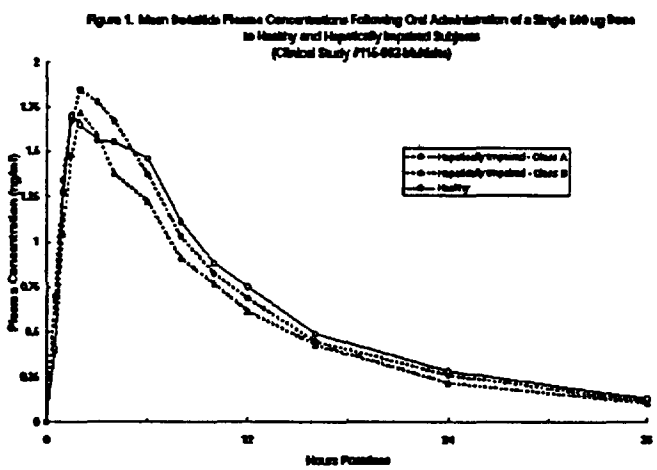
Table 3. Pharmacokinetic Parameters (Mean±SD) of Dofetilide Following Oral Administration of Single and Multiple Twice Daily 500 μg Doses to Hepatically Impaired (HI) and Healthy (HE) Subjects

Parameter	HI- Class A		HI-Class B		HI-ALL		HE	
	Day 1	Day 11	Day 1	Day 11	Day 1	Day 11	Day 1	Day 11
Cmax (ng/ml)	2.0±0.3	3.2±0.7	1.7±0.4	2.6±0.5	1.9±0.4	2.9±0.7	1.9±0.5	2.7±2.1
AUCτ (ng.h/ml)	15±2.3	25.3±5.3	12.1±2.1	20.5±4.4	13.8±2.5	23.2±5.3	14.1±3.3	20.2±15.2
AUC0-∞ (ng.h/ml)	23.8±4.1	-	20.4±4.8	-	22.1±4.7	-	23.6±6.1	-
T1/2 (h)	8.6±1.3	9.3±1.9	9.0±2.7	10.6±2.0	8.80±2.0	9.9±1.9	9.2±1.6	11.6±2.6
Tmax (h)	2.8±1.7	1.8±1.1	3.3±1.6	1.9±0.7	3.0±1.6	1.8±0.9	2.3±1.3	2.1±1.7
CLr (ml/min)	218±57	248±92	270±98	124±72	235±73	207±102	226±99	2190±55
AR	-	1.7±0.4	-	1.7±0.2	-	1.6±0.2	-	1.7±0.5

AR = Accumulation ratio (AUCτ on Day 11/ AUCτ on Day 1)



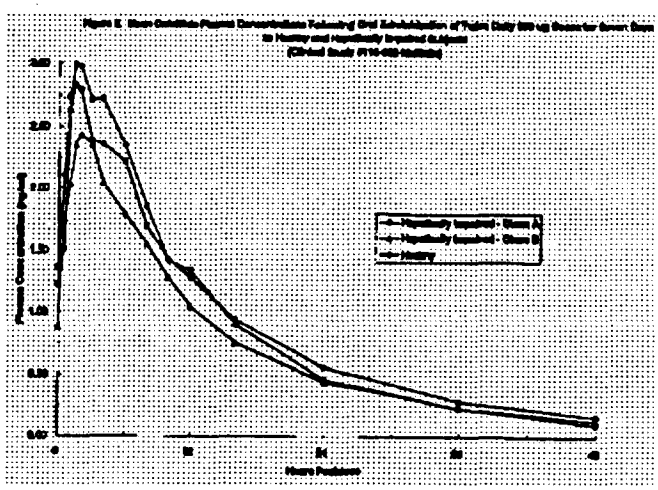


FIGURE 3
DOFETILIDE PROTOCOL 002
MEAN LEAD II QTC CHANGES FROM PRE-DOSE ON DAYS 1 AND 11

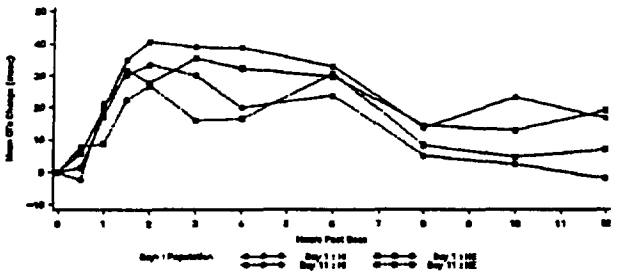


FIGURE 4
DOFETILIDE PROTOCOL 002
CMAX VERSUS CHILD-PUGH CLASSIFICATION TOTAL SCORE

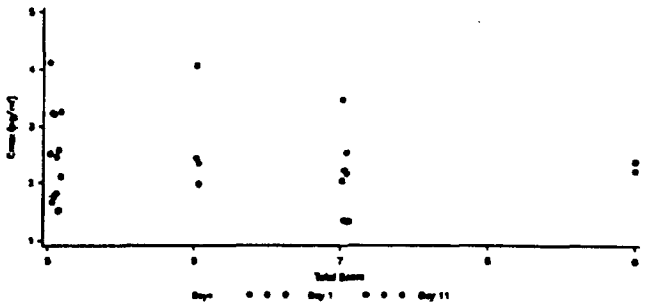
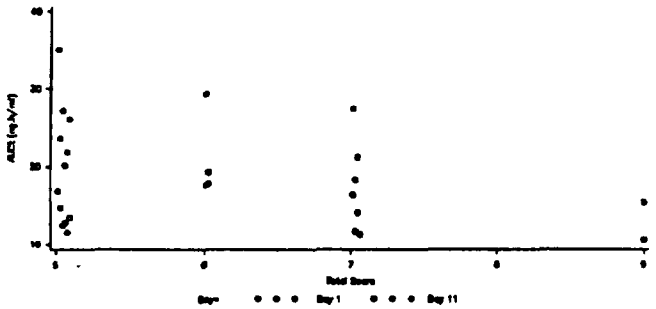


FIGURE 5
DOFETILIDE PROTOCOL 002
AUCT VERSUS CHILD-PUGH CLASSIFICATION TOTAL SCORE



CONCLUSIONS: The data obtained from the study showed that there were no significant differences in the pharmacokinetic and pharmacodynamic profiles of dofetilide in patients with stable chronic hepatic impairment (Class B or Class A, according to the Child-Pugh classification criteria) compared to healthy subjects.

AGE EFFECT STUDY

STUDY 115-235 **VOLUME: 2.50**

INVESTIGATOR AND LOCATION:

STUDY DATE: March to May 1991.

STUDY OBJECTIVE: To assess the effect of age on the pharmacokinetic and pharmacodynamic profiles of dofetilide following single oral and intravenous doses and to evaluate its safety and toleration in young and elderly healthy, male subjects after both routes of administration.

DRUG ADMINISTRATION:
Dofetilide: 25mcg/ml free base in 10ml solution for intravenous injection, FID 0952, Lot Number 746-27; Capsules containing the equivalent of 500mcg free base as the monohydrate salt, FID 0964, Lot 904-05.
Diluent: Mannitol solution (50mg/ml) with citric acid monohydrate solution (4mg/ml) adjusted to pH 3.5 with a solution of sodium hydroxide in sterile water (FID 0950, Lot 746-31).
Dosing: The intravenous solution was diluted such that 500mcg was infused over 30 minutes at a constant rate of 80ml/h. Two capsules were taken with 240ml water. The dosing interval was 1 week and both treatments were given to fasted subjects.

STUDY DESIGN:
This was an open, randomised cross-over study in which eleven elderly and ten young subjects received dofetilide 1000mcg orally and 500mcg by intravenous (iv) infusion. Blood was sampled for plasma concentrations of dofetilide at the same times as 3-lead ECG measurements for up to 72 hours after each dose. Plasma samples were taken at 5, 10, 15, 20, 30, 35, 40, 45 and 50 minutes, then 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 28, 34, 48 and 72 hours after the start of the iv infusion or at 0.25, 0.5 and 0.75 minutes, then 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 28, 34, 48 and 72 hours after oral dosing. Total urine output was collected during the periods 0-24, 24-48 and 48-72 hours after dosing.

ASSAYS:

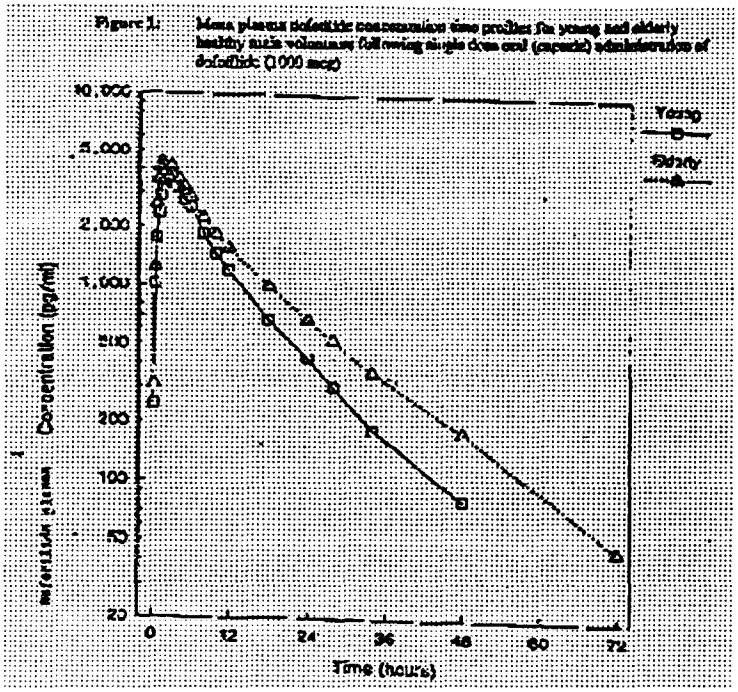
DATA ANALYSIS:
Cmax, Tmax, AUC, Kel, T1/2, renal clearance (CLr), non-renal clearance (CLnr) and systemic bioavailability were derived from plasma and urine concentrations of dofetilide using standard pharmacokinetic calculations. Creatinine clearance (CLcr) was estimated (Cockroft and Gault) from baseline data. QTc values were calculated using Bazett's formula. The relationship between plasma concentrations of dofetilide and change in QTc from baseline was examined using linear regression analysis after oral dosing.

RESULTS: Table 1 and Figures 1-5 summarize the pharmacokinetic and pharmacodynamic data obtained from the study.

Table 1: Mean (SD) of PK and PD parameters for dofetilide

	ORAL (1000 mcg)		INTRAVENOUS (500 mcg over 30 mins)	
PARAMETER	YOUNG	ELDERLY	YOUNG	ELDERLY
C_{max} (ng/ml)	5.94 (0.65)	4.89 (1.58)	5.19 (0.92)	5.39 (0.15)
T_{max} (h)	2.35 (0.97)	2.34 (0.83)	0.41 (0.15)	0.43 (0.09)
AUC (ng.h/ml)	41.96 (7.21)	58.79 (7.32)	23.28 (3.60)	28.58 (4.02)
k_{el} (h^{-1})	0.0733 (0.0100)	0.0528 (0.0067)	0.0801 (0.0123)	0.0608 (0.0080)
$t_{1/2}$ (h)	9.45	13.13	8.65	11.40
CL (ml/min)	-	-	366 (55)	297 (41)
CL_R (ml/min)	235 (75)	169 (30)	190 (100)	195 (60)
CL_{NR} (ml/min)	-	-	176 (76)	102 (37)
V (L)	-	-	276 (33)	398 (57)
F	0.84 (0.15)	0.91 (0.21)	-	-
[b]Slope (msec/ng/ml)	23.7 (5.7)	13.6 (3.3)	22.7 (7.1)	20.9 (5.9)
[a]QTc (msec)	132.1 (29.8)	86.1 (34.9)	96.8 (26.4)	79.2 (27.6)

[a] Mean maximum changes from baseline
[b] Excluding subject 23 (see text)


Young
Elderly
Concentration (pg/ml)
10,000
5,000
2,000
1,000
500
200
100
50
20
0
12
24
36
48
60
72
Time (hours)

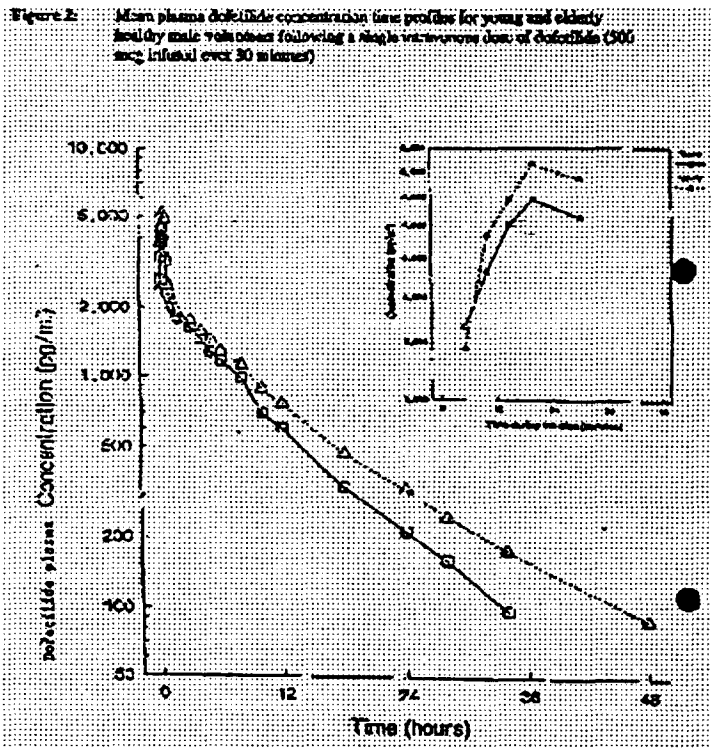

10,000
5,000
2,000
1,000
500
200
100
50
0
12
24
36
48
Time (hours)

