CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20931

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA 20-931 **SUBMISSION DATES:** NOV. 25, 1997
Priority: 1 S DEC. 1, 1997
TYKOSYN™ (Dofetilide, UK-68,798) MARCH 9, 1998
Capsules (0.125, 0.25 and 0.5 mg) JUNE 3, 1998
JUNE 25, 1998
JULY 31, 1998
AUG. 7, 1998
OCT. 9, 1998
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DEC. 10, 1998.

IND

PFIZER CENTRAL RESEARCH **REVIEWER**: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: Original NME

SYNOPSIS:

TIKOSYN (Dofetilide) is a Class III antiarrhythmic drug developed for the treatment of reenterant tachyarrhythmia. Dofetilide selectively inhibits the rapid component of the delayed rectifier potassium current I_{Kr}. The proposed indications for dofetilide are (1) the maintenance of normal sinus rhythm with associated symptoms relief in patients with supraventricular arrhythmias such as atrial fibrillation, atrial flutter and paroxysmal supraventricular tachycardia and (2) the conversion of atrial fibrillation and atrial flutter to normal sinus rhythm. The sponsor has studied the pharmacokinetics, pharmacodynamics, the relationship between the two, the bioavailability, bioequivalency, interaction with food and drugs, safety and toleration of dofetilide in normal healthy volunteers as well as in special patient populations relevant to its potential use. Absolute bioavailability is about 98% and dofetilide pharmacokinetics were approximately linear with both single and multiple dose administration. The mean percentage of dosed radioactivity recovered in the urine was 80% following IV administration and 78% following oral administration. Only a small proportion of dofetilide was recovered in the feces (2% and 10% after IV and oral administration, respectively). *In vitro* human microsomal metabolic studies showed that dofetilide is

metabolized by CYP3A4 and does not significantly inhibit metabolism of known CYP 2C9, CYP2D6 and CYP3A4 substrates over the concentration range μM. Studies in healthy volunteers have shown that dofetilide does not affect the pharmacokinetics of concomitant medications such as: warfarin, digoxin, propranolol, phenytoin, theophylline, and oral contraceptives. In addition, in healthy volunteers, amlodipine, phenytoin, glyburide, ranitidine, omeprazole, antacid (aluminum and magnesium hydroxides such as Maalox) and theophylline do not affect the pharmacokinetics of dofetilide. Dofetilide exposure is increased when co-administered with cimetidine in a dose related fashion with an approximately 50% increase in dofetilide exposure with 400mg cimetidine bid. The combination of dofetilide and cimetidine administration is contra-indicated. Co-administration of dofetilide with verapamil resulted in increases in dofetilide peak plasma levels of 40%. In volunteers with varying degrees of renal impairment and patients with arrhythmias the clearance of dofetilide decreases with decreasing creatinine clearance. In clinical studies the half-life of dofetilide is also extended in subjects with lower creatinine clearances. Thus, dosage adjustment is required based on creatinine clearance. There was no clinically significant alteration in the pharmacokinetics of dofetilide in volunteers with mild to moderate hepatic impairment compared to healthy volunteers. Population pharmacokinetic analyses of dofetilide given orally indicate that the plasma concentrations in patients with supraventricular and ventricular arrhythmias are similar to normal healthy volunteers after adjusting for renal function. Studies with intravenously administered dofetilide showed that there is no difference in pharmacokinetic parameters between patients with ischemic heart disease and healthy volunteers. Apparent clearance was significantly lower and plasma concentrations 25% higher in elderly (>65 years) compared to young healthy volunteers. This reduced clearance is accounted for primarily by a reduction in renal function which occurs in the elderly and any dosage adjustment should be made on the basis of creatinine clearance. In healthy volunteers and in patients with supraventricular and ventricular tachyarrhythmias, the relationship of dofetilide plasma levels and QTc were linear. The concentration-QTc relationship in ischemic heart disease patients is similar to that in healthy volunteers after intravenous dosing of dofetilide. The clinical trial formulations are bioequivalent to the to-be-marketed formulations. An *in vitro* dissolution method has been provided and but the recommended dissolution specification of Q % at minutes should be changed to Q % at minutes. Bioequivalence was demonstrated between "cross-linked" capsule formulation with low dissolution (mean %dissolved at minutes %) and the capsules with isolated hydrophobic effect (mean %dissolved at minutes %) to capsules with normal dissolution profile (mean %dissolved at minutes %) showing that proposed dissolution method is not reflective of the bioavailability of dofetilide. Therefore, this will be an interim dissolution specification until a dissolution method that will correlate *in vitro* dissolution to *in vivo* perfomance is developed.

RECOMMENDATION:

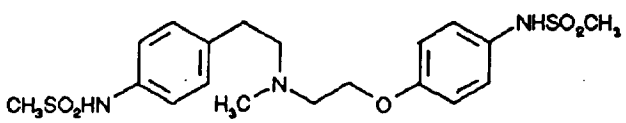
The Division of Pharmaceutical Evaluation I has reviewed the sponsor's NDA 20-931 and recommends that the sponsor should respond to the comments below (pages 22-23).

TABLE OF CONTENTS:

Appendix (Study Summaries)

BACKGROUND: Dofetilide (UK-68,798) has been classified as the first oral Vaughan Williams Class III antiarrhythmic and has the structure shown in Figure 1. An intravenous (i.v.) formulation of dofetilide has been used in pharmacokinetic, mechanistic and clinical studies, but this is not being developed commercially. A total of 74 clinical pharmacology studies have been conducted with dofetilide but many of these studies were not relevant to this NDA. A total of 44 pharmacokinetics and pharmacodynamics studies, 3 *in vitro* studies and 3 population pharmacokinetics and pharmacodynamic analyses were reviewed. The most serious overall adverse reaction is Torsades de Pointes. The recommended dosing is 0.5 mg twice daily.

FIGURE 1. Structural formula of Dofetilide



Molecular Formula of Dofetilide: $C_{19}H_{27}N_3O_5S_2$

Molecular Weight of Dofetilide: 441.6

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

Physical and Chemical Characteristics

Solubility: Solubility data for dofetilide in (a) various solvents (20°C - 23°C) and (b) aqueous media (20°C)are provided below.

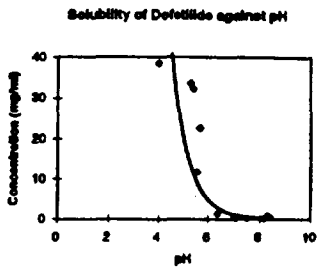
(a)

Solvent	Solubility (mg/mL)
diethyl ether	<0.1
hexane	<0.1
toluene	<0.1
water	<0.1
propan-2-ol	0.4
absolute ethanol	2.1
dichloromethane	2.7
ethyl acetate	3.1
methanol	12.6
acetonitrile	18.7
0.1M aqueous sodium hydroxide	21.0
0.1M aqueous hydrochloric acid	36.8
acetone	50.4
N,N-dimethylformamide	271.8

(b)

Buffer/Media	Final pH	Saturation solubility (mg/mL)
Glycine	6.4	32.2
Citrate pH3	4.0	38.5
Lactate	5.3	33.7
Acetate	5.5	11.8
Citrate pH6	6.4	1.24
Phosphate	7.1	0.260
Tris[1]	8.2	0.067
SGN[2]	6.4	22.8
1mM HCl	7.1	0.561
Saline	6.2	0.103
SIN[3]	6.8	0.545
Water	6.5	0.070
SIF[4]	7.5	0.149

[1] Tris is tromethamine buffer
[2] SGN is simulated gastric fluid, no pepsin
[3] SIN is simulated intestinal fluid, no pancreatin
[4] SIF is simulated intestinal fluid (with NaCl)



Ionization Constant (pKa): The ionization constants for dofetilide in water were determined by potentiometric titration against 0.5M aqueous potassium hydroxide. The results are as follows:
Solvent : Water at 26°C
pKa1 = 7.89 ± 0.03
pKa2 = 8.83 ± 0.03
pKa3 = 9.38 ± 0.03
pKa1 corresponds to the protonation of the tertiary amine, pKa2 and pKa3 are due to removal of the N-H proton from the sulphonamido groups attached to the phenethyl ring and the phenoxy ring respectively.

