Table 49a: Laboratory data CHF

SUMMARY OF ADVERSE EVENTS GENERATED BY LABORATORY TESTS: INTENT-TO-TREAT POPULATION

NUMBER(%) OF SUBJECTS:	DOFETILIDE				PLACEBO			
Evaluable for lab. adverse events	762				756			
With lab. adverse events	78	(9.6)			61	(8.1)		
Discontinued with lab. adverse events	0				1	(0.1)		
Number of lab. adverse events	78				61			
BODY SYSTEM / COSTART Preferred Term	n(%)		SEV.* MILD	MOD.	SEV.	n(%)		SEV.* MILD	MOD.	SEV.
DIGESTIVE	1	(0.1)	1	0	0	2	(0.3)	0	1	1
Liver damage	1	(0.1)	1	0	0	2	(0.3)	0	1	1
HEMIC AND LYMPHATIC	3	(0.4)	0	1	2	6	(0.8)	2	0	4
Acute myeloblastic leukemia	0		0	0	0	1	(0.1)	0	0	1
Cyanosis	0		0	0	0	3	(0.4)	0	0	3
Ecchymosis	1	(0.1)	0	0	1	0		0	0	0
Iron deficiency anemia	0		0	0	0	1	(0.1)	1	0	0
Lymphangitis	0		0	0	0	1	(0.1)	1	0	0
Myeloma	1	(0.1)	0	0	1	0		0	0	0
Refractory anemia	1	(0.1)	0	1	0	0		0	0	0
METABOLIC AND NUTRITIONAL	49	(6.4)	21	26	2	38	(5.0)	7	30	1
Diabetes mellitus	46	(6.0)	20	24	2	38	(5.0)	7	30	1
Diabetic coma	1	(0.1)	0	1	0	0		0	0	0
Edema	3	(0.4)	1	2	0	0		0	0	0
UROGENITAL	23	(3.0)	12	8	3	15	(2.0)	3	9	3
Acute kidney failure	2	(0.3)	0	1	1	1	(0.1)	0	1	0
Hematuria	22	(2.9)	12	8	2	14	(1.9)	3	8	3

Table 49b: Laboratory data MI

DOFETILIDE PROTOCOL 400 - DIAMOND MI STUDY
SUMMARY OF ADVERSE EVENTS GENERATED BY LABORATORY TESTS: INTENT-TO-TREAT POPULATION

NUMBER(%) OF SUBJECTS:	DOFETILIDE				PLACEBO			
Evaluable for lab. adverse events	749				761			
With lab. adverse events	60	(8.0)			44	(5.8		
Discontinued with lab. adverse events	0				1	(0.1		
Number of lab. adverse events	62				46			
BODY SYSTEM / COSTART Preferred Term	n(%)		SEV.* MILD	MOD.	SEV.	n(%)		SEV.* MILD	MOD.	SEV
HEMIC AND LYMPHATIC	5	(0.7)	2	2	1	2	(0.3)	1	2	
Cyanosis	4	(0.5)	1	2	1	0		0	0	
Ecchymosis	1	(0.1)	1	0	0	0		0	0	
Iron deficiency anemia	1	(0.1)	1	0	0	0		0	0	
Lymphangitis	0		0	0	0	1	(0.1)	0	1	
Petechia	0		0	0	0	1	(0.1)	0	1	
Purpura	0		0	0	0	1	(0.1)	1	0	
METABOLIC AND NUTRITIONAL	35	(4.7)	16	19	0	22	(2.9)	9	11	
Diabetes mellitus	32	(4.3)	15	17	0	21	(2.8)	8	11	
Edema	2	(0.3)	1	1	0	1	(0.1)	1	0	
Electrolyte depletion	1	(0.1)	0	1	0	0		0	0	
UROGENITAL	20	(2.7)	10	8	3	21	(2.8)	12	8	
Acute kidney failure	1	(0.1)	0	0	1	1	(0.1)	0	0	
Hematuria	20	(2.7)	10	8	2	20	(2.6)	12	8	

10.13 Quality of life

No definitive conclusions could be drawn from this study because the studies commenced at least one month after the commencement of the study. Furthermore, there was no difference in the time to death in both treatment groups and the magnitude of clinical benefit, by age and sex, was not prospectively evaluated between the treatment groups.

11.0 Overall Summary: DIAMOND STUDIES

Dofetilide appears to be a useful drug for the conversion and maintenance of chronic supraventricular arrhythmias in patients with left ventricular dysfunction and structural heart disease. Significant safety issues have been identified in the trials, but for most part represent selective drug effect on Ikr channel which it blocks. These safety issues should not be overlooked in the face of population PK/PD data analysis based on 908 plasma concentrations and 1469 QTc measurements from 117 patients derived from four pivotal studies (Biopharm. Review). The observed linear relationship between QTc interval and plasma Dofetilide concentration is highly significant across studies in this NDA. There is also a higher frequency of Torsades in patients receiving Dofetilide (500mcg bid) which is reduced by creatinine clearance dependent dosing. There is an increased susceptibility to Torsades by females compared to males but this is reduced by creatinine clearance dependent dosing regimen. The safety issues require close monitoring in the post-marketing period.

The sponsors did not carry out PK/PD analysis in the RI substudy even though the patients were in steady state. The possible effect of Dofetilide on asymptomatic patients with supraventricular tachycardia cannot be resolved from this study because all the patients enrolled were very sick, and Dofetilide showed no mortality or morbidity benefit in patients with ventricular tachyarrhythmias compared to placebo.

One of the main reasons for treating symptomatic or asymptomatic atrial arrhythymias is the conversion and maintenance of the arrhythmias to sinus rhythm which in turn leads to improved quality of life, increased exercise tolerance, increased cardiac function, measured by increase of ejection fraction , stroke volume and cardiac output. There is, however, a potentially significant risk in treating asymptomatic patients with a benign disease with Dofetilide because of its pro-arrhythmogenic property, particularly Torsades, regardless of dose levels.

In the combined CHF/MI data, there were more cardiac deaths among patients who had cardiac arrests in the Dofetilide treated patients (65/1511 [4.3%] compared to 54/1517 [3.56%]) in the placebo group. Although this difference is not significant, during the first seven days of treatment, there was a 2 fold difference in cardiac mortality in the Dofetilide group compared to placebo (31 patients : 16 patients). The prolongation of the QT/QTc intervals in the Dofetilide group consistently observed in the early days of therapy may have contributed to this excess mortality. Even after downward titration of Dofetilide, based on creatinine clearance, there was still a 1.5 fold increase of cardiac arrests and deaths in the Dofetilide group compared to placebo(25:16). These data suggest that the risk of cardiac mortality appears to be greater in Dofetilide treated patients during the first week of treatment (<7 days) compared to placebo .

Evaluation of the risk-benefit of Dofetilide becomes a critical issue in therapy because any increase in plasma concentration of Dofetilide above the optimal concentration for efficacy has the potential for a proportional prolongation of QTc interval. The sponsor therefore claims that predictability of the recommended clinical dosing regimen minimizes the risks of TdP and sudden death. Dose adjustments for creatinine clearance levels, which came into effect after the commencement of the studies, resulted in a neutral mortality outcome for all the primary and secondary mortality endpoints. It was after the implementation of the creatinine clearance dependent dosing, effected after May 1 1994, that downward titration of drug dosage levels reduced frequencies of prolonged QT/QTc, TdP and sudden deaths compared to placebo. The total mortality data from these studies may therefore be an underestimate because reduced doses for conversion of AF to SR were administered to a significant proportion of patients because of AF/AFL, renal impairment and other reasons including prolonged QT/QTC intervals (Tables 50a and 50b) .

Table 50a: Dose adjustments, time, AF/AFl-DIAMOND-CHF /MI

	CHF (N=1518)		MI (N=1510)		CHF and MI
Dosage adjustments	Dofetilide	Placebo	Dofetilide	Placebo	Total N=3028
Day 1					
No of patients< 500mcg bid:	976 (64.3%)	-	736 (48.7)	-	1712/3028
Patients with AF	323 (33.1%)	-	95 (12.9%)	-	418
Patients with ↓RF	637 (65.3%)	-	619 (84.1%)	-	1256
Other reasons< 500mcg bid	26/762 (3.4%)	14/756 1.9%)	26/749 (3.5%)	8/761 (1.1%)	74/3028
Duration of study					
Other reasons< 500mcg bid	84/762 (11.0%)	38/756 (5%)	99/749 (13.2)	35/761 (4.6%)	256/3028

RF=Impaired renal function. See Table 50b for summary.

Table 50b: Summary dose adjustments - DIAMOND-CHF/MI

No of patients randomized to 500mcgbid	No of patients on 500mcgbid - duration of study	No of patients downtitrated <500 mcg bid or discontinued
CHF 762	187 (25%)	575 (75%)
MI 749	287 (38.5%)	462 (61.5%)

In summary the clinical benefits of Dofetilide are marginal compared to placebo (Table 50c). The studies have satisfied the prespecified indications for conversion and maintenance of sinus rhythm in the presence of structural heart disease but have not shown a reduction in mortality as prespecified in the protocol. The reviewer's conclusion to approve this drug for these indications are therefore based on the data which shows that the mortality of the study population is not increased, despite the fact that the patients were not only very sick but the reduced renal fraction of the cardiac output predisposed them to reduced renal drug clearance which in turn led to QT prolongation, Torsades, and bradycardia.

In making this recommendation special attention must be paid to labeling which should stipulate initial treatment in a hospital environment to deal with the Torsades during the first 4 days, creatinine clearance dose dependent adjustments, for both sexes, particularly for females, and body weight , all being covariates that may influence Dofetilide pharmacodynamic effects. It is against this background that Dofetilide efficacy and safety should be evaluated in the post-marketing period.

NDA #20931
A.O.Williams, M.D.

Table 50c: Overall summary of DIAMOND STUDIES-CHF/MI

PARAMETER	Congestive Heart Failure		Myocardial Infarction	
	DOFETILIDE	PLACEBO	DOFETILIDE	PLACEBO
1) Structural Heart disease	++	++	++	++
2) CHF NYHA baseline	+++	+++	++	++
3) CHF NYHA (EOS)	++	+++	++	++
4) Morbidity EOS	++	++	++	++
5) Total Mortality EOS	++	++	++	++
6) Cardiac Mortality EOS	++	++	++	++
7)Conversion to SR	+	++	+	++
8)Maintenance of SR	+	++	+	++
9) TAD EOS	++	+	++	+
10) Torsades EOS	+	-	+	-
11) Thromboembolic events	+	+	+	+
12) Re-Hospitalization	+	++	+	++

- = not present /minimal; + = mild; ++ = moderate; +++ = severe; EOS = End of study.TAD=Total arrhythmic deaths; SR=Sinus rhythm.

Reviewer's Conclusions

The evidence obtained from the DIAMOND studies in randomized patients with CHF and, or MI with left ventricular dysfunction, structural heart disease, and supra-ventricular tacchycardias at baseline shows a neutral net benefit in terms of Dofetilide safety as an anti-arrhythmic agent.While Dofetilide therapy failed to show reduction in total or cardiac mortality, compared to placebo, it is not associated with increased mortality, as has been described for other anti-arrhythmics. DIAMOND studies recruited only patients with chronic supraventricular arrhythmias and heart failure and patients with paroxysmal supraventricular tachycardias (PSVT) were not included. Therefore, no conclusions can be made for this indication. There are other sections of this NDA that adresses the efficacy and safety of Dofetilide in PSVT.

The evidence obtained from the DIAMOND AF substudy, though flawed in design, shows increased mortality in the Dofetilide group of 97 patients (p=0.04) compared to 81 placebo patients , but analysis of all 506 AF patients in the DIAMOND studies also failed to show a reduction in mortality in 249 Dofetilide treated patients compared to 257 placebo patients (p=0.63)(Figure 5, page 32). However, anti-arrhythmic efficacy at the supraventricular level is striking in the AF substudy(p=0.001).

The risk of Torsades is significantly higher in this very sick population exposed to Dofetilide compared to placebo, and female patients who were either dosed or not dosed according to their creatinine clearance showed a higher frequency of Torsades compared to males. The constellation of QT prolongation, bradycardia, and Torsades reflect adverse drug effects which may either contribute and, or result in mortality and sudden death among Dofetilide treated patients. Taking this constellation of effects listed above, the reviewer is unable to justify Dofetilide therapy in asymptomatic supraventricular tacchycardia or in "benign" PSVT.

The sponsor has conducted the mortality trials in such a way that serious adverse events were reduced by dose adjustments and by so doing, succeeded in achieving similar survival rates in both treatment groups. Table 50b below shows the frequecy distribution of dose adjustments from day 1 in the DIAMOND studies and illustrates imbalances between the treatment groups. However, compared to quinidine, Dofetilide shows some superiority in mortality over quinidine. Quinidine has been approved as an antiarrhythmic that can be used in the presence of structural heart disease. On this basis, the reviewer recommends approval of Dofetilide with strict attention to dosing regimens and careful and vigilant clinical management.

12.0 Reviewer's Recommendations - DIAMOND STUDIES

- At the present time, I estimate Dofetilide's therapy benefit to risk relationship as being acceptable for the proposed patient population.
- Dofetilide should be approved for the conversion and maintenance of sinus rhythm in patients with symptomatic supraventricular tachyarrhythmias (AF/AFl) and congestive heart failure, and or myocardial infarction, that require hospitalization, regardless of the presence of structural heart disease.
  - Dofetilide should not be approved for the treatment of asymptomatic supraventricular tachyarrhythmias, particularly when hospitalization is not required for systemic embolization, and or left ventricular dysfunction.

Approval should be subject to labeling issues noted below:

- Adjustment of Dofetilide doses based on age, sex, weight, and creatinine clearance may help in the control of frequencies of adverse reactions including Torsades and sudden cardiac death in patients with symptomatic supraventricular arrhythmias and congestive heart failure.
- Adjustment of Dofetilide doses based on age, sex, weight, and renal function may help in the control of adverse reactions including Torsades and sudden cardiac death in patients with supraventricular arrhythmias, myocardial infarction and congestive heart failure.
- Adjustment of Dofetilide doses based on age, sex, weight, and renal function may help in the control of adverse reactions including Torsades and sudden cardiac death in patients with symptomatic supraventricular arrhythmias in the presence of structural heart disease.
- Dofetilide should be contraindicated in patients with congenital or acquired causes of QT/QTc prolongation or in patients receiving any QT prolonging drugs. Dofetilide should be contraindicated in patients with severe chronic renal impairment (CLcr < 40ml/min).

NDA 20-931 : 115-400 AF/AFL SUBSTUDY

13.0 Title: Dofetlide in treatment of atrial fibrillation/flutter in patients with reduced left ventricular function - A DIAMOND substudy

Introduction
Atrial fibrillation/flutter (AF/AFl) is a widespread complication in patients with congestive heart failure (CHF), and acute myocardial infarction (MI) (Alpert 1988). With AF/AFl, there are increased risks of mortality and/or morbidity (Pritchett, 1992), thromboembolic complications (Stroke Prevention Investigators 1992), and the potential to precipitate or aggravate heart failure. The DIAMOND studies provide an opportunity to evaluate the efficacy and safety of Dofetilide in patients with underlying structural cardiac disease and AF/AFl at baseline. It should also provide valuable information on the viability of DC cardioversion as a routine treatment of AF/AFl.

It was anticipated that the overall population with AF/AFl at baseline from the combined DIAMOND CHF and MI studies would generate at least 450 subjects and most would enter this substudy, designed to explore the long term benefits of being in sinus rhythm (SR) compared to the disadvantages of being in AF/AFl under controlled conditions.

Study Dates: 11 November 1993 to 1 July 1997

Study objectives
This substudy was designed to evaluate the potential for Dofetilide to restore sinus rhythm in an AF/AFl population with reduced left ventricular function and its ability to maintain SR over a 12 month period in subjects in whom SR had been restored by either Dofetilide or DC cardioversion. As a secondary objective, the substudy was to evaluate the impact of Dofetilide on morbidity and mortality in this population.

13.1 Claims
The sponsor claims that Dofetilide can restore SR and, once restored, maintain normal rhythm for up to one year of treatment in a sub-population taken from the two major studies.

Study Design: This substudy was a non-randomized study that recruited previously randomized patients to the DIAMOND CHF and MI study populations with AF/AFl at baseline, within the period of hospitalization. A total of 3000 subjects were to be enrolled in DIAMOND - 1500 each into the CHF and MI studies. Studies published prior to approval of this protocol suggested that at least 15% of those patients recruited would suffer from AF/AFl at baseline and it was anticipated that most of these patients would be recruited into the substudy, thereby providing an expected population of 450 subjects. The eligible population was anticipated to be 450 subjects equally divided between the two treatment groups. Subjects still in AF/AFl at the Month 1 visit were treated with DC cardioversion.

