Means (U/L)

	dofetilide								placebo	
	<250 mcg bid n/N=167/217		250 mcg bid n/N=332/392		500 mcg bid n/N*=837/1058		>500 mcg bid n/N=42/51		n/N=652/759	
	baseline	mean change ±sem	baseline	mean change ±sem	baseline	mean change ±sem	baseline	mean change ±sem	baseline	mean change ±sem
SGPT U/L	24.74	2.92 ±1.71	23.89	3.38 ±2.31	26.32	4.63 ±1.28	22.4	10.38 ±6.28	27.95	2.15 ±1.43
SGOT U/l	23.98	2.44 ±1.01	21.89	3.76 ±2.09	23.46	4.21 ±1.18	19.52	7.07 ±3.05	25.66	11.82 ±1.31
alk phos U/L	105.16	-5.32 ±2.47	88.73	0.32 ±1.25	103.01	1.91 ±1.07	115.17	28.85 ±16.19	90.44	-1.26 ±1.02

*for all dose groups except 500 mcg bid the number of evaluable patients is nearly the same for all of the above parameters; for 500 mcg bid, n=837 for SGPT, 798 for SGOT, and 721 for alk phos.

Including the placebo group, there are dose dependent trends with increasing dofetilide dose for SGPT and SGOT.

6.2.3 Renal function and electrolytes

The table below shows the baseline mean and mean change from baseline for the dofetilide and placebo patients for renal function tests. The table represents patients in relevant phase II/III placebo controlled trials.

Means

	dofetilide in placebo controlled trials n=1418			placebo n=759		
parameter	no. evaluable patients	baseline mean	mean change from baseline±SEM	no. evaluable patients	baseline mean	mean change from baseline±SEM
BUN (mg/dl)	639	17.95	0.69±0.32	388	17.94	1.43±0.44
creatinine (mg/dl)	1203	1.13	-0.01±0.01	661	1.15	0.00±0.01
urea (mg/dl)	564	36.27	-0.71±0.48	267	34.67	0.09±0.72
calcium (mg/dl)	1196	9.29	-0.01±0.02	652	9.28	0.01±0.03
chloride (mEq/l)	832	103.39	-0.14±0.20	381	103.29	-0.30±0.35
magnesium (mg/dl)	1197	2.07	0.01±0.02	652	2.08	-0.01±0.01
sodium (mEq/l)	1198	140.39	-0.26±0.14	656	140.39	-0.28±0.17
potassium (mEq/l)	1183	4.39	0.04±0.02	647	4.39	0.04±0.03

H.6.16.2

The tables below shows the number and percent of patients in relevant Phase II/III placebo controlled trials who had an abnormal BUN, creatinine, sodium or potassium value.

Clinically significant abnormalities

		dofetilide in placebo controlled trials n=1244		placebo n=687	
parameter	criteria for clinically significant change from baseline	number evaluable	number and (percent) abnormal	number evaluable	number and (percent) abnormal
Renal function					
BUN (mg/dl)	>1.3 x ULN	656	30 (4.6)	405	25 (6.2)
creatinine (mg/dl)	>1.3 x ULN	1237	20 (1.6)	687	14 (2.0)
urea (mg/dl)	>1.3 x ULN	581	21 (3.6)	281	15 (5.3)
Electrolytes					
sodium (mEq/l)	<0.95 x LLN	1236	14 (1.1)	687	9 (1.3)
sodium (mEq/l)	>1.05 x ULN	1236	4 (0.3)	687	1 (0.1)
potassium (mEq/l)	<0.9 x LLN	1231	5 (0.4)	686	4 (0.6)
potassium (mEq/l)	>1.1 x ULN	1231	33 (2.7)	686	18 (2.6)

H.6.12.2

There was little difference between treatment groups regarding the reporting of renal or electrolyte abnormalities and reporting severe laboratory abnormalities was rare. No patient in either dofetilide or placebo groups had a creatinine value >3 x ULN, a potassium value <0.6 x LLN, a magnesium value <0.6 x LLN, or a magnesium value >2 x ULN. There were 4 (0.3%) dofetilide patients and 4 placebo patients (0.6%) who had a potassium value >1.4 x ULN (H.6.15.9).

6.2.4 Glucose, lipid profiles, bicarbonate,

The incidence rates for abnormalities of random glucose, cholesterol, and triglyceride values are similar for the dofetilide and placebo treatment groups.

Because there were so few dofetilide patients who were evaluated for bicarbonate (3.1%, 36/1170 in the SVA placebo controlled trials), the data cannot be interpreted.

Overall, there is no evidence that dofetilide use can be linked to any abnormal laboratory values.

However, the sponsor omitted discussion of urinalysis, inorganic phosphorus, uric acid, albumin and globulin levels and, as stated above, very few patients were evaluated for bicarbonate.

7.0 Electrocardiograms and vital signs

7.1 ECG intervals other than QT/QTc

Mean baseline and mean change from baseline for the RR, PR, and QRS intervals are shown below for patients in relevant phase II/III trials.

Means (msec)

	placebo controlled trials					
	RR interval		PR interval		QRS interval	
	dofetilide n=1375	placebo n=737	dofetilide n=507	placebo n=378	dofetilide n=1199	placebo n=648
baseline	812	836	174	172	94	98
change from baseline	87	60	-7	2	3	1

H.6.20.2

There is no indication that dofetilide prolongs the QRS or the PR intervals. However, it does prolong the RR interval.

The table below shows the number and percent of patients who had more than a 25% change from baseline in the ECG intervals by treatment group, placebo controlled trials only, for the first 3 days of treatment.

Number and percent of patients with changes

25% change from baseline	dofetilide n=1376	placebo n=737	placebo subtracted %
RR interval increase	510 (37.1)	216 (29.3)	7.8
RR interval decrease	179 (13.0)	90 (12.2)	0.8
PR interval increase	22 (1.6)	16 (2.2)	-0.6
QRS increase	103 (7.5)	53 (7.1)	0.4
QRS decrease	39 (2.8)	19 (2.6)	0.2

H.6.19.2

More patients on dofetilide had a ≥25% increase from baseline in the RR interval compared to patients on placebo. The other changes are similar for the 2 treatment groups.

Mean changes from baseline for heart rate in protocol 372 are shown below for the dofetilide 500 mcg bid and placebo groups.

Mean heart rates (bpm)

	dofetilide^	placebo^
baseline	76	70
change from baseline 2-4 hours after 1st dose	1	-1
change from baseline 2-4 hours after 6th dose	-11	-4
change from baseline week 1	-7	2
change from baseline week 26	-6	2

^n ranged from 20-38 per group
appendix 1 Table 6 study report

Dofetilide decreases heart rate by about 6 bpm.

7.2 Blood pressure

Baseline blood pressures and changes from baseline for protocol 372 are shown below.

Mean supine SBP/DBP (mm Hg)

	dofetilide^	placebo^
baseline	130/80	127/80
change from baseline 2-4 hours after 1st dose	-1/-4	-2/-1
change from baseline 2-4 hours after 6th dose	0/-1	-1/-1
change from baseline week 1	1/-1	-3/-2
change from baseline week 26	-2/0	-4/-3

^n ranged from 20-38 per group
appendix 1 Table 7 study report

Dofetilide does not have an obvious effect on blood pressure.

8.0 Special population

This section includes discussion of safety based on age, race, gender, kidney function, liver impairment, and heart failure.

8.1 Age

Pharmacokinetics study

Protocol 235 was an open, randomized cross-over study designed to evaluate the effects of age on the pharmacokinetics and pharmacodynamic profiles of dofetilide following single oral (1000 mcg) and intravenous (500 mcg) doses in young and elderly (64 to 75 years) healthy, male subjects. Females were not studied. Blood was obtained for plasma concentrations of dofetilide at the same times as 3-lead ECG measurements for up to 72 hours after each dose. Ambulatory ECGs were monitored for 24 hours after each treatment.

A total of 11 elderly (64-73 years) and 10 young (19-38 years) males received dofetilide. The elderly on average were about 10 kg heavier than their young counterparts. One elderly (00370026) subjects was discontinued when his QT/QTc was prolonged after receiving oral dofetilide.

The PK parameters for both groups, oral formulation only, are shown below.

	ORAL(1000 mcg)	
PARAMETER	**YOUNG**	**ELDERLY**
C_{max} (ng/ml)	3.94 (0.65)	4.89 (1.38)
T_{max} (h)	2.35 (0.97)	2.38 (0.83)
AUC (ng.h/ml)	41.96 (7.21)	58.79 (7.32)
k_{el} (h^{-1})	0.0733 (0.0100)	0.0528 (0.0087)
$t_{1/2}$ (h)	9.45	13.13

The Cmax and AUC were higher and the $T_{1/2}$ was longer in the elderly male population. Individual 12-hour dofetilide concentrations for young and elderly males are shown below. Note that the y-axis is different for the 2 figures.

FIGURE 8
DOFETILIDE PROTOCOL 235
INDIVIDUAL DOFETILIDE PLASMA CONCENTRATIONS UP TO 12 HOURS POST-DOSE
TREATMENT=DOFETILIDE 1000 mcg CAPSULE (YOUNG)

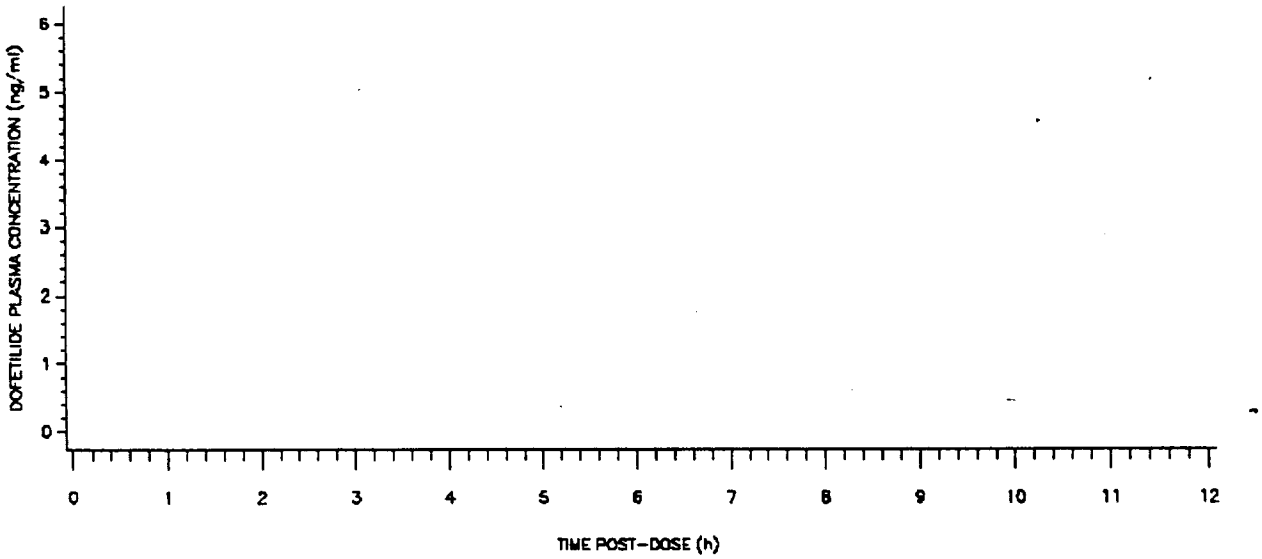
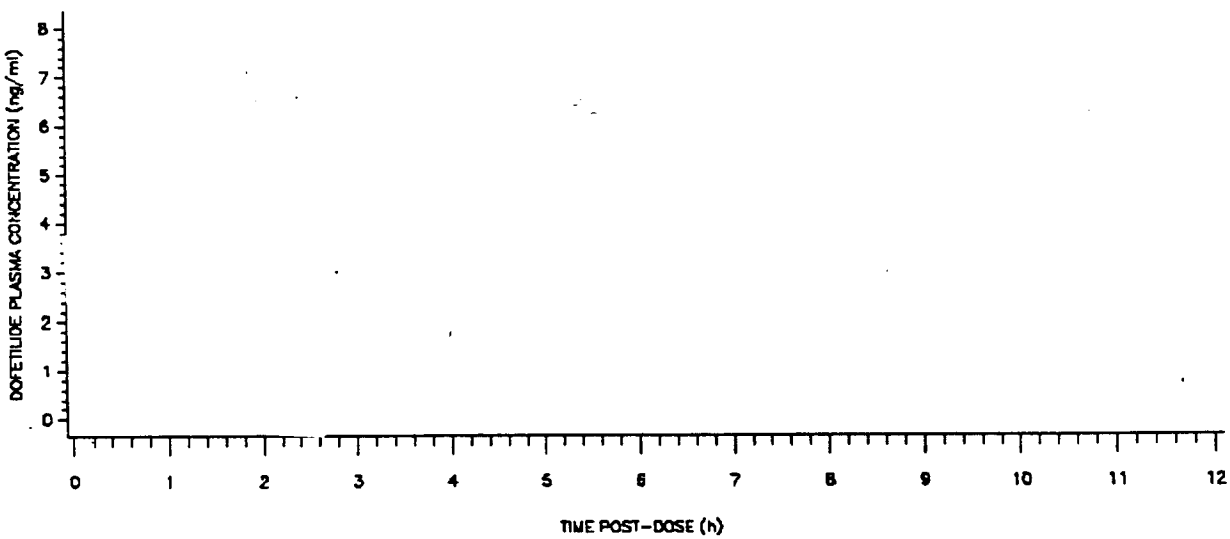