Partition Coefficient:
The log D value for dofetilide at pH 7.4 (n-octanol – buffer) has been measured as 0.93, the average of three determinations (0.94, 0.91, 0.93). The log D values for dofetilide at pH 6.4 and 5.4 have also been measured as -0.09 and -1.05.

Melting point: 163°C

Hygroscopicity: Not hygroscopic

Isomerism: Contains no chiral centers and does not exist in other isomeric forms

SUMMARY OF BIOAVAILABILITY / PHARMACOKINETICS / PHARMACODYNAMICS

I. BIOAVAILABILITY/BIOEQUIVALENCE:

A. Absolute Bioavailability: With reference to a 500 mcg IV dose (infusion), the absolute bioavailabilty of dofetilide given as 500 mcg capsule averaged 98.0% (CV=9.3; Study 115-212). Exposure and elimination rates are closely equivalent between intravenous and capsule formulations. The capsule formulation is bioequivalent to the dofetilide solution (Study 115-210)

B Bioequivalence: Bioequivalence was evaluated on log-transformed parameters and 90% confidence intervals were reported. Study 115-012 compared the proposed 500 mcg commercial oral capsule formulation of dofetilide (FID #QC2445), and the 500 mcg clinical oral capsule formulation of dofetilide (FID #0964) while Study 115-013 compared the 125 mcg commercial oral capsule formulation of dofetilide (FID #QC2442), and the 500 mcg clinical oral capsule formulation of dofetilide (FID #0964). The clinical batches and the final commercial formulations were bioequivalent.
Study 115-254 determined the bioavailability of dofetilide 500mcg when administered as a (i) 500mcg capsule with a stability effect on extended storage at elevated temperatures and humidity (ICH accelerated conditions; labeled as 'cross-linked'), (ii) 500mcg capsule with an isolated hydrophobic effect manufacture effect giving a non-standard water dissolution profile (labeled = non-standard or hydrophobic effect capsules) and (iii) 500mcg commercial capsule with a standard water dissolution profile. 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 bioavailability of dofetilide. The stability effect capsule was associated with an average of 1.1 hours delay in Tmax relative to the other two formulations.

C. Food effect: The effect of a standard breakfast on the absorption of dofetilide administered as the proposed 500 mcg commercial capsule was evaluated (Study 115-015). Food did not affect the bioavailability (bioequivalence was observed) but there was a 2-hour delay in absorption of dofetilide from the commercial capsule. The effect of a high fat breakfast on the biavailability dofetilide administered as the proposed 250 mcg commercial capsule was evaluated (Study 115-244). Bioequivalence was observed with regard to Cmax but AUC was increased by about 5% and Tmax delayed by about 0.8 hour.

Table 1: Food Effect Study 115-015 - Statistical assessment of bioequivalence

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

II. PHARMACOKINETICS:

Pharmacokinetics of dofetilide were evaluated in several studies in healthy volunteers as well as in the target population of patients with heart disease. Oral doses up to and including 1250 mcg and intravenous doses up to and including 12.5 mcg/kg were administered (Tables 2-5). Maximum observed plasma concentrations occur at about 2 - 3 hours in fasted subjects and at about 3 - 4 hours when dofetilide capsules are taken with food. The terminal half-life is approximately 10 hours and the systemic clearance is about 350 ml/min (range 348-366 ml/min). Volume of distribution is ranged from 228-276 L. The renal clearance ranged from 190- 260ml/min and the non-renal clearance ranged from 176-197 ml/min. Steady-state plasma concentrations are attained within 3-5 days and can be predicted from a single oral dose. Over the clinical dose range, plasma concentrations increase in a predictable, linear fashion for both single and multiple dosing. Variability in plasma concentrations within and between subjects is low. Once daily dosing did not seem to lead to accumulation, but under a twice daily dosing regimen, the accumulation index ranged from 1.5 to 2.

Table 2: Summary of Pharmacokinetic Data from Single Dose Administrations of mcg/kg Body Weight Basis

			Pharmacokinetic parameters; Mean *						
Protocol 115	Dose (mcg/kg)	N	AUC_t (ng.h/ml)	AUC (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)	% renally excreted	$t_{1/2}$ (h)	k_{el} (/h)
201	5 (sol)	1		N/A	1.12	1.0	-		
	7.5 (sol)	5		23.38	2.06	2.6	58%	7.5	0.093
	10 (sol)	6		35.57	2.83	2.9	64%	8.6	0.081
	12.5 (sol)	4		41.63	3.78	2.3	67%	7.7	0.090
202	2 (sol)	7	3.81	N/A	0.54	2.50	51.0%	N/A	N/A
	5 (sol)	10	13.62	15.82	1.29	2.40	62.2%	7.7	0.090
	7.5 (sol)	6	21.63	24.84	2.43	2.00	66.8%	7.6	0.091
	10 (sol)	6	29.47	33.0	2.77	1.20	57.8%	8.4	0.082

* Geometric mean for AUC_t, AUC and C_{max}; arithmetic mean for T_{max}. % renally excreted drug and k_{el}. Mean $t_{1/2}$ calculated from mean k_{el}

Table 3: Summary of Mean Pharmacokinetic Results from Protocol 115-203

	dofetilide 100mcg bid	dofetilide 200mcg od	dofetilide 200mcg bid	dofetilide 400mcg bid
Day 1				
C_{max} (ng/ml)	0.50	0.83	0.83	1.81
T_{max} (h)	2.5	2.1	2.6	2.0
AUC_t (ng.h/ml)	3.0	7.7	5.8	12.5
Day 10				
C_{max} (ng/ml)	0.59	0.87	1.19	2.73
T_{max} (h)	2.6	2.1	2.3	1.9
k_{el} (/h)	0.081	0.120	0.098	0.076
$t_{1/2}$ (h)	8.6	5.8	7.1	9.1
AUC_t (ng.h/ml)	4.4	7.6	8.5	19.1
Renal Clearance (ml/min)	287	289	217	195

Table 4: Summary of Pharmacokinetic Data from Single Fixed Dose Administrations of Dofetilide (Study Reports 115-216 and 115-212)

Protocol 115-	Dose (mcg)	N	Pharmacokinetic parameters; Mean *					
			AUC_τ (ng.h/ml)	AUC (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	k_{el} (/h)
216	500	3		21.2	2.98	1.3	7.7	
235	500 (young)	10		23.0	5.11	0.41	8.7	0.080
212 (iv)	500	9	22.3	24.6	8.21	0.17	7.4	0.093

* Geometric mean for AUC_τ, AUC and C_{max}; arithmetic mean for T_{max} and k_{el}. Mean $t_{1/2}$ calculated from mean k_{el}.