Figure 3: QTc up to 12 hours post dose: Mean change from baseline

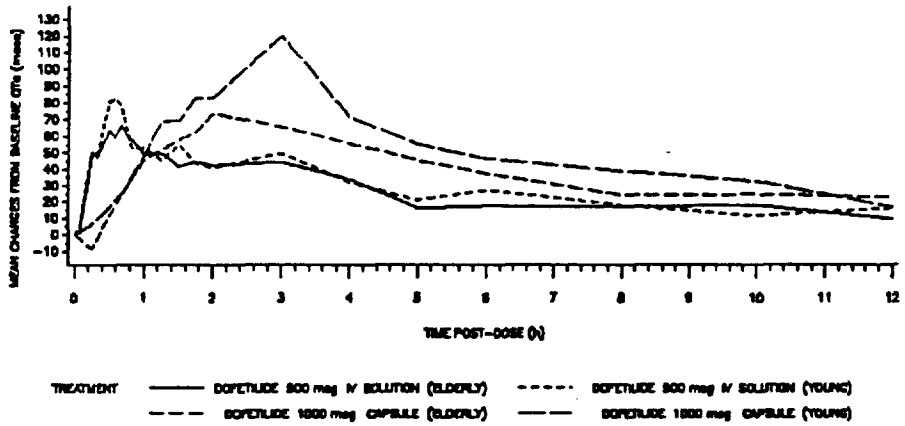


Figure 4: Relationship between age and creatine clearance

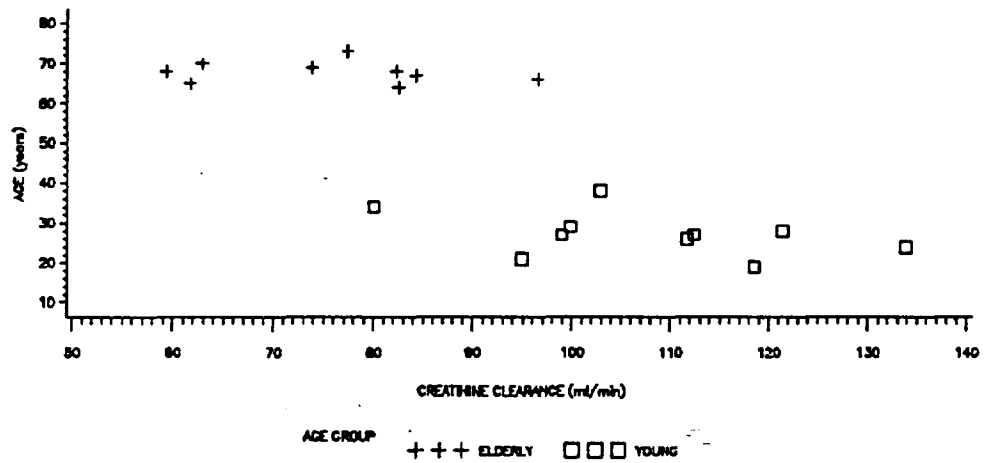
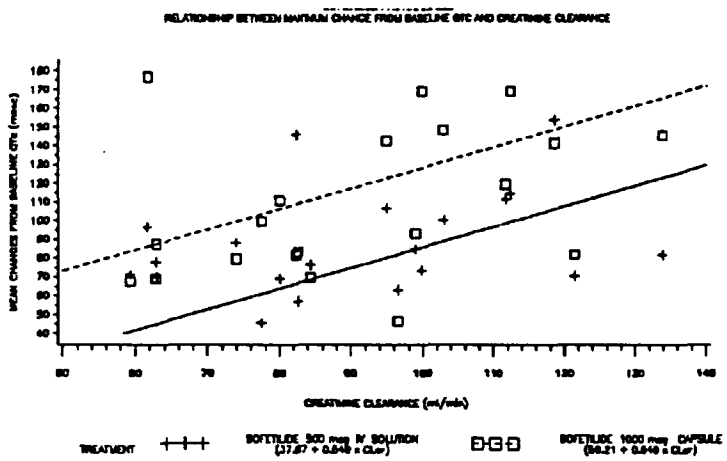


Figure 5:



CONCLUSIONS

Data from the study show that Cmax was greater in the elderly group (about 25% increase after PO) and there were significant differences between the age groups in AUC (40% increase after PO and 23% increase after IV in the elderly), Kel (about 30% decrease after PO and 25% decrease after IV in the elderly) and half life (40% increase after PO and 30% increase after IV), QTc max (35% decrease after PO and 18% decrease after IV) and PK-PD slope (40% decrease after PO and 8% decrease after IV), resulting in greater exposure but less sensitivity to dofetilide in the elderly population. Differences were eliminated statistically when these data were corrected for baseline creatinine clearance. An age group difference shown for non-renal clearance (30% decrease after PO), indicating that hepatic metabolism of dofetilide was reduced in the elderly, was not explained by creatinine clearance. Data from this study indicate that the elderly population was exposed to higher concentrations of dofetilide for a longer period of time. There was a significant relationship between the drug clearance, renal clearance and creatinine clearance. The decreased clearance of drug in the elderly was mostly accounted for by reduced renal function as evidenced by lower creatinine clearance.

In the elderly subjects, there was an apparent decrease in sensitivity when the drug was administered orally in comparison to intravenous administration.

Dosage adjustment may be necessary in the elderly, particularly those with compromised renal function

PHARMACOKINETICS AND PHARMACODYNAMICS IN PATIENTS WITH STABLE AF AND REDUCED LEFT VENTRICULAR EJECTION FRACTION

STUDY 115-005 **VOLUME**: 2.11

INVESTIGATOR AND LOCATION:

STUDY DATE: November 1994 - February 1997.

RATIONALE:
Atrial fibrillation with reduced cardiac output, could alter dofetilide's pharmacologic profile either by effects on its pharmacokinetics, as a consequence of modifications in end-organ responsiveness, or both. In normal volunteers, about 30% of a given dose is eliminated by non-renal routes, and about 70% by renal elimination. In patients with atrial fibrillation and reduced cardiac output, renal perfusion will be reduced, and hepatic congestion could impair metabolism. The concept of compensatory non-renal elimination does not apply to all cases. When patients with atrial fibrillation are exposed to dofetilide, some of them convert to sinus rhythm. Such conversion could alter the pharmacokinetics and pharmacodynamics of dofetilide, and the effect of such changes on the responsiveness to the drug deserves evaluation.

STUDY OBJECTIVE: To evaluate the pharmacokinetics of dofetilide following single and multiple dosing in subjects with stable atrial fibrillation/flutter and reduced left ventricular ejection fraction, to examine the pharmacokinetic/pharmacodynamic relationship of dofetilide in this subject population, to determine whether the pharmacokinetic and/or pharmacodynamic profile of dofetilide changes in subjects who convert to sinus rhythm following dofetilide administration, and to compare the pharmacokinetic/pharmacodynamic relationship in these subjects with values obtained from a control population matched for age, sex, weight, and race.

DRUG ADMINISTRATION:
Dofetilide intravenous formulation, 100mcg/mL FID #QC2052, Lot #N6118A-G1 and FID #QC2052A, Lot #ED-O-251-893
Dofetilide capsule, 250mcg, FID #0963, Lot # 503-15
Dofetilide capsule, 500mcg, FID #0964, Lot # 503-20
Placebo capsule, FID #0034, Lot #748-45

Dosing : Day 1, single oral dose of placebo
Day 8, dofetilide 8mcg/kg IV infusion over 30min
Days 15-29, 500mcg dose of dofetilide orally bid (only the morning dose was administered on Day 29); subject 06030001 received dofetilide 250mcg bid starting from the second dose on Day 15

STUDY DESIGN:

This was a placebo-controlled, single-blind study. All subjects with stable atrial fibrillation took warfarin for the duration of the study. Subjects received a single oral placebo capsule on Day 1, single dofetilide 8mcg/kg IV infusion over 30 minutes on Day 8, and dofetilide 500mcg oral capsules bid from Day 15 to Day 29 (only the morning dose was administered on Day 29). If QT interval prolongation during the first 12 hours post oral dofetilide dosing (Day 15) exceeded 15% of the subject's baseline value, subsequent doses were reduced to 250mcg bid (one subject). Subjects with atrial fibrillation who converted to normal sinus rhythm during or after intravenous dofetilide administration completed all scheduled evaluations for that day (Day 8). Subjects with atrial fibrillation who converted to normal sinus rhythm during oral dofetilide administration (Days 15-29) and those who did not convert completed the 14-day dosing schedule and all the evaluations scheduled for Days 15-29. Pharmacokinetic and pharmacodynamic measurements were taken on Days 1, 8, 15 and 29. Dofetilide plasma concentrations were monitored at hours 0 (just prior to dosing), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 and 48 hours post morning dosing on Days 1 and 29. Additionally, blood was collected at hour 72 after the dose on study Day 29. On Day 15, plasma samples were collected per the above schedule but only through the 12h post-dose sampling. On Day 8, blood samples were collected at 0, 5, 10, 15, 30, 45, 60min, and at 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 and 48 hours from the beginning of the infusion. In addition, pre-dose blood samples for dofetilide concentration were obtained during the visits on Days 20, 22, 24 and 26. Urine samples were collected during the 12 hours following the morning dosing on Days 1, 8, 15 and 29. The total urine volume collected during each day was measured and after thorough mixing, aliquots were analyzed for dofetilide concentrations. An overall safety evaluation was performed based on Holter data, 12-lead ECGs, rhythm strip data, blood pressure, heart rate, reported or observed adverse events and clinical laboratory data.

ASSAYS:

DATA ANALYSIS:

Cmax, Tmax, AUC, Kel, CLr, Emax and AUEC were computed.

RESULTS: Tables 1-2 and Figures 1-6 summarize the pharmacokinetic and pharmacodynamic data obtained from the study.

Table 1:
Mean Pharmacokinetic Parameters, Atrial Fibrillation (N=5) vs. Healthy (N=4)*

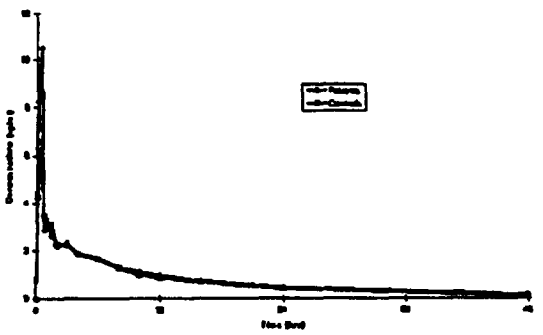
	Day	AF	Healthy	Ratio**/Difference	90% Confidence Limits
AUC (ng·h/mL)	8	42.32	36.38	116.3%	(86.8%, 155.8%)
Cmax (ng/mL)		10.53	6.70	157.2%	(116.9%, 211.5%)
Tmax (h)		0.45	0.40	0.06	(-0.15, 0.26)
Kel (/h)		0.0528	0.0656	-0.0127	(-0.0246, -0.0008)
CLr (mL/min)		166.7	239.9	-73.2	(-193.8, 47.5)
AUCτ (ng·h/mL)	15	18.34	15.90	115.4%	(97.8%, 136.2%)
Cmax (ng/mL)		2.86	1.99	143.3%	(99.0%, 207.3%)
Tmax (h)		2.25	4.50	-2.25	(-5.39, 0.89)
CLr (mL/min)		96.7	250.5	-153.8	(-196.9, -110.7)
AUCτ (ng·h/mL)	29	50.34	38.60	130.4%	(101.4%, 167.8%)
Cmax (ng/mL)		4.26	3.23	131.9%	(88.2%, 197.3%)
Tmax (h)		2.75	1.25	1.50	(0.71, 2.29)
Kel (/h)		0.0385	0.0483	-0.0097	(-0.0236, 0.0042)
CLr (mL/min)		168.9	261.7	-92.9	(-154.5, -31.2)

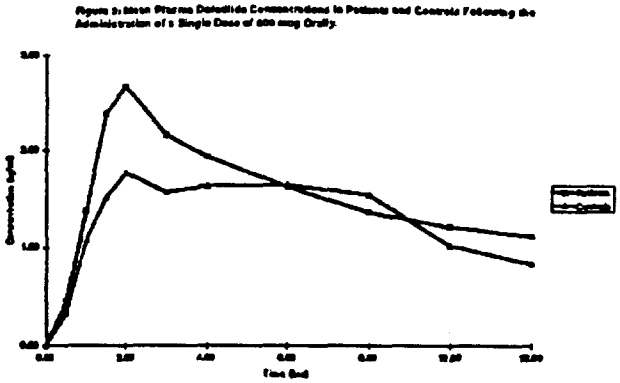
* All means are adjusted arithmetic means except for AUC, AUCτ and Cmax, which are adjusted geometric means.
** Ratios are expressed in %.