FIGURE 8
DOFETILIDE PROTOCOL 235
INDIVIDUAL DOFETILIDE PLASMA CONCENTRATIONS UP TO 12 HOURS POST-DOSE
TREATMENT=DOFETILIDE 1000 mcg CAPSULE (ELDERLY)



Blood levels were higher and remained elevated longer in the elderly males, probably in part because of reduced creatinine clearance. QTc intervals change from baseline at 1-6 hours after the oral dose for the 2 age groups are shown below. The baseline for the young and elderly were 397 and 425 msec, respectively.

QTc (msec) change from baseline

	young	elderly
hour 1	49	46
hour 2	83	74
hour 3	120	66
hour 4	72	56
hour 5	56	46
hour 6	46	37

study report table 6.1

Surprisingly, although the elderly had higher dofetilide concentrations, the young had larger QTc increases from baseline. This is puzzling.

Phase II/III

The percents of patients in the Phase II/III studies who received oral dofetilide (N=1941) and reported a proarrhythmic event and/or experienced sudden unexpected cardiac death, by age category, are shown below.

Number and (percent) of patients

proarrhythmic event	<45 years n=137	45-64 years n=864	≥65 years n=940	total N=1941
new sustained VT	1 (0.7)	2 (0.2)	3 (0.3)	6 (0.3)
New VF	0	2 (0.2)	1 (0.1)	3 (0.2)
Resistant VT	0	1 (0.1)	0	1 (0.1)
SUCD	0	10 (1.2)	10 (1.1)	20 (1.0)
TdP	3 (2.2)	9 (1.0)	15 (1.6)	27 (1.4)

H.6.11.12.1 and .2

Without age matched controls it is difficult to draw conclusions from these data. However, nothing appears to be highly unusual. The next table includes only patients enrolled in the *relevant* Phase II/III studies and there are age matched controls. Of the 1418 patients who received dofetilide in these studies, 5.6% were < 45 years, 41.7% were 45-64 years, and 52.8% were ≥ 65 years.

The table below shows the number of dropouts for safety reasons.

Number and (percent) discontinuations

	<45 years		45-64 years		≥ 65 years	
	dofetilide n=79	placebo n=62	dofetilide n=591	placebo n=328	dofetilide n=748	placebo n=369
any reason	28 (35.4)	23 (37.1)	278 (47.0)	199 (60.7)	355 (47.5)	195 (52.8)
adverse event	5 (6.3)	4 (6.5)	51 (8.6)	27 (8.2)	58 (7.8)	40 (10.8)
lab abnormality	1 (1.3)	0	3 (0.5)	2 (0.6)	6 (0.8)	1 (0.3)
↑ QT/QTc	1 (1.3)	0	17 (2.9)	0	35 (4.7)	1 (0.3)
withdrew consent	5 (6.3)	1 (1.6)	6 (1.0)	6 (1.8)	16 (2.1)	12 (3.3)
death	0	1 (1.6)	2 (0.3)	0	7 (0.9)	0

H.6.1.2.1

There was an age related increase in QT and the 7 deaths reported for patients ≥ 65 years old were all in the dofetilide group.

Serious adverse events

The number and percent of patients who reported serious adverse events in the relevant and other phase I/II/III studies (N=2669 for all dofetilide and N=1034 for placebo) are shown in the table below.

Number and (percent) of patients

	<18-64 years		65-84 years		≥85 years	
adverse event	dofetilide n^=1709	placebo n^=639	dofetilide n^=950	placebo n^=392	dofetilide n^=10	placebo n^=3
total number of events	469 (27.4)	201 (31.4)	729 (76.7)	269 (68.6)	12	0
VT	86 (5.0)	18 (2.8)	72 (7.6)	25 (6.4)	1 (10)	0
heart failure+	15 (0.9)	5 (0.8)	44 (4.6)	20 (5.1)	2	0
VF	16 (0.9)	2 (0.3)	13 (1.4)	3 (0.8)	0	0
death including sudden	8	0	7	2	0	0
syncope	10	5	17	5	0	0
dizziness	6	0	9	1	0	0
GI hemorrhage	1	0	6	2	0	0
ven arrhythmia	6	0	2	0	0	0
bradycardia	4	1	6	4	0	0

^numbers of patients are from fax dated 6-12-98
+includes cardiac failure, left cardiac failure, worsening heart failure
H.6.8.1.1

Ventricular tachycardia in the younger population was more likely to occur in patients on dofetilide (5.0%) compared to the age matched placebo population (2.8%). One percent of dofetilide patients > 65 years of age reported VT compared to no placebo patient in this age group.

ECG changes

The incidence of clinically significant changes from baseline in ECG intervals for dofetilide and placebo patients who participated in relevant Phase II/III trials, by age group.

Number and (percent) of patients

	<45 years		45-64 years		≥ 65 years	
	dofetilide n=77	placebo n=62	dofetilide n=571	placebo n=316	dofetilide n=728	placebo n=359
any significant change	47 (61.0)	29 (46.8)	329 (57.6)	157 (49.7)	453 (62.2)	192 (53.5)
RR >25% increase	25 (32.5)	10 (16.1)	203 (35.6)	99 (31.3)	282 (38.7)	107 (29.8)
PR >25% increase	0	2 (3.2)	6 (1.1)	1 (0.3)	16 (2.2)	13 (3.6)
QRS >25% increase	7 (9.1)	5 (8.1)	43 (7.5)	18 (5.7)	53 (7.3)	30 (8.4)
QT >25% increase	9 (11.7)	1 (1.6)	113 (19.8)	23 (7.3)	134 (18.4)	18 (5.0)
QTc >25% increase	4 (5.2)	0	17 (3.0)	3 (1.0)	28 (3.9)	5 (1.4)

H.6.19.2.1

Older dofetilide patients were more likely to have RR, QT and QTc increases of >25% from baseline compared to the placebo patients.

In summary, there is increased concern with elderly patients experiencing VT and the higher dofetilide plasma levels shown in elderly males seen in study 235 require further investigation.

8.2 Race

There were very few non white patients in the Phase II/III dofetilide program. In all, there were 38 black and 2 Asian patients compared to 1883 white patients who received dofetilide. Only white patients reported TdP or other proarrhythmic events. There were 3 SUCD that occurred in blacks. The effect of race on the safety of dofetilide is unknown.

8.3 Gender

Combined data from 4 phase I studies (115-012,-013, -014, and-015) in which a total of 49 healthy females and 31 healthy males received oral doses of 500 mcg showed an increase in both the mean AUC and Cmax. This is shown below along with the results derived from an ANCOVA model.

Estimated geometric means ±SE

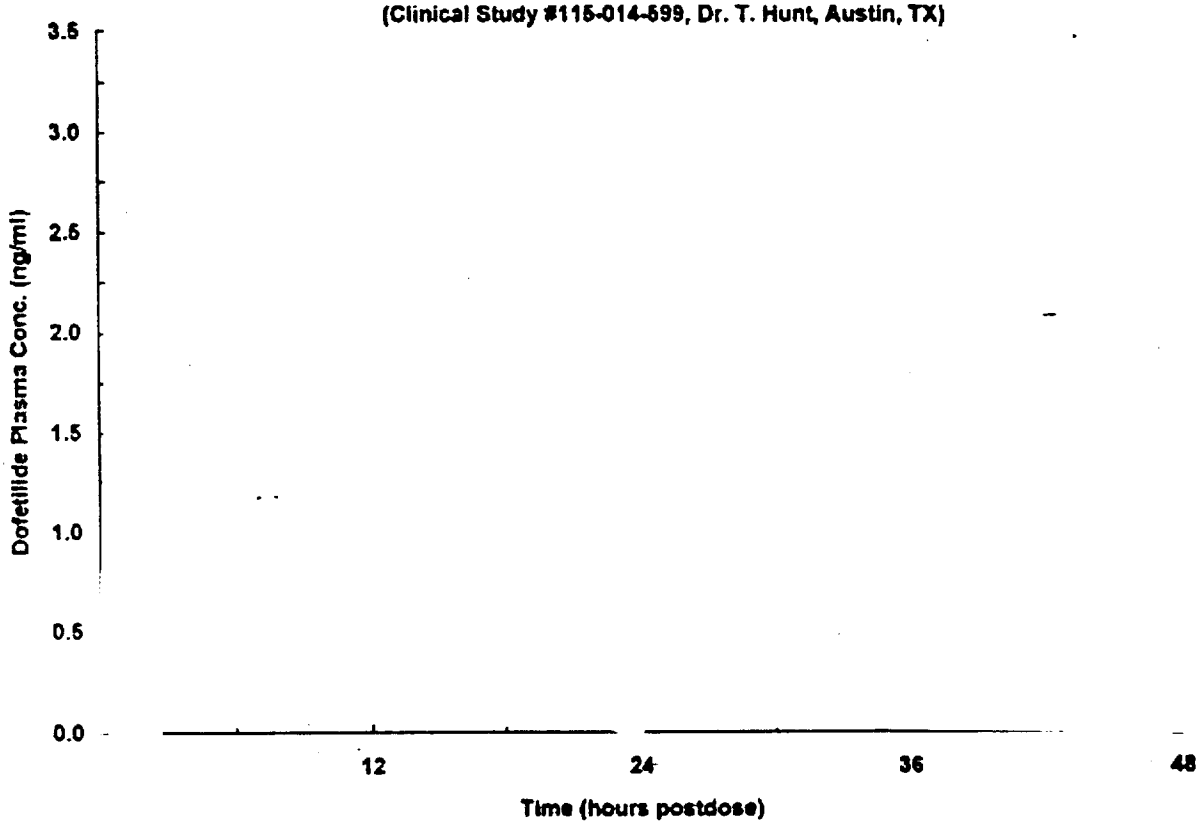
	AUC (ng.h/ml)		Cmax (ng/ml)	
	males n=31	females	males	females
actual data	22.9 ±0.69	26.34 ±0.69	2.07 ±0.10	2.49 ±0.09
derived^	22.98	25.72	2.02	2.42

^adjusted for gender, treatment and body weight from fax dated 10-16-98

Even with the adjustments, there was a 12% increase in the AUC and a 20% increase in the Cmax for females compared to males. The possibility that the use of oral contraceptives (OC) by 37% of the female study subjects was interfering with the metabolism of dofetilide was rejected when the Cmax and AUC were both found to be lower in the OC user compared to the non OC user.