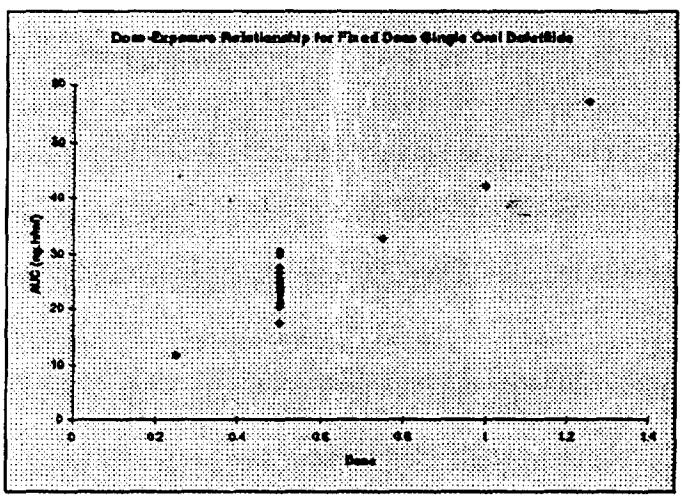
Table 5: Summary of Pharmacokinetics (Means) from Study 115-229

	330mcg tid	500mcg bid	500mcg tid	750mcg bid	830mcg tid	1250mcg bid
Day 1						
C_{max} (ng/ml)	1.70	2.64	2.26	3.54	3.55	5.47
T_{max} (h)	2.29	2.00	2.13	2.13	2.29	1.57
AUC_τ (ng h/ml)	8.61	17.03	10.81	23.55	18.89	37.50
Slope *(msec.ml/ng)	20.7	15.6	18.1	14.5	15.1	16.2
Day 5						
C_{max} (ng/ml)	3.04	3.80	4.78	5.23	7.71	10.07
T_{max} (h)	2.29	2.00	2.00	1.88	2.14	1.57
AUC_τ (ng h/ml)	16.75	25.39	25.54	37.50	40.10	62.07
K_{el} (/h)	0.070	0.066	0.073	0.069	0.073	0.069
Slope *(msec.ml/ng)	16.0	19.2	13.0	13.3	11.2	11.1

Note τ is 8 hours for tid and 12 hours for bid dosing

* = Slope of change in QTc/ plasma dofetilide concentration

Figure 2: Linearity of the Pharmacokinetics of Dofetilide (From various studies)



III. METABOLISM:

The mean percentage of dosed radioactivity recovered in the urine was 80% following IV administration and 78% following oral administration (Table 6) . Only a small proportion of dofetilide was recovered in the feces (2% and 10% after IV and oral administration, respectively) i.e most orally administered dofetilide is absorbed from the gastroiñtestinal tract. Analysis of the 0-24hr urine samples indicated that unchanged dofetilide made up the majority of radioactivity present in the urine (mean 83%), representing 66% of the administered

dofetilide. Five polar metabolites were detected in the urine, four of which were identified. The metabolite profiles were similar for both routes of administration. No single metabolite accounted for more than 3.5% or less than 1% of urine radioactivity in any individual. The two most lipophilic of these metabolites were the N-oxide and the N-desmethyl forms of dofetilide, the major metabolite is N-desmethyl-dofetilide (UK-71,385). Two other components were the carboxylic acid and secondary amine metabolites resulting from N-dealkylation type metabolism of dofetilide around the basic nitrogen. The metabolites are clinically inactive (below the lower limit of quantification in plasma and potency 20 or more fold lower than that of dofetilide) and therefore are not expected to contribute to the therapeutic or side effect profile of the compound.

In vitro human microsomal metabolic studies showed that dofetilide is metabolized by CYP3A4 and does not significantly inhibit metabolism of known CYP2C9, CYP2D6 and CYP3A4 substrates over the concentration range 0.01-100 μM (several orders of magnitude above therapeutic concentrations). In vitro N-demethylation of dofetilide is inhibited by CYP3A4 inhibitors (ketoconazole and TAO) and induced by CYP3A4 inducers (AFN).

Table 6: Metabolic Profiling of Dofetilide (Study 115-216) - Mean pharmacokinetic parameters (+SD)

Parameter	Oral		Intravenous	
	Dofetilide	Radioactivity	Dofetilide	Radioactivity
C_{max} (ng/ml)	1.65±0.6	2.2±0.9	2.98±0.9	3.4±1.0
T_{max} (h)	2.3±1.5	1.3±0.6	1.3±0.3	1.4±0.1
AUC_{0-24} (ng.h/ml)	17.5±3.2	24.9±4.1	21.2±4.5	27.3±4.8
$t_{1/2}$ (h)	8.0±2.0	7.2±0.6	7.7±0.6	7.8±0.8
Excretion of radioactivity (% dose):				
Urine 0-168 hours	77.53±2.98		80.04±3.59	
Feces 0-144 hours	10.27±4.01		2.23±1.48	
Total Recovery	87.80±6.42		82.27±2.17	

VI. SPECIAL POPULATIONS:

A. Renal Impairment: Protocol 115-219 was a renal impairment study comparing data obtained with small numbers of renally impaired patients to those from a healthy volunteer study (data from Protocol 115-244). Dofetilide pharmacokinetics are highly dependent on renal function. Cmax and AUC were proportionally greater, $t_{1/2}$ increased and Tmax extended in the severely impaired subjects compared to the moderately impaired subjects (Table 7). Other studies, including the metabolism and excretion study Protocol 115-216 which used radio-labeled dofetilide, have estimated dofetilide to be 60-70% renally excreted.

Table 7: Summary of Dofetilide Pharmacokinetic Data from Protocol 115-219

Dose	Population	N	Pharmacokinetic parameters; Mean *					
			CL/f (L/h)	AUC (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	k_{el} (/h)
500mcg capsule	Normal data from study 115-244	18	21.7	23.5	1.97	3.1	9.8	0.0708
500mcg capsule	moderate impairment (CL_{cr} 29.3-39.5 ml/min)	5	7.59	89.5	2.69	3.3	21.7	0.0320
500mcg capsule	severe impairment (CL_{cr} 8.7-17.4 ml/min)	6	4.55 (n=5)	116.7 (n=5)	3.11	4.5	31.5	0.0220 (n=5)

* Geometric mean for AUC, AUC and C_{max}; arithmetic mean for T_{max} and k_{el}. Mean $t_{1/2}$ calculated from mean k_{el}.

Exploratory work confirmed a linear relationship between creatinine clearance and apparent clearance of dofetilide:

CL/f = 2.81+0.17xCLCr, with r^2= 0.88 or approximately CL/f = 0.2xCLCr.

Based on this relationship, an algorithm was designed to normalize exposure for subjects with different creatinine clearances, taking a CLCr of 100-150ml/min to be normal. On this basis, subjects with a creatinine clearance larger than 60 ml/min should not require adjustment of their intended dose, subjects with creatinine clearances between 40 and 60ml/min should reduce the intended dose by half, and subjects with creatinine clearances between 20 and 40ml/min should use a further reduction by half to normalize their predicted exposure to dofetilide.

A sub-population from the primary studies of DIAMOND CHF and MI, who were taking randomized treatment for at least one month and whose renal function was defined by creatinine clearance (CLCr) levels as normal (CLCr >60ml/min), mildly impaired (>40-<60ml/min) or moderately impaired (>20-<40ml/min) provided blood and urine samples across a dose interval to measure concentrations of dofetilide (Table 8).

Table 8: Summary of Pharmacokinetic Results from Protocol 115-400 (DIAMOND)-RI

	Degree of Impairment		
Parameter (mean (n))	Normal	Mild	Moderate
AUC_{ss} * (ng.h/ml)	25.7 (7)	20.7 (9)	28.7 (10)
Cmax * (ng/ml)	3.4 (7)	2.4 (9)	2.0 (10)
Cavss * (ng/ml)	2.1 (7)	1.7 (9)	1.2 (10)
CL/f (L/h)	20.6 (10)	12.5 (10)	8.8 (10)
CLr (L/h)	12.6 (10)	6.4 (8)	4.5 (9)
Protein binding (%)	62.9 (10)	64.9 (10)	67.9 (8)

* geometric mean

B. Hepatic Impairment: Protocol 115-002 explored dofetilide pharmacokinetics after a single (first) dose and at steady-state in patients with hepatic impairment (Table 9). Dofetilide pharmacokinetics were not affected by hepatic failure following either a single dose or at pseudo steady-state. Patients with mild to moderate hepatic failure do not require adjustment of their dofetilide dose.