Table 2

Mean Pharmacodynamic Parameters, Atrial Fibrillation (N=5) vs. Healthy (N=4)

	Day	AF	Healthy	Difference	95% Confidence Limits
AUECτ (msec·h)	1	104.05	-22.63	126.68	(-195.05, 448.40)
Emax (msec)		31.60	17.25	14.35	(-13.10, 41.80)
AUECτ (msec·h)	8	220.85	386.56	-165.71	(-725.37, 393.95)
Emax (msec)		61.40	56.75	4.65	(-53.57, 62.87)
AUECτ (msec·h)	15	155.31	361.50	-206.19	(-678.09, 265.72)
Emax (msec)		53.50	47.00	6.50	(-57.59, 70.59)
AUECτ (msec·h)	29	349.81	401.75	-51.94	(-346.59, 242.72)
Emax (msec)		36.25	30.75	5.50	(-4.53, 15.53)





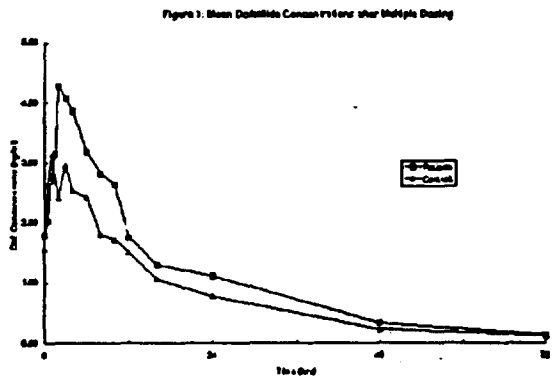


FIGURE 4
DOFETILIDE PROTOCOL 005
MEAN EXPERT RHYTHM STRIP QTC CHANGES FROM PRE-DOSE ON DAYS 1, 8, 15 AND 29

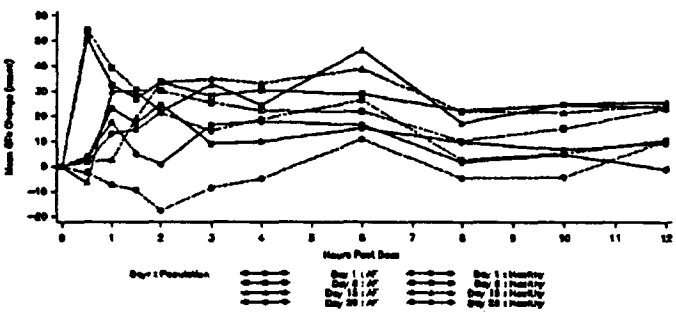
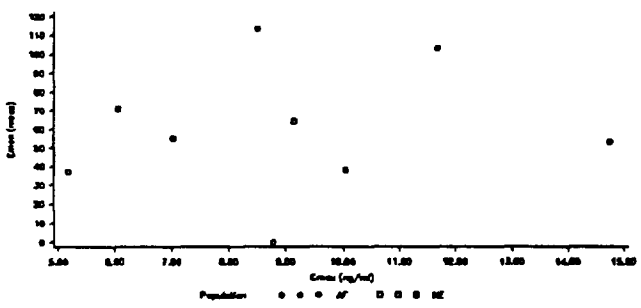
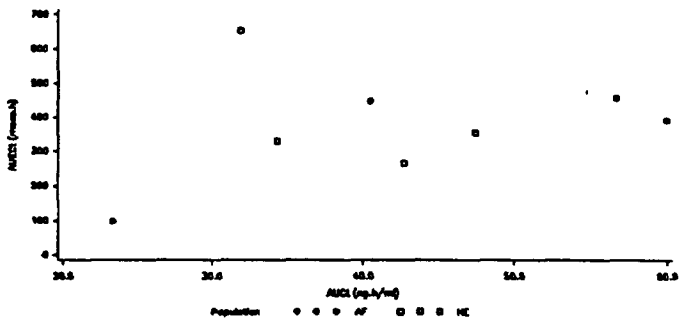


Figure 6

FIGURE 5
DOFETILIDE PROTOCOL 005
EXPERT RHYTHM STRIP QTC EMAX VS CMAX – DAY 8



EXPERT RHYTHM STRIP QTC AUECT VS AUCT – DAY 29



CONCLUSIONS: Although the study sample size is small, the data obtained from the study show that AUC and Cmax of dofetilide are increased and the renal clearance reduced in patients with Atrial Fibrillation (AF) when compared with healthy volunteers after both oral and IV administration. The maximum change in QTc from baseline (Emax) is also greater in patients with AF when compared with healthy volunteers.

FOOD EFFECT STUDY

STUDY 115-015 **VOLUME**: 1.26

INVESTIGATOR AND LOCATION:

STUDY DATE: November - December 1996.

STUDY OBJECTIVE: To determine the effect of food on the pharmacokinetics of dofetilide when administered as the proposed 500mcg commercial capsule formulation to healthy subjects.

DRUG ADMINISTRATION:
Dofetilide 500mcg commercial capsule FID# QC2445, Lot No. N6179-G1

STUDY DESIGN:
This was an open-label, randomized, two period, two treatment, crossover study in 20 healthy subjects and a washout period of 7 days. On days 1 and 8 and after fasting for 8 hours, subjects received the proposed 500mcg commercial capsule in either a fasted or fed state (after ingestion of a standard breakfast). Blood samples (sufficient to yield 3ml of plasma) weres collected from each subject at 0 (baseline, just prior to dosing), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post dosing with study drug.
The standard breakfast comprised of two eggs fried in butter, two strips of bacon, six ounces of hash brown potatoes, two slices of toast with two pats of butter, and eight ounces of whole milk. This meal was consumed over a 20 minute interval and dofetilide administered immediately thereafter.

ASSAYS:

DATA ANALYSIS:
Plasma concentrations were used to determine pharmacokinetic parameters (AUC, Cmax, Tmax, and Kel).

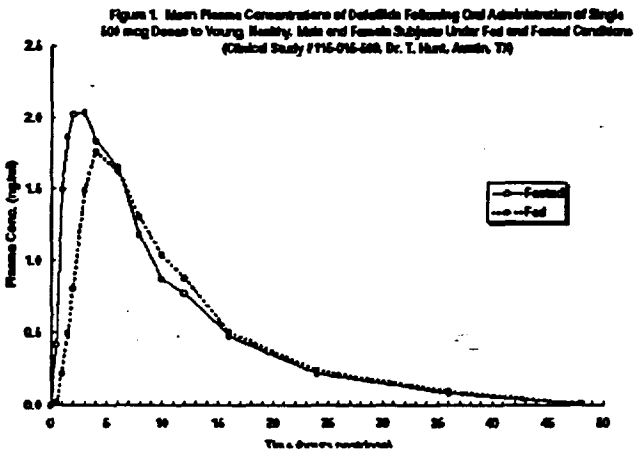
RESULTS: Table 1 and Figure 1 summarize the pharmacokinetic data obtained from the study.

Table 1:

Pharmacokinetic Results: Mean Pharmacokinetic Parameters (n=20)

	FID #QC2445 Fed	FID #QC2445 Fasted	Ratio	90% Confidence Limits
AUC (ng•hr/ml)*	22.50	23.99	93.8%	(88.5%, 99.4%)
Cmax (ng/ml)*	2.01	2.22	90.7%	(82.0%, 100.4%)
			Difference	
Tmax (h)**	4.8	2.8	2.0	(1.0, 2.9)
Kel**(/h)	0.0989	0.0984	0.0004	(-0.0038, 0.0047)

* Adjusted Geometric Mean **Adjusted Arithmetic Mean



CONCLUSIONS:

Food did not affect the extent of absorption or the maximum plasma concentration obtained. However, food did cause a 2-hour delay in absorption of dofetilide from the commercial capsule.

FOOD EFFECT STUDY

STUDY 115-211 **VOLUME: 2.32**

INVESTIGATOR AND LOCATION:

STUDY DATE: March - May 1989.

STUDY OBJECTIVE: The objectives of this study were to assess the effect of food on the pharmacokinetic profile, and assess the safety and toleration, of dofetilide.

DRUG ADMINISTRATION:
Test Product: Capsules containing 500mcg dofetilide, FID# 0964, Lot 772-02.

STUDY DESIGN:
Twelve subjects were studied in this open, randomised, crossover study in 12 healthy subjects and a washout period of 7 days. Following 12 hours of fasting each subject received 500 mcg dofetilide as a capsule with a standard breakfast (half way through a standard breakfast) and the same dose without breakfast. Blood samples for estimation of plasma concentrations of dofetilide were collected immediately prior to dosing and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 hours afterwards. A 12-lead resting ECG was to be recorded at the pre-study screen, during the control period and 1, 2, 4, 8, 12 and 24 hours after dosing.
The meal consisted of bacon and egg filled buttered rolls and a decaffeinated beverage with milk.

ASSAYS:

DATA ANALYSIS:
Plasma concentrations were used to determine pharmacokinetic parameters (AUC, Cmax, Tmax, and Kel).

RESULTS: Tables 1-3 and Figures 1-2 summarize the pharmacokinetic and phramcodynamic data obtained from the study.

Table 1: MEAN (SD) PHARMACOKINETIC PARAMETERS

Parameter	Treatment	
	With food (A)	Without Food (B)
Cmax (pg/ml)	2387 (329)	2432 (598)
Tmax (hours)	3.3 (1.2)	2.5 (1.2)
AUC_t (pg.h/ml)	28551 (3845)	29635 (3963)
AUC_∞ (pg.h/ml)	29950 (3895)	30731 (4017)
Terminal rate constant ($hours^{-1}$)	0.0716 (0.0235)	0.0691 (0.0189)
Half-life (hours)	9.7	10.0

Table 2:

DOFETILIDE PROTOCOL 111
ANALYSIS OF DOFETILIDE PHARMACOKINETIC PARAMETERS SUMMARY

COMPARISON: Dofetilide 500 mcg (Fasted) - Dofetilide 500 mcg (Fed)

	DIFFERENCE BETWEEN ADJUSTED MEANS	90% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS LOWER	UPPER		P-VALUE
Kel (/h)	-0.0024	-0.0119	0.0070	(-17%, 10%)	0.6521

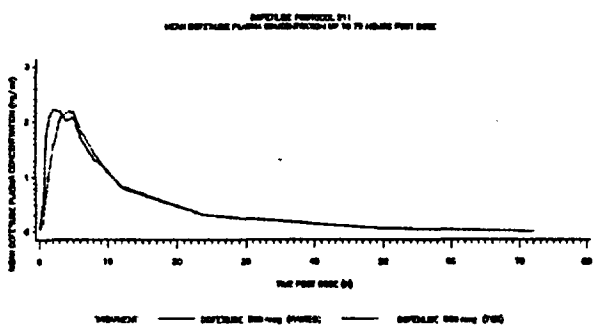
	LOG TRANSFORMED DATA			ANTI-LOG*			
	DIFFERENCE BETWEEN ADJUSTED MEANS	90% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS LOWER	UPPER	RATIO BETWEEN MEANS	90% CONFIDENCE LIMITS ON RATIO BETWEEN MEANS LOWER	UPPER	P-VALUE
AUC (0-24h) (ng.h/ml)	0.04	-0.01	0.09	103.9%	99.1%	108.8%	0.1698
AUC (ng.h/ml)	0.03	-0.01	0.06	102.6%	99.3%	106.1%	0.1889
Cmax (ng/ml)	0.00	-0.07	0.08	100.2%	92.9%	108.1%	0.9601

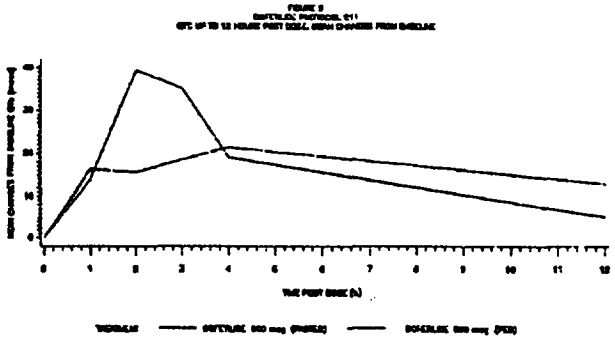
Table 3:

QTc SUMMARY, MEAN CHANGES FROM BASELINE

QTc INTERVAL BAZETTS (msec)

		TIME POST DOSE (h)						
		BASE-LINE	1	2	3	6	12	24
TREATMENT								
DOFETILIDE 500 mcg (FASTED)	MEAN	413.52	13.76	99.39	25.08	19.10	5.02	1.03
	S.E.	4.54	5.35	17.20	12.04	2.67	3.35	3.78
	N	12	12	8	4	12	12	12
DOFETILIDE 500 mcg (FED)	MEAN	407.51	16.94	15.56		21.25	12.92	4.66
	S.E.	4.74	5.25	5.72		4.60	3.12	3.24
	N	12	12	12		12	12	12





CONCLUSIONS:

The plasma dofetilide concentration profiles were similar whether the subjects were fed or fasted, but Cmax occurred earlier (0.8 hour faster) in the fasted state than it did in the same subjects after feeding. The mean QTc value increased after dosing under both regimens, the fasted group achieving their maximum response 1 - 2 hours earlier than the fed group, in line with observed Tmax values. The apparent anomaly between the maximum observed change from baseline in QTc between the treatment groups was due to one abnormally high value recorded from a single subject 2 hours after dosing in the fed state.

