

One of the endpoints was the number of patients who did not have sustained ventricular tachycardia induced during PES. Seven patients did not have complete acute phase data. Forty-six patients receiving dofetilide and 43 subjects receiving sotalol did not experience sustained ventricular tachycardia during PES (Table 333.3). There was no significant difference between treatment groups.

**Table 333.3. Proportion of Patients Responding to Therapy**

	Dofetilide	Sotalol
# patients receiving therapy in acute phase	132	131
# patients with incomplete acute phase data	4	3
# patients who did not have sustained VT induced in the acute phase	46 (36%)	43 (34%)

Responders in the acute phase were eligible to continue on to the chronic phase. A patient's drug regimen in the chronic phase depended on which drug(s) the patient responded to in the acute phase. If they responded to both therapies, the drug in the second crossover phase was administered in the chronic phase. Table 333.4 shows the number of patients who continued on into the chronic phase and the number who withdrew prematurely. Ten patients in each group discontinued prematurely. At 3, 6, 9 and 12 months, the 95% confidence intervals for each treatment overlapped suggesting no difference between treatment groups. This result does not prove that the treatments are the same.

**Table 333.4. Chronic Phase Data**

	Dofetilide	Sotalol
# patients in chronic phase	41	26
# patients withdrawing prematurely	10	10

**Study 334 and 334A. Acute Phase: Double Blind Crossover Study to Assess the Therapeutic Value (Efficacy and Safety) of Oral Dofetilide Versus Oral Sotalol in Patients with Sustained Ventricular Tachycardia of Ischemic Origin. Chronic Phase: Double Blind Study to Assess the Long Term (6 Months) Therapeutic Value (Efficacy And Safety) of Dofetilide Versus Sotalol**

Study Dates: 11/9/93 - 3/13/96 (Study 115-334)

Study Dates: 8/1/94 - 1/29/97 (Study 115-334A)

**Protocol**

This was a randomized, double-blind, 2 period crossover trial in patients with a history of ischemic heart disease and a history of sustained ventricular tachycardia that was inducible by EP testing<sup>54</sup>. The trial consisted of an acute phase (Study 334), a non-randomized, double-blind, long term (6 months) treatment phase (Study 334) and an optional extension phase (Study 334A). In the acute phase, patients were treated with dofetilide 500 mcg bid and sotalol 160 mg bid for 3 - 6 days<sup>55</sup> during different intervals that were separated by a 2 - 3 day washout period. EP testing was performed to assess the inducibility of ventricular tachycardia on drug therapy. Patients whose ventricular tachycardia was not inducible on therapy were eligible to continue the chronic phase. If patients respond to the first treatment drug, the patient will continue on long-term follow-up on this treatment<sup>56</sup>. The study expected to randomize 50 patients. The study endpoint in the acute phase was the prevention of induction of ventricular tachycardia by programmed electrical stimulation (PES)<sup>57</sup>. The study endpoints in the chronic period were the number of VT attacks, symptomatic benefit<sup>58</sup>, the frequency of side effects and the number of dropouts.

<sup>54</sup> During the screening for enrollment, subjects were to have an EPS to ensure that VT could be induced by programmed electrical stimulation in a drug free state. Sustained ventricular tachycardia will be defined as ventricular tachycardia > 30sec or < 30sec but requiring emergency intervention (cardioversion). Non-sustained VT is defined as VT lasting for less than 30sec and not requiring emergency intervention (cardioversion).

<sup>55</sup> An amendment to the protocol allowed for a dose reduction of 50% if the calculated creatinine clearance was between 40 and 60 ml/minute.

<sup>56</sup> They would not crossover to the other therapy.

<sup>57</sup> Complete response to study drug is defined as prevention of induction of more than 10 beats of ventricular tachycardia (VT) at all levels of stimulation.

<sup>58</sup> (number of hospitalizations, patient symptom diaries, doctors visits, etc.)

## Results

The study was conducted at 10 centers in Spain. The study randomized all Caucasians, 98 % male with a mean age of 63 years. Table 334.1 outlines the disposition of patients in the acute and long term phase. Forty patients were randomized to dofetilide (n = 20) or sotalol (n = 20) in the first crossover period. Whether those patients proceeded into the second crossover period depended on their response in the initial treatment period. Because patients who were responders in the initial period were not exposed to the other therapy, it is difficult to make comparisons of response rate between the two treatments. For the 23 patients who received both therapies, only two had a response to the second therapy (sotalol 2 of 13 and dofetilide 0 of 10). Thus, this study provides no relevant comparative data.

**Table 334.1. Disposition of Patients**

Acute Phase		Long Term Phase	Extension
<b>Sequence #1</b>			
Crossover Period 1 Dofetilide (N = 20)	Crossover Period 2 Sotalol		
6 Responders →	→	Dofetilide N = 6 →	Dofetilide N = 6
1 Withdrew			
13 Non-Responders to Period 2 →	Sotalol N = 13		
	2 Responders →	Sotalol N= 2	Sotalol N= 1
	2 Withdrew	1 withdrew	
	9 Non-Responders		
<b>Sequence #2</b>			
Crossover Period 1 Sotalol (N = 20)	Crossover Period 2 Dofetilide		
10 Responders →	→	Sotalol N= 10 →	Sotalol N= 5
0 Withdrew		4 withdrew	
10 Non-Responders to Period 2 →	Dofetilide N = 10		
	0 Responders →	Dofetilide N = 0	
	1 Withdrew		
	9 Non-Responders		

Table 334.2 lists the patients withdrawn during the study.

**Table 334.2. Patients Discontinued**

Acute Phase					
Patient ID	Sex	Age	Treatment	Day	Reason Discontinued
00750008	male	70	dofetilide	7	Discontinued due to lack of efficacy of drug.
00810021	male	63	dofetilide	5	Asked to be withdrawn from the study.
00750006	male	67	sotalol	4	Laboratory abnormality. [Creatinine clearance low]
00780029	male	74	sotalol	7	Laboratory abnormality. [urinary infection, low creatinine clearance]
Chronic or Extension Phase					
Patient ID	Sex	Age	Treatment	Day	Reason Discontinued
A00750044	male	66	dofetilide	460	Adverse event. [sustained VT, death 24 days later]
A00780037	male	68	dofetilide	370	Discontinued due to lack of efficacy of drug.
A03110039	male	75	dofetilide	419	Patient died. [cardiac failure, sudden death]
00760010	male	66	sotalol	120	Laboratory abnormality. [Elevation of SGOT, Elevation of SGPT]

**Table 334.2. (con't) Patients Discontinued**

Patient ID	Sex	Age	Treatment	Day	Reason Discontinued
00760061	male	68	sotalol	34	Adverse event. [skin allergic reaction, acute pulmonary edema]
00770035	male	57	sotalol	9	Adverse event. [Symptomatic sinus bradycardia]
00780038	male	49	sotalol	108	Adverse event. [dyspnea, Bronchitis]
03110041	male	69	sotalol	61	Adverse event. [angina pectoris, cardiac failure, death due to infection post CABG on day 115]

**Study 104. An Open-Label Dose Titration Study of Orally Administered Dofetilide in Patients with Sustained Ventricular Tachycardia**

Study Dates: 4/24/91 - 8/18/93

This was an open-label, multi-center, dose titration trial in patients with a history of sustained ventricular tachycardia (VT) and inducible sustained VT<sup>59</sup> with EP testing. The primary purpose of the study was to define the clinical electrophysiological effects and the range of effective oral doses of dofetilide in subjects. The trial consisted of an acute in-hospital phase and a chronic phase. In the acute phase, patients who had inducible VT were started on dofetilide 250 mcg tid. The dose was titrated up to 500 mcg tid and then 750 mcg tid<sup>60</sup> if VT was inducible with electrophysiological testing. Patients who responded to dofetilide (not inducible) were eligible to continue chronic dofetilide therapy for 1 year at the dose that prevented VT. In the acute phase, clinical efficacy was measured by the ability of dofetilide to prevent the induction of sustained VT. In the chronic phase, clinical efficacy was measured by the ability of dofetilide to prevent the recurrence of sustained ventricular tachycardia.<sup>61</sup> There was no sample size justification and no pre-specified statistical analysis planned.

The study was conducted at 17 centers in the United States<sup>62</sup>. The study proposed to enroll 60 patients. Sixty-one patients received dofetilide during the acute phase. All but two subjects were white and only five were female. Nine of these patients were complete responders<sup>63</sup> to dofetilide and continued into the chronic phase for dofetilide therapy. Of the remaining 51 patients, 29 discontinued and 23 continued into the chronic phase as control subjects. Table 104.1 lists the patient disposition. Overall, 9 subjects were classified as responders, 44 subjects did not respond at any dofetilide level at which they were evaluated, and 8 subjects received dofetilide but did not have EP testing at any dosing level. No further efficacy evaluations were done during the chronic period. Five dofetilide subjects and 14 control subjects remained in the study to the end of the 12 month follow-up period.

**Table 104.1. Patient Disposition in Study 104**

	Number of Patients
Number Entering the Acute Phase	61
Number Discontinued in the Acute Phase	29
Reason Discontinued	
Lack of Efficacy	16
Adverse Event	2
Protocol Violation	1
Asked to be Withdrawn	1
QT Prolongation	1
Torsades de Pointes	2
Proarrhythmic	4
Other	2

<sup>59</sup> (>30 seconds or requiring emergency cardioversion prior to 30 seconds)<sup>60</sup> if tolerated and QT did not prolong to greater than 500 msec<sup>61</sup> There are eight additional acute measures of efficacy and 1 additional chronic measure of efficacy.<sup>62</sup> Five centers did not enroll patients.<sup>63</sup> Complete response: Prevention of induction of sustained VT at all levels of stimulation; Partial response: a) Induction of sustained VT whose cycle length is > 100 msec above that at baseline and not associated with hemodynamic compromise.

**Table 104.1. (con't) Patient Disposition in Study 104**

Entered the Chronic Phase	Number of Patients	
	32	
	Dofetilide	Control
	9	23
Completed 12 months	5	14
Discontinued	4	9
Reason Discontinued		
Lack of Efficacy	2	2
Adverse Event	1	0
Asked to be Withdrawn	1	2
Death	0	1
Lost to Follow-up	0	3
Low EF	0	1

**Study 308. An Open, Multi-center Study Using Programmed Electrical Stimulation to Assess the Safety and Efficacy of Oral Dofetilide in the Treatment of Patients with Sustained Ventricular Tachycardia**

Study dates: 12/90 - 4/93

**Protocol**

This was an open label study to assess efficacy, pharmacokinetics, electrophysiological effects (EP), safety and toleration of oral dofetilide in subjects susceptible to sustained ventricular tachycardia (VT). The trial consisted of an acute phase and a chronic phase. In the acute phase, patients undergoing electrophysiological evaluation who have sustained VT induced by PES and fulfilled the exclusion criteria could be started on dofetilide therapy (250 mcg, 500 mcg, 750 mcg or 1000 mcg every 12 hours). Each subject received a single dose regimen for 3 - 6 days. Dosing could be terminated for proarrhythmia, prolongation of the QT interval and intolerable side effects. Eight subjects would complete a dose level before subjects could receive the next highest dose. While on therapy, patients had PES repeated again at trough on day 4, 5, 6 or 7 (12 hours post dosing). Patients who had a complete or partial response<sup>64</sup> during the acute phase were eligible to continue dofetilide for up to one year as outpatients. Visits during the chronic phase were scheduled for 2 weeks, 4 weeks, 2 months, 3 months, 6 months, 9 months and 12 months.

The endpoints are listed in Table 308.1.

**Table 308.1. Endpoints in the Study**

Acute Phase Endpoints	Chronic Phase Endpoints
Prevention of induction of sustained VT	Prevention of recurrence of sustained VT
Cycle length of induced sustained VT	Mortality
Effective refractory periods in the atria, the AV nodes and the ventricles (VERP) during atria or ventricular pacing at cycle lengths of 600, 500 and 400 msec.	
PR, QRS, RR, QT, PA, AH and HV intervals during sinus rhythm; the Wenckebach point; QTc during sinus rhythm	
Correlation between dofetilide levels and the electrophysiological effect	
Sinus node recovery time	

<sup>64</sup> **Complete** response to study drug is defined as prevention of induction of ventricular tachycardia (VT) at all levels of stimulation. **Partial** response to study drug is defined as: (1) more difficult to induce VT (more extra stimuli are required or shorter stimulation length required). (2) VT when induced, less severe, as defined (a) longer cycle length (>100 msec above that seen at baseline) and/or (b) without hemodynamic compromise (ii indeed hemodynamic compromise was present pre-dose) and/or (c), only possible to induce non-sustained VT when previously sustained VT could be induced.

The procedures performed during the study are outlined in Table 308.2.

**Table 308.2. Flowchart**

	Screen	Acute Phase Days					Chronic Phase						
					Prior to EPS	at 2 <sup>nd</sup> EPS	Weeks		Months				
		1	2	3	3 - 6	4 - 7	2	4	2	3	6	9	12
Treatment		x	x	x	x		----->						
Clinical Examination	x						x	x	x	x	x	x	x
Weight	x												
Labs	x	x					x	x	x	x	x	x	x
Plasma Concentration		x		x	x		x	x	x	x	x	x	x
EPS		x				x							
ECG	x	x		x	x	x	x	x	x	x	x	x	x
Vital Signs	x	x		x	x		x	x	x	x	x	x	x
24 hours Holter		x			x				x	x			x
EF Determination	x	x							x	x			x

<sup>A</sup> Dofetilide was discontinued 12 hours prior to the 2<sup>nd</sup> EPS.

### Results

The study was conducted at six centers in Germany (5 centers) and the Netherlands (1 center). Thirty-five patients were entered into the acute phase: 8 in 250 mcg, 10 in 500 mcg, 7 in 750 mcg and 10 in 1000 mcg. All patients completed the acute phase except for one patient in the 1000 mcg group. Of these, 17 entered the chronic phase and nine completed 12 months of follow-up. Eight patients withdrew during the chronic phase. Six patients completed  $\geq$  351 days in the chronic phase while three patients completed  $<$  351 days but are not counted as premature withdrawals from the study. Table 308.3 shows the patient disposition by treatment. Table 308.4 lists the patients discontinued in the chronic phase and the reason for discontinuation.

**Table 308.3. Patient Disposition.**

	250 mcg	500 mcg	750 mcg	1000 mcg	Total
Entered Acute Phase	8	10	7	10	35
Withdrew in Acute Phase	0	0	0	1 <sup>A</sup>	1
Entered the Chronic Phase <sup>B</sup>	4	5	4	4	17
Withdrew in Chronic Phase <sup>C</sup>	2	2	1	3	8
Completed 351 days <sup>B</sup>	1	1	3	1	6
Completed $<$ 351 days <sup>D</sup>	1	2			3

<sup>A</sup> Patient 310006 for Torsades de Pointes. <sup>B</sup> from table 3.1.2. <sup>C</sup> from table 4.2.2. <sup>D</sup> Not counted as withdrawal by sponsor.

**Table 308.4. Patients Discontinued in the Chronic Phase**

Patient ID	Sex	Age	Dose	Day	Reason
310005	Male	66	1000 mcg	1	Sudden Death.
310007	Male	49	1000 mcg	27	Discontinued due to lack of efficacy of drug.
310008	Female	55	1000 mcg	1	Discontinued due to lack of efficacy of drug. (breathless, RR decreased, recurrent VT, intubation)
310001	Female	65	250 mcg	33	Discontinued due to lack of efficacy of drug. (EPS measurement 16/ 4/ 91 ventricular tachycardia induced under medication)
320002	Male	60	250 mcg	8	Other. (Patient underwent anti-tachycardia surgery)
320003	Male	66	500 mcg	1	Discontinued due to lack of efficacy of drug.
330005	Male	56	500 mcg	175	Discontinued due to lack of efficacy of drug.
110007	Male	34	750 mcg	2	Discontinued due to lack of efficacy of drug. (worsening of arrhythmias)

Table 308.5 lists the demographic characteristics of the patients enrolled. They were predominately male, almost exclusively Caucasian with a mean age of 60 years.