Table 9: Summary of Dofetilide Pharmacokinetic Data in Hepatic Failure

		N	Pharmacokinetic parameters; Mean *					
			AUC_{∞} (ng.h/ml)	CLr (ml/min)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	k_{el} (/h)
500mcg capsule first dose	Normal	12	14.07	226.13	1.86	2.38	8.8	0.0786
	All hep. Imp.	13	13.54	243.89	1.87	3.02	8.2	0.0843
	Child-Pugh A	7	14.50	217.95	1.95	2.94	8.6	0.0802
	B	6	12.65	269.83	1.79	3.10	7.8	0.0885
last dose	Normal		20.23	219.20	2.67	2.04	11.0	0.0631
	All hep. Imp.		22.37	185.89	2.62	1.78	9.7	0.0717
	Child-Pugh A		24.89	247.78	3.10	1.94	9.2	0.0751
	B		20.11	124.00	2.56	1.63	10.1	0.0683

* Geometric mean for AUC_{∞}, AUC and C_{max}; arithmetic mean for T_{max} and k_{el}. Mean $t_{1/2}$ calculated from mean k_{el}.

C. Age and Gender: Protocol 115-235 was an open, cross-over study comparing the safety, pharmacokinetic and pharmacodynamic profiles of oral and intravenous doses of dofetilide in 11 elderly. The QTc response to dofetilide was significantly different between age groups and between and oral dosing. Mean maximum QTc increases from baseline were 79 and 86 msec for i.v. and orally dosed elderly respectively, and 97 and 132 msec for i.v. and orally dosed young respectively (Table 10). Although the difference by age lost its significance after adjustment for creatinine clearance, the difference by dose route remained. Non-renal clearance was different for young (176ml/min) and elderly (102ml/min) subjects following intravenous dosing, even after adjustment for creatinine clearance, indicating a reduction in liver metabolism with diminishing renal function. 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.

There is a difference in the pharmacokinetic of dofetilide between males and females (Figures 4 & 5). Body weight accounts for some of the observed difference but does not account for the total difference. Population pharmacokinetics analyses of Phase II and Phase III data indicated females had, on average, 18% and 12% respectively lower CL/F than males. The sponsor is conducting additional Phase I studies to provide data to better understand gender differences in dofetilide pharmacokinetics

Table 10: Summary of Dofetilide Pharmacokinetic Data by Age (Study 115-235)

PARAMETER	ORAL (500 mcg)		IV (2.5 mcg over 20 min)	
	YOUNG	ELDERLY	YOUNG	ELDERLY
C_{max} (ng/ml)	3.94 (0.65)	4.89 (1.30)	3.19 (0.92)	3.39 (0.25)
T_{max} (h)	2.33 (0.97)	2.38 (0.83)	0.41 (0.15)	0.43 (0.08)
AUC (ng.h/ml)	41.94 (7.21)	38.79 (7.32)	23.28 (3.40)	22.38 (4.02)
k_{el} (hr^{-1})	0.0725 (0.0100)	0.0558 (0.0087)	0.0804 (0.0125)	0.0608 (0.0088)
$t_{1/2}$ (h)	9.45	13.13	8.85	11.48
CL (ml/min)	-	-	366 (53)	297 (41)
CL_R (ml/min)	255 (73)	169 (39)	190 (100)	185 (40)
CL_{NR} (ml/min)	-	-	176 (74)	102 (37)
V (L)	-	-	274 (33)	206 (37)
F	0.84 (0.15)	0.91 (0.21)	-	-
^{a}Slope (msec/ng/ml)	23.7 (3.7)	13.6 (1.3)	23.7 (7.1)	20.9 (3.9)
^{a}QTc (msec)	113.1 (29.8)	86.1 (34.9)	94.6 (26.4)	79.3 (27.4)

a Mean maximum change from baseline
b Excluding subject 23 (see text)

Figure 4: Gender Differences in Dofetilide Pharmacokinetics (Study 115-014)

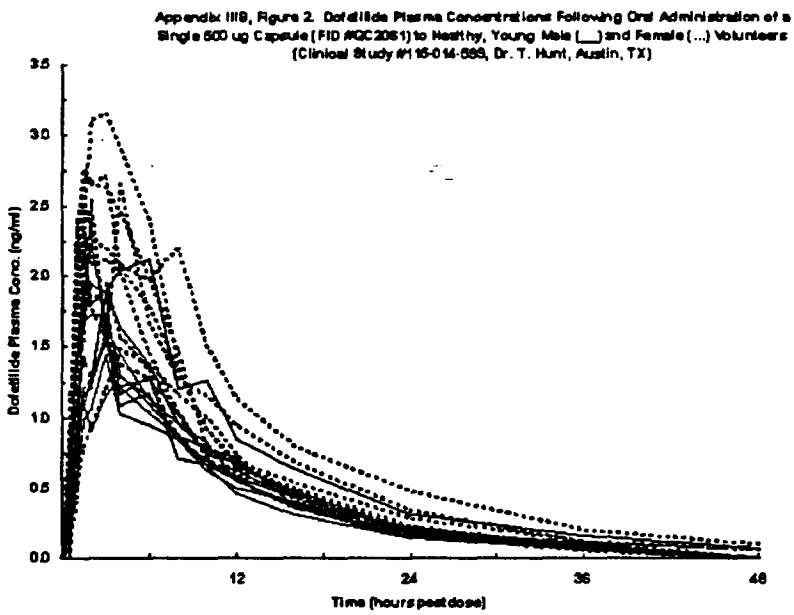
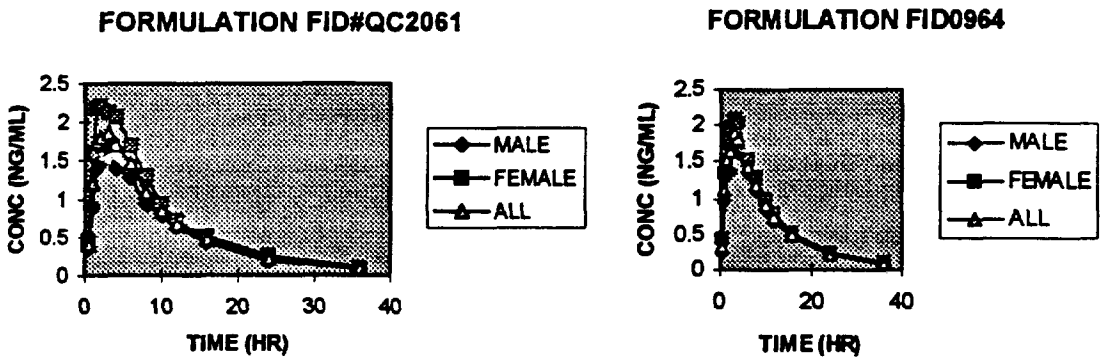


Figure 5: Mean Plasma Profiles Following Administration of Formulation FID #QC2061 and FID0964 (Study 115-014)



D. Dofetilide Pharmacokinetics in Patients with Atrial Fibrillation and Reduced Left Ventricular Ejection Fraction: Protocol 115-005 studied dofetilide pharmacokinetic and pharmacodynamic behavior in patients with stable atrial fibrillation (AF) and left ventricular dysfunction as compared to healthy volunteers (Table 11). In a single-blind, placebo-controlled, fixed sequence cross-over design, a total of 10 (5 evaluable in the AF and 4 in the control group) subjects received a capsule of placebo on Day 1. On Day 8, after a 7 day wash-out, they received an intravenous infusion of 8mcg/kg dofetilide. After another wash-out period of 7 days, they received 14 days of dofetilide 500mcg bid (to be reduced to 250mcg bid in case of QT prolongation exceeding 15%) from Day 15 to Day 29, inclusive. There was no correlation between dofetilide clearance and LVEF. There was a weak correlation between dofetilide clearance and age (r2= 0.28) and body weight (r2= 0.26) and a strong correlation between dofetilide clearance and creatinine clearance (r2= 0.79). When dofetilide clearance was corrected for creatinine clearance, the weak relationships with age and body weight were no longer demonstrated. There was a correlation (r2= 0.64) between dose normalised Cmax and creatinine clearance. The data support dosage adjustment recommendations based on creatinine clearance in order to achieve a consistent exposure in subjects with impaired renal function

Table 11: Summary of Dofetilide Pharmacokinetic Data in Patients with Atrial Fibrillation and Reduced Left Ventricular Ejection Fraction (Study 115-005)