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 115-012 **VOLUMES**: 1.23

INVESTIGATOR AND LOCATION:

STUDY DATE: November - December 1996.

OBJECTIVES:
To determine the bioequivalence of a proposed 500mcg commercial oral capsule formulation of dofetilide (FID #QC2445), and the 500mcg clinical oral capsule formulation of dofetilide (FID #0964).

FORMULATIONS:
500mcg commercial capsule formulation (FID #QC2445; Lot No. N6179-G1)
500mcg clinical capsule formulation (FID #0964; Lot No. 503-19-G1)

STUDY DESIGN:
This was an open, randomized, two-period, two-treatment crossover study of the pharmacokinetics of a commercial capsule formulation and the clinical capsule formulation of dofetilide in twenty healthy subjects (4 male and 16 female) and a washout period of seven days. After fasting for eight hours, subjects were administered single 500mcg oral doses of dofetilide as either the FID #QC2445 (commercial) formulation or FID #0964 (clinical) formulation. They fasted for an additional four hours and received a standard meal. Blood samples for the determination of plasma dofetilide concentrations were collected prior to (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours after each dose of study drug.

ASSAYS:

DATA ANALYSIS:
AUC, Cmax, Tmax, and Kel were determined.

RESULTS: Table 1 and Figures 1-3 summarize the pharmacokinetic data obtained from the study.

Table 1. Bioequivalence of the two formulations

Mean Pharmacokinetic Parameters, Commercial vs. Clinical Formulation (n=20)

Pharmacokinetic Parameter	Commercial	Clinical	Comparison	90% Confidence Limits
	Adjusted Geometric Mean		Ratio	
AUC (ng•hr/mL)	26.52	27.60	96.1%	(91.2%, 101.2%)
Cmax (ng/mL)	2.40	2.47	97.1%	(89.8%, 105.0%)
	Adjusted Arithmetic Mean		Difference	
Tmax (hr)	2.5	2.3	0.2	(-0.3, 0.7)
Kel (/hr)	0.0969	0.0967	0.0002	(-0.0066, 0.0070)

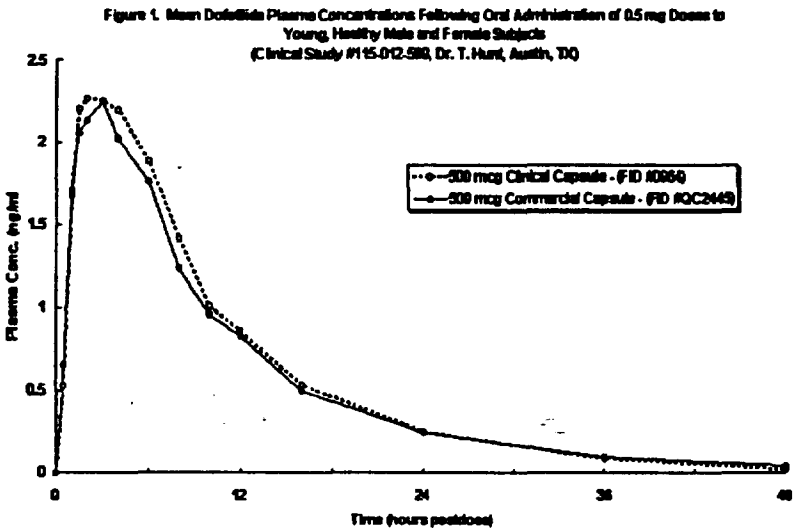


Figure 2:

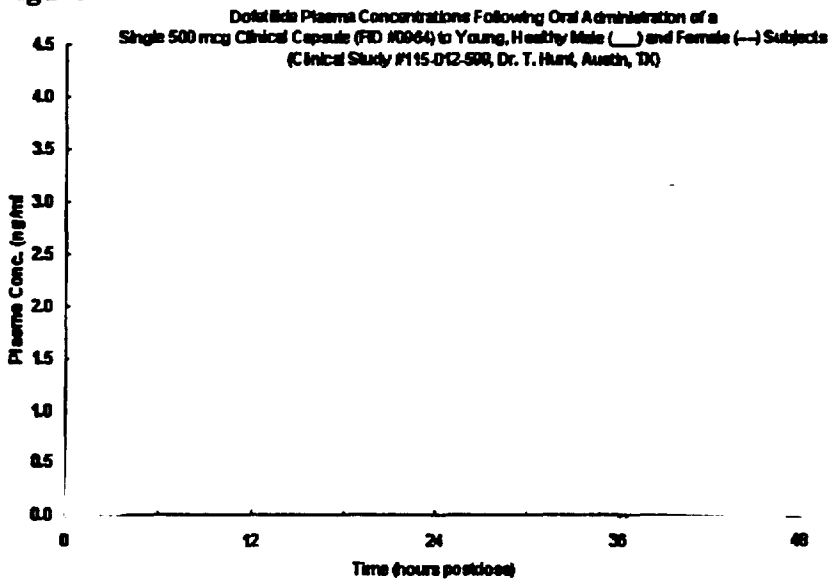
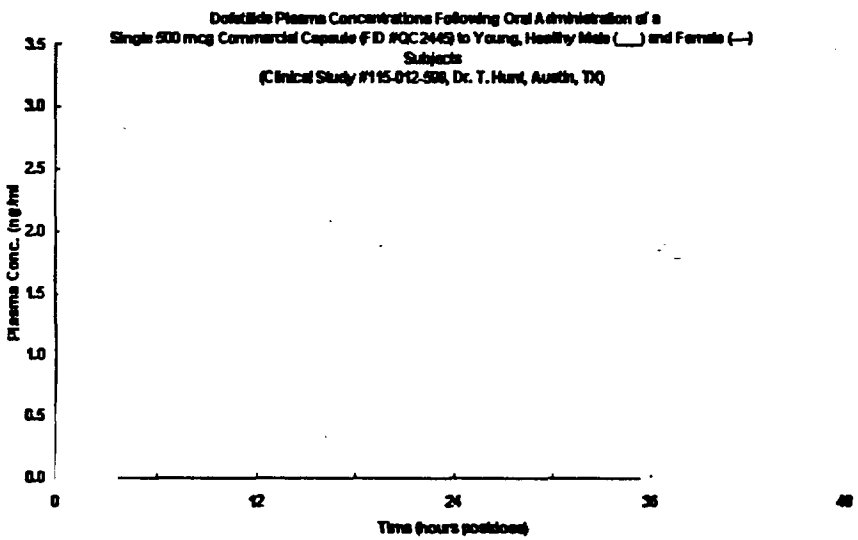


Figure 3:



CONCLUSIONS:

The results obtained from the study indicated that the two capsule formulations of dofetilide were bioequivalent. Individual plasma profiles (Figures 2 & 3) indicate that female subjects generally displayed higher level of dofetilide for both formulations.

BIOAVAILABILITY / BIOEQUIVALENCE STUDY

STUDY 115-013 **VOLUMES**: 1.24

INVESTIGATOR AND LOCATION:

STUDY DATE: November - December 1996.

OBJECTIVE:
To determine the bioequivalence of a proposed 125mcg commercial capsule formulation of dofetilide relative to the standard 500mcg clinical capsule formulation..

FORMULATIONS:
500mcg clinical capsule, FID #0964, Lot No. 503-19-G1
125mcg commercial capsule, FID #QC2442, Lot No. N6178-G2

STUDY DESIGN:
This was an open, randomized, two-period, two-treatment crossover study in twenty healthy subjects (7 male and 13 female) and a washout period of seven days. After fasting for eight hours, subjects were administered dofetilide 500mcg either as a single 500mcg clinical capsule or four 125mcg commercial capsules. Dofetilide plasma concentrations were monitored on Days 1 and 8 at hour 0 (just prior to dosing), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post dosing.

ASSAYS:

DATA ANALYSIS:
AUC, Cmax, Tmax, and Kel were determined.

RESULTS: Table 1 and Figures 1-3 summarize the pharmacokinetic data obtained from the study.

Table 1. Bioequivalence of the two formulations

Mean Pharmacokinetic Parameters, Commercial vs. Clinical (n=20)

	Commercial	Clinical	Ratio	90% Confidence Limits
AUC (ng.h/mL)*	25.02	25.63	97.6%	(92.2%, 103.5%)
Cmax (ng/mL)*	2.41	2.32	103.7%	(91.4%, 117.6%)
			Difference	
Tmax (h)**	2.5	2.7	-0.1	(-0.6, 0.3)
Kel (/h)**	0.0888	0.0918	-0.0030	(-0.0096, 0.0036)

* Adjusted Geometric Mean ** Adjusted Arithmetic Mean

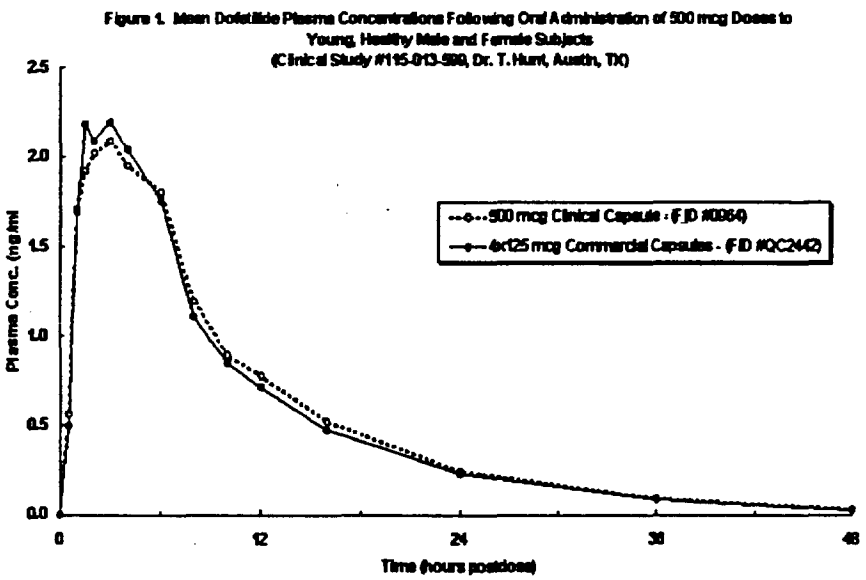


Figure 2:

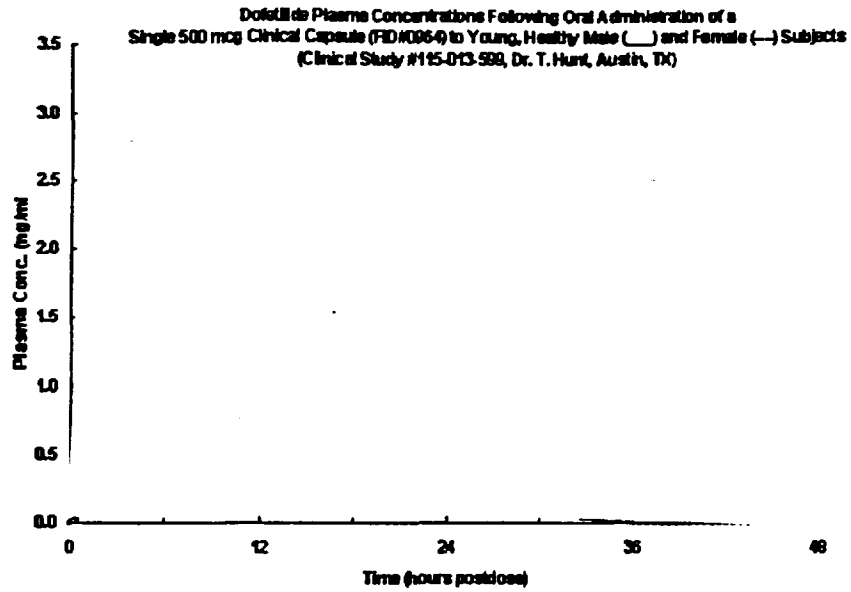
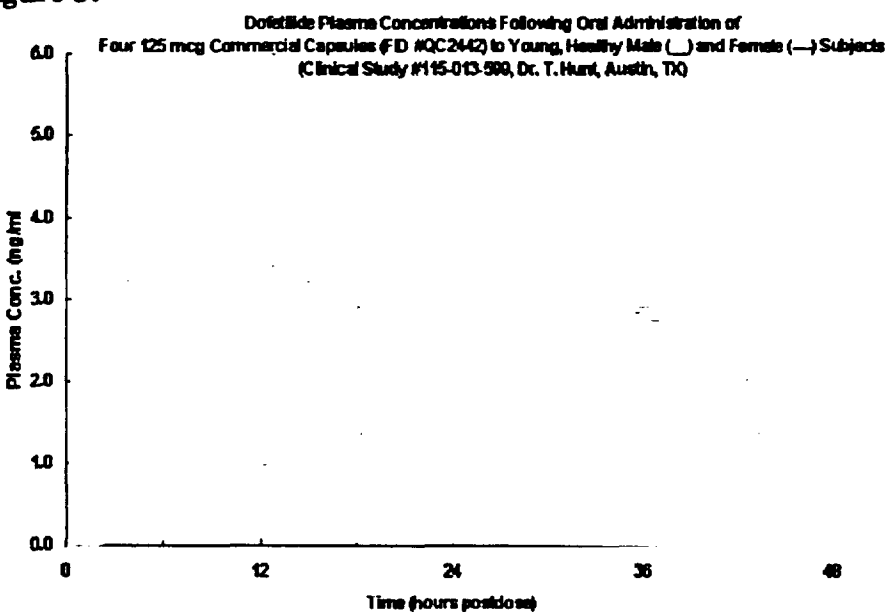


Figure 3:



CONCLUSIONS:

The results obtained from the study indicated that indicate that a single 500mcg clinical capsule (FID #0964) was bioequivalent to four 125mcg commercial capsules (FID #QC2442). Individual plasma profiles (Figures 2 & 3) indicate that female subjects generally displayed higher level of dofetilide for both formulations.

