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D-Willard
DEC 15 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
REVIEW OF SAFETY

N.A. #20,931
Drug name: Dofetilide (Tikosyn™)
Sponsor: Pfizer, Inc
Medical reviewer: Maryann Gordon, MD
Completion date: 12-14-98

/S/ / /
MD

(N.B. This document includes the safety review of the pooled dofetilide studies. A safety review of the DIAMOND trial is included in a separate review of that study.)

cc
orig.
HFD 110
HFD 110/D Roeder/M Gordon

REVIEW OF SAFETY
TABLE OF CONTENTS

Summary

Dofetilide is an oral agent developed for 1) maintenance of normal sinus rhythm with associated symptom relief in patients with supraventricular arrhythmias including atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia and 2) conversion of atrial fibrillation and atrial flutter to normal sinus rhythm.

QT/QTC prolongation

Dofetilide, a Class III antiarrhythmic, delays cardiac repolarization via inhibition of the cardiac ion channels carrying the potassium current. There is a correlation between dofetilide concentration and QT/QTc prolongation. Oral doses of 500 mcg bid are associated with mean maximum QT/QTc interval increases from baseline of 52/30 msec, with about 20% of the dofetilide patients (all doses combined, placebo subtracted) having at least a 15% increase in the QTc interval from baseline.

Proarrhythmia

The incidence rate for the reporting of TdP during the dofetilide development program is 1.7% (59/3452). Many of the TdP events were symptomatic and required an intervention such as cardioversion with some events degenerating into ventricular fibrillation. Dofetilide was nearly always withdrawn as a result. TdP was not reported by placebo patients.

The table below shows the number and percent of patients who reported TdP in the Phase II/III and were included in the population pharmacokinetics study, by daily AUC and Cmax.

Number and percent of patients

daily AUC (ng.h/ml)						daily Cmax (ng/ml)				
<20	20-40	40-60	60-80	80-100	>100	0-2	2-4	4-6	6-8	>8
0	3 (0.5)	4 (0.7)	10 (3.4)	2 (1.7)	10 (18)	3 (0.4)	11 (1.2)	7 (3.7)	5 (38.4)	3 (69.2)

Table 2 Population pharmacokinetic report

Reports of TdP increase with increasing AUC and Cmax.

The table below shows the number of proarrhythmic events by randomized dose.

Number and (percent) of patients-supraventricular arrhythmia trials

	oral dofetilide (mcg)				placebo
arrhythmia event	< 250 mcg bid n=217	250 mcg bid n=388	500 mcg bid n=703	>500 mcg bid n=38	n=677
TdP	0	2 (0.5)	6 (0.9)	4 (10.5)	0
VF	1 (0.5)	1 (0.3)	1 (0.1)	1 (2.6)	1 (0.1)
VT	2 (0.9)	3 (0.8)	5 (0.7)	1 (2.6)	7 (1.0)

There is a striking increase in the incidence rates of TdP and VF with doses above 500 mcg bid.

Mortality

(N.B. During a meeting held with the sponsor on April 22, 1992, the Division recommended that the sponsor demonstrate the benefits of maintaining normal sinus rhythm with dofetilide. One suggested study design consisted of two treatment groups; one group would be cardioverted to normal sinus rhythm and maintained with dofetilide; the other group would not be cardioverted but given an anticoagulant and possibly digoxin. Possible clinical endpoints included incidence of stroke, bleeding, proarrhythmia, and mortality. A clinical outcome of "not worse than" anticoagulation therapy combined with efficacy in the studies designed to show prolongation of the time to recurrence of AF were sufficient to obtain a claim for the treatment of AF. At a subsequent meeting with FDA on April 9, 1993 it was agreed that a meta-analysis or pooled analysis of the AF database would support safety claims in the target population and would replace the need to demonstrate the benefits of maintaining normal sinus rhythm and whether the benefits outweigh the risks of inducing proarrhythmic events.)

An meta analysis limited to patients with AF/AFL plus those with pSVT reported mortality rates of 0.9% (12/1346) for dofetilide and 0.4% (3/677) for placebo. The estimated hazard ratio for death associated with dofetilide (as compared to placebo) is 1.4 (95% CI 0.4, 5.1). Excess mortality (and arrhythmias) occurred with dofetilide even though the studies carefully selected patients and routinely discontinued dofetilide or lowered the dose if prolonged QT/QTc interval was observed.

Narrow therapeutic window

The effective dose being proposed by the sponsor is 500 mcg bid, with adjustments based on creatinine clearance and QT/QTc prolongation. Doses 750 mcg and above were dropped from the development program because of excessive proarrhythmia. One patient (#115-400-0282) erroneously received 2 doses of 500 mcg 1 hour instead of 12 hours apart while under nursing care and developed ventricular fibrillation and cardiac arrest about 2 hours after the second dose.[1]

Drug interactions

To avoid higher dofetilide concentrations and, as a consequence, greater increases in the QT/QTc intervals, dofetilide should not be co-administered with cimetidine, oral contraceptives, and verapamil. A study investigating the interaction of dofetilide and ketaconazole is ongoing. Until the results of that study are known, it is reasonable to suspect that drugs that are inhibitors of p 450 CYP3A4 interfere with the metabolism of dofetilide and should be avoided.

Special populations

Females and elderly males (elderly females were not evaluated) were shown to have higher blood concentrations (AUC and Cmax) compared to males. The univariate analysis of TdP in the dofetilide subjects for gender was significant (p=0.01) with a relative risk for females of 3.77 (95% CI 1.74, 8.17). (This finding was confirmed by the DIAMOND trial.)

The mean increase in QTc at baseline after multiple dosing in the hepatically impaired patients was twice the mean increase for healthy volunteers. Patients with liver impairment have a larger dofetilide-

[1]There were 2 other cases of overdose: a patient underwent gastric aspiration 30 minutes after receiving 28 capsules and a patient who apparently received undiluted dofetilide solution IV push (multiples of the recommended dose in a fraction of time) and experienced no events.

induced prolongation of QTc interval compared to healthy volunteers. Dose adjustment for these patients, in addition to the adjustment for renal impairment, should be considered.

Risk factors

While the number of reported TdP events decreased after 4 days of dosing, this may reflect an elimination of the most vulnerable patients rather than a true risk reduction. Also, if there is an increase in risk immediately after starting dofetilide, patients who stop drug and then restart it on their own may be at a high risk for TdP.

Labs and vital signs

Overall, there is no evidence that dofetilide use can be linked to any abnormal laboratory values. Dofetilide does lower the heart rate by approximately 6 bpm. It has no effect on blood pressure.

Conclusions

Dofetilide prolongs the QT/QTc intervals in a dose related manner, is associated with proarrhythmias including TdP, shows potentially dangerous drug-drug interactions, has a narrow therapeutic window, and has unknown effects on the testes[2]. Females taking dofetilide, compared to males, have higher plasma concentrations and more TdP; it is likely that the benefit risk ratios for males and females taking dofetilide are different.

[2]testicular atrophy and reduction in testicular weight was observed in all species (rat, mouse, and dog). The no effect AUC in dogs and rats was about 1.3 and 4 times, respectively, the human AUC. In the rat (only species tested) the effects were not reversible.

1.0 Introduction

IND for intravenous dofetilide was submitted to FDA on November 17, 1989. IND for oral dofetilide was submitted on June 28, 1990. NDA #20,931 for the oral formulation was submitted on March 9, 1998 and the 120-day safety update was submitted on June 9, 1998.

The sponsor is seeking the approval of the oral formulation, only, for 1) maintenance of normal sinus rhythm with associated symptom relief in patients with supraventricular arrhythmias such as atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia.2) conversion of atrial fibrillation and atrial flutter to normal sinus rhythm. No NDA either for the intravenous formulation or for the ventricular arrhythmia indication has been submitted.

The majority of this safety review focuses upon those patients who took part in Phase II/III studies for supraventricular and, to a large extent, ventricular arrhythmias. The safety of dofetilide, both routine and serious, was determined primarily from these studies. Patients and subjects who participated in the Phase I studies, the DIAMOND mortality studies, the Japanese studies, and the intravenous studies without an oral component were reviewed and are discussed separately.

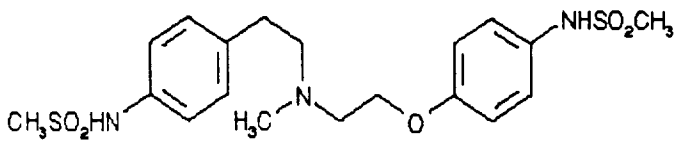
Numerous volumes (via the CANDA) from the NDA as well as the Safety Update were examined during this review. The sources of tables, figures and appendices from the NDA used to create tables in this review are identified. Optical images or the paper copy of the case report forms for numerous deaths, serious safety, and withdrawals for safety were examined by this reviewer.

1.1 Chemistry

Dofetilide is a methanesulphonamide molecule of relatively low molecular weight, is achiral, and has no isomeric forms.

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

The chemical structure is shown below:



1.2 Mechanism of action

Dofetilide exhibits Vaughan Williams Class III antiarrhythmic actions. It prolongs the effective refractory period by specifically inhibiting the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current, Ikr. Consistent with its Class III effect, dofetilide prolongs the QT/QTc intervals.

1.3 Human pharmacokinetics summary

Absorption and Bioavailability: Dofetilide from capsules is >90% systemically available, with absolute bioavailability of up to 98%. Maximum observed plasma concentrations occur at about 2-3 hours after dosing.

Metabolism, and Elimination: The majority (about 80%) of dofetilide is excreted mostly unchanged in the urine; the rest is metabolized predominantly by the P450 isoenzyme, CYP3A4. Metabolites occur at very low concentrations relative to the parent and have no significant activity. Terminal half life of dofetilide is approximately 10 hours; no radioactivity was detected in blood samples collected 24 hours or more after dosing.

Study 221 was a single blind study with 12 normal volunteers received 3 single doses of oral dofetilide 250, 750 and 1250 mcg with a single oral dose of placebo and a single iv dose of dofetilide (10 mcg/kg) randomly introduced into the sequence. There was a 1 week washout period between doses. Selected PK parameters for the iv dose and the oral doses are shown below.

4. A summary of the key pharmacokinetic parameters is presented below (the results are expressed as means and standard deviations).

Dose level	C_{max} (ng/ml)	T_{max} (h)	k_{el} (/h)	AUC (ng.h/ml)	Systemic availability
10mcg/kg iv	9.94 (2.65)	0.48 (0.06)	0.0985 (0.0163)	36.06 (7.21)	-
250mcg oral	0.98 (0.19)	3.00 (1.73)	0.1024 (0.0191)	11.20 (2.72)	0.91 (0.10)
750mcg oral	3.30 (0.78)	1.74 (0.92)	0.0919 (0.0102)	33.17 (5.56)	0.91 (0.10)
1250mcg oral	4.98 (0.93)	3.38 (2.14)	0.0875 (0.0172)	56.34 (8.65)	0.93 (0.09)

5. C_{max} and AUC increased linearly with dose following oral dosing. As an approximation, C_{max} (ng/ml) = 0.006 . oral dose (mcg) and AUC (ng.h/ml) = 0.05 . oral dose (mcg).