**Table 308.5. Demographics.**

	250 mcg	500 mcg	750 mcg	1000 mcg	Total
Male/Female	7/1	10/0	6/1	7/3	30/5
Caucasian/Other	8/0	10/0	6/1	10/0	34/1
Mean Age	61	61	60	57	
< 65 / ≥ 65 Years	5/3	7/3	5/2	6/4	23/12

Table 308.6 lists the number of responders. There is no difference between treatment groups. Fourteen patients were considered responders to therapy and were eligible to continue into the chronic phase. Seventeen patients entered the chronic phase.

**Table 308.6. Acute Phase Responders**

	250 mcg	500 mcg	750 mcg	1000 mcg	Total
Number Entered	8	10	7	10	35
Complete Responders	3	4	2	4	13
Partial Responders	1	0	0	0	1

Marked increases in QTc were observed between the baseline and final EP procedures for all doses of dofetilide, but the responses increased with dose but not in purely linear fashion for the ITT population <sup>65</sup>(p= 0.057). The range of mean increases in QTc for ITT was 32msec (~8%) to 84msec (~20%).

Ventricular effective refractory period (VERP) were not recorded consistently from all subjects. There were no important differences in baseline values between the treatment groups and there were dose-related increases in mean values after 250, 500 and 1000 mcg bid dosing.

**Study 335 and 336. A Double Blind Comparative Study to Assess the Efficacy and Safety of Dofetilide Versus Amiodarone in the Management of Ventricular Arrhythmias in Subjects with Dilated Cardiomyopathy (Study 335) or Hypertrophic Cardiomyopathy (Study 336)**

Study Dates: 11/10/93 - 5/6/96

**Protocol**

These were double-blind, double-dummy, parallel-group, multi-center studies of dofetilide and amiodarone in the control of ventricular arrhythmias. The efficacy, safety and toleration of dofetilide and amiodarone were to be assessed in subjects with dilated cardiomyopathy in Study 115-335 and in subjects with hypertrophic cardiomyopathy in Study 115-336<sup>66</sup>. In both studies, subjects were to be randomized, according to a computer-generated pseudo-random code, to receive up to 26 weeks treatment with either oral dofetilide or amiodarone. Dofetilide was to be administered as 500 mcg bid and amiodarone was to administered as a 400 mg bid loading dose for the first week, followed by 300 mg daily (200 mg in the morning and 100 mg in the evening) for the rest of the treatment period.<sup>67</sup> Additional double-blind follow-on supplies were to be provided for the investigator to administer amiodarone as a clinical measure, at the end of the study.

Subjects with dilated or hypertrophic cardiomyopathy were to be screened for inclusion 2-15 days prior to the start of treatment. Screening was to consist of a full medical examination including medical history, recording of ECG data, echocardiography, Holter monitoring and collection of blood samples for laboratory testing. Suitable subjects were to be hospitalized for the first 2-3 days of treatment in order to be monitored closely. During this hospitalization,

<sup>65</sup> excludes eight patients with bundle branch blocks

<sup>66</sup> The studies were eventually combined (amendment V) because of slow recruitment.

<sup>67</sup> Should the QTc interval at any time during the double-blind treatment period exceed 550msec and/or the QTc interval increase more than 25% from baseline, study medication was to be discontinued and the subject withdrawn. In the event that a subject developed proarrhythmia (as defined in Appendix C of the protocol), a blood sample (5ml) was to be obtained for determination of serum magnesium and serum potassium concentrations. A plasma sample was to be frozen for later assessment of plasma dofetilide concentration and a 12-lead ECG was to be recorded immediately after the event, as well as 8 and 24 hours after the event with measurement of the QTc interval.

subjects were to have a 12-lead ECG recording, 48 hour Holter recording, a blood sample taken for pharmacokinetic analysis and blood pressure recorded. If the QTc interval exceeded 500 msec at any time during the first two days of hospitalization, the subject was to remain hospitalized for the third day. Otherwise, the subject was to be discharged 48 hours after the start of treatment. If the QTc interval remained above 500 msec on the third day, the case was to be discussed with the sponsor in order to decide whether or not the subject should continue in the study. If the QTc interval increased to greater than 25% above baseline or exceeded 550 msec at any time during the study, the subject was to be withdrawn immediately. The investigators were instructed to monitor subjects for any changes in ECG that suggested evidence of proarrhythmic events, particularly Torsades de Pointes. Throughout the follow-up treatment period (up to 26 weeks) subjects were to visit as outpatients at Weeks 4, 12-13 and 26 (Days 28, 84 - 91 and 182, respectively) at the same time of day. Table 335.1 lists the procedures performed during the study.

**Table 335.1. Study Flowchart**

	Screening <sup>A</sup>	Initiation of Therapy (Hospitalization)				Out Patient Visit (Weeks)		
		Day 1	Day 2	Day 3	Discharge	4	12 -13	26
		Clinical Evaluation	x				x	x
Echo	x							
48 hour Holter	x	x				x	x	
Treatment		x	x	x		x	x	
ECG/ BP	x	x <sup>B</sup>	x <sup>B</sup>			x	x	
Lab test	x					x	x	
PK Level		x <sup>C</sup>	x <sup>C</sup>			x	x	
Concomitant therapy	x				x	x	x	
Quality of Life					x	x	x	

<sup>A</sup> 2 - 15 days before dosing. <sup>B</sup> 0, 2, 4, 8, 12 h. <sup>C</sup> 0, 1 - 3 h, 3 - 6 h, 6 - 12 h

After the 26 week double-blind treatment period, there was to be a 3-day washout before subjects were to receive one week of amiodarone treatment, if clinically warranted. This follow-on amiodarone treatment was to be supplied blinded so that the investigator could start amiodarone treatment as a clinical measure at the end of the study. Subjects who had previously received amiodarone would receive the 300 mg/day maintenance dose but those who had previously received dofetilide would receive the 400 mg bid loading dose. There was to be a final follow-up visit after the one week of follow-on amiodarone treatment (Week 28, Day 191).

There were six protocol amendments; each applied to both studies except amendment II, which applied only to center 121 in Study 115-335.

- Amendment I introduced the quality of life assessment, which was to be measured at baseline and Weeks 4, 12-13 and 26 using a self administered questionnaire. It also amended the serum chemistry assays to include total T3, T4 and TSH, and added the follow-up safety assessments for subjects receiving the extra week of amiodarone treatment at the end of the study period.
- Amendment II described the source data verification procedure to be used at center 121.
- Amendment III introduced extra Holter monitoring and echocardiographic assessment prior to the start of the study due to the high degree of variability of ventricular arrhythmias in the subject populations being studied. It also clarified the calculation of left ventricular ejection fraction (LVEF).
- Amendment IV excluded subjects with a creatinine clearance less than 60 ml/min (any subject developing creatinine clearance of less than 60 ml/min was to be withdrawn from the study) and subjects receiving cimetidine were to be prescribed an alternative treatment or be withdrawn from the study. This amendment was made as other studies have shown that exposure to dofetilide is proportional to renal impairment and creatinine clearance, and that cimetidine competes with dofetilide at the renal binding site, resulting in higher exposure to dofetilide.
- Amendment V was issued to combine the two studies; the studies were terminated due to slow recruitment and combined so that the power for the safety analyses would be achieved. Amendment V also revised the hepatic safety criteria to be more appropriate for subjects with cardiac conditions.
- Amendment VI revised the patient information sheet.

Inclusion Criteria

- Males and females of non-child-bearing potential (at least two years post menopausal or surgically sterilized), aged 18 to 85 years.
- Written informed consent was to be given.
- Study 115-335 - documented dilated cardiomyopathy, defined as: unexplained dilation of the left and/or right ventricular cavity (left ventricular end diastolic dimension > 5.6cm); LVEF < 50% by angiography or < 40% by echocardiography; and absence of ischemic heart disease.
- Study 115-336 - documented hypertrophic cardiomyopathy, defined as: left ventricular wall thickness > 1.5cm (or > 1.3cm in subjects with a family history of hypertrophic cardiomyopathy) and no evidence of identifiable cardiac or systemic cause to hypertrophy.
- Documented ventricular arrhythmia, defined in Study 115-335 as at least 750 multiform ventricular premature contractions (VPC)/24 hours and in Study 115-336 as at least 500 multiform VPC/48 hours, and an episode of VT defined (in both studies) as three or more consecutive ventricular extrasystoles with mean rate > 110 bpm.

Exclusion Criteria

Subjects with any of the following were not eligible for participation in the study:

- Uncompensated congestive heart failure (NYHA Class IV).
- Myocardial infarction, unstable angina pectoris or survival from sudden cardiac death (within the previous three months for Study 115-336).
- For Study 115-335, clinical evidence of ischemic heart disease or symptomatic sustained VT (VT  $\geq$  30 seconds).
- Known symptomatic abnormalities of the sinus node.
- AV block greater than first degree.
- Systolic blood pressure < 80mmHg or diastolic blood pressure > 110mmHg.
- Major hematologic, hepatic or renal disease likely to interfere with the evaluation of the safety or efficacy of the compound.
- Serum potassium < 3.6 mmol/L or > 5.5 mmol/L or serum magnesium < 0.6 mmol/L or > 1.25 mmol/L.
- Concomitant therapy with: other antiarrhythmic drugs, drugs known to prolong QT, drugs associated with incidence of Torsades de Points. Additionally, previous treatment with such drugs was to be prohibited within the period corresponding to five times the relevant half life prior to receiving study treatment.
- Previous treatment with amiodarone within six months resulting in good clinical response and good toleration, or resulting in discontinuation of amiodarone due to lack of efficacy or serious adverse events.
- A history of substance abuse or dependence including alcohol.
- Subjects who received an experimental drug within the past three months.
- Subjects with ICD devices.
- Baseline QTc > 440 msec and/or abnormal ventricular repolarization, including long QT syndrome.
- Any contraindication to amiodarone therapy.
- Creatinine clearance less than 60 ml/min (protocol amendment IV).
- Concomitant treatment with cimetidine (protocol amendment IV).
- Donation of blood was prohibited during the study and for four weeks after the end of the study (or withdrawal).

Study Endpoints

- Incidence of documented ventricular arrhythmias (compared to screening and between dofetilide or amiodarone treated patients).
- Incidence of adverse effects, between patients on dofetilide or amiodarone.

Statistical Plan

Fifty subjects per treatment group were to be randomized in Study 115-335 and 25 subjects per treatment group were to be randomized into Study 115-336. The sample sizes were originally calculated as follows:

- Study 115-335 - in subjects with dilated cardiomyopathy, assuming an adverse event rate of 55% on amiodarone and 20% on dofetilide, a sample size of 50 subjects per treatment group was considered sufficient to detect the 35% difference between the treatments with 90% power, using a two-tailed test at the 5% significance level.
- Study 115-336 - in subjects with hypertrophic cardiomyopathy, assuming an adverse event rate of 55% on amiodarone and 10% of dofetilide, a sample size of 25 subjects per treatment group was considered sufficient to

detect the 45% difference between the treatments with 80% power using a two-tailed test at the 5% significance level.

The protocol specified analyses are listed in table 335.2.

**Table 335.2. Protocol Specified Analyses**

Variable	Analysis
VPCs	<ul style="list-style-type: none"> <li>total number of VPCs per 24 hours will be derived for each patient at each timepoint;</li> <li>patients classified as responder if they have a 90% reduction in total PVCs/24 hours;</li> <li>Comparisons between the response rate for the two treatment groups will be made using an appropriate chi-squared test;</li> <li>LOG e (PVC/24 hour + 0.01) will be compared between treatment groups using an analysis of variance model.</li> </ul>
Episodes of ventricular tachycardia	same as VPCs
Treatment related adverse events	Chi-Squared test

## Results

### Disposition

The study was conducted at 32 centers in Poland, Spain, France, Germany, Italy, the Czech Republic, Austria and Croatia. One-hundred and forty-five patients were screened and 110 were randomized. Fifty-six were randomized to dofetilide and 54 were randomized to amiodarone. Table 335.3 lists the patient disposition in the study. Table 335.4 lists the patients discontinued prematurely. The majority of patients discontinued due to adverse events. Three dofetilide patients died on therapy while none of the amiodarone patients died.

**Table 335.3. Patient Disposition**

	All Patients		Study 335. Dilated Cardiomyopathy		Study 336. Hypertrophic Cardiomyopathy	
	dofetilide	amiodarone	dofetilide	amiodarone	dofetilide	amiodarone
Randomized	56	54	38	37	18	17
Completed Study	37	45	22	32	15	13
Discontinued Study	19	9	16	5	3	4
Reason Discontinued						
Adverse Event	9	6				
Lack of Efficacy	3	0				
Death	3	0				
Other	1	0				
QT Prolongation	2	0				
Lab Abnormality	1	2				
Protocol Violation	0	1				

**Table 335.4. Patients Discontinued Prematurely**

Randomized to Dofetilide					
Study/Patient #	Sex	Age	Treatment	Day	
336/01280039	male	68	Dofetilide	16	Adverse event. [acute ischemia left lower extremity, bradycardia, hypotension, right femoral artery embolism]
335/00960015	male	44	Amiodarone (Open) ^	113	Adverse event. [increased frequency of VT, increased number of PVCs]

**Table 335.4. Patients Discontinued Prematurely**

335/01290091	male	40	Dofetilide	9	Adverse event. [non- sustained ventricular tachycardia]
335/01290109	male	44	Dofetilide	6	Adverse event. [non sustained VT]
336/01290043	female	49	Dofetilide	12	Adverse event. [palpitations, recurrent non- sustained VT]
335/01290022	male	46	Dofetilide	6	Adverse event. [polymorphic VT]
335/01290092	male	39	Dofetilide	7	Adverse event. [recurrent non- sustained VT, sustained ventricular tachycardia ]
335/01290021	male	49	Dofetilide	105	Adverse event. [ventricular tachycardia]
335/01420033	male	58	Dofetilide	2	Adverse event. [worsening ventricular tachycardia]
335/01280020	female	38	Dofetilide	116	Discontinued due to lack of efficacy of drug.
335/01450025	male	51	Dofetilide	148	Discontinued due to lack of efficacy of drug.
335/02120057	male	34	Dofetilide	135	Discontinued due to lack of efficacy of drug.
335/01280085	female	52	Dofetilide	137	Laboratory abnormality. [elevated transaminases]
335/01160008	male	75	Dofetilide	1	Other. [creatinine clearance <60ml/ min.]
335/00340066	male	66	Dofetilide	143	Patient died. (lung cancer)
335/01290110	female	53	Dofetilide	8	Patient died. (sudden)
335/02850169	female	65	Dofetilide	4	Patient died. (sudden)
335/01160006	male	54	Dofetilide	1	QT/ QTc prolongation.
336/02900060	male	36	Dofetilide	2	QT/ QTc prolongation.
Randomized to Amiodarone					
Study/Patient #	Sex	Age	Treatment	Day	
335/00960014	male	61	Amiodarone	35	Laboratory abnormality. [dizziness]
336 01280040	male	57	Amiodarone	140	Adverse event. [cornea amiodarone deposits, left eye papillitis]
336 01290057	female	71	Amiodarone	6	Adverse event. [fever, herpes simplex of mouth, skin allergy, syncopal episodes, viral infection of respiratory tract]
335/02130064	male	20	Amiocarone	109	Adverse event. [hyperthyroidism]
335/01280017	male	30	Amiodarone	1	Adverse event. [hypotension, multiple focus ventricular extra beats]
335/01430047	male	62	Amiodarone	10	Adverse event. [metallic taste in mouth, nausea]
336 01210002	male	34	Amiodarone	78	Adverse event. [stroke]
335/01290023	male	40	Amiodarone (Open)	191	Laboratory abnormality. [low lymphocyte count, low triiodothyronine T <sub>3</sub> count, raised transaminases, serum creatinine raised]
336 01280024	female	47	Amiodarone	184	Protocol violation.

<sup>^</sup> on dofetilide in double-blind period

### Demographics

The patients were almost exclusively Caucasian with approximately 76% males. About one quarter were female. Table 335.5 lists the demographics of each treatment group.