FOOD EFFECT STUDY

STUDY 115-244 **VOLUME: 2.55**

INVESTIGATOR AND LOCATION: [redacted]

STUDY DATE: December 1992, to March 1993.

STUDY OBJECTIVE: To compare the bioavailability of oral dofetilide research capsules with oral dofetilide commercial capsules in fasted healthy males, and determine whether food affects the bioavailability of the commercial capsules.

DRUG ADMINISTRATION:
Test Product: 250mcg dofetilide oral capsules - commercial (FID S00114AA, Lot No. 2958-013) and research (FID 0963, Lot No. 503-15)..

STUDY DESIGN:
This was an open, randomized, three-way, crossover study in which 18 healthy males who received, on three separate occasions, a single oral dose of 500mcg (2 x 250mcg) dofetilide. On two of the occasions subjects fasted and received dofetilide as the commercial or research capsule, and on one occasion subjects received dofetilide as the commercial capsule after a standardised high fat breakfast. Blood samples were taken at regular intervals after dosing for up to 48 hours post-dose and twelve-lead ECG and haemodynamic recordings were made at regular intervals up to 32 hours post-dose.
The high fat breakfast (estimated fat content = 53g) consisted of of 100 g scrambled eggs, two 100 g white rolls, 20g butter or margarine, and 140ml whole milk.

ASSAYS: [redacted]

DATA ANALYSIS:
Plasma concentrations were used to determine pharmacokinetic parameters (AUC, Cmax, Tmax, and Kel). ANOVAs were performed to compare the log-transformed AUCt and Cmax for the commercial and research capsules after fasting, and for the commercial capsule after fasting and food.

RESULTS: Tables 1-4 and Figures 1-2 summarize the pharmacokinetic and phramcodynamic data obtained from the study.

Table 1: PK and PD Parameters from the three treaments

		A: Dofetilide 500mcg research capsule (fasted)	B: Dofetilide 500mcg commercial capsule (fasted)	C: Dofetilide 500mcg commercial capsule (fed)
1. Pharmacokinetics:				
Mean ± SD	Cmax (ng/ml)	1.97 ± 0.45 ‡	2.06 ± 0.49 † ‡	2.08 ± 0.31 †
	Tmax (h)	3.08 ± 1.74	2.25 ± 1.39	3.00 ± 1.49
	AUCt (ng.h/ml)	21.7 ± 3.5 ‡	21.7 ± 3.2 † ‡	22.5 ± 3.2 †
	AUC (ng.h/ml)	23.5 ± 3.6	23.3 ± 3.5	24.5 ± 3.2
	Kel (/h)	0.071 ± 0.013	0.074 ± 0.021	0.068 ± 0.012
Geometric Mean	t1/2 (h)	9.8	9.4	10.1
2. Pharmacodynamics				
Max change in QTc (msec, mean ± SE)		31.58 ± 7.21	33.21 ± 6.11	29.45 ± 8.81
Time of mean, max change of QTc (h)		4	2	2

†, ‡ = means sharing these symbols are equivalent (90% confidence intervals on ratio between means within range 80-125%).

Table 2:

ANALYSIS OF DOFETILIDE PHARMACOKINETIC PARAMETERS SUMMARY
(ALL CAPSULES DOFETILIDE 500 MCG)

COMPARISON: Commercial capsule (Fasted)/Research capsule (Fasted)

	LOG TRANSFORMED DATA			ANTI-LOG*		
	DIFFERENCE BETWEEN MEANS	90% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS LOWER	UPPER	RATIO BETWEEN MEANS	90% CONFIDENCE LIMITS ON RATIO BETWEEN MEANS LOWER	UPPER
AUCt (ng.h/ml)	0.00	-0.02	0.03	100.1%	97.7%	101.7%
Cmax (ng/ml)	0.01	-0.05	0.07	101.1%	95.2%	107.6%

Table 3:

ANALYSIS OF DOFETILIDE PHARMACOKINETIC PARAMETERS SUMMARY
(ALL CAPSULES DOFETILIDE 500 MCG)

COMPARISON: Commercial capsule (Fasted)/Commercial capsule (Fed)

	LOG TRANSFORMED DATA			ANTI-LOG*		
	DIFFERENCE BETWEEN MEANS	90% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS LOWER	UPPER	RATIO BETWEEN MEANS	90% CONFIDENCE LIMITS ON RATIO BETWEEN MEANS LOWER	UPPER
AUCt (ng.h/ml)	-0.04	-0.06	-0.01	96.6%	94.0%	98.8%
Cmax (ng/ml)	-0.01	-0.07	0.05	99.1%	93.3%	105.3%

Figure 3:

Table 4:

QTC SUMMARY, MEAN CHANGES FROM BASELINE
(ALL CAPSULES DOFETILIDE 500 MCG)

QTc INTERVAL BAZETTS (msec)

		TIME POST-DOSE (h)						
		Baseline	2	4	6	8	12	22
TREATMENT								
COMMERCIAL CAPSULE (FASTED)	MEAN	406.97	33.21	22.97	16.26	13.24	6.70	-2.98
	S.E.	3.29	6.11	3.51	4.92	6.14	3.26	3.84
	N	18	18	18	18	18	18	18
COMMERCIAL CAPSULE (FED)	MEAN	407.20	29.45	23.53	20.63	6.98	0.77	-4.81
	S.E.	3.00	8.81	5.11	3.75	1.92	2.01	2.61
	N	18	18	18	18	18	18	18
RESEARCH CAPSULE (FASTED)	MEAN	407.25	30.94	21.58	17.05	11.44	4.52	-5.27
	S.E.	4.59	5.69	7.21	2.83	2.09	3.19	3.64
	N	18	18	18	18	18	18	18

FIGURE 1
DOFETILIDE PROTOCOL 244
QTC UP TO 12 HOURS POST DOSE, MEAN CHANGES FROM BASELINE
(ALL CAPSULES DOFETILIDE 500 MCG)

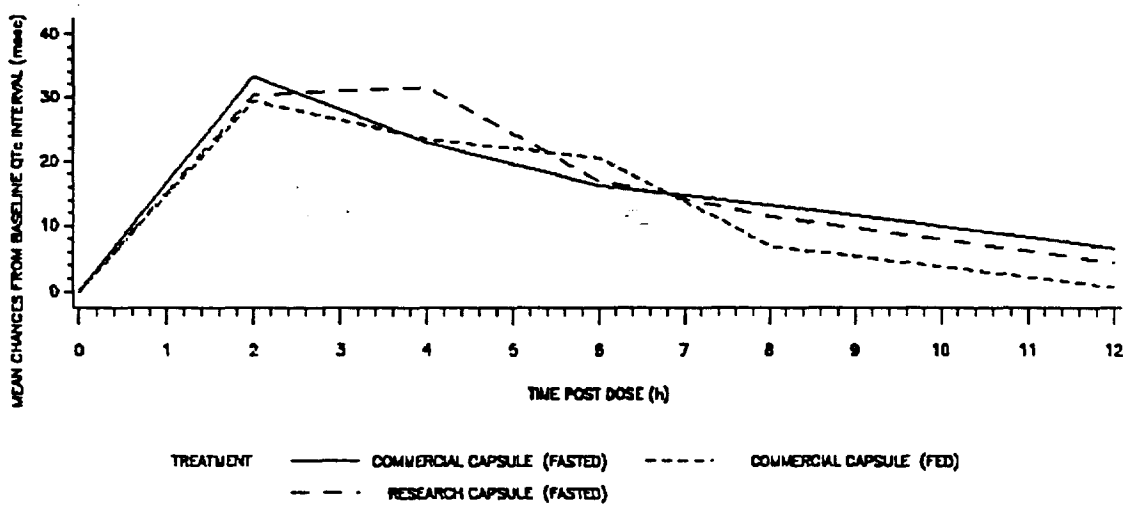
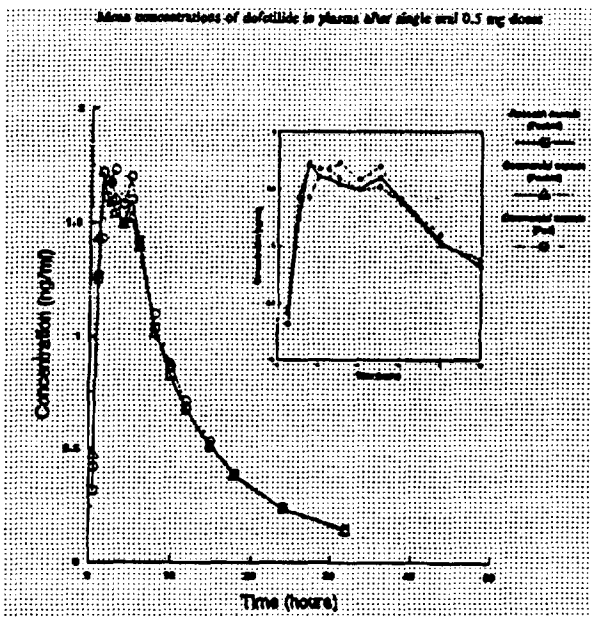


Figure 2:



CONCLUSIONS:

The plasma dofetilide concentration profiles were similar for the three treatments and the 90% on the ratio between the treatment means of AUCt and Cmax were within the range 80-125% but the sponsor did not calculate the confidence intervals for the $AUC_{0\text{-inf.}}$ so that a statement on the equivalence of the three treaments cannot be made. With co-administration of the commercial capsules with a high fat meal Cmax occurred earlier (0.8 hour faster) in the fasted state than it did in the same subjects after feeding.

The mean changes in QTc from baseline to 32 hours post-dose had similar profiles for the three treatments (Table 4 and Figure 1). Mean maximum observed increases from baseline were at 2 hours post-dose for the commercial capsule, both fasted and fed subjects, and were 33.21 ± 6.11 and 29.45 ± 8.81msec (mean ± SE), respectively. Mean maximum observed increases from baseline for the research capsule plateaued out between 2 and 4 hours (30.34 ± 5.69 and 31.58 ± 7.21msec, respectively).

BIOAVAILABILITY STUDY

STUDY 115-212 **VOLUMES: 2.33**

INVESTIGATOR AND LOCATION:

STUDY DATE: April to June 1989.

OBJECTIVES:
To compare the safety, toleration, pharmacokinetics and bioavailability of dofetilide administered orally and intravenously to healthy subjects.

FORMULATIONS:
Dofetilide injection 250mcg in 10ml (FID 0952, Lot No. 733-42).
Capsules suitable for oral intake containing 500mcg dofetilide (FID 0964, Lot No. 772-02).

STUDY DESIGN:
A single centre, randomized, two-way, cross-over study in nine healthy male subjects and a washout period of at least seven days. Each subject received a single dose of 500mcg dofetilide by oral capsule and intravenous infusion. For the intravenous dose blood samples were withdrawn immediately prior to the infusion, immediately on completion of the infusion, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 hours after completion of the infusion. For the oral dose blood samples were withdrawn immediately prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72 and 96 hours afterwards. The volumes of urine excreted during the hour prior to drug administration and over the periods 0-12, 12-24 and 24-48 hours post-dosing were measured. Twelve-lead ECG recordings were to be made at screening, during the control period, by the end of all intravenous infusions, and at 1, 2, 3, 4, 8, 12 and 24 hours after dosing.

ASSAYS:

DATA ANALYSIS:
AUC, Cmax, Tmax, and Kel were determined.

RESULTS: Table 1 and Figures 1-3 summarize the pharmacokinetic data obtained from the study.