		N	Pharmacokinetic parameters; Mean *					
			AUC ** (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	k_el (/h)	CLr (ml/min)
AF patients		5						
Day 8	8mcg/kg i.v.		42.32	10.63	0.45	13	0.053	166.7
Day 15	500mcg (first dose)		18.34	2.86	2.25		N/A	96.7
Day 29	500mcg (last dose)		60.34	4.26	2.75	18	0.039	168.9
Volunteers		4						
Day 8	8mcg/kg i.v.		36.38	6.70	0.40	10	0.066	239.9
Day 15	500mcg (first dose)		15.90	1.99	4.50		N/A	250.5
Day 29	500mcg (last dose)		38.60	3.23	1.25	14	0.048	261.7

* Geometric mean for AUC and C_{max}; arithmetic mean for T_{max} and k_el. Mean $t_{1/2}$ calculated from mean k_el

** AUC on Day 15 truncated to 12 hours because of bid dosing

V. DRUG INTERACTIONS:

A. Digoxin: Protocol 115-214 investigated the effect of 250mcg dofetilide bid for 5 days on the pharmacokinetics of steady-state digoxin, There were no significant differences between treatment groups for the Day 12 minus Day 7 digoxin pharmacokinetic data, nor for trough digoxin concentrations during the same period (Table 12).

Table 12: Digoxin Pharmacokinetics Results (Study 115-214)

	C_{max} * (nmol/l)	T_{max} (h)	$AUC_{(\tau=ss)}$* (nmol.h/ml)	CLr (ml/min)
Dofetilide (n=8)				
Day 7	2.02	1.25	20.51	149.16
Day 12	1.93	0.88	16.74	143.92
Placebo (n=5)				
Day 7	1.98	0.80	21.86	135.66
Day 12	1.88	1.10	17.83	155.26

* Geometric Means

B. Warfarin: An initial study (Protocol 115-213) looking for any potential interaction of dofetilide with warfarin concluded that dofetilide did not appear to have any effect on warfarin-induced mean increments in prothrombin time. This study used dofetilide 250mcg given bid, with a single dose of 20 mg of warfarin, but the increases in prothrombin time observed indicated that this dose was clinically marginal and the study was repeated using 40 mg of warfarin (Study 115-242). There was no statistically significant difference between the treatment groups in the mean AUECt values for prothrombin time. Administration of a single dose of warfarin had no apparent effect on the pharmacokinetics of dofetilide.

C. Propranolol: Protocol 115-215 was set up to investigate the effects of oral dofetilide, 250mcg bid for 4 days, on the pharmacodynamics and pharmacokinetics of steady-state propranolol. Dofetilide did not alter the pharmacodynamics or pharmacokinetics of propranolol. Plasma concentrations of dofetilide were within anticipated limits.

D. Cimetidine / Ranitidine: Protocol 115-004 was an observer-blind, randomized, placebo-controlled, multiple-dose, parallel group study. Dofetilide only was administered 500mcg bid for 9 days, with only the morning dose given on Day 10. On Day 5 the subjects were randomly assigned to receive either cimetidine 400 mg bid or placebo for 7 days. The concomitant administration of cimetidine with dofetilide resulted in an increase in AUC and Cmax. The increases in mean Cmax of 52% and in mean AUCτ of 58% in the group treated with cimetidine plus dofetilide from Day 4 to Day 10 were statistically significant (Table 13). Much of the increase in AUC and Cmax for the subjects treated with dofetilide and cimetidine could be attributed to a 44% decrease in renal clearance, a decrease which was statistically significant. Cimetidine is a non-specific cytochrome P450 inhibitor and also a potent inhibitor of the renal tubular secretion of several organic cations by competing for active tubular secretion by the organic transport system in the proximal tubule of the kidney.

Table 13: Pharmacokinetic and Pharmacodynamic (Change from Baseline in QTc) Results (Study 115-004)

	Group A (n=12)		Group B(n=12)	
	Dofetilide Day 4	Dofetilide + Cimetidine Day 10	Dofetilide Day 4	Dofetilide + Placebo Day 10
Pharmacokinetic Results				
AUC_{τ} (ng.h/ml)*	17.4	27.6 **	16.6	17.3
C_{max} (ng/ml)*	2.26	3.44 **	2.10	2.17
T_{max} (h)	2.6	2.6	3.1	2.3
K_{el} (h^{-1})	–	0.0534	–	0.0651
CL_r (ml/min)	343.7	192.9 **	419.2	334.3
Pharmacodynamic (change from baseline QTc) Results				
	Dofetilide Day 4	Dofetilide + Cim Day 10	Dofetilide Day 4	Dofetilide + Placebo Day 10
$AUEC_{\tau}$ (msec.h)	199.9	204.0	257.6	176.2
E_{max} (msec)	45.6	46.4	46.5	41.3

* Geometric means.

** Differences between Day 4 and Day 10 were statistically significant. Differences between the two treatment groups were significant for AUC_{τ} and C_{max} ($p \leq 0.0001$).

Protocol 115-253 was designed to investigate the effects of a lower dose of cimetidine (100 mg bid) on the pharmacokinetics and pharmacodynamics (i.e. change in QTc) of dofetilide, to determine the effects of cimetidine and ranitidine on QTc intervals in the absence of dofetilide and to evaluate the safety and toleration of dofetilide whilst being given concurrently with cimetidine and ranitidine. Subjects received cimetidine (C) (100 mg and 400 mg both bid), ranitidine (R) (150 mg bid) or placebo during four treatment periods of four days each with a single dose of dofetilide (D) (500mcg) on Day 2. Exposure to dofetilide increased when dosed concomitantly with cimetidine 400 mg: mean AUC_{0-48} was statistically significantly increased as well as mean Cmax, arising predominantly from a statistically significant decrease in the renal clearance of dofetilide. Cimetidine 100 mg caused a much smaller reduction in elimination arising from a modest decrease in the renal clearance of dofetilide. No clinically or statistically significant differences in renal or non-renal clearance were observed with ranitidine 150 mg when compared to placebo. A single dose of ranitidine 150 mg or cimetidine 100 mg alone did not significantly affect QTc. Thereafter, when dofetilide was dosed, QTc increased in line with increases in dofetilide plasma concentration. The change in maximum QTc after cimetidine 400 mg was statistically significantly larger than the change observed with placebo. After ranitidine 150 mg the QTc response was similar to the response after placebo.

E. Verapamil: Protocol 115-001 was designed to investigate whether any clinically significant pharmacokinetic or pharmacodynamic interaction occurs between dofetilide and verapamil. The concomitant administration of dofetilide and verapamil did not result in change in verapamil or norverapamil pharmacokinetic parameters. Cmax of dofetide increased by 42% while AUC(0- 4) and AUC(0- 12) increased by 24% and 14% respectively and Tmax decreased from 2.2 hours to 1.5 hours. This is consistent with verapamil increasing gut blood flow which, in turn, is responsible for the increased speed of absorption of dofetilide and with the inhibition of CYP3A4 by verapamil.

F. Amlodipine: Protocol 115-255 investigated the effect of multiple dose amlodipine on the

steady-state pharmacokinetics and pharmacodynamics of dofetilide. Co-administration of amlodipine with dofetilide had no significant effect on dofetilide pharmacokinetics and pharmacodynamics.