**Table 335.5. Demographics**

	Dofetilide	Amiodarone
Randomized	56	54
Males	43 (77%)	41 (76%)
Females	13 (23%)	13 (24%)
Caucasians	56	52
Negro	0	1

**Table 335.5. Demographics**

	Dofetilide	Amiodarone
Asian	0	1
Mean Age	50	48
NYHA Class I	16%	17%
NYHA Class II	66%	63%
NYHA Class III	18%	20%
Ejection Fraction	42%	38%

**Endpoints**

There was no difference between treatments with regard to the number of patients who experienced at least one adverse event (45% for dofetilide and 52% for amiodarone;  $p = .44$ ). The probability of withdrawing for safety reasons was greater in the dofetilide group compared to the amiodarone group (probability of withdrawal at 6 months was .27 for dofetilide vs. .13 for amiodarone; logrank  $p = .058$ ). Table 335.6 shows the response rate<sup>68</sup> for reduction in PVCs per 24 hours. Amiodarone had a greater percentage of patients with > 90% reduction.

**Table 335.6. PVC Responders**

	Dofetilide	Amiodarone
Responders at 12 weeks <sup>A</sup>	3/39 (8%)	24/37 (65%)
Responders at 26 weeks <sup>A</sup>	3/36 (8%)	24/39 (64%)

<sup>A</sup> Responder defined as 90% reduction from baseline

Table 335.7 shows the change in mean PVCs per 24 hours over time. Both dofetilide and amiodarone reduced overall VPC count during treatment. VPC count was reduced to 63.9% of the baseline count for dofetilide (a reduction of approximately 36%) and to 5.7% of the baseline count for amiodarone (a reduction of approximately 94%) when data were averaged over the Week 12-13 and Week 26 visits. The difference between the treatments was statistically significant ( $p < 0.001$ ). The PVC response was consistent between both populations of patients (Dilated vs. Hypertrophic).

**Table 335.7. Mean PVCs per 24 Hour**

	Baseline		Week 12		Week 26		Average wk. 12 and 26	
	Dofet.	Amiod.	Dofet.	Amiod.	Dofet.	Amiod.	Dofet.	Amiod.
(Study 335)								
Mean	10243.6	6217.6	7114.3	1026.9	7996.3	905.1	7586.5	1021
S. E.	1995.9	944.3	2135.7	524.2	2013.7	299.7	1762.2	362.8
N	38	34	25	28	21	30	28	32
(Study 336)								
Mean	1795	3915	478.5	293.3	635.2	340	557.6	280.3
S. E.	590.5	1497.2	97.8	139.4	169.3	184.5	103.5	109.6
N	18	16	14	13	15	13	15	15
Total Mean	7528	5480.7	4732.2	794.3	4929.2	734.2	5134.6	784.6
S. E.	1461.6	807.2	1454.1	362.6	1316.3	218.6	1252.4	253.3
N	56	50	39	41	36	43	43	47

A VPC count greater than 12000 per 24 hours is considered exceptionally high. Nine subjects with dilated cardiomyopathy in the dofetilide group had exceptionally high VPC counts at baseline (Subjects 00960015, 00960130, 01160006, 01210118, 01290022, 01290091, 01290106, 01450025, 01450026). Five of these subjects were withdrawn due to VT, QT/QTc prolongation or lack of efficacy; three had worsened during treatment and two had shown slight improvement. The remaining four subjects completed the study but showed only slight improvement. In the amiodarone

<sup>68</sup> Response rate is defined as a 90% reduction in the number of PVCs

group, seven subjects had exceptionally high VPC counts (Subjects 01210117, 01430045, 02120058, 02130064, 03700146, 01210002, 01280047), five had dilated cardiomyopathy and two had hypertrophic cardiomyopathy. None of these subjects was withdrawn for lack of efficacy and six of the seven showed clinically significant improvement.

The mean number of ventricular tachycardia episodes per 24 hours was 106 for dofetilide and 59 for amiodarone patients. Both treatment reduced the number of VT episodes over time. The reduction with amiodarone was greater than dofetilide when measured as a function of baseline. The average reduction (week 12 and 26) of VT attacks was 55% with dofetilide and 97% with amiodarone (Table 335.8).

**Table 335.8. Number of VT Episodes per 24 hours.**

	Baseline		Week 12		Week 26		Average wk. 12 and 26	
	Dofet.	Amiod.	Dofet.	Amiod.	Dofet.	Amiod.	Dofet.	Amiod.
Mean	105.9	58.5	24.3	1.2	60.3	1	41.4	1.2
S. E.	51.32	38.58	9.22	0.44	45.01	0.33	21.97	0.35
N	56	50	39	41	36	43	43	47

**Study 109. Comparative Evaluation of Uk-68,798 and Procainamide in Patients with Hypertrophic Cardiomyopathy and Inducible Sustained Ventricular Tachycardia or Ventricular Fibrillation**

Study dates: 1/7/91 - 10/26/93

The purpose of this study was to evaluate the efficacy and safety of intravenous and oral dofetilide in the prevention of inducible ventricular tachycardia in patients with hypertrophic cardiomyopathy and inducible VT. The trial consisted of three phases:

1. acute open label, randomized, in-hospital intravenous phase during which PES was performed to assess the ability of dofetilide or procainamide in preventing induction of sustained VT or VF by programmed electrical stimulation (PES);
2. an evaluation as in Phase 1 of 3 days of orally administered dofetilide (250mcg or 375mcg tid), or procainamide (1000mg tid);
3. a one year, outpatient evaluation in responders<sup>69</sup> of open-label, oral treatment (dofetilide 250 mcg or 375 mcg bid).

The primary endpoint of Phases 1 and 2 was to be prevention of induction of sustained ventricular tachycardia/ventricular fibrillation (VT/VF) by programmed electrical stimulation (PES). Without going into great detail, 17 subjects were entered into the study. There were numerous deviations from the protocol that ranged from failure to meet the entrance criteria (14 patients) to not receiving study drug as specified in the protocol (9 patients) to not having labs done (6 subjects). Sixteen of the 17 received intravenous dofetilide<sup>70</sup> in the first phase. In summary, of the 16 subjects who received intravenous dofetilide at some stage of the study, 7 were responders, 5 were partial responders, and 4 subjects had no response. All 17 patients continued into phase 3. Of note, during the third phase, three patients died suddenly while on dofetilide therapy (375 mcg tid or 250 mcg tid) after 8, 14 and 17 months.

Because of the limited size of the study, there is limited information to support any efficacy endpoints.

**Study 330. The Efficacy and Safety of Dofetilide in the Acute Termination of Sustained Ventricular Tachycardia**

Study Dates: 7/5/93 - 8/9/95

This was an open, multi-center pilot study to assess the efficacy of dofetilide in the termination and prevention of sustained VT. The study enrolled patients who had hemodynamically stable VT induced by PES. The study was divided into three phases: infusion phase, acute oral phase and long-term oral phase. During the infusion phase, dofetilide (6mcg/kg iv over 10 minutes) was administered during hemodynamically stable sustained VT induced in the electrophysiology (EP) laboratory. Subjects were then to enter the acute oral phase and receive dofetilide (500 mcg bid)

<sup>69</sup> Subjects were to be categorized as complete responders if induction of sustained or non-sustained (greater than or equal to 5 beats) VT/VF was prevented at all levels of stimulation. Partial responders with an ICD device implanted could continue.

<sup>70</sup> Nine subjects were randomized to dofetilide and 8 to procainamide. Seven of the 8 procainamide patients were switched to iv dofetilide because of a proarrhythmic effect of procainamide.

for 3-6 days. Electrophysiology testing was performed again while on oral therapy. Subjects showing clinical benefit were to enter the long-term oral phase (1 year) with dofetilide (500 mcg bid).

Thirty subjects were screened at 9 centers<sup>71</sup> in Europe and 19 (17 male, 2 female; 19 Caucasian) received intravenous dofetilide. Eighteen completed the intravenous phase. During the intravenous phase, two of eighteen patients had VT terminated by dofetilide. Eighteen patients entered the acute oral phase even though only patients who were responders in the acute intravenous phase should have received dofetilide in the acute oral phase. In the acute oral phase, three patients had non-inducible VT by PES.

**Table 330.1. Patient Disposition**

	Acute Intravenous Phase	Acute Oral Phase	Chronic Oral Phase
Entered	19	18	7
Completed	18	7	4
Withdrawn	1	11	3
Responder	3 <sup>A</sup> 2 <sup>B</sup>	3 <sup>B</sup>	

<sup>A</sup> Terminated VT. <sup>B</sup> VT non-inducible

Table 330.2 lists the patients discontinued from the study.

**Table 330.2. Patients Discontinued From Study 330.**

Patient ID	Sex	Age	Phase	Day	Reason Discontinued.
1050008	male	64	Intravenous	1	Discontinued due to lack of efficacy of drug.
110063	male	45	Acute Oral	7	Discontinued due to lack of efficacy of drug.
440027	female	72	Acute Oral	4	Adverse event. [Torsades de Pointes]
870017	male	61	Acute Oral	6	Discontinued due to lack of efficacy of drug.
890023	male	49	Acute Oral	7	Discontinued due to lack of efficacy of drug.
1050006	male	70	Acute Oral	3	Discontinued due to lack of efficacy of drug.
1130037	female	67	Acute Oral	6	Discontinued due to lack of efficacy of drug.
1130045	male	60	Acute Oral	4	Adverse event. [Ventricular fibrillation]
1130046	male	65	Acute Oral	6	Other. [Investigator decided not to continue into chronic therapy]
1130047	male	62	Acute Oral	5	Discontinued due to lack of efficacy of drug.
1130048	male	53	Acute Oral	4	Discontinued due to lack of efficacy of drug.
1140041	male	71	Acute Oral	4	Discontinued due to lack of efficacy of drug.
110062	male	68	Chronic Oral	155	Adverse event. [Myocardial infarction]
880021	male	73	Chronic Oral	14	Discontinued due to lack of efficacy of drug.
1140039	male	71	Chronic Oral	56	Discontinued due to lack of efficacy of drug.

Tables 330.3a - 330.3c lists various parameters measured during the intravenous infusion of dofetilide.

**Table 330.3a. Mean Change ( $\Delta$ ) from Pre-Dose in ECG Parameters during EP Study**

		Pre-Treatment	IV Phase ( $\Delta$ )	Acute Oral ( $\Delta$ )
RR interval ( msec)	mean	829	-28.4	73.6
	SE	32.91	29.49	28.49
	N	16	16	13
QT interval ( msec)	mean	388	39.8	48.5
	SE	11.28	7.12	6.66
	N	14	14	11

<sup>71</sup> 5 other centers did not randomize any patients

**Table 330.3a. Mean Change ( $\Delta$ ) from Pre-Dose in ECG Parameters during EP Study**

		Pre-Treatment	IV Phase ( $\Delta$ )	Acute Oral ( $\Delta$ )
QRS width ( msec)	Mean	116.9	2.8	0.3
	SE	7.19	3.54	2.33
	N	16	16	13

**Table 330.3b. Mean Change ( $\Delta$ ) from Pre-Dose in EP Parameters at 400 msec Pacing Cycle Length**

		Pre-Treatment	IV Phase ( $\Delta$ )	Acute Oral ( $\Delta$ )
VERP (msec)	mean	230	-2.7	-12.2
	SE	4.39	8.1	9.4
	N	13	11	9
VFRP (msec)	mean	259.3	-3.7	-10.2
	SE	6.02	8.37	10.2
	N	8	7	6
QTv (after 30 sec constant pacing) ( msec)	mean	368.2	-30	-13.6
	SE	5.58	9.92	11.63
	N	10	9	8

**Table 330.3c. Mean Change in Tachycardia Cycle Length and Systolic and Diastolic Blood Pressure During Intravenous Infusion of Dofetilide**

		Baseline	1	2	3	4	5	6	7	8	9	10	15
Tachycardia Cycle Length	mean	350.3	0.9	1.5	4.8	7.3	6.9	9.8	7.8	9.6	10.2	13.1	15.5
	SE	20.9	1.7	2.1	2.3	2.7	2.7	3.2	3.9	4.6	4.5	4.4	6.1
	N	17	16	17	15	16	14	14	13	14	13	14	11
Systolic Blood Pressure	mean	113.5		3		2.2		1.8		2.3		2.5	
	SE	5.1		4.1		4.7		4.1		4.7		5.2	
	N	19	0	16	0	17	0	16	0	16	0	15	0
Diastolic Blood	mean	77.6		3.2		4.2		4.3		4.4		0.9	
	SE	3.6		2.7		2.2		2.0		2.0		1.8	
	N	19	0	16	0	17	0	16	0	16	0	15	0

**Study 331. The Concordance of Intravenous and Oral Dofetilide in the Management of Sustained Ventricular Tachycardia**

Study Dates: 8/5/93 - 10/4/95

Study 331 was similar in design to study 330 with regard to the phases, the patients enrolled, the procedures performed and the measurements of efficacy. There were differences in the drug administration. Subjects received a 15 minute intravenous infusion of dofetilide (6mcg/kg). If VT could still be induced, subjects received a second infusion of dofetilide (4mcg/kg). Oral dofetilide (250 or 500mcg bid) was administered for 3-6 days (acute oral phase). Subjects showing clinical benefit were given long-term (one year) oral dofetilide.

The study was conducted at 7 centers in Europe<sup>70</sup> and enrolled 27 subjects. The subjects were 11% female, all Caucasian and with a mean age of 57 years. Table 331.1 lists the patient disposition in the study. Eighteen of 27 patients were responders in the acute intravenous phase. In the acute oral phase, 11 of 14 were responders<sup>71</sup>.

**Table 331.1. Patient Disposition.**

	Acute Intravenous Phase	Acute Oral Phase	Chronic Oral Phase
Entered	27	25	14
Completed	25	14	8
Withdrawn	2	11	6
Responder	18	11	

Table 331.2 lists the patients who discontinued from the study and the reason for discontinuation. Two patients died suddenly during the chronic phase.

**Table 331.2. Patients Discontinued in Study 331.**

Patient #	Sex	Age	Phase	Day	Reason Discontinued
310047	male	66	Infusion	1	Discontinued due to lack of efficacy of drug.
310049	male	63	Infusion	1	Adverse event. [Ventricular fibrillation]
110066	female	31	Acute Oral	3	Adverse event. [Non sustained VT, Torsades de Pointes]
110067	male	47	Acute Oral	9	Discontinued due to lack of efficacy of drug.
310050	male	37	Acute Oral	7	Discontinued due to lack of efficacy of drug.
310051	male	51	Acute Oral	4	Discontinued due to lack of efficacy of drug.
310052	female	73	Acute Oral	5	Discontinued due to lack of efficacy of drug.
310053	male	63	Acute Oral	6	Discontinued due to lack of efficacy of drug.
310054	male	62	Acute Oral	10	Discontinued due to lack of efficacy of drug.
870025	male	70	Acute Oral	9	Discontinued due to lack of efficacy of drug.
870027	male	46	Acute Oral	6	Discontinued due to lack of efficacy of drug.
890017	male	65	Acute Oral	6	Discontinued due to lack of efficacy of drug.
1140043	male	63	Acute Oral	6	Other. [Physicians decision]
110064	male	52	Chronic Oral	22	Adverse event. [Dizzy, Nausea, Sinus bradycardia]
110068	male	40	Chronic Oral	6	Asked to be withdrawn from the study.
110075	male	54	Chronic Oral	17	Adverse event. [Ventricular tachycardia]
110078	female	71	Chronic Oral	134	Patient died.
440024	male	46	Chronic Oral	190	Patient died.
1140044	male	65	Chronic Oral	9	Adverse event. [ischemic heart disease]

The QTc interval and ventricular effective refractory period increased during the intravenous infusion and acute oral therapy.

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Concur: K. Mahjoob, Ph.D. *[Signature]*

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cc: orig.  
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HFD710 / J. Hung / G. Chi / K. Mahjoob

<sup>70</sup> 7 other centers did not enroll any patients

<sup>71</sup> Complete response to study drug is defined as prevention of induction of more than 10 beats of ventricular tachycardia at all levels of stimulation. Partial response to study drug is defined as prolongation of ventricular tachycardia cycle length of more than 100msec and the tachycardia cycle length is more than 350msec and is hemodynamically tolerated.

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**APPEARS THIS WAY  
ON ORIGINAL**

Figure 120.5. Symptom Questionnaire Completed by Patients in Study 120.

DURING THE PAST TWO WEEKS HAVE YOU EXPERIENCED ANY OF THE FOLLOWING SYMPTOMS?

- Palpitations
- Shortness of Breath
- Lightheadedness
- Chest Pain (Discomfort)
- Worry (Concern)
- Fatigue (Tiredness)
- Other (specify):

Yes  
If Yes, estimate  
frequency below.