Table 1. Pharmacokinetic Parameters

Pharmacokinetics (Mean ± SDM, n = 9, [a]n = 8)

	500mcg Intravenous Dofetilide	500mcg Oral Dofetilide
Cmax(ng/ml)	8.21 ± 3.44[a]	2.26 ± 0.58
Tmax(h)	0.167 ± 0[a]	2.556 ± 1.286
AUCt	22.3 ± 3.7	21.5 ± 4.5
AUC	24.6 ± 4.3	24.2 ± 5.5
kel(h)	0.093 ± 0.014	0.097 ± 0.009
t 1/2 (h)	7.4	7.1
Systemic availability	N/A	0.98 ± 0.09
Systemic Clearance (ml/min)	348 ± 59	N/A
Volume of Distribution (l)	228 ± 52	N/A

Table 2: Urinary Data

Route of administration	% Dose Excreted	Mean F_{abs}
IV	54 ±7	-
PO	49 ±7	93 ±15

Table 3:

ANALYSIS OF DOFETILIDE PHARMACOKINETIC PARAMETERS SUMMARY

COMPARISON: Dofetilide 500 mcg Capsule - Dofetilide 500 mcg IV Solution

	DIFFERENCE BETWEEN ADJUSTED MEANS	90% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS LOWER	UPPER		P-VALUE
Kel (/h)	0.0044	-0.0065	0.0153	(-7%, 17%)	0.4594

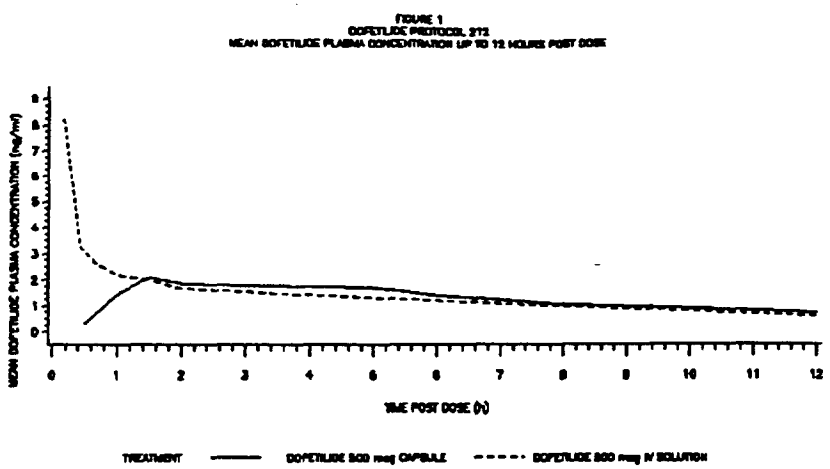
	LOG TRANSFORMED DATA			ANTI-LOG*			
	DIFFERENCE BETWEEN ADJUSTED MEANS	90% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS LOWER	UPPER	RATIO BETWEEN MEANS	90% CONFIDENCE LIMITS ON RATIO BETWEEN MEANS LOWER	UPPER	P-VALUE
AUC (ng.h/ml)	-0.03	-0.09	0.04	97.3%	91.2%	104.1%	0.4864
AUCt (ng.h/ml)	-0.04	-0.10	0.02	96.0%	90.5%	101.8%	0.2289

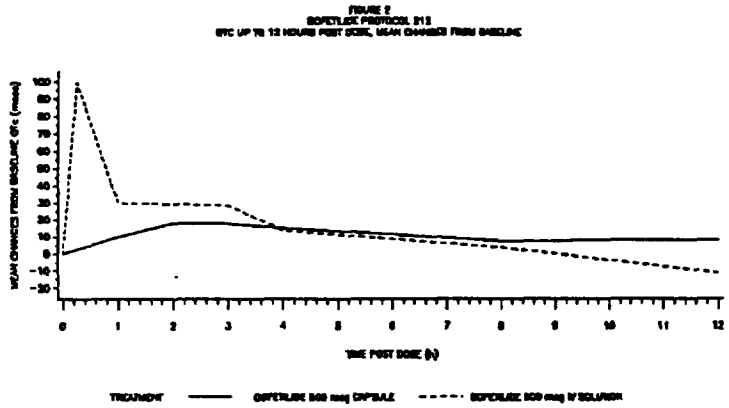
Table 4:

QTC SUMMARY, MEAN CHANGES FROM BASELINE

QTc INTERVAL BAZETT'S (msec)

		TIME POST DOSE (h)								
		BASE-LINE	END OF INFU-SION	1	2	3	4	8	12	24
TREATMENT										
DOFETILIDE 500 mcg CAPSULE	MEAN	406.00		9.74	17.92	17.69	15.09	7.67	7.96	-5.20
	S.E.	6.94		7.74	9.93	8.61	9.55	10.24	9.81	9.38
	N	9		9	9	9	9	9	9	9
DOFETILIDE 500 mcg IV SOLUTION	MEAN	404.91	99.52	29.93	29.38	28.34	13.59	3.58	-11.18	-6.40
	S.E.	8.29	29.72	22.93	12.85	12.95	11.42	10.19	9.68	6.04
	N	9	9	9	9	9	9	9	9	9





CONCLUSIONS

This study showed that the bioavailability of 500mcg oral dofetilide was 98%, and the total systemic exposure and the rate of elimination from the blood were similar to that seen after 500mcg intravenous dofetilide. The intravenous dose caused marked prolongation of QT and QTc in some subjects. The study was terminated early (nine out of twelve subjects having been recruited) because QTc was prolonged to over 500msec in three subjects immediately after the intravenous infusion

BIOAVAILABILITY STUDY

STUDY 115-254 **VOLUMES: 2.60**

INVESTIGATOR AND LOCATION:

STUDY DATE: February to March 1996.

OBJECTIVES:
To determine whether the bioavailability of dofetilide 500mcg differed when administered as a 1) 500mcg capsule with a stability effect on extended storage at elevated temperatures and humidity (ICH accelerated conditions) labelled as 'cross-linked' in the protocol and tables and as stability effect capsules in the text, 2) 500mcg capsule with an isolated hydrophobic effect manufacture effect giving a non-standard water dissolution profile (label = non-standard or hydrophobic effect capsules) and 3) 500mcg commercial capsule with a standard water dissolution profile. To evaluate the safety and toleration of this dose in healthy male subjects.

FORMULATIONS:
Dofetilide standard dissolution capsule 500mcg (Lot No 4503-043),
dofetilide Stability Effect capsule 500mcg (Lot No 4503-016)
and dofetilide hydrophobic effect capsule 500mcg (Lot No 4503-042).
All capsules had an expiry date of July 1996.

STUDY DESIGN:
This was an open, randomised (Latin square), three-way crossover study investigating the bioavailability of a single 500mcg dose of dofetilide administered as different batches of commercial capsule. The study consisted of three, 48-hour treatment periods (separated by a seven-day minimum washout) On Day 1 of each study period, 5ml blood samples (to provide 1.5ml plasma) were taken for the assessment of plasma concentrations of dofetilide. The samples were to be collected in heparinised tubes at time 0 (baseline pre-dose)
and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose.

ASSAYS:

DATA ANALYSIS:
AUC, Cmax, Tmax, and Kel were determined. ANOVA was performed.

RESULTS: Table 1 and Figure 1 summarize the pharmacokinetic data obtained from the study.

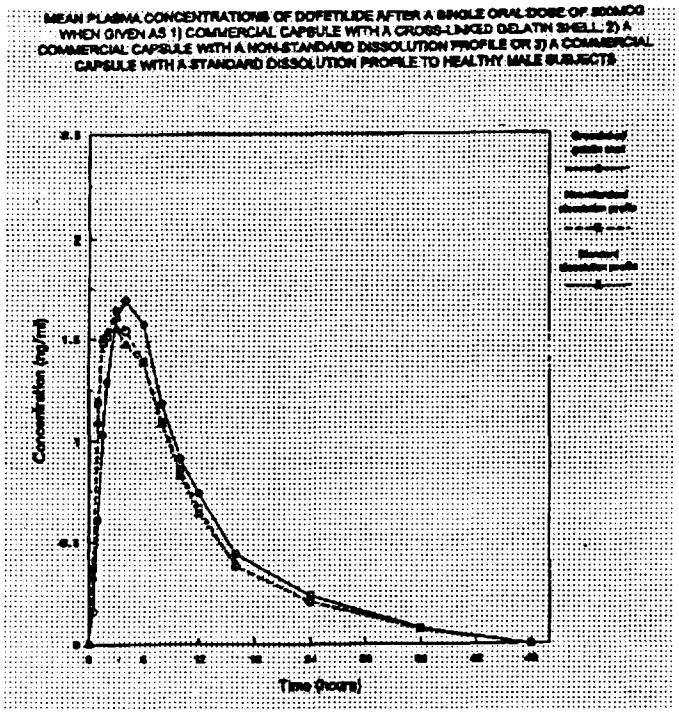
Table 1. Pharmacokinetic Parameters

Parameter mean[a]	Standard (reference)	Stability Effect	Ratio (%) or difference between means	n	90% CIs
Cmax (ng/ml)	1.75		100.6%	18	94.9%; 106.6%
Tmax (h)	2.8	1.77	1.1 h	18	0.5; 1.8
AUC (ng.h/ml)	20.39	3.9	106.2%	18	102.4%; 110.2%
Kel (/h)	0.089	21.66	0.001 h	18	-0.003; 0.006
t½ (h)[b]	7.8	0.090	0.1 h	18	-
		7.7			
	Standard	Hydrophobic Effect			
Cmax (ng/ml)	1.75	1.69	100.0%	18	94.3%; 105.9%
Tmax (h)	2.8	2.8	0.1 h	18	-0.6; 0.7
AUC (ng.h/ml)	20.39	20.97	102.8%	18	99.1%; 106.7%
Kel (/h)	0.089	0.087	-0.002 h	18	-0.006; 0.003
t½ (h)[b]	7.8	8.0	-0.2 h	18	-

[a] = adjusted means - geometric = Cmax, AUC, arithmetic = Tmax, Kel
[b] harmonic mean
CIs = 90 % confidence intervals back-transformed from the log scale

[a] = adjusted means - geometric = Cmax, AUC, arithmetic = Tmax, Kel
[b] harmonic mean
CIs = 90 % confidence intervals back-transformed from the log scale

Figure 1:



CONCLUSIONS:

This study showed that the three formulations of dofetilide were bioequivalent with respect to Cmax, and AUC therefore indicating that cross-linking of the gelatin capsule does not affect the bioavilability of dofetilide. The stability effect capsule was associated with an average of 1.1 hours delay in Tmax relative to the other two formulations.

APPEARS THIS WAY
ON ORIGINAL

BIOAVAILABILITY STUDY

STUDY 115-246 **VOLUMES: 2.57**

INVESTIGATOR AND LOCATION: [redacted]

STUDY DATE: July to August 1994.

RATIONALE:
Dofetilide is a potent antiarrhythmic drug and to-date, there are no mechanistically specific antagonists for dofetilide available in the case of excessive pharmacological effects. Activated charcoal has been generally recognised as an effective adsorbent of many drugs and other potentially toxic substances. Activated charcoal appreciably reduces the gastrointestinal absorption of various drugs when administered promptly. There is also evidence that it increases the clearance of drugs that have already been absorbed and are in the systemic circulation. This study was designed to assess the effect of activated charcoal, administered at two different timepoints, on the pharmacokinetics of dofetilide.

OBJECTIVES:
To determine the effect of activated charcoal given at two timepoints, on the pharmacokinetics of dofetilide following a single oral dose of 500mcg administered as a capsule.

FORMULATIONS:
Dofetilide 500mcg capsules FID No S00145AB, Lot No 2958-070).
Activated charcoal provided as Carbomix (Penn Pharmaceuticals).

STUDY DESIGN:
This was an open, randomized, three-way crossover study in 18 healthy volunteers. Each subject received three dose regimens in random order, each separated by a period of 1-2 weeks. Subjects received either a single dose of dofetilide (500mcg), or a single dose of dofetilide (500mcg) followed by activated charcoal (50g as a slurry, total volume 500ml) at either 15 minutes or 4 hours afterwards. On each visit, blood samples (about 6ml) sufficient to provide 3ml plasma were to be collected in heparinised tubes at time 0 (baseline pre-dose) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32 and 48 hours post-dose.

ASSAY:
[redacted]

DATA ANALYSIS:
AUC, Cmax, Tmax, and Kel were determined. ANOVA was performed.

RESULTS: Table 1 and Figure 1 summarize the pharmacokinetic data obtained from the study.

Table 1. Pharmacokinetic Parameters

	Dofetilide 500mcg (mean ± SD (n))		Dofetilide 500mcg + charcoal (15mins) (mean ± SD (n))		Dofetilide 500mcg + charcoal (4hrs) (mean ± SD (n))	
Cmax (ng/ml)	1.86 ± 0.50	(18)	0.20 ± 0.26	(18)	1.98 ± 0.57	(18)
Tmax (h)	2.5 ± 0.7	(18)	2.9 ± 5.0	(11)	2.4 ± 1.2	(18)
T1/2 (h)	7.4[a]	(13)	[b]		7.4[a]	(17)
AUCt (ng.h/ml)	19.1 ± 3.0	(18)	1.2 ± 1.6	(18)	17.9 ± 3.1	(18)
Kel (/h)	0.093 ± 0.020	(13)	[b]		0.093 ± 0.021	(17)

[a] Harmonic mean; [b] Could not be calculated

Table 2:

DOFETILIDE PROTOCOL 246
ANALYSIS OF DOFETILIDE PHARMACOKINETIC PARAMETERS SUMMARY

COMPARISON: Dofetilide 500mcg +charcoal (15mins) / Dofetilide 500mcg

	LOG TRANSFORMED DATA			ANTI-LOG*		
	DIFFERENCE BETWEEN MEANS	90% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS LOWER	UPPER	RATIO BETWEEN MEANS	90% CONFIDENCE LIMITS ON RATIO BETWEEN MEANS LOWER	UPPER
AUCt (ng.h/ml)	-2.43	-2.77	-2.08	8.8%	6.3%	12.4%
Cmax (ng/ml)	-2.02	-2.33	-1.70	13.3%	9.8%	18.2%

Table 3:

ANALYSIS OF DOFETILIDE PHARMACOKINETIC PARAMETERS SUMMARY

COMPARISON: Dofetilide 500mcg +charcoal (4hrs) / Dofetilide 500mcg

	LOG TRANSFORMED DATA			ANTI-LOG*		
	DIFFERENCE BETWEEN MEANS	90% CONFIDENCE LIMITS ON DIFFERENCE BETWEEN MEANS LOWER	UPPER	RATIO BETWEEN MEANS	90% CONFIDENCE LIMITS ON RATIO BETWEEN MEANS LOWER	UPPER
AUCt (ng.h/ml)	-0.06	-0.32	0.19	92.8%	72.4%	121.3%
Cmax (ng/ml)	0.05	-0.20	0.31	105.6%	82.2%	135.8%

CONCLUSIONS

This study therefore showed that charcoal given 4 hours after dofetilide did not significantly affect absorption, but there was a large decrease in plasma levels and in the effects of the drug, caused by charcoal given 15 minutes after dofetilide. Little benefit would be obtained by giving charcoal 4 hours post dose, but charcoal would be useful in preventing absorption of dofetilide when given sufficiently early.