Plasma concentration profiles from study 115-014 for 11 males (solid lines) and 11 females (dotted lines) who received a single 500 mcg dose of dofetilide are shown below.

Appendix IIIB, Figure 1. Dofetilide Plasma Concentrations Following Oral Administration of a Single 500 ug Capsule (FID #0964) to Healthy, Young Male (__) and Female (...) Volunteers (Clinical Study #115-014-599, Dr. T. Hunt, Austin, TX)



There were 2 subjects who were discontinued because of excessive QT prolongation, and both were female. Overall, females tend to have higher dofetiiide concentrations and are at greater risk of proarrhythmic event such as TdP.

Phase II/III studies

The effects of gender on QT/QTc prolongation and reports of proarrhythmic events are discussed below.

QT/QTc intervals

The table below shows the mean baseline and the mean change from baseline for QT and QTc, by gender, for patients enrolled into a placebo controlled relevant Phase II/III trial.

Means (msec)

	male		female	
interval	dofetilide n=923/655^	placebo n=497/396^	dofetilide n=450/321^	placebo n=236/202^
baseline QT	373	377	370	379
mean change	44	9	48	– 8
baseline QTc	411	413	413	410
mean change	36	1	32	3

^n=QT/n=QTc
H.6.20.2.3

Mean baseline and mean changes from baseline are similar for the sexes in both treatment groups.

Proarrhythmic events

The percents of patients in the Phase II/III studies who received oral dofetilide (N=1941) and reported a proarrhythmic event and/or experienced sudden unexpected cardiac death, by gender, are shown below.

Number and (percent) of patients

proarrhythmic event	male n=1392	female n=549
new sustained VT	2 (0.1)	4 (0.7)
new VF	2 (0.1)	1 (0.2)
resistant VT	1 (0.1)	0
SUCD	12 (0.9)	8 (1.5)
TdP	11 (0.8)	16 (2.9)
at least one of the above	28 (2.0)	29 (5.3)

H.6.11.11.1 and.2

The univariate analysis of TdP in the dofetilide subjects for gender was significant (p=0.01) with a relative risk of 3.77 (95% CI 1.74, 8.17). H.6.11.5

The table below shows the number of TdP reports by gender in the DIAMOND trial (pooled CHF and MI). There were no reports of TdP in the placebo group of either gender.

DIAMOND Number and (percent) of patients

proarrhythmic event	male n=1088	female n=423
TdP	17 (1.6)	15 (3.5)

H.6.11.11.6

The univariate analysis of TdP in the dofetilide DIAMOND subjects for gender (discrete) was also significant (p=0.02) with a relative risk of 2.32 (95% CI 1.15, 4.68). H.6.11.10

Serious adverse events

The reporting rates by dofetilide and placebo patients, by gender, for selected serious adverse are shown below.

Number[a] and (percent) of patients

adverse event	male		female	
	dofetilide n^=2023	placebo n^=755	dofetilide n^=646	placebo n^=279
any report	935 (46.2)	335 (44.4)	275 (42.6)	135 (48.8)
VT	117 (5.8)	40 (5.3)	42 (6.5)	3 (1.1)
VF	19 (0.9)	4 (0.5)	10 (1.5)	1 (0.4)
death including sudden	11 (0.5)	2 (0.3)	4 (0.6)	0
heart failure+	52 (2.5)	21 (2.8)	9 (1.4)	4 (1.4)
syncope	24 (1.2)	8 (1.0)	3 (0.5)	2 (0.7)
dizziness	14 (0.7)	0	1 (<0.1)	1 (0.4)
chest pain	24 (1.2)	8 (1.0)	4 (0.6)	5 (1.8)
MI	16 (0.8)	8 (1.0)	4 (0.6)	2 (0.7)
angina pectoris#	28 (1.4)	6 (0.8)	5 (0.8)	0
CVA*	17 (0.8)	6 (0.8)	12 (1.9)	3 (1.1)
GI hemorrhage	7	2	0	0
ven arrhythmia	6	0	2	0
bradycardia	9	3	1	2
cardiac arrest	4	5	3	0
QT increase	6	1	2	0
dyspnea	6	2	1	1
pneumonia	15	7	4	1
acute renal failure	3	4	1	0

a patient could have more than 1 event per category and thus be counted more than once but this should be rare.
^numbers are from fax sent 6-12-98
+includes cardiac failure, left cardiac failure, worsening heart failure
#includes angina pectoris aggravated
*includes cerebral hemorrhage, cerebral vascular disorder, intracranial hemorrhage
H.6.8.1.3

Compared to females on placebo, females on dofetilide reported more VT, VF, and died more often. The risks for VT and VF by gender are shown below.

	males	females	F/M
VT	1.1 (5.8/5.3)	5.9 (6.5/1.1)	5.4
VF	1.8 (0.9/0.5)	3.8 (1.5/0.4)	2.1

Females taking dofetilide are at substantially higher risk for VT as well as VF.

Discontinuations

Discontinuations for safety reasons in the *relevant* Phase II/III studies by gender are shown below. The number of patients in these studies who received dofetilide is 1418.

Number of events and (percent) of patients

	male		female	
	dofetilide n=953	placebo n=516	dofetilide n=465	placebo n=243
any reason	444 (46.6)	296 (57.4)	217 (46.7)	121 (49.8)
adverse event	78 (8.2)	50 (9.7)	36 (7.7)	21 (8.6)
lab abnormality	4 (0.4)	1 (0.2)	6 (1.3)	2 (0.8)
increase in QT	35 (3.7)	1 (0.2)	18 (3.9)	0
withdrew consent	18 (1.9)	12 (2.3)	9 (1.9)	7 (2.9)

H.6.1.2.3

Except for lab abnormality, the drop out rates for specific reasons are similar for males and females.

Supraventricular arrhythmia studies

The table below shows reports of TdP and SUCD by gender and treatment group in the SVA studies.

Number and (percent) of patients-SVA

	males		females	
	placebo controlled trials		placebo controlled trials	
	dofetilide n=889	placebo n=438	dofetilide n=457	placebo n=239
TdP	3 (0.3)	0	8 (1.8)	0
SUCD	3 (0.3)	0	3 (0.7)	2 (0.8)

Tables 3 and 4 document from sponsor drafted 10-98

Consistent with the all studies evaluation, the incidence rate of reported TdP in females was higher than that for males. Rates for SUCD in these studies were similar. However, the percents of SUCD reported in the ventricular arrhythmia studies for male and female patients taking dofetilide were 0.9 (3/347) and 6.8% (3/44), respectively (corresponding placebo rates were not provided).

Overall, females taking dofetilide, compared to males, tend to have higher blood levels of dofetilide, a higher risk of serious proarrhythmic events such as TdP, and it is likely that the benefit risk ratios for males and females are different. Finally, the dofetilide levels in the oral contraceptive interaction study were alarmingly high (see section 9.2).

8.4 Renal impairment (protocol 219)

Dofetilide is mainly excreted unchanged by the kidneys. This study was an open, pilot study to evaluate the influence of renal impairment on the pharmacokinetics, pharmacodynamics and safety of a single, 500mcg oral dose of dofetilide. Study subjects included 8 with severe renal impairment (creatinine clearance below 20ml/min but not requiring dialysis) and 4 with moderate impairment (creatinine clearance 20-40ml/min).

The pharmacokinetic parameters for subjects with moderately and severely impaired renal function are shown below and are compared to the parameters for normals from study 244.

Means±SD

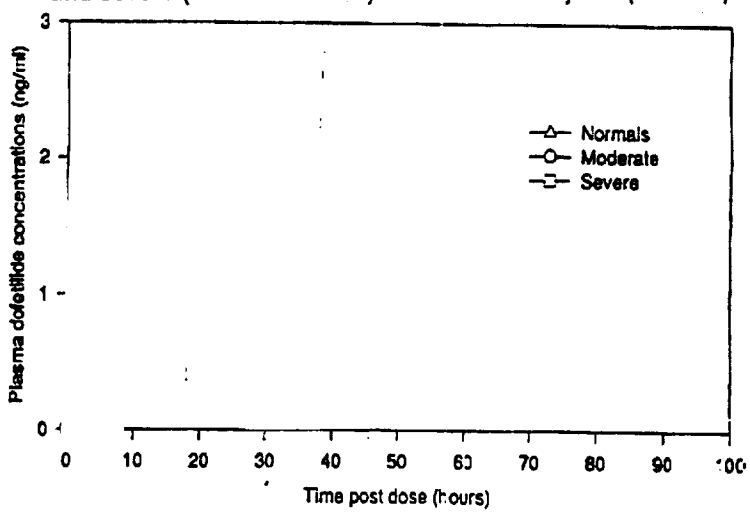
	normal (study 244)	moderate	severe
Cmax (ng/ml)	1.97±0.45	2.69±0.62	3.11±0.64
Tmax (hrs)	3.1±1.7	3.3±1.3	4.5 ±2.1
AUC (ng.h/ml)	23.5±3.6	69.5±15.4	116.7±24.2
T1/2 (hrs)	9.8	21.7	31.5

Tables 6.3.1 and 6.3.2 study reports

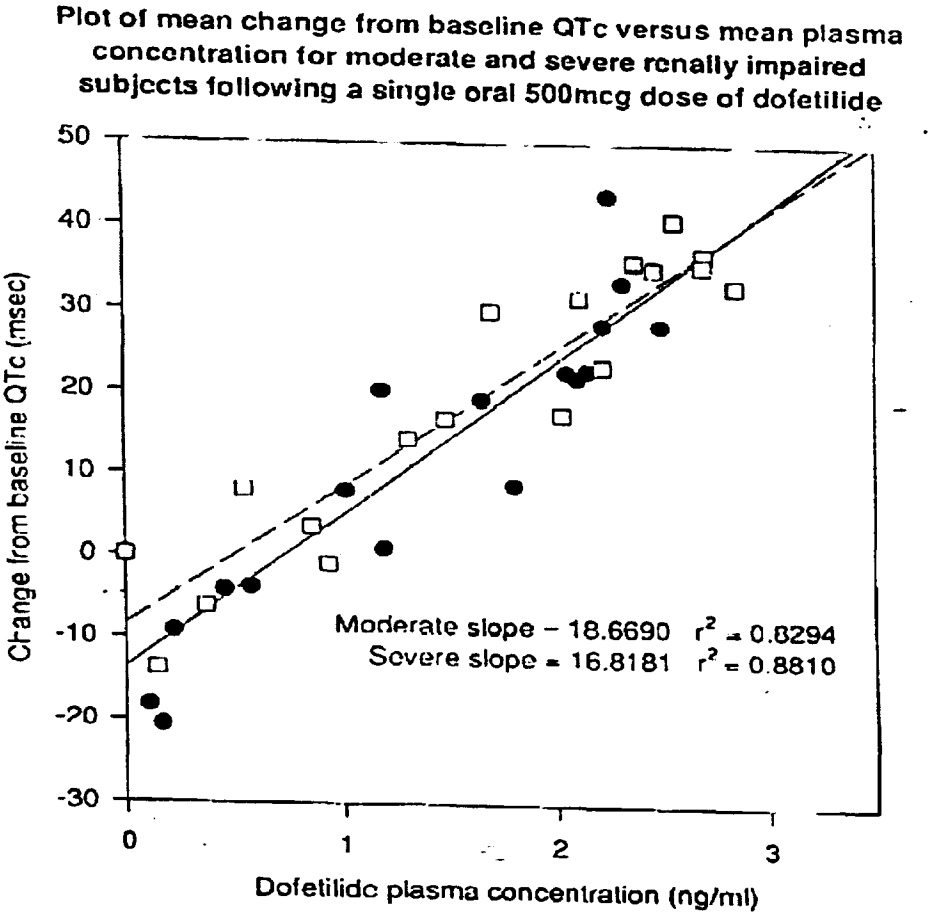
All parameters increase with worsening renal function. Plasma concentration profiles of dofetilide for normal subjects and moderate and severe renal failure patients are shown in the figure below.

Figure 3
DOFETILIDE PROTOCOL 219

Plasma concentrations of dofetilide after single, oral 500mcg dose of dofetilide in normal males (115-244), in moderate (CLcr 20-40ml/min) and severe (CLcr <20ml/min) renal failure subjects (115-219).



The correlation between plasma concentration and change from baseline for the QTc interval, by severity of renal impairment, is shown below.



The table below shows the mean QTc interval change from baseline for the patients with moderate and several renal impairment, at maximum and at 12 hours after the dose.

QTc intervals (+SD) msec

	normal n=6	moderate n=5	severe n=6
QTc max	50 (13)	57 (25)	52 (17)
QTc at 12 hours	7 (14)	19 (23)	32 (18)

Table 6.4 study report

While the maximum increases from baseline for the QTc are similar for the 3 groups, the QTc interval increases from baseline at 12 hours after drug intake are greater for the moderately and, especially, the severely impaired groups compared to the normals.

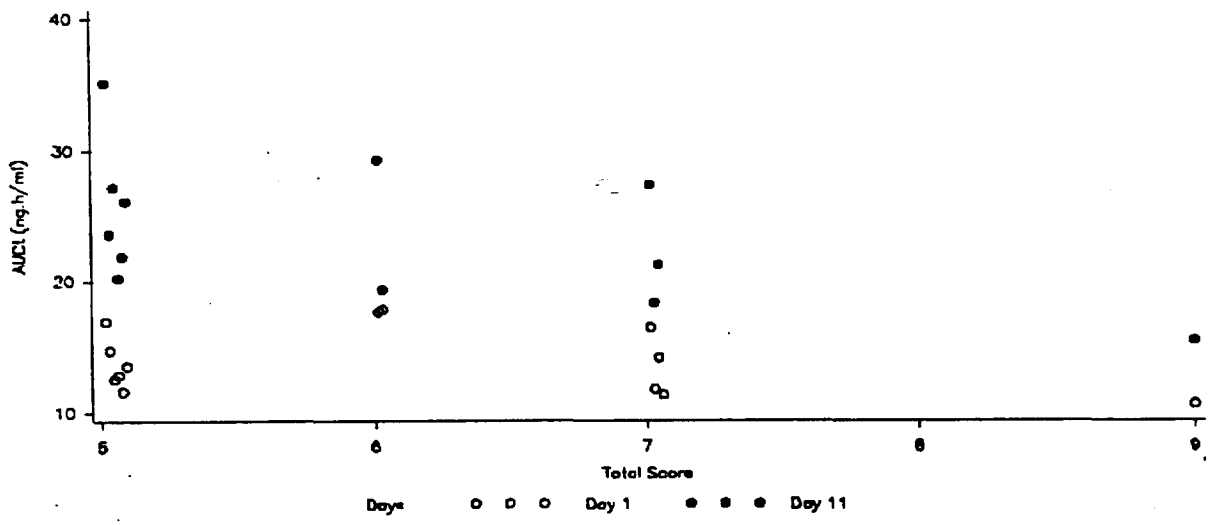
Reduced creatinine clearance results in higher dofetilide concentrations and extended QTc interval prolongation. The sponsor is recommending using Cockcroft's formula in determining the dose for patients with renal impairment.

8.5 Liver impairment

Protocol 0002 was an open, non-randomized, parallel group, single and multi-dose 500 mcg dose study in patients with liver impairment. Dofetilide was administered as a single dose on days 1 and 11, withheld days 2-4, and administered bid for days 5-10. PK/PD was collected on day 1 and day 11.

The figures below show the AUC and Cmax versus various degrees of liver impairment (higher score means more severe) after the 1st dose of dofetilide (day 1) and then at steady state (day 11).

FIGURE 5
DOFETILIDE PROTOCOL 002
AUCT VERSUS CHILD–PUGH CLASSIFICATION TOTAL SCORE

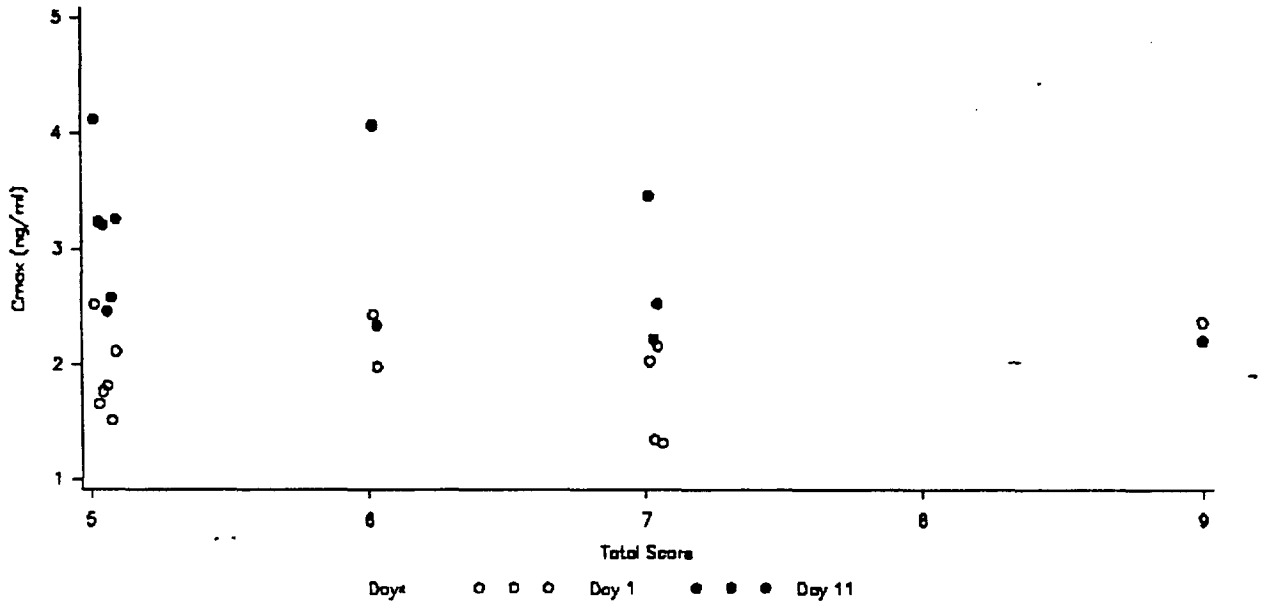


D: 27AUG97
T: 27AUG97(16:33)

Source: Table 6.1.1 and Appendix V Table 2.4

* Day relative to the start of study therapy (Day 1).
Includes only Hepatically Impaired Subjects.

FIGURE 4
DOFETILIDE PROTOCOL 002
CMAX VERSUS CHILD–PUGH CLASSIFICATION TOTAL SCORE



D: 27AUG97
T: 27AUG97(16:32)

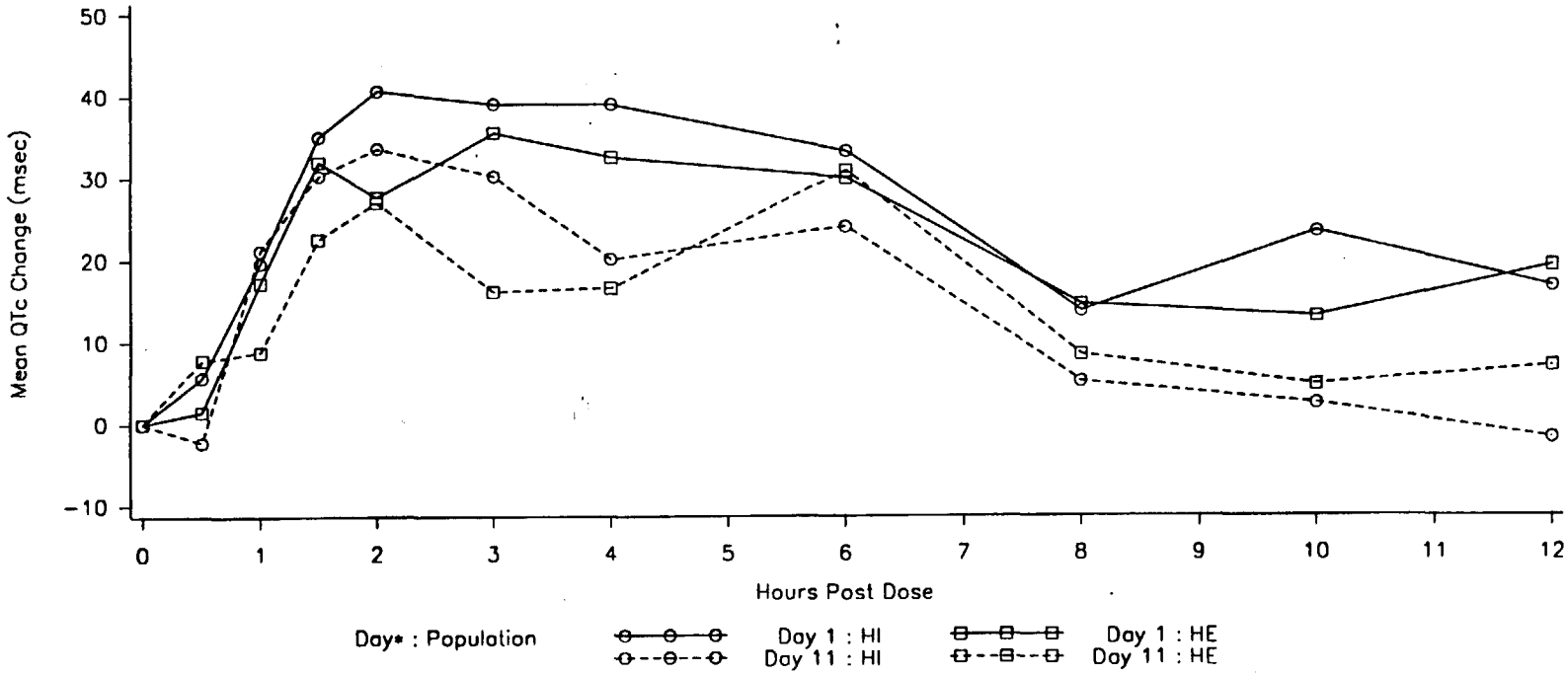
Source: Table 6.1.1 and Appendix V Table 2.4

* Day relative to the start of study therapy (Day 1).
Includes only Hepatically Imparied Subjects.

The AUC and Cmax were generally higher at steady state, implying drug accumulation, but are not higher in patients with liver impairment.

The changes in QTc interval from baseline with a single dose (day 1) compared to multiple dose (day 11) for all liver impaired subjects and healthy subjects are shown below.

FIGURE 3
DOFETILIDE PROTOCOL 002
MEAN LEAD II QTC CHANGES FROM PRE-DOSE ON DAYS 1 AND 11



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Source: Appendix IV Table 2.1

HI = Hepatically Impaired HE = Healthy
Pre-dose defined as the 0-hour redding on Day 1 or Day 11.
Days for subject 05650026 are relative to the first date the reduced dofetilide dose was given.
* Day relative to start of study therapy (Day 1).

The QTc interval was increased for both groups after single and multiple dosing but the increase was greater for the hepatically impaired subjects. Of the 17 hepatically impaired subjects, 10 (59%) had at least one (and usually numerous) episode of QTc interval > 500 msec compared to 2 (17%) of the healthy volunteers (1 episode each). The maximum increase in QTc for the impaired patients was 587 msec compared to 538 msec for the healthy.

The table below shows the mean QTC interval at baseline and changes from baseline at steady state (day 11: 12 and 24 hours after the last dose).

APPENDIX I TABLE 6.1
DOFETILIDE PROTOCOL 052
MEAN 12 LEAD QTC INTERVAL (BAZETTS) CHANGES FROM BASELINE

Page 1 of 1

QTc Interval (Bazetts) (msec)

		DAY*		
		1	11	12
		HOURS POST DOSE	HOURS POST DOSE	HOURS POST DOSE
		Baseline	0	24
POPULATION				
Medically Impaired	Mean	417.6	26.3	10.3
	SE	7.7	7.5	6.7
	N	13	12	9
Healthy	Mean	394.1	12.5	7.6
	SE	6.7	6.4	8.2
	N	11	10	11

By: DOSE(C)
To: DOSE(ST(20:25))

Source: Appendix IV Table 1.1

Baseline defined as the 0-hour pre-dose reading on Day 1.
* Day relative to start of study therapy (Day 1).
Days for subject [illegible] are relative to the first date the reduced dofetilide dose was given.

The mean increase in QTc at baseline after multiple dosing (day 11) in the hepatically impaired patients was twice the mean increase for healthy volunteers (26 msec and 13 msec, respectively). Patients with liver impairment have a larger dofetilide-induced prolongation of QTc interval compared to healthy volunteers. Dose adjustment for these patients should be considered.

8.6 Heart failure

Cardiac hemodynamics

The objective of study 127 was to evaluate the effects of dofetilide on left ventricular (LV) function, systemic hemodynamics and myocardial oxygen consumption in patients with congestive heart failure and depressed systolic function. The study was randomized, double-blind, parallel, placebo-controlled comparison of intravenous dofetilide and amiodarone conducted at a single site. There were 30 patients with mild to moderate NYHA Class II or III CHF and LVEF $\leq$ 35% who underwent left and right heart catheterization and were included in the efficacy evaluations: 12 received 8mcg/kg dofetilide, 6 received 5mg/kg amiodarone, and 12 received placebo infused over 30 minutes.

The table below shows the mean change from baseline ± S.E. for the various cardiovascular parameters. ('Landmark' is used to define parameters derived from the difference between the end diastolic and end systolic angiographic volumes while 'maximum' denotes parameters derived from the difference between the minimum and maximum LV angiographic volumes in the complete cardiac cycle).

	Dofetilide	Amiodarone	Dof. vs Amio. P-value	Placebo	Dof. vs Pbo P-value
Landmark CI (L/min/m^2)	0.07(±0.12)	-0.37(±0.28)	0.346	-0.10(±0.24)	0.390
Max CI (L/min/m^2)	-0.21(±0.20)	-0.45(±0.24)	0.922	-0.42(±0.28)	0.473
Heart rate (bpm)	-8.08(±1.66)	-7.33(±2.20)	0.463	-2.58(±1.90)	0.013
LV end diastolic volume index (ml/m^2)	3.95(±2.77)	6.36(±3.05)	0.611	-4.10(±3.02)	0.054
LV end systolic volume index (ml/m^2)	-1.37(±1.36)	7.93(±2.58)	0.028	-3.97(±2.87)	0.425
Landmark stroke vol (ml)	10.17(±3.99)	-2.67(±6.77)	0.151	-0.17(±5.49)	0.131
Landmark ejection fraction (%)	2.22(±0.79)	-1.20(±1.93)	0.175	-0.07(±1.43)	0.157
Landmark cardiac output (L/min)	0.14(±0.23)	-0.66(±0.48)	0.294	-0.19(±0.45)	0.394
QT dispersion	-2.82(±1.49)	5.50(±5.96)		1.38(±1.39)	
QTc single-lead	82.49(±12.22)	-2.95(±8.65)		-4.46(±7.98)	
Myocardial oxygen consumption (ml/min)	-1.64(±0.97)	-0.22(±0.62)		-1.02(±1.91)	

It's difficult to determine the value of this study. All the noteworthy safety events occurred in the dofetilide group: 1 patient had polymorphic VT, 1 patient had VT and 3 were discontinued for QT/QTc prolongation.

Proarrhythmia and low EF/structural heart disease

The following tables show the number and percent of patients reporting TdP and/or other

proarrhythmic events by ejection fraction and the presence or absence of structural heart disease. Patients were defined as having structural heart disease if they had a medical history of diseases predisposing for SHD including hypertension, valvular disease, etc. The number of patients with determinations of LVF was small (22.4%, 435/1941)

Number and (percent) of patients

proarrhythmic event	LVEF ≤ 35% n=160	LVEF >35% n=275
TdP	0	7 (2.5)
new sustained VT	3	1
new VF	1	0
sudden unexpected cardiac death	4	4

H.6.11.17.1 and .2

The table below shows the number of patients with proarrhythmic events grouped by whether they had structural heart disease or not.

Number and (percent) of patients

proarrhythmic event	Yes SHD n=937	No SHD n=887
TdP	17 (1.8)	7 (0.8)
new sustained VT	5 (0.5)	1 (0.1)
new VF	1 (0.1)	2 (0.2)
SUCD	8 (0.9)	7 (0.8)

H.6.11.18.1 and .2

Compared to patients without SHD, more patients with SHD reported TdP and this was borderline significant (p=0.051). The estimated risk of TdP for patients with SHD was 2.32 (95% CI 0.96, 5.63). The sudden unexpected cardiac death rates were similar for the 2 groups.

9.0 Drug interactions

Approximately 70-80% dofetilide is excreted unchanged in the urine and the rest is metabolized primarily by cytochrome P450 CYP3A4 (study report DM18). Circulating metabolites in plasma occur at very low concentrations relative to the parent; three of the metabolites display class III activity, but only at concentrations at least 20-fold higher than dofetilide.

The studies showing an interaction include drugs that are substrates and/or inhibitors of 3A4: verapamil, cimetidine, and oral contraceptives (ethinylestradiol). It is unclear how many other drugs that are metabolized by 3A4 will interfere with the metabolism and increase the concentration of dofetilide. This is of great concern because dofetilide has a very narrow therapeutic window.

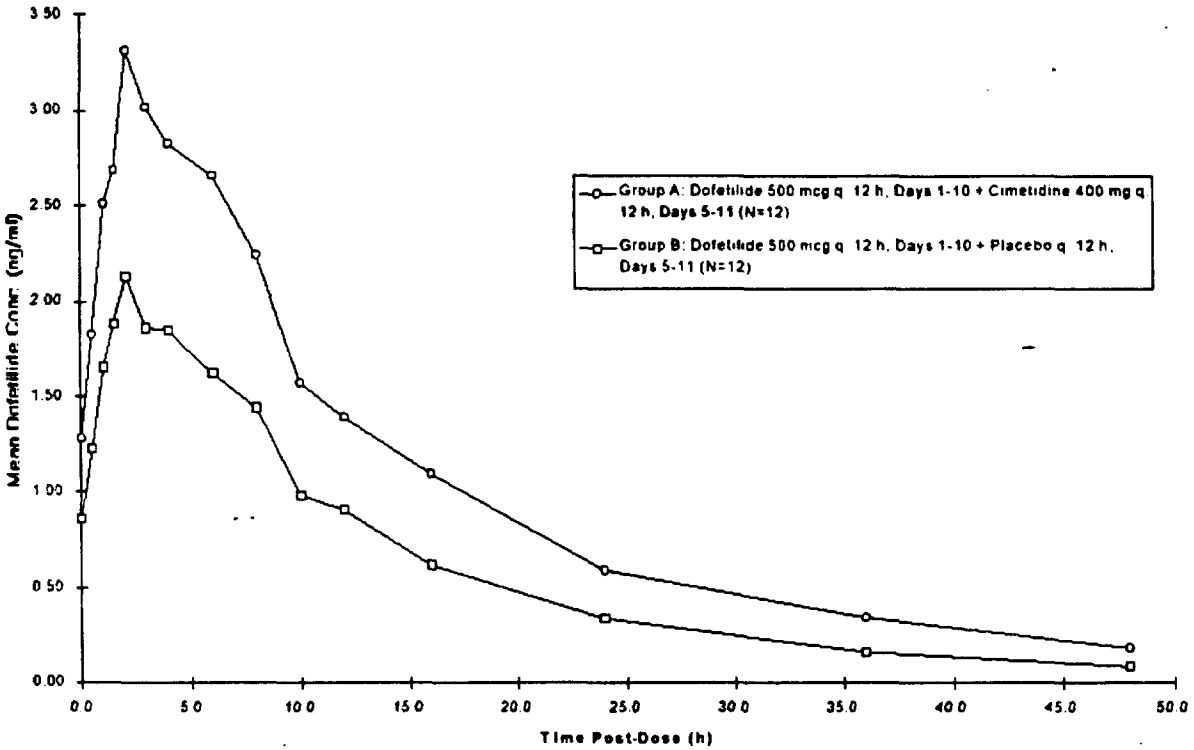
Although there was no placebo group for comparison, there were greater decreases in heart rate and blood pressure when dofetilide was given concomitantly with propranolol compared to propranolol alone which could pose a hazard for an older, sicker population.

9.1 Cimetidine (protocol 004)

This was a single-blind, placebo-controlled, multi-dose, parallel group study of the pharmacokinetic and pharmacodynamic interaction between cimetidine (400 mg bid) and dofetilide (500 mcg bid). All subjects received dofetilide Days 1 to 9. On Day 5, the 24 subjects were randomly assigned to receive either cimetidine or placebo for 7 days. Blood samples and Lead II ECG rhythm strips were obtained simultaneously at various times throughout days 4 and 10.

The figure below shows the dofetilide concentration when dofetilide is used concomitantly with cimetidine (group A) and when dofetilide is used concomitantly with placebo (group B).

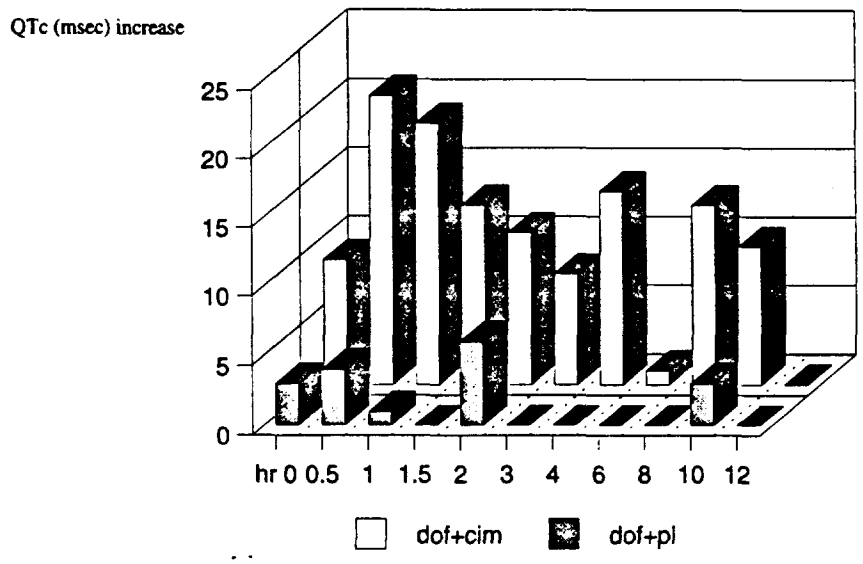
Figure 2. **Mean Dofetilide Plasma Concentrations on Day 10 Following Multiple Oral Doses of Dofetilide (500 mcg q. 12 h) With Either Cimetidine (400 mg q. 12 h) or Placebo (q. 12 h) to Healthy Male Subjects**



Both AUC and Cmax of dofetilide are substantially increased when the drug is coadministered with cimetidine.

The figure below shows the mean <u>additional</u> increase in QTc interval at day 10.

QTc interval (msec) Mean change from Day 4 at Day 10



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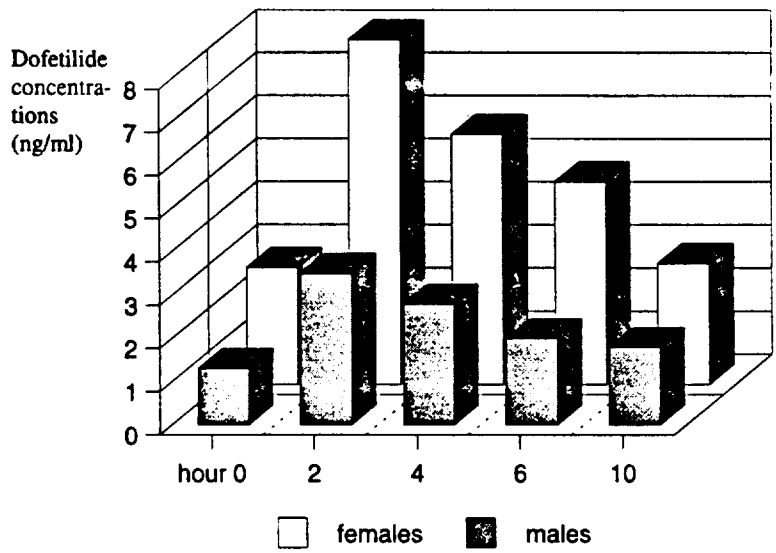
There were additional increases (up to 20 msec) in the QTc interval in the combination group compared to dofetilide alone. Cimetidine and dofetilide should not be co-administered.

9.2 Oral contraceptive (Protocol 236)

The objective of this double-blind, placebo-controlled, crossover study was to investigate the effect of dofetilide 750mcg bid for 6 days on the plasma concentrations of a combined oral contraceptive (60mcg ethinylestradiol, an inhibitor of p 450 3A4, and 300mcg levonorgestrel). Eighteen healthy female subjects were randomized in equal numbers to either dofetilide or placebo for 6 days with the first dose taken between days 1 and 3 of the start of menstruation. On Day 4, all received a single dose of oral contraceptive 2 hours after the morning dose of dofetilide or placebo. Blood samples were taken at intervals following the morning dose of dofetilide on Day 4 for assay of plasma dofetilide and at intervals following the morning dose of oral contraceptive on Day 4 for assay of plasma ethinylestradiol and levonorgestrel. The results of the study showed no effects on plasma ethinylestradiol and levonorgestrel. Concentrations of dofetilide other than during day 4 were not obtained.

The figure below shows the mean dofetilide concentration profile in females when one dose of OC was administered with steady state dofetilide (day 4) as well as the profile in males with steady state dofetilide 750 mg alone (from study protocol 242, table 1 of appendix III) for comparison.

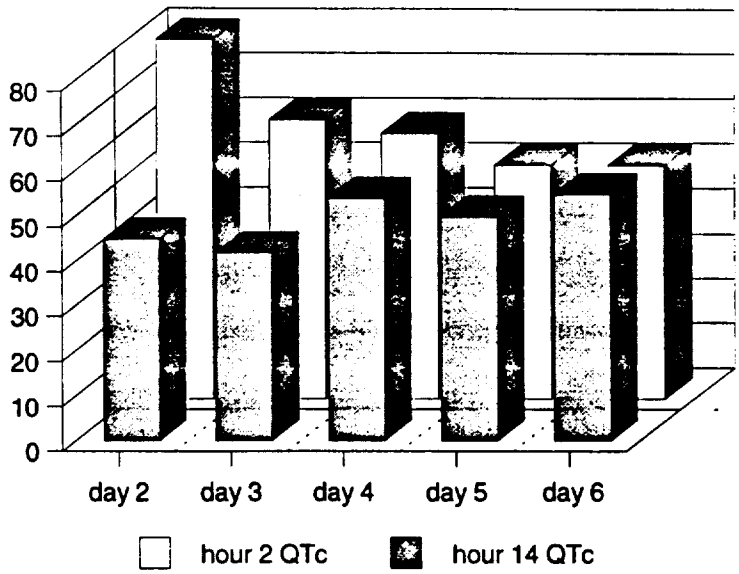


Note: the last value obtained for males was at 8 hours. The information from males is from study 242.

The dofetilide concentrations in the females were much higher than what occurred in males; mean Cmax was 8 ng/ml in females, compared to 3.7 ng/ml in males.

In the interaction study, 3 female subjects discontinued the study as a result of: QTc > 550 msec (actual values were as high as 622 msec), a 4-beat non-sustained VT, and a second degree heart block on holter monitor.

ECGs in the study were measured each day 2 and 14 hours after the dose of dofetilide. The results of the QTc intervals mean change from baseline for dofetilide and placebo groups are shown below (appendix table 6.2 study report).



The largest mean change was 80 msec on day 2 hour 2. While there was a small decline over time, the mean QTc increases remained at or above 40 msec.

The dofetilide levels in this study were higher than what is expected with the 750 mcg dose and it is disturbing that the OC was administered 2 hours after the dose of dofetilide. Clearly, the results of this study should provoke further trials to determine if blood levels of dofetilide alone are higher in females than in males; the interaction trial with ketaconazole will be important to determine if inhibitors/substrates of CYP 3A4 inhibit the metabolism of dofetilide. From the results of this trial, the concomitant use of oral contraceptives and dofetilide should be contraindicated.

9.3 Verapamil (protocol 001)

This was a non-randomized, single-blind, fixed-sequence, placebo-controlled study to compare the pharmacokinetics and pharmacodynamics of verapamil (80 mg tid) and dofetilide (500 mcg bid) administered individually and concomitantly. Study drugs were administered according to the following fixed sequence: Days 1-3: verapamil, Days 4-6: placebo, Days 7-11: dofetilide, Days 12-14: dofetilide and verapamil.

Results: there was no effect on verapamil or norverapamil levels. Dofetilide PK parameters at day 11 (dofetilide alone at steady state) and day 14 (dofetilide and verapamil steady state) are shown below.

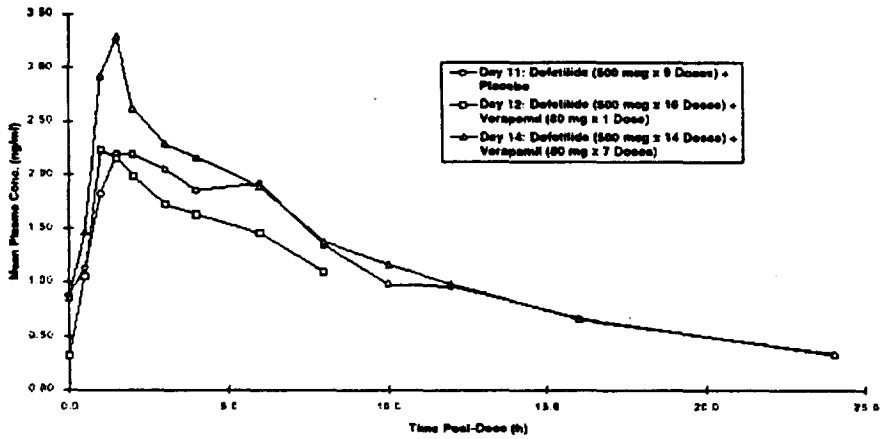
Dofetilide: Means±SD

AUC (0-4)		AUC (0-12)		Cmax		Tmax	
day 11	day 14	day 11	day 14	day 11	day 14	day 11	day 14
7.4±1.0	9.2±1.4	18.4±3.4	21.0±3.6	2.4±0.4	3.43±0.7	2.2±1.4	1.5±0.5

Table 6.1.1 study report

The concomitant use of verapamil increases dofetilide AUC (0-4) and AUC (0-12) by 24% and 14%, respectively, increases Cmax by 43% and decreases Tmax by 32%. The following figure shows dofetilide concentrations at the different time points.

Figure 1. Dofetilide Mean Plasma Concentrations Following Multiple Oral Doses (500 mcg q. 12 h) in the Absence and *Presence of Single and Multiple Oral Doses of Verapamil (80 mg q. 8 h)* to Healthy Male Subjects (Clinical Study #115-001-561, Dr. J. Venitz, Richmond, VA)



Source Data: Appendix IIIB Table 1

The concomitant use of verapamil increases the plasma concentrations of dofetilide, particularly at Cmax. The mean QTc intervals for steady state verapamil alone, dofetilide alone and the combination for hours 0-4 hours are shown below.

Means± SE

	hour 0	hour 0.5	hour 1	hour 1.5	hour 2	hour 3	hour 4
ver alone	379±5.4	376±4.0	384±4.6	388±5.4	387±6.0	381±4.2	379±6.1
placebo	377±5.9	374±5.4	369±4.6	372±4.8	362±5.7	378±4.8	366±5.3
dof alone	395±8.0	382±6.1	400±4.6	412±5.4	413±6.2	415±6.8	410±6.3
dof + ver	403±4.7	390±5.1	414±4.5	429±7.0	416±3.8	410±7.2	400±6.0

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At hour 1.5, dofetilide plus verapamil had a 17 msec increase in the mean QTc interval compared to dofetilide alone. In conclusion, the combination dofetilide and verapamil increases the Cmax of dofetilide and further prolongs the QTc interval compared to dofetilide alone.

9.4 Propranolol (protocol 215)

In this study, healthy male volunteers received 40 mg propranolol bid for days 1 through 8, inclusive, and dofetilide 250mcg bid or placebo on days 5 to 8, one hour before each propranolol dose. (The propranolol doses are lower than the usual maintenance dosage: usual maintenance 120 mg to 240 mg per day and up to 640 mg a day). Pharmacokinetics for propranolol were obtained on days 4 (steady state propranolol) and 8 (steady state propranolol and dofetilide); trough levels for dofetilide were obtained at trough on days 5 and 8. Subjects underwent an exercise test at baseline and 3 hours after the morning dose of propranolol on days 4 and 8. Maximal exercise heart rate was to be measured within 5 seconds after the completion of the exercise.

There were only small differences in exercise heart rate in the combination group compared to propranolol alone. However, routine standing and supine blood pressure and heart rate decreases from baseline on day 8 at hours 1, 2 and 4 after dosing, shown below, were always larger for the combination compared to propranolol alone.

Change from baseline Day 8

	propranolol +dofetilide			propranolol alone		
time (hr) post dose	1	2	4	1	2	4
standing SBP/DBP mmHg	-16/-6	-18/-12	-20/-8	-9/-4	-14/-5	-8/0
supine SBP/DBP mmHg	-13/-7	-13/-11	-13/-7	-6/-2	-3/-2	-9/-3
heart rate bpm	-8	-11	-4	-3	-3	3

Table 6.5 and appendix I table 6

Although there was no placebo group, the potential for excessive decreased BP and heart rate could pose a problem for an older, sicker population. The additional problem of both drugs being tested at low doses would necessitate a recommendation to decrease the dose of a beta blocker if used with dofetilide.

9.5 Digoxin (protocol 214)

This double-blind, placebo-controlled, randomized parallel group study was designed to investigate the effects of oral dofetilide 250mcg bid for 5 days with steady-state digoxin (titrated to 250 mcg) in healthy male volunteers. Subjects received digoxin for 7 days followed by digoxin plus dofetilide or placebo for 5 additional days.

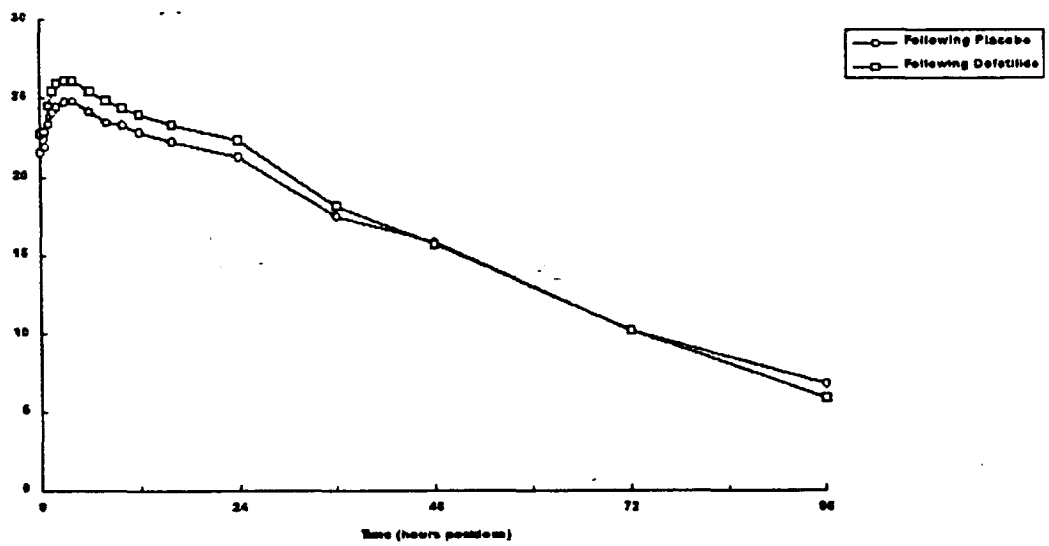
There were only minor differences in the PK of digoxin in the combination group. Dofetilide levels, determined only at trough, are shown below.

Mean dofetilide levels increased from 0.36 ng/ml day 8 (first day of dosing with the combination) and to 0.46 ng/ml which may reflect the accumulation usually seen with dofetilide. It is not possible to determine if dofetilide concentration is altered with the concomitant use of digoxin from this study.

9.6 Phenytoin (protocol 006)

This was a single blind, placebo-controlled, parallel-group study of the pharmacokinetic and pharmacodynamic interaction, under steady-state conditions, between phenytoin once daily and dofetilide bid after multiple doses. All subjects received phenytoin sodium, 300mg (equivalent to 274.8mg phenytoin) from Day 1 through Day 15. Depending upon plasma concentrations of phenytoin, subjects were either randomized or remained on phenytoin for another 15 days. The randomized treatment groups were phenytoin sodium with or without dofetilide 500 mcg and treatment was for 15 days. Plasma concentration profiles of phenytoin with and with dofetilide are shown below. Dofetilide concentrations were obtained only at trough on days 27-30.

Figure 2. Mean Phenytoin Plasma Concentrations Following Multiple Daily Oral Doses and Either Dofetilide or Placebo Twice Daily for 16 Days in Healthy, Male Volunteers (Clinical Study #116-006-5001, Dr. Scavone, MTRA, Boston, MA)



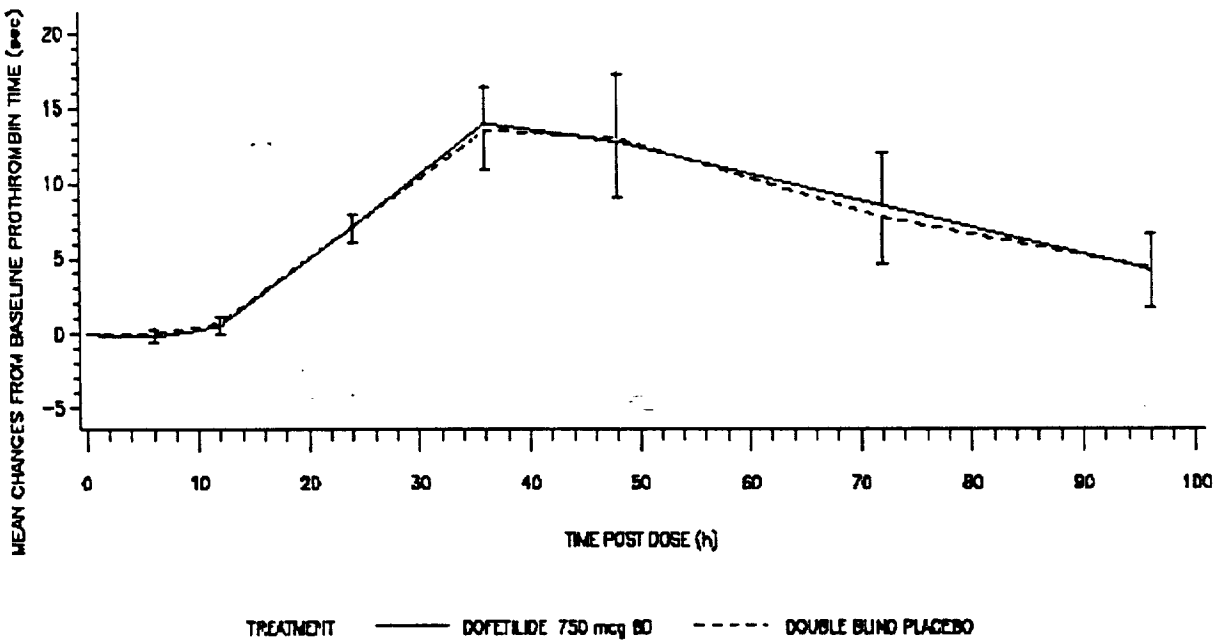
The plasma concentrations of phenytoin with and without dofetilide were similar, as were the dofetilide concentrations obtained at trough. While, it is unknown if the Cmax of dofetilide was altered by its use with phenytoin, no subject experienced an arrhythmia while on dofetilide and only one subject had a QTc value greater than 500msec (534msec), indicating that dofetilide levels were not excessive.

9.7 Warfarin

This was a double-blind, randomised, two period cross-over study with a total of 14 healthy male subjects. Dofetilide 750mcg bid or placebo bid was administered for 7 days with a single dose of warfarin 40 mg given 2 hours after the morning dose of dofetilide on day 5 of each study period. There was a minimum of a week washout between study periods. Prothrombin times were measured pre-dose on Days 1, 3, 4 and 5 and at intervals up to 96 hours after dosing with warfarin. An additional measurement was also made 2 hours post-dose on Day 4.

The figure below shows the change from baseline on day 5 for the prothrombin time for the 2 treatment groups.

FIGURE 1
DOFETILIDE PROTOCOL 242
PROTHROMBIN TIME, MEAN CHANGES FROM BASELINE ON DAY 5



Dofetilide does not affect the pharmacodynamics of a single dose of warfarin.

10.0 Clinical pharmacology

Number of patients

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

Study Discontinuations

The number and percent of subjects who discontinued from a Phase I trial are shown below.

Number and (percent) of patients

	placebo controlled trials		active/uncontrolled trials	
	dofetilide n=304	placebo n=258	dofetilide n=503	active control n=38
discontinued for any reason	29 (9.5)	14 (5.4)	49 (9.7)	0
adverse events	7 (2.3)	6 (2.3)	12 (2.4)	0
lab abnormality	1 (0.3)	2 (0.8)	1 (0.2)	0
special safety test	11 (3.6)	4 (1.6)	8 (1.6)	0
withdrew consent	4 (1.3)	1 (0.4)	3 (0.6)	0

H.6.1.1

Dofetilide patients in the placebo controlled trials were more likely to drop out for special safety test (prolonged QT/QTc) than for any other safety reason.

Reported arrhythmic events

Incidence rates for selected arrhythmic events are shown below.

Number and (percent) of patients

	placebo controlled trials		active/uncontrolled trials	
	dofetilide n=304	placebo n=258	dofetilide n=503	active control n=38
TdP	0	0	1 (0.2)	0
VF	1 (0.3)	0	0	0
VT	1 (0.3)	0	5 (1.0)	0

H.6.10.1, H.6.11.1.1

These arrhythmic events were reported only in the dofetilide groups.

Laboratory abnormalities

Reports of selected sponsor defined clinically significant test abnormalities from the placebo controlled phase I trials only are shown below.

Number and (percent) of patients

		dofetilide N=299		placebo N=254	
parameter	criteria	n tested	n and (%) abnormal	n tested	n and (%) abnormal
Hematology					
hematocrit (F) %	>20%dec	35	0	29	0
hematocrit (M) %	>20%dec	234	1 (0.4)	198	1 (0.5)
hemoglobin (F) g/dl	>20%dec	35	0	29	0
hemoglobin (M) g/dl	>20%dec	235	3 (1.3)	199	1 (0.5)
platelets $10^3/mm^3$	<75	294	0	238	1 (0.4)
WBC $10^3/mm^3$	<2.5	296	1 (0.3)	241	0
Liver function					
SGPT IU/L	>3xULN	286	2 (0.7)	232	1 (0.4)
SGOT IU/l	>3xULN	275	1 (0.4)	223	0
alk phos IU/L	>3xULN	268	0	220	0
LDH IU/L	>3xULN	105	0	86	0
total bilirubin mg/dl	>1.5xULN	297	4 (1.3)	238	3 (1.3)
Kidney function					
BUN mg/dl	>1.3xULN	70	3 (4.3)	44	0
creatinine mg/dl	>1.3xULN	298	3 (1.0)	238	0
urea mg/dl	>1.3xULN	228	0	194	1 (0.5)

H.6.12.1

There is no signal from these data that dofetilide adversely affects any laboratory parameters.

Conclusions: safety data in the Phase I studies are not different from safety data in Phase II/III studies.

11.0 Japanese studies (serious safety and deaths)

As of May 14, 1997, 610 subjects had been enrolled in 18 dofetilide studies conducted in Japan. Of these, 3 patients discontinued because of TdP (1 with oral and 2 with intravenous formulations). There were 42 patients who discontinued for safety-related reasons and there were 15 serious adverse events (8 were VF, VT, and/or TdP), including 2 deaths. The events are similar to those reported in the pooled, non Japanese studies.

TdP

68 year old female received oral dofetilide for the treatment of paroxysmal AF. Study drug was titrated from 250 mcg/day up to 500 mcg/day for a total of 13 days. Baseline QTc was 430 msec which increased by 12% after start of treatment. Dose was increased despite a 42% increase in QTc over baseline. The subject experienced TdP which was terminated by DC cardioversion. Medical history included prior MI and congestive heart failure. Concomitant medications included digoxin, denopamine and furosemide.

Discontinuations

-8 patients discontinued in early oral Phase II studies: 1 syncope, 1 VF/VT, 2 dizziness, 1 TdP, 1 suspected VT, 1 acute pancreatitis. Total daily doses ranged from 500 to 1000 mcg, days on drug ranged from 1 to 6.
-11 subjects discontinued in late oral Phase II studies: 4 prolonged QT/QTc, 1 VT, 2 epigastric complaints, 2 respiratory distress, 1 rash, 1 induction of AF and aggravation of heart failure. Total daily doses ranged from 250 to 750 mcg, days on drug ranged from 1 to 10.
-17 patients discontinued in ongoing oral Phase II/III studies: 9 prolonged QT/QTc, 1 sinus arrest, 1 VF, 1 VT, 1 relapse of AF, 1 junctional rhythm, 1 VPC, 1 gastric carcinoma, 1 pruritus. Total daily doses ranged from 375 to 500 mcg, days on drug ranged from 1 to 138. The blind was not broken for all cases.
-4 subjects discontinued in oral and intravenous Phase I studies: all prolonged QT/QTc.