No  
If No, check appropriate  
information below.

**Only patients answering YES to the above question should complete the following information**

HOW WOULD YOU DESCRIBE THE SYMPTOMS THAT YOU HAVE EXPERIENCED (✓ the appropriate box for each symptom)

SYMPTOM	Code	NONE (1)	VERY MILD (2)	MILD (3)	MODERATE (4)	SEVERE (5)	VERY SEVERE (6)
Palpitations	(544)						
Shortness of Breath	(540)						
Lightheadedness	(53)						
Chest Pain (Discomfort)	(553)						
Worry (Concern)	(457)						
Fatigue (Tiredness)	(718)						
Other (specify):							

HOW OFTEN DURING THE PAST TWO WEEKS HAVE YOU EXPERIENCED THESE SYMPTOMS?

(✓ the appropriate box for each symptom)

SYMPTOM	Code	NONE (1)	3-4 DAYS (2)	5-6 DAYS (3)	7-10 DAYS (4)	EVERY DAY (5)
Palpitations	(544)					
Shortness of Breath	(540)					
Lightheadedness	(53)					
Chest Pain (Discomfort)	(553)					
Worry (Concern)	(457)					
Fatigue (Tiredness)	(718)					
Other (specify):						

IN GENERAL, HOW WOULD YOU DESCRIBE YOUR OVERALL SYMPTOMS IN THE PAST TWO WEEKS?

- (2) Very Mild     (3) Mild     (4) Moderate     (5) Severe     (6) Very Severe

ON YOUR WORST DAY, HOW WOULD YOU DESCRIBE YOUR OVERALL SYMPTOMS?

- (2) Very Mild     (3) Mild     (4) Moderate     (5) Severe     (6) Very Severe

**Table 120.7. Discontinuations Prior to Entering the Maintenance Period in Study 120.**

Patient #	Treatment	Sex	Age	Day	Reason
05680088	Placebo	Male	76	1	Adverse Event: Bradycardia Pulse Less Than 50 bpm, Pulse Less Than 50 Bpm Bradycardia, RR Interval Greater Than 4 Sec
05870216	Placebo	Male	75	2	Adverse Event: New V Tachycardia
05100197	Placebo	Male	65	3	Patient Failed To Electrically Cardiovert
05090172	Placebo	Male	61	3	Unable to Cardiovert
05180505	Placebo	Male	55	3	Unable to Cardiovert
05280187	Placebo	Male	74	3	Unable to Cardiovert
05760141	Placebo	Male	56	3	Unable to Cardiovert
05780217	Placebo	Female	73	3	Unable to Cardiovert
05790131	Placebo	Male	67	3	Unable to Cardiovert
05830282	Placebo	Male	53	3	Unable to Cardiovert
05890268	Placebo	Male	47	3	Unable to Cardiovert
06390353	Placebo	Male	58	3	Unable to Cardiovert
06610447	Placebo	Male	75	3	Unable to Cardiovert
06610545	Placebo	Male	76	3	Unable to Cardiovert
05120079	Placebo	Male	69	3	Unable to Cardiovert
05100490	Placebo	Male	62	5	Failed To Hold NSR During Hospital Stay
50020279	500 mcg	Female	82	1	QT/ QTc Prolongation. QTc 21%, QT 34%
05790336	500 mcg	Male	68	2	Asked To Be Withdrawn From The Study. Pt's Family Withdrew Consent
05790130	500 mcg	Male	58	2	QT/ QTc Prolongation. 43%
50021033	500 mcg	Male	62	2	QT/ QTc Prolongation. Increase From Baseline 33%
05680086	500 mcg	Male	60	3	Adverse Event: Non-sustained Ventricular Tachycardia, Sinus Pauses
05680485	500 mcg	Male	38	3	Adverse Event: Torsades De Pointes, Ventricular Fibrillation
05830284	500 mcg	Female	68	3	Didn't Remain In NSR
06610450	500 mcg	Female	74	3	Didn't Remain In NSR
05470089	500 mcg	Male	63	3	Failed To Convert To NSR After Electrocardioversion X3
05910342	500 mcg	Male	62	3	Unable to Cardiovert
50020456	500 mcg	Male	63	3	Unable to Cardiovert
05760142	500 mcg	Male	66	3	Unable To Electrically Convert
05910255	500 mcg	Male	66	4	Did Not Cardiovert Remained In Atrial Fib
05100196	500 mcg	Male	64	4	Patient Did Not Maintain NSR For 24 Hours
05890266	500 mcg	Male	68	4	Unable To Cardiovert
06921012	250 mcg	Male	79	1	QT/ QTc Prolongation. 15.6%
50021032	250 mcg	Female	66	2	Adverse Event: Torsades De Pointes, Ventricular Fibrillation
05870215	250 mcg	Male	67	3	Adverse Event: Sino-atrial Pause
05670125	250 mcg	Female	66	3	Didn't Maintain NSR
50020472	250 mcg	Male	70	3	Failed Cardioversion
05790361	250 mcg	Male	68	3	Failed To Convert
06090385	250 mcg	Female	57	3	Failure To Cardiovert

**Table 120.7. Discontinuations Prior to Entering the Maintenance Period in Study 120.**

Patient #	Treatment	Sex	Age	Day	Reason
05420149	250 mcg	Male	75	3	Patient Failed Electrocardioversion After 3 Attempts
07000521	250 mcg	Male	65	3	Patient Failed To Cardiovert
05100200	250 mcg	Male	63	3	Patient Failed To Electrically Cardiovert
05760143	250 mcg	Male	76	3	Pharmacological + Electrical cardioversion Unsuccessful
05760493	250 mcg	Male	71	3	QT/ QTc Prolongation. Increase From Baseline 33.6% QT
05670124	250 mcg	Male	80	3	Unable To Cardiovert
05680349	250 mcg	Male	65	3	Unable To Cardiovert
05790129	250 mcg	Male	60	3	Unable To Cardiovert
06390355	250 mcg	Male	58	3	Unable To Cardiovert
06461024	250 mcg	Male	66	3	Unable To Cardiovert
05120324	250 mcg	Male	68	3	Unable To Convert Electrically To Sinus Rhythm
06640393	250 mcg	Male	64	4	Did Not Maintain NSR For 24 Hours
06461026	250 mcg	Male	69	4	Failed To Maintain NSR
05381018	250 mcg	Male	65	4	Unable To Cardiovert- NSR Lasted Only 20- 30 Minutes Post Cardioversion
05470090	125 mcg	Male	47	1	Adverse Event: Intermittent Nausea, Intermittent R Sided Pain, Intermittent Vomiting, Non- Sustained 7 Beat Run V Tachycardia, R Sided Pain Intermittent
50020280	125 mcg	Female	65	1	QT/ QTc prolongation. 28%
05100199	125 mcg	Male	60	2	Failed Cardioversion
05180509	125 mcg	Male	68	2	Adverse Event: Monomorphic VT
05060441	125 mcg	Male	70	3	Patient Failed Cardioversion
05180506	125 mcg	Male	71	3	Unable To Cardiovert
05420148	125 mcg	Male	54	3	Failed DC Electrical Cardioversion
05420318	125 mcg	Male	72	3	Pt Did Not Convert To Sinus Rhythm
05670126	125 mcg	Male	55	3	Unable To Cardiovert
05680087	125 mcg	Male	56	3	Patient Did Not Convert
05720100	125 mcg	Male	63	3	Unable To Cardiovert
05790132	125 mcg	Male	72	3	Did Not Cardiovert
05860340	125 mcg	Male	77	3	Failure To Cardiovert
05870212	125 mcg	Male	54	3	Adverse Event: Chest Pain, Hypotension, V- Tachycardia
05870417	125 mcg	Male	60	3	Unable to convert
50020275	125 mcg	Male	45	3	Failure to cardiovert
50020348	125 mcg	Male	70	3	Unsuccessful cardioversion
50021031	125 mcg	Male	68	4	Did not maintain NSR for 24 hrs. post-cardioversion
50021035	125 mcg	Female	80	4	Did Not Remain In NSR For 24hrs Post Cardioversion
50021044	125 mcg	Male	72	4	Patient Failed Cardioversion
06610445	125 mcg	Female	78	5	Patient died.
05120321	125 mcg	Male	81	7	Unable To Maintain NSR

**Table 120.21a. Percentage of Patients with Severity Score in Each Category at Baseline and Final Visit (NSR vs. Relapsed)**

			None	Very Mild	Mild	Moderate	Severe	Very Severe
Score ⇒			0	1	2	3	4	5
Symptoms ↓	Visit ↓	Group ↓						
Palpitations	Baseline	NSR	66	16	11	7	0	0
	Final Visit		78	8	3	8	1	2
	Baseline	Relapsed	64	19	9	7	1	0
	Final Visit		54	9	20	15	2	0
Shortness of Breath	Baseline	NSR	48	18	22	7	5	1
	Final Visit		75	7	7	10	1	0
	Baseline	Relapsed	55	17	13	14	1	0
	Final Visit		53	12	15	17	3	0
Lightheadedness	Baseline	NSR	79	9	8	4	0	0
	Final Visit		83	7	3	7	1	0
	Baseline	Relapsed	80	7	8	4	1	0
	Final Visit		77	9	7	7	0	0
Chest Pain	Baseline	NSR	80	8	7	2	3	0
	Final Visit		82	3	7	5	2	2
	Baseline	Relapsed	84	8	6	2	0	0
	Final Visit		79	5	13	1	0	1
Worry	Baseline	NSR	58	19	8	10	3	2
	Final Visit		73	6	11	6	3	2
	Baseline	Relapsed	64	15	12	5	3	0
	Final Visit		57	9	18	13	2	1
Fatigue	Baseline	NSR	42	17	15	19	4	3
	Final Visit		63	8	8	15	4	1
	Baseline	Relapsed	47	12	15	20	5	0
	Final Visit		47	9	20	19	4	1

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**Table 311.1a. Premature Discontinuations from Protocol 311.**

Patient #	Sex	Age	Dose	Day	Reason for discontinuation
00110003	Male	45	250 mcg	10	Discontinued due to lack of efficacy of drug. (recurrence of AF -> amiodarone started)
00120094	Female	62	250 mcg	25	Discontinued due to lack of efficacy of drug.
00220043	Male	65	250 mcg	15	Discontinued due to lack of efficacy of drug.
00390103	Male	67	250 mcg	2	Side effect possibly related to study drug. (ventricular tachycardia)
00390108	Male	55	250 mcg	42	Not related asked to be withdrawn from the study. (palpitations)
00390111	Male	75	250 mcg	49	QTc prolongation (syncope and non-sustained ventricular tachycardia)
00390113	Male	61	250 mcg	3	Torsades de Points during intravenous infusion of dofetilide 10mcg/kg on day 1.
00110009	Male	60	500 mcg	7	Discontinued due to lack of efficacy of drug.
00120084	Male	50	500 mcg	3	Discontinued due to lack of efficacy of drug.
00120092	Male	58	500 mcg	36	Side effect probably related to study drug. (watery rhinitis)
00120093	Male	61	500 mcg	1	Discontinued due to lack of efficacy of drug.
00380068	Male	67	500 mcg	4	Discontinued due to lack of efficacy of drug.
00390107	Female	57	500 mcg	334	Discontinued due to lack of efficacy of drug.
00390109	Male	63	500 mcg	132	Not related discontinued due to inter- or concurrent illness.
00220070	Female	74	500 mcg	2	Side effect probably related to study drug. (Torsades de Point)
00110002	Male	67	750 mcg	2	Discontinued due to lack of efficacy of drug.
00120082	Male	71	750 mcg	3	Discontinued due to lack of efficacy of drug.
00120089	Female	56	750 mcg	15	Discontinued due to lack of efficacy of drug.
00120095	Male	53	750 mcg	3	QT prolongation. (QTc exceeds 550msec)
00120097	Male	63	750 mcg	22	Adverse Event. (ventricular fibrillation)
00380066	Female	69	750 mcg	4	Discontinued due to lack of efficacy of drug. (study drug stopped before treatment of AF with dc shock, calcium entry blockers)
00380080	Male	67	750 mcg	16	Discontinued: safety and lack of efficacy of drug.
00410053	Female	69	750 mcg	14	QT prolongation. (ventricular tachycardia)
00110001	Male	58	placebo	8	Discontinued due to lack of efficacy of drug.
00110006	Male	67	placebo	118	Asked to be withdrawn from the study. (Intercurrent illness)
00110012	Male	63	placebo	14	Discontinued due to lack of efficacy of drug.
00120088	Male	48	placebo	14	Discontinued due to lack of efficacy of drug.
00120096	Female	48	placebo	1	Discontinued due to lack of efficacy of drug.
00120099	Male	58	placebo	198	Discontinued due to lack of efficacy of drug.
00390106	Female	66	placebo	3	Discontinued due to lack of efficacy of drug.
00390114	Male	41	placebo	260	Lost to follow up.

**Table 119.5. List of Patients Discontinued from Double blind Therapy During In-Hospital Period and Not Included in Intent Treat Analysis (from sponsor's table 4.2)**

Patient ID	Sex	Randomized Dose	Age	Actual Dose	Day WD	Reason
6910249	Male	250 mcg	67	250 mcg	2	Adverse event. [intermittent periods of sinus arrest, paroxysmal atrial fibrillation, paroxysmal atrial flutter]
7070951	Male	250 mcg	77	125 mcg	2	Adverse event. [non- sustained ventricular tachycardia]
6850830	Male	250 mcg	79	125 mcg	3	Adverse event. [persistent SVT unresponsive to medication]
6350048	Male	250 mcg	75	250 mcg	3	Not in NSR.
6250304	Male	250 mcg	62	250 mcg	4	Adverse event. [chest pain]
5860326	Male	250 mcg	48	250 mcg	4	Not in NSR.
5880282	Male	250 mcg	74	125 mcg	4	Not in NSR.
6230005	Male	250 mcg	52	125 mcg	4	Not in NSR.
6230760	Male	250 mcg	56	250 mcg	4	Not in NSR.
5060297	Male	375 mcg	62	375 mcg	1	QT/ QTc prolongation. [42%]
6340074	Male	375 mcg	79	250 mcg	2	QT/ QTc prolongation. [23%]
6230001	Male	375 mcg	72	375 mcg	3	Not in NSR.
6250041	Male	375 mcg	78	250 mcg	3	QT/ QTc prolongation. [23%]
7070898	Male	375 mcg	89	250 mcg	3	Not in NSR.
5100131	Female	375 mcg	54	375 mcg	4	Not in NSR.
5280208	Male	375 mcg	45	375 mcg	4	Not in NSR.
5280210	Male	375 mcg	78	250 mcg	4	Not in NSR.
5860325	Male	375 mcg	73	250 mcg	4	Not in NSR.
6250727	Male	375 mcg	71	375 mcg	4	Not in NSR.
6270101	Male	375 mcg	42	375 mcg	4	Not in NSR.
6330133	Female	375 mcg	74	250 mcg	4	Not in NSR.
7070935	Female	375 mcg	76	250 mcg	4	Not in NSR.
6250303	Male	375 mcg	32	375 mcg	3	Not in NSR.
6900745	Male	375 mcg	78	250 mcg	5	Not in NSR.
5420613	Male	Placebo	60	Placebo	2	Adverse event. [monomorphic non- sustained VT]
5680609	Male	Placebo	73	Placebo	2	Asked to be withdrawn from the study.
6390627	Male	Placebo	78	Placebo	2	Adverse event. [sinus arrest]
6740140	Female	Placebo	69	Placebo	2	Asked to be withdrawn from the study.
5210319	Male	Placebo	59	Placebo	3	Not in NSR.
5600309	Female	Placebo	70	Placebo	3	Not in NSR.
5680792	Female	Placebo	60	Placebo	3	Not in NSR.
5880281	Male	Placebo	46	Placebo	3	Not in NSR.
6230759	Female	Placebo	71	Placebo	3	Not in NSR.
6250039	Male	Placebo	76	Placebo	3	Not in NSR.
6250728	Male	Placebo	60	Placebo	3	Not in NSR.
6350220	Female	Placebo	77	Placebo	3	Not in NSR.
5680791	Male	Placebo	61	Placebo	4	Not in NSR.
6250037	Male	Placebo	34	Placebo	4	Adverse event. [atrial fibrillation ]

**Table 119.5. List of Patients Discontinued from Double blind Therapy During In-Hospital Period and Not Included in Intent Treat Analysis (from sponsor's table 4.2)**

Patient ID	Sex	Randomized Dose	Age	Actual Dose	Day WD	Reason
7060908	Male	Placebo	62	Placebo	4	Not in NSR.
50020925	Female	Placebo	65	Placebo	4	Not in NSR.
5830287	Male	Placebo	84	Placebo	5	Not in NSR.
6790188	Female	Placebo	58	Placebo	5	Not in NSR.