PHARMACOKINETICS-PHARMACODYNAMICS STUDY

STUDY 115-234 **VOLUME: 2.49**

INVESTIGATOR AND LOCATION:

STUDY DATES: June to September 1991

STUDY OBJECTIVES:
To examine the pharmacokinetics and pharmacodynamics, safety and tolerance of dofetilide after initial iv dosing followed by 3.5 days of oral administration.

Drug administration:
Dofetilide suitable for intravenous infusion provided as free base in solution (25 mcg/ml; FID No 0952, 746-33) and was diluted with the diluent.
Dofetilide suitable for oral dosing provided as two capsules per dose composed of the appropriate numbers of 250 mcg (FID No 0963, Lot No 904-04) and 500 mcg (FID No 0964, Lot No 904-05) capsules.
Matched placebo (solution and capsule) and diluent (FID No 0950, Lot No 953-45).

STUDY DESIGN:
This study was of a double-blind, placebo-controlled, randomized 3-way crossover design in 9 healthy male subjects. Subjects received all three treatments and were randomised to a sequence of dosing: regimen 1 (6mcg/kg intravenous dofetilide, immediately followed by oral doses of dofetilide (750 mcg bid)); regimen 2 (6 mcg/kg intravenous dofetilide immediately followed by oral doses of dofetilide (1000 mcg bid)) and regimen 3 (single intravenous dose of placebo followed immediately by oral doses of placebo bid). There was a 7 day washout period between regimens. All subjects were given a single intravenous infusion over 0.5 hours, followed immediately by oral doses at 12-hourly intervals for 3.5 days. Blood samples (approximately 4mls) were taken at the following times relative to the start of the intravenous dose on Day 1; pre-dose, 5, 10, 20, 30 (end of iv infusion), 35, 40, 45, 50, 55, 60 minutes and 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12 (prior to the second oral dose) and 24 hours (prior to the third oral dose). On the morning of Day 4 (following the seventh oral dose) blood was sampled as follows: pre-dose, 15, 30, 45, 60 minutes and at 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36 and 48 hours.

ASSAYS:

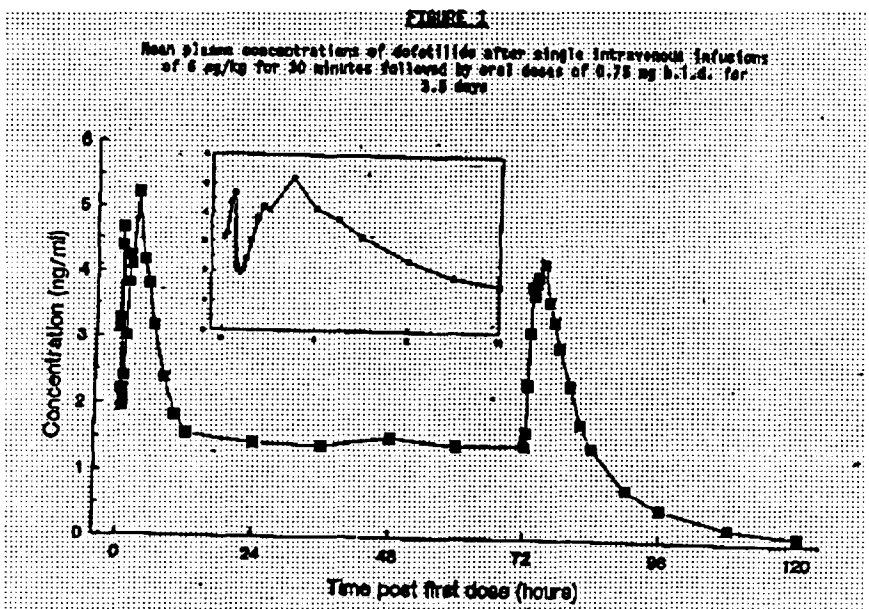
DATA ANALYSIS:
Cmax, Tmax, AUC, AUCt, Kel, T 1/2 were computed. 3-lead ECGs were recorded and PR, QRS, QT, QTc and RR intervals were determined.

RESULTS: Table 1-4 and Figures 1-6 summarize the data obtained from the study

Table 1. Pharmacokinetics and Pharmacodynamics of Dofetilide

Parameter	Regimen 1 (post iv infusion)	Regimen 1 (last oral dose)	Regimen 2 (post iv infusion)	Regimen 2 (last oral dose)
Cmin (ng/ml)	1.82 ± 0.21	1.44 ± 0.26	2.01 ± 0.30	1.98 ± 0.55
Cmax (ng/ml)	4.80 ± 1.63[1]	4.98 ± 0.82[2]	5.63 ± 1.12[3]	6.57 ± 1.43
Tmax (h)	0.52 ± 0.15	2.19 ± 1.43	0.48 ± 0.11	2.42 ± 1.22
AUC(0-12) (ng.h/ml)	-	33.18 ± 3.32	-	46.06 ± 9.73
Kel (/h)		0.071 ± 0.004		0.076 ± 0.006
T1/2 (h)		9.77		9.11

	Regimen 1	Regimen 2	All data
Slope (msec/ng/ml)[4]	12.1±3.7	11.7±3.9	11.8



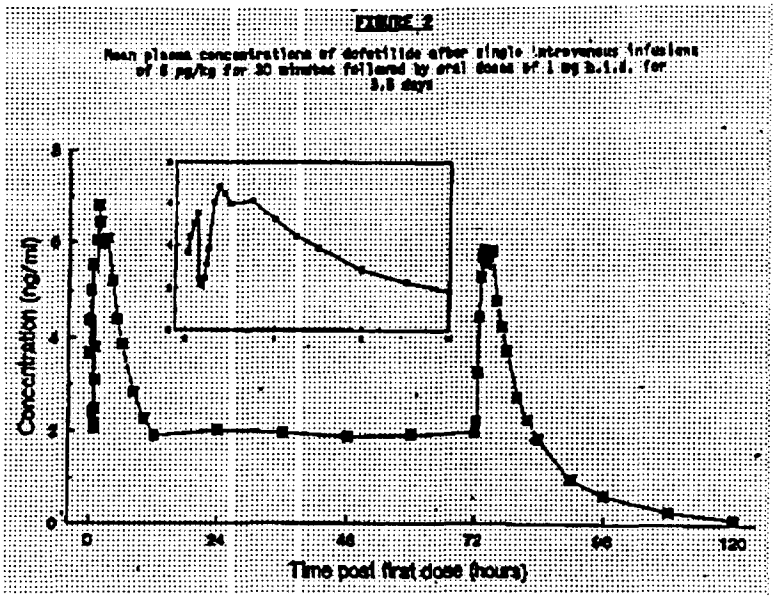

Concentration (ng/ml)
Time post first dose (hours)

Figure 3:

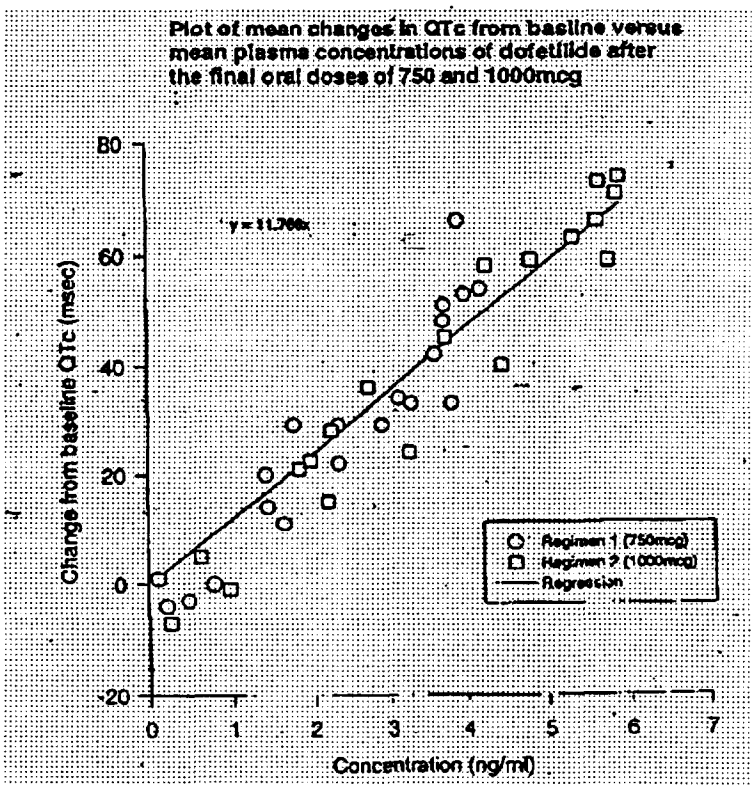

Plot of mean changes in QTc from baseline versus mean plasma concentrations of dofetilide after the final oral doses of 750 and 1000mcg
Change from baseline QTc (msec)
Concentration (ng/ml)
Regimen 1 (750mcg)
Regimen 2 (1000mcg)
Regression

Figure 4:

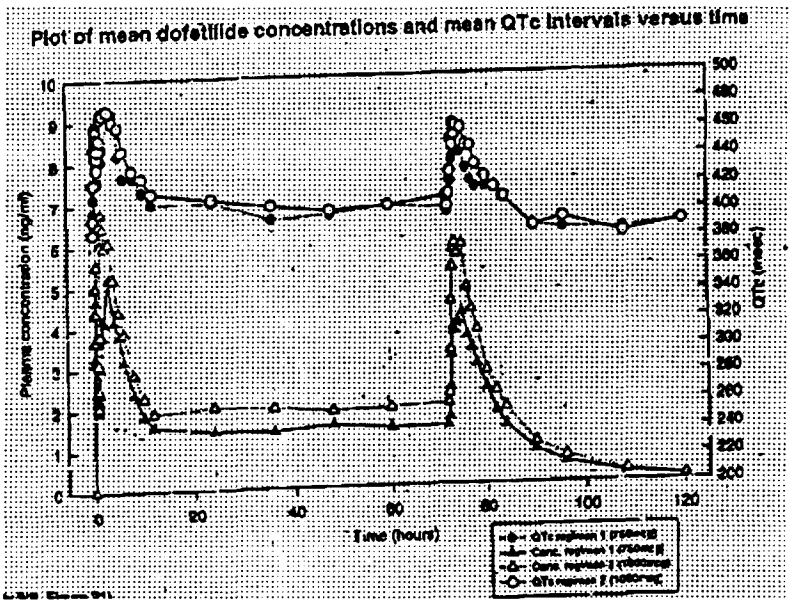


Figure 5:

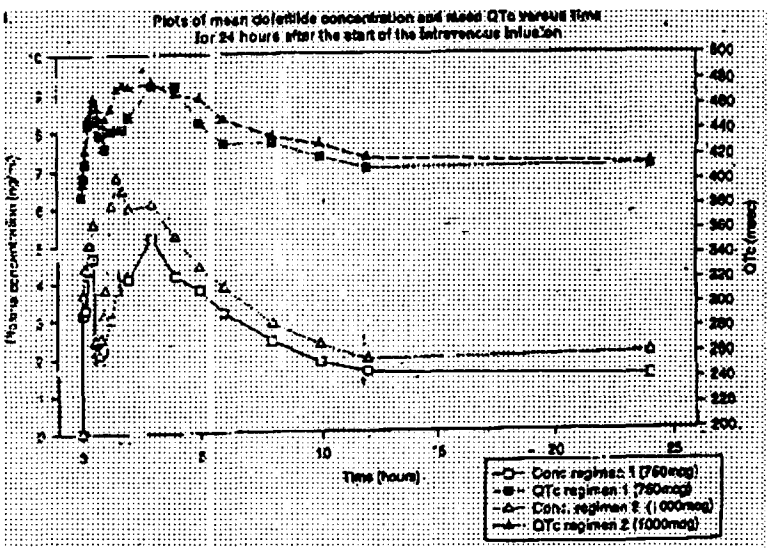
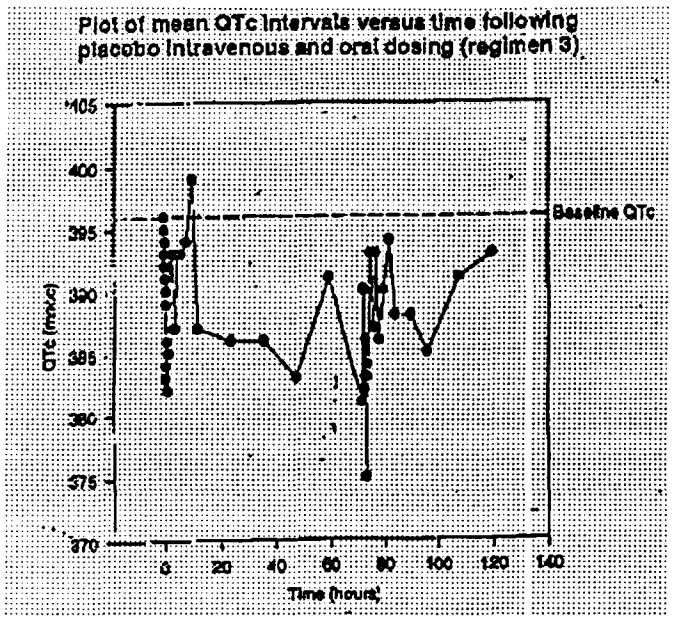


Figure 6:



CONCLUSIONS: This double-blind, placebo-controlled, 3-way crossover study in healthy male volunteers showed that the change in QTc versus plasma concentration was similar for regimens 1 and 2. It was concluded that a suitable dosing regimen could be designed to maintain appropriate plasma dofetilide concentrations and QTc prolongation by the oral route following rapid attainment by the intravenous route.