G. Phenytoin: Protocol 115-007 was an observer-blind, placebo-controlled, multi-dose, parallel group study of the pharmacokinetic and pharmacodynamic interaction between dofetilide and phenytoin. Concomitant administration of 300 mg of phenytoin sodium with dofetilide at a dose of 500mcg bid at steady-state had no clinically significant effects on dofetilide pharmacokinetics or pharmacodynamics. Protocol 115-006 was an observer-blind, placebo-controlled, multi-dose, parallel group study of the pharmacokinetic and pharmacodynamic interaction between dofetilide and phenytoin. Concomitant administration of 300 mg of phenytoin sodium with dofetilide at a dose of 500mcg bid at steady-state had no clinically significant effects on phenytoin pharmacokinetics or pharmacodynamics

H. Theophylline: Protocol 115-008 was an observer-blind, randomized, placebo-controlled, parallel group study of the effect of theophylline, administered as the sustained-release formulation, Theo-Dur, at a dose of 450 mg bid, on the pharmacokinetics and pharmacodynamics of dofetilide. The concomitant administration of theophylline and dofetilide resulted in increases in mean dofetilide AUCt (14%) and Cmax (6%) but no significant effect on the pharmacodynamics of dofetilide as assessed by QTc intervals. Protocol 115-009 was an observer-blind, randomized, placebo-controlled, parallel group study of the effect of dofetilide, on the pharmacokinetics and pharmacodynamics of theophylline (administered as the sustained-release formulation, Theo-Dur, at a dose of 450 mg bid). The concomitant administration of theophylline and dofetilide resulted in increases in mean dofetilide AUCt (16%) and Cmax (14%) but no significant effect on the heart rate pharmacodynamics of theophylline.

I. Glibenclamide: Protocol 115-011 was an observer-blind, placebo-controlled, randomized, crossover study of glibenclamide 5 mg daily on the pharmacokinetics and pharmacodynamics of dofetilide (500mcg bid) after multiple dosing. Coadministration of glibenclamide and dofetilide did not affect the pharmacokinetics and pharmacodynamics of dofetilide.

J. Oral contraceptive: Protocol 115-236 was a double-blind, two-way, placebo-controlled, crossover study conducted in two identical stages to investigate the safety and toleration of dofetilide and its influence on plasma oral contraceptive concentrations in healthy (surgically sterilized) women. There were no statistically significant treatment effects on the mean values of Cmax for both ethinylestradiol and levonorgestrel but their AUC increased by 21% and 15% respestively (the variability in the pharmacokinetic parameters were high - %CV = 40-75%). Although the objective of this study was not the investigation of the effect of oral contraceptive on the pharmacokinetics of dofetilide, it appears that the mean Cmax of 8 ng/ml obtained from this study is rather high and suggests possible interaction of oral contraceptive with dofetilide. The sponsor is conducting a Phase I study to determine the effect of hormone replacement therapy on dofetilide pharmacokinetics.

K. Activated Charcoal: Protocol 115-246 was an open, randomized, 3-way, cross-over study designed to assess the usefulness of activated charcoal in the treatment of overdoses. When given within 15 minutes of overdosing, absorption of 500mcg of dofetilide is effectively prevented, with only 6-12% of normal exposure. At 4 hours after the overdose, exposure levels are approaching the expected normal levels and charcoal treatment is ineffective.

Table 14: Summary of dofetilide pharmacokinetics with and without activated charcoal

	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

L. Omeprazole/Maalox: Protocol 115-003 was an open, randomized, placebo-controlled, 3-way, cross-over study of 500mcg dofetilide from capsules. Pretreatment with omeprazole or Maalox (an aluminum/magnesium hydroxide antacid) does not change the systemic availability of dofetilide. Dofetilide was well tolerated, with these results suggesting that pre-treatment with Maalox or omeprazole did not alter the single-dose pharmacokinetics of dofetilide.

Table 15: Summary of dofetilide pharmacokinetics with and without omeprazole / Maalox

Treatment	N		$AUC(0-\infty)$ (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	0.0796[c]	8.7[c]	329.6	73
		(SD)	(3.8)	(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

VI. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP:

In the dofetilide Pharmacokinetic / Pharmacodynamic (PK/PD) studies, QTc determinations were made and plasma samples obtained at regular intervals. For each individual subject, the plasma dofetilide concentration to time curve was fitted to poly-exponential models (one or two compartment models generally produced the best fit). The PK/QTc relationship was determined by linking the QTc response data to the PK model. Where loop-shaped curves emerged with counter-clockwise hysteresis, the curves were collapsed by introducing an effect-compartment with equilibration rate constant. A linear relationship generally described the data best and parameters (slope of the QTc response:concentration curve and equilibration half-life, where appropriate) were estimated for each individual. Group mean results are presented.

Following intravenous dosing of dofetilide, the QTc response:concentration relationship displays counter-clockwise hysteresis because the rapid build-up of plasma concentrations with intravenous dosing leads to non-instantaneous equilibrium between plasma and the effect compartment. Following collapse of the hysteresis loop, a linear QTc response:concentration relationship emerges. Oral dofetilide displays near instantaneous equilibrium between plasma and the effect compartment without appreciable counter-clockwise hysteresis. This lack of hysteresis indicates that slow absorption of dofetilide from capsules allows near instantaneous equilibration between the central and effect compartments. The linear QTc response:concentration relationship observed following intravenous dosing is also present for dofetilide from capsules. Highly similar PK/PD slopes are observed across several dose levels and across bid and tid dosing frequencies on both the first and fifth day of oral dosing. Sensitivity to dofetilide decreases with time to reach a stable state by Day 5 of dosing; conversely, dofetilide accumulates under the recommended bid dosing regimen to reach pharmacokinetic steady-state by Day 5. These counteracting processes produce an overall QTc response to dosing over time, increasing to a discrete maximum around Day 2-3 of dosing and then decreasing to reach a stable state by Day 5 of dosing. A similar pattern of QTc response over time was observed with sotalol in a study that found sotalol 240 mg bid to cause equivalent QTc increases to dofetilide 750 mcg bid (Study 115-245).

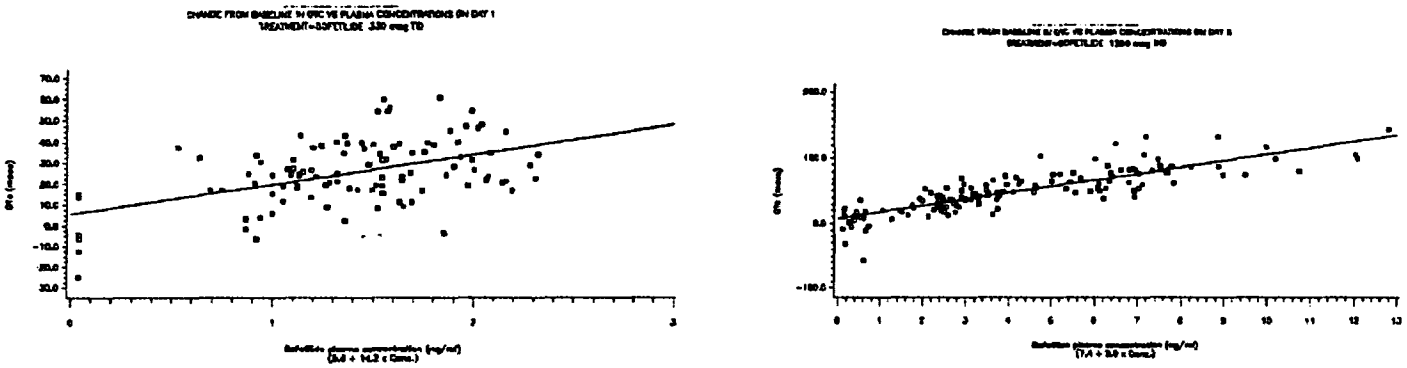
Protocol 115-229 was an exploratory, double-blind investigation of dofetilide in three separate groups of volunteers. Within each group a given daily dose (1000, 1500 or 2500 mcg orally) was administered as equally divided increments, either twice or thrice daily. Comparison of the mean changes from baseline for QTc with mean plasma concentrations shows a direct relationship with no indication of QTc lagging behind the plasma profile for any dose on either day (Figures 6). Unlike plasma concentrations, there was no accumulation of effect on QTc, with profiles on Day 5 being of similar order to those on Day 1 (Table 16). The relationships of the changes in QTc with plasma concentrations on Day 1 were linear and similar between all doses (Figure 5), bid dosing (range 14.5 - 16.2 msec.ml/ng) being about the same as the tid dosing (15.1 - 20.7 msec.ml/ng). On Day 5 at steady-state, these values were significantly lower than on Day 1 ($p=0.0001$) and there were no real differences between any of the doses over the range 11.1 - 13.3 msec.ml/ng, with the exception of the slope for 330mcg tid which was unusually high on Days 1 (20.7+4.5 msec.ml/ng) and 5 (16.0+4.5 msec.ml/ng). Consistent with the close linear relationship between plasma concentration and QTc increase, the mean AUECt on Day 1 increased predictably with dose on both regimens. Increases in QTc remained constant over the dosing cycles, the relationship between QTc and plasma concentration (Slope) being significantly different between Days 1 and 5. Slope on Day 5 was essentially similar across all doses, indicating that the frequency of dose administration does not affect this response.