WD = withdrawn

**Table 119.6a. List of Patients Discontinued from Double blind Therapy after an Event (from sponsor's table 4.2)**

Patient ID	Sex	Randomized Dose	Age	Actual Dose	Day WD	Reason
6250040	Male	250 mcg	67	125 mcg	283	Adverse event. [coronary artery bypass]
7070931	Male	250 mcg	67	125 mcg	157	Adverse event. [headache]
6610264	Female	250 mcg	60	125 mcg	205	Asked to be withdrawn from the study.
5470661	Male	250 mcg	78	125 mcg	5	Lack of Efficacy. [worsening pSVT]
6610115	Male	250 mcg	55	250 mcg	386	Other. [non-compliance]
6340673	Female	250 mcg	76	125 mcg	254	Patient died.
5980766	Female	375 mcg	40	375 mcg	42	Adverse event. [atrial tachyarrhythmias]
5360059	Female	375 mcg	70	375 mcg	253	Adverse Event. [discontinued medication due to intercurrent illness]
5860087	Female	375 mcg	81	250 mcg	324	Adverse event. [right hemispheric cerebrovascular accident]
5420017	Male	375 mcg	64	375 mcg	3	Asked to be withdrawn from the study.
6610117	Male	375 mcg	66	250 mcg	249	Asked to be withdrawn from the study.
6610259	Male	375 mcg	37	375 mcg	60	Asked to be withdrawn from the study.
6350045	Female	375 mcg	31	375 mcg	32	Laboratory abnormality. [elevated liver functions]
5280341	Male	375 mcg	70	250 mcg	305	Lack of Efficacy
7070950	Male	375 mcg	69	375 mcg	19	Lack of Efficacy. [rapid atrial fibrillation, ventricular tachycardia]
5210320	Male	375 mcg	48	375 mcg	49	Lack of Efficacy. [worsening of atrial fibrillation symptoms]
5980764	Male	375 mcg	64	375 mcg	159	Other. [had developed AV node reentrant tachycardia requiring ablation]
6330136	Female	375 mcg	78	250 mcg	37	QT/QTc prolongation. [24%]
5680607	Female	Placebo	60	Placebo	26	Adverse event. [memory loss (forgetfulness)]
5860872	Female	Placebo	76	Placebo	182	Laboratory abnormality. [elevated liver function tests]
5280206	Male	Placebo	62	Placebo	343	Lack of Efficacy. [exacerbation of SVT, recurrent atrial fibrillation]
5420015	Male	Placebo	67	Placebo	9	Lack of Efficacy. [pt reached clinical endpoint. Relapsed into symptomatic AF.]
5360656	Male	Placebo	78	Placebo	222	Protocol violation. [received wrong meds]
5360657	Male	Placebo	68	Placebo	205	Protocol violation. [received wrong meds]

Note: Where QT/QTc prolongation is the reason for withdrawal, the % increase from baseline, as given by the physician, is presented in [ ]. WD = withdrawn

**Table 128.4. Patients Discontinued During the In-hospital Period ( Not Included in the Efficacy Analysis)**

Patient ID	Sex	Age	-. Dose	Day*	Reason Discontinued
5350450	male	72	1000 mcg	3	Adverse event. [bacteremia]
6370170	male	59	500 mcg	4	Adverse event. [monomorphic ventricular tachycardia]
7740423	female	75	500 mcg	2	Adverse event. [sponsor requested patient withdraw due to sinus Bradycardia]
7570233	female	66	500 mcg	4	Did not meet selection criteria. [AF on day four - patient did not enter efficacy period]
5880068	male	85	250 mcg	4	Did not meet selection criteria. [AF on index ECG]
50020108	female	81	250 mcg	4	Did not meet selection criteria. [AF ]
7650342	female	82	250 mcg	3	Did not meet selection criteria. [day 4 ECG denoted AF - patient did not enter efficacy phase.]
5880221	female	61	1000 mcg	3	Did not meet selection criteria. [day 4 ECG in AF]
7650476	male	77	500 mcg	3	Did not meet selection criteria. [failed to convert to NSR during hospitalization]
7470145	female	70	500 mcg	3	Did not meet selection criteria. [in AF at discharge]
7110159	male	68	250 mcg	3	Did not meet selection criteria. [index ECG does not show NSR]
7640365	female	62	1000 mcg	3	Did not meet selection criteria. [index ECG does not show NSR]
7060216	female	74	500 mcg	3	Did not meet selection criteria. [index ECG indicates AF]
6370172	male	45	500 mcg	3	Did not meet selection criteria. [not in NSR on day 4]
5680461	male	74	1000 mcg	3	Did not meet selection criteria. [remained in AF on day of discharge]
5680350	female	68	500 mcg	3	Discontinued due to lack of efficacy of drug.
5880067	female	68	1000 mcg	4	Discontinued due to lack of efficacy of drug.
7400027	male	58	1000 mcg	2	Discontinued due to lack of efficacy of drug.
7690329	female	73	250 mcg	3	Discontinued due to lack of efficacy of drug.
7430126	male	75	250 mcg	3	Qt/QTc prolongation. [17%]
7750373	female	72	250 mcg	1	Qt/QTc prolongation. [17%]
6350377	female	73	250 mcg	3	Qt/QTc prolongation. [24%]
7100046	female	72	500 mcg	2	Qt/QTc prolongation. [28%]
7560477	female	74	250 mcg	2	Qt/QTc prolongation. [28%]
7470146	female	72	0 mcg	3	Adverse event. [suspected Torsades]
7600384	male	72	0 mcg	2	Adverse event. [ventricular tachycardia]
7060215	female	71	0 mcg	2	Asked to be withdrawn from the study.
5680292	male	78	0 mcg	3	Did not meet selection criteria. [AF at day 4]
5100177	female	80	0 mcg	3	Did not meet selection criteria. [day 4 ECG does not show NSR]
7110202	male	63	0 mcg	4	Did not meet selection criteria. [day 4 index ECG showed AF]
7030262	male	64	0 mcg	3	Did not meet selection criteria. [did not achieve NSR]
7030074	male	57	0 mcg	4	Did not meet selection criteria. [did not achieve NSR]
7300078	male	82	0 mcg	3	Did not meet selection criteria. [did not convert to normal sinus rhythm on day 4]
7400025	male	58	0 mcg	4	Did not meet selection criteria. [did not convert to NSR at day 4]
7560355	female	65	0 mcg	3	Did not meet selection criteria. [failed to have sinus rhythm on day 4]
7550306	male	62	0 mcg	3	Did not meet selection criteria. [index ECG - AF ]

**Table 128.4. Patients Discontinued During the In-hospital Period ( Not Included in the Efficacy Analysis)**

Patient ID	Sex	Age	Dose	Day*	Reason Discontinued
6440062	male	78	0 mcg	4	Did not meet selection criteria. [index ECG did not show NSR (day 4)]
7330054	male	67	0 mcg	3	Did not meet selection criteria. [index ECG did not show NSR. Patient did not enter efficacy evaluation period]
7070011	male	88	0 mcg	3	Did not meet selection criteria. [index ECG does not show NSR]
7450091	male	57	0 mcg	3	Did not meet selection criteria. [index ECG does not show NSR]
7750376	male	68	0 mcg	3	Did not meet selection criteria. [index ECG does not show NSR]
5870183	male	64	0 mcg	4	Did not meet selection criteria. [index ECG does not show NSR]
6980168	male	65	0 mcg	4	Did not meet selection criteria. [index ECG does not show NSR]
7110160	male	63	0 mcg	3	Did not meet selection criteria. [index ECG show AF ]
7120443	male	72	0 mcg	4	Did not meet selection criteria. [not in NSR day 4 discharge]
6440061	male	43	0 mcg	4	Did not meet selection criteria. [patient in AF on day 4 ECG.]
7290200	male	54	0 mcg	4	Did not meet selection criteria. [patient not in NSR]
7300077	female	57	0 mcg	3	Did not meet selection criteria. [pt did not convert to normal sinus rhythm on day 4]
6610425	male	69	0 mcg	4	Did not meet selection criteria. [subject not in NSR on day 4]
7290197	male	81	0 mcg	4	Discontinued due to lack of efficacy of drug.
7600381	male	55	0 mcg	4	Discontinued due to lack of efficacy of drug.
5880223	female	60	0 mcg	4	Discontinued due to lack of efficacy of drug..
7120442	male	70	0 mcg	5	Other. [ECG noted SVT]
5680349	female	74	0 mcg	3	Other. [investigator withdrew patient due to continuous AF]
7600357	female	53	0 mcg	2	Protocol violation. [QTc interval 466 at baseline]

\* Day Discontinued; \*\*total daily dose after adjustment for creatinine clearance and/or QTc prolongation.

**Table 128.6. Patients Discontinued at or after Qualifying as an Event in Study 128 (from sponsor's table 4.2 and Sponsor's Appendix IIIA, table 1.1)**

Patient ID	Sex	Age	Dose**	Day*	Reason Discontinued
5880065	female	61	0 mcg	53	Adverse event. [complaint of change in character of pal, continued fatigue, diarrhea, headache, syncope]
7060214	female	50	0 mcg	234	Adverse event. [small bowel obstruction]
5280083	male	69	0 mcg	135	Adverse event. [small occipital infarct]
7330053	male	54	0 mcg	132	Adverse event. [thyrotoxicosis]
5760149	male	70	0 mcg	223	Asked to be withdrawn from the study.
5280081	male	41	0 mcg	33	Discontinued due to lack of efficacy of drug.
5360192	male	64	0 mcg	25	Discontinued due to lack of efficacy of drug.
5680289	female	73	0 mcg	148	Discontinued due to lack of efficacy of drug.
5870181	female	64	0 mcg	13	Discontinued due to lack of efficacy of drug.
5980137	male	64	0 mcg	14	Discontinued due to lack of efficacy of drug.
6350058	female	73	0 mcg	148	Discontinued due to lack of efficacy of drug.
6370169	male	53	0 mcg	106	Discontinued due to lack of efficacy of drug.
6370517	male	72	0 mcg	20	Discontinued due to lack of efficacy of drug.

**Table 128.6. Patients Discontinued at or after Qualifying as an Event in Study 128 (from sponsor's table 4.2 and Sponsor's Appendix IIIA, table 1.1)**

Patient ID	Sex	Age	Dose**	Day*	Reason Discontinued
6390245	female	66	0 mcg	8	Discontinued due to lack of efficacy of drug.
6610257	male	79	0 mcg	93	Discontinued due to lack of efficacy of drug.
6610428	female	74	0 mcg	52	Discontinued due to lack of efficacy of drug.
6980167	male	82	0 mcg	35	Discontinued due to lack of efficacy of drug.
7030073	female	58	0 mcg	7	Discontinued due to lack of efficacy of drug.
7030261	male	78	0 mcg	35	Discontinued due to lack of efficacy of drug.
7060122	female	77	0 mcg	141	Discontinued due to lack of efficacy of drug.
7060218	female	65	0 mcg	17	Discontinued due to lack of efficacy of drug.
7110203	male	64	0 mcg	17	Discontinued due to lack of efficacy of drug.
7410001	male	41	0 mcg	24	Discontinued due to lack of efficacy of drug.
7450089	female	51	0 mcg	43	Discontinued due to lack of efficacy of drug.
7450093	male	46	0 mcg	40	Discontinued due to lack of efficacy of drug.
7470147	male	58	0 mcg	97	Discontinued due to lack of efficacy of drug.
7510133	male	47	0 mcg	15	Discontinued due to lack of efficacy of drug.
7560354	male	60	0 mcg	77	Discontinued due to lack of efficacy of drug.
7570236	female	57	0 mcg	95	Discontinued due to lack of efficacy of drug.
7650475	male	71	0 mcg	81	Discontinued due to lack of efficacy of drug.
7740422	male	68	0 mcg	78	Discontinued due to lack of efficacy of drug.
7740424	female	74	0 mcg	9	Discontinued due to lack of efficacy of drug.
50020105	male	48	0 mcg	100	Discontinued due to lack of efficacy of drug.
50020317	male	62	0 mcg	18	Discontinued due to lack of efficacy of drug.
50020318	male	63	0 mcg	67	Discontinued due to lack of efficacy of drug.
7680333	male	70	1000 mcg	22	Adverse event. [pAF with uncontrolled rate response]
50020110	male	69	500 mcg	48	Asked to be withdrawn from the study.
5280084	female	74	500 mcg	23	Discontinued due to lack of efficacy of drug.
5350449	male	52	1000 mcg	18	Discontinued due to lack of efficacy of drug.
5680352	male	66	500 mcg	29	Discontinued due to lack of efficacy of drug.
5760151	male	68	500 mcg	71	Discontinued due to lack of efficacy of drug.
5980138	female	60	1000 mcg	72	Discontinued due to lack of efficacy of drug.
6230117	female	61	1000 mcg	34	Discontinued due to lack of efficacy of drug.
6390246	female	78	250 mcg	78	Discontinued due to lack of efficacy of drug.
7030076	male	67	1000 mcg	105	Discontinued due to lack of efficacy of drug.
7070010	female	75	500 mcg	303	Discontinued due to lack of efficacy of drug.
7070016	female	63	1000 mcg	12	Discontinued due to lack of efficacy of drug.
7100045	male	40	1000 mcg	36	Discontinued due to lack of efficacy of drug.
7110201	male	47	1000 mcg	72	Discontinued due to lack of efficacy of drug.
7290198	male	62	500 mcg	38	Discontinued due to lack of efficacy of drug.
7370274	male	57	500 mcg	151	Discontinued due to lack of efficacy of drug.
7470148	male	60	1000 mcg	160	Discontinued due to lack of efficacy of drug.
7470242	female	55	500 mcg	155	Discontinued due to lack of efficacy of drug.
7510134	male	54	750 mcg	35	Discontinued due to lack of efficacy of drug.
7550305	male	57	500 mcg	20	Discontinued due to lack of efficacy of drug.
7550308	female	78	250 mcg	78	Discontinued due to lack of efficacy of drug.
7560353	male	56	250 mcg	93	Discontinued due to lack of efficacy of drug.

**Table 128.6. Patients Discontinued at or after Qualifying as an Event in Study 128 (from sponsor's table 4.2 and Sponsor's Appendix IIIA, table 1.1)**

Patient ID	Sex	Age	Dose**	Day*	Reason Discontinued
7560356	female	82	250 mcg	29	Discontinued due to lack of efficacy of drug.
7600360	male	43	500 mcg	159	Discontinued due to lack of efficacy of drug.
7600383	male	58	500 mcg	78	Discontinued due to lack of efficacy of drug.
7740421	male	54	500 mcg	5	Discontinued due to lack of efficacy of drug.

\* Day Discontinued; \*\*total daily dose after adjustment for creatinine clearance and/or QTc prolongation.

**Table 365.7. Patients Discontinued from Therapy After Experiencing an Event or After 24 Weeks of Follow-up**

Patient #	Treatment	Sex	Age	Day	Reason
3270251	dofetilide	Male	65	21	Adverse event. [fatigue]
1170103	dofetilide	female	63	50	Adverse event. [relapse to symptomatic atrial fibrillation]
4190209	dofetilide	Male	38	4	Lost to follow up. <sup>A</sup>
3990310	dofetilide	female	74	20	Other. [thyroid toxic adenoma - treated with I <sup>131</sup> ]
4180170	dofetilide	female	73	98	Protocol violation. [she was enrolled in the SYST-EUR study with hypotension]
4000332	placebo	Male	71	140	Adverse event. [atrial fibrillation]
4180173	placebo	female	71	76	Adverse event. [hospitalization due to pAF]
4180187	placebo	female	70	8	Adverse event. [hospitalization due to pAF]
4180228	placebo	Male	70	14	Adverse event. [hospitalization due to pAF]
4180152 <sup>B</sup>	placebo	Male	54	171	Asked to be withdrawn from the study.
4360355	placebo	Male	50	7	Asked to be withdrawn from the study.

<sup>A</sup> Was noted to be alive as of 11/16/98

<sup>B</sup> patient 4180152 completed 24 weeks of therapy without an event and is censored at 24 weeks in the analysis

**Table 113.4b. Patients Discontinued During the Chronic Phase**

Patient ID	Sex	Age	Treatment	Day	Reason discontinued
5520203	male	61	dofetilide	20	Adverse experience related to disease under study. [sustained polymorphic ventricular tachycardia]
5520004	male	70	dofetilide	16	Adverse experience related to disease under study. [sustained ventricular tachycardia]
5630074	male	76	dofetilide	15	Discontinued due to lack of efficacy of drug.
6020134	male	70	dofetilide	120	Discontinued due to lack of efficacy of drug.
7071145	male	60	dofetilide	39	Discontinued due to lack of efficacy of drug.
6701089			dofetilide	306	Not provided.
5520201	male	63	dofetilide	23	Other. [investigator error- pt discontinued due to misinterpretation of the arrhythmia]
5880124	male	67	dofetilide	4	QT/ QTc prolongation.
6230138	male	58	dofetilide	26	Side effect probably related to study. [Side effect not provided in data]
5881098	male	79	dofetilide	4	Side effect probably related to study drug. [qt prolongation with inappropriate response to isoproterenol]
5540241	male	74	Placebo	42	Adverse experience related to concurrent illness. [atrial fib with rapid ventricular response with ICD shocks x4]
6150381	male	70	Placebo	60	Adverse experience related to concurrent illness. [new onset AF]
6100141	male	64	Placebo	9	Adverse experience related to concurrent illness. [patient had continued multiple ICD firings]

**Table 113.4b. Patients Discontinued During the Chronic Phase**

Patient ID	Sex	Age	Treatment	Day	Reason discontinued
5980115	male	41	Placebo	16	Adverse experience related to disease under study. [149 discharges from ICD for SVT]
5160235	male	56	Placebo	80	Adverse experience related to other event. [subdural hematoma - a fall down a flight of stairs.]
5690101	male	70	Placebo	68	Asked to be withdrawn from the study.
7071136	male	69	Placebo	77	Asked to be withdrawn from the study. [patient saw accupuncturist she told patient he shouldn't take medication]
5160233	male	70	Placebo	206	Asked to be withdrawn from the study. [pt ran out of drug & refused to be hospitalized to restart drug]
6020326	male	54	Placebo	30	Discontinued due to lack of efficacy of drug.
6021119	male	52	Placebo	186	Discontinued due to lack of efficacy of drug.
6050322	male	33	Placebo	37	Discontinued due to lack of efficacy of drug.
6751062	female	58	Placebo	34	Discontinued due to lack of efficacy of drug.
6751253	male	68	Placebo	262	Discontinued due to lack of efficacy of drug.
5280072	male	63	Placebo	4	Discontinued due to lack of efficacy of drug.
5520001	male	71	Placebo	5	Other. [inability of ICD to deliver therapy]
6051053	male	37	Placebo	77	Other. [patient had heart transplant - AICD removed]
6531081	female	71	Placebo	38	Other. [sponsor requested patient withdrawal due to a history of Torsades]
5260025	male	56	Placebo	5	Other. [supra ventricular tachycardia requiring treatment not permitted in protocol]

APPEARS THIS WAY  
ON ORIGINAL

D. Weder  
FEB 10 1999

NDA 20-931  
Tikosyn (Dofetilide)  
February 10 1999

**DOFETILIDE: HOW BEST TO USE THIS DRUG AND HOW BEST TO PRESCRIBE**

BY

A. Olufemi Williams

The following are suggestions based on DIAMOND studies, and they address management of risks of Dofetilide in the post-marketing period. Assuming that the review has identified the major life-threatening risks among survivors, management of drug-induced risks is a logical sequel. The Division's meeting on February 9 with Dr Lipicky, Division Director, requested all members present to think about management of potential risks of Dofetilide taking into account the labeling, and comments of members of the Advisory Committee meeting of 1/28/99.

- 1) Use only in patients with chronic atrial fibrillation/flutter who are symptomatic and are in NYHA class II at least.
- 2) Do not use in patients with creatinine clearance below 40ul/min outside the hospital environment in order to minimize risk of Torsades, particularly in females.
- 3) Discontinue therapy in patients with QT >450msec regardless of sex or age and regardless of the baseline length of QT. Do not rely on increased %tage in QY prolongation. The exclusion criteria in DIAMOND stipulated increase >20% but labeling suggests 15%.
- 4) For the first 2/3 years FDA should mandate a) Monitoring of Creatinine and b) QT intervals, and c) symptoms monthly in order to gather information during post-marketing period.
- 5) Simultaneously, physicians prescribing the drug should be mandated to a) Monitor Creatinine, b) evaluate QT intervals, and c) correlate symptoms monthly for the first year on therapy.
- 6) Adverse events should be reported to the sponsor and collated for onward transmission to the FDA.
- 7) Set up a 1 800 number
- 8) Patients on the drug should carry ID cards on them (just like epileptics or diabetics) with the dose they are taking so that if they develop Torsades or cardiac arrest due to ventricular arrhythmias or life threatening episodes they can be defibrillated by paramedics or physicians.
- 9) Data generated over the next one or two years will provide data for needs assessments, and analyses of risks consequent on therapy and this will in turn aid management of risks and post-approval policy formulation by FDA for risk management.
- 10) Educate pharmacists, nurses and patients on the potential dangers of the drug.

cc  
Division File,  
NDA 20-931  
HFD 110-A O Williams  
HFD110-Shaw Chen  
HFD110-David Roeder  
HFD110-R. Lipicky

*JS*  
\_\_\_\_\_  
A.O. Williams, M.D.

D. Roeder  
DEC 29 1998

NDA 20-931  
Tikosyn  
DIAMOND STUDIES  
SAFETY REVIEW  
DECEMBER 18, 1998

The attached document is the medical officer's review of DIAMOND STUDIES which addresses Dofetilide (TIKOSYN) safety. Additional review of Dofetilide safety is in other parts of this NDA.

Medical Officer.....  
A.O. Williams, M.D.

*ISI*

- cc:  
NDA 20-931  
HFD110-Division File  
HFD110-David Roeder  
HFD110-A.O. Williams  
Dr Shaw Chen M.D., Ph.D.

**Cardio-Renal Drug Product Division  
HFD110  
DIAMOND STUDIES**

NDA#: 20-931	NDA Volumes 1 and 2
Drug Name: Dofetilide	Sponsor: Pfizer Pharmaceuticals
Date Received March 11 1998	Date completed: December 7, 1998
Type of document: Electronic	Correspondence Date: March 9, 1998
Medical Review : DIAMOND STUDIES AF/AFL SUBSTUDY RI SUBSTUDY	Type of Documents: Electronic Dates: March 14, 1998; July 14, 1998; August 1998
Medical Reviewer: A.O. Williams, M.D.	

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## 1.0 Title of Study

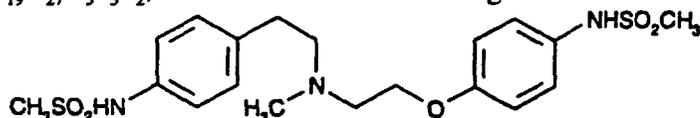
- ◆ A double-blind, placebo-controlled trial to evaluate the efficacy and safety of Dofetilide in high risk patients with reduced systolic left ventricular function and congestive heart failure - DIAMOND CHF.
- ◆ A double-blind, placebo-controlled trial to evaluate the efficacy and safety of Dofetilide in high risk patients with reduced systolic left ventricular function and congestive heart failure and recent myocardial infarction - DIAMOND MI.

## 1.1 Study objectives

- ◆ To evaluate whether treatment with Dofetilide reduces total mortality and morbidity of high risk subjects with left ventricular dysfunction in association with congestive heart failure,
- ◆ and / or recent myocardial infarction without adversely affecting morbidity from CHF and incidence of re-infarction.

## 1.2 Background and History of Protocol Development

The chemical name for Dofetilide is N-[4-(2-(2-[4-(methanesulphonamido) phenoxy]-N-methylethylamino) ethyl) phenyl]methanesulphonamide. The molecular formula is  $C_{19}H_{27}N_3O_5S_2$ , and it has a molecular weight of 441.6. The structural formula is :



The relatively high incidence of mortality associated with arteriosclerotic heart disease and myocardial infarction is invariably due to sudden unexpected death (SUCD) which can be attributed to cardiac arrhythmias. Previous studies have so far shown no safe and effective agents that are considered therapeutically safe in reducing mortality and or preventing SUCD. For example, quinidine has a negative influence by increasing mortality despite its efficacy in reducing the frequency of premature ventricular contractions. Amiodarone and propafenone, however, showed positive influence on mortality from SUCD in the absence of structural heart disease. Therefore, excess mortality in clinical trials with patients on anti-arrhythmic therapy and structural heart disease continues to be a therapeutic problem particularly in the area of safety. Although Dofetilide and Amiodarone share similar mechanisms of action, the sponsor claims that Dofetilide appears to cause less significant side effects compared to amiodarone and can be administered in the presence of structural heart disease.

## 1.3 Mechanism of action

Dofetilide acts by complete blockade, at nanomolar concentrations, of the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current,  $I_{Kr}$ . Over several orders of magnitude of concentration, the drug produces a block of  $I_{Kr}$  and no relevant block of the other repolarizing potassium currents (i.e.,  $I_{KS}$ ,  $I_{K1}$ ,  $I_{o'}$ ,  $I_{KATP}$ ), the hyperpolarization activated current ( $I_f$ ), the fast sodium current or the voltage-dependent calcium current. It has no affinity for a range of classical receptors including adrenergic alpha- and beta receptors at concentrations associated with the proposed therapeutic doses. Dofetilide demonstrates Vaughan Williams Class III anti-arrhythmic activity through its selective blockade of  $I_{Kr}$  which in turn blocks re-entry by prolonging the effective refractory period. At clinically relevant concentrations (1-5 ng/ml), Dofetilide does not have any effect on sodium channels (associated with Class I effect), calcium channels (associated with Class IV effect), or other potassium channels, and has no beta-blocking (Class II) effect.

#### 1.4 Protocols

Two protocols (DIAMOND CHF and DIAMOND MI) were designed to find out if Dofetilide therapy is associated with reduced morbidity and mortality in patients with reduced left ventricular function and structural heart disease. An additional substudy was designed to test whether in a sub-population with supraventricular arrhythmias (AF/AFL), taken from the two major studies, Dofetilide can restore sinus rhythm (SR) and, once restored, maintain normal sinus rhythm for up to at least one year, thus reducing the risks of embolization, stroke and cardiac failure.

#### 1.5 Protocol Amendments

The following protocol amendments and statistical analysis plans have been adopted for the analysis of the DIAMOND CHF/MI studies:

Protocol: 21 May 1993

Amendments: I 6 August 1993; II 13 January 1994; III 22 February 1994;  
IV 19 April 1994; V 31 October 1994; VI 18 February 1995;  
VII 6 March 1995; VIII 26 April 1996.

Statistical Analysis Plan: 16 August 1996; Amendment I: 11 March 1997

Where amendments to endpoints occurred after the beginning of the study, they were made at the suggestion of the sponsor's independent Steering Committee.

#### 1.6 Definitions

CHF is defined as a recent history (defined as within 1 month) of shortness of breath at rest or with minimal exertion or paroxysmal nocturnal dyspnoea (equivalent to NYHA Class III and IV). Eligible patients must have echocardiographically proven left ventricular dysfunction with a wall motion index (WMI) < 1.2.

Myocardial infarction or reinfarction is defined as the presence of at least two of the following clinical features: Chest pain > 20 min; ECG changes suggestive of MI, and elevation of enzymes. Diagnostic enzyme changes of MI include elevated ASAT, LDH, LDH1, CK, CKMB, CKB or Troponin T fraction of at least twice the upper limit of normal.

#### 1.7 The Claims

- ◆ In CHF studies, Dofetilide demonstrated no effect on total or cardiac mortality in the high risk population of CHF, but conferred significant benefit in delaying the progression of underlying heart failure.
- ◆ In MI studies, although modest benefits were shown in favor of Dofetilide, there was no significant difference on total or cardiac mortality compared to placebo.
- ◆ Furthermore, that in a patient population with recent MI and an ejection fraction < 35%, Dofetilide can safely be given without adverse effects on cardiac performance as frequently experienced with other types of anti-arrhythmic drugs.

#### 1.8 Proposed Indications

The two indications proposed for Dofetilide are:

- (a) Maintenance of normal sinus rhythm with associated symptom relief in patients with supraventricular arrhythmias, and
- (b) Conversion of atrial fibrillation and atrial flutter to normal sinus rhythm.

#### 1.90 Study design and Treatment

This was a multicenter, randomized, intent-to treat, double-blind, routine-treatment, placebo-controlled, parallel group study.

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The studies were carried out in 37 centers in Europe and each center was expected to recruit about 100 patients. Dofetilide was given as 500mcg bid, placebo as matched capsules b.i.d. to subjects without AF/AFl or renal impairment (RI). Patients with CLcr lower than 60ml/min (Cockcroft and Gault (1976) estimates, or with AF/AFl at baseline were given reduced doses of Dofetilide (250mcg bid or matched placebo), and those with CLcr below 40ml/min were given 250mcg od. Further dose adjustments to the minimum of 250mcg od were made as necessary for excessive QT/QTc prolongation or adverse events (See Table 50a, page 47). After discharge, patients were seen at Month 1, Month 3 and at 3 monthly intervals thereafter until 12 months after randomization of the final recruit (Figures 1 and 2). The total observation periods were approximately 3 years for the CHF study (End of Study EOS=Dec10, 1996), and 3.5 years for the MI study (EOS=July 1, 1997), which was slower to recruit.

### 1.91 Enrollment/Recruitment of patients-CHF/MI

Patients were consented and screened for the study within 7 days of their primary event of hospitalization for CHF or MI. Study treatment was monitored using telemetric observation of rhythm and heart rate for at least the first 3 days of uninterrupted medication.

### 1.92 Study Dates

DIAMOND CHF -11th November 1993-10th December 1996 (End of study=EOS).

DIAMOND MI -11th November 1993-1st July 1997 (End of study=EOS).

Figure 1: Study Design for CHF

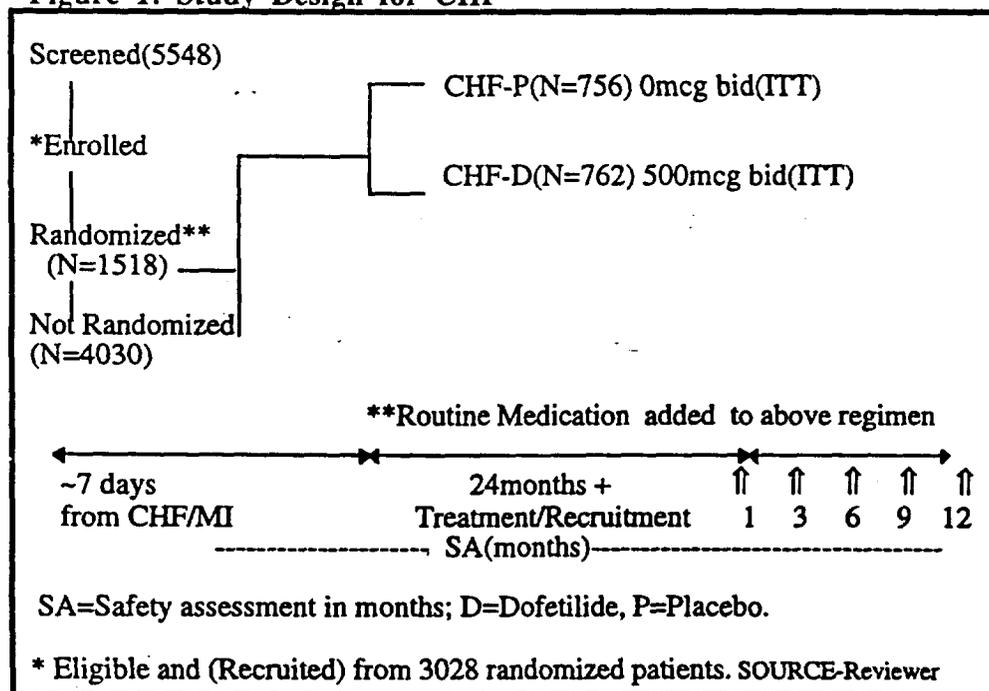
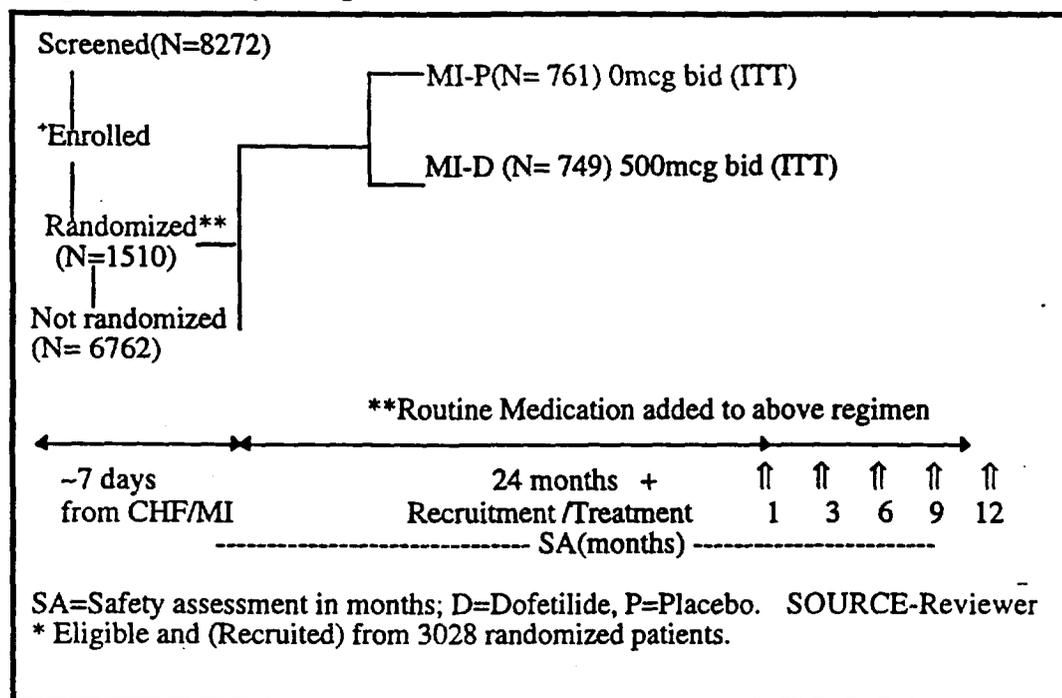


Figure 2: Study Design for MI



\*Two patients were enrolled and randomized after December 10 1995 for the CHF study and one patient was enrolled on July 1 1996, which was the last day for recruiting patients for MI study.

### 1.93 Randomization

Randomization to Dofetilide or placebo was based on a computer-generated list blocked by center, and stratified for NYHA classification and either Wall Motion Index (WMI) of  $\geq 0.8$  to  $\leq 1.2$ , or WMI  $\leq 0.8$ , respectively. At randomization, the median duration of CHF since first diagnosis was 12 months (range 0 - 324 months) and about 70% of each treatment group had WMI values between 0.8 and 1.2, corresponding to a left ventricular ejection fraction (LVEF) between 25% and 35%.

Table 1 summarizes the investigational plan before randomization at baseline. These included a clinical examination, including recording of blood pressure, a blood sample for laboratory safety test, and a 12-lead surface ECG, and QTc estimations. When feasible, patients had a 24-hour Holter monitoring (pre-treatment) performed at baseline. Prior to administration of the first dose, and for the following 3 days, the patient was monitored by telemetry. Patients were Holter-monitored for 24 hours on Day 3 of treatment when feasible.

### 1.94 Schedule of Assessment

The schedule of assessment is presented in Table 1. The results of video-taped echocardiographs were sent to investigators before randomization so that WMI results could be used to assign patients to treatment groups. It is noteworthy that no subsequent WMI measurements were carried out during the study, particularly for characterization of worsening heart failure for hospitalization and also for objective assessment of LVEF.

Table 1: Investigational Plan for CHF/MI-Diamond Studies-Section 1.94

Parameters	Screen	*B L	D1	D2	D3	D4	M 1	3	6	9	12	15	1 8	21	24	27	30	33	3 6	
Demographic s	+																			
Medical History	+																			
Clin. examination		+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood pressure		+				+	+		+		+		+		+		+		+	+
ECG include QTc		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Concomitant Med.	+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Laboratory safety		+					+	+	+	+	+	+	+		+		+		+	+
Telemetry			+	+	+															
Chest XRay (CHF-pts)	+																			
AE-recording		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Echocardiography	+																			
Event monitoring	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Quality of life assess							+	+	+	+	+	+	+	+	+	+	+	+	+	+
Socioeconomic assessments							+	+	+	+	+	+	+	+	+	+	+	+	+	+
NYHA classification		+					+	+	+	+	+	+	+	+	+	+	+	+	+	+
Holter -24hr		+			+															

D = Day; M = Month; \* = Randomization; BL = Baseline.

### 1.95 Organization and Monitoring of studies

The conduct of the study was coordinated by a

The follow-up of randomized patients for mortality was effected using data derived from the central personal registry (CPR). The CPR is a unique repository of information containing actual dates of deaths of all Danish citizens regardless of their geographic location.

### 2.0 Statistical analyses: Plan of data analyses

#### Primary analysis

#### Data Analyses: Primary Efficacy Analysis

The principal analysis will be all cause mortality of all ITT patients including the outcome of patients lost to follow-up. Patients who remained in the study until study termination will be censored at the last patient's visit plus seven days. The survival time will be treated as censored on the date of operation for those patients receiving heart transplants. The primary analyses will be carried out for CHF and MI cohorts separately; a secondary analysis pooling the MI and CHF cohorts will also be carried out, testing for consistency of treatment effect over the cohorts, and also for an overall treatment effect allowing for cohort.

- ◆ The survival distribution for each treatment group will be estimated using the Kaplan-Meier method and the main assessments of efficacy will be based upon a logrank test. Cox's proportional hazard model will be used to confirm differences in survival times among the two treatment groups after allowing for the following risk factors: wall motion index, age, sex, etiology of heart failure, i.e. ischemic and non-ischemic, level of serum potassium at baseline, number of previous MI, smoking history and arrhythmia at baseline. Estimates of relative risks and corresponding 95% confidence intervals will be presented.

- ◆ Kaplan-Meier estimates of the survival curve for each treatment are presented together with the yearly estimates of mortality and corresponding 95% confidence intervals. These are presented pooled across WMI categories and separately for each WMI category (WMI <0.8 and WMI > 0.8). The log-rank statistic, stratified by center and WMI category, was calculated from the observed and censored survival times.

### Secondary analyses

- ◆ An investigation of the influence of pre-defined risk factors using Cox's proportional hazards model for both the "ITT population - end of study" analysis and "ITT population - on treatment" analysis will be carried out.
- ◆ An on-treatment analysis, in which only deaths occurring whilst receiving study medication were considered as events, with all others being censored at the date of last study medication.
- ◆ An ITT analysis for subjects randomized after the Protocol Amendment (Amendment IV) allowing for dosage adjustment according to their level of creatinine clearance.
- ◆ An on-treatment analysis including a 30 day lag period, in which only deaths occurring up to and including 30 days after discontinuing study medication were considered as events, with all other events being censored at the date of last study medication plus a 30 day lag period.

### Secondary efficacy endpoints

- ◆ Cardiac mortality;
- ◆ Incidence of Total Arrhythmic Death (TAD);
- ◆ Cardiac mortality plus resuscitated cardiac arrest;
- ◆ Incidence of arrhythmia requiring treatment and withdrawal of study drug;
- ◆ Worsening of CHF;
- ◆ Number of infarctions/reinfarctions
- ◆ In subjects with AF at baseline, separate analysis combining total mortality/number of strokes/number of systemic embolisms;
- ◆ Total mortality, cardiac mortality and incidence of TAD on subjects randomized from the time of the implementation of the protocol amendment allowing for dosage adjustment according to the calculated creatinine clearance. Implementation date: 1st May, 1994;
- ◆ Total mortality, cardiac mortality and incidence of TAD for the first year of treatment after randomization. This was not intended to support the regulatory filing so has not been included in this report.

### Secondary analysis

The analyses of cardiac mortality will be the same as those for total mortality with between-treatment comparison of the time to cardiac deaths in the ITT analysis using log-rank test at the 5% level (2-sided), stratified for two variables - WMI and center. In addition, analyses of subjects randomized after the protocol amendment allowing for dosage adjustment according to their creatinine clearance, using a Cox's Proportional Hazards Model, will also be performed. The estimate of survival at 1 year will be tabulated and presented graphically in each of these analyses without formal statistical comparisons.

## 2.2 Populations For Analyses

- ◆ Prior to study closure and whilst the data remained blinded to the sponsor, three populations were defined for analyses:  
**Intent-to-Treat (ITT)**  
The ITT population included all randomized subjects, their treatment groups being defined according to the drug to which they were randomized. All events occurring on treatment for subjects withdrawn from the study and events occurring up to and including the date of the last scheduled visit for every subject still receiving treatment were considered for analysis. Subjects withdrawn prior to their final scheduled visit were also considered for mortality assessments up to the date of the final study visit of the last subject enrolled for DIAMOND CHF.
- ◆ **On-treatment (OT)**  
This group included every randomized subject who received at least one dose of study medication. In contrast to the ITT population, treatment for the OT population was defined as the drug actually received. Events recorded up to and including the day of discontinuation of randomized treatment for an individual subject were considered for analysis. A second analysis extended the observation time of the OT population to 30 days after discontinuation of randomized treatment to confirm the validity of the OT analysis.
- ◆ **Screened-only (SO)**  
This analysis included every subject who was screened for entry to the study but who was not subsequently randomized. Subjects who had multiple screening visits but were not randomized to treatment only had the details from their final screening visit included for assessment.
- ◆ Prior to unblinding of the study, a review of the data identified that all subjects had received at least one dose of the correct study medication. Consequently the ITT and OT populations contain identical numbers of subjects and the only difference between them is the period of follow up used in the analysis. Therefore these populations will be defined as the ITT population - end of study analysis and ITT population - on treatment analysis, respectively, throughout the report.

## 2.3 Sample Size

Sample size calculations were based on estimated one year mortality rate of 25% (Lachlin 1981). Using a power of 90% and a 5% significance level (2-sided) a total sample size of 1050 subjects was considered sufficient to detect a reduction in the one year mortality rate from 25% to 18.75%, assuming approximately 402 deaths over the course of the study. The number of subjects randomized to each study exceeded the minimum calculated sample size for this type of study, and this was considered adequate.

## 3.0 Case Report Forms (CRF)

The CRFs were filled by investigators prospectively for patients when seen at scheduled clinic visits and retrospectively for patients who were either not seen at scheduled visits for some reason or the CRO informed investigators of reasons including SAEs that had affected the patients.

## 4.0 Labeling

- ◆ Since DIAMOND studies are trials specifically designed to evaluate drug safety on mortality in the presence of structural heart disease, the sponsor proposes the following:

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- ◆ In general, Dofetilide showed no statistically significant effect on mortality in treated subjects compared to placebo subjects, regardless of the severity and extent of underlying structural heart disease. This makes the drug usable in patients with concurrent structural cardiac diseases who may potentially benefit from anti-arrhythmic therapy.
- ◆ Compared to other approved anti-arrhythmic agents, active controls, and placebo group in DIAMOND, mortality was not increased in Dofetilide treated patients. Furthermore, there is a relatively lower frequency of "drug-related" side effects (AEs) in patients receiving Dofetilide in both studies (CHF and MI).

### 5.0 Investigators and Sites of Investigation

Principal Investigators: Drs: M. Møller; J. Videbaek; H Bagger, N. Keller; K.Norgaard Hansen; F. Frandsen; J. Markenvard; K. Lyngborg; J.J. Kjaergaard; H.Depcik; Per Fritz Hansen; L. Køber; C. Torp Pedersen; F.J. Gammelgaard; K.Egstrup; S.E. Jensen; E. Agner; K. Skagen; E. Klarholt; E. la Cour Petersen; D.Hansen; Dalstrøm; H. Vagn Nielson; A. Johannesen; Ib Frimodt Lindbjerg; M.Scheibel; M. Asklund; T. Glud; B. Broch Møller; T.L. Svendsen; S. Bach; J.Larsen; I. Nielsen; E. Kjølner; H.A. Sørensen; V. Mohr Drewes; P. Eliassen; F.Egede; M. Brøns; B. Dorff; A. Deding; M. Tangø; O. Lederballe Petersen; H.K.Nielsen; J. Lindskov; K. Garde; T. Gjørup; H. Nielsen; E. Steinmetz; J. Rokkedal Nielsen; S Zabel Abildstrøm. Thirteen centres (0018, 0029, 0164, 0166, 0167, 0168, 0169, 0170, 0171, 0172, 0174, 0182, 0187), were involved in the study.

### 6.0 Inclusion Criteria - CHF

1. Males and females of non-childbearing potential i.e. who were at least 2 years past the menopause or who had been surgically sterilized.
2. Above 18 years of age.
3. Subjects with CHF requiring treatment. This could be a new diagnosis or based on their medical history, but subjects were to have been hospitalized with CHF within the previous 7 days. To be eligible for entry, subjects were to have echocardiographically proven left ventricular dysfunction determined as a WMI of less than or equal to 1.2.
4. Written informed consent.

### Exclusion criteria - CHF

1. Subjects with a resting ventricular rate of less than 50 bpm when awake and at time of randomization.
2. Sick sinus syndrome unless treated with a well-functioning pacemaker.
3. Second or third degree AV block at time of randomization unless treated with a well-functioning pacemaker.
4. History of polymorphic ventricular tachycardia (VT) secondary to treatment with anti-arrhythmic drugs or with other drugs which have been associated with the genesis of Torsade de Pointes VT.
5. QTc interval exceeding 460msec in the drug-free state at the time of randomization. In cases of increased QRS width, i.e.  $\geq 120$ msec e.g. due to bundle branch block (BBB), a QTc interval of up to 500msec was to be accepted.
6. Diastolic blood pressure  $>115$ mmHg or systolic blood pressure  $<80$ mmHg at time of randomization.
7. Subjects who were to be likely to die from other causes during the course of the trial (i.e. cancer including treatment with anti-neoplastic drugs).
8. Serum potassium  $<3.6$ mmol/L or  $>5.5$ mmol/L at time of randomization.
9. Concomitant therapy with Class I or III anti-arrhythmic drugs, or with other drugs known to be associated with the genesis of Torsade de Pointes VT or those receiving such treatment in the period of time corresponding to five times the relevant half-life prior to receiving study treatment.

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10. Amiodarone treatment within the last 3 months.
11. Those who had taken part in studies with an experimental drug in the previous 3 months.
12. Subjects who had previously received Dofetilide.
13. Chronic alcoholism, drug addiction, dementia or other conditions where subjects could not cooperate in the study.
14. Clinically significant liver dysfunction, e.g. cirrhosis, or clinically significant reduced kidney function, originally defined as serum creatinine below 250mcmol/L, later modified in generic amendment V to creatinine clearance below 20ml/min.
15. Subjects on urgent cardiac transplantation list.
16. Acute myocarditis.
17. Subjects with planned cardiac surgery including surgery for valvular heart disease, coronary artery bypass grafts (CABG) and percutaneous transluminal coronary angioplasty (PTCA).
18. Subjects with aortic stenosis. This was to be interpreted as haemodynamically unstable aortic stenosis.
19. Subjects who had cardiac surgery within the preceding 4 weeks.
20. Subjects with an implantable cardioverter defibrillator (ICD).
21. Subjects receiving Cimetidine who could not be offered alternative anti-ulcer therapy (e.g. omeprazole). A list of prohibited medications was used to monitor protocol violation.

#### 6.1 Inclusion criteria - MI

1. Males and females of non-childbearing potential i.e. who were at least 2 years past the menopause or who had been surgically sterilized.
2. Minimum age was to be 18 years.
3. Subjects who had experienced MI within the previous 7 days and who had a WMI of less than or equal to 1.2. WMI was to be measured by echocardiography between the second and sixth day following the MI.

MI for this study was to be defined by an elevation of those enzymes usually considered to be diagnostic of MI (see below) in combination with either chest pain lasting for at least 20 minutes and/or ECG changes, such as 2mm elevation of the ST segment in two or more contiguous leads or new pathologic Q-waves.

Increases greater than twice the upper limit of normal of the local analytical laboratory in the following enzymes, either singly or in combination, would be considered as diagnostic of MI:

\_\_\_ Creatinine kinase (CK) CKMB or CKB; An isolated elevation of CK with negative CKMB or CKB would not be acceptable for the diagnosis.

\_\_\_ Lactate dehydrogenase (LDH) or LDH1,

\_\_\_ Troponin T.

\_\_\_ Aspartate transaminase (aspartate aminotransferase - SGOT, ASAT, AST).

The investigator was required to ensure that there were no other medical conditions which could explain the raised enzymes.

4. Written informed consent.

#### Exclusion criteria - MI

1. Subjects with a resting ventricular rate of less than 50bpm when awake and at time of randomization.
2. Sick sinus syndrome unless treated with a well-functioning pacemaker.
3. Second or third degree AV block at time of randomization unless treated with a well-functioning pacemaker.
4. History of polymorphic ventricular tachycardia (VT) secondary to treatment with antiarrhythmic drugs or with other drugs\* which have been associated with the genesis of Torsade de Pointes VT.
5. QTc interval exceeding 460msec in the drug-free state at the time of randomization.

In cases of increased QRS width, i.e.  $\geq 120$ msec e.g. due to bundle branch block (BBB), a QTc interval of up to 500msec was to be accepted.

6. Diastolic blood pressure >115mmHg or systolic blood pressure <80mmHg at time of randomization.
7. Subjects who were to be likely to die from other causes during the course of the trial (i.e. cancer including treatment with anti-neoplastic drugs).
8. Serum potassium <3.6mmol/L or >5.5mmol/L at time of randomization.
9. Concomitant therapy with Class I or III antiarrhythmic drugs, or with other drugs\* known to be associated with the genesis of Torsade de Pointes VT or those receiving such treatment in the period of time corresponding to five times the relevant half-life prior to receiving study treatment.
10. Amiodarone treatment within the last 3 months.
11. Those who had taken part in studies with an experimental drug in the previous 3 months.
12. Subjects who had previously received Dofetilide.
13. Chronic alcoholism, drug addiction, dementia or other conditions where subjects could not co-operate in the study.
14. Clinically significant liver dysfunction, e.g. cirrhosis, or clinically significant reduced kidney function, originally defined as serum creatinine below 250µmol/L, later modified in generic amendment V to creatinine clearance below 20ml/min.
15. Subjects on urgent cardiac transplantation list.
16. Acute myocarditis.
17. Subjects with planned cardiac surgery including surgery for valvular heart disease, coronary artery bypass grafts (CABG) and percutaneous transluminal coronary angioplasty (PTCA).
18. Subjects with aortic stenosis. This was to be interpreted as haemodynamically unstable aortic stenosis.
19. Subjects who had cardiac surgery within the preceding 4 weeks.
20. Subjects with an implantable cardioverter defibrillator (ICD).
21. Subjects receiving Cimetidine who could not be offered alternative anti-ulcer therapy (e.g. omeprazole).

## 6.2 Withdrawal criteria CHF/MI

Subjects withdrawn prior to their final scheduled visit, regardless of the reason, were censored for mortality assessments up to the date of the final study visit of the last subject enrolled for DIAMOND CHF and MI studies.

## 6.3 Drug administration

Study drug was administered in addition to the best available treatment offered to each patient (Tables 3-4)). Randomization to treatment was stratified according to WMI, patients being allocated to Dofetilide 0.5 mg bid or matched placebo capsules bid, subject to meeting one or more of the following criteria:

- ◆ Patients with AF/AFl at baseline were allocated to half of the nominal dose - 0.25mg Dofetilide b.i.d. or one placebo capsule b.i.d.
- ◆ Patients with creatinine clearance (CLcr) levels estimated from the Kampmann nomogram (1974) or Cockcroft and Gault equation (1976) between 40 and 60ml/min were also allocated 0.25mg Dofetilide bid or one placebo capsule bid, those with estimated values between 20 and 40ml/min were allocated 0.25mg Dofetilide od or one placebo capsule od. This dosing regimen has been estimated to offer a similar exposure to Dofetilide in subjects with reduced CLcr as 0.5mg b.i.d. in subjects with normal renal function (115-219 study report).

- ◆ In the DIAMOND studies, Amendment IV required that subjects with very low estimates of CLcr (<20ml/min) were no longer considered for entry, and those subjects with low estimates who were already in the studies were withdrawn. Single dose adjustments were made for subjects with levels between 40 and 60ml/min and double adjustment for subject with levels between 20 and 40ml/min by either reducing the number of capsules, increasing the dose interval, or a combination of both, i.e 0.5mg bid was changed to 0.25mg bid and 0.25mg bid was changed to 0.25mg od.
- ◆ Subjects whose CLcr was below 20ml/min at screening were not accepted for treatment and those whose levels fell below this limit during the study were withdrawn from treatment. Thus study treatment, either Dofetilide or placebo, could be adjusted. Further, as treatment progressed, dose adjustments were made as a result of subjective adverse events, the occurrence of atrial fibrillation or to reduce excessive QTc prolongation, defined for the study as increases > 550msec or 20% from baseline. The same restrictions were applied to QT intervals for subjects in a continuous paced rhythm. Subjects were only allowed to have two dose adjustments from the nominal dose and were withdrawn when events required a third adjustment.

### 7.0 Summary of comments on Protocol

The DIAMOND protocol seeks to find out whether Dofetilide therapy reduced morbidity and mortality in the defined high risk population of patients with left ventricular dysfunction and structural heart disease using a prespecified dose-range. The actual dose was dependent on creatinine clearance, the presence of atrial fibrillation or flutter, or prolonged QT interval. These adjustments were carried out on an individual patient basis in order to reduce adverse events when compared to placebo. Safety evaluation between treatment groups was difficult because dose adjustments had to be targeted to individual patient defined risks. Variable proportions of patients were therefore managed for risks rather than for efficacy (Table 50a page 47). As a result, the incidence of AES was reduced in the Dofetilide group. The study however, was powered for total mortality regardless of dose adjustments, and dose adjustments were effected after the study commenced.

The dosage adjustments, designed to reduce QT prolongation and Torsades, would appear to have favorably affected mortality outcome and safety issues. This is a clinical approach to individual drug-risk profiling, rather than individual disease-risk profiling in both DIAMOND studies. Creatinine clearance appeared to be the determining variable for risk profiling rather than disease severity for which an indication is sought. Since total drug exposure was reduced in the cohorts of patients with QT or QTc prolongation >20% change (See Figures 30-34; page 36-38), the impact of concomitant medication between treatment groups makes objective comparisons difficult.

Torsades and prolongation of QT interval was higher in Dofetilide treated patients prior to creatinine clearance dependent dosing regimen, and was still higher after the regimen was instituted compared to placebo. When creatinine dependent dosing of patients with renal impairment was instituted, the incidence of Torsades was reduced but still higher in the Dofetilide group compared to placebo. Targeting care to the individual defined risk and management of risks was a prominent feature in DIAMOND studies. This was not adequately controlled for in the protocol and could be a limiting factor in its use for the indications sought. The relative lack of Torsades in placebo patients highlights the issue of Dofetilide safety at therapeutic levels.

The CLcr level of >60ml/min was adopted for normal patients. This cut off level that was used for dose adjustment is not in accordance with the "FDA guidelines on PK and renal disease". This relatively low level is acceptable to the reviewer because of the reduced LVEF in the patients.

One of the exclusion criteria in DIAMOND studies was QTc interval exceeding 460msec in the drug-free state at the time of randomization, and in cases of increased QRS width,  $\geq 120$ msec e.g. due to bundle branch block (BBB), a QTc interval of up to 500msec was to be accepted. While the exclusion of patients with long QT/QTc is clinically sound, the exclusion of an "at-risk" special population, who may be responders with single oligonucleotide changes in their  $I_{K_r}$  cardiac channel, has not been studied. The possible role of single nuclear polymorphism of the  $I_{K_r}$  channel in the general population and in high risk populations with left ventricular dysfunction requires further evaluation in Dofetilide safety. In general, the selection of patients based on phenotypic features may be problematic when pharmacological mode of drug action was based on a "genotypic" feature.

Although one of the criteria for enrollment of CHF patients is that they must require treatment, about 6.4% of patients were enrolled with NYHA class I [(195/3028 (6.4%)). There was also an imbalance in the numbers of patients recruited between ischemic and non-ischemic groups based on severity of heart failure, using the NYHA classification. There was a relatively higher frequencies of NYHA class II in randomized MI patients ( 54% ) compared to CHF patients (37.5%) (Section 8.4 page 14). The hazard ratio of WMI for MI-ITT is 0.48, whereas for CHF-ITT, it was 0.71 (p values for both  $\leq 0.001$ ). While both showed decreased hazard with increased WMI, the risk was less with MI compared to CHF.

The study design allowed for an intervening period between the final clinic visit date and the designated dates for end of studies. Follow up among patients recruited in the 12 months preceding the end of study dates was carefully evaluated, particularly the mortality data. Two CHF-ITT patients were recruited after the dates they should have been recruited but the dates of the final recruited MI-ITT patients were consistent with the protocol.

Twelve patients were included in the primary efficacy analysis who had not been followed for 360 days as specified in the protocol. The investigators did not physically examine all the patients at the end of study. Completion of data on deaths and SAEs in CRFs was effected by two means : (1) When a subject died in hospital, the investigator was notified at the next scheduled clinic visit and (2) The CRO ran a monthly CPR search and any deaths at home were notified to the investigator for inclusion in the final visit entry (CRF or SAE forms). As a result, the dates of deaths entered into the CRF forms for patients not seen are dates notified to investigators and correspond to the actual dates of deaths in the CPR. The magnitude of the validation of these entries was about 52/632 (5%) patients for CHF and 32/785 (4%) patients for MI patients (Table 18, page 17). Primary analyses of mortality was not impacted by this procedure since the integrity of the randomization was preserved until the end of studies.

For evaluation and analysis of worsening heart failure that required hospitalization, randomized patients were to satisfy one of the following criteria: (a) Symptoms were severe enough to require cardiovascular heart failure hospitalization for at least 24 hours. (b) Adjustment of heart failure therapy, i.e. introduction of ACE inhibitors, digoxin or diuretics not previously received, or an increase in dose of Frusemide or addition of a second diuretic on an inpatient basis also qualifies as an endpoint. If adjustment of heart failure therapy were done on an outpatient basis (e.g minimal adjustment to diuretic dose), this did not qualify as an endpoint. NYHA classification, albeit an insensitive measure for objective assessment of worsening of heart failure on hospitalization, would have been additive to the clinical assessment of patients hospitalized for worsening heart failure.

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There was no data on NYHA when patients were hospitalized for worsening heart failure. Furthermore, the revision of secondary endpoints in the Generic Protocol Amendment VIII/115 (Clarification of Administrative details) in the DIAMOND studies stipulated removal of the requirement to collect data on the dose and frequency of concomitant medication (Tables 3 and 4; see page 16). In effect, the clinical benefit of time to first hospitalization was solely based on the investigators clinical decision and not on the documentation of the worsening of heart failure. Heart failure studies regard hospitalization as a surrogate endpoint for death only when stringent criteria are applied. The application of data and results from analysis of time to first event of worsening heart failure cannot be easily justified as a surrogate for death.

Studies on quality of life in the DIAMOND studies commenced after the patients had been on therapy for one month and were in steady state. Evaluation of the data on quality of life did not add much to the overall assessment of Dofetilide efficacy and safety.

## Results

### 8.0 Study Population

A total of 13820 subjects were screened to enter both DIAMOND studies: 5548 for CHF and 8272 for MI; some subjects being screened on more than one occasion. From the screened population, a total of 3028 (18%) patients were randomized into both studies, 1518 and 1510 for CHF and MI, respectively (Figures 1 and 2). About 9% each of patients were randomized to the CHF and MI studies. About 4.5% of the screened population received either Dofetilide or placebo. The primary reason for non-randomization of 82% of screened patients was left ventricular ejection fraction (LVEF) >35% (WMI >1.2).

The majority of non-randomized subjects had WMI >1.2, equivalent to an LVEF >35%. The symptoms associated with their disease state were less severe than those of the randomized population. There were small demographic differences between the screened only and the randomized populations. The only significant difference between the screened only and randomized populations was in the severity of their heart failure. It is conceivable that some of these patients had left ventricular diastolic dysfunction but this was not specifically looked for.

The screened only population had a higher percentage of females than the group randomized to study treatment, 36.2% compared to 26.5%, but, based on the reasons for non-randomization, there was no evidence to suggest a recruitment bias towards males. The only criterion specifically for females (no childbearing potential) resulted in the non-selection of only five subjects (0.2%) out of the screened female population (Appendix Tables 1A and 1B). Other reasons for non-randomization are summarized in Appendix Table 1 (pages 95-96).

### Double-blind period of study

Eligible patients (3028) were randomly allocated to one of the treatment arms with Dofetilide or matching placebo, at the earliest, on the 3rd day for MI patients, and the latest, on the 7th day following MI or 7th day after admission or diagnosis of CHF, with some exceptions. The screening of consecutive subjects and randomization by WMI and NYHA insured that no major differences existed between the treatment groups.

### 8.1 Drug supplies and administration

For drug administration see section 6.3 above. For drug supplies, see Table 2 below.

**Table 2: Drug supplies - CHF/MI**

	Route	Product number
Placebo	Oral	FIDSOO117AA(Lot 2833-122)
		FIDSOO117AA(Lot 2968-078)
Dofetilide	Oral 0.25mg	FIDSOO114AB(Lot 2833-130)
		FID2958-069X (Lot 2833-183)

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## 8.2 Concurrent Medication for CHF/MI

On entry to the study, every subject was taking some medication - mainly cardiovascular drugs (Tables 3 and 4), and the number of medications increased during the study. The increased administration of diuretics and anticoagulants was identical between the treatment groups but each of the remaining medications was prescribed for more subjects receiving placebo than Dofetilide. Tables 3 and 4 summarize the increased frequencies of patients on concurrent medication with progression of the study.

### Concurrent medication for CHF/MI

**Table 3: Percent Frequency of patients taking Medication-CHF**

	Medication On Entry		During Study	
	Dofetilide	Placebo	Dofetilide	Placebo
Diuretics	94	96	98	98
ACE Inhibitors	72	76	87	90
Calcium Antagonists	20	23	31	36
Glycosides	63	61	72	76
Vasodilators	48	53	62	67
Anticoagulants	24	25	36	36
Beta-blocking Agents	9	11	21	24
Anti-arrhythmics	0.1	0	1.3	3

**Table 4: Percent Frequency of patients taking Medication-MI**

Medication	Medication On Entry		During Study	
	Dofetilide	Placebo	Dofetilide	Placebo
Diuretics	71	68	83	83
ACE Inhibitors	59	57	85	86
Calcium Antagonists	17	17	32	39
Glycosides	28	28	40	43
Vasodilators	79	78	88	88
Anticoagulants	19	17	33	32
Beta-blocking Agents	36	37	47	55
Anti-arrhythmics	0.3	0	1	0.9
Aspirin	91	91	95	95
Anti-platelet Agents	0.3	0.4	3	3

## Demographics

### 8.3 Clinical Features and Baseline characteristics-CHF/MI

There were 852 CHF patients (56%) experienced shortness of breath at rest and 1493 CHF patients (98%) had difficulty breathing on minimum exertion. Approximately 67% were suffering from ischemic heart disease, and 51% had suffered one or more infarctions. On entry into the study, 97% (1469) were experiencing at least one disease or syndrome other than CHF (Tables 5a-b).

The baseline characteristics of randomized MI patients showed that 99.6% and 96% had evidence of structural heart disease as shown by elevated enzymes and myocardial dysfunction (Table 5c). There was no significant imbalance between treatment groups at baseline.