BIOAVAILABILITY STUDY

STUDY 115-003 **VOLUMES: 1.22**

INVESTIGATOR AND LOCATION:

STUDY DATE: January - March 1993.

RATIONALE:
The absorption of several drugs is altered secondary to changes in gastric pH. Dofetilide is a mildly basic drug (pka=7), and the effect of gastric pH on its bioavailability is not known. Although omeprazole may also interfere with the metabolism of drugs metabolized by the cytochrome P450 enzyme system either by enzyme inhibition or induction, such interference has been described only following repeated dosing for at least 7 days. In this study, involving acute treatment with omeprazole to determine the effect of omeprazole-induced increase in gastric pH on the relative bioavailability of dofetilide, effects on hepatic enzyme activity were not expected to be significant.
Absorbed antacids neutralize gastric acidity to elevate gastric pH and may also alter urinary pH, affecting the rate of renal elimination of some drugs. Because there is a possibility that co-administration of dofetilide and antacids may occur in practice, Maalox suspension (aluminum hydroxide 100 mg/ml & magnesium hydroxide 90 mg/ml) was to be used in this study to assess its effect on the relative bioavailability of dofetilide.

OBJECTIVES:
To (1) determine the effect of omeprazole on the relative bioavailability of dofetilide and (2) assess the effect of the antacid Maalox on the relative bioavailability of dofetilide.

FORMULATIONS:
Dofetilide 500 mcg research capsule formulation (FID #0964, Lot #503-20); Omeprazole 20 mg commercial capsule (Prilosec); Maalox Xtra Strength Plus 30ml (Rhone Pharm.); placebo capsule (FID #0034, Lot #748-17).

STUDY DESIGN:
This was an open, randomized, placebo-controlled, three-way, cross-over study with 3 treatment periods, each separated by at least 7 days. Dofetilide (500 mcg) was to be administered as a single dose only on days 1, 8, and 15. The individual treatments were dofetilide after treatment with omeprazole, dofetilide after treatment with placebo, and dofetilide after treatment with the antacid Maalox. Blood samples for determination of plasma concentrations were collected predose on study Days 1, 8, and 15, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours post-dofetilide dosing. All urine voided during the 24 hours following each dosing with dofetilide (on Days 1, 8, and 15) was to be collected in a single container. The total volume of each 24-hour urine collection for each subject was to be measured.

ASSAY:

DATA ANALYSIS:
AUC, Cmax, Tmax, and Kel were determined. Natural log-transformed AUC and Cmax and untransformed Tmax, Kel, excretion percentage and CLr were analyzed using an analysis of variance (ANOVA).

RESULTS: Tables 1-3 and Figure 1 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

Table 1. Mean Dofetilide Pharmacokinetic Parameters

Treatment	N		AUC(0-∞) (ng•h/ml)	Cmax (ng/ml)	Tmax (h)	Kel (hr^{-1})	T1/2[b] (h)	CL_r (ml/min)	Urinary Excretion (%)
Omeprazole[a]	12	Arithmetic	21.9[c]	1.95	2.4	0.0798[c]	8.7[c]	329.6	73
		(SD)	(3.6)	(0.57)	(0.8)	(0.0100)	–	(76.0)	(11)
		Geometric	21.6	1.88	–	–	–	–	–
Placebo[a]	12	Arithmetic	22.4[d]	1.86	3.0	0.0781[d]	8.9[d]	329.1	73
		(SD)	(4.9)	(0.55)	(1.5)	(0.0058)	–	(84.5)	(9)
		Geometric	21.9	1.80	–	–	–	–	–
Maalox[a]	12	Arithmetic	21.8[e]	1.71	3.2	0.0724[e]	9.6[e]	316.5	68
		(SD)	(2.9)	(0.27)	(1.1)	(0.0136)	–	(80.2)	(14)
		Geometric	21.6	1.69	–	–	–	–	–

a- Omeprazole 40 mg x 2 doses (@2200 and 0600) prior to Dofetilide 500 µg x 1 dose (@ 0800).
Placebo x 2 doses (@2200 and 0600) prior to Dofetilide 500 µg x 1 dose (@ 0800).
Maalox 30 ml x 3 doses (@2200, 0600, and 0730) prior to Dofetilide 500 µg x 1 dose (@ 0800).
b- ln 2/mean Kel.
c- N = 11
d- N = 9
e- N = 10

Table 2:

ANALYSIS OF DOFETILIDE PHARMACOKINETIC PARAMETERS SUMMARY
(ALL DOFETILIDE CAPSULES 500 MCG)

Pharmacokinetic Parameter	Comparison			90% Confidence Limits
		Adjusted Geometric Means	Ratio	
AUC (ng.h/ml)	D + M vs. B + P	21.10 vs. 22.04	95.7%	(91.1%, 100.6%)
	D + C vs. B + P	21.74 vs. 22.04	98.6%	(94.1%, 103.3%)
Cmax (ng/ml)	D + M vs. B + P	1.69 vs. 1.90	94.1%	(83.0%, 106.1%)
	D + C vs. B + P	1.84 vs. 1.90	104.7%	(94.5%, 115.9%)
		Adjusted Arithmetic Means	Difference	
Tmax (h)	D + M vs. B + P	2.2 vs. 2.0	0.2	(-0.5, 1.0)
	D + C vs. B + P	2.4 vs. 2.0	-0.5	(-1.2, 0.2)
Kel (/h)	D + M vs. B + P	0.0716 vs. 0.0775	-0.0060	(-0.0139, 0.0012)
	D + C vs. B + P	0.0786 vs. 0.0775	0.0010	(-0.0055, 0.0081)
CLr (ml/min)	D + M vs. B + P	316.3 vs. 329.1	-12.7	(-40.2, 14.9)
	D + C vs. B + P	329.6 vs. 329.1	0.5	(-27.1, 28.0)
Excretion Percentage	D + M vs. B + P	68.44 vs. 72.55	-4.12	(-8.26, 0.03)
	D + C vs. B + P	73.01 vs. 72.55	0.46	(-3.68, 4.61)

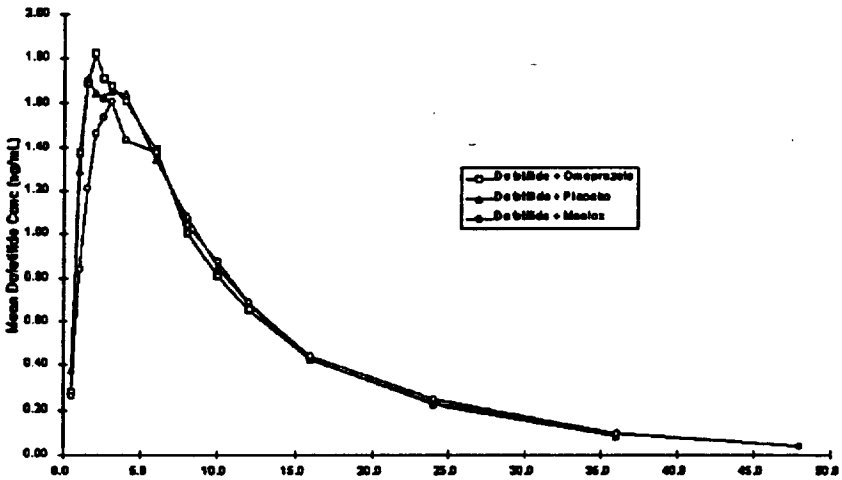
Table 3:

MEAN LEAD II QTC CHANGES FROM BASELINE FOR EACH TREATMENT
(ALL DOFETILIDE CAPSULES 500 MCG)

QTc Interval (msec)

		TIME POST DOSE		
		Baseline	2 Hours	24 Hours
TREATMENT				
DOFETILIDE+ MAALOX	Mean	273.0	26.9	9.0
	SE	3.2	5.6	4.5
	N	12	12	12
DOFETILIDE+ OMEPRAZOLE	Mean	273.5	25.6	5.9
	SE	4.0	2.5	2.6
	N	12	12	12
DOFETILIDE+ PLACEBO	Mean	269.2	42.3	8.8
	SE	4.3	4.3	4.0
	N	12	12	12

Figure 1. Mean Dofetilide Plasma Concentrations Following Single Oral 500 mcg Doses After Pre-Treatment With Omeprazole (40 mg x 2 Doses), Placebo (x 2 Doses), and Maalox (30 ml x 3 Doses) to Healthy Male Subjects



CONCLUSIONS: The geometric mean dofetilide AUC and Cmax values following pre-treatment with either omeprazole or Maalox were very similar to those following pre-treatment with placebo. The mean Kel, renal clearance, and excretion percentage of dofetilide dose were also similar across all 3 treatments.
Statistical examination of the AUC ratios and Cmax ratios for the treatment comparisons of dofetilide with Maalox and dofetilide with omeprazole to those of dofetilide with placebo showed no statistically significant difference. A statistical comparison of the differences in means for Tmax, Kel, renal clearance, and excretion percentage for the dofetilide + Maalox and dofetilide + omeprazole treatments vs dofetilide + placebo showed no statistically significant difference. Dofetilide was well tolerated, with these results suggesting that pre-treatment with Maalox or omeprazole did not alter the single-dose pharmacokinetics of dofetilide.

SINGLE DOSE-RANGING STUDY

STUDY 115-201 **VOLUMES: 2.21**

INVESTIGATOR AND LOCATION:

STUDY DATE: June - November 1988.

OBJECTIVES:
To evaluate the safety, toleration, and pharmacokinetics of escalating single oral doses of dofetilide in healthy volunteers. To establish the dose of dofetilide required to produce measurable changes in QT interval.

FORMULATIONS:
1, 2, 5, 7.5, 10, 12.5, 15 mcg/kg (5 mg in 100 ml) of dofetilide in solution in a total volume of 100 ml (FID No. 0954, Lot No. 733-37), dofetilide powder 5 mg (Lot No 686-02). Placebo diluent - 100 ml of 0.002M HCl (FID No. 0925, Lot No 686-03). 0.002M HCl diluent for dofetilide, 100 ml (FID No. 0925,Lot No 733-34).

STUDY DESIGN:
This was a four-way, double-blind, randomized, placebo controlled, crossover study in sixteen subjects and a washout period of 7 days. Dofetilide was administered in order of increasing dose, and progression to higher doses was determined by the safety and toleration of the preceding doses. One dose of placebo was randomly inserted into the dosing scheme. The doses of dofetilide which were studied were 1 mcg/kg, 2 mcg/kg,5 mcg/kg, 7.5 mcg/kg, 10mcg/kg, 12.5 mcg/kg, and 15 mcg/kg. Blood samples for estimation of drug concentration were obtained immediately prior to dosing, and 1, 2, 3 and 4 hours post dose for doses 1 mcg/kg - 10 mcg/kg and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 48 hours after dose for doses 5 mcg/kg and 15 mcg/kg.

ASSAY:

DATA ANALYSIS:
AUC, Cmax, Tmax, Kel, t½ and urinary excretion were determined.

RESULTS: Table 1 and Figures 1-4 summarize the pharmacokinetics and pharmacodynamics data obtained from the study.

Table 1.

Pharmacokinetic Results:	Dofetilide			
Mean ± SD	5mcg/kg (n=1)	7.5mcg/kg (n=5)	10mcg/kg (n=8)	12.5mcg/kg (n=4)
Cmax (ng/ml)	1.12	2.06 ± 0.49	2.63 ± 0.43	3.78 ± 0.35
Tmax (h)	1.0	2.6 ± 1.3	2.9 ± 1.2	2.3 ± 0.9
AUC (ng.h/ml)	n/a	23.38 ± 8.55	35.57 ± 3.73*	41.63 ± 4.43
Kel (/h)	n/a	0.093 ± 0.027	0.081 ± 0.024*	0.090 ± 0.007
t½ (h)	n/a	7.5	8.6	7.7
Urinary excretion(%)	n/a	58 ± 6	64 ± 8	67 ± 6*

Plasma concentrations were below quantification with doses less than 5mcg/kg
n = number of subjects evaluated, * = 1 subject not evaluated, n/a = not applicable

Figure 1: