14] In the sponsors summary, the term completed describes patients who had a relapse or completed 12 months of therapy.

Table 120.10. Patients Prematurely Discontinued During the Maintenance Period in Study 120.

Patient #	Treatment	Sex	Age	Day	Reason
06640395	Placebo	Male	73	110	Adverse Event: Palpitation
05120329	Placebo	Male	81	184	QT/ QTc Prolongation. Increase From Baseline 19% - Patient On Treatment OD -No Room For Down Titration
05800059*	Placebo	Female	72	307	Discontinued Due To Lack Of Efficacy Of Drug.
05420473	500 mcg	Male	73	2	Adverse Event: Slow Ventricular Rate < 40 bpm
07000524	500 mcg	Male	64	3	Adverse Event: Monomorphic Ventricular Tachycardia
05670122	500 mcg	Male	78	3	QT/ QTc Prolongation. QT 42% Above Baseline, QTc 27.9% Above Baseline
05060438	500 mcg	Male	73	4	QT/ QTc Prolongation. 32%
05120330	500 mcg	Male	76	6	Asked To Be Withdrawn From The Study.
05120077	500 mcg	Male	69	8	Patient Died.
05790363	500 mcg	Male	56	12	Protocol Violation. Missed 4 Doses Of Drug
05720102	500 mcg	Female	66	13	Patient Died.
05940237	500 mcg	Male	65	67	Asked To Be Withdrawn From The Study.
05120325	500 mcg	Male	70	70	Protocol Violation. Non Compliance
50020399	500 mcg	Female	69	225	Patient Moving Out Of State
05940233	500 mcg	Male	63	312	Protocol Violation. Pt Non-compliant W/ Study Medication. (Missed 22 Doses)
05890265	250 mcg	Male	64	20	Adverse Event: Chest Pain, Shortness of Breath
05120332	250 mcg	Male	86	27	Adverse Event: Decline In Mental Status; Inability To Take Oral Drug
05090170	250 mcg	Male	39	31	Asked To Be Withdrawn From The Study.
05120426	250 mcg	Male	70	155	Asked To Be Withdrawn From The Study.
05120289	250 mcg	Male	66	190	Adverse Event: Runs Of AV Nodal Re- Entrant Tachycardia
06610448	250 mcg	Male	73	194	Subject Moved To Mexico, Unable To Follow Closely
05120328	250 mcg	Male	62	211	Patient Died.
05120502	250 mcg	Male	73	291	Adverse Event: Intermittent Supra Ventricular Tachycardia
05940235	250 mcg	Male	74	309	Adverse Event: Atrial Tachycardia, Unstable Angina
06020457	250 mcg	Male	74	328	Adverse Event: Aortic Insufficiency, Aortic Valve Replacement, Chest Pain, Congestive Heart Failure, Fatigue, Polymorphic Ventricular Tachycardia
05920177	125 mcg	Male	71	5	QT/ QTc prolongation.
50051001	125 mcg	Male	58	8	Adverse Event: Sustained Ventricular Tachycardia
06921011	125 mcg	Female	58	16	Ethic committee stopped the project
06640396	125 mcg	Male	88	116	Moved out of state
05420151	125 mcg	Male	73	181	Adverse Event: Non Q Wave MI, R/ O MI, Unstable Angina
05120501	125 mcg	Male	76	239	Patient Died.

* Patient was counted as an event in the sponsor's analysis but did not have a recurrence of AF/AFl.

Primary Endpoint - Patients in NSR at 6, 9 and 12 months

Relapse of AF/AFl required documentation of the arrhythmia for 24 hours. The primary endpoints were the Kaplan-Meier estimates of the proportion of patients remaining in NSR at 6, 9 and 12 months. There was no adjustment specified in the protocol to account for the multiple primary endpoints. Because the study sample size was calculated using a 6 month placebo rate, the 6 month analysis is viewed as the primary endpoint analysis. Table 120.11 shows the number of patients who had a relapse of AF/AFl, prematurely discontinued or completed the study at 6 months (180 days), 9 months (270 days) and 12 months (at least 351 days)[15].

[15] Patients who were seen at least 2 weeks prior to their 1 year anniversary date were counted as completing 1 year of follow-up.

Table 120.11. Outcome of Patients in Maintenance Phase (Intent-to-Treat Population)

Randomized Dose [A]	Dofetilide			Placebo
	125 mcg bid	250 mcg bid	500 mcg bid	
Number Randomized	82	82	77	84
Outcome in Maintenance Phase @ 6 months (180 days)				
AF/AFl	54	51	36	58
Complete 6 months	23 (28%)	27 (33%)	32 (42%)	22 (26%)
Premature Withdrawal	5	4	9	4
Outcome in Maintenance Phase @ 9 months (270 days)				
AF/AFl	55	53	37	63
Complete 9 months	21 (26%)	22 (27%)	30 (39%)	17 (20%)
Premature Withdrawal	6	7	10	4
Outcome in Maintenance Phase @ 12 months (351 days)				
AF/AFl	57 [E]	56 [E]	38	64 [D]
Complete 12 months	17 (21%)	13 (16%)	27 (35%)	15 (17%)
Premature Withdrawal	6	10	12	5
< 351 days of follow-up and not Premature Withdrawal	2 [B]	3 [C]	0	0

[A] Does not represent the actual dose received.; [B] Patient 05940236 and 50020454;
[C] Patient 05680484, 05420146 and 05920178. [D] The sponsor's number is 65 because they erroneously counted patient 5800059 as an event. [E] Counts 2 relapses after day 351;
NSR = Normal Sinus Rhythm; DC = Discontinuation. Results Confirmed by the Reviewer's Analysis.

Table 120.12 lists the proportion (from Kaplan-Meier Curve) remaining in NSR at 180, 270 and 360 days along with their 95% CI. The log rank test[16] comparing all treatment groups at 180 (6 months) days yields an unadjusted p = .125. The log rank test comparing all treatment groups at 270 days and 1 year yields an unadjusted p values of .059 and .035 respectively. If the 6 month time is viewed as the principal primary endpoint, which is not unreasonable because the size of the study was powered based on the 6 month time point, the study does not have a significant outcome.

At 6 months, the comparison of 500 mcg bid versus placebo yields a p = .051. The 125 mcg and 250 mcg treatment groups were not significantly different from placebo.

Table 120.12. Probabilities of Remaining in NSR at the Primary Endpoint Times of 180, 270 and 360 Days in the Intent-to-Treat Population. (Based on Kaplan-Meier Estimates)

	Dofetilide			
	125mcg (N = 82)	**250mcg (N = 82)**	**500mcg (N = 77)**	**Placebo (N = 84)**
Probability at:				
180 days	0.32	0.37	0.50	0.30
270 days	0.31	0.34	0.48	0.23
360 days	0.29	0.28	0.47	0.20
P-value (overall treatment comparisons)[A]:				
180 days	P = 0.125			
360 days	P = 0.035			
P-value (vs. placebo):				
180 days	p = 0.90	p = 0.54	p = 0.051	
360 days	p = 0.65	p = 0.41	p = 0.008	

[16] Stratified log rank by center

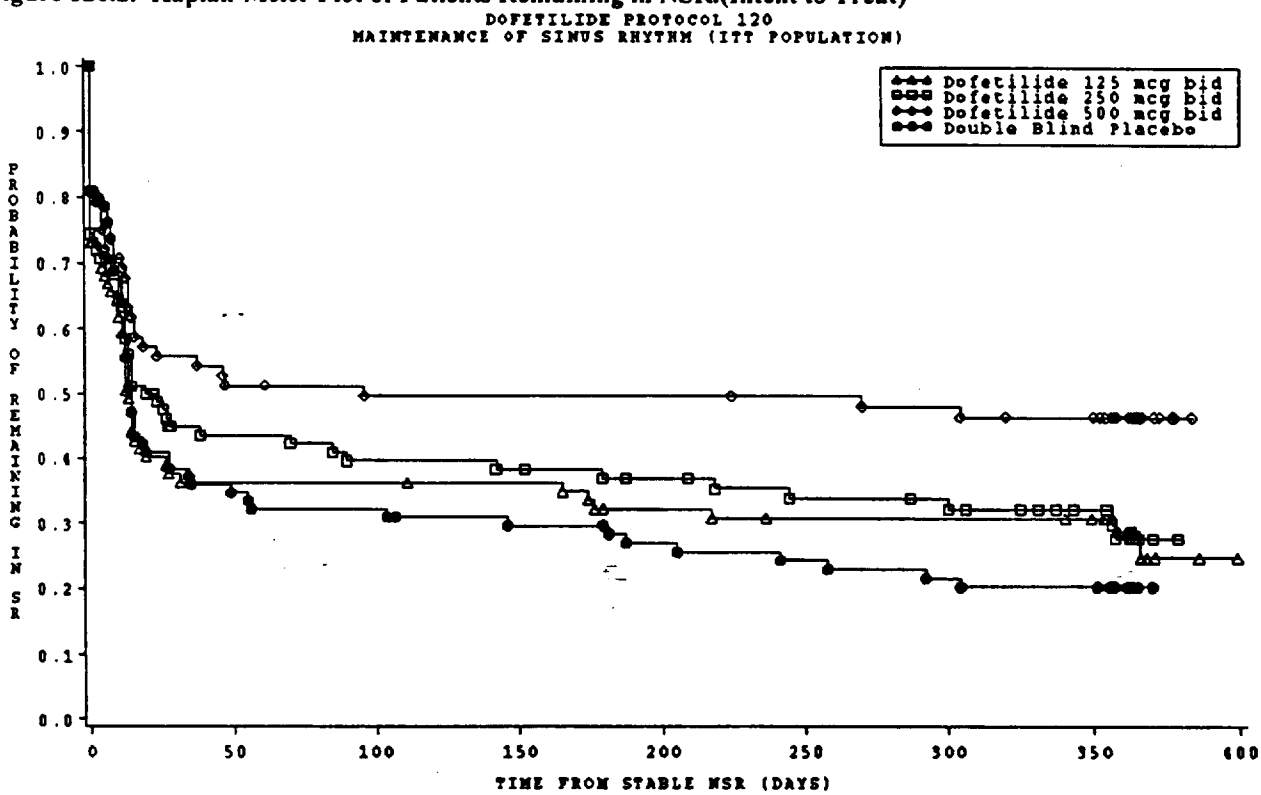
Table 120.12. Probabilities of Remaining in NSR at the Primary Endpoint Times of 180, 270 and 360 Days in the Intent-to-Treat Population. (Based on Kaplan-Meier Estimates)

	Dofetilide			
	125mcg (N = 82)	250mcg (N = 82)	500mcg (N = 77)	Placebo (N = 84)
Hazard Ratio [95% CI] vs. placebo	0.92 0.64-1.32	0.86 0.60-1.23	0.58 0.38-0.87	

^ Primary analysis
* Results Confirmed by the Reviewer's Analysis.

Figure 120.2 illustrates the data listed in Table 120.12. There is clearly a separation of active therapy groups compared to placebo. The ordering of the treatment groups in the Kaplan-Meier plot is suggestive of a dose response relationship. The Kaplan-Meier curve for the 125 and 250 mcg groups are almost superimposable.

Figure 120.2. Kaplan-Meier Plot of Patients Remaining in NSR.(Intent to Treat)



There were 24 patients who developed AF/AFl during the maintenance period but did not fulfill the 24 hour criteria for duration of the arrhythmia. This included four placebo, three 125 mcg, twelve 250 mcg and five 500 mcg patients. Of these 24 patients, eleven relapsed into AF/AFl at a later time. [17]

Other Analyses of the Primary Endpoint

One of the problems with the intent-to-treat analysis for the primary endpoint is that it includes patients who did not even maintain NSR after attempted cardioversion. These patients could not relapse because they were never in a rhythm from which they could relapse. This study could be analyzed (and other studies in the NDA with similar design) in two parts. The first part of the study evaluates the ability of the drug to convert patients from AF/AFl to

[17] Based on information included in fax dated 6/5/98.

NSR[18]. The second part evaluates the ability of the drug to maintain NSR in only those patients who converted to NSR. For the purpose of this discussion, the **Maintenance Population** refers to those patients who successfully convert to NSR. Table 120.12a, 120.12b and figure 120.3 reflect an analysis of the Maintenance Population. The log rank test comparing all treatment groups at 180 days yields an unadjusted p = .062. The log rank test comparing all treatment groups at 270 days and 1 year yields an unadjusted p values of .016 and .011 respectively. The Kaplan-Meier curve for the Maintenance Population is similar to the Intent-to-Treat Population.

Table 120.12.a. Outcome of Patients By Randomized Dose (Only Patients Entering Maintenance Phase)

Randomized Dose [A]	Dofetilide			Placebo
	125 mcg bid	250 mcg bid	500 mcg bid	
Number Randomized	82	82	77	84
Number Converting to NSR and Entering Maintenance	60 (73.1%)	61 (74.4%)	62 (80.5%)	68 (81.0%)
Outcome in Maintenance Phase @ 6 months (180 days)				
AF/AFl Recurrence	32 (53%)	30 (49%)	21(34%)	42 (62%)
Complete 6 months	23 (38%)	27 (44%)	32 (52%)	22 (32%)
Premature Withdrawal	5	4	9	4
Outcome in Maintenance Phase @ 9 months (270 days)				
AF/AFl Recurrence	33 (55%)	32 (52%)	22 (36%)	47 (67%)
Complete 9 months	21 (35%)	22 (36%)	30 (48%)	17 (25%)
Premature Withdrawal	6	7	10	4
Outcome in Maintenance Phase @ 12 months (351 days)				
AF/AFl Recurrence	35 [D] (58%)	35* (57%)	23 (38%)	49 (72%)
Complete 12 months	17 (28%)	13 (21%)	27 (44%)	14 (21%)
Premature Withdrawal	6	10	12	5
< 351 days of follow-up and not Premature Withdrawal	2 [B]	3 [C]	0	0

[A] Does not represent the actual dose received.; NSR = Normal Sinus Rhythm; DC = Discontinuation
[B] Patient 05940236 and 50020454; [C] Patient 05680484, 05420146 and 05920178.
[D] Counts 2 relapses after day 351. Results Confirmed by the Reviewer's Analysis.

Table 120.12.b. Probabilities of Remaining in NSR at the Primary Endpoint Times of 180, 270 and 360 Days in the Maintenance Population. (Based on Kaplan-Meier Estimates)

	Dofetilide			
	125mcg (N=60)	250mcg (N=61)	500mcg (N=61)	Placebo (N=68)
Probability at:				
180 days	0.44	0.50	0.62	0.37
270 days	0.42	0.46	0.60	0.28
360 days	0.40	0.37	0.58	0.25
P-value (overall treatment comparisons):				
180 days	P=0.062			
360 days	P=0.011			
P-value (vs. placebo):				
180 days	p = 0.55	p = 0.15	p = 0.014	
360 days	p = 0.21	p = 0.10	p = 0.001	

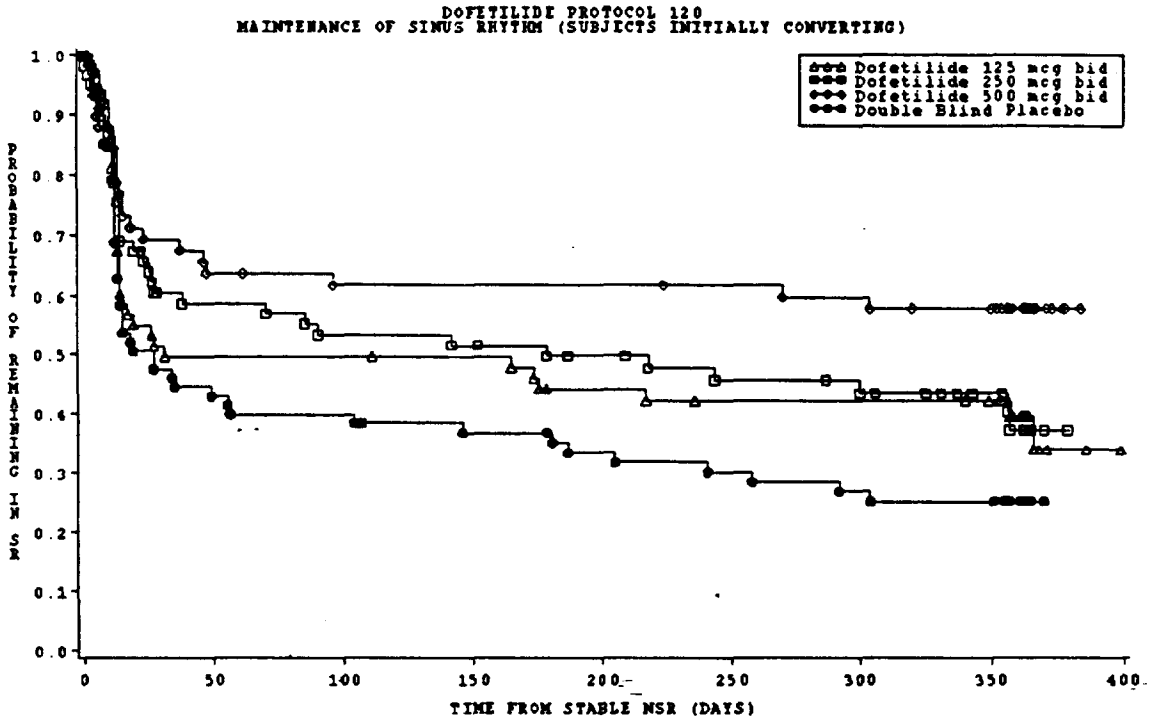
[18] This is a secondary endpoint in this trial.

Table 120.12.b. Probabilities of Remaining in NSR at the Primary Endpoint Times of 180, 270 and 360 Days in the Maintenance Population. (Based on Kaplan-Meier Estimates)

	Dofetilide			
	125mcg (N=60)	250mcg (N=61)	500mcg (N=61)	Placebo (N=68)
Hazard Ratio [95% CI] vs. placebo	0.75 0.48-1.18	0.69 0.45-1.08	0.44 0.26-0.73	

Reviewer's Analysis.

Figure 120.3. Kaplan-Meier Plot of Patients Remaining in NSR (Maintenance Population).



The actual dose a patient received in the study was dependent on their calculated creatinine clearance and whether they experienced QT interval prolongation after the first dose. Table 120.13.a and 120.13.b shows the actual dose ingested by patients in the maintenance period. For the 500 mcg dose, 53% of the patients remained on 500 mcg at the start of maintenance. For the 125 and 250 mcg dose groups, 80% and 79% remained on the initial dose.

Table 120.13.a. Dose* At Start of Maintenance (Intent to Treat population)

	Dofetilide			Placebo	
	125 mcg	250 mcg	500 mcg		Total
Dofetilide 62.5 mcg	15 (18%)	0	0	0	15
Dofetilide 125 mcg	67 (82%)	21 (26%)	0	0	88
Dofetilide 250 mcg	0	61 (74%)	35 (45%)	0	96
Dofetilide 500 mcg	0	0	42 (55%)	0	42
Double Blind Placebo	0	0	0	84	84
Total	82	82	77	84	325

* Start of maintenance reflects the later of the conversion date or the date of the fifth dose.
Actual Dose for subjects discontinuing reflects last dose taken. [from sponsor's Table 3.3.1]
The number of placebo patients receiving reduced placebo doses is not provided.

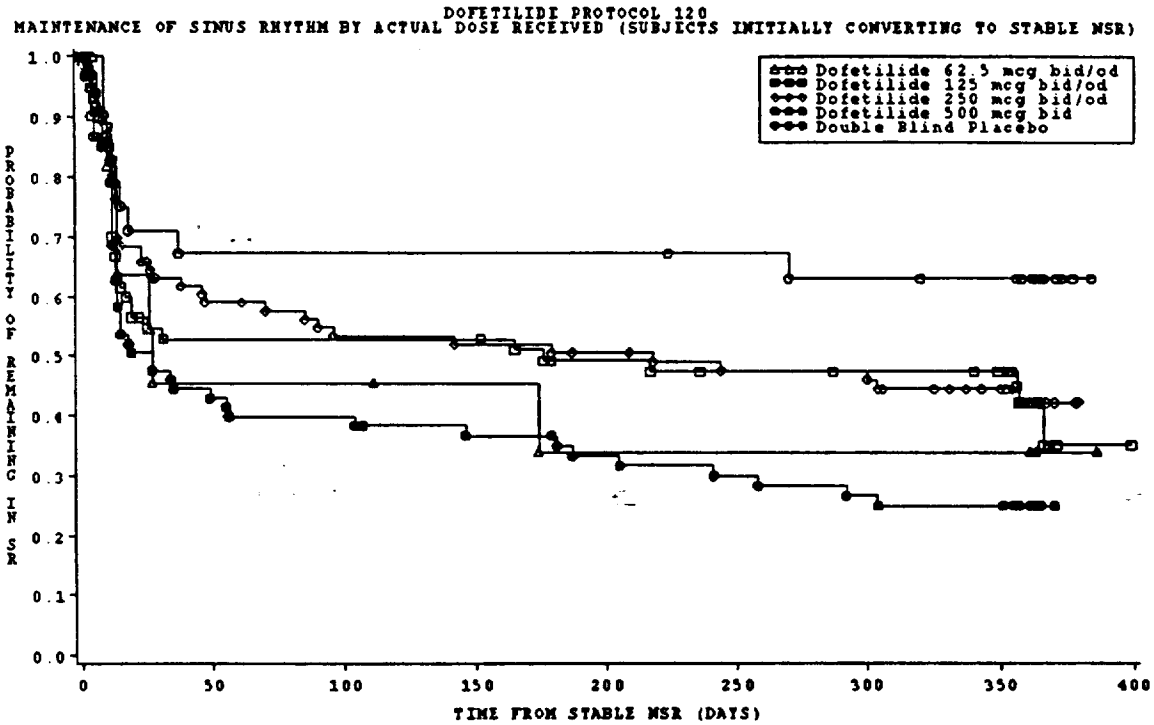
Table 120.13.b. Dose at the Start of Maintenance (Maintenance Population)

	Dofetilide			Placebo	
	125 mcg	250 mcg	500 mcg		Total
Dofetilide 62.5 Mcg	12 (20%)	0	0	0	12
Dofetilide 125 Mcg	48 (80%)	13 (21%)	0	0	61
Dofetilide 250 Mcg	0	48 (79%)	28 (45%)	0	76
Dofetilide 500 Mcg	0	0	33 (53%)	0	33
Double Blind Placebo	0	0	0	68	68
Total	60	61	61	68	250

* Start of maintenance reflects the later of the conversion date or the date of the fifth dose.
[from sponsor's Table 3.3.2] The number of placebo patients receiving reduced placebo doses is not provided.

Figure 120.4 shows the Kaplan-Meier plot for the actual dose received. The ordering of the dose groups is similar to the plots for the randomized dose Kaplan-Meier analysis.

Figure 120.4. Kaplan-Meier Plot of Patients Remaining in NSR Based on Actual Dose Received at the Start of Maintenance. (Maintenance Population).



Impact of Dropouts on Efficacy Results

Patients prematurely discontinued from therapy were censored at the time of discontinuation If the distribution of dropouts is unevenly distributed between treatment groups, this can have an impact on the analysis. The distributions of censoring time for maintenance of NSR are compared between the 500 mcg group and the placebo group. As illustrated in Table 120.14, the 500 mcg group generally had a shorter premature censoring time and about twice as many premature censored cases than the placebo group. Thus, the traditional analysis, such as logrank test, may be biased in favor of the 500 mcg.

Table 120.14. Distributions of Censoring Time (in days) for Maintenance of NSR * (Intent-to-Treat Population)

	< 360 days		< 270 days		< 180 days	
	500 mcg	Placebo	500 mcg	Placebo	500 mcg	Placebo
# randomized	77	84	77	84	77	84
# of premature censored cases	19 (25%)	10 (12%)	10 (13%)	4 (5%)	9 (12%)	4 (5%)
Max	358	357	224	179	61	179
99th %tile	358	357	224	179	61	179
95th	358	357	224	179	61	179
90th	358	357	143	179	61	179
75th	356	356	12	143	10	143
50th	224	353	5	61	4	61
Mean	184	243	70	84	11	75
25th	4	107	2	8	2	8
10th	1	1	1	1	1	1
5th	1	1	1	1	1	1
1st	1	1	1	1	1	1
Min	1	1	1	1	1	1

* Reviewer's Analysis

To assess the worst possible impact of such a bias, the worse case analysis was performed in which all the premature censored cases (i.e.. censoring time < 360 days or < 180 days) were treated as events in the 500 mcg group and nonevents in the placebo group. An alternative analysis that treated all premature censored cases as events in both treatment groups was performed.

Regardless of analysis, the 500 mcg group had a numerically smaller incidence rate of relapse than the placebo group (Table 120.15). The nominal p-value can change in the range of 0.051 to .33 for the 6 month comparison. A similar analysis using the maintenance population is provided in Table 120.15a.

Table 120.15. Incidence of Relapse in the Maintenance Phase (Intent to Treat Population)*

	500 mcg (N=77)	Placebo (N=84)	hazard ratio (95% CI)	P-value**
At 180 days				
Pre-specified analysis	36 (46.8%)	58 (69.0%)	0.66 (0.43, 1.01)	0.051
alternative analysis@	45 (58.4%)	62 (73.8%)	0.77 (0.52, 1.14)	0.19
worse case analysis$	45 (58.4%)	58 (69.0%)	0.82 (0.55, 1.22)	0.33
At 270 days				
Pre-specified analysis	37 (48.1%)	63 (75.0%)	0.60 (0.40, 0.90)	0.014
alternative analysis@	47 (61.0%)	67 (79.8%)	0.72 (0.49, 1.05)	0.084
worse case analysis$	47 (61.0%)	63 (75.0%)	0.76 (0.52, 1.12)	0.16
At 360 days				
Pre-specified analysis	38 (49.4%)	65 (77.4%)	0.58 (0.38, 0.87)	0.008
alternative analysis@	57 (74.0%)	75 (89.3%)	0.69 (0.48, 0.99)	0.040
worse case analysis$	57 (74.0%)	65 (77.4%)	0.80 (0.55, 1.16)	0.23

** nominal p-value obtained from logrank test

@ all premature censored cases are treated as events in both treatment groups

$ premature censored cases are treated as events in the treated group but non-events in the placebo group

* Reviewer's Analysis

Table 120.15a. Incidence of Relapse in the Maintenance Phase (Maintenance Population) *

	500 mcg (N=61)	Placebo (N=68)	hazard ratio (95% CI)	P-value**
At 180 days				
Pre-specified analysis	21 (34.4%)	42 (61.8%)	0.52 (0.30, 0.89)	0.014
alternative analysis@	29 (47.5%)	46 (67.6%)	0.66 (0.41, 1.05)	0.080
worse case analysis$	29 (47.5%)	42 (61.8%)	0.72 (0.44, 1.16)	0.17
At 270 days				
Pre-specified analysis	22 (36.1%)	47 (69.1%)	0.46 (0.27, 0.77)	0.002
alternative analysis@	31 (50.8%)	51 (79.8%)	0.60 (0.38, 0.95)	0.027
worse case analysis$	31 (50.8%)	47 (69.1%)	0.65 (0.41, 1.03)	0.063
At 360 days				
Pre-specified analysis	23 (37.7%)	49 (72.1%)	0.44 (0.26, 0.73)	0.001
alternative analysis@	41 (67.2%)	59 (86.8%)	0.58 (0.380, 0.89)	0.011
worse case analysis$	41 (67.2%)	49 (72.1%)	0.70 (0.45, 1.09)	0.12

** nominal p-value obtained from logrank test;
@ all premature censored cases are treated as events in both treatment groups
$ premature censored cases are treated as events in the treated group but nonevents in the placebo group
* Reviewer's Analysis

Subgroup Analysis

Because an insufficient number of Black and Asian patients were enrolled in the study, any analysis as a function of race is not interpretable. Female and male patients appear to have similar relapse rates. Age does not appear to make a difference in relapse rate although there is a slight difference in the subjects receiving 500 mcg. Table 120.16and Tables 120.16a through 120.16.c provides the results for the subgroups.

Table 120.16. Number (%) of Patients Who Relapsed by Subgroups. (Intent to Treat)*

	125 mcg (N=82)	250 mcg (N=82)	500 mcg (N=77)	Placebo (N=84)
All Patients	57/82 (70%)	56/82 (68%)	38/77 (49%)	65/84 (77%)
Gender				
Male	48/68 (71%)	48/69 (70%)	31/63 (49%)	54/73 (74%)
Female	9/14 (64%)	8/13 (62%)	7/14 (50%)	11/11 (100%)
Race				
White	51/76 (67%)	51/75 (68%)	36/70 (51%)	59/77 (77%)
Black	3/3 (100%)	3/5 (60%)	1/6 (17%)	3/4 (75%)
Asian	1/1 (100%)	0/0	0/0	3/3 (100%)
Other	2/2 (100%)	2/2 (100%)	1/1 (100%)	0/0
Age				
< 65 years	23/33 (70%)	17/23 (74%)	18/28 (64%)	19/25 (76%)
>= 65 years	34/49 (69%)	39/59 (66%)	20/49 (41%)	46/59 (78%)

* Reviewer's Analysis

Table 120.16a. Number (%) of Patients Who Relapsed by Subgroups. (Maintenance population)*

	125 mcg (N=60)	250 mcg (N=61)	500 mcg (N=61)	Placebo (N=68)
All Patients	34/60 (57%)	35/61 (57%)	23/61 (38%)	49/68 (72%)
Gender				
Male	28/49 (57%)	30/51 (59%)	19/50 (38%)	39/58 (67%)
Female	6/11 (55%)	5/10 (50%)	4/11 (36%)	10/10 (100%)

Table 120.16a. Number (%) of Patients Who Relapsed by Subgroups. (Maintenance population)*

	125 mcg (N=60)	250 mcg (N=61)	500 mcg (N=61)	Placebo (N=68)
Race				
White	31/56 (55%)	30/54 (56%)	21/54 (39%)	46/64 (72%)
Black	2/2	3/5	1/6	2/3
Asian	0/1	0/0	0/0	1/1
Other	1/1	2/2	1/1	0/0
Age				
< 65 years	14/24 (58%)	12/18 (67%)	10/20 (50%)	12/18 (67%)
>= 65 years	20/36 (56%)	23/43 (53%)	13/41 (32%)	37/50 (74%)

* Reviewer's Analysis

Table 120.16b. Probability of Remaining in NSR at 12 Months by Subgroup. (Intent-to-treat Population)

	Dofetilide						Placebo	
	125 mcg		250 mcg		500 mcg			
	N	Prob.	N	Prob.	N	Prob.	N	Prob.
Males	68	.28	69	.26	63	.46	73	.24
Females	14	.32	13	.37	14	.47	11	0
< 65 years	33	.27	23	.20	28	.32	25	.21
≥ 65 years	49	.31	59	.30	49	.55	59	.20

Table 120.16c. Probability of Remaining in NSR at 12 Months by Subgroup. (Maintenance Population)

	Dofetilide						Placebo	
	125 mcg		250 mcg		500 mcg			
	N	Prob.	N	Prob.	N	Prob.	N	Prob.
Males	49	.39	51	.35	50	.57	58	.30
Females	11	.41	10	.48	11	.60	10	0
< 65 years	24	.37	18	.26	20	.45	18	.29
≥ 65 years	36	.43	43	.50	41	.64	50	.23

Primary Endpoint - Frequency and Severity of Symptoms

The protocol did not pre-specify details of the analysis for the primary endpoint related to the frequency and severity of symptoms. The sponsor has chosen to calculate the mean symptom scores at various time points of follow-up. A questionnaire assessing symptom severity and frequency was completed by patients at baseline, at each visit and at intervals between visits. The investigators completed the same symptom severity questions at each visit. Figure 120.5 (in the appendix of this review) shows a copy of the questionnaire completed by the patients[19]. The severity (none, very mild, mild, moderate, severe and very severe) and frequency[20] of symptoms (palpitations, shortness of breath, lightheadedness, chest pain, worry, fatigue) were specifically asked in the patient questionnaire and by the investigator (severity only). Each category of symptoms and frequency response was assigned a value of 0 through 5. Table 120.17 shows the values assigned for each category of symptom or frequency.

[19] The physician completed the same symptom severity questions.

[20] how many days in the past two weeks did the patients experience symptoms

Table 120.17. Value Assigned to Severity and Frequency Categories

Value	Severity	Frequency
0	None	None
1	Very Mild	1 - 4 days
2	Mild	5 - 8 days
3	Moderate	9 - 13 days
4	Sever	every day
5	Very Severe	

The total score was calculated for each assessment by summing the scores of the individual symptoms and dividing by 5. This provided a mean severity score that could range from 0 to 5. This provided a mean frequency score that could range from 0 to 4. The sponsor has performed multiple analyses that compares symptom scores at different time points between patients remaining in NSR with those who relapsed and between treatment groups. Table 120.18 lists the mean baseline symptom scores for severity and frequency. The mean baseline values for the severity scores is less than one for all symptoms except fatigue. This suggests that on average most patients had no symptoms or very mild symptoms.

Table 120.18. Subject Assessment of Arrhythmia Associated Symptoms Analysis. Baseline Scores for Converters to NSR

		Severity		Frequency	
	N	Mean	SE	Mean	SE
Palpitations	249	0.62	0.06	0.84	0.09
Shortness of Breath	249	0.98	0.08	1.18	0.10
Lightheadedness	249	0.38	0.05	0.50	0.07
Chest Pain	249	0.31	0.05	0.37	0.06
Worry	249	0.75	0.07	0.92	0.09
Fatigue	249	1.28	0.09	1.49	0.11
Total Symptoms	249	0.72	0.05	0.88	0.06

Note: 251 patients converted to NSR

The sponsor's analysis of the change from baseline in the scores was conducted by an analysis of covariance (SAS proc GLM) for the end of study (nominally 360-day) time points (Table. 120.19). The dependent variable was the score change from baseline, with the primary comparison by assigned rhythm status. Baseline score and center were included in the model as covariates.

Table 120.19. Total Symptoms Scores Based on Final Value (Final value carried forward.)

	Relapsed	N	Baseline	Change	SE	p value
Total Severity Score	NSR	105	0.77	-0.22	0.07	.0002
	Relapsed	140	0.68	0.18	0.07	
Total Frequency Score	NSR	105	0.92	-0.40	0.09	.011
	Relapsed	140	0.87	-0.13	0.08	
Total Severity Score	dofetilide 500 mcg	58	0.83	-0.05	0.10	.93
	placebo	68	0.69	0.01	0.09	
Total Frequency Score	dofetilide 500 mcg	58	1.07	-0.41	0.12	.39
	placebo	68	0.85	-0.15	0.11	

Table 120.20 shows the mean change in severity symptom scores for the individual symptoms based on whether the patient remained in NSR or relapsed into AF/AFl.

Table 120.20. Mean Change from Baseline to Final Score for Severity Score of Individual Symptoms

Symptom	Population	N	Mean Change	SE	p value
Palpitations	NSR	105	-0.12	0.11	0.0002
	Relapsed	140	0.37	0.10	
Shortness of Breath	NSR	105	-0.56	0.09	<0.0001
	Relapsed	140	0.13	0.11	
Lightheadedness	NSR	105	0.00	0.10	0.69
	Relapsed	140	0.08	0.09	
Chest Pain	NSR	105	0.01	0.10	0.70
	Relapsed	140	0.14	0.07	
Worry	NSR	105	-0.26	0.14	0.01
	Relapsed	140	0.29	0.11	
Fatigue	NSR	105	-0.50	0.13	0.0052
	Relapsed	140	0.05	0.13	

Final Score is last value carried forward.

Although several nominal p values are less than .05 in the analysis of symptom severity and frequency, it is difficult to interpret these results for the following reasons.

- In the analysis, the categories are treated as continuous variables where the calculation of mean values and changes in mean values are compared between groups. In doing this, it implies that a fraction of a category has some meaning. When the changes calculated are a fraction of a category (e.g. < 1), it is difficult to determine the clinical benefit derived especially when the majority of subjects did not have symptoms or had very mild symptoms at baseline.
- A change in the mean value from baseline may reflect either a shift of several categories by a few patients or a shift of one category by a lot of patients.

For these reasons, the analysis performed by the sponsor is not ideal. A categorical analysis seems more reasonable for the type of data collected. Table 120.21 lists the number of patients that improved, worsened or had no change from baseline to their final visit based on rhythm status (NSR vs. relapsed). Nominal p values calculated by the Chi-Square test showed that the changes for palpitations, shortness of breath, worry and fatigue were less than 0.05. Table 120.21a (see table in appendix of this review) lists the percentage of patients in each category for the each symptom.

Table 120.21. Change in Status from Baseline to Final Visit

		Change in Status			
		Improved	No Change	Worsened	P value ^
palpitations	NSR	25 (24%)	66 (62%)	15 (14%)	0.004
	Relapsed	20 (14%)	74 (54%)	44 (32%)	
Shortness of Breath	NSR	42 (40%)	56 (53%)	8 (8%)	0.001
	Relapsed	29 (21%)	77 (56%)	32 (23%)	
Lightheadedness	NSR	16 (15%)	76 (72%)	14 (13%)	.746
	Relapsed	19 (14%)	96 (70%)	23 (17%)	
Chest Pain	NSR	15 (14%)	78 (74%)	13 (12%)	0.55
	Relapsed	14 (10%)	103 (75%)	21 (15%)	
Worry	NSR	35 (33%)	54 (51%)	17 (16%)	.002
	Relapsed	22 (16%)	74 (54%)	42 (30%)	
Fatigue	NSR	42 (40%)	49 (46%)	15 (14%)	0.056
	Relapsed	37 (27%)	69 (50%)	32 (23%)	

^ Chi-Square

Secondary Endpoints

Table 120.22 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. The 125 and 250 mg group converted 4.9% and 8.6% respectively.

Table 120.22. Number of Patients Pharmacologically Converting to NSR

	Dofetilide			Placebo
	125 mcg bid	250 mcg bid	500 mcg bid	
Number of Subjects	82	82	77	84
Subjects Converting to NSR Pharmacologically	5 (6.1 %)	8 (9.8 %)	23 (29.9 %)	1 (1.2 %)
Difference From Placebo (%)	4.9	8.6	28.7	
95% Confidence Interval	-0.8 To 10.6	1.7 To 15.4	18.2 To 39.2	
P- Value *	0.098	0.015	<0.001	

Substudy 120X

For the exercise substudy, 56 patients had baseline exercise test performed. All patients should have had a post-conversion exercise test performed regardless of rhythm status (NSR or persistent AF/AFL). If patients failed to enter the maintenance period or relapsed to AF/AFL prior to day 60, they should have had a Termination visit exercise test performed. Table 120.23 shows the disposition of patients with regard to the number who had exercise tests performed. As illustrated in Table 120.23, ninety-five percent of the patients in NSR at 60 days who were part of the substudy had exercise testing performed whereas only 38% of the patients who relapsed or who failed to convert to NSR had a termination exercise visit performed.

Table 120.23. Disposition of Patients in Exercise Substudy

Number with Baseline Exercise Test	56
Number in NSR after Conversion	29
Number in NSR at 60 days	19
Number in NSR at 60 days with 60 day exercise test	18 (95%)
Number Failing to Convert and/or Enter Maintenance or Relapse to AF/AFL by Day 60	37
Number Failing to Convert and/or Enter Maintenance or Relapse to AF/AFL by Day 60 with a Termination Visit Exercise Test	14 (38%)

There were two primary endpoints in the exercise study:

1. the change in exercise time from baseline in patients remaining in NSR at 60 days, and
2. a comparison of the change from baseline for those remaining in NSR versus those who remained in AF/AFl or relapsed into AF/AFl.

The sponsor has provided an analysis for subjects, irrespective of treatment, that compared the exercise times at each time point to baseline for patients who remained in NSR after 60 days. Exercise time increased by 27.1% (154.5 seconds)[21] at 60 days post conversion in patients who remained in NSR. From these results the sponsor concludes that there is "an improvement in exercise tolerance with conversion to and maintenance of sinus rhythm". This result, however, is difficult to interpret because there is no comparator group and one cannot exclude the possibility of a training effect.

The more important endpoint involves the comparison of patients in NSR at 60 days versus those in AF/AFl at 60 days. Because the majority of subjects who failed to convert or relapsed to AF/AFl did not have Termination visit exercise testing performed, an adequate comparison to those remaining in NSR at day 60 cannot be interpreted. There is too much missing data. Based on the results included in the submission, there is insufficient evidence to indicate that exercise tolerance improves in patients who remain in NSR.

[21] From Table 6.18 of sponsor's study report.

Study 345. A Double Blind, Placebo Controlled, Dose Ranging Comparative Study to Assess the Safety, Toleration and Efficacy of Oral Dofetilide and Sotalol in the Prevention of Recurrence of Atrial Fibrillation/Atrial Flutter
Study Dates: 5/3/94 - 1/15/97

Protocol
Design

This is a randomized, double-blind, multi-center (Europe and Australia), placebo controlled study in patients with AF/AFl to define the dose response, efficacy and safety relationships for dofetilide in AF/AFl subjects compared to placebo and sotalol. The study was similar in design to Study 120 in that there was a conversion phase and a maintenance phase.

During the **Conversion** phase, eligible patients entered the hospital for an attempt at pharmacologic conversion to NSR with placebo, sotalol or dofetilide. Prior to the first dose, a quality of life questionnaire was to be completed by the subject and they were to be given the patient-activated ECG recorder (Hertcard) to make a pre-dose recording. Subjects were also to be given a symptom diary to record symptoms which the subject usually associated with the underlying condition. If after receiving five doses (the fifth dose is the day 3 morning dose) of double-blind randomized therapy the patient was still in AF/AFl, electrical conversion was performed within 4 hours of the morning dose. Patients who converted to NSR, either pharmacologically or electrically, and remained in this rhythm for one hour entered the **Maintenance** phase.

During the maintenance phase, patients in NSR were continued on randomized therapy as outpatients. Patients who did not maintain NSR were discontinued from the study. Those who entered the maintenance phase were to be discharged from the hospital and return for clinic visits after 1, 3, 6, 9 and 12 months. Patients remaining in NSR were followed for 12 months with the option of an additional 3 months of follow-up (15 months total). Patients discontinued as a consequence of therapeutic failure or adverse event completed the schedule of visits indicated in the flowchart, with the exception of the month 15 visit. At these visits, the assessments related to health economic and quality of life elements of the study were performed, and an ECG recorded.

Table 345.1 lists the procedures scheduled during the course of the trial. Quality of life questionnaires were completed by the patients and by an observer. At some time after the restoration of NSR and prior to discharge, the transthoracic echocardiography was performed to provide a baseline for left atrial size and left ventricular end-systolic and end-diastolic dimensions.[22]

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[22] Transthoracic echocardiography was also performed at screening to determine left atrial size.

Table 345.1. Flowchart of Procedures Performed in Study 345

		Day			Month						
	Screen[a]	1	2	3	1	3	6	9	12	15	Withdrawal
Medical History	x										
Clinical Exam	x										x
Body Weight	x	x			x	x	x	x	x	x	x
DC Conversion				x[b]							
Hospitalization		x	x	x							
Initiate Therapy		x									
Lab Safety	x	x			x	x	x	x	x	x	x
ECG and BP	x	x[c]	x[c]	x[c]	x	x	x	x	x	x	x
Echocardiography	x[d]		x	x		x[e]			x[e]		x[e]
Quality of Life		x			x[i]		x[i]		x[i]		x[i]
Health Economics					x[i]	x[i]	x[i]	x[i]	x[i]		x
Population PK		x[f]	x[f]	x[g]	x[h]	x[h]	x[h]	x[h]	x[h]		x[h]

a. Within 14 days prior to cardioversion. b. If required

c. Prior to every dose, and at 1 - 3, and 3 - 6, and 6 - 12 hours after the morning dose every day. Also, 1 hour after electrical conversion on Study Day 3, if performed and prior to discharge.

d. Must be during AF/AFl within the preceding 28 days; for left atrial diameter ONLY.

e. During sinus rhythm; for atrial and ventricular dimensions. If withdrawal is due to relapse to AF/AFl then left atrial diameter ONLY to be measured.

f. Prior to and at 1 - 3, 3- 6, and 6 - 12 hours after the first dose (Day 1) and morning dose (Day 2).

g. Before the morning dose on Day 3, and at discharge.

h. Before the morning dose, or at 1 - 3 or 3 - 6 or 6 - 12 hours after the morning dose.

i. To be collected regardless of withdrawal from study drug therapy.

Inclusion Criteria

- Patients with AF/AFl of between 1 week and 2 years duration.
- Patients in whom a clinical indication for cardioversion of AF/AFl and drug therapy for prevention of relapse to AF/AFl is present.
- Patients aged 18 years or older
- Patient capable of giving written informed consent.

The inclusion of a patient more than once in the same clinical trial was not permissible.

Exclusion criteria

- Female patients of child-bearing potential (i.e., less than 2 years post-menopausal or not surgically sterilized).
- Patients with clinically unstable heart failure.
- Patients with a resting ventricular rate of less than 60 beats per minute during AF/AFl measured from the screening or Study Day 1 pre-dose ECG.
- For patients receiving chronic beta receptor antagonism the ventricular rate during AF/AFl at these times must be not less than 80 beats per minute.
- Patients with QRS > 180 msec and/or QT > 440 msec, or with daytime pauses during AF/AFL exceeding 4 seconds, measured from the screen or Study Day 1 pre-dose ECG.
- Patients with uncontrolled thyrotoxicosis, or with other reversible predisposing conditions.
- Patients with myocardial infarction or unstable angina pectoris or cardiac surgery or survival from sudden cardiac death within the preceding 3 weeks.
- Patients with known symptomatic abnormalities of the sinus node.
- 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 diastolic blood pressure > 110 mmHg, or systolic blood pressure < 90 mmHg, despite medical management.
- Patients with major hematologic disorders (such as aplastic anemia or agranulocytosis), hepatic disease or renal impairment (serum creatinine greater than 2 times upper limit of normal) likely to interfere with the safety or efficacy evaluation of the compounds.

- Patients with serum potassium < 3.6 mmol or > 5.5 mmol, or serum magnesium < 0.6 mmol or > 1.25 mmol at screen.
- Acute intravenous supplementation of K^+ or Mg^{2+} is not permissible.
- Patients receiving concomitant therapy with class I, III (including sotalol or d-sotolol) or IV (verapamil, diltiazem or bepridil) antiarrhythmic agents, heterocyclic antidepressant, anticonvulsants or phenothiazines, or other drugs reported to be associated with QT interval prolongation and/or Torsades de Pointes, or receiving such treatment in the period of time corresponding to five times the relevant half-life prior to receiving study treatment.
- Patients receiving amiodarone treatment within the previous 12 weeks or known to have an amiodarone blood level > 0.3 mg/ml.
- Patients who previously have participated in any Dofetilide study.
- Patients taking any experimental medication, or who have taken such medication within the preceding 4 weeks.
- Patients contra-indicated to sotalol (e.g., patients with metabolic acidosis, history of bronchospasm, diabetic ketoacidosis).
- Patients with a recent history of substance dependency/abuse.
- Patients with any concomitant disease likely to be fatal within one year.

Treatment Groups

Patients were randomized to one of the following treatment groups:

- Dofetilide 125 mcg bid
- Dofetilide 250 mcg bid
- Dofetilide 500 mcg bid
- Sotalol 80 mg bid
- Placebo bid.

An amendment was added (date?) to the protocol that permitted a decrease in dose based on calculated creatinine clearance. For patients with creatinine clearance > 60 ml/min there was no dose adjustment. For calculated creatinine clearances 40 - 60 ml/min., subjects were given once a day dosing rather than bid dosing[23]. Patients with a calculated creatinine clearance < 40 ml/min were excluded from the trial. Patients were withdrawn if the QTc increased above pre-specified parameters either after the first dose or at anytime during the conduct of the study.

Endpoints - Primary

The primary efficacy endpoint is the time to therapeutic failure while receiving double-blind therapy, as determined in a Kaplan-Meier analysis. From this will be derived the proportions of patients remaining in NSR after 3, 6, 9 and 12 months, to facilitate comparison with published literature. Therapeutic failure was defined as one of the following:

1. a single, documented (by patient-activated ECG or otherwise) recurrence of AF/AFl persisting for more than 24 hours, OR
2. a single, documented recurrence of AF/AFl requiring medical intervention prior to that time, in the clinical judgment of the investigator, OR
3. repetitive, documented recurrences of AF/AFl, which neither persist for 24 hours nor require medical intervention prior to that time, but which, had they occurred in a patient not enrolled to a clinical trial, would have precipitated a change of drug therapy; OR
4. the discontinuation of study drug due to an adverse event or intolerable drug-related symptoms[24].

The category of therapeutic failure will be indicated in the case report form (CRF).

Endpoints - Secondary

The safety end-point is the incidence of adverse events occurring during double-blind therapy.

The secondary endpoints included:

- Ventricular rate during symptomatic attacks of AF/AFl during double-blind therapy, determined from a 30 second rhythm strip obtained via patient-activated ECG or otherwise, prior to administration of any additional medication for ventricular rate control.

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[23] In study 120, patients were given twice a day dosing.

[24] The statistic section of the protocol contradicts the inclusion of these patients as therapeutic failures. Patients who withdraw for reasons other than recurrence of AF/AFl during the study will be treated as censored on the date of withdrawal.

- Number of documented paroxysms of AF/AFl during double-blind therapy.
- Adjunctive utility of double-blind therapy in the restoration of SR, assessed from: the electrical energy required for conversion, the rate of conversion, the incidence of early, i.e., pre-discharge, relapse to AF/AFl and the incidence of pharmacological conversion to SR.
- Disease-related symptoms frequency and severity, assessed from the CRF.
- The relationship between symptoms and relapse to AF/AFl will be demonstrated by the recording of symptoms by the patient on a diary card, and simultaneous patient-activated ECG recording.
- Adverse event related symptoms frequency, severity, and interference with the patient's daily life activities, assessed by a standardized interviewer-administered adverse event impact questionnaire.
- Impact of the disease and the study treatment on the patient's quality of life will be assessed from a patient self-administered questionnaire.
- Health Care Resource Utilization data, including extra, i.e., not required by the study protocol. visits, extra diagnostic and therapeutic procedures, extra hospital admissions and management of adverse events. These data will be collected in natural units for subsequent costing. They will be assessed from review of the CRF, and by interview of patients withdrawn from double-blind therapy within 12 months of the start of the study.
- Number of days off work in employed patients, assessed from the CRF.
- Population pharmacokinetics during double-blind therapy.

Statistical Plan

The projected sample size of 100 patients per treatment group (500 patients in total) would be sufficient to detect at the 5% (2-sided) level of significance with 90% power an improvement from 25% (placebo) to 50% (dofetilide) in the proportion of patients remaining in sinus rhythm at 12 months. This calculation is based on survival times, and assumes that each patient is treated for a maximum of twelve months[25]. The calculation allows for a 30% drop-out rate. These estimates of response rates are based on the quinidine meta analysis[26]. No efficacy difference was expected compared to sotalol. The sample size of 100 patients per treatment group (500 patients in total) is sufficient to detect as statistically significant, a difference between a 40% adverse event incidence for sotalol (Anderson, et al, J. Am. Col. Cardiol., 1986. 8: 752-62/ Singh, et al, Drugs, 1987. 34:311-49/ Singh, et al, Am. Heart J., 1987. 114: 121-39) and a 20% adverse event incidence for dofetilide, with at least 80% power. The calculation is based on a 5% 2-sided level of significance.

Patients achieving an end-point are considered to have completed the therapeutic part of this study. Socio-economic follow-up was to be performed in all patients achieving an end-point before the Month 12 visit.

The principal analysis is the survival distributions for each treatment group which are estimated using the Kaplan-Meier method and presented graphically. This principal analysis includes data up to the first 12 months of therapy. A log rank test stratified by country was used to compare the survival distributions for each of the treatment groups. Primary comparisons are made between each of the active dofetilide dose groups and the placebo dose group. The **Maintenance Population** was composed of all patients in whom NSR was attained and maintained for 1 hour.

A secondary analysis using Cox's proportional hazard model[27] will compare the difference in time to recurrence of sustained AF/AFl among the treatment groups. Patients who withdraw for reasons other than recurrence of AF/AFl during the study were treated as censored on the date of withdrawal. Estimates of the relative risks and corresponding 95% confidence intervals are also be presented. An analysis, using a Chi-squared statistic, will compare between the dofetilide treatment groups and the sotolol treatment group, the proportion of patients with treatment related adverse events during double blind therapy. No interim analyses were planned for this study.

Efficacy Results

There are two differences in study design compared to protocol 120 that are worth noting.

- In study 120, patients had to remain in NSR for 24 hours before continuing into the maintenance phase whereas in study 345 they were required to remain in NSR for one hour to be counted as a converter.

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[25] (Lachin. Controlled Clinical Trials. 198 1; 2: 93-113)

[26] (Coplen et al. Circulation, 1990; 82: 1106-16)

[27] The following risk factors will be considered for inclusion as covariates in the model: age, sex, left atrial size, etiology of underlying heart disease, cardiac history and duration of arrhythmia.

- The primary analysis in study 120 included all randomized patients. The primary analysis for study 345 only includes those patients entering the maintenance phase.

The protocol states [28] that the double-blind code was broken for each patient after completion of the month 15 visit.[29] As a general rule, it is not good procedurally to unblind the investigator to a patient's treatment prior to finalizing the case report form.

Disposition

During the conversion phase, patients received up to five doses of randomized therapy before undergoing electrical cardioversion. Tables 345.2 and 345.2a. provides the disposition of patients throughout the trial. The majority of dropouts in the conversion phase were due to failure to convert to NSR. The number of patients entering the maintenance phase was similar between treatment groups except for the 250 mg dofetilide group because they had 50% fewer dropouts in the conversion phase.

Table 345. 2. Patient Disposition During the Conversion Phase (derived from Table 6.1 of sponsor's report)

Randomized Dose [A]	Dofetilide			Sotolol	Placebo
	125 mcg	250 mcg	500 mcg	80 mg	
Number Randomized	135	133	129	137	137
Number Not Entering the Maintenance Phase	32 (24%)	15 (11%)	29 (22%)	29 (21%)	31 (24%)
Reasons Patients Did not Enter the Maintenance Phase					
Unable to Convert [B]	27	12	21	23	27
Adverse Event	2	2	1	4	1
Lab Abnormality	0	0	1	0	0
QT/QTc prolonged	0	0	5	0	0
Protocol Violation	0	0	1	1	1
Other	2	0	0	1	2
Withdrew Consent	1	1	0	0	0
Number Converting to NSR and Entered Maintenance	103 (76%)	118 (90%)	100 (79%)	108 (80%)	106 (77%)
Conversion Information					
Number Randomized	135	133	129	137	137
Successful Pharmacologic Conversion	8 (5.9%)	14 (10.5)%	38 (29.5%)	7 (5.1%)	2 (1.5%)
?Withdrew during Pharmacologic Conversion	3	1	8	3	1
# Eligible for Electrical Conversion (AF/AFl @ day 3)	124	118	86	127	134
Electrical Conversion Not Attempted	2	0	3	1	1
Electrical Conversion Attempted	122	118	83	126	133
Successful Electrical Cardioversion	104	109	70	107	108
Unsuccessful Electrical Cardioversion	18	9	13	19	25
# Reverting AF/AFl within 1 hour after Successful Cardioversion	9	3	6	5	4
Total Converting to NSR (Electrical + Pharmacological)	112	123	108	114	110

[A] Does not represent the actual dose received.; [B] Did not Maintain NSR for 1 hour after conversion attempt
NSR = Normal Sinus Rhythm; * from Table 5 of sponsor report

The primary reason for premature discontinuation during the maintenance phase was because of adverse

[28] Page 25
[29] All patients who wished to continue on drug were unblinded at the completion of the 15 month visit.

events.

Table 345. 2a. Disposition During the Maintenance Phase (from 7/24/98 sponsor submission)

Randomized Dose	Dofetilide			Sotolol	Placebo
	125 mcg	250 mcg	500 mcg	80 mg	
Number Randomized	135	133	129	137	137
Number Entered Maintenance	103 (76%)	118 (90%)	100 (79%)	108 (80%)	106 (77%)
Number Relapsing into AF/AFl	61 (59%)	55 (47%)	32 (32%)	48 (44%)	83 (78%)
Revised Number Relapsing into AF/AFl [B]	60	55	32	49	81
Number Prematurely Discontinuing	17	12	21	28	8
Adverse Event	9	4	9	16	4
Lab Abnormality	1	0	2	4	1
QT/QTc prolonged	2	3	2	2	0
Protocol Violation	1	2	3	1	1
Other	2	0	1	1	2
Withdrew Consent	2	3	2	4	0
Lost to Follow Up	0	0	1	0	0
Patient Died	0	0	1	0	0
Number Completing 1 Year of Treatment Without Relapse [A]	25 (24%)	51 (43%)	47 (47%)	32 (30%)	15 (14%)
Revised Number Completing 1 Year of Treatment Without Relapse [B]	26	50	49	34	17

A listing of patients withdrawn in the Conversion phase and Maintenance phase are not included in this review because the Table in the sponsor's submission was 69 pages and could not be easily formatted for this document.

[A] Eighteen patients had less than 351 days of follow-up but were not counted as premature discontinuations. Patients were to be followed for at least one year unless relapse to AF/AFl or discontinuation of medication. Allowing for +/- 2 weeks from one year, the minimum follow-up should be no less than 351 days. The sponsor reviewed the CRFs (the CRFs were not included with the NDA) for these patients and did not note any circumstances (e.g., adverse events) that would have encouraged premature discontinuation.

[B] During the review of study 345, there were inconsistencies between tables in the sponsor's submission that warranted further clarification. Five patients were listed as having events but were censored in the primary analysis. Nine additional patients were censored (n =5) or not included in the primary analysis (n = 4) when they should have been counted as events or included in the analysis but censored. The sponsor performed a new analysis after making appropriate changes to the database and there is essentially little or no difference in the calculations of p values or probabilities of remaining in NSR at various timepoints. The analyses included in this review are based on the original SAS database.

Demographics

The study randomized 671 subjects at 79 centers in 8 countries. The number of subjects randomized per treatment group ranged from 129 to 137. The number of subjects per center ranged from 0 to 45.[30] Approximately 70% of the subjects were male and almost exclusively Caucasian. The average age was 64 years. Ninety percent of the patients were in atrial fibrillation and ten percent were in atrial flutter. The majority of the patients had AF/AFl for less than 6 months (69% of the AF and 78% of the AFl). The majority of subjects were categorized as NYHA Class I. Table 345.3 lists the demographics for patients by treatment group. The treatment groups were similar with respect to demographic variables.

[30] Eighteen centers randomized zero patients. Twenty-four randomized > 10 patients.

Table 345.3. Demographics of Randomized Subjects

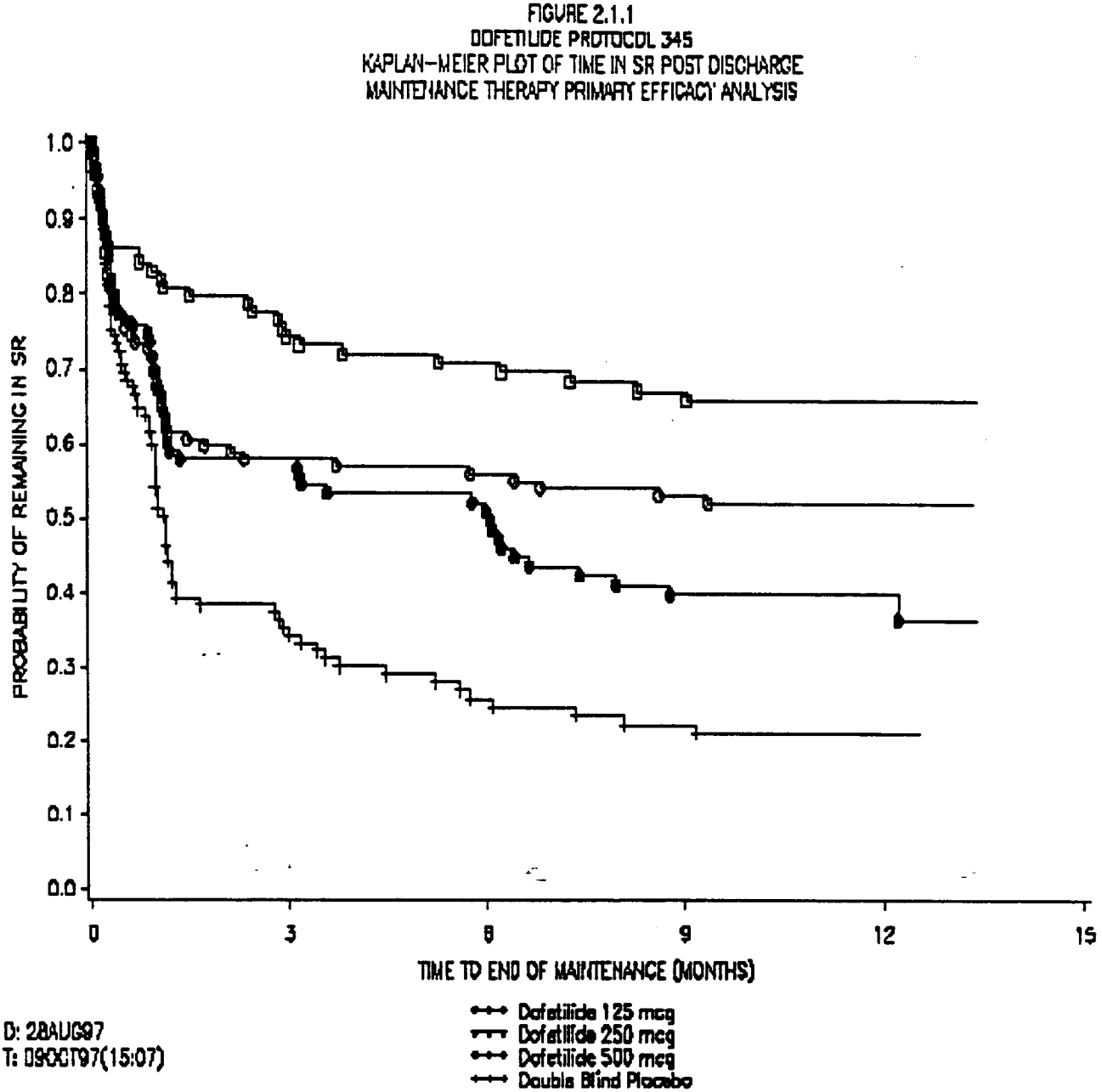
	Dofetilide				
	125 mcg	250 mcg	500 mcg	Sotolol 80 mg	Placebo
N	135	133	129	137	137
Mean Age (years)	64	66	64	64	63
White	135	133	129	136	136
Other /Asian	0	0	0	1	1
Male	94 (70%)	85 (64%)	87 (67%)	102 (74%)	103 (75%)
Female	41	48	42	35	34
AF	121	119	114	125	120
AFl	12	13	15	12	17
AF/AFl	2	1			
NYHA Class					
I	78 (58%)	63 (47%)	67 (52%)	75 (55%)	76 (55%)
II	47 (35%)	62 (47%)	55 (43%)	55 (40%)	54 (39%)
III	10 (7%)	8 (6%)	7 (5%)	7 (5%)	7 (5%)
Essential Hypertension	33%	38%	40%	42%	38%
Valvular Heart Disease	19%	12%	12%	12%	15%
Congestive Heart Failure	4%	9%	8%	8%	7%
Ischemic Heart Disease	15%	14%	10%	12%	16%

Results Confirmed by Reviewer's Analysis

Primary Endpoint

The primary analysis is performed on the Maintenance Population at 12 months. Figure 345.1 shows the Kaplan-Meier plot for the patients remaining in NSR (Maintenance Population). The log rank test yielded a p value of .0001 for an overall treatment effect.

Figure 345.1. Kaplan-Meier Plot of Patients Maintained in NSR (Maintenance Population)



Source: Appendix III. Tables 2.1 to 2.3

Table 345.4 lists the probabilities of remaining in NSR after entering the maintenance phase. Patients had to remain in AF/AFl for 24 hours to be counted as an event.[31] All active treatment groups are significantly different from placebo. At one year, the probability of remaining in NSR for the placebo group was .21 compared to .66, .52 and .40 for the dofetilide 500 mcg bid, 250 mcg bid and 125 mcg groups respectively. There were statistically significant differences between each of the active treatments and placebo.

[31] 43 patients (7 on 125 mcg, 7 on 250 mcg, 20 on 500 mcg, 7 on sotalol and 2 placebo patients) did not relapse but had at least one episode of paroxysmal AF/AFl of < 24 hours duration recorded on the Hertcard recorder

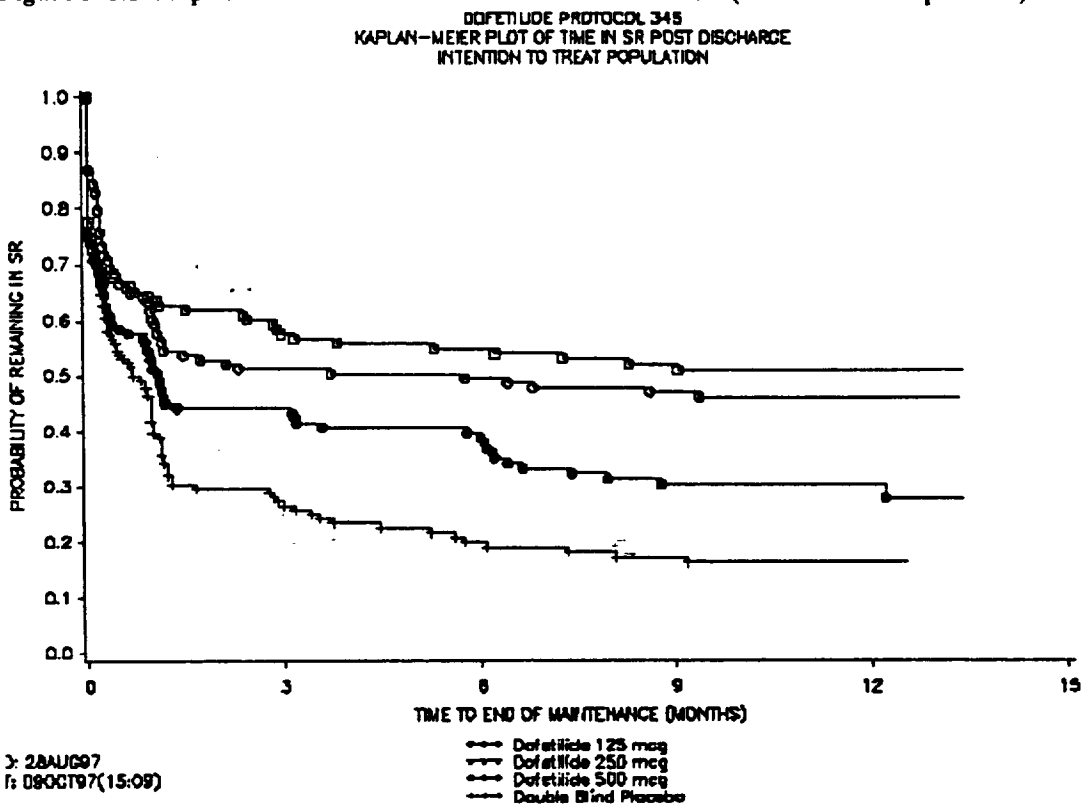
Table 345.4. Probability of Remaining in NSR for Maintenance Population. (Based on Kaplan-Meier Estimates)

	Dofetilide			Sotalol	Placebo
	125mcg bid	250mcg bid	500mcg bid	80mg bid	
Month 3	0.56	0.58	0.74	0.63	0.34
Month 6	0.50	0.56	0.71	0.57	0.26
Month 9	0.39	0.53	0.67	0.51	0.22
Month 12	0.39	0.51	0.66	0.49	0.21
P- value [A]	0.0059	0.0001	0.0001	0.0001	n/ a
Hazard Ratio	0.61	0.48	0.29	0.45	n/ a
CI for Hazard Ratio	(0.43, 0.87)	(0.34, 0.68)	(0.19, 0.44)	(0.31, 0.64)	

[A] Comparison to placebo. n/a = not applicable. Source: Sponsor's Tables 6.3 and 6.4.1.
Results Confirmed by Reviewer's Analysis

Figure 345.2 shows the Kaplan-Meier plot for the patients remaining in NSR for the **Intent-to-Treat Population**. The log rank test yielded a p value of .0001 for an overall treatment effect.