Table 16: Dofetilide Pharmacokinetics/Pharmacodynamics Paramters (Means + SE) from Stsudy 115-229

	330mcg tid	500mcg bid	500mcg tid	750mcg bid	830mcg tid	1250mcg bid
Day 1						
Cmax (ng/ml)	1.70 ± 0.07	2.64 ± 0.11	2.26 ± 0.09	3.54 ± 0.21	3.55 ± 0.14	5.47 ± 0.29
Tmax (h)	2.29 ± 0.18	2.00 ± 0.31	2.13 ± 0.13	2.13 ± 0.13	2.29 ± 0.18	1.57 ± 0.20
AUCτ (ng.h/ml)	8.61 ± 0.43	17.03 ± 0.82	10.81 ± 0.34	23.55 ± 1.32	16.89 ± 0.75	37.50 ± 1.27
Slope*(msec/ng/ml)	20.7 ± 4.5	15.6 ± 2.4	18.1 ± 4.5	14.5 ± 4.1	15.1 ± 3.8	16.2 ± 2.7
Day 5						
Cmax (ng/ml)	3.04 ± 0.19	3.80 ± 0.19	4.78 ± 0.25	5.23 ± 0.29	7.71 ± 0.60	10.07 ± 0.70
Tmax (h)	2.29 ± 0.18	2.00 ± 0.22	2.00 ± 0.00	1.88 ± 0.40	2.14 ± 0.14	1.57 ± 0.30
AUCτ (ng.h/ml)	16.75 ± 0.86	25.39 ± 1.49	25.54 ± 1.74	37.80 ± 2.62	40.10 ± 2.05	62.07 ± 2.92
Kel (/h)	0.070 ± 0.0020	0.068 ± 0.0029	0.073 ± 0.0024	0.069 ± 0.0022	0.073 ± 0.0023	0.069 ± 0.0026
Slope*(msec/ng/ml)	16.0 ± 4.1	13.2 ± 2.3	13.0 ± 2.9	13.3 ± 2.2	11.2 ± 1.6	11.1 ± 2.1

Where τ is the dosing interval of 8 hours for tid and 12 hours for bid
* = Slope of ΔQTc/ plasma dofetilide concentration ± SD

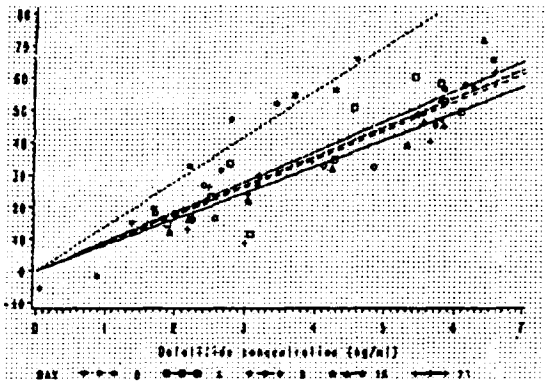
Figure 5: Change in QTc Versus Concentration (Study 115-229)



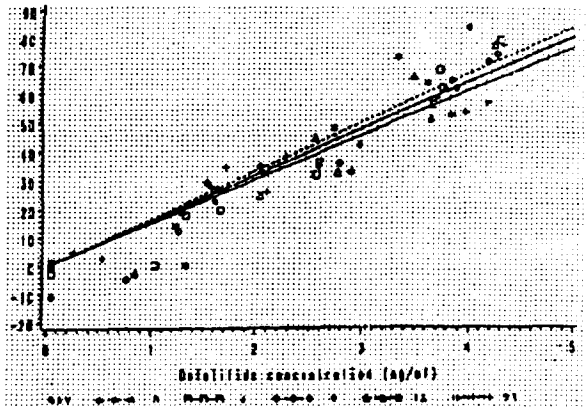
A subsequent study (Protocol 115-239) was designed to investigate further the time course of the attenuation of sensitivity reported in study 115-229. This was a single-blind, placebo-controlled parallel group study to assess the pharmacokinetics, pharmacodynamics and PK/PD to 24 days of 1000 mcg dofetilide bid continuous intermittent dosing. This study demonstrated that dofetilide pharmacokinetics, as expected from the bid dosing regimen and terminal half-life, have reached steady-state by Day 5 of dosing . The intermittent dosing regimen did not lead to accumulation. With continuous dosing, the slope of the concentration response relationship had attenuated by Day 5 of dosing to approximately 60-65% of the Day 1 value. No attenuation was seen with intermittent dosing. Taken together, the end result for QTc with continuous dosing was a prolongation over Days 1-24 with a discrete maximum in increase on Days 2 and 3 of dosing and a stable steady-state from Day 5 onwards (Figure 6). With intermittent dosing, prolongation of QTc without the above described change over time was observed, and no QTc prolongation was seen with placebo. Having demonstrated this effect with dofetilide, Protocol 115-245 investigated if this was a dofetilide-specific effect by comparison with (d,l-)sotalol. For both dofetilide and sotalol, the slope of the QTc plasma concentration relationship was significantly lower on Day 6 of continuous dosing. As in Protocol 115-239, the final slope was approximately 60% of the initial one and this was similar for the two treatments.

Figure 6: Mean changes in QTc versus dofetilide concentration (Protocol 115-239)

(a) continous regimen



(b) intermittent regimen



VII. POPULATION PHARMACOKINETICS/PHARMACODYNAMICS:

A population pharmacokinetic and pharmacodynamic analysis was conducted, using on data from four Phase II oral dose ranging studies (115-104, 115-105, 115-308 and 115-310), comprising 908 plasma concentrations and 1469 QTc measurements from 117 patients. Eight different dosage regimens (250, 500, 750, 1000 & 1250 mcg bid and 250, 500 & 750 mcg tid) were investigated in these studies. An additional 11 individuals from study 115-219 were incorporated into the overall analysis in order to provide information from patients over a range of renal dysfunction. A one-compartment model with Tlag was found adequately to describe the pharmacokinetics of dofetilide. The population typical values (Relative Standard error (R.SE)) were 17.4 L/h (3%) for apparent clearance (CL/F), 216 L (4%) for apparent volume of distribution (V/F; equivalent to a t1/2 of 10.8 h), 2.55 /h (18%) for Ka and 0.632 h (8%) for Tlag. The pharmacokinetics of dofetilide were linear over the dose range studied, exhibiting dose proportionality. Creatinine clearance (CLCr) was shown to be the most influential covariate for CL/F ($p<0.001$). Gender was shown to influence CL/F to a statistically significant degree (females possessing, on average, 18% lower CL/F than males). Following inclusion of the renal impairment data, the population mean CL/F for males and females changed by 1.9 L/h and 1.6 L/h, respectively, for every 10 ml/min that CLCr changed from the median value. Non-renal CL/F was estimated to be 2.7 L/h and 2.3 L/h for males and females, respectively (<20% of the typical value for CL/F 17.4 L/h). Volume was influenced by body weight ($p<0.001$) with V/F estimated to be 3.4 L/kg. The analysis shows that dofetilide exhibits predictable pharmacokinetics with low levels of both interindividual and residual variabilities. A linear model with components for baseline and slope (an indicator of drug sensitivity) was used to relate the predicted plasma concentration to the QTc intervals. The population typical values (mean (R.SE)) were 437 msec (1%) for baseline and 10.9 msec.ml/ng (8%) for slope.