Diagnoses and Criteria for Inclusion of Subjects
Subjects from the DIAMOND CHF or MI populations were required to have continuous (24 hour) AF/AFl, which was not the result of another illness and were to tolerate and receive anticoagulation therapy for 1 month prior to and 2 months after DC cardioversion, if this was required to achieve SR.

13.2 Study Monitoring

The 25 centers participating in this substudy were monitored routinely as part of DIAMOND CHF and DIAMOND MI studies. The blinding restrictions of the primary studies were not compromised by DIAMOND AF/AFl.

Principal Investigators: Drs: J. Videbaek; H. Bagger; N. Keller; K. Lyngborg; J. Kjaergaard; H. Depcik; P. Fritz Hansen; L. Køber; F. Gammelgaard; K. Egstrup; S. Jensen;; E. Agner; K. Skagen; E. Klarholt; E. la Cour Petersen; H. Vagn Nielsen;; A. Johannesen; Ib Frimodt Lindbjerg; M. Scheibel; M. Asklund; T.Lysbo Svendsen; S. Bach; J. Larsen; I. Nielsen; E. Kjøller; H. Ancher Sørensen; V. Mohr Drewes; P. Eliasen; M. Brøns; B. Dorff; A. Deding; M. Tangø; O. Lederballe; H.Kraemmer Nielsen; K. Garde.

Drug Administration

Dosing was as outlined in the primary protocol with no change for the substudy (Table 52).

Table 51: Drugs supplied

	Dose	Lot no
Dofetilide	250mcg oral	3833-183
Placebo	Matching capsules oral	2968 -078

Efficacy Evaluations:
Primary Endpoints

- The number of subjects with drug-induced conversions to SR within one month.
- The number of subjects converted to SR with DC cardioversion.
- The recurrence rate of AF/AFl within 12 months of DC cardioversion.
- The recurrence rate of AF/AFl for all subjects converted to SR.
- Recurrence of AF/AFl was to be confirmed from a second ECG recorded at least 24 hours after a first recording showing AF/AFl. Further evidence of relapse to AF/AFl would be taken as the requirement for DC conversion without documented electrocardiographic support. There were no other specific directions to obtain the substudy endpoints because the routine assessments from the primary DIAMOND studies were considered adequate.

Secondary Endpoints

- Severity of heart failure
- Total mortality
- Cardiovascular mortality
- Thromboembolic complications
- Energy needed for DC conversion.

Statistical Methods: All planned analyses prespecified in the protocol were employed .

Study Design

There was no separate randomization for DIAMOND AF/AFl, subjects participating in the substudy were selected from the DIAMOND CHF and MI study populations. This time difference between randomization and enrollment into the substudy allowed the entry of subjects who had received study treatment and may have experienced a change in rhythm status, even a pharmacological conversion to SR. The duration of the arrhythmia was to be recorded as part of each subject's medical history and could be based on either electrocardiographic documentation or the patient's history provided this gave specific dates for the onset of symptoms, such as palpitations.

In order to reduce the thromboembolic complications associated with DC conversion, those subjects consenting to take part in the substudy who were not already taking anticoagulants were to be started on anticoagulant treatment prior to discharge. It was anticipated that they would complete a minimum period of four weeks of anticoagulation, three at a therapeutic level, prior to cardioversion.

At their first out patient visit for the primary study (Month 1) the investigator was to assess the rhythm status of each subject and evaluate whether those remaining in AF/AFl were in optimal anticoagulation (International Normalized Ratio between 2 and 3) for DC cardioversion one week later. Subjects who failed this evaluation but were still considered to be potential candidates could be re-evaluated at weekly intervals for up to 3 weeks. Thereafter they were not to be considered eligible for the substudy but exclusion here would not affect their continuation in the primary studies. Subjects whose medical condition deteriorated sufficiently to warrant DC cardioversion prior to the Month 1 visit could be included into the substudy provided the cause of their deterioration did not violate the selection criteria.

Cardioversion was to be performed in the morning after an overnight fast in accord with local techniques and guidelines (Ewy, 1992). Subjects not responding to this procedure, and remaining arrhythmic, were to be withdrawn from the substudy without compromise to the primary studies.

Selection Criteria

Subjects entering the AF/AFl substudy would in addition to fulfilling the selection criteria of the primary studies fulfill the specific selection criteria listed below.

Inclusion Criteria

1. Subjects were to have continuous AF/AFl with a duration of more than 24 hours at the time of randomization. For the purposes of this substudy AF was to be identified from an ECG showing an absence of P waves or the presence of rapid, irregular atrial activity at a rate of 350 - 600 cycles/minute (cpm) and irregular ventricular depolarisation. AFl was to be identified from an ECG showing the presence of P waves and a rapid regular atrial activity rate of 250 - 350cpm and regular or irregular ventricular depolarisation.

Exclusion Criteria

1. Subjects with paroxysmal AF/AFl whereby the fibrillation/flutter lasted less than 24 hours with at least 24 hours between attacks.
2. Subjects with AF/AFl due to acute infections, pulmonary embolism, pericarditis, myocarditis, alcohol abuse, surgery or thyrotoxicosis.
3. Subjects with contraindications to anticoagulant treatment.

Safety Assessments

The only safety tests additional to those defined for the primary studies was a requirement to confirm anticoagulation control and monitor plasma electrolytes one week prior to DC cardioversion. Anticoagulation would be considered 'controlled' when the international normalized ratio (INR) was above 2.0 and preferably below 3.0 (Petersen, 1989).

Data analysis : Sample Size

From the literature it was anticipated that 15% of the combined populations from DIAMOND CHF and DIAMOND MI populations would have AF/AFl at baseline, equating to a substudy population of 450 patients but only 410 patients participated in the substudy. The total number of subjects studied was not powered enough to detect a significant difference and there was imbalance between the treatment groups at the end of study.

Results

13.3 Study Population

Five hundred and six (506) patients in DIAMOND presented with AF/AFl at baseline, representing 17% of the overall population. Of the 506 patients, 401 from 25 centers participated in the substudy. One hundred and ninety six (196) of these subjects were allocated to Dofetilide and 205 to placebo. Of these, only 97 and 81 respectively were enrolled in the substudy, representing 49.5% and 39.5% of the available treatment populations. More patients were randomized to Dofetilide (97) compared to placebo(81) treatment groups. Over one third of each group was recruited after randomization, 34 subjects receiving Dofetilide (35%) and 26 subjects (34%) given placebo. Further, 17 of these subjects receiving Dofetilide (18%) and 9 (12%) given placebo were recruited after 30 days, i.e. at their Month 1 visit. Only 35% of the total DIAMOND population with AF/AFl was recruited to the substudy. 34% of the final population were recruited at their month 1 visit - after the start of study treatment.

13.4 Demography and baseline characteristics

The demographics of the patients are in Table 52. There were slight differences in the percentage of patients with AF/AFl at baseline, 25% randomized to Dofetilide compared to 27% randomized to placebo. These differences, however, were not considered to be significant to influence the effects of study treatment. The baseline characteristics of the patients in this substudy are in Tables 53-56.

Table 52: Demographics of subjects entering maintenance phase(MP) - AF/AFL

	Dofetilide			Placebo		
	Males	**Females**	**Total**	**Males**	**Females**	**Total**
n MP (ITT) of pts.	66 (76)	18 (21)	84 (97)	39 (65)	11 (16)	50 (81)
Age(yrs)						
<18	0	0	0	0	0	0
18-44	0	0	0	1(2.6)	0	1(2.0)
45-64	20(30.3)	4(22.2)	24(28.6)	5(12.8)	1(9.1)	6(12.0)
65-74	24(36.4)	6(33.3)	6(35.7)	19(48.7)	3(27.3)	22(44.0)
75-84	21(31.8)	7(38.9)	7(33.3)	14(35.9)	6(54.5)	20(40.0)
>=85	1(1.5)	1(5.6)	2(2.4)	9	1(9.1)	1(2.0)
Age range(yrs)	51-85	59-87	51-87	42-84	64-89	42-89
Mean Age(yrs)	70	73	71	71	75	72
Race						
White	66(100)	18(100)	84(100)	39(100)	11(100)	50(100)
Black	-	-	-	-	-	-
Other	-	-	-	-	-	
Weight Range(kg)	56-110	43-97	43-110	63-99	45-92	45-99
Mean weight(kg)	80	71	78	78	72	77
Height Range(cm)	150-189	150-174	150-189	166-186	149-172	149-186
Mean Height(cm)	175	162	172	176	161	173
Alc. consumption (units /week)	0-35	0-7	0-35	0-28	0-5	0-28
Median values	3	0	2	4	0	2
Not known	3	0	3	0	0	0

The baseline characteristics of the patients are presented in Tables 53-56 below.

Table 53: Baseline characteristics AF/AFl-CHF/MI-ITT

	Dofetilide	Placebo
Number (%) of subjects enrolled	97	81
Completed substudy	64(66)	45(55.6)
Discontinued substudy	33(34)	36(44.4)
Maintenance phase	84(86.6)	50(61.7)
Completed	57(59.9)	34(42.0)
Discontinued	27(27.8)	16(19.8)
Analyzed-ITT	97(100)	81(100)
Efficacy	96(99)	81(100)
Subjects entering maintenance phase	84(86.6)	50(61.7)

Table 54: Baseline characteristics AF/AFl-CHF/MI-ITT

	Dofetilide	Placebo
Number (%) of subjects	78	65
Shortness of breath with minimum exertion		
Present	77(98.7)	65(100)
Absent	1(1.3)	0
Shortness of breath with paroxysmal nocturnal		
Present	33(42.3)	29(43.1)
Absent	45(57.7)	37(56.9)
Shortness of breath at rest Present		
Absent	44(56.4)	35(53.9)
	34(43.6)	30(46.1)

Table 55: Baseline disease characteristics-AF/AFL-ITT

Baseline Characteristics	Dofetilide (N=97)	Placebo (N=81)
NYHA at Baseline		
I	1(1.1)	4(4.9)
II	50(53.2)	39(48.15)
III	41(43.6)	36(44.4)
IV	2(2.1)	2(2.5)
Not available	3	0
Creatinine clearance (ml/min)		
20-<40	19(19.6)	14(17.3)
40-,60	39(40.2)	31(38.3)
>=60	39(40.2)	36(44.4)
Mean	60.6	63.1
Std	25.4	28.5
N	97	81

Table 56: Baseline disease characteristics-ITT-AF/AFL

Baseline Characteristics	Dofetilide (N=97)	Placebo (N=81)
Number of previous MI		
0	65	46
1	23	19
2	6	8
3	2	4
>3	1	4
Number of previous cardiac arrests		
0	96	78
1	1	3
Ischemic Heart Disease		
Yes	45(46.4)	46(56.9)
No	52(53.6)	35(43.3)
Wall Motion Index		
<0.8	14(14.4)	17(21.0)
>=0.8 -<=1.2	83(85.6)	64(79.0)
Median	1.0	1.0
Range	(0.4 - 1.2)	(0.5 - 1.2)
Number of complications		
Thrombolytic treatments	4(4.1)	8(9.9)
Reinfarctions	0	0
Cardiac Arrests	0	1(1.2)
Arrhythmias requiring treatment	53(54.6)	43(53.1)
Other	48(49.5)	40(49.4)

Subject Disposition

All 178 subjects had been randomized to treatment in one of the main studies. The discrepancies in recruitment described above resulted in a treatment imbalance between the groups. More subjects entering the substudy had been allocated to Dofetilide (97) treatment, compared to placebo (81) treatment, resulted in an overall imbalance of 54:46 (%) in the substudy population. Further, at Month 1, proportionally twice as many subjects in the placebo group failed to respond to DC cardioversion, 19 of 61 = 31% compared to 5 of 35, 14%. This resulted in a higher percentage of the Dofetilide population entering the maintenance phase, 87% (84 subjects) compared to 62% (50 subjects) allocated to placebo and a greater imbalance to 63:37 (%) in the final population.

The allocation of patients resulted in an imbalance of 78:65 patients (54.5:45.5 %) which was further enhanced by the end of the study because of the failure of patients in the placebo group to respond to DC cardioversion. There was a greater imbalance of 63% Dofetilide to 37% placebo in the final population at the end of study.

Table 57: Evaluable Groups

	Dofetilide	Placebo
Total AF/AFl population	249	257
Eligible population	196	205
Entered study	97	81
Completed substudy	64	45
Entered maintenance phase	84	50

Safety data included in DIAMOND CHF and DIAMOND MI reports.

Table 58: Responders to cardioversion - AF/AFL

	Responders to cardioversion	Non-Responders to cardioversion	Total (%)
Dofetilide	49	29	78(54.5%)
Placebo	24	41	65(45.5%)
Total	73	70	143(100%)
χ=8.6; df=1; p=0.003			

The selection bias enhanced by response to cardioversion is statistically significant (p=0.003) and forms the basis for the flaw in design and conduct of the study. Although the findings in this substudy are not suitable for efficacy, a review of essential data follows.

Duration of follow up

The duration of AF/AFL in patients entering the maintenance phase is presented in Table 59 below.

Table 59: Duration of AF/AFl in subjects entering maintenance phase (MP)

	Dofetilide			Placebo		
	Males	**Females**	**Total**	**Males**	**Females**	**Total**
Number of subjects	66	18	84	39	11	50
Duration AF (days)						
1-7	12(18.2)	7(38.9)	19(22.6)	5(12.8)	1(9.1)	6(12.0)
>7 days	30(45.5)	3(16.7)	33(39.3)	18(46.2)	4(36.4)	22(44.0)
Median AF duration	213		27	91	25 (57)	91
Not known	15(22.7)	3(16.7)	18(21.4)	8(20.5)	4(36.4)	12(24.9)
Duration of AFL(days)						
1-7	3(4.5)	1(5.6)	4(4.8)	2(5.1)	0	2(4.0)
>7 days	5(7.6)	2(11.1)	7(8.3)	3(7.7)	1(9.1)	4(8.0)
Median AFL duration(days)	30	183	46	9	244	126
Not known	1(1.5)	2(11.1)	3(3.6)	3(7.7)	1(9.1)	4(8.0)

The duration of observation time for mortality endpoints is presented in Table 60 below.

Table 60: Total observation time for mortality endpoints AF/AFL

Baseline Characteristics	Dofetilide (N=97)	Placebo (N=81)
Duration of study		
<1 day	0	0
2days<2weeks	1	0
1month<3months	1	0
3months<6months	8	3
6months,12months	4	5
12months<18months	11	6
18months<24months	24	22
24months<36months	29	21
36months<48months	19	23
>48	0	1
Median Duration (days)	534	561
Range(days)	12-981	46-1102

Protocol violations/Deviations

One patient who was randomized to Dofetilide substudy arm had converted to SR prior to receiving his first dose of study treatment. Since this substudy permitted selection of patients after randomization and selection continued after the start of treatment, subjects whose arrhythmias had been converted to SR were still acceptable. About 34% of the study population were recruited into the substudy after the start of the study treatment. This irregularity predisposed may have predisposed to results which require cautious interpretation. The other violations are in Table 61 below.

Table 61: Protocol violations

Number of subjects	Dofetilide N=97 (%)	Placebo N=81 (%)
No. of Subj. with at least 1 deviation	5(5.2)	9(11.1)
Reason for deviation Disallowed anti-arrhythmic therapy	5(5.2)	9(11.1)

Concomitant medication in AF/AFl

Every patient was on concomitant medication on entry and throughout the study. The relevant medications are presented in Table 62 below.

Table 62: Concomitant medication in AF/AFl

Medication	% Patients Taking Medication			
	On entry		During Study	
Anti-arrhythmics	Dofetilide	Placebo	Dofetilide	Placebo
for VT	1	1	1	0
for SVT	0	0	0	2(3%)
Calcium Antagonists	28(29%	25(31%)	37(38%)	39(48%)
Beta-blocking Agents	12(12%)	13(16%)	22(23%)	25(31%)
Glycosides	91(94%)	72(89%)	93(96%)	79(98%)

13.4 Primary efficacy end-point

Conversion of AF/AFL to SR

Based on ECG data and the investigators documented opinion, 56 subjects given Dofetilide were in SR 30 days after the start of study treatment, showing a conversion rate of 22.5%, compared to 7 subjects and a conversion rate of 3% from the placebo group. Using data collected at the Month 1 visit, there was also a significant difference between treatment groups in the maintenance of SR in both the CHF and MI populations for those subjects who had converted to SR (Table 63).