Deaths

76 year old female received oral dofetilide 375 mcg/day for the treatment of ventricular premature contractions and VT. Approximately 139 days after the start of treatment the patient lost consciousness and was found to be in ventricular fibrillation. CPR was ineffective and the patient died that day. Concomitant medications were metildigoxin, furosemide, spironolactone, amlodipine, ticlopidine, benidipine, etizolam, magnesium oxide, isosorbide dinitrate, clotiazepam, teprenone, rilmazafone hydrochloride and phenovalin. Medical history included cerebral infarction, previous myocardial infarction, atrial fibrillation, angina and hypertension.

74 year old male received oral dofetilide 250 mcg/day for the treatment of paroxysmal AF. Approximately 127 days after the start of treatment, he was hospitalized for pneumonia and heart failure and was treated with mexiletine and digoxin for premature ventricular contractions and atrial fibrillation. The patient suffered a cerebral infarction and died. Cause of death was pneumonia and heart failure.

12.0 Short term use

This section examines the serious safety of oral dofetilide when used to convert patients from AF/AFl to normal sinus rhythm. The studies required patients to be hospitalized and on a cardiac monitor for the first 3 days (or 5 doses) of dosing. The terminal half life of dofetilide is approximately 10 hours.

There was one death during the first 3 days of treatment with dofetilide: patient #115-365-327-0273, a 71 year old white female with pAF/AFl, received one dose of 500 mcg, developed vomiting and hemiplegia, and then became comatose and died of a stroke. She had a history of ischemic heart disease and CHF.

Patients who were discontinued during the conversion phase (study days 1-3) for adverse events in protocols 120 and 345 are shown in the table below.

Number and (percent)

	dofetilide dose			placebo
	125 mcg	250 mcg	500 mcg	
protocol 120	3/82 (3.7)	2 /82 (2.4)	4/77 (5.2)	3/84 (3.6)
reasons for discontinuation	all VT	av block, VT/VF	bradycardia, VT/av block, VT/VF, VT	bradycardia, av block, VT
protocol 345	2/135 (1.5)	2/133 (1.5)	4/129 (3.1)	1/137 (0.7)
reasons for discontinuation	headache, bronchitis	angioedema, av block	VT, VT/VF, dizziness/arrhythmia, VT	nausea

Appendix IA table 1 study reports

The dofetilide discontinuations are discussed below.

Protocol 120
dofetilide 125mcg, 3 patients discontinued for VT with onset on days 1 (about 8 hours after first dose), 2 (17 beat run of VT with chest pain and hypotension) and 3;

dofetilide 250mcg group, 2 patients discontinued for 1) TdP which degenerated into VF with onset on day 2 (this patient had been downtitrated to 125 mcg because of QT prolongation) and 2) heart block with onset on day 3;

dofetilide 500mcg group, 4 patients discontinued for 1) bradycardia with onset on day 2; 2) VT and AV block with onset on day 3; and 3) TdP degenerating into VF with onset on day 3; and 4) VT on day 3.

Study 345
dofetilide 125mcg bid, 2 patients discontinued for 1) severe headache on day 1, and 2) fever and bronchitis on day 2

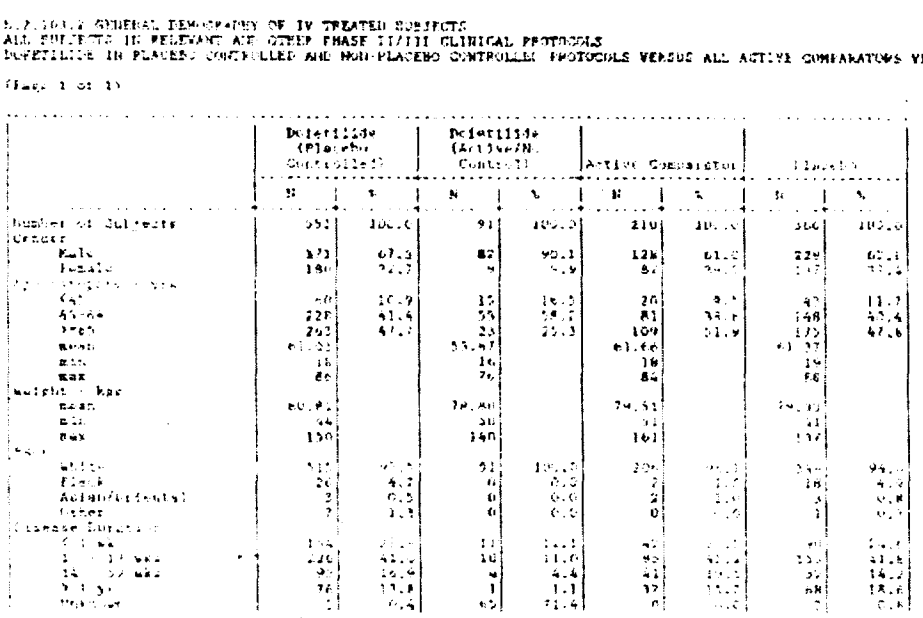
dofetilide 250mcg bid, 2 patients discontinued for 1) angioedema on day 2, and 2) second degree AV block on day 2.

dofetilide 500mcg bid, 4 patients discontinued for 1) dizziness with prolonged QTc interval and arrhythmia on day 1, 2) TdP on day 3, 3) TdP/VF on day 3, and 4)TdP on day 3.

Roughly 2.4% of patients who receive dofetilide for conversion only (3 days of treatment) will discontinue for adverse events (primarily VT with some degenerating into VF).

13.0 Intravenous use

There were 643 patients who received iv dofetilide. The demographics for these patients and the control groups are shown below.



Most patients were male and white. The mean age was around 61 years and the majority of patients had their disease for 13 weeks or less.

Proarrhythmia

The percents of patients in the clinical trials who discontinued study drug because of a proarrhythmia are shown below.

Percent of patients

	Placebo controlled trials		active/uncontrolled trials	
Event	dofetilide n=551	placebo n=366	dofetilide n=91	active control n=210
heart arrest	0.2	0	0	0
QT prolongation	1.3	0.3	0	0
ventricular arrhythmia	0.2	0	0	0
VF	0.4	0	0	0
VT	2.5	0	1.1	0

H.6.106.2a

The incidence rates for the discontinuations are higher in the dofetilide than the control groups. The placebo subtracted rate of VT for dofetilide in the placebo controlled trials is 2.5%

The reporting rates for all reported proarrhythmias including sudden unexpected cardiac death are shown below.

Percent of patients

	Placebo controlled trials		active/uncontrolled trials	
Event	dofetilide n=551	placebo n=366	dofetilide n=91	active control n=210
TdP	3.6	0	1.1	0
QT prolongation	1.5	0.3	0	0.5
ventricular arrhythmia	2.0	0.5	0	0.5
VF	0.5	0	1.1	0
VT	6.5	0.5	5.5	0
SUCD	0.2	0	1.1	0

H.6.104.2a, H.6.111.2.1 and H.6.111.2.2

The rates for these events are much higher for the patients who received dofetilide. The placebo subtracted rate for VT is 6%.

Serious adverse events other than proarrhythmias not necessarily leading to discontinuation reported in 2 or more dofetilide patients included heart failure (4), pneumonia (3), myocardial infarction (2), and pulmonary embolism (2). H.6.108.1.3

Gender

The differences in reporting rates of proarrhythmias for males and females in the placebo controlled trials are shown below. The patient numbers could be slightly underestimated because they are counted up to May 14, 1997 and the number of events are counted up to September 15, 1997.

Number and (percent) of patients

	males		females	
Event	dofetilide n=371	placebo n=229	dofetilide n=180	placebo n=137
QT prolongation	1 (0.3)	0	1 (0.6)	0
ventricular arrhythmia	1 (0.3)	0	3 (1.7)	0
VF	2 (0.5)	0	3 (1.7)	1 (0.7)
VT	11 (3.0)	1 (0.4)	17 (9.4)	0
death	6 (1.6)	0	1 (0.6)	1 (0.7)

H.2.103.2, H.6.108.1.3

Females who received intravenous dofetilide were more likely to experience VT, VF, or ventricular arrhythmias or have QT prolongation compared to their male counterparts. The death rate, however, was higher in males.

14.0 Safety Update

The Division agreed that the sponsor would include in the Safety update only serious adverse events (defined as those that were fatal, life threatening, resulted in permanent disability; required inpatient hospitalization or prolongation of hospital stay; or involved congenital anomaly, cancer or drug overdose, or any other adverse experience considered by the investigator to be serious) reported to the sponsor between September 16, 1997 (cut off for NDA was September 15, 1997) and January 5, 1998.

There were 9 protocols conducted during the 4 month interval:115-108B, 115-113B, 115-119A, 115-120A, 115-128A, 115-397, 115-398, 115-399, 115-400B. Protocols 115-108B, 115-397, 115-398, and 115-399 were compassionate use programs. The remaining were study extensions, all but 1 (115-397) requiring previous dofetilide study enrollment.

While there is some imprecision about the numbers of patients, there were apparently 243 subjects enrolled as of September 16, 1997 and of these, 23 (9.5%) were discontinued as of January 5, 1998. Of the 243 patients, 216 received dofetilide and 27 received placebo (protocol 115-128A). The estimated enrollment in dofetilide clinical studies in Japan during this time frame is 14.

Deaths

There were 3 deaths (1.2%) that occurred during or within 30 days of therapy. One additional patient (115-345-122-0869) died of colon cancer more than 30 days off treatment.

Patient number	age/race/ sex	total daily (dose mcg) /duration (d)	comedications	comments
115 119A-627-0356 pAF	82/w/male	250/648	lisinopril, furosemide, atenolol, aspirin, colchicine, allopurinol, and digoxin.	sudden death, unwittnessed. Medical history of CHF, mitral insufficiency, hypertension, hyperlipidemia, gout, chest pain, MI, CABG, and PUD.
115-113B-516-0040 VT	70/w/male	500/1180	digoxin,captopril,isosorbi dedinitrate, lorazepam, prochlorperazine, acetaminophen/ hydrocodone, acetaminophen/ oxycodone.	Died off drug 2 days. Diagnosed with lung cancer 7 months earlier. History of ICD, COPD hypertension, and aortic aneurysm and MI.

115-113B-528-0271	72/w/male	1000/1140	dipyridamole,aluminum salts/aspirin/magnesium salts, captopril, digoxin, pentoxifylline, ranitidine, lovastatin, nitroglycerin, nicotinic acid, nifedipine, alginic ac/aluminum hydroxide/sodium bicarbonate/magnesium, lorazepam, furosemide, fexofenadine, and acetaminophen/hydrocodone.	Died about 7 days after being diagnosed with lung cancer and superior vena cava syndrome. Medical history included ICD, COPD, pAF, PVD, hyperlipidemia, MI, cardiac arrest, CABG and chronic pancreatitis.

There were 2 reports of proarrhythmia that met the sponsor's definition: patient 115-119A-627-0356 had sudden death (discussed above) and patient 115-398-288-0002, a 70 year old white male who had VF after 2 years of dofetilide (total daily dose 1000 mcg reduced to 500 mcg) for the treatment of sustained VT. Resuscitation attempts were successful and study treatment was permanently discontinued. QTc values are not available. Medical history included ischemic heart disease, MI, angina, hypertension, valvular heart disease and hypertrophic prostate.

One patient (71 year old white male) was permanently discontinued from long term treatment with 500 mcg dofetilide because of worsening creatinine clearance.

In addition, 4 dofetilide patients reported VT compared to 0 placebo patients. None of the patients was discontinued because of this event.

This additional safety information is similar to what was reported for the Integrated Safety Summary.