Figure 345.2. Kaplan-Meier Plot of Patients Maintained in NSR (Maintenance Population)



Source: Appendix III. Tables 3.1 to 3.3

Table 345.5 lists the probabilities of remaining in NSR for the Intent-to-Treat Population. Because patients who did not convert to NSR in the conversion phase are included in this analysis, the proportion of patients remaining in NSR at one year is lower for all groups compared to the results of the analysis of the Maintenance Population.

Table 345.5. Probability of Remaining in NSR for the Intent-to-Treat Population (Based on Kaplan-Meier Estimates)

	Dofetilide 125mcg bid	Dofetilide 250mcg bid	Dofetilide 500mcg bid	Sotalol 80mg bid	Placebo
Month 3	0.43	0.51	0.58	0.51	0.27
Month 6	0.39	0.50	0.55	0.45	0.20
Month 9	0.30	0.47	0.52	0.42	0.17
Month 12	0.30	0.45	0.51	0.38	0.16
P- value*	0.030	0.0001	0.0001	0.0002	n/ a
Hazard ratio	0.73	0.50	0.47	0.56	n/ a
CI for Hazard Ratio	(0.55, 0.97)	(0.37, 0.68)	(0.34, 0.64)	(0.42, 0.76)	

*Comparison to placebo. n/a = not applicable. Source: Sponsor's Tables 6.4.2.1 - 6.4.2.4
Results Confirmed by Reviewer's Analysis

Impact of Dropouts on Efficacy Results

The distributions of censoring time for maintenance of NSR are compared between the treatment groups. As illustrated in Table 345.6 (maintenance population) and 345.7 (intent to treat population), the three dofetilide groups and the sotalol group generally had a shorter premature censoring time and about twice as many premature censored cases than the placebo group. Thus, the traditional analysis, such as logrank test, may be biased in favor of the dofetilide groups and the sotalol group.

Table 345.6. Distributions of Censoring Time (Days) for Maintenance of NSR in Patients Prematurely Withdrawn (< 365 Days) - Maintenance Population*

	Dofetilide				
	125 mcg (N=103)	250 mcg (N=118)	500 mcg (N=100)	Sotalol 80 mg (N=108)	Placebo (N=106)
# of premature censored cases	25 (24%)	28 (24%)	34 (34%)	42 (39%)	18 (17%)
Max	364	364	363	364	364
99th %tile	364	364	363	364	364
95th	364	364	362	364	364
90th	363	363	357	363	361
75th	361	361	353	359	357
50th	194	351	237	242	346
Mean	195	249	213	201	235
25th	53	82	57	26	104
10th	5	1	1	3	7
5th	3	1	1	1	6
1st	1	1	1	1	6
Min	1	1	1	1	6

* Reviewer's Analysis

Table 345.7. Distributions of Censoring Time (Days) for Maintenance of NSR in Patients Prematurely Withdrawn (< 365 Days) - Intent to Treat Population

	Dofetilide				
	125 mcg (N=135)	250 mcg (N=133)	500 mcg (N=129)	Sotalol 80 mg (N=137)	Placebo (N=137)
# of premature censored cases	25 (19%)	28 (21%)	34 (26%)	42 (31%)	18 (13%)
Max	364	364	363	364	364
99th %tile	364	364	363	364	364
95th	364	364	362	364	364
90th	363	363	357	363	361

Table 345.7. (con't) Distributions of Censoring Time (Days) for Maintenance of NSR in Patients Prematurely Withdrawn (< 365 Days) - Intent to Treat Population

	Dofetilide				
	125 mcg (N=135)	250 mcg (N=133)	500 mcg (N=129)	Sotalol 80 mg (N=137)	Placebo (N=137)
75th	361	361	353	358	357
50th	173	350	237	188	346
Mean	190	252	213	193	235
25th	53	115	57	21	104
10th	5	1	1	3	7
5th	3	1	1	1	6
1st	1	1	1	1	6
Min	1	1	1	1	6

Reviewer's Analysis

To assess the impact of such a bias, an alternative analysis was performed in which all the premature censored cases (censoring time < 365 days) were treated as events in all treatment groups. In addition, the worse case analysis that treated all premature censored cases as events in the active treatment groups and nonevents in the placebo group is also performed. The results of these analysis are listed in Table 345.8. The alternative analysis gave the same conclusion as the pre-specified analysis. The superiority of 250 mcg and 500 mcg over placebo is still concluded by the worse case analysis. Thus, the potential bias due to the imbalance in the censoring distribution does not appear to have a great adverse impact on the conclusion drawn for the efficacy of dofetilide 250 mcg and 500 mcg. The analysis in the intent to treat population gives the same conclusion (Table 345.9).

Table 345.8. Incidence of Relapse in the Maintenance Phase (365 days) for Maintenance Population *

	125 mcg (N=103)	250 mcg (N=118)	500 mcg (N=100)	Sotalol 80 mg (N=108)	Placebo (N=106)
pre-specified analysis					
# of events (%)	58 (56%)	53 (45%)	31 (31%)	48 (44%)	81 (76%)
p-value vs. plbo*	0.0088	0.0001	0.0001	0.0001	
alternative analysis@					
# of events (%)	83 (81%)	81 (69%)	65 (65%)	90 (83%)	99 (92%)
p-value vs. plbo*	0.020	0.0001	0.0001	0.0014	
worse case analysis$					
# of events (%)	83 (81%)	81 (69%)	65 (65%)	90 (83%)	81 (76%)
p-value vs. plbo*	0.41	0.021	0.0003	0.11	

* nominal p-value obtained from logrank test; @ all premature censored cases are treated as events in all treatment groups

$ premature censored cases are treated as events in the treated groups but nonevents in the placebo group

* Reviewer's Analysis

Table 345.9. Incidence of Relapse in the Maintenance Phase (365 days) for the Intent-to-Treat Population *

	Dofetilide				
	125 mcg (N=135)	250 mcg (N=133)	500 mcg (N=129)	Sotalol 80 mg (N=137)	Placebo (N=137)
pre-specified analysis					
# of events (%)	90 (67%)	68 (51%)	60 (47%)	77 (56%)	111 (81%)
p-value vs. plbo*	0.040	0.0001	0.0001	0.0002	
alternative analysis@					
# of events (%)	115 (85%)	96 (72%)	94 (73%)	119 (87%)	129 (94%)
p-value vs. plbo*	0.058	0.0001	0.0001	0.0044	
worse case analysis$					

Table 345.9. Incidence of Relapse in the Maintenance Phase (365 days) for the Intent-to-Treat Population *

	Dofetilide				
	125 mcg (N=135)	250 mcg (N=133)	500 mcg (N=129)	Sotalol 80 mg (N=137)	Placebo (N=137)
# of events (%)	115 (85%)	96 (72%)	94 (73%)	119 (87%)	111 (81%)
p-value vs. plbo*	0.55	0.0027	0.0028	0.14	

* nominal p-value obtained from logrank test; @ all premature censored cases are treated as events in all treatment groups
$ premature censored cases are treated as events in the treated groups but nonevents in the placebo group
* Reviewer's Analysis

The randomized dose could be adjusted down based on the calculated creatinine clearance at baseline but not for prolongation of the QT interval. Table 345.10 shows the actual dose received by patients at the start of the maintenance period. Seventy to eighty percent of patients in each treatment group remained on their assigned randomized therapy.

Table 345.10. Dose at the Start of Maintenance in Study 345. (Maintenance Population)

	Randomized Dose				
Actual Dose Received	Dofetilide BID			Placebo	Sotalol
⇩	125 mcg	250 mcg	500 mcg		
Dofetilide 125 mcg OD	26 (25%)	0	0	0	0
Dofetilide 125 mcg BID	77 (75%)	0	0	0	0
Dofetilide 250 mcg OD	0	34 (29%)	0	0	0
Dofetilide 250 mcg BID	0	84 (71%)	0	0	0
Dofetilide 500 mcg OD	0	0	30 (30%)	0	0
Dofetilide 500 mcg BID	0	0	70 (70%)	0	0
Reduced Placebo	0	0	0	21 (20%)	0
Full Dose Placebo	0	0	0	85 (80%)	0
Reduced Sotalol	0	0	0	0	19 (18%)
Full Dose Sotalol	0	0	0	0	89 (82%)
Total	103	118	100	106	108

Start of maintenance reflects the later of the conversion date or the date of the fifth dose.
(from sponsor's trial report Table 3.2)

Table 345.11 lists the probabilities of remaining in NSR based on the actual dose received at the start of the Maintenance period. There still appears to be a dose response relationship consistent with the primary analysis.

Table 345.11. Probability of Remaining in NSR Based on Actual Dose Received at Hospital Discharge (Maintenance Population)

	Dofetilide							Sotalol	
	500 bid	500 od	250 bid	250 od	125 bid	125 od	placebo	80 bid	80 od
Total Daily Dofetilide Dose (mcg)	1000	500	500	250	250	125			
N	70	30	84	34	77	26	106	89	19
N in NSR	39	10	41	9	19	7	17	30	4
Prob. NSR @ 3 mths.	.80	.60	.61	.49	.54	.64	.34	.62	.64
Prob. NSR @ 6 mths.	.77	.56	.60	.46	.51	.46	.26	.57	.58
Prob. NSR @ 9 mths.	.74	.52	.56	.46	.38	.41	.22	.51	.50
Prob. NSR @ 12 mths.	.74	.47	.56	.38	.38	.41	.21	.48	.50
% in NSR @ 12 months	56%	33%	49%	26%	25%	27%	16%	34%	21%
Probability of Difference From Placebo (p value)	.0001	.0057	.0001	.0743	.0172	.0565		.0001	.023

Subgroup Analysis