Table 63: Pharmacological and spontaneous conversions-AF/AFl at baseline (N=506)

	CHF		MI	
Number with AF/AFl at entry	Dofetilide (n=190)	Placebo(n=201)	Dofetilide(n=59)	Placebo(n=56)
Total conversion	84	28	22	7
Probability of remaining in AF/AFl at 12 months	0.44(0.35,0.52)	0.83(0.76,0.89)	0.37(0.17,0.56)	0.81(0.68.0.94)
For comparison with probability of remaining in SR in DIAMOND studies at 1 year see Table 64 below on page 76				

Table 64: Probability of remaining in SR for subjects with AF at baseline - CHF/MI

	CHF		MI	
	Dofetilide	Placebo	Dofetilide	Placebo
No. in SR at entry	n = 556	n = 534	n = 683	n = 697
Probability of remaining in SR				
At 1 year	0.99 (0.98, 1.0)	0.94 (0.92, 0.97)	0.99 (0.98, 1.00)	0.97 (0.96, 0.99)
At the End of the Study	0.95 (0.92, 0.98)	0.81 (0.69, 0.92)	0.97 (0.95, 0.99)	0.90 (0.80, 1.00)

Conversion of AF/AFL to SR in Combined CHF/MI

There was a significant difference favoring Dofetilide in the maintenance of SR in both the CHF and MI populations, regardless of how SR was induced (Tables 63-66). Including subjects who were successfully given DC cardioversion as part of the AF/AFl substudy with those showing a pharmacological or spontaneous conversion to SR there were 154 subjects from the Dofetilide treatment group compared to 92 patients on placebo, who had AF/AFl at baseline but who were in SR at the Month 1 visit . From this subgroup, 70 subjects receiving Dofetilide remained in SR at 1 year with a probability of 0.75 (CI: 0.68, 0.83), compared to 21 subjects receiving placebo with a probability of 0.40 (CI: 0.28, 0.52). There was also a significant difference between the groups in the numbers of subjects remaining in SR at the end of the study ($p<0.001$).

Table 65: Drug-induced conversions to SR-AF/AFL

Number of subjects	Dofetilide (N=97)	Placebo (N=81)
Number of Subjects with drug-induced conversion-SR	49 (51%)	6 (7.4%)
χ^2=37.8; p<0.001		

Table 66: Maintenance of SR in AF/AFL studies

Number of subjects	Dofetilide	Placebo
Number of subjects entering maintenance Phase	84	50
Number of subj who relapse	26 (31%)	35 (70%)

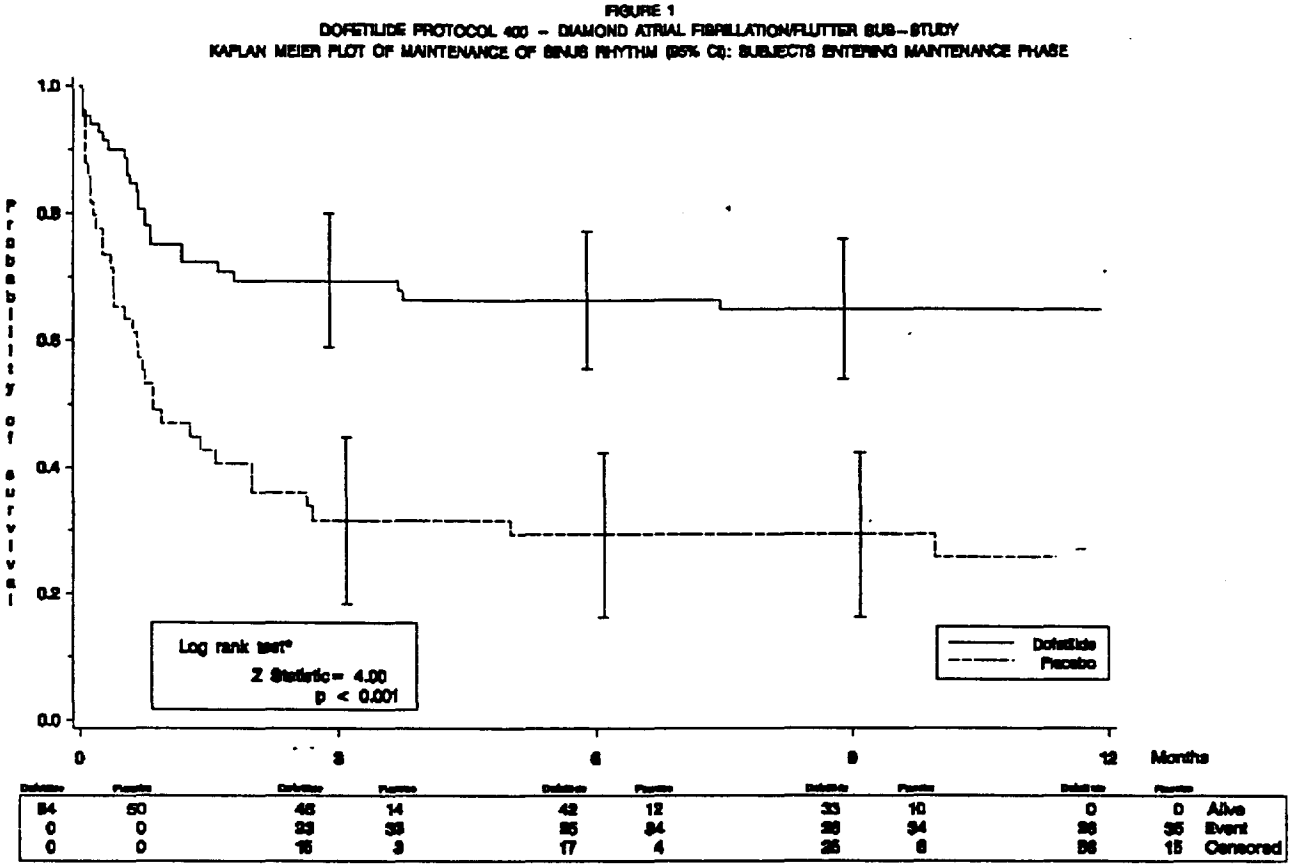
The severity of the disease state of the DIAMOND populations is such that many subjects would be expected to develop AF/AFl, particularly amongst those with CHF, so an additional analysis showed a benefit in preventing AF/AFl at the end of 12 months and the differential between treatments progressively increased with time, as shown in Tables 64 and 67).

Table 67: Time to Relapse in AF/AFL studies

	Log Rank Test			Dofetilide			Placebo		
	Z statistic	p- value	Month of event free	Probability of event free	Lower 95%CI	Upper 95% CI	Probability of event free	Lower 95%CI	Upper 95%CI
Time to First Relapse	4.0007	0.0001	3months	0.994	0.589	0.799	0.315	0.182	0.448
			6months	0.664	0.555	0.772	0.292	0.162	0.423
			9months	0.647	0.537	0.758	0.292	0.162	0.423
			End of Study	0.647	0.537	0.758	0.256	0.123	0.388

See Figure 44

Figure 44 (Table 67)



13.5 Mortality

The mortality data from the AF/AFl substudy differed from the results of the primary studies (Table 68).

Primary Endpoint-Total Mortality

Total Mortality AF/AFl

There was a difference in total mortality between the two groups in this substudy, more subjects from the Dofetilide treatment group dying during the early part of the substudy. Thereafter, the death rate was similar between the two groups, but the early separation in this population carried through to the end of the observation period for both the substudy and the primary studies. Twenty four (24) of the 96 subjects enrolled from the Dofetilide group (25%) had died at 12 months compared to 14 of the 81 (17%) from the placebo group, the corresponding figures being 34 (35%) and 21 (26%) respectively at the end of the observation period. In contrast, when the total population with AF/AFl at baseline was examined, there were no differences between the treatment groups p = 0.6326
The difference between treatment groups in total mortality in the substudy was a reflection of the early non-cardiac deaths, where the difference between groups achieved borderline significance (p = 0.076). There were 10 (10%) non-cardiac deaths in the Dofetilide treatment group and 3 (4%) in the placebo treatment group. There were no differences between the treatment groups in any of the other secondary endpoints.

Table 68: Total mortality CHF/MI-Overall WMI

Total Mortality at 3 monthly intervals	Dofetilide (N=96)	Placebo (N=81)
Baseline	96	81
Total dead	34 (35.4%)	21(25.9%)
Probability of survival:		
3months	0.896 0.835 0.957	0.963 0.922 1.000
6 months	0.854 0.784 0.925	0.901 0.836 0.966
9 months	0.781 0.699 0.864	0.840 0.760-0.919
12 months	0.750 0.663 0.837	0.827 0.745 0.910
24 months	0.636 0.523 0.750	0.732 0.621 0.843
36 months		0.513 0.204 0. 821
EOS	0.452 0.248 0. 656	0.513 0.204 0.821

Z=--2.0383 p=0.0415 (Table 70)

The mortality rate showed an initial separation between the treatment groups and in favor of placebo (Figure 29). This separation was statistically significant and the difference was maintained throughout the study and mirrored in both the CHF and MI cohorts. In contrast to the substudy, mortality data from the total population with AF/AFl at baseline showed no differences between either the overall treatment groups (p = 0.633) (Table 67) or in the treatment groups by primary study.

This substudy, though flawed in design, shows increased mortality from the Dofetilide group compared to placebo group suggesting that Dofetilide was associated with increased mortality compared to placebo. This could probably be explained by the selection bias but taking other safety data into account, it would appear that the safety issue of prolonged QTc and TdP with Dofetilide therapy may be contributory to the observed increase in mortality (Table 69).

Table 69: Comparison of Mortality AF/AFl in patients from DIAMOND studies and from substudy

	CHF			MI			DIAMOND SUBSTUDY	
	Dofetilide	Placebo		Dofetilide	Placebo		Dofetilide	Placebo
AF/AFL	n=190	n=201	p	n=59	n=56	p	n=97	n=81
Deaths at 1 year	56(42%)	61(44%)	0.733	21(55%)	20(56%)	0.489	**24 (25%)	14 (17%)
Probability of survival*	0.71	0.69		0.64	0.64		0.75	0.82
Significant difference in mortality in substudy accompanied by highly significant efficacy of Dofetilide in maintenance of SR compared to placebo. In contrast no significant difference in mortality in DIAMOND studies.								

*Log rank test for 12 months mortality in substudy. ** Significant p=0.0415 see Table 71.

Mortality data on patients recruited to the primary studies (CHF/MI) on or before the first day of substudy treatment showed no difference between the treatment groups.

However when the combined data from the primary studies are separated by treatment group, mortality among the total AF/AFl populations is higher than those of total mortality.

Secondary analysis of "On treatment plus 30 days" was not significant (Z=-0.2877; p=0.7736) in this group, and cardiac mortality was also not significant Z=-1.3374 ; p= 0.1811 (Table 67). If total or cardiac mortality in this substudy, which had a relatively higher number of patients on Dofetilide, had been positive either before or after cardioversion, Dofetilide safety could have been eliminated. But overall, it would appear that in the primary studies, with no apparent flaws in design, Dofetilide is not superior to placebo in mortality rates. In this substudy with a flaw in design, albeit insignificant, mortality is higher in Dofetilide treated patients compared to placebo. While the flaw in design is associated with superiority of Dofetilide therapy in the maintenance of SR compared to placebo (Tables 65-66), it is evident that in order to achieve this level of efficacy, a significantly higher mortality is inevitable. The observed increase in mortality raises the issue of risk benefits of Dofetilide therapy in patients with asymptomatic supraventricular arrhythmias associated with CHF.

Although the sponsor does not wish to claim Dofetilide efficacy because of the flaw in allocation of subjects, the reviewer is of the opinion that the design flaw could not selectively account for the striking difference in efficacy (maintenance of SR for 12 months) between the treatment groups (p=0.001) without the attendant increase in mortality (p=0.0415) between Dofetilide responders compared to placebo (Tables 68-69, and 71). This substudy shows that increased mortality was observed regardless of reduced Dofetilide dosage (even at 50% reduction of 250mcg bid, and 250mcg od) for AF/AFL and reduced creatinine compared to placebo (Table 72).

Table 70: Hazard ratio. for SR-AF/AFl

*Variable	Hazard Ratio	95% CI		
		Lower	Upper	p-value
Treatment group	0.364	0.217	0.612	0.0001
Alc.consumption	1.610	0.912	2.944	0.1007
Wall motion Index	0.519	0.291	0.955	0.0351

*Subjects entering maintenance phase

Table 71: Study end-points AF/AFL studies

	Log Rank Test			Dofetilide N=96			Placebo N=81		
	Z statistic	p value	Month of event free	Probability of event free	Lower 95%CI	Upper95% CI	Probability of event free	Lower95 %CI	Upper95 %CI
Total Mortality	-2.0383	0.0415							
*(CHF/ MI)			12months	0.750	0.663	0.837	0.827	0.745	0.910
			24months	0.636	0.523	0.750	0.732	0.621	0.843
			EOS(981dys)	0.452	0.248	0.656	0.513	0.204	0.821
CHF	-1.5940	0.1109							
MI	-1.6163	0.1060							
CHF = NS; MI = NS; Combined CHF and MI = p 0.0415. CHF and MI with AF/AFL p = 0.6326 NS N=506									

Table 72: Number of patients with AF/AFL at baseline ITT-Dose adjustment

	Patients n (%)		
Creatinine clearance	20<=Clcr < 40	40<= CLcr < 60	CLcr > = 60
Dofetilide			
0.25mg od	17(89.5%)	2(5.1%)	0
0.25mgbid	2(10.5%)	37(94.9%)	39(100%)
Placebo			
0.00mg od	12(85.7%)	2(6.5%)	1(2.8%)
0.00mgbid	2(14.3%)	29(93.5%)	35(97.2%)

See Table 50a and 50b

Figure 45

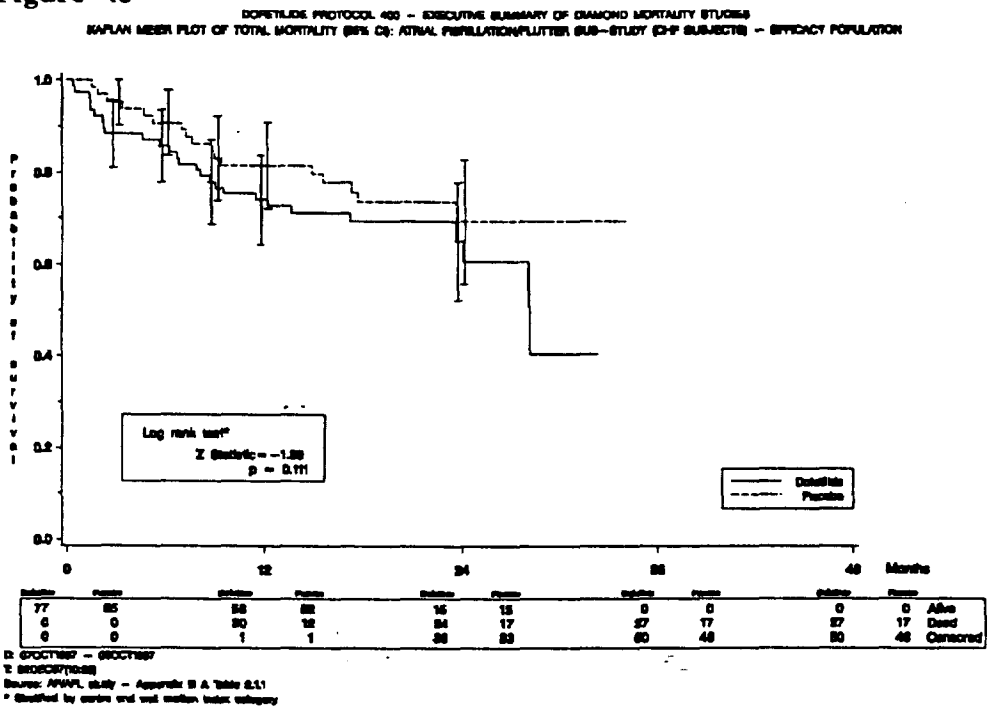
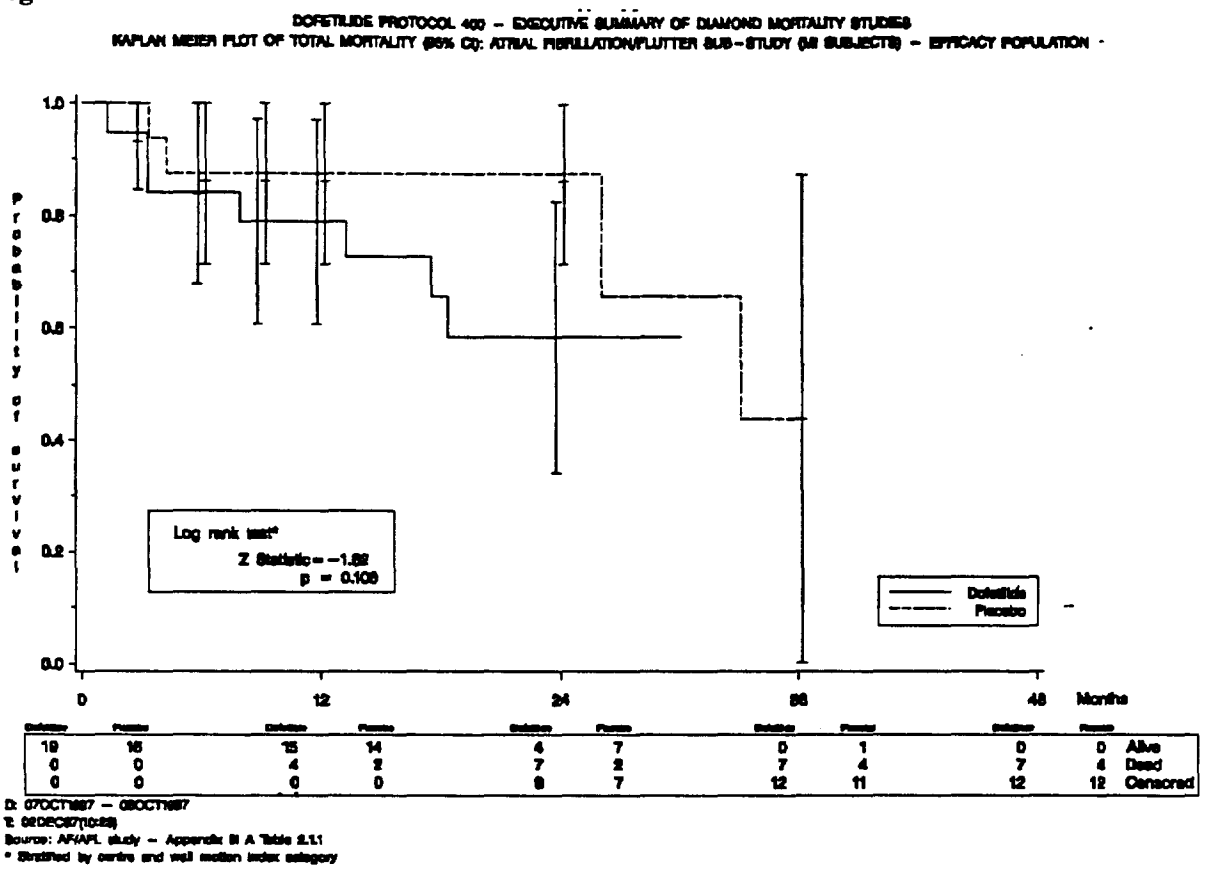