The following figures shown the 12 hour plasma profiles for dofetilide from study 203. The doses studied were single and multiple doses of 100 mcg to 400 mcg bid. Day 1 shows plasma levels after a single dose and day 10 shows plasma levels after multiple doses. Note that the y-axis is different for the two figures.

FIGURE 1.1

DOFETILIDE PROTOCOL 203
MEAN DOFETILIDE PLASMA DRUG CONCENTRATIONS

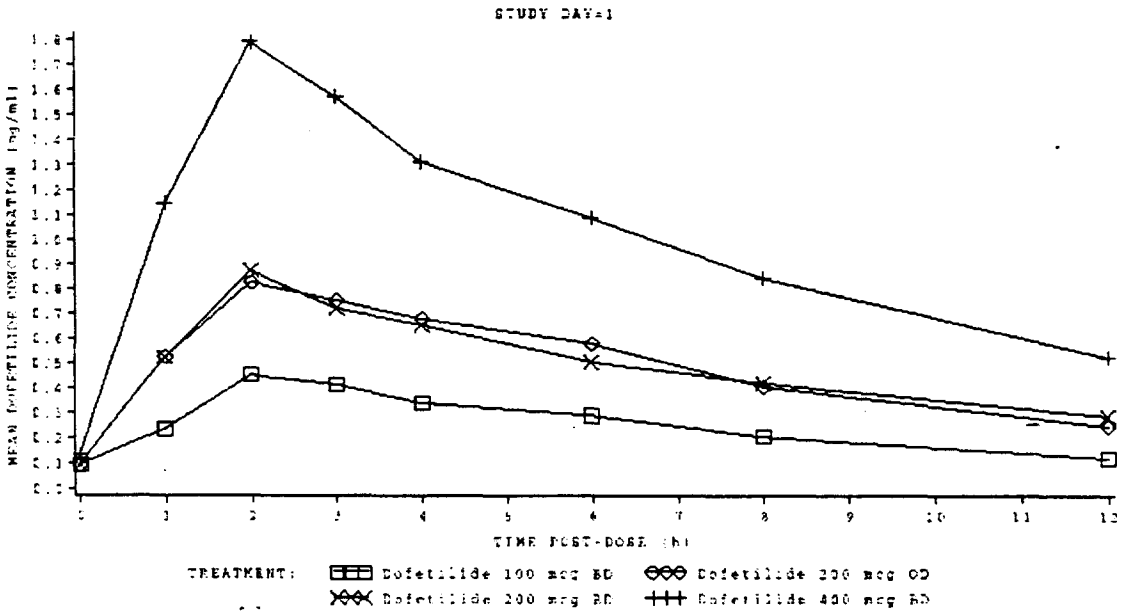
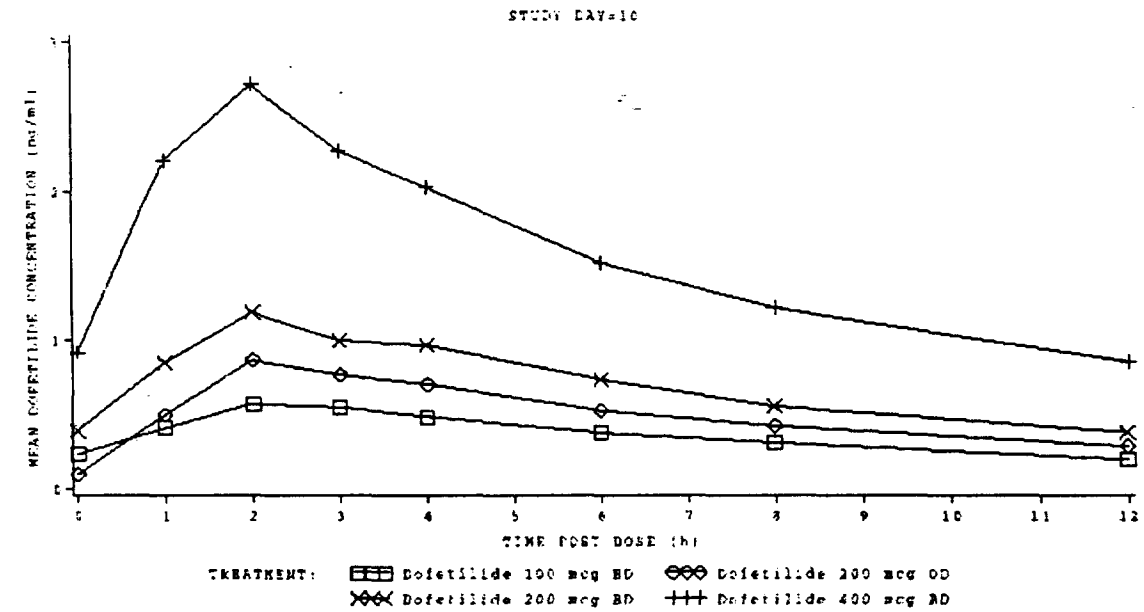


FIGURE 1.2

DOFETILIDE PROTOCOL 203
MEAN DOFETILIDE PLASMA DRUG CONCENTRATIONS



Both Cmax and AUC increased with multiple dosing. The 400 mcg bid dose produced plasma concentrations throughout the 12 hour dosing interval that were much higher than the lower doses.

1.4 Foreign marketing history

Dofetilide is not marketed in any country.

2.0 Overview of clinical program

2.1 All trials

This NDA includes a total of 150 clinical studies with dofetilide, employing intravenous and/or oral formulations, and investigating supraventricular as well as ventricular arrhythmias. The sponsor combined 126 studies of these studies as the basis of the integrated safety summary. These 126 studies include 75 Clinical Pharmacology studies and 51 Phase II/III studies. The studies not combined for analysis include the 18 studies conducted in Japan, the DIAMOND mortality trial and 2 others (protocol numbers 400B and 128A, the first a small extension study and the second without patients enrolled).

For this submission, the cutoff dates for non serious and serious safety data were May 14, 1997 and September 15, 1997, respectively. A listing of the protocol numbers by type of study (oral and/or intravenous) and location (US or non US) is shown below.

Dofetilide protocol numbers

Type of Study	US studies	Non US studies
oral		
Phase II/III[a] Relevant	104, 113, 119/119A, 120/120X, 128	308, 311/311A, 320/320A, 330,331, 333, 334/334A, 335, 336, 345, 363, 365, 372
Phase II/III Other	108B, 109, 111, 113B, 114/114A/114C, 120A	307, 330, 331, 337, 337A, 364, 397, 398, 399 (oral leg only)
Diamond mortality (CHF and MI)		400
Clinical Pharmacology[b] Relevant and Other	001, 002, 003, 004, 005 (oral leg only), 006, 007, 008, 009, 011, 012, 013, 014, 015, 105	201, 202, 203, 208, 209, 210, 211, 212 (oral leg only), 213, 214, 215 216 (oral leg only), 219, 220, 221 (oral leg only), 222 (oral leg only), 227, 229, 234 (oral leg only), 235 (oral leg only), 236, 237, 238, 239, 240, 242, 243 (oral leg only), 244, 245, 246, 250, 253, 254, 255, 310, 313
Japan		18 total (see below)
intravenous[c]		
Phase II/III	103, 106, 107, 117, 123	302, 306, 318, 319, 331, 360, 361, 362, 366, 371, 399 (IV leg only)
Clinical Pharmacology[b]	005 (IV leg only), 010, 102, 110, 112, 127	204, 205, 206, 207/207A, 212 (IVleg only), 216 (IV leg only), 217, 218, 221 (IV leg only), 222 (IV leg only), 223, 224, 228, 231, 232, 234 (IV leg only), 235 (IV leg only), 252, 301, 303, 304, 305, 318, 322

[a] "Relevant" Phase II/III clinical trials for the combined safety analysis is defined by the sponsor as trials that used oral dofetilide and evaluated the efficacy of dofetilide in the treatment of supraventricular or ventricular arrhythmias.

[b] Clinical Pharmacology studies includes all Phase I studies, plus Phase II pharmacodynamic Studies: 105, 310, and 313 (oral) and 102, 110, 112, 127, 301, 303, 304, 305, 318, and 322 (IV). These studies are not included in Phase II/II studies.

[c] IV studies include only studies in which no oral dofetilide was administered, or the IV leg of studies in which the IV and oral doses were separated by a washout period.

Studies by indication

Dofetilide was evaluated in patients with supraventricular as well as in patients with ventricular arrhythmias; the indication for the latter is not being sought by the sponsor. The protocol numbers for listed in the tables below

Studies for supraventricular arrhythmias

placebo controlled	placebo and active controlled	active controlled
120, 120X, 311, 311A, 114, 114A, 119, 128, 320, 320A, 365,	345+, 372 #, 363&	114C^

+ comparator was sotalol
# comparator was propafenone
^ study design was open label vs. digoxin
& comparator was quinidine

Studies for ventricular arrhythmias

placebo controlled	active controlled	uncontrolled
113	333*, 334* , 334A* , 335^, 336^, 109#	104, 308, 330, 331

*versus sotalol
^versus amiodarone
#versus procainamide

The protocols that evaluated dofetilide in the supraventricular and ventricular arrhythmias, by formulation, are shown below.

Protocol numbers

supraventricular arrhythmias			ventricular arrhythmias		
Oral Dofetilide	Intravenous Dofetilide		Oral Dofetilide	Intravenous and Oral Dofetilide	Intravenous Dofetilide
114/114A/114C^!	106^	319^	104+	109+!%	112^
119^	107^	360^	113^	330+	301~
120/120X^	117^%	361^	308+	331+	315*!
128^	123^	362^	333^&		103*!
311^*	302^	366^	334/334A&		
320/320A^!	306+	371^	335/336@		
345^&			337*		
363^∝					
365^					
372^++					
400AF/AFL#					
364*					
307+*					

+open label study
^placebo controlled with or without active comparator
#substudy of 400 (DIAMOND)
!discontinued
&versus sotalol, @verses amiodarone, %versus procainamide, ++versus propafenone, ∝versus quinidine
~no control
*non-relevant study

The long term extension studies that are still ongoing include 108B, 113B, 119A, 120A, 128A, 397, 398, 399, 400B.

Clinical Studies in Japan

The studies conducted in Japan are shown below. The safety from these studies are not included in the pooled analyses, but are discussed in section 11.

Oral studies
DOF-JP-91-001 Phase I Study of Dofetilide (Single Dose Study)
DOF-JP-91-002 Phase I Study of Dofetilide (Effects of Meals on Absorption of Dofetilide)
DOF-JP-91-003 Phase I Study of Dofetilide (Multiple Doses Study)
DOF-JP-92-001 Early Phase II Study of Dofetilide (Clinical Study of Orally Administered Dofetilide in Patients with VPC or SVPC)
DOF-JP-93-601 Early Phase II Study of Dofetilide (Clinical Study of Orally Administered Dofetilide in Patients with PSVT or PAf / AF)
DOF-JP-93-602 Late Phase II Study of Dofetilide (Clinical Study of Orally Administered Dofetilide in Patients with VPC)
DOF-JP-93-603 Late Phase II Study of Dofetilide (Clinical Study of Orally Administered Dofetilide in Patients with PSVT or PAf / AF)
DOF-JP-93-605 Clinical Phase II Study of Dofetilide Capsules in Tachyarrhythmias- Effects on Autonomic Nerve Function -

Accompanied by Lowered Renal or Hepatic Function- A Pharmacokinetics Study -
Intravenous studies

DOF-JP-91-004 Phase I Study of Dofetilide (Single Intravenous Study)
DOF-JP-92-002 Early Phase II Study of Dofetilide (Clinical Study of Intravenously administered Dofetilide in Patients with Premature Contractions, Tachycardia Atrial Fibrillation /Flutter)
DOF-JP-92-003 Phase II Study of Dofetilide (The Evaluation of the Hemodynamic Effects of Intravenously Administered Dofetilide in Patients with Premature Contractions, Tachycardia or Atrial Fibrillation / Flutter)
DOF-JP-92-004 Phase II Study of Dofetilide (The Evaluation of the Electrophysiologic Effects of Intravenously Administered Dofetilide)
DOF-JP-94-601 Late Phase II Dose-Finding, Double-Blind Study of Dofetilide IV in Ventricular premature Contraction (VPC), or Paroxysmal Supraventricular Tachycardia (PSVT)and Paroxysmal Atrial Fibrillation / Flutter (PAf / AF)
DOF-JP-94-602 Late Phase II Clinical Study of Dofetilide IV in Ventricular Tachycardia (VT)
DOF-JP-94-603 Phase II Study of Dofetilide IV : The Evaluation the Electrophysiologic Effects Intravenously Administered Dofetilide in Patients with Paroxysmal Atrial Fibrillation
* : ongoing

2.2 Number of patients

The approximate total number of patients in all studies is 9110 which includes 5472 patients in oral and intravenous dofetilide studies in the US and Europe, 3028 (1518 CHF and 1510 MI) patients in the Diamond study, and 610 patients in the Japanese studies.

Total number of study patients

US and Europe	Diamond	Japan
5472	3028	610

The number of patients who received dofetilide in a clinical trial, by type of study and formulation, is shown below.

Number of patients who received dofetilide

	oral formulation^	iv formulation+
Phase I	807	489
Phase II/III	1941	642
Diamond mortality	1511	0
total	4259	1131

^H.2.A
+H.6.101.2, H.6.106.1 The iv formulation includes studies that used the iv formulation only, as well as data from studies where iv and oral doses were separated by a washout period sufficient to allow attribution of events to either the IV or oral formulation. Data from iv/oral studies without washout between the iv and oral doses are included in the oral studies.

Oral formulation

Clinical pharmacology studies

The table below shows the total number of subjects (normal volunteers and patients) in *all* clinical pharmacology studies who received oral dofetilide (in a placebo controlled trial or in an active or uncontrolled trial) and the number of patients in these trials who received an active comparator or placebo.

Number of subjects

	dofetilide			
	placebo controlled	active/ no control	active comparator	received placebo
total treated	304	503^	38	258

^H.2.1.2 states 455 instead of 503
H.6.C.3.a

Phase II/III studies

The table below shows the total number of patients in *all* Phase II/III studies who received dofetilide (in a placebo controlled trial or in an active or uncontrolled trial) and the number of patients in these trials who received an active comparator or placebo. The open label studies were 306, 104, 308, 330, 331, 109. There were no uncontrolled supraventricular arrhythmia studies.

Number of patients

	dofetilide			active comparator	placebo
	placebo controlled	active	no control		
total treated	1479	252	210+	496	778

+fax sent 11-25-98
includes protocols: 115-: 104, 108B, 109, 111, 113, 113B, 114, 119, 120, 120X, 128, 303, 307, 308, 310, 311, 320, 330, 331, 333, 334, 335, 336, 337, 337A, 345, 363, 364, 365, 372, 397 and 399
H.6.C.2.a

The table below, a subgroup of the above table, shows the total number of patients treated in the *relevant* ("Relevant" Phase II/III clinical trials for the combined safety analysis were trials that used oral dofetilide and evaluated the efficacy of dofetilide in the treatment of supraventricular or ventricular arrhythmias) Phase II/III studies, by treatment assignment. The studies excluded from this grouping were: 108B, 109, 111, 113B, 114,303, 307, 310, 337, 337A, 364, 365, 397, and 399.

Number of patients

	dofetilide			
	placebo controlled	active/ no control	active comparator	placebo
total treated	1418	358	476	759

Protocols included: 115-: 104, 113, 119, 120, 120X, 128, 308, 311, 320, 330, 331, 333, 334, 335, 336, 345, 363, 365 and 372
H.6.C.1.a

The number of patients who participated in an oral phase II/III study, by index arrhythmia and treatment group, is shown below. The category "other" is not included.

Number of patients

supraventricular arrhythmias				ventricular arrhythmias				
placebo controlled		active controlled		placebo controlled		active controlled		uncontrolled
dof	pla	dof	active	dof	pla	dof	active	
1346	677	31	235	102	101	296	250	210

fax sent 11-25-98 and H.6.1.6

There were no uncontrolled supraventricular arrhythmia trials. In the ventricular arrhythmia program, there were 210 patients enrolled into uncontrolled/compassionate use studies.

Number of patients by randomized dose

The usual dose range studied with oral dofetilide was from 125 mcg bid to 1000 mcg bid. Doses > 500 mcg bid (studies 311, 114, 320, 104) were deemed to be unsafe and were subsequently dropped from development.

All studies with oral formulation (excluding Japan and DIAMOND)

Table below shows the number of dofetilide patients by randomized dose and study type. Four studies are excluded from the table: 104 (no fixed dose), 201 and 202 (oral solution), and 227 (sustained release formulation).

Number of patients

study type	<250 mcg bid	250 mcg bid	500 mcg bid	>500 mcg bid
clinical pharmacology	54	288	306	128
supraventricular arrhythmias	217	388	705	38
ventricular arrhythmias	0	9	329	24
misc. and terminated studies	3	46	122	4
total	274	711	1462	194

H.2.1.5

The majority of patients received 500 mcg bid as their randomized dose.

Number of patients by actual dose (information obtained from submission dated 7-10-98)

Many studies allowed downward dose titration for safety reasons, i.e., for prolongation of QT/QTc, and during the first quarter of 1994 the sponsor determined that patients were to be dosed by

their baseline creatinine clearance, calculated by the equation of Cockcroft and Gault[1], in order to minimize the risk of proarrhythmia.

The table below shows the number of patients randomized to various doses of dofetilide as well as the number of patients who actually received a particular dose. The table is limited to the 1331 dofetilide patients randomized in a supraventricular arrhythmia study (excludes the 15 patients in discontinued study 115-114).

Number of patients

<250 mcg bid		250 mcg bid		500 mcg bid		>500 mcg bid+	
randomized	actual	randomized	actual	randomized	actual	randomized	actual
217	375	384	497	697	426	33	33

+doses >500 mcg bid were eliminated for safety reasons

Approximately 39% of patients randomized to 500 mcg bid had to be titrated to a lower dose.

The table below shows the number of patients, at hospital discharge, who stayed on 500 mcg bid and the number who were down titrated, died or discontinued the study.

Number and (percent) of patients

number of patients randomized to dofetilide 500 mcg bid	were on 500 mcg bid at hospital discharge	down titrated to dose < 500 mcg bid, died or discontinued study
Diamond CHF (n=762)	187 (24.5)	575 (75.5)^
Diamond MI (n=749)	287 (38.3)	462 (61.7)+

^includes 71 patients who were withdrawn entirely from study drug and 8 with no discharge date
+includes 96 patients who were withdrawn entirely from study drug and 10 with no discharge date
table 3.3 study reports

About 25 percent of patients with CHF and 38 percent of patients with MI who were randomized to dofetilide were discharged from the hospital on the 500 mcg bid dose. Most patients had a dose decrease because of creatinine clearance < 60 ml/min.

One explanation for being unable to distinguish dofetilide from placebo in DIAMOND is that the dofetilide patients were unable to tolerate an effective dose.

Supraventricular arrhythmia studies

The table below shows the percent of patients who were not maintained on the 500 mcg bid dose, by demographics.

---

[1]Clcr MALE= [(140-age in years)(body weight in kg)]/[72 X serum creatinine (mg/100ml)]
Clcr FEMALE= CLCR MALE x 0.85.

characteristic	not remaining on 500 mcg bid n=271
female	42% (265/154)+
male	38% (432/272)
%>65 years	48.2%/37.3%
structural heart disease-yes	43% (322/182)
structural heart disease-no	35% 375/244

+(n=randomized/n=actual)

Forty two percent of females (256/154, randomized/actual) did not remain on 500 mcg bid compared to 38% (432/272) of the males. The mean age was lower (60.0 years) and the mean weight was higher (85.4 kgs) for the actual dose group compared to the randomized dose group (62.9 years and 82.7 kgs, respectively). Left ventricular ejection fraction (LVEF) was obtained in only a small fraction of study patients. There were 6 patients randomized to 500 mcg bid who were identified with LVEF $\leq$ 35% and only 3 of these remained on that dose. Overall, while these changes may reflect only that patients were placed on a lower dose because of reduced creatinine clearance, this may also indicate that patients who are older, female, of lighter weight, with structural heart disease, and reduced LVEF may not tolerate the 500 mcg bid dose and should begin treatment with a lower dose.

2.3 Patient type

Patient characteristics for those enrolled into a Phase II/III study, by study drug, are shown below.

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8.2.3.10 GENERAL DEMOGRAPHY OF ORALLY TREATED SUBJECTS
ALL SUBJECTS IN RELEVANT AND OTHER PHASE II/III CLINICAL PROTOCOLS
DOFETILIDE IN PLACEBO CONTROLLED AND NON-PLACEBO CONTROLLED PROTOCOLS VERSUS ALL ACTIVE COMPARATORS VERSUS PLACEBO

(Page 1 of 1)

	Dofetilide (Placebo Controlled)		Dofetilide (Active/NO Control)		Active Comparator		Placebo	
	N	%	N	%	N	%	N	%
Number of Subjects	1479	100.0	462	100.0	495	100.0	778	100.0
Gender								
Male	1006	68.0	386	83.5	371	75.0	530	68.1
Female	473	32.0	76	16.5	124	25.0	248	31.9
Age category yrs								
<45	85	5.7	52	11.3	55	11.1	63	8.1
45-64	618	41.8	246	53.2	247	49.9	339	43.6
>=65	776	52.5	164	35.5	195	39.9	376	48.3
mean	65.7[illegible]		58.38		[illegible]		61.3[illegible]	
min	16		25		17		18	
max	89		81		86		88	
Weight (kgs)								
mean	82.43		77.43		72.55		82.83	
min	41		40		[illegible]		41	
max	147		141		143		161	
Race								
White	1425	96.4	457	98.9	491	99.0	739	95.0
Black	35	2.4	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Asian/Oriental	2	0.1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Other	15	1.0	[illegible]	[illegible]	[illegible]	0.2	6	[illegible]
Unknown	[illegible]	0.0	[illegible]	[illegible]	[illegible]	[illegible]	0	[illegible]
Disease Duration								
< 1 wk	95	6.4	42	9.1	44	8.9	67	8.6
1 - 13 wks	492	33.3	104	22.5	171	34.5	216	27.8
14 - 52 wks	288	19.5	42	9.1	95	19.2	122	15.7
> 1 yr	337	22.8	101	21.9	151	30.4	201	25.8
Unknown	266	18.0	173	37.4	35	7.1	172	22.1

The majority of patients were male, white, and with a mean age of about 60 years.

The table below shows the number of patients by primary diagnosis for the Phase II/III studies.

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H.5.1.1 PRIMARY DIAGNOSIS AND DURATION OF DISEASE IN ORALLY TREATED SUBJECTS
ALL SUBJECTS IN RELEVANT PHASE II/III CLINICAL PROTOCOLS
DOFETILIDE IN PLACEBO CONTROLLED AND NON-PLACEBO CONTROLLED PROTOCOLS VERSUS ALL ACTIVE COMPARATORS VERSUS PLACEBO

Page 1 of 2

	Dofetilide (Placebo Controlled)		Dofetilide (Active/No Control)		Active Comparator		Placebo	
	N	%	N	%	N	%	N	%
Chronic atrial fibrillation								
Number of Subjects	642	45.1	0.0	0.0	225	26.3	212	27.8
Mean Duration (months)	5.07		0		7.03		7.92	
Minimum Duration (months)	0		0		1		1	
Maximum Duration (months)	83		0		21		48	
Unknown Duration	20	1.4	0.0	0.0	1	0.1	5	0.7
Chronic atrial flutter								
Number of Subjects	83	5.8	0.0	0.0	11	1.3	40	5.2
Mean Duration (months)	4.34		0		6.73		3.69	
Minimum Duration (months)	0		0		1		1	
Maximum Duration (months)	47		0		12		21	
Unknown Duration	5	0.4	0.0	0.0	0	0.0	1	0.1
Paroxysmal atrial fibrillation								
Number of Subjects	487	34.2	0.0	0.0	98	11.5	317	41.5
Mean Duration (months)	48.01		0		45.11		51.05	
Minimum Duration (months)	0		0		0		0	
Maximum Duration (months)	372		0		300		333	
Unknown Duration	133	9.4	0.0	0.0	1	0.0	83	10.9
Paroxysmal atrial flutter								
Number of Subjects	67	4.7	0.0	0.0	8	1.0	65	8.5
Mean Duration (months)	33.76		0		30.71		29.45	
Minimum Duration (months)	0		0		1		1	
Maximum Duration (months)	372		0		144		240	
Unknown Duration	21	1.5	0.0	0.0	2	0.0	21	2.8
Paroxysmal supraventricular tachycardia								
Number of Subjects	75	5.3	0.0	0.0	51	6.4	63	8.3
Mean Duration (months)	104.50		0		149.12		63.92	
Minimum Duration (months)	1		0		5		1	
Maximum Duration (months)	340		0		480		276	
Unknown Duration	11	0.8	0.0	0.0	0	0.0	3	0.4
Ventricular tachycardia								
Number of Subjects	66	4.6	303	50.0	241	50.6	64	8.5
Mean Duration (months)	0.06		24.55		24.22		0.02	
Minimum Duration (months)	0		1		1		0	
Maximum Duration (months)	1		252		216		2	
Unknown Duration	42	3.0	62	10.2	13	4.8	44	5.8
Other primary diagnoses								
Number of Subjects	0.0	0.0	39	6.4	0.0	0.0	0.0	0.0

Most patients had chronic or paroxysmal atrial fibrillation and the mean duration of disease was between 4 and 6 months for chronic AF/AFl and 33-48 months for paroxysmal AF/AFl.

The next table shows the number and percent of study patients with regard to special demographics including abnormal renal function, structural heart disease, size of left atrium, underlying cardiac disorder, LVEF (mostly unknown), and NYHA class.

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[illegible] DEMOGRAPHY OF [illegible] TREATED SUBJECTS
ALL SUBJECTS IN RELEVANT AND OTHER PHASE II/III CLINICAL PROTOCOLS
DOFETILIDE IN PLACEBO-CONTROLLED AND NON PLACEBO CONTROLLED PROTOCOLS VERSUS ALL ACTIVE COMPARATORS VERSUS PLACEBO

(Page 1 of 2)

	Dofetilide (Placebo-Controlled) N	%	Dofetilide (Active-Control) N	%	Active Comparator N	%	Placebo N	%
Number of Subjects	1472	100.0	462	[illegible]	494	100.0	[illegible]	[illegible]
Gender								
Male	1006	68.0	386	[illegible]	372	75.0	[illegible]	[illegible]
Female	473	32.0	76	[illegible]	126	25.0	[illegible]	[illegible]
Creatinine Clearance - ml/min								
<20	0	0.0	0	0.0	0	0.0	0	[illegible]
20-<40	[illegible]	[illegible]	12	[illegible]	6	1.2	[illegible]	[illegible]
40-<60	301	20.4	65	14.1	60	12.1	[illegible]	[illegible]
>=60	[illegible]	60.5	223	48.3	269	54.2	186	[illegible]
Unknown	[illegible]	15.6	162	35.1	161	32.5	207	[illegible]
Structural Heart Disease								
Absent	[illegible]	52.9	105	[illegible]	175	35.3	[illegible]	[illegible]
Present	[illegible]	46.6	307	[illegible]	310	62.5	[illegible]	[illegible]
N/A	[illegible]	0.5	50	10.8	11	2.2	[illegible]	[illegible]
Left Atrial Diameter - mm								
<40	[illegible]	[illegible]	22	4.8	50	10.1	206	[illegible]
>=40	[illegible]	[illegible]	47	10.2	142	28.6	[illegible]	[illegible]
Unknown	[illegible]	22.7	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]								
Ischaemic Heart Disease	[illegible]	6.7	247	53.5	184	37.1	66	[illegible]
Hypertrophic Cardiomyopathy	0	0.0	35	7.6	26	5.2	[illegible]	[illegible]
Dilated Cardiomyopathy	11	0.7	44	[illegible]	40	8.1	14	[illegible]
Cardiomyopathy	11	[illegible]	1	[illegible]	[illegible]	0.9	4	[illegible]
Mixed	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
N/A	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Left Ventricular Ejection Fraction - %								
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	44	8.9	[illegible]	[illegible]
Unknown	[illegible]	[illegible]	[illegible]	[illegible]	380	76.6	[illegible]	[illegible]
New York Heart Association Class								
Class 1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	21.2	[illegible]	[illegible]
Class 2	[illegible]	[illegible]	144	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Class 3	[illegible]	[illegible]	21	[illegible]	16	3.2	[illegible]	[illegible]
Class 4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Other	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.0	[illegible]	[illegible]

Most patients had a creatinine clearance > 60 ml/min, more than half of the dofetilide patients in the placebo controlled trials did not have structural heart disease and most patients were NYHA class I or II.

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Supraventricular arrhythmia studies

Patient characteristics for those enrolled into a supraventricular study, by study drug, are shown below.

N.2.3.6 GENERAL DEMOGRAPHY OF ORALLY TREATED SUBJECTS BY INDICATION
ALL SUBJECTS IN RELEVANT PHASE II/III CLINICAL PROTOCOLS
DOFETILIDE IN PLACEBO CONTROLLED AND NON-PLACEBO CONTROLLED PROTOCOLS VERSUS ALL ACTIVE COMPARATORS VERSUS PLACEBO

(Page 1 of 3)

Supraventricular

	Dofetilide (Placebo Controlled)		Dofetilide (Active/No Control)		Active Comparator		Placebo	
	N	%	N	%	N	%	N	%
Number of Subjects	1331	100.0	0	0.0	235	100.0	672	100.0
Gender								
Male	877	65.9	0	0.0	150	63.8	436	64.9
Female	454	34.1	0	0.0	85	36.2	236	35.1
Age Category - yrs								
<45	78	5.9	0	0.0	27	11.5	57	8.5
45-64	554	41.6	0	0.0	114	48.5	291	43.3
>=65	699	52.5	0	0.0	94	40.0	324	48.2
mean	63.80		0		59.35		62.03	
min	18		0		17		18	
max	89		0		85		86	
Weight - kgs								
mean	81.46		0		79.43		80.38	
min	43		0		49		41	
max	147		0		145		161	
Race								
White	1756	56.4	0	0.0	232	98.7	635	94.5
Black	30	2.3	0	0.0	1	0.4	20	3.0
Asian/Oriental	2	0.2	0	0.0	1	0.4	9	1.3
Other	18	1.0	0	0.0	0	0.0	6	0.9
Disease Duration								
< 1 wk	50	3.8	0	0.0	2	0.9	38	5.7
1 - 13 wks	493	37.0	0	0.0	85	36.2	215	32.0
14 - 52 wks	285	21.4	0	0.0	68	28.9	107	15.9
> 1 yr	321	24.4	0	0.0	79	33.6	195	29.0
Unknown	176	13.2	0	0.0	1	0.4	109	16.2

The majority of patients were around 60 years of age, male, and white. Additional patient characteristics are shown below.

[illegible] SPECIAL DEMOGRAPHY OF ORALLY TREATED SUBJECTS BY INDICATION
ALL SUBJECTS IN RELEVANT PHASE OF [illegible] CLINICAL PROTOCOLS
DOFETILIDE IN PLACEBO CONTROLLED AND NON-PLACEBO CONTROLLED PROTOCOLS VERSUS ALL ACTIVE COMPARATORS VERSUS PLACEBO

(Page 1 of 6)

Supraventricular

	Dofetilide Placebo Controlled		Dofetilide Active/No Control		Active Comparator		Placebo	
	N	%	N	%	N	%	N	%
Number of Subjects	1331	100.0	0	0.0	235	100.0	671	100.0
Gender								
Male	877	65.9	0	0.0	151	64.3	434	64.7
Female	454	34.1	0	0.0	84	35.7	237	35.3
Creatinine Clearance - ml/min								
<20	0	0.0	0	0.0	0	0.0	1	0.1
20-<40	47	3.5	0	0.0	1	0.4	23	3.4
40-<60	261	19.6	0	0.0	25	10.6	130	19.4
>=60	973	73.1	0	0.0	177	75.3	474	70.6
Unknown	50	3.8	0	0.0	32	13.6	43	6.4
Structural Heart Disease								
Absent	764	57.4	0	0.0	118	50.2	350	52.2
Present	567	42.6	0	0.0	117	49.8	321	47.8
N/A	0	0.0	0	0.0	0	0.0	0	0.0
Left Atrial Diameter - mm								
<40	361	27.1	0	0.0	37	15.7	114	17.0
>=40	775	58.2	0	0.0	100	42.6	344	51.3
Unknown	195	14.7	0	0.0	98	41.7	213	31.7
Underlying Disorder								
Ischaemic Heart Disease	0	0.0	0	0.0	0	0.0	0	0.0
Hypertrophic Cardiomyopathy	0	0.0	0	0.0	0	0.0	0	0.0
Dilated Cardiomyopathy	0	0.0	0	0.0	0	0.0	0	0.0
Cardiomyopathy	0	0.0	0	0.0	0	0.0	0	0.0
Mixed	0	0.0	0	0.0	0	0.0	0	0.0
N/A	1331	100.0	0	0.0	235	100.0	671	100.0
Left Ventricular Ejection Fraction - %								
<=35	21	1.6	0	0.0	0	0.0	9	1.3
>35	120	9.0	0	0.0	0	0.0	37	5.5
Unknown	1210	90.9	0	0.0	235	100.0	625	93.2
New York Heart Association Class								
Class 1	419	31.5	0	0.0	35	14.9	156	23.2
Class 2	364	27.4	0	0.0	34	14.5	180	27.2
Class 3	31	2.3	0	0.0	2	0.9	19	2.8
Class 4	0	0.0	0	0.0	0	0.0	21	3.1
Other	3	0.2	0	0.0	0	0.0	4	0.6
Unknown	511	38.3	0	0.0	178	75.7	208	31.0
Disease Duration								
< 1 wk	50	3.8	0	0.0	2	0.9	38	5.7
1 - 13 wks	493	37.0	0	0.0	55	23.4	215	32.0
14 - 52 wks	285	21.4	0	0.0	68	28.9	122	18.2
> 1 yr	325	24.4	0	0.0	79	33.6	197	29.3
Unknown	178	13.4	0	0.0	1	0.4	100	14.9

Most patients had creatinine clearance of ≥ 60 ml/min, about half were without structural heart disease, and most had no CHF.

2.4 Patient exclusions

Patients were routinely excluded from participating in studies for the following reasons (not all

protocols had identical exclusions). The following exclusions are from the 3 main efficacy trials 120 (120X), 345 and 372.

-Pregnant women, women of childbearing potential, and women who were breast feeding.
-Inability to tolerate withdrawal from current antiarrhythmic therapy.
-History of undiagnosed cause of syncope in the six months preceding the study.
-Active thyrotoxicosis or atrial fibrillation/flutter resulting from other reversible non-cardiac diseases (e.g. pericarditis or alcohol intoxication).
-Uncompensated or rapidly progressive congestive heart failure.
-Myocardial infarction or unstable angina pectoris within the preceding 1 month or PTCA within the preceding 3 months, cardiac surgery within the preceding 2 months.
-Significant abnormalities of the sinus node (including sick sinus syndrome) or atrio-ventricular block greater than first degree, unless treated with a proper functioning pacemaker.
-ECG intervals exceeding the following limits in the drug-free state and in the absence of pre-excitation syndrome and BBB: QRS >180msec, QT/QTc >440msec. In the case of BBB, QT/QTc was not to exceed 500msec. RR interval greater than 3.5 seconds, ventricular rate of less than 50 beats/minute (less than 80 beats per minute during AF/AFl for subjects receiving chronic beta-receptor antagonists)
-Systolic blood pressure <90mm Hg, or diastolic blood pressure >110mm Hg (or >105mm Hg for Canadian Centers).
-Major hematologic, pulmonary, hepatic, or renal disease (serum creatinine >2.5mg/dl or calculated creatinine clearance <20ml/min).
-Serum potassium <4.0mEq/L (<3.6 in some protocols) or >5.5mEq/L, or serum magnesium <1.5mEq/L or >2.5mEq/L.
-Concomitant therapy with: other antiarrhythmic agents, verapamil, cimetidine, diltiazem, diuretics (unless serum potassium was within the limits specified above), antihistamines, tri-cyclic antidepressants, anticonvulsants, or phenothiazines. Therapy with digoxin was allowed provided the dosage was kept constant throughout the study.
-Amiodarone blood level >0.3mcg/ml.
-History of polymorphic ventricular tachycardia associated with the use of antiarrhythmic drugs or with other classes of drugs known to prolong the QT/QTc interval.
-Patients with known substance abuse/dependency (i.e. alcohol, controlled drugs, etc.), or inability to give informed consent.
-daytime pauses during AF/AFl exceeding 4 seconds
-survival from sudden cardiac death within the preceding 3 weeks;
-diabetic subjects known to be poorly controlled or found to be unstable
-subjects with a creatinine clearance of less than 60 ml/min at baseline were excluded, and any subject who fell below this value at any time during the double blind period was withdrawn from the study.

2.5 Duration of therapy

The table below shows the duration of therapy for patients in the supraventricular studies by randomized as well as by actual dose. The actual dose and randomized dose are the same for the dose groups >500 mcg bid and placebo.

	<250 mcg bid		250 mcg bid		500 mcg bid		>500 mcg bid	placebo
	actual	randomized	actual	randomized	actual	randomized		
n	375	217	497	384	426	697	33	672
mean duration (wks)	19.45	18.2	22.38	23.52	22.85	21.79	15.23	16.10
% with Rx ≥1 yr	19	18	19	23	15	14	0	8

submission 7-10-98 page 7

Only around 15% of patients (63) in the supraventricular arrhythmia studies actually received 500 mcg bid for 1 year or longer.

3.0 Proarrhythmia

Dofetilide exhibits Vaughan Williams Class III antiarrhythmic actions. It prolongs the effective refractory period by specifically inhibiting the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current, Ikr. Consistent with its Class III effect, dofetilide prolongs the QT/QTc intervals and provokes ventricular arrhythmias, specifically *torsades de pointes* (TdP).

3.1 QT/QTc interval prolongation (Bazett's formula was used to calculate QTc)

Protocol 203

This study was designed to investigate the pharmacokinetic and pharmacodynamic effects of single and multiple doses of oral dofetilide up to 400 mcg bid. (The 12 hour plasma concentration profiles are shown in section 1.3 of this review.) ECG 12-hour profiles were obtained on day 1 (single dose) and day 10 (steady state) in 8 normal males per treatment group. The mean change from baseline for the QT/QTc intervals for both days and all doses as well as placebo are shown in the figures below.

FIGURE 2.1

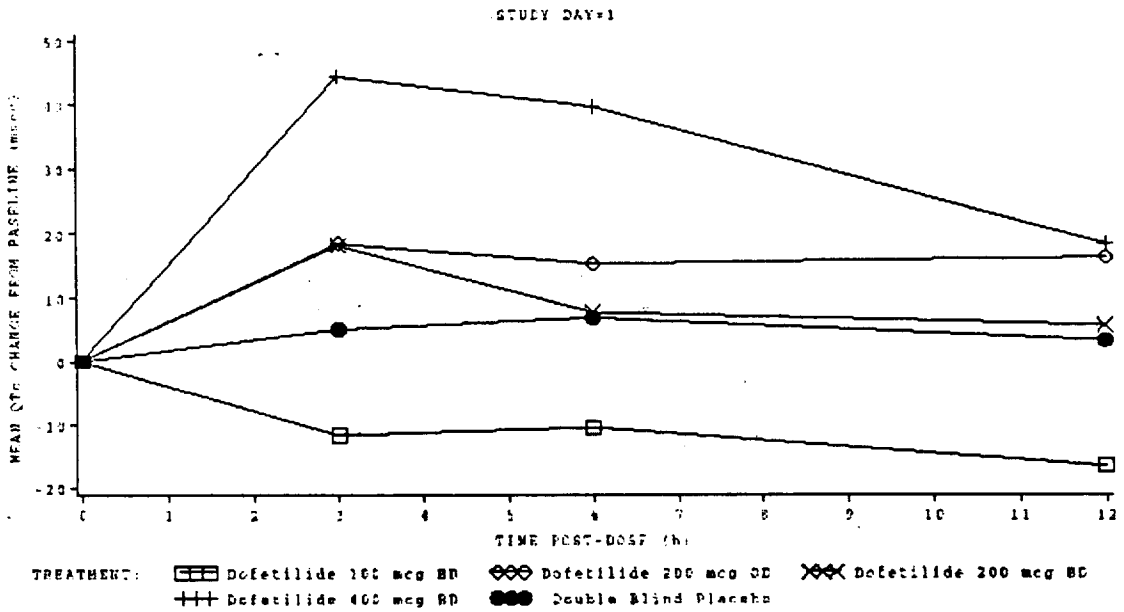
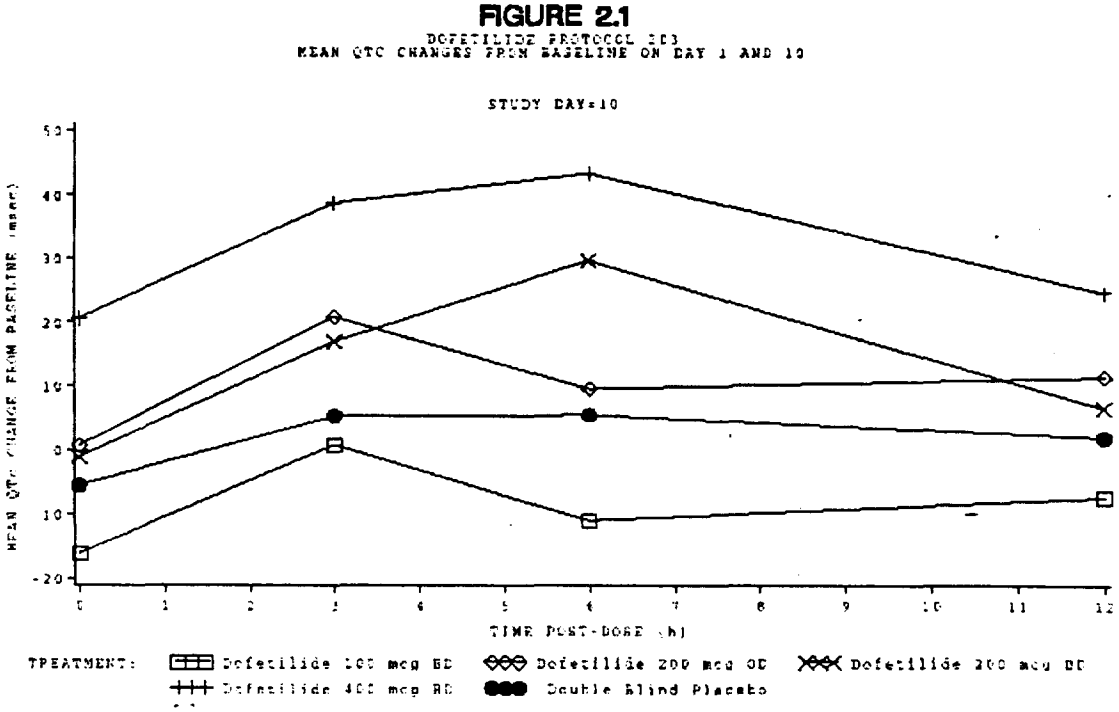


FIGURE 2.1



Dofetilide doses above 100 mcg substantially increased the QTc compared to baseline after the first dose as well as at steady state. The 400 mcg twice daily dose showed the greatest increase (about 45 msec) at hour 3 and the increase, although smaller, was still present at hour 12 (about 25 msec). The 200 mcg dose when given once a day produced a smaller increase (about 20 msec) and the maximum effect was earlier (hour 3) compared to the 200 mcg bid dose (about 30 msec at 6 hours). Placebo produced minimal change.

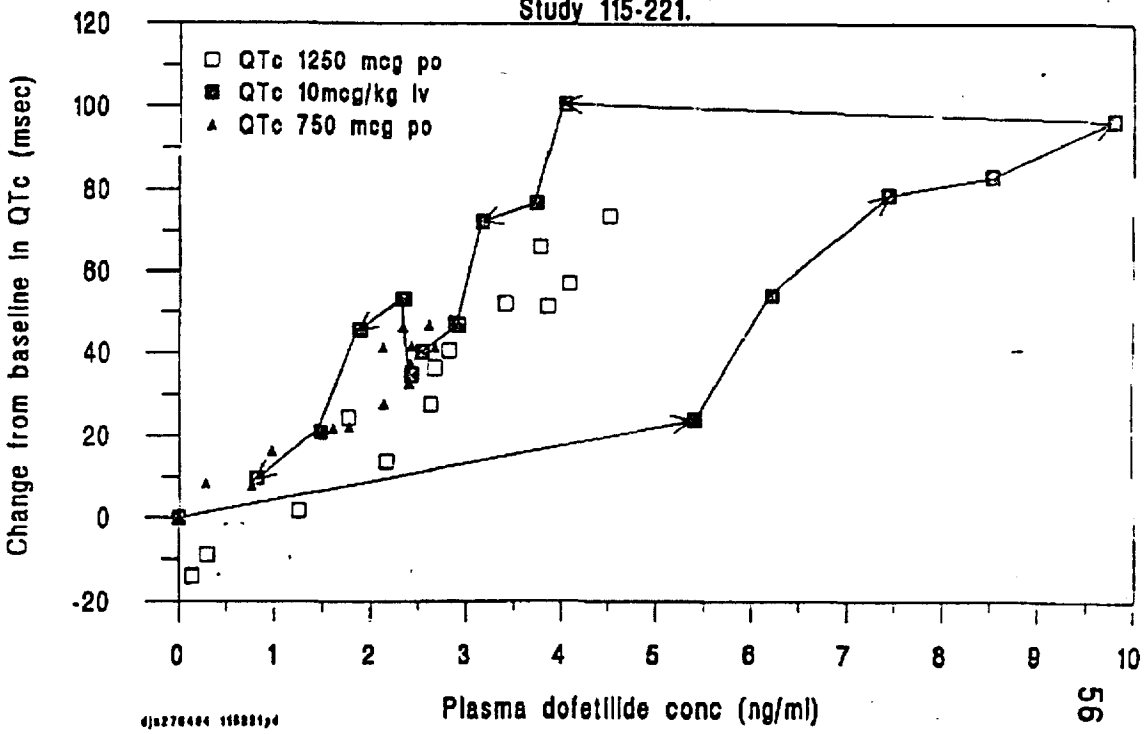
Protocol 221

This study was designed to investigate the relationship between plasma concentrations and QTc intervals of the oral and iv dofetilide formulations compared to placebo. The subjects were 12 healthy males who received, in a random fashion and separated by 1 week, 3 single oral doses of dofetilide (250, 750 and 1250 mcg), a single oral dose of placebo, and a single iv dose of dofetilide (10 mcg/kg). Blood for plasma concentrations of dofetilide and ECGs were collected up to 48 hours after each dose. Ambulatory ECGs were monitored for 24 hours after each treatment.

The figure below shows the relationship between plasma concentration, dose, and change from baseline for the QTc interval.

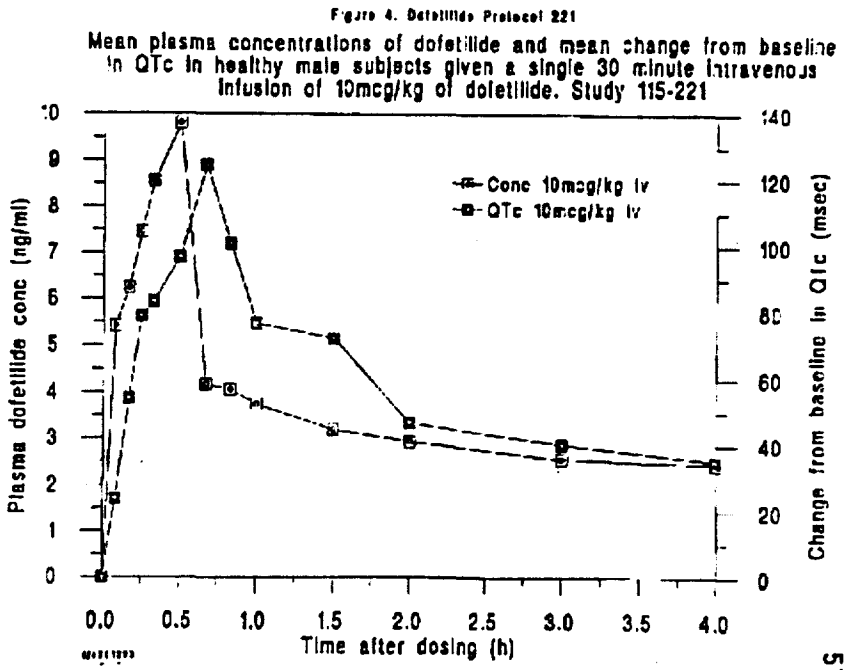
Figure 3. Dofetilide Protocol 221

Relationship between mean change from baseline in QTc and mean plasma dofetilide concentration in healthy male subjects given a single 30 minute intravenous infusion of 10mcg/kg dofetilide, a 750mcg and a 1250mcg oral capsule. Study 115-221.



The higher the plasma concentration of dofetilide, the larger the increase in mean QTc from baseline.

With the infusion, an anticlockwise hysteresis curve was demonstrated for the plasma concentration and QTc change from baseline. The delay between peak plasma concentration and maximum increase from baseline for QTc is less than 0.5 hours with the iv dose and is shown in the figure below.



Phase II/III trials

Study patients generally were hospitalized and monitored, usually with telemetry, for at least one day after the start of the iv studies and for at least five doses after the start of the oral studies. Some studies also obtained Holter recordings at baseline and post baseline.

The tables below show the mean baseline and the mean maximum change from baseline for the QT and QTc intervals by treatment group. The measurements were over the first 1 to 3 days of dosing.

Mean QT (msec)

	placebo controlled trials		active/non controlled trials	
parameter	dofetilide n=1373	placebo n=733	dofetilide n=251	active comparators n=395
baseline	372	378	392	378
maximum change	45	9	53	62

H.6.20.2

Mean QTc (msec)

	placebo controlled trials		active/non controlled trials	
parameter	dofetilide n=976	placebo n=598	dofetilide n=194	active comparators n=254
baseline	412	412	420	413
maximum change	35	1	43	27

H.6.20.2

Dofetilide substantially increased QT/QTc intervals from baseline as did the active comparators. The QTc for placebo showed little change.

The table below shows the number and percent of patients in various categories of percent increases in QTc from baseline. Only data from the first 3 days of treatment in the placebo controlled trials are included in the table.

Number and (percent) of patients

QTc interval increase from baseline	dofetilide n=1304	placebo n=661	placebo subtracted %
15-20%	194 (14.9)	34 (5.1)	9.8
20-25%	83 (6.4)	7 (1.1)	5.3
25-30%	40 (3.1)	9 (1.4)	1.7
>30%	59 (4.5)	8 (1.2)	3.3

H.6.21.2 (table was corrected by sponsor fax 4-17-98 and again 12-4-98)

The QTc interval in patients on dofetilide tended to increase $\leq 25\%$ from baseline.

The changes for other ECG intervals are shown below for the dofetilide and placebo patients, placebo controlled trials.

Mean (msec)

	dofetilide			placebo		
parameter	n	baseline	change from baseline	n	baseline	change from baseline
RR	1375	812	87	737	836	60
PR	507	174	-7	378	172	-4
QRS	1199	94	3	648	98	1

H.6.20.2

The RR interval was increased in the dofetilide group compared to placebo. The other mean changes from baseline were similar for the 2 groups.

3.2 Proarrhythmic events

Beginning in November 1991, an independent expert panel defined criteria for the diagnosis of proarrhythmia for the dofetilide program.

The following categories of proarrhythmic events were defined:
1. TdP, defined as polymorphic ventricular tachycardia of >10 beats associated with twisting of the axis and prolonged repolarization which need not be continuously present (recorded in the absence of rate correction)
2. New ventricular fibrillation
3. VT resistant to cardioversion
4. New sustained VT (>30 seconds at a rate of >100 beats per minute) provided no ventricular rhythm longer than a triplet had previously been documented off drug.
5. Development of sustained (>5 minutes) supraventricular tachycardia (supraventricular tachycardia at a rate of >120 beats per minute, or atrial fibrillation or flutter at any rate) in a patient in whom these rhythms had never been previously documented or suspected on clinical grounds.
6. Supraventricular tachycardia (with the exception of atrial fibrillation) which previously had been terminated with pacing and/or intravenous AV nodal blocker (verapamil or adenosine) and in whom these therapies are no longer effective ('incessant ventricular tachycardia").
7. Sudden cardiac death (CAST-like mortality), except in studies where SUCD is an endpoint rather than a proarrhythmia (e.g. the DIAMOND studies).

For all cases meeting the above criteria, and any other cases where a diagnosis of TdP was considered, the details were sent to an independent expert (Prof. A.J. Camm for European cases, Prof. D. Roden for US and Japanese cases). **Where the investigator highlighted an event in the case report form as a serious electrophysiological event but it did not meet the protocol criteria for proarrhythmia it was still reported in the study report tables but was indicated as not meeting the protocol criteria for proarrhythmia. Such events were not included in the analyses of proarrhythmic events presented in the NDA integrated safety summary and therefore, there could be an underestimation of the incidence of proarrhythmia in patients taking dofetilide, in particular TdP.**

In addition, Dr. Roden reviewed all death and identified those he considered to be sudden and cardiac, arrhythmic or presumed arrhythmic and occurring during treatment or within 7 days of stopping treatment. These deaths are referred to as sudden unexpected cardiac deaths (SUCD).

The incidence rate for the reporting of TdP during the dofetilide development program is 1.7% (59/3452). Many of the TdP events were symptomatic and required an intervention such as cardioversion. Numerous events degenerated into ventricular fibrillation. Dofetilide was nearly always withdrawn. TdP was not reported by placebo patients.

The table below shows the reporting of TdP by study type.

Number and (percent)

Diamond MI n=749	Diamond CHF n=762	SVA n=1377	VT n=443	other n=121	total 3452
7 (0.9)	25 (3.3)	12 (0.9)	11 (2.5)	4 (3.3)	59 (1.7)

H.6.11.3.b.3, and submission from sponsor

The table below shows the number and percent of patients with serious ventricular arrhythmic events. The patients are those who participated in relevant and other Phase I/II/III studies including compassionate use and uncontrolled studies.

Number of events

	dofetilide n^=2669	placebo n^=1034
VT	159	43
VF	29	5
ventricular arrhythmia	8	0

^numbers from fax sent 6-12-98
H.6.8.1.3

The table below shows the occurrence of proarrhythmic events reported while patients were receiving dofetilide, all doses combined, during the *relevant* Phase II/III Clinical trials, as well as the placebo, and active comparator rates.

Number and (percent) of patients

proarrhythmic event	dofetilide n=1776	placebo n=759	active comparator n=476
TdP	24 (1.4)	0	0
new sustained VT	6 (0.3)	1 (0.1)	4 (0.8)
new VF	3 (0.2)	1 (0.1)	1 (0.2)
other	2 (0.1)	0	1 (0.2)
SUCD	12 (0.7)	3 (0.4)	1 (0.2)
any of the above	47 (2.6%)	5 (0.7%)	7 (1.5%)

H.6.11.2.1 and 2

The sponsor argues that the patients on dofetilide were followed longer than the patients in the other treatment groups and thus had increased opportunity to report adverse events and/or die. However, there are no data to support this conclusion.

The table below shows the number and percent of patients who reported TdP in the Phase II/III and were included in the population pharmacokinetics study, by daily AUC and Cmax.

Number and percent of patients

daily AUC (ng.h/ml)						daily Cmax (ng/ml)				
<20	20-40	40-60	60-80	80-100	>100	0-2	2-4	4-6	6-8	>8
0	3 (0.5)	4 (0.7)	10 (3.4)	2 (1.7)	10 (18)	3 (0.4)	11 (1.2)	7 (3.7)	5 (38.4)	3 (69.2)

Table 2 Population pharmacokinetic report

The reporting of TdP increases with increasing AUC and Cmax.

Supraventricular arrhythmia studies

The table below shows the number of patients with reports of TdP, VF and VT, by *randomized* dose, in the supraventricular arrhythmia studies. Classification was done by Dr. Dan Roden.

Number and (percent) of SVA patients

	dofetilide (mcg)					placebo
arrhythmia event	< 250 mcg bid n=217	250 mcg bid n=388	500 mcg bid n=703	>500 mcg bid n=38	all doses combined n=1346	n=677
TdP	0	2 (0.5)	6 (0.9)	4 (10.5)	12 (0.9)	0
VF^	1 (0.5)	1 (0.3)	1 (0.1)	1 (2.6)	4 (0.3)	1 (0.1)
VT	2 (0.9)	3 (0.8)	5 (0.7)	1 (2.6)	11 (0.8)	7 (1.0)
SUCD	2 (0.9)	0	3 (0.4)	0	5 (0.4)	2 (0.3)

^includes patients who had TdP as well as VF
H.6.10.5, H.6.11.5.1, H.6.11.5.2 and fax sent 11-25-98

The higher the dose of dofetilide, the higher the event rate for TdP and VF. VT, described as monomorphic VT, was independent of dose. SUCD in this population was rare.

The table below shows the number of patients with reports of TdP, VF and VT, by *actual* dose, in the supraventricular arrhythmia studies (dofetilide n=1346).

Number and (percent) of patients

	dofetilide (mcg)				placebo
arrhythmia event	< 250 mcg bid n=375	250 mcg bid n=497	500 mcg bid n=426	>500 mcg bid n=38	n=677
TdP	0	3 (0.6)	5 (1.2)	4 (10.5)	0
VF	2 (0.5)	0)	1 (0.3)	1 (2.6)	1 (0.1)
VT	3 (0.8)	5 (1.0)	2 (0.5)	1 (2.6)	7 (1.0)
SUCD	2 (0.5)	0	3 (0.7)	0	2 (0.3)

fax 12-4-98
Submission 7-10-98 pages 18-19

Adjusting the dose of dofetilide based on QT/QTc prolongation and creatinine clearance did not greatly change TdP and VF event rates.

Events reported by investigators as proarrhythmic but excluded from NDA safety summary--- supraventricular placebo controlled studies only

As stated earlier in this section, if the investigator highlighted an event in the case report form as a serious electrophysiological event but it did not meet the protocol criteria for proarrhythmia it was still reported in the study report tables but was indicated as not meeting the protocol criteria for proarrhythmia. Such events were not included in the analyses of proarrhythmic events presented in this safety summary in NDA. The discussion below is an attempt to determine if there is under reporting of proarrhythmia.

All reports of ven arrhythmia^ not included in safety summary

protocol number	dofetilide	placebo
120	4	0
311	0	0
372	0	0
345	1	0
128	0	1

^excludes ventricular premature beats
table 7.4 of study reports

Events not included in proarrhythmia tables, by study
protocol 120
Dofetilide
05470090, a 68-year-old male, experienced, about 8 hours after his first dose of 125mcg, a 7 beat run of monomorphic VT that was asymptomatic and self-limiting.

05870212, a 55-year-old male who was receiving 125mcg bid, had a 17 beat run of **VT**, chest pain and hypotension on Day 2. The event was terminated with dobutamine and lidocaine.
06020457, a 75-year-old male, was hospitalized for an aortic valve replacement revision, reverted to AF and then experienced two short bursts of **VT** which were considered to be TdP by his personal cardiologist, but were later classified as pause-dependent polymorphic VT by the cardiology consultant. The event resolved after treatment with oral potassium, IV magnesium sulfate and lidocaine. The subject had received 250mcg bid for 10.5 months.
07000524, a 64-year-old male, after 6 doses of 500mcg given bid, had a 14-beat run of monomorphic **VT** which resolved without treatment.
protocol 345
Dofetilide
Subject 00120353 experienced non-sustained **VT** (23 beats, 190 beats/minute) 3 hours after cardioversion from AF on Day 3. Dofetilide 125 mcg bid was permanently discontinued for safety considerations.
protocol 128
Placebo
Subject 07600384 experienced a 15-beat episode of VT on day 2 of dosing which spontaneously converted to sinus rhythm. The study drug was discontinued.

Ventricular arrhythmia studies

The number of reported proarrhythmic events in patients enrolled into a Phase II/III ventricular arrhythmia study is shown below.

Number and (percent) of patients

	placebo controlled trials		active/uncontrolled trials	
event	dofetilide n=96	placebo n=69	dofetilide n=347	active comparator n=250
TdP	4 (4.2)	0	7 (2.0)	0
VT	32 (33.0)	27 (39.0)	36 (10.3)	6 (2.4)
VF	3 (3.1)	1 (1.4)	4 (1.7)	1 (0.4)
SUCD	1 (1.0)	1 (1.4)	7 (2.0)	1 (0.4)

H.6.11.6.1, H.6.11.6.2 and fax 12-4-98

The TdP rate in the VA population was higher than the rate in the SVA population (4.2% and 0.9%, respectively). The placebo subtracted VF rate for dofetilide in the VA population was 1.7% compared to 0.2% for the SVA population.

DIAMOND studies

The investigators were required to report all cases of proarrhythmia. In order to promote consistency between them, the sponsor offered guidelines defining proarrhythmic events which had been agreed by a panel of experts, the key requirement in DIAMOND being that the investigator considered that the events had a causal relationship to treatment. The sponsor stated that "the boundaries between an arrhythmic event classified as proarrhythmic, thus relating to treatment, and an arrhythmic event resulting from the progression of the underlying CHF were very subjective so it was decided that the true index of proarrhythmia would be the event rate for Torsade de Pointes, as defined by the Arrhythmic Events Committee. For this reason the report has not included all narratives of the other event."

The number of reports of proarrhythmia (TdP, VT and VF) for the DIAMOND CHF and MI that were selected by the Arrhythmic Events Committee are shown below by treatment groups.

Number and (percent) of patients

	DIAMOND CHF		DIAMOND MI		DIAMOND total	
	dofetilide n=762	placebo n=756	dofetilide n=749	placebo n=761	dofetilide n=1511	placebo n=1517
TdP	25 (3.3)	0	7 (0.9)	0	32 (2.1)	0
VF	43 (5.6)	26 (3.4)	39 (5.2)	48 (6.3)	82 (5.4)	74 (4.9)
VT	84 (11.0)	85 (11.2)	55 (7.3)	54 (7.1)	139 (9.2)	139 (9.2)

H.6.11.3B.3 and .4

In the combined results, the incidence rate for TdP was 2.1% for dofetilide compared to 0% for placebo. VF was reported slightly more often by the dofetilide patients.

Ventricular arrhythmic events reported by the investigators but judged not to be a proarrhythmic event by the Committee are shown below.

All reports of ven arrhythmia not included in safety summary

protocol number	dofetilide	placebo
diamond-chf	5	3
diamond-mi	6	1

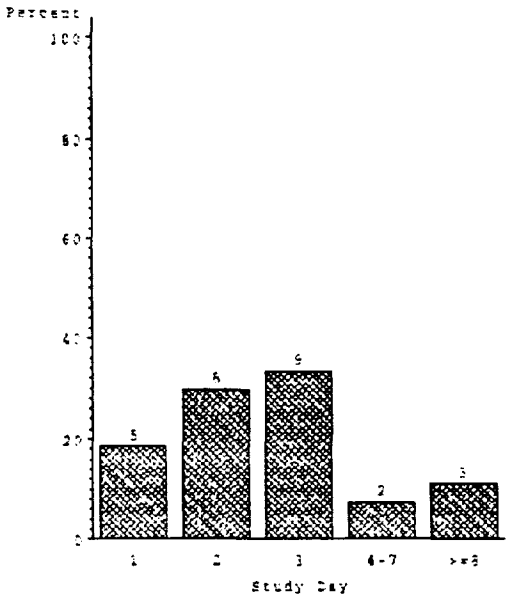
table 7.5.3 of study reports

3.2.1 Time to event

The figures below show the relationship between the start of dofetilide dosing and the occurrence of TdP and other potentially proarrhythmic events in the Phase II/III clinical trials.

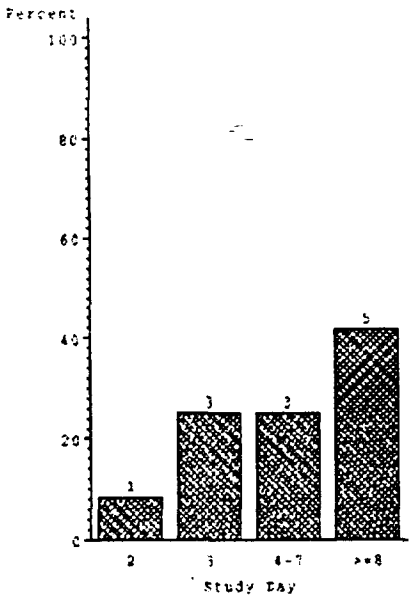
H.8.11.10.3 PROARRHYTHMIA GRAPH

FREQUENCY OF QTcI > 500 MSEC DOFETILIDE SUBJECTS VERSUS STUDY DAY
PATIENTS IN RELEVANT PHASE II/III CLINICAL AND OTHER STUDIES
PERCENTAGE IN EACH GROUP WITH AND WITHOUT TORSADES DE POINTES



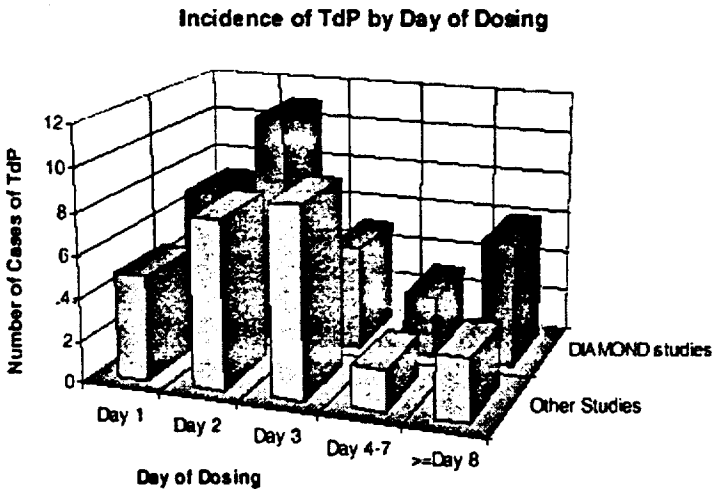
H.8.11.10.4 PROARRHYTHMIA GRAPH

FREQUENCY OF POTENTIALLY PROARRHYTHMIC EVENTS IN DOFETILIDE SUBJECTS VERSUS STUDY DAY
PATIENTS IN RELEVANT PHASE II/III CLINICAL AND OTHER STUDIES
PERCENTAGE IN EACH GROUP WITH AND WITHOUT POTENTIALLY PROARRHYTHMIC EVENTS



Many, but not all, reports of TdP occurred before day 4 of treatment

The figure below shows the incidence of TdP reported for the DIAMOND trial as well as the pooled other trials relative to start of dofetilide dosing.



These 3 figures illustrate that the risk of TdP and other proarrhythmic events does not disappear after the first few days of starting treatment with dofetilide. This risk remains throughout therapy despite the care that was taken to discontinue or lower the dose of dofetilide in those patients thought to be most at risk, such as those with excessively prolonged QT/QTc intervals.

3.2.2 Risk factors

The sponsor reviewed their extensive data on TdP and identified potential risk factors for the development of this proarrhythmia. The following is their description of the analysis.

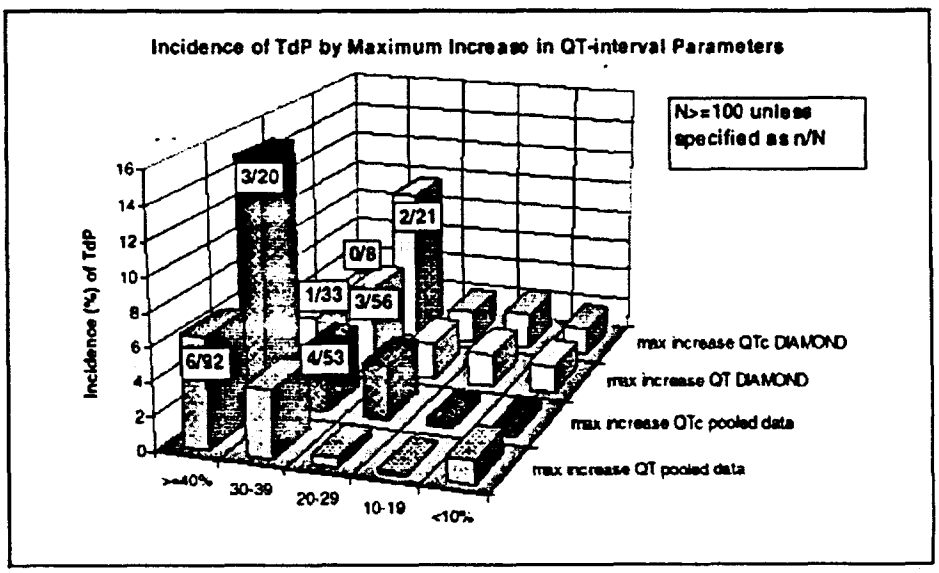
> A univariate analysis was done for TdP to investigate the association of the factor with the risk of TdP (i.e., which were predictors of TdP). Continuous parameters were analyzed in strata and/or continuously. Significant risk factors (predictors of TdP) were selected and in cases of risk factors that are by definition dependent (e.g., baseline QT, baseline QTc, maximum increase in QT and maximum increase in QTc), a choice was made for the most significant and/or clinically useful predictor. These factors were then to be fed into a multiple

logistic regression analysis to detect which remained significant risk factors in the presence of the other factors determined to be significant in the univariate analyses. However, data on the factor LVEF was collected in a subset of subjects only (435/1941). Because the multiple logistic regression analysis requires complete data on all subjects, the analysis would be unnecessarily restricted. Therefore, this factor was excluded from the final analyses.

The factors that were highly significant predictors of TdP were maximum QTc increase of ≥ 50% compared to baseline during day 1-3, baseline QT > 450 msec, female gender, presence of structural heart disease, and primary diagnosis of VT.

Maximum increase QT/QTc from baseline

The risk of TdP was between 4 and 42 times higher for subjects with a ≥50% increase as compared to those with <50% increase in QT/QTc , observed over the first 3 days of dosing. The figure below shows the incidence of TdP versus the percent increase in maximum QT/QTc prolongation (the highest increase is to the left) for the pooled clinical data excluding DIAMOND as well as for DIAMOND alone.



Ref: Tables H.6.11.23/24.1/6

Generally, the larger the maximum increase from baseline QT/QTc, the higher the TdP incidence rate.

The table below shows the number and percent of patients with TdP, new VF and or SUCD, by maximum increase in QTc interval. All or nearly all protocols instructed investigators to decrease the dose or discontinue study patients if their QT/QTc interval increased >15% compared to baseline.

Number and (percent) of patients

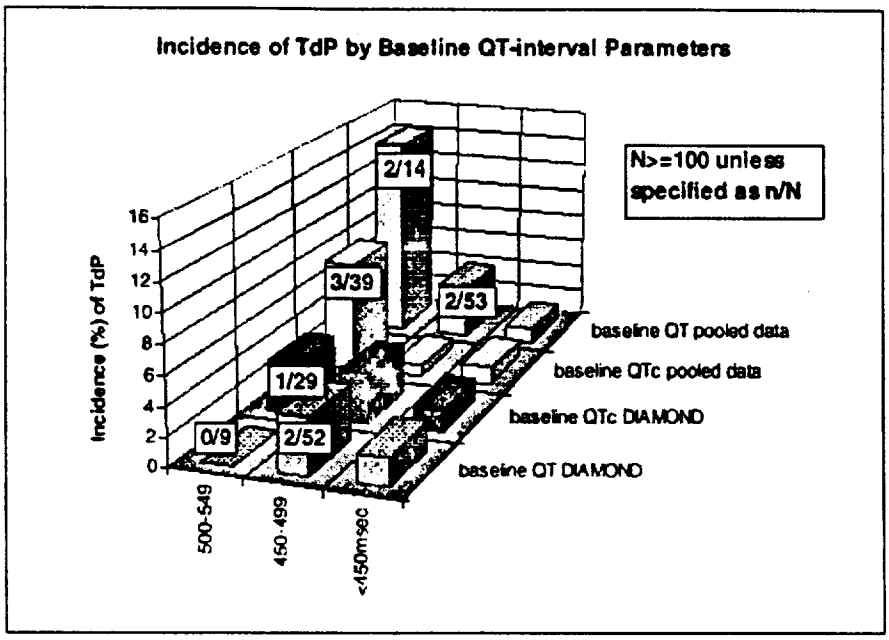
	increase from baseline QTc				
	<10% n=744	10-19% n=612	20-29% n=184	30-39% n=53	≥ 40% n=20
TdP	2 (0.3)	2 (0.3)	6 (3.3)	4 (7.5)	3 (15.0)
New VF	0	1 (0.2)	1 (0.5)	0	0
SUCD	3 (0.4)	4 (0.7)	2 (1.1)	1 (1.9)	0

H.6.11.21.1 and H.6.11.24.2

While there is a direct correlation between the rate of TdP and SUCD and the increase from baseline in QTc, there was still a risk even if the QTc increase was less than 10%.

Baseline QT interval

Patients with a baseline QT interval >450msec had an 8 fold increase in risk compared to those with intervals ≤450msec. Surprisingly, this was not true for QTc but the sponsor reasonably surmised that this was the result of the difficulty in obtaining reliable QTc measurements in patients with AF. (In the pooled data from DIAMOND, it was QTc and not QT that was the significant risk factor.) The figure below shows the incidence of TdP versus the baseline QT/QTc prolongation (the highest baseline is to the left) for the pooled clinical data excluding DIAMOND as well as for DIAMOND alone.



Ref: Tables H.6.11.20.21.1/6

Generally, the larger the baseline QT/QTc, the higher the TdP incidence rate.

The table below shows the number and percent of patients with TdP, new VF and or SUCD, by baseline QT interval. Most patients were not enrolled into a dofetilide study if their baseline QT/QTc exceeded >440 msec.

Number and percent of patients

	baseline QT (msec)			
	<450 n=1719	450-499 n=53	500-549 n=14	550-599+ n=1
TdP	18 (1.0)	2 (3.8)	2 (14.3)	1 (100)
new VF	2 (0.1)	0	0	0
SUCD	13 (0.8)	0	0	0

+no patients with baseline QT >599 were enrolled
H.6.11.20.1, .2

For the few patients who were protocol violators, their chance of reporting a TdP event increased with increasing baseline intervals. Even with careful screening, one can conclude that at least 1% of patients taking dofetilide will report TdP.

Females

The estimated risk (95% CI) for females was 3.77 (1.74, 8.17) times that of males.

Structural heart disease

The estimated risk (95% CI) for patients with structural heart disease was 2.32 (0.96, 5.63) times that of patients without structural heart disease.

Primary arrhythmia diagnosis

The estimated risk (95% CI) for patients with a primary diagnosis of VT was 2.9 (1.27, 6.61) times that of patients with a primary diagnosis of SVA.

Other factors that were less convincing included potentially abnormal potassium and magnesium levels, creatinine clearance, and baseline heart rate. However, correcting electrolyte imbalances was an entry criterion in all studies, a large number of subjects in the "creatinine clearance" analysis already had their dose adjusted on the basis of creatinine clearance, and most protocols had a lower limit of 50 bpm for heart rate as an entry criterion and many subjects were in AF at baseline with potentially high ventricular rates.

Factors that were not predictors of TdP included the lowest heart rate observed over the first 3 days of dosing, age, race, and presence or absence of a pacemaker.

While there were no cases of TdP reported in patients with ejection fraction $\leq 35\%$ in the pooled database, the data from the pooled DIAMOND studies show that TdP does occur in this patient category.

Multiple logistic regression analyses

These results are presented in the tables below.

Summary of Multiple Logistic Regression Risk Factor Analysis with Baseline QTc Pooled Database				
	Relative Risk / Slope	95% Confidence Interval		p-value
		Lower limit	Upper limit	
Gender (Female : Male)	4.206	1.35	13.15	0.0135
Baseline QTc (continuous)	0.015	0.00	0.03	0.0479
Structural Heart Disease (Present : Absent)	1.652	0.54	5.05	0.378
Potentially abnormal K+ or Mg++ (Present : Absent)	1.640	0.53	5.04	0.387
Creatinine Clearance (>60 : =<60)	0.991	0.97	1.01	0.435
Ref Table H.6.11.26.1				

A high baseline QT/QTC and female gender are significant risk factors for the development of TdP.

Population pharmacokinetics (from amendment F section 6)

The sponsor used the results from the population pharmacokinetic analysis to try to determine the relationship between the derived pharmacokinetic parameters (AUC and Cmax) and the incidence of TdP and other serious arrhythmias.

Of the 1,445 patients included in this analysis, 14 (6 AF/AFl, 8 VT) experienced an episode of TdP. All but 2 patients were receiving total daily doses of 1000 mcg; the other 2 were receiving 125 mcg and 500 mcg. The time from first dose to the reporting of TdP ranged from 0 to 1036 days with 7 events occurring prior to day 3. Mean AUC and range were 73.5 and 12-187 $ng.ml^{-1}.h$, respectively. Mean Cmax and range were 3.6 and 0.6-8.5 $ng.ml^{-1}.h$, respectively.

The figures below show the AUC and Cmax for the dofetilide by creatinine clearance. The black boxes in each figure represent an episode of TdP.

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