Figure 46



Worsening of Heart Failure

No significant difference was observed in time to worsening of heart failure regardless of WMI between the treatment groups. The treatment interactions are presented in Table 69 All other parameters including age, etiology of AF, sex, smoking, hypertension, and cardiovascular drugs (digoxin, beta-blockers) were not statistically significant at the 10% level.

13.6 Safety

The safety issues are discussed under the primary studies. No significant differences were seen in the complications during the study between the treatment groups (Table 72).

Table 73: Complications during study in CHF/MI of AF/AFl

	Dofetilide (N=96)	Placebo (N=81)
Bleeding	6 (3.125%)	3 (3.7%)
Thromboembolic complications	4 (4.2%)	3 (3.7%)

13.7 Comments on Protocol and data

- The protocol allowed recruitment after randomization and initiation of treatment.
- Only one third of total AF/AFl population (506) was recruited.
- There was an imbalance between the treatment groups.

Some of the concerns with this substudy and the data generated are as follows:

- The protocol design allowed enrollment, hence an opportunity for selection, over the period of hospitalization (generally 4 days), even after the start of study treatment.
- Recent data indicate that efficacy in AF/AFl may be apparent as early as Day 1, consequently candidates whose AF status had changed to SR were still acceptable.
- Only one third of total AF/AFl population (506) was recruited into the substudy.
- Of the population recruited to the substudy, one third of the patients were not enrolled whilst receiving treatment.
- There was an imbalance in the numbers of subjects recruited to each treatment group from an equally balanced treatment population.
- The marked superiority of Dofetilide over placebo treatment in restoring SR was neither representative of the total AF/AFl population receiving Dofetilide in DIAMOND nor the overall Dofetilide program.
- The mortality curves from the substudy were neither representative of the total mortality of the AF/AFl population in DIAMOND nor of the overall mortality by AF/AFl treatment groups.

13.8 Conclusions and summary

- The primary efficacy endpoint of this substudy is to examine the ability of Dofetilide to restore and maintain SR for up to 1 year of treatment. The selection of patients was flawed in this substudy, because enrollment to the substudy was allowed over 4 days, hence offering an opportunity for selection, and pharmacological restoration of SR may have occurred as early as Day 1. Consequently patients whose rhythm status had changed to SR were still accepted into the study. Furthermore, only one third of the eligible population was recruited, with no obvious explanation for the selection.
- As a result of the above selection bias, there is a significant difference in the maintenance of SR in patients who had received Dofetilide compared to placebo. This difference is evident in both the CHF and MI studies regardless of how the conversion was induced. Out of 154 and 92 patients with AF/AFl at baseline and in SR at 1 month visit, and who received Dofetilide and placebo respectively, 70 Dofetilide-treated patients remained in SR at 1 year (Probability 0.75; CI: 0.68,0.83) whereas only 21 patients receiving placebo remained in SR (Probability 0.40; CI: 0.28,0.52). This significant difference remained to the end of the study ($p<0.001$). These data are not acceptable because of the study design.
- Taking into consideration the inherent deficiencies in the conduct of this substudy, and assuming that the results will not be used for Dofetilide efficacy, the increased mortality rate observed among Dofetilide responders in this substudy should not be overlooked as a signal for two reasons. Firstly the drug has demonstrated proarrhythmic proclivity in this substudy and secondly a similar pattern has been observed in other studies in the NDA.
- Since Dofetilide therapy showed no mortality benefit over placebo in the DIAMOND studies, which are not flawed in design or conduct, and in view of increased Torsades in Dofetilide treated patients compared to placebo, this substudy shows similar trends in QTc prolongation as in the primary studies. There is a significant difference in total mortality between the two groups in this substudy as more subjects from the Dofetilide treatment group died early and during the early part of the substudy as observed in the primary DIAMOND studies. The similarities in mortality between this substudy and the primary studies would suggest that Dofetilide exposure is associated with increased proarrhythmic events, and Torsades which may explain the increased mortality in this substudy.

- This study presents two distinct signals. One signal is related to QTc prolongation and bradycardia, and the other is related to safety including mortality. The safety issues which are patently demonstrated in this substudy and in the primary studies are of such magnitude as to justify the conclusion that Dofetilide therapy cannot be recommended in asymptomatic tachyarrhythmias, regardless of the presence of structural heart disease. The signal relating to prolongation of QT interval represents, for the most part, selective drug effect on Ikr cardiac channel.

13.9 Recommendation

From a purely regulatory standpoint, this substudy must be deemed to have failed to support the clinical relevance of Dofetilide in the maintenance of SR for up to 1 year of treatment because it is non-randomized and also the selection bias observed between the treatment groups. Overall, the unexplained imbalance between the treatment groups at entry leading to a further imbalance in the maintenance phase appears to have impacted the results. No claim can be made on this substudy because of the inherent faults in the study design.

115-400 Renal Impaired (RI)

14.0 Title: Pharmacokinetics, pharmacodynamics, safety and tolerance of oral Dofetilide in subjects with renal impairment (DIAMOND RI substudy).

14.1 Protocol development and background

The protocol for this substudy was based on an amendment to the DIAMOND protocol 115-400 CHF/MI because of the pharmacokinetic and pharmacodynamic profiles of Dofetilide during the primary trials. Two studies in this NDA (115-219 and 115-308) examined the effects of Dofetilide in patients with normal and impaired renal function. The two studies provide the baseline data for dosing regimens proposed to maintain Dofetilide levels in patients with renal impairment similar to those in healthy volunteer subjects. The study was designed to confirm the relationship between CL/f and CLcr established in other studies in this NDA. DIAMOND Renal Impairment (RI) recruited patients with normal to moderately impaired renal function from the primary study.

Study 219 in this NDA showed that decreased renal function alone could not account for the total decrease in drug clearance. Patients with moderate renal impairment showed a decrease in non-renal clearance of approximately 47% compared to those with normal renal function. It was therefore hypothesized that a concomitant mechanism existed that may be responsible for decreased drug clearance in patients with renal impairment. The non-renal mechanism remains unclear in the absence of a demonstrable increase in protein binding. Available data suggest that with decreased renal function, non-renal function is also diminished.

Renal failure is intimately linked to cardiac disease, and based on earlier studies with Dofetilide, individual dosing in the DIAMOND studies was adjusted according to calculated values of creatinine clearance, on entry and during the study. As the study progressed, dose adjustments were also made for safety findings (Tables 50 a-b).

Although patients with heart failure and renal failure have been shown to have increased α1-acid glycoprotein (Ghan, 1989; Movin-Osswald, 1993), this study showed no increased protein binding. Therefore, levels of α1-acid glycoprotein were not carried out as planned in this substudy. Results from this substudy are meant to provide justification that exposure to Dofetilide can be maintained within reasonable levels by dose adjustments according to estimated creatinine clearance in a haemodynamically compromised population.

Comments on Protocol

A total of 67 subjects were screened and entered into the DIAMOND RI substudy. Thirty-five were randomized to placebo treatment and 32 to Dofetilide. There was no female with CHF and normal renal function in the substudy and there was also no female patient with mild impairment of renal function and MI. Every subject completed the DIAMOND RI substudy. The sponsor did not include enough females in the study groups and did not carry out pharmacodynamic studies in any of the patients as specified in the substudy protocol. There are, however, data from other studies in this NDA (115-250) that provide some additional information on pharmacodynamic effects in a double blind placebo controlled study design. It is noteworthy that patients enrolled in DIAMOND studies have reduced LVEF which is associated with proportionately reduced glomerular filtration fraction, impaired renal clearance and correspondfing increase in plasma drug concentration.

Significant safety issues ensue if the plasma drug concentration exceeds the optimal concentration for efficacy, and this is the basis of the dose adjustments in the primary studies. Efficacy and safety are therefore closely interrelated in the dosing regimen for Dofetilide, and renal function is a critical factor in the dosing regimen and in therapy.

14.1.1 Study objectives
The primary objectives of DIAMOND RI were to define the pharmacokinetics of Dofetilide in patients with reduced creatinine clearance and to relate the PK and protein binding to the pharmacodynamics as assessed by QTc changes. The substudy will define the pharmacokinetic profile (PK), and protein binding of Dofetilide in patients with normal and impaired renal function. Renal function was defined by creatinine clearance (CLcr) levels as normal (CLcr>60ml/min), mildly impaired (>40-<60ml/min), or moderately impaired (>20-<40ml/min).

Study Design
Patients in the RI substudy were recruited from the DIAMOND study populations after taking randomized treatment for at least one month. In order to maintain their routine dose regimen, subjects who consented to this substudy were to remain under observation from the day prior to the study day until completion of the final safety evaluations. For this substudy, they were to provide blood samples to measure Dofetilide concentrations, creatinine clearance, protein binding and α1-acid glycoprotein should their protein binding be outside the normal range in addition to those required for the routine safety evaluations. Urine was to be collected across the dose interval and assayed for Dofetilide and creatinine concentrations.

On the study day, further blood and urine samples were to be collected across each subject's dose interval to provide a full pharmacokinetic profile and EKGs were to be measured at corresponding times. Routine safety checks of vital signs were to be performed prior to discharge, anticipated to be 24 hours after dosing or on administration of the next dose of study treatment.

Principal Investigators:

Study Dates: 19 January 1995 - 03 January 1996.

Duration of study: One day within the duration of the primary studies.

Diagnoses and Criteria for Inclusion of Subjects
Males and females with renal function, defined above, who had participated in DIAMOND CHF or MI for at least 1 month and with serum albumin ≤30g/l.

Drug Administration
Dosage Form Dofetilide, 250mcg oral capsules (FID S00114AB Lot 2833-130 and FID2958-069X, Lot 2833-183), and placebo as matching oral capsules (FID S00117AA, Lot 2833-122 and FID S00117AA, Lot 2968-078). Dosing 500mcg bid (normal function), 250mcg bid (mild impairment) 250mcg od (moderate impairment) unless adjusted for QTc intervals beyond prescribed limits or adverse events.

14.2 Pharmacokinetic/Pharmacodynamic and Safety Evaluations
Blood and urine samples were taken across one dose interval to measure Dofetilide plasma concentrations. ECGs were monitored throughout for QTc measurement and safety. All safety assessments were done as part of the primary DIAMOND studies.

Statistical Methods
These are as specified in the protocol.

Study Population
Two centers participated in the RI substudy. Sixty seven (67) subjects were screened and accepted for entry, 32 receiving Dofetilide treatment and 35 receiving placebo.
A minimum of 60 subjects, with at least one month's participation in either of the two primary DIAMOND studies, were recruited to the DIAMOND Renal Impairment (RI) substudy. Twenty subjects were to have normal renal function, 20 mild renal impairment and 20 moderate impairment. Each subject was to complete a separate written CRF for this substudy.

Selection Criteria
Subjects entering the RI substudy fulfilled the following selection criteria of the primary studies and in addition, they were to fulfill the specific criteria below.
They would have been enrolled in the primary study for at least one month prior to recruitment to the RI study, so would be at steady state with their study treatment.

Inclusion Criteria
1. Subjects were to have stable renal function within one of the three categories listed below:
Normal CLcr above 60 ml/min
Mild CLcr within the range >40 - <60ml/min
Moderate CLcr within the range >20 - <40ml/min
calculated according to the Cockroft and Gault equations:
For males: CLcr(ml/min) = (140-age)(body weight)/(72.scr),
For females: CLcr(ml/min) = CLcr (males) x 0.85,
2. Subjects' serum albumin was to be greater than or equal to 30g/l.
3. Serum potassium was to be within 3.6 and 5.5mmol/l.
4. On clinical examination, subjects were to have no clinically significant abnormality and the only acceptable ECG abnormalities were those associated with renal insufficiency, heart failure or MI.
5. They were to have no clinically significant abnormal laboratory test data other than those parameters influenced by renal insufficiency, heart failure or MI.

Exclusion Criteria
1. Subjects who had received a renal transplant.
2. Subjects with any condition likely to influence the absorption of study treatment.

Dosage Form
Dofetilide was supplied as 250mcg oral capsules (FID S00114AB Lot 2833-130 and FID2958-069X, Lot 2833-183), and placebo as matching oral capsules (FID S00117AA, Lot 2833-122 and FID S00117AA, Lot 2968-078).

Pharmacokinetic Assessments
On the assessment day, suitable blood samples (8ml) were obtained pre-dose, and 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours after dosing to measure concentrations of Dofetilide. In addition, protein binding was assayed. Urine output was collected over 12 hourly periods across the dose interval and assayed for Dofetilide by and a separate 10ml sample was assayed for creatinine.

Pharmacokinetic Analysis
The following PK parameters were derived for each subject from the plasma concentration time profiles and the amounts of Dofetilide excreted in the urine: Aetau, AUCtau, Cmax, Cmin, Tmax, and Cavss that allows for direct comparison between unequal groups was calculated as the average plasma concentration of Dofetilide during a dose interval at steady state calculated as AUCtau/Dose Interval (ng/ml).
Clcr: For males CLcr(ml/min) = (140-age)(body weight)/(72.scr).
For females CLcr(ml/min) = CLcr (males) x 0.85.
CL/f: Apparent clearance, calculated as dose/AUCtau (L/h)
CLr : Renal clearance, calculated as Aetau/AUCtau (L/h).
CL/fnr Apparent non-renal clearance, calculated as CL/f - CLr (L/h).
Cmax and Cavss were log transformed and assessed between the groups using analyses of variance techniques. A second analysis of variance was performed allowing for grouping by CLcr, the primary diagnosis of MI and CHF, and an interaction between primary diagnosis and CLcr.

Pharmacodynamic Assessments
Triplicate measures of 12 lead ECG were recorded predose and at 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours after dosing with an additional 24h recording in subjects receiving the od regimen. Accurate measures of QT/QTc were made from Leads II, AVF and V5 using the same equipment.

Pharmacodynamic Analyses
For each group, QTc data from the 12 lead ECG were summarized pre-dose and 2 - 4 hours after dosing on the study and follow-up days.

Safety Assessments
Safety events specifically relevant to this protocol were generated in this substudy from DIAMOND CHF/MI. However, the ECG data collected for pharmacodynamic assessment were evaluated for safety and blood pressures and heart rate were measured.
The pre-dose blood sample was to be sufficient to allow for the additional assay of serum α1-acid glycoprotein concentrations in patients only where plasma protein binding showed an increase.

Safety Analysis
Adverse events reported directly or observed from the safety test data from the study day were considered pertinent to the primary studies and have been included in the safety data presented in the DIAMOND CHF and DIAMOND MI reports.

Study Monitoring
The centers participating in this substudy were monitored routinely as part of DIAMOND CHF and DIAMOND MI studies. The blinding restrictions of the primary studies were not compromised.

14.3 Data analysis
Sample Size
Formal sample sizing was not undertaken but the minimum number of 60 participants, 20 per group, was chosen to provide 10 patients per group receiving active treatment.

14.4 Results
Population For Analyses
Based on calculated values of creatinine clearance (CLcr), and hence renal function, 3 study groups received Dofetilide and one group for placebo (Table 74).
The underlying cause of ventricular dysfunction was not a factor.

Table 74: Evaluable Groups for PK - 115-400RI

No of subjects	Mild	Moderate	Normal	Placebo
Entered Study	11	11	10	35
Completed study	11	11	10	35
Evaluated for PK	10	10	10	0
Safety*	11	11	10	35

*Reported as part of DIAMOND CHF/MI

Baseline Creatinine clearance

Of the 32 patients receiving Dofetilide double-blind, 10, 11, 11 were classified as having normal renal function, CLcr range 68 to 114 ml/min, mild renal impairment, 43- 59ml/min, and moderate renal impairment, 23-40ml/min, respectively (Table 75).

Table 75: Baseline creatinine clearance - 115-400RI

	Evaluable population		
	Moderate n=11	Mild n=11	Normal n=10
Arithmetic Mean ± sd	32.5 ± 5.5	51.7 ± 6	87 ± 15.2
Range	23-40	43-59	68-114

Demographics

Of the 32 patients, 18 were recruited from DIAMOND MI (16 males and 2 females), and 14 from DIAMOND CHF (9 males and 5 females). The male/female ratio was 25:7 and the group with normal renal function was generally younger (Mean 56 yrs) compared to mild and moderate renal impairment, being 70 and 75 years, respectively (Table 76).

Table 76: Demographics - 115-400 RI

	Dofetilide					
	Mild (n=11)		Moderate (n=11)		Normal (n=10)	
	Males	Female	Males	Female	Males	Female
n of patients	8	3	8	3	9	1
Age(yrs)						
<18	0	0	0	0	0	0
18-44	0	0	0	0	0	0
45-64	0	1	1	0	9	1
65-84	8	2	7	3	0	0
>=85	0	0	0	0	0	0
Age Range (yrs)	66-77	64-67	63-82	75-81	50-61	58-58
Mean Age(yrs)	72	65	73	79	55	58
Race						
White	100%	100%	100%	100%	100%	100%
Black	-	-	-	-	-	-
Other	-	-	-	-	-	-
Weight Range(kg)	59-93	50-69	61-82	55-72	70-97	66-66
Mean weight(kg)	78	61	70	63	81	66
Height range(cm)	158-185	156-170	163-178	152-162	173-182	165-165
Mean Height(cm)	175	162	171	158	177	165
DIAMOND CHF MI	 3 5	 3 0	 4 4	 2 1	 2 7	 0 1

Study subjects: Patient Disposition
A total of 67 subjects were screened and entered DIAMOND RI, 35 randomized to placebo treatment and 32 to Dofetilide. There was no female with CHF and normal renal function in the substudy and there was also no female patient with mild impairment of renal function and MI. Every subject completed the DIAMOND RI substudy (Table 74).

Exclusions from Evaluation
Thirty-five subjects that received placebo in this substudy in order to maintain the blinding were not included in any of the analyses. Nine subjects who received Dofetilide were excluded from evaluation of at least one pharmacokinetic assessment.

Drug administration
Patients with normal renal function were randomized to Dofetilide 500mcg b.i.d or matched placebo capsules bid; mild impairment of renal function had their dose adjusted to 250mcg bid and those with moderate impairment of renal function received 250mcg od. Further dose adjustments were also made for 1 subject with AF/AFl, 2 subjects with prolongation of QTc beyond recommended limits, and those who experienced adverse or other events on their initial regimen which the investigator considered warranted a lower dose. Five subjects (3 normal and 2 mild RI) who entered DIAMOND RI received doses of Dofetilide which were adjusted for unknown reasons other than CLcr (Table 77).

Table 77: Drug administration in evaluable subjects

	Dofetilide RI Substudy		
	Mild	Moderate	Normal
No of subjects	11	11	10
0.50mg bid	0	0	7(70)
0.25mg bid	9(81.8)	0	3(30)
0.25 od	2(18.2)	11(100)	0

Study Drug Discontinuations
No subject was discontinued from the substudy.

Protocol deviations
There were five subjects who deviated from the protocol:-
Consent form specific to DIAMOND RI not completed- 1 subject.
Taking reduced doses of Dofetilide - 2 Subjects and
incomplete blood and or urine sampling 1 Subject.

14.5 Pharmacokinetic Results
For PK assessments, the dose (0.25mg od) for all moderately impaired renal patient is similar , whereas in 2 mild, and 3 normal patients, the dose was down titrated from 0.5mg bid to 0.25mg od and 0.25 bid, respectively. Because the patients had been on therapy, and were in steady state, Cavss was calculated to allow direct comparison across the 3 groups (Table 78) . This is not an ideal way to assess comparisons among cohorts receiving different drug dosage. However, the mean plasma concentrations of Dofetilide in patients with renal impairment were below the mean concentration in subjects with normal renal function (Table 79 and Figure 1 RI). Cavss showed a similar relationship to Cmax (Tables 78 -80). Cmax occurred earlier in patients with normal renal function at 1.7h compared to 2.2h (mild) and 2.8h (moderate) (Figure 1 RI and 2 RI). All values were within the limits observed in the other Dofetilide studies (Study 115-219).

Table 78: **Pharmacokinetic Results

	Degree of Impairment Parameter (mean ± sd (n)) Normal	Mild	Moderate
AUCtau (ng.h/ml)	25.7 ±6.8 (7)	20.7 ±5.4 (9)	28.7 ±3.6 (10)
Cmax * (ng/ml)	3.4 ±1.4 (7)	2.4 ±1.3 (9)	2.0 ±1.2 (10)
Cavss * (ng/ml)	2.1 ±1.3 (7)	1.7 ±1.3 (9)	1.2 ±1.1 (10)
CL/f (L/h)	20.6 ±5.1 (10)	12.5 ±2.9 (10)	8.8 ±1.1 (10)
CLr (L/h)	2.6 ±3.4 (10)	6.4 ±1.7 (8)	4.5 ±0.9 (9)
Protein binding (%)	62.9 ±3.7 (10)	64.9 ±8.5 (10)	67.9 ±5.5 (8)

* Geometric mean ** Data does not separate the 5 patients receiving different doses.
Linear regression of total and renal clearance against CLcr gave the following equations:
CL/f (L/h) = 1.385 + 0.2190 x CLcr, R 2(adj) = 0.808 CLr (L/h) = -1.148 + 0.1554 x CLcr, R2 (adj) = 0.816

Table 79: *Cmax/Cavss (ng/ml) of evaluable patients

	Dofetilide and Renal Impaired patients (ng/ml)		
	Mild (n=9)	Moderate (n=10)	Normal (n=7)
Mean Cmax ± sd	2.5±0.7	2.1±0.5	3.5±1.3
CV(%)	27.7	23.3	37.5
Geometric mean±sd	2.4±1.3	1.0±1.2	3.4±1.4
Cavss geometric	1.2±1.1	1.7±1.3	2.1±1.3
mild-normalp=0.026; moderate-normalp= <0.001;mild-moderate p=0.151@90%			

*Invalid comparisons and p-values because dose varied among subjects

Table 80: Cmax and Cavss in RI substudy

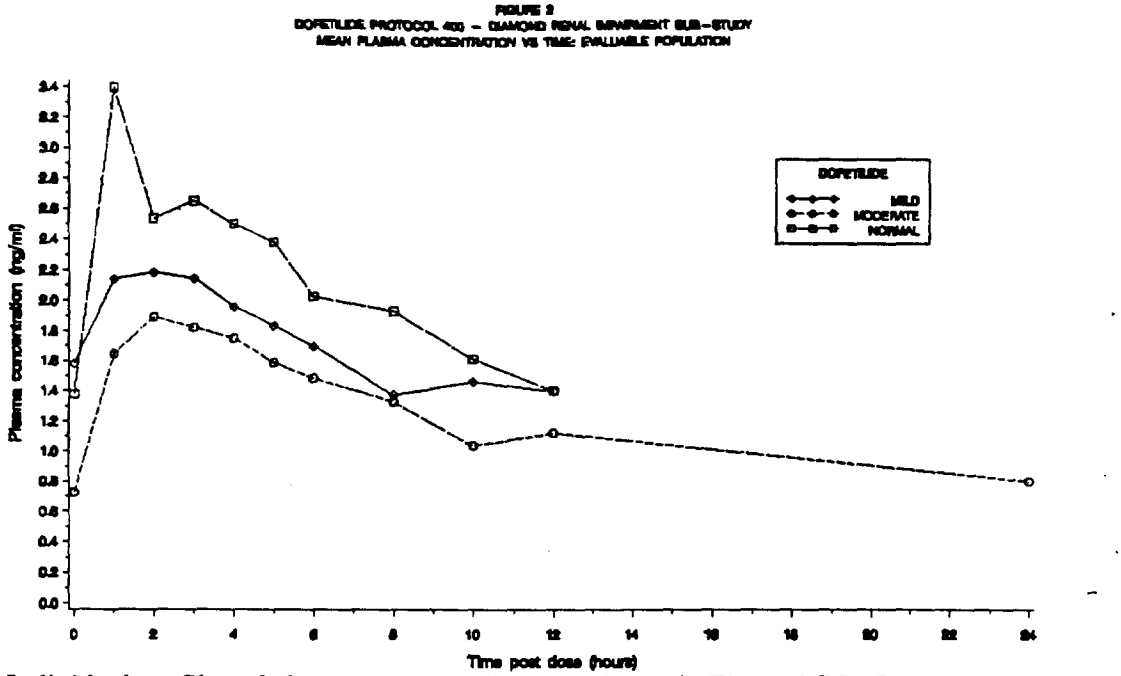
TABLE 6.2
DOFETILIDE PROTOCOL 400 - DIAMOND RENAL IMPAIRMENT SUB-STUDY
SUMMARY OF ANALYSIS OF PHARMACOKINETIC PARAMETERS: EVALUABLE POPULATION

CONTRAST

Dofetilide Comparison	Log Transformed Data: Difference	SED	90% Confidence Limits on Difference: Lower	Upper	P-value	Anti-Log: Ratio Between Geometric Means (%)	90% Confidence Limits: Lower (%)	Upper (%)
Cmax (ng/ml)								
MILD - MODERATE	0.2	0.1	0.0	0.4	0.152	120	97	149
MILD - NORMAL	-0.8	0.1	-0.6	-0.1	0.026	72	57	91
MODERATE - NORMAL	-0.5	0.1	-0.7	-0.3	<0.001	60	48	76
Cavss (ng/ml)								
MILD - MODERATE	0.3	0.1	0.2	0.5	0.002	141	119	167
MILD - NORMAL	-0.2	0.1	-0.4	0.0	0.062	81	67	97
MODERATE - NORMAL	-0.6	0.1	-0.7	-0.4	<0.001	57	48	69

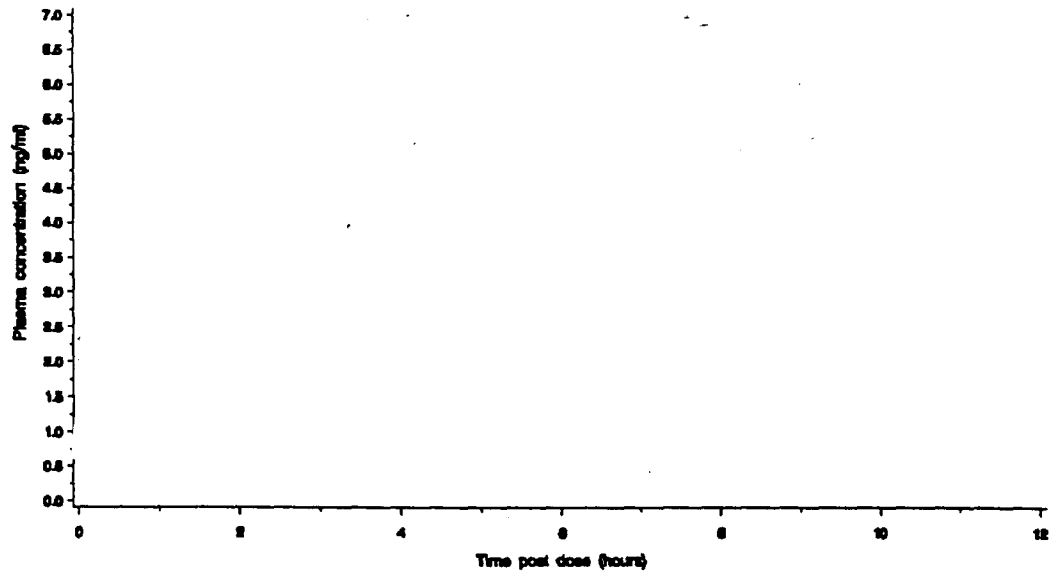
D: 28MAY1997 - 03JUL1997
T: 05AUG97 (15:19)
Page 1 of 1

Figure 1 RI



Individual profiles of plasma concentrations are shown in Figure 2 RI. Cmax was greater in subjects with normal renal function, using geometric mean of 3.4ng/ml ±1.4(sd) compared to groups with mild and moderately impaired renal function with 2.4ng/ml ±1.3 and 2.0ng/ml ± 1.2 , respectively, ($p = 0.026$ and $p<0.001$).

Figure 2 RI



NDA #20931
A.O.Williams, M.D.

Urinary excretion

The amount of Dofetilide and proportion of dose excreted in the urine showed slight differences between the groups corresponding with their renal function, the normal group excreting 321mcg (64% of the dose) Dofetilide across the dose interval; 136.4mcg (55%) in mild impairment group, and 128.1mcg (51%) in moderate impairment group. Apparent clearance of Dofetilide (CL/f) decreased with decreasing renal function, normal subjects clearing 20.6 ±5.1L/h compared to 12.5±2.9L/h (mild impairment) and 8.8 ± 1.1 L/h (moderate impairment) as did renal clearance (CLr = 12.6± 3.4L/h, 6.4± 1.7L/h and 4.5 ± 0.9L/h), respectively. There were strong linear relationships with creatinine clearance for both Dofetilide clearance and renal clearance (r2= 0.81 and 0.82 respectively,(Figures 3 RI and 4 RI). The decrease in renal clearance did not completely account for the reduction in total clearance.

Figure 3 RI

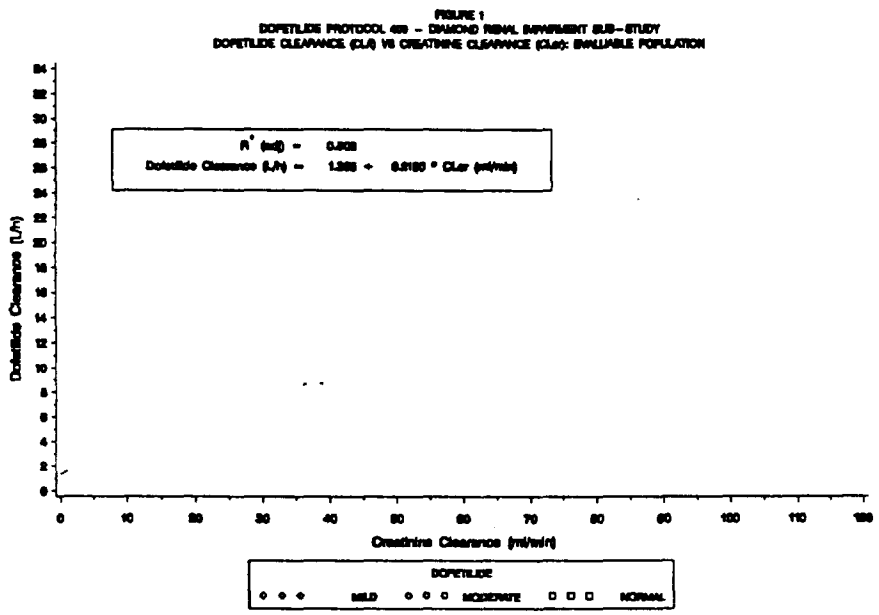
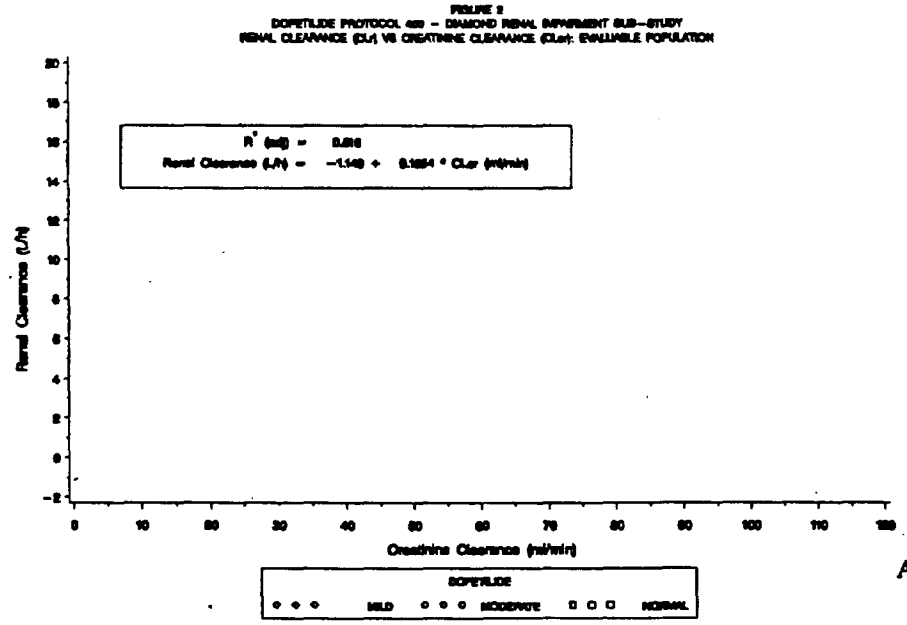


Figure 4 RI



Although there were no significant differences between the treatment groups in protein binding, there are data on protein binding in healthy volunteers which show that the drug is not highly bound to protein (See Dr Fadiran's review - Biopharm). However, the percentage range of protein binding was 53.6% - 77%; the simple mean values (± sd) were 62.9% ± 3.7 for the patients with normal renal function, 64.9 ± 8.5 for those with mild impairment and 67.9 ± 5.5 for those with moderate impairment. In 3 subjects there were no data on the protein binding, and in the mild group there were no data on 2 subjects. No reasons were given for the lack of data. Urinary clearance in normal subjects is 20.6 ±5.1L/h compared to 12.5±2.9L/h (mild impairment) and 8.8 ± 1.1 L/h (moderate impairment) and similarly renal clearance (CLr = 12.6 ± 3.4L/h, 6.4 ± 1.7L/h and 4.5 ± 0.9L/h respectively).

14.6 Pharmacodynamic Assessment

QTc for each group 2 - 4 hours after dosing on the study day (Day 1) were not available for all the sampling times. QT data for days 1-4 are graphically represented in Figure 5 RI below. The mean increase in QT interval post-dose from the group with normal renal function was generally larger than those observed from the groups with impaired renal function. However, there was considerable overlap between the range values in the group and the differences between the groups are unlikely to have any clinical implications (Table 81). No reasons were given for not evaluating the QTc intervals of patients at the presspecified times in the protocol, particularly when the patients were in steady state.

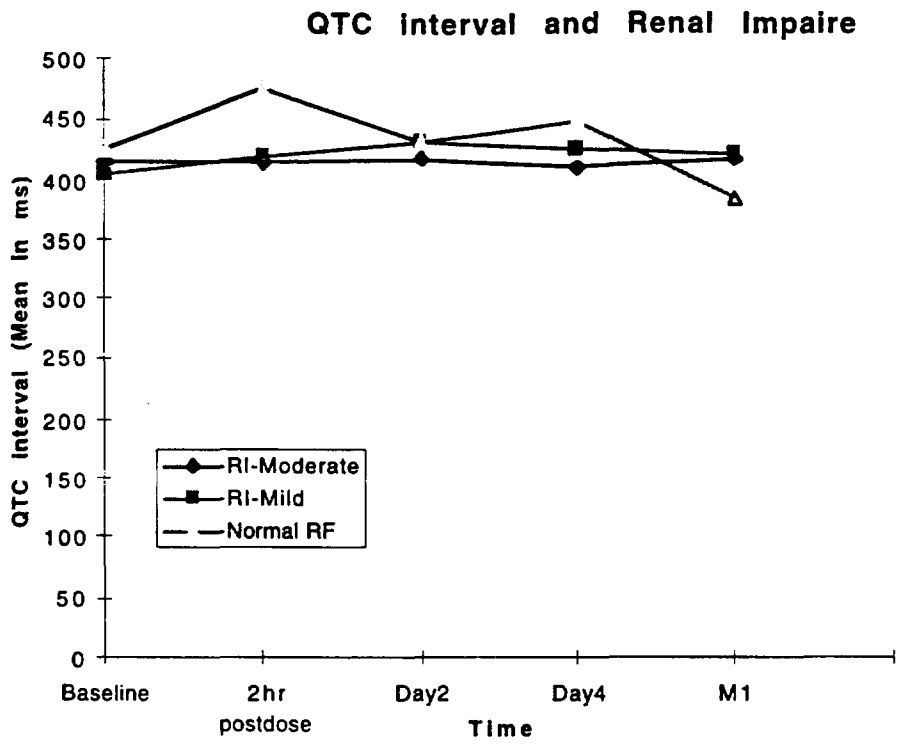
Table 81: Summary of QTc changes in RI substudy

TABLE 6.3
DOFETILIDE PROTOCOL 400 - DIAMOND RENAL IMPAIRMENT SUB-STUDY
QTC SUMMARY: EVALUABLE POPULATION

DAY *		DOFETILIDE MILD IMPAIRMENT	DOFETILIDE MODERATE IMPAIRMENT	DOFETILIDE NORMAL RENAL FUNCTION
Day 1	Arithmetic Mean	402.1	415.7	421.3
	Std. Dev.	52.8	32.3	27.2
	N	8	6	6
	Range			
	Missing	3	5	4
Day 1 *	Arithmetic Mean	420.7	418.1	490.9
	Std. Dev.	54.8	39.0	72.1
	N	10	8	8
	Range			
	Missing	1	3	2
Day 2 *	Arithmetic Mean	433.8	425.5	437.1
	Std. Dev.	63.2	41.1	43.0
	N	9	8	7
	Range			
	Missing	2	3	3
Day 4 *	Arithmetic Mean	427.8	421.0	450.1
	Std. Dev.	68.5	40.9	30.6
	N	9	6	7
	Range			
	Missing	2	5	3

D: 23MAY1997 Page 1 of 1
T: 09SEP97(11:09)

Figure 5 RI: QTc changes in RI substudy



Source : Reviewer

14.7 Safety

Results: Safety data are presented in DIAMOND CHF and DIAMOND MI reports.

14.8 Discussion

This is a substudy which derived patients from the primary DIAMOND studies. Any conclusions from this substudy should be taken with caution for the following reasons. The sample size is small, there is imbalance between the sexes, the NYHA classification was not considered as a factor in recruitment, and data derived from patients randomized to placebo were not included in the analysis. The sponsor did not carry out PK/pd analysis as prespecified in the protocol.

Reduction in LVEF predisposes to reduced creatinine clearance and all eligible patients randomized to DIAMOND had reduced LVEF (<25 or < 35%), suggesting that there was reduced creatinine clearance at baseline. Therefore, for a drug like Dofetilide which has at least a 60% renal clearance of parent drug, reduction of creatinine clearance is expected to result in increased drug exposure and reduced drug clearance. This should inevitably lead to increased Cmax and extended Tmax in patients with impaired renal function.

Conclusions

AUCt and AUC values in moderately and severely renally impaired patients were approximately 3 and 5 fold higher, respectively, compared to healthy volunteers. Similarly, the terminal half life of Dofetilide was 2.5 and 3.5 fold longer respectively, compared to healthy volunteers. Cmax was approximately 50% higher in renally impaired patients compared to normal subjects.

Evaluation of data from DIAMOND RI study shows a linear relationship between renal and creatinine clearance and confirms that, at steady state, CLcr is directly proportional to CLr and is consistent across the dose range of 250mcg od to 500mcg bid in renally impaired patients. Although thepatients had structural heart disease, the severity of left ventricular dysfunction was not validated in the subjects enrolled in the substudy. Furthermore there was a gender imbalance of 3.5 males to 1 female which gives a limited value on the interpretation of the results for both sexes. The arbitrary limits for CLcr in apparently healthy population (above 60ml/min) is not in accordance with FDA " guidelines on PK studies in renally impaired subjects".

The linear relationship between Dofetilide clearance and CLcr with chronic dosing in subjects with impaired renal function is similar to what has been described with single dosing in an otherwise healthy population (Study 115-244), and in renally impaired patients (Study 115-219). (The slopes which fitted the equations were equal to 0.17 x CLcr (R2= 0.88) for study 115-229, and 0.22 x CLcr, (R2= 0.81) in 115-400 DIAMOND RI) .

QTc changes in patients with impaired renal function showed some degree of overlap with those from subjects with patients with normal renal function and relatively higher rates of Clcr (Figure 5RI). Efficacy has been shown in other studies (115-120, 115-345) using doses of Dofetilide adjusted according to Clcr. The clinical benefit of Dofetilide is therefore dose-dependent for any clinical indication. Regardless of the exact mechanisms of drug clearance in patients, increased drug exposure exposes patients to the risk of QTc prolongation, bradycardia, Torsades and sudden death. Dose adjustments, based on calculated levels of CLcr may successfully reduce these potential risks in patients with mild and moderate renal impairment from what would be anticipated to be standard therapeutic clinical dose.

This study had to reduce Dofetilide dosage in 3/10 (30%) patients with apparently normal renal function in order to achieve reduced drug concentration and reasonable urinary excretion. All 3 patients had increased QTc interval. Two of the 3 patients had MI and the third had atrial fibrillation and "digitalis effect".

The potential risk of Torsades and sudden death, particularly in patients with asymptomatic supraventricular tachycardia and mild heart failure (NYHA <class III) in renally impaired patients with recent MI poses a safety concern. The risks are probably greater in females who appear to have higher plasma concentrations of Dofetilide compared to males. Safety issues were not assessed in the cohort studied in DIAMOND RI. The lack of enough female patients in this substudy is not desirable in view of the apparent increase in female susceptibility to adverse events in other studies where Dofetilide was administered to females in this high risk population.

As observed in other studies in this NDA, the protein binding of Dofetilide in normal patients is not statistically significantly different compared to patients with mild or moderate renal impairment (Study 115-219). Other studies in this NDA (115-004, 115-007, 115-011, 115-255) showed that Dofetilide exposure predisposed to higher levels of drug concentrations in patients with renal impairment, and that renal and oral clearance of drug was significantly reduced in patients with renal impairment.

15.0 Recommendations

On the basis of population PK data derived from other studies in this NDA (115-004, 115-007, 115-011, 115-255), and the pharmacokinetic data and pharmacodynamic effects generated from this substudy (115-400RI), there is compelling evidence to recommend dose adjustments and, or lengthening of dosing interval of drug therapy in hemodynamically compromised patients with renal impairment. Creatinine clearance dose-dependent regimen is indicated in patients with renal impairment and, or patients with prolonged QTc in order to reduce the risk of serious adverse events, including Torsades and sudden cardiac death.

16.0 Appendix Table 1A

REASONS FOR NON-RANDOMIZATION: SCREENED NON-RANDOMIZED MI POPULATION

NUMBER(%) OF SUBJECTS	6762
Percentage of patients not meeting selection criteria *:	
Patient is female and of child bearing potential	32 (0.5)
Patient has WMI >1.2	5857 (86.7)
Patient has not suffered from MI / CHF within previous 7 days	113 (1.7)
Patient gave no written informed consent	2109 (31.2)
Patient has sick sinus node syndrome	5 (0.1)
Patient could die from causes other than cardiovascular	23 (0.3)
Patient has serum potassium < 3.6 mmol/L or > 5.5 mmol/L	73 (1.1)
Patient is receiving concomitant therapy with class I or III anti-arrhythmic drugs	82 (1.2)
Patient has received Amiodarone within the last 3 months	16 (0.2)
Patient has participated in an experimental drug study in the past 3 months	10 (0.1)
Patient suffers from chronic alcoholism, drug addiction, dementia or some other condition	63 (0.9)
Patient has clinically significant reduced kidney function	54 (0.8)
Patient has acute myocarditis 1	
Patient has planned cardiac surgery	16 (0.2)
Patient has aortic stenosis	13 (0.2)
Patient has had a cardiac operation in the preceding 4 weeks	2
Patient has a resting ventricular rate of < 50 bpm when awake	10 (0.1)
Patient has second or third degree AV block	18 (0.3)
Patient has QTc>460 msec in the absence of BBB or has QTc>500 msec in the presence of BBB	34 (0.5)
Patient has diastolic bp > 115 mmHg or systolic bp < 80 mmHg	9 (0.1)
Reasons for non-randomization:	
Did not meet selection criteria	6259 (92.6)
Protocol violation	1
Asked to be withdrawn prior to randomization	267 (4.0)
Patient died prior to randomization	**74 (1.1)**
Others	156 (2.3)
Missing	5

* Patients may have more than one reason for non-randomization

Appendix Table 1B

DIAMOND CHF STUDY- REASONS FOR NON-RANDOMIZATION: SCREENED NON-RANDOMIZED POPULATION

TOTAL NUMBER (%) OF SUBJECTS	4030
Percentage of patients not meeting selection criteria *:	
Patient is female and of child bearing potential	5 (0.1)
Patient has WMI >1.2	2996 (74.3)
Patient has not suffered from MI / CHF within previous 7 days	52 (1.3)
Patient gave no written informed consent	1480 (36.7)
Patient has sick sinus node syndrome	10 (0.2)
Patient has a history of polymorphous VT	19 (0.5)
Patient could die from causes other than cardiovascular	20 (0.5)
Patient has serum potassium < 3.6 mmol/L or > 5.5 mmol/L	86 (2.1)
Patient is receiving concomitant therapy with class I or III anti-arrhythmic drugs	154 (3.8)
Patient has received amiodarone within the last 3 months	45 (1.1)

Patient has participated in an experimental drug study in the past 3 months	10 (0.2)
Patient suffers from chronic alcoholism, drug addiction, dementia or some other condition	84 (2.1)
Patient has clinically significant reduced kidney function	70 (1.7)
Patient has acute myocarditis	3 (0.1)
Patient has planned cardiac surgery	20 (0.5)
Patient has aortic stenosis	73 (1.8)
Patient has had a cardiac operation in the preceding 4 weeks	5 (0.1)
Patient has a resting ventricular rate of < 50 bpm when awake	8 (0.2)
Patient has second or third degree AV block	7 (0.2)
Patient has QTc>460 msec in the absence of BBB or has QTc>500 msec in the presence of BBB	44 (1.1)
Patient has diastolic bp > 115 mmHg or systolic bp < 80 mmHg	6 (0.1)
Reasons for non-randomization:	
Did not meet selection criteria	3565 (88.5)
Asked to be withdrawn prior to randomization 260 (6.5)	
Patient died prior to randomization	**19 (0.5)**
Other	186 (4.6)

* Patients may have more than one reason for non-randomization

APPENDIX Table 2: Mean (range) duration of follow up at EOS - CHF/MI

	CHF (n=888/1518 58.5%)		*MI(n=1034/1510 68.5%)	
Patients censored	Dofetilide(449)	Placebo(439)	Dofetilide(517)	Placebo(517)
Adverse events	52 196(1-1002)	36 155(1-717)	45 138(1-1006)	42 239(1-1085)
Asked to be withdrawn from study	46 160(1-774)	47 207(2-807)	55 148(1-756)	63 248(1-917)
Completed study*	**315 643(343-1099)**	**304 658(349-1094)**	**383 742(342-1300)**	**395 741(342-1300)**
Did not meet selection criteria	1 67	1 27	-	-
Laboratory abnormality	6 398(34-644)	7 446(81-801)	2 169(105-232)	1 42
Lost to follow up	2 499(412-587)	2 297(47-546)	4 417(4-939)	2 447(105-788)
Others	10 209(5-482)	32 141(6-674)	12 390(6-1235)	10 326(8-737)
Protocol violation	5 18(5-41)	8 199(3-749)	5 114(6-247)	1 69
QT/QTc prolongation	12 114(2-723)	2 295(18-571)	11 52(3-183)	3 117(3-244)

First Row = Number of patients; Second Row=Mean duration of follow up and ( )=minimum and maximum duration of follow up (days). *Sponsors figures are 519 and 518 for drug and placebo, respectively in MI study. Source: Reviewer

APPENDIX Table 3: Mean (range) duration of follow up - CHF/MI permanently discontinued patients

	CHF (N=630) 629		MI (N=657) 655	
Final status of patients	Dofetilide (138+174)312	Placebo (133+184)317	Dofetilide (229) +1	Placebo (241)+2
Patient died before LVD	174	184	229	241
Adverse events	57 172(1-932)	48 104(1-931)	38 103(1-836)	40 125(1-597)
Asked to be withdrawn from study	43 183(1-758)	54 116(1-570)	28 111(1-697)	38 66(1-625)
Did not meet selection criteria	-	1 33	-	1 29
Laboratory abnormality	4 204(108-345)	4 354(240-449)	2 (6-105)	1 233
Lost to follow up	1 324	2 602(432-771)	2 493(161-825)	1 517
Others	20 171(4-804)	16 238(2-680)	5 220(14-410)	14 220(9-764)
Protocol violation	2 10(5-15)	3 28(2-64)	-	1 40
QT/QTC prolongation	2 50(5-95)	1 102	8 36(2-126)	-

LVD=Last visit date; First Row = Number of patients; Second Row = Mean duration of follow up and () = minimum and maximum duration of follow up. Source: Reviewer. See Appendix Table 18 page 24) for the last 3 months of both studies.

APPENDIX Table 4

The slope/hazard ratio together with the 95% confidence interval for the variables/factors included in the model are summarised below. For the continuous variables of age and creatinine clearance the parameter estimate (slope) is presented.

Summary of Cox's Proportional Hazards Model for Total Mortality: Intent-to-Treat Population - End of Study Analysis				
Variable	Slope/Hazard Ratio	95% CI	p-value	Conclusions
Treatment	0.94	0.81 to 1.11	0.470	Equivalence with trend towards decreased hazard on dofetilide compared to placebo
Age *	0.02	0.01 to 0.03	<0.001	Increased hazard with increasing age
Creatinine Clearance *	-0.01	-0.02 to -0.01	<0.001	Decreased hazard with increased creatinine clearance
Presence of AF/AFl	1.18	0.98 to 1.41	0.084	Increased hazard with the presence of AF/AFl
Presence of Ischaemia	1.33	1.11 to 1.60	0.003	Increased hazard with the presence of Ischaemia
NYHA II III IV	 1.32 1.76 2.54	 0.69 to 2.52 0.92 to 3.37 1.28 to 5.06	 0.401 0.089 0.008	Increased hazard (relative to NYHA I) with increasing NYHA score
WMI	0.71	0.60 to 0.84	<0.001	Decreased hazard with increased WMI

APPENDIX Tables 5

The slope/hazard ratio together with the 95% CI for the variables/factors included in the model are summarised below. For the continuous variable, age, the parameter estimate (slope) is presented.

Summary of Cox's Proportional Hazards Model for Total Mortality: Intent-to-Treat Population - On Treatment Analysis				
Variable	Slope/Hazard Ratio	95% CI	p-value	Conclusions
Treatment	0.86	0.64 to 1.17	0.341	Equivalence with trend towards decreased hazard on dofetilide compared to placebo
Age *	0.03	0.01 to 0.05	<0.001	Increased hazard with increasing age
NYHA II III IV	 2.43 3.05 6.43	 0.57 to 10.44 0.71 to 13.18 1.43 to 28.95	 0.231 0.135 0.015	Increased hazard (relative to NYHA I) with increasing NYHA score

For continuous variables (*) the slope is presented which is interpreted as the increase in hazard by unit (age = years).

The relative hazard of dofetilide versus placebo, having adjusted for important prognostic factors, is 0.86 with 95% confidence interval ranging from 0.64 to 1.17.

APPENDIX Table 6

Summary of Cox's Proportional Hazards Model for Total Mortality: Intent-to-Treat Population - End of Study Analysis				
Variable	Slope/Hazard Ratio	95% CI	p-value	Conclusions
Treatment	0.97	0.80 to 1.17	0.733	Equivalence with trend towards decreased hazard on dofetilide compared to placebo
Creatinine Clearance *	-0.02	-0.015 to -0.024	<0.001	Decreased hazard with increased creatinine clearance
Presence of AF/AFl	1.46	1.07 to 1.97	0.016	Increased hazard with the presence of AF/AFl
Cimetidine	0.61	0.37 to 0.99	0.045	Decreased hazard with use of cimetidine at any time during study
Presence of Ischaemia	1.39	1.13 to 1.71	0.002	Increased hazard with the presence of Ischaemia
NYHA II III IV	 2.32 3.78 7.96	 1.42 to 3.77 2.29 to 6.25 4.37 to 14.50	 <0.001 <0.001 <0.001	Increased hazard (relative to NYHA I) with increasing NYHA score
WMI	0.56	0.42 to 0.75	<0.001	Decreased hazard with increased WMI

For continuous variables (*) the slope is presented which is interpreted as the increase in hazard by unit (age = years, creatinine clearance = ml/min).

APPENDIX Table 7

Summary of Cox's Proportional Hazards Model for Total Mortality: Intent-to-Treat Population - On Treatment Analysis				
Variable	Slope/Hazard Ratio	95% CI	p-value	Conclusions
Treatment	0.92	0.66 to 1.28	0.618	Equivalence with trend towards decreased hazard on dofetilide compared to placebo
Creatinine Clearance*	-0.02	-0.015 to -0.033	<0.001	Decreased hazard with increased creatinine clearance
Cimetidine	0.41	0.13 to 1.27	0.122	Decreased hazard with use of cimetidine at any time during study
NYHA II III IV	 1.80 3.32 2.18	 0.82 to 3.94 1.51 to 7.31 0.68 to 6.95	 0.142 0.003 0.190	Increased hazard (relative to NYHA I) with increasing NYHA score
Sex	0.59	0.39 to 0.90	0.014	Decreased hazard for females relative to males
Smoking Ex-Smoker Smoker	 0.58 0.69	 0.37 to 0.90 0.46 to 1.05	 0.016 0.086	Decreased hazard for smokers and ex-smokers (relative to non-smokers)
WMI	0.48	0.30 to 0.75	0.001	Decreased hazard with increased WMI

For continuous variables (*) the slope is presented which is interpreted as the increase in hazard by unit (creatinine clearance = ml/min).

APPENDIX Table 8

ANALYSIS ON QT BY TIME: 95% CI FOR THE DIFFERENCE

obs	time	n_d	n_p	se_d	se_p	mean_d	mean_p	diff	ll95	ul95	p_val
1	Day1	700	688	1.34	1.00	25.97	2.71	23.26	19.9746	26.5454	0.00000
2	Day2	669	673	1.67	1.15	36.97	4.89	32.08	28.1100	36.0500	0.00000
3	Day4	621	632	1.68	1.33	39.49	4.37	35.12	30.9284	39.3116	0.00000
4	M1	569	572	2.16	6.84	24.56	4.27	20.29	6.2007	34.3793	0.00485
5	M3	519	503	2.27	1.97	27.43	-0.28	27.71	21.8045	33.6155	0.00000
6	M6	461	431	2.32	2.21	28.86	-1.18	30.04	23.7425	36.3375	0.00000
7	M12	388	365	2.71	2.20	26.07	1.62	24.45	17.5592	31.3408	0.00000
8	M18	238	238	3.39	2.77	29.73	3.30	26.43	17.8495	35.0105	0.00000
9	M24	133	129	5.18	4.49	29.88	-5.77	35.65	22.1816	49.1184	0.00000
10	M30	49	52	11.25	7.33	21.48	3.04	18.44	-7.5800	44.4600	0.16794

APPENDIX Table 9

ANALYSIS ON QTC CHANGE BY TIME: 95% CI FOR THE DIFFERENCE

obs	time	n_d	n_p	se_d	se_p	mean_d	mean_p	diff	ll95	ul95	p_val
1	Day1	697	684	1.42	1.21	19.39	1.60	17.79	14.1276	21.4524	0.00000
2	Day2	666	670	1.66	1.34	21.54	-0.61	22.15	17.9712	26.3288	0.00000
3	Day4	618	628	1.75	1.53	21.93	-1.13	23.06	18.5085	27.6115	0.00000
4	M1	566	570	2.13	8.13	13.22	1.99	11.23	-5.2933	27.7533	0.18309
5	M3	515	499	2.25	1.98	11.41	-5.47	16.88	10.9923	22.7677	0.00000
6	M6	457	426	2.27	2.39	11.86	-7.27	19.13	12.6731	25.5869	0.00000
7	M12	385	362	2.64	2.32	9.58	-8.91	18.49	11.5677	25.4123	0.00000
8	M18	236	236	3.42	2.86	8.36	-8.33	16.69	7.9518	25.4282	0.00020
9	M24	133	128	5.12	4.89	11.54	-14.75	26.29	12.3958	40.1842	0.00025
10	M30	49	52	10.97	6.94	9.08	-8.89	17.97	-7.1662	43.1062	0.16428

APPENDIX Table 10

ANALYSIS ON HEART RATE CHANGE BY TIME: 95% CI FOR THE DIFFERENCE

obs	time	n_d	n_p	se_d	se_p	mean_d	mean_p	diff	ll95	ul95	p_val
1	Day1	704	699	0.41	0.39	-3.78	-0.59	-3.19	-4.29930	-2.08070	0.00000
2	Day2	670	687	0.45	0.47	-7.69	-2.21	-5.48	-6.75625	-4.20375	0.00000
3	Day4	627	647	0.55	0.53	-8.44	-2.56	-5.88	-7.37656	-4.38344	0.00000
4	M1	574	584	0.67	0.67	-5.72	-0.92	-4.80	-6.65728	-2.94272	0.00000
5	M3	525	511	0.73	0.75	-7.23	-2.14	-5.09	-7.14099	-3.03901	0.00000
6	M6	463	436	0.79	0.87	-7.80	-2.51	-5.29	-7.58872	-2.99128	0.00001
7	M12	388	369	0.87	0.83	-7.82	-3.07	-4.75	-7.11100	-2.38900	0.00009
8	M18	239	242	1.10	1.04	-9.15	-4.52	-4.63	-7.59613	-1.66387	0.00234
9	M24	134	133	1.50	1.47	-8.04	-2.44	-5.60	-9.71679	-1.48321	0.00814
10	M30	49	52	2.60	2.16	-6.07	-4.63	-1.44	-8.03452	5.15452	0.66959

APPENDIX Table 11

ANALYSIS ON QRS CHANGES BY TIME: 95% CI FOR THE DIFFERENCE

obs	time	n_d	n_p	se_d	se_p	mean_d	mean_p	diff	ll95	ul95	p_val
1	Day1	706	701	0.64	0.51	-0.63	-0.07	-0.56	-2.16526	1.0453	0.49425
2	Day2	672	688	0.68	0.59	-0.92	0.06	-0.98	-2.74186	0.7819	0.27581
3	Day4	628	648	0.76	0.68	1.63	0.50	1.13	-0.86583	3.1258	0.26733
4	M1	576	583	1.00	0.82	1.81	0.61	1.20	-1.33179	3.7318	0.35309
5	M3	525	514	1.19	0.97	3.43	0.51	2.92	-0.09585	5.9359	0.05801
6	M6	462	440	1.11	1.14	2.63	0.28	2.35	-0.76844	5.4684	0.14002
7	M12	388	370	1.20	1.25	2.09	0.74	1.35	-2.04486	4.7449	0.43598
8	M18	240	242	1.58	1.72	6.82	2.35	4.47	-0.10937	9.0494	0.05632
9	M24	132	134	2.43	2.72	6.42	1.42	5.00	-2.15530	12.1553	0.17197
10	M30	49	53	3.40	3.19	9.47	2.15	7.32	-1.80904	16.4490	0.11920

APPENDIX Table 12

TABLE 8
DOFETILIDE PROTOCOL 400 - DIAMOND CHF STUDY
INCIDENCE OF CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES: INTENT-TO-TREAT POPULATION

				DOFETILIDE			PLACEBO		
NUMBER(%) OF SUBJECTS:									
Evaluable for laboratory abnormalities				646			639		
With clinically significant laboratory abnormalities				476		(73.7%)	492		(77.0%)
GROUP	PARAMETER	UNITS	CRITERIA	N	n	(%)	N	n	(%)
HAEMATOLOGY	HGB (M)	G/DL	>20% decrease*	468	38	(8.1%)	479	32	(6.7%)
	HGB (F)	G/DL	>20% decrease*	178	10	(5.8%)	155	9	(5.8%)
	Platelets	10**3/MM**3	>700	641	3	(0.5%)	634	2	(0.3%)
			<75	641	8	(1.2%)	634	8	(1.3%)
	WBC	10**3/MM**3	>17.5	641	6	(0.9%)	634	5	(0.8%)
			<2.5	641			634		
LIVER FUNCTION	Total Bilirubin	MG/DL	>1.5 x ULN	643	41	(6.4%)	634	57	(9.0%)
	Total Protein	G/DL	>1.1 x ULN	643	10	(1.6%)	634	6	(0.9%)
			<0.9 x LLN	643	12	(1.9%)	634	14	(2.2%)
	Albumin	G/DL	>1.1 x ULN	643	1	(0.2%)	634	1	(0.2%)
			<0.9 x LLN	643	75	(11.7%)	634	80	(12.6%)
	SGOT (AST)	IU/L	>3 x ULN	643	7	(1.1%)	634	6	(0.9%)
	SGPT (ALT)	IU/L	>3 x ULN	643	11	(1.7%)	634	17	(2.7%)
	AP	IU/L	>3 x ULN	643	7	(1.1%)	634	13	(2.1%)
RENAL FUNCTION	Urea	MG/DL	>1.3 x ULN	643	313	(48.7%)	634	326	(51.4%)
	Creatinine	MG/DL	>1.3 x ULN	643	112	(17.4%)	634	141	(22.2%)
ELECTROLYTES	Sodium	MEQ/L	>1.05 x ULN	643	1	(0.2%)	634	1	(0.2%)
			<0.95 x LLN	643	32	(5.0%)	634	32	(5.0%)
	Potassium	MEQ/L	>1.1 x ULN	627	37	(5.9%)	629	38	(6.0%)

D: 14MAY1997
T: 22MAY97(05:50)

Page 1 of 2

Source: Appendix V Table 11

Note: N=total number of subjects with at least one observation
of the lab. parameter while on study treatment or during lag time
n=number of subjects with a clinically significant abnormality.
* Change from baseline

APPENDIX Table 13

TABLE 8
DOFETILIDE PROTOCOL 400 - DIAMOND CHF STUDY
INCIDENCE OF CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES: INTENT-TO-TREAT POPULATION

				DOFETILIDE			PLACEBO		
GROUP	PARAMETER	UNITS	CRITERIA	N	n	(%)	N	n	(%)
ELECTROLYTES	Potassium	MEQ/L	<0.9 x LLN	627	4	(0.6%)	629	10	(1.6%)
	Calcium	MG/DL	>1.1 x ULN	643	2	(0.3%)	634	2	(0.3%)
			<0.9 x LLN	643	5	(0.8%)	634	5	(0.8%)
	Glucose (random)	MG/DL	>1.5 x ULN	628	164	(26.1%)	629	148	(23.5%)
			<0.8 x LLN	628	14	(2.2%)	629	12	(1.9%)
	Magnesium	MG/DL	>1.1 x ULN	643	69	(10.7%)	634	83	(13.1%)
			<0.9 x LLN	643	2	(0.3%)	634	1	(0.2%)
URINE	Urine Protein	No unit	>=2+	606	39	(6.4%)	606	48	(7.9%)
	Urine Glucose	No unit	>=2+	606	70	(11.6%)	606	59	(9.7%)
	Urine Hemoglobin	No unit	>=1+	606	110	(18.2%)	606	122	(20.1%)

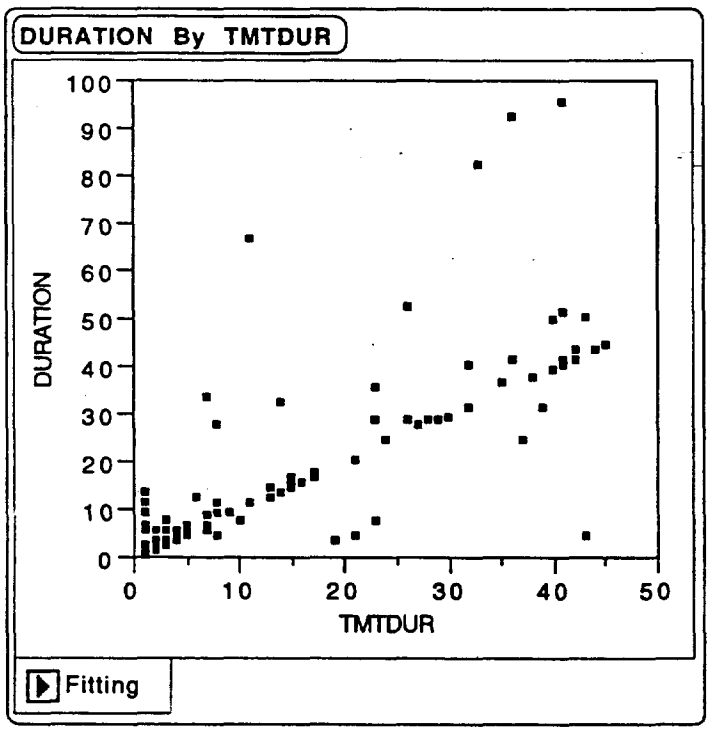
D: 14MAY1997
T: 22MAY97(05:50)

Source: Appendix V Table 11

Note: N=total number of subjects with at least one observation
. of the lab. parameter while on study treatment or during lag time
. n=number of subjects with a clinically significant abnormality.
* Change from baseline

16.1
Appendix Figures 1-8 Source: Reviewer
Treatment duration by duration of follow up and deaths

Deaths <1Month visitdate-CHF

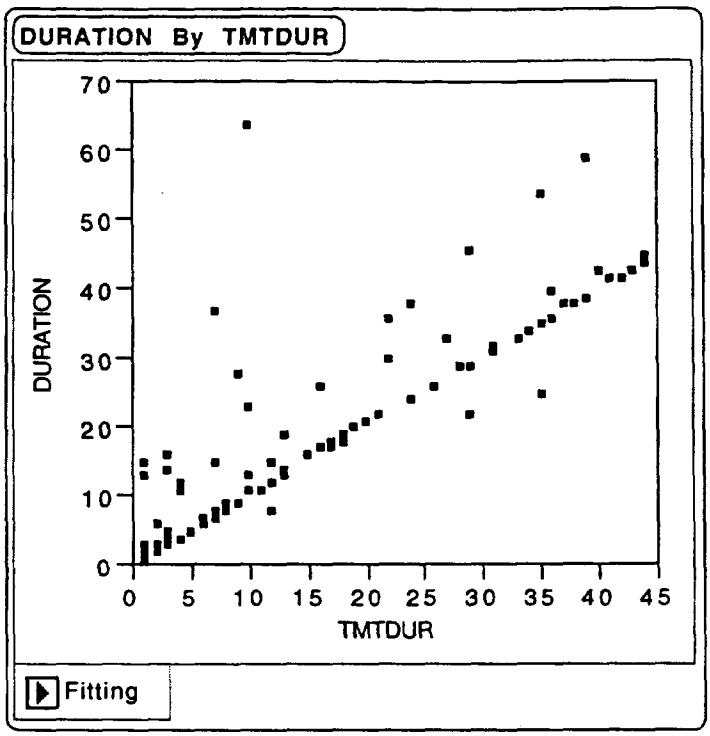


N=108(1-45days) Duration followup;Tmtduration

Dofetilide scatter plot above compared to Placebo below.

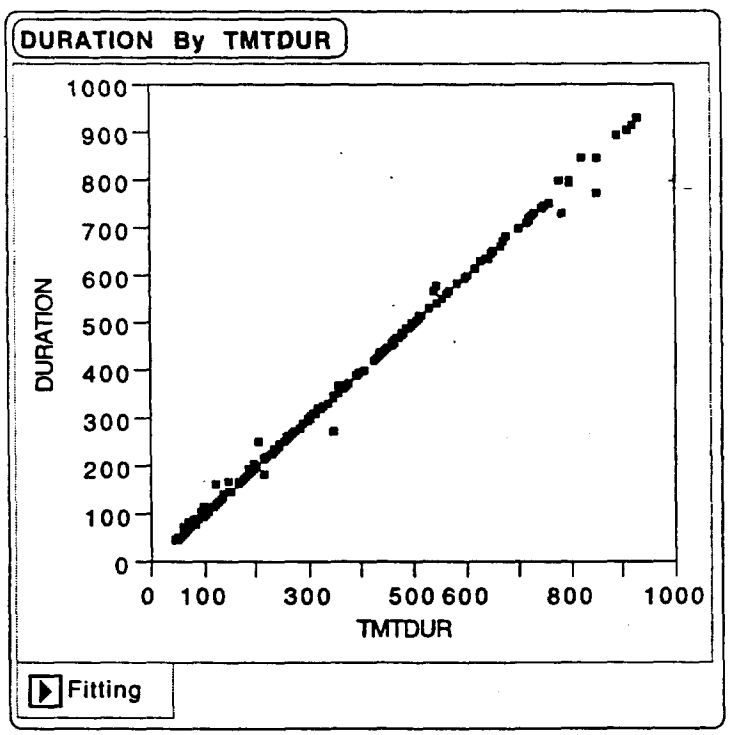
NDA #20931
A.O.Williams, M.D.

Deaths <1mth PlcboCHF



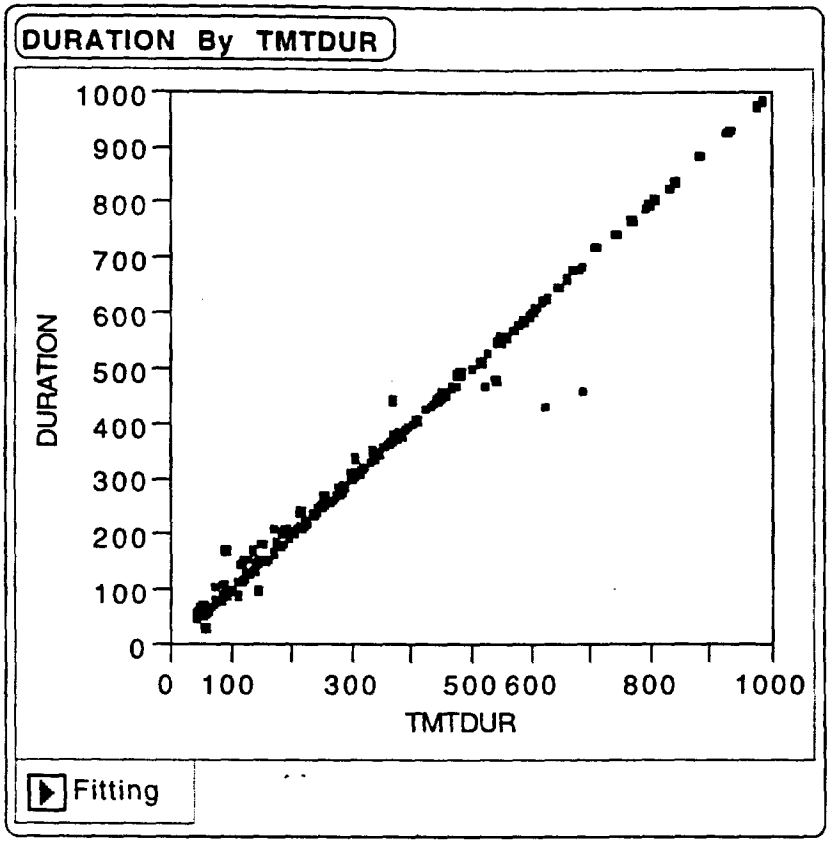
N=105 (1-45days) Duration of follow up. Treatment

Deaths>45daysDofetilide-CHF



N=203(45-EOS) Duration of follow uo;Tmtduration

Deaths>45daysPlcbo-CHF

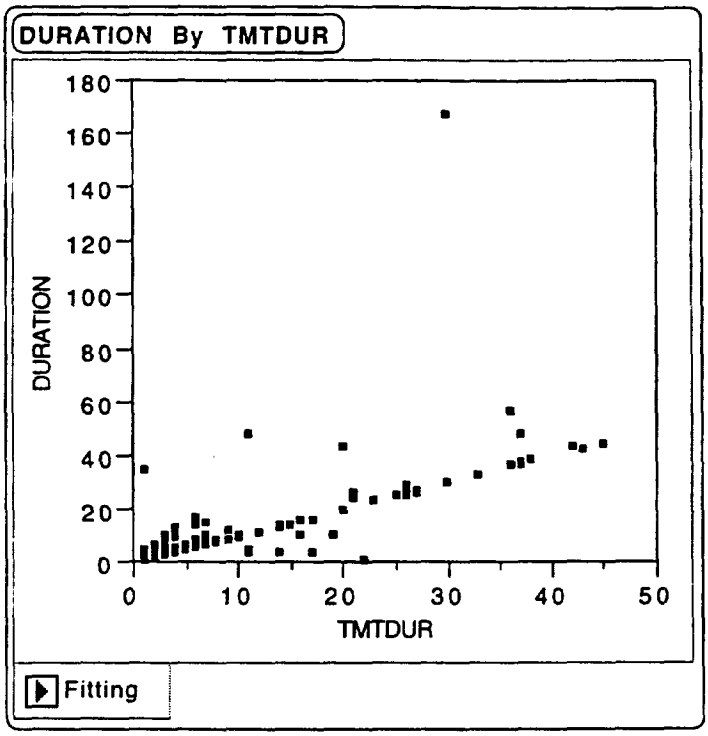


N=212(45d-EOS) Duration of followup; Treatment duration

Footnote

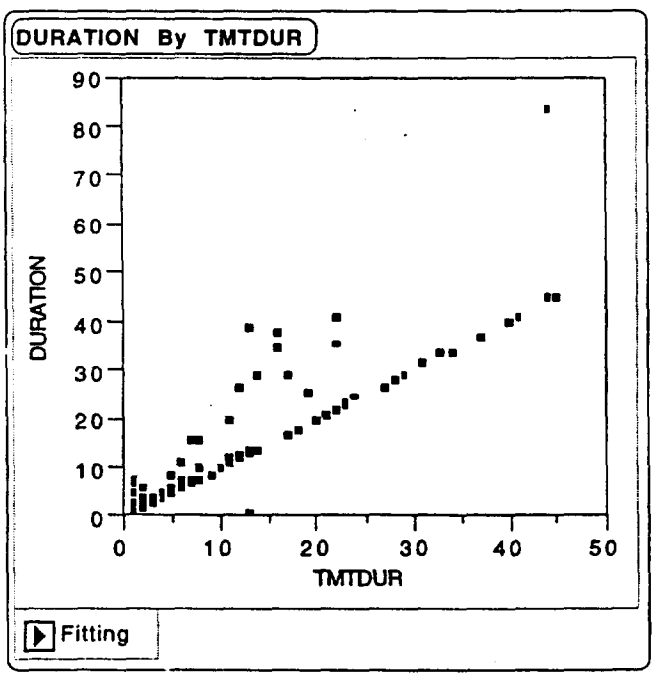
r=0.988 p <0.0001 for CHF Placebo and Dofetilide

Deaths< 1mthvisitdateDof-MI



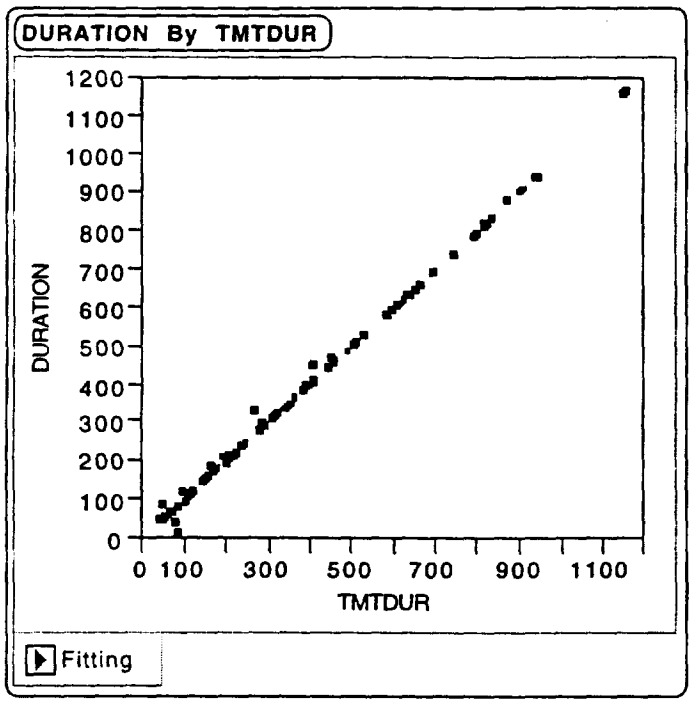
N=118(1-45)Duration of follwup;Tmtduration

Deaths<1mth visitdatePlcboMI



N=108(1-45days)Duration of follow up; TMT duration

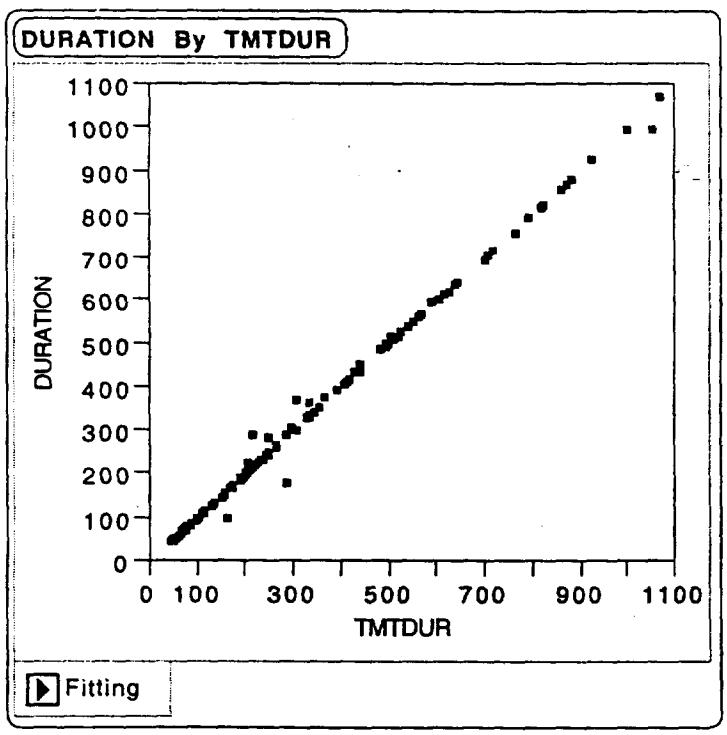
Deaths>1monthsvisitdateDof-MI



N=112(45-EOS)Duration of follwup;Tmtduration

r=0.99 ; p=0.0001

Deaths >45daysPlcbo-MI



N=135(45-EOS); Duration of follow up, Tmt duration

17.0 REFERENCES

Behrens S, Ney G, Fisher SG, et al. The effects of amiodarone on the circadian pattern of sudden cardiac death. Results from the Congestive Heart Failure-Survival Trial of Antiarrhythmic Therapy. J. Am. Coll. Cardiol 1997:29(suppl 2):33A-34A

Berning J, Hoilund-Carlsen PF, Nielsen GG, et al. Critical appraisal of bedside echocardiographic estimates of left ventricular ejection fraction. Importance of wall motion index. Am J Noninvas Cardiol 1992;6(N5 Sept-Oct):269-278.

Biswas A, Dey SK, Banerjee AK, et al. Low-dose amiodarone in severe chronic heart failure. Indian Heart J. 1996;48 (4):361-4.

Cockroft DW and Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:3141.

Gentile S, Vignoli A, Tommasielli G, et al. Effect of low dose amiodarone on the incidence of sudden death in elderly patients with congestive heart failure: a double-blind, placebo-controlled study. Arch. Gerontol. Geriatr. 1996;23(suppl 5):191-195.

Køber L, Torp-Pedersen C, Carlsen J, et al. An echocardiographic method for selecting high risk patients shortly after acute myocardial infarction, for inclusion in multicentre studies as used in the TRACE study. Eur Heart J 1994;15:1616-1620.

Nicklas JM, McKenna WJ, Stewart RA, et al. Prospective, double-blind, placebo-controlled trial of low-dose amiodarone in patients with severe heart failure and asymptomatic frequent ventricular ectopy. Am. Heart J. 1991;122(4 Pt 1):1016-21.

Pinto JV, Ramani K, Neelagaru S, et al. Amiodarone therapy in chronic heart failure and myocardial infarction: a review of the mortality trials with special attention to STAT-CHF and GESICA trials. Prog. Cardiovasc Dis. 1997;40(1):85-93.

Schiller NB, Shah PM, Crawford M, et al. Recommendations for Quantitation of the Left Ventricle by Two-Dimensional Echocardiography. J American Society of Echocardiography 1989;2:358-367.

Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. New Engl. J Med. 1995;333(2):77-82.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron, 1976:31-41.

Nichols DJ. Preliminary Report of Pharmacokinetic and Pharmacodynamic Data from STudy 115-219 Renal Impairment Study of Dofetilide, 1994.

Movin-Osswald G, Boelaert J, Harnmarlund-Undenaes M, Nilsson LB. The Pharmacokinetics of Remoxipride and Metabolizes in Patients with Various Degrees of Renal Function. Br J Clin Pharmac, 1993; 35:615-622.

Ghan G L-Y, Axelson JE, Price JDE, McErkme KM, Kerr CR. In Vitro Protein Binding of Propafenone in Normal and Uraemic Human Sera. Eur J Clin Pharmacol, 1989; 36: 495-499.