A population pharmacokinetic analysis was conducted on data from 14 Phase III dofetilide clinical trials, comprising 10335 plasma concentration values from 1445 patients. Both once and twice daily dosing regimens were encountered, with a range of oral doses from

62.5mcg to 500mcg. A one-compartment disposition model with first order absorption proved to be adequate to model this data. The population typical values (Relative Standard Error (R.SE)) were 14.1 L/h (1%) for apparent clearance (CL/F), 247 L (1.5%) for apparent volume of distribution (V/F), 1.69 /h (9.7%) for Ka. The pharmacokinetics of dofetilide were linear over the dose range studied, exhibiting dose proportionality. Creatinine clearance (CLCr) was by far the most influential factor accounting for interindividual variability of dofetilide CL/F ($p<0.001$). CL/F changed by 1.3 L/h for every 10 ml/min that CLCr changed from the median value of 75 ml/min. The slope and intercept calculated for the relationship between dofetilide CL/F and CLCr were 0.128 L/h per ml/min and 4.5 L/h, respectively. The V/F changed by 18.5 L for every 10 kg that weight changed from the median value of 80 kg. Gender effect was found ($p<0.001$) on CL/F (a 12% lower CL/F for females was estimated).

A population PK/PD analysis of dofetilide safety and efficacy data was performed with the following objectives: (1) To determine the relationship between the derived pharmacokinetic parameters (AUC and Cmax) and the incidence of certain adverse events, (2) To explore the relationship between dofetilide pharmacokinetics and specific efficacy endpoints from these studies and (3) To use the pharmacokinetic, pharmacokinetic/safety and pharmacokinetic/efficacy data to assess the phase III dosage algorithm. The results of the analyses showed that the prevalence of both TdP and the other potentially proarrhythmic events recorded within

the Phase III pharmacokinetic population increased with AUC and Cmax. The majority of the episodes were associated with AUCs > 60 $ng.ml^{-1}.h$. The prevalence of TdP within the full Phase II/III program was also shown to increase with increasing AUC and Cmax. For AUCs < 60 $ng.ml^{-1}.h$, the prevalence (<1%) was reduced, compared to AUCs > 60 $ng.ml^{-1}.h$ (>2.9%). The prevalence of TdP was also shown to increase with increasing Cmax. Adherence to the Phase III dosage algorithm greatly reduced the incidence of TdP in patients with low CLcr (<60$ml.min^{-1}$).

The percentage of patients with paroxysmal arrhythmia in SR after 12 weeks of treatment was 31% and 37% for the placebo and the dofetilide treated patients with AUCs < 60 $ng.ml^{-1}.h$, respectively. However, AUCs > 60 $ng.ml^{-1}.h$ were associated with an increased response rate of 47%. In comparison to patients with CLcr < 60 $ml.min^{-1}$, a higher percentage of patients with CLcr> 60 $ml.min^{-1}$ were in SR at 6 months. The difference between the two groups varied over the observed AUC ranges but was greatest in the AUC range of between 40 to 60 $ng.ml^{-1}.h$. This analysis demonstrated that the Phase III dosage algorithm improved the risk-benefit ratio of dofetilide.

VIII. FORMULATION: The three capsule formulations to be marketed are 0.125, 0.25 and 0.5 mg and their compositions are shown in Table 17 (Attached).

IX. DISSOLUTION: The proposed dissolution method of USP Apparatus I (baskets) at 100 rpm, in 0.001M hydrochloric acid is acceptable as an interim method. Although a tighter dissolution specification could be justified based on data on batches N6179 and N6178 used for the pivotal BE study (maximum dissolution reached in less than minutes), the data from the "cross-linked" capsules with stability effect (mean %dissolved at minutes %) and the capsules with isolated hydrophobic effect (mean %dissolved at minutes %) which

demonstrated bioequivalency to capsules with normal dissolution profile (mean %dissolved at minutes %) show that the proposed dissolution method is not reflective of the bioavailability of dofetilide capsule formulations. The recommended dissolution specification of Q % at minutes should be changed to Q % at minutes. This will be an interim dissolution specification until a dissolution method that will correlate *in vitro* dissolution to *in vivo* perfomance is developed (see comments below).

X. ASSAY:

XI. PLASMA PROTEIN BINDING: Plasma protein binding of dofetilide is 60-70%, is independent of plasma concentration ng/ml) and is unaffected by renal impairment.

XII. PEDIATRIC POPULATION: The pharmacokinetics of dofetilide has not been described in the pediatric population.

XIII. LABELING: The clinical pharmacology section of the labeling is deficient and the firm has been advised to modify it accordingly

XIV. INFLUENCE OF RACE: The influence of race on the pharmacokinetics of dofetilide has not been studied.

COMMENTS TO BE SENT TO THE SPONSOR:

LABELING COMMENTS:

The following subsections of the Clinical Pharmacology section of the labeling should be edited as shown below:

/S/

12/10/98

Emmmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by A. Parekh, Ph.D. ----------/S/ 12/10/98

Biopharm Day - 11/20/98: Lesko, Chen, Mehta, Parekh, Marroum, Selen, Miller, Williams, Gordon, Ganley, Robbie, Sadrieh, Lau, Madani, Colangelo.

cc: NDA 20-931, HFD-110, HFD-860 (Fadiran), CDR (Attn: Barbara Murphy), Chron, Drug, Review, HFD-340 (Vish).

COMPOSITION OF THE FORMULATIONS

The compositions of dofetilide capsules containing dofetilide equivalent to 0.125 mg, 0.25 mg and 0.5 mg are as follows:

TABLE 17: Quantitative Composition of Dofetilide Capsules Formulations

Component	Grade	Function	0.125 mg Capsule (mg/Unit)	0.25 mg Capsule (mg/Unit)	0.5 mg Capsule (mg/Unit)
Dofetilide	Pharm[1]	Active			
Microcrystalline Cellulose	NF	Diluent			
Corn Starch (dried)[2]	NF[2]	Diluent/Disintegrant			
Colloidal Silicon Dioxide	NF	Glidant			
Magnesium Stearate	NF	Lubricant			
# 4 Orange Opaque/ White Opaque Printed Capsule	Pharm[1]	Shell			
# 4 Peach Opaque/Peach Opaque Printed Capsule	Pharm[1]	Shell			
# 2 Peach Opaque/ White Opaque Printed Capsule	Pharm[1]	Shell			
Fill Weight					
Total Weight					

[1] Pharm grade material is released to a Pfizer specification.

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APPENDIX

METABOLIC PROFILING

STUDY NUMBER: 115-216 **VOLUME**: 2.37 **PAGES**: 1-270

INVESTIGATOR AND LOCATION:

STUDY PERIOD: February 1990 - April 1990.

OBJECTIVES: The primary aims of the study were to define the metabolic profile of dofetilide administered as a single oral or IV dose to healthy male volunteers, and to identify thepossible metabolites of dofetilide in man.

FORMULATIONS:
Dofetilide 500mcg intravenous solution, containing 20mcCi (734 KBq) ^{14}C-labelled dofetilide, was administered as a single dose, either orally, or as an IV infusion. (FID 0952, Lot No. 788-43). For oral administration, 500mcg was given as two 2 x 10ml ampoules.
For the intravenous administration, the ampoules were reconstituted with diluent (FID0950, Lot No. 788-38) and were given as a 50ml infusion over a 90 minute period at a rate of 0.6ml/min.

STUDY DESIGN:
This was an open study in healthy male volunteer subjects. Within 2 weeks of a screening visit, seven subjects (three subjects for po and 4 subjects for IV) were received single dose of 500mcg ^{14}C-dofetilide containing 20mcCi (734KBq), either orally (oral (po) dofetilide treatment group), or as an IV 50ml infusion over 90 minutes at a rate of 0.6ml/min (IV dofetilide treatment group). Venous blood samples were withdrawn into heparinised containers at pre-dose (immediately before dosing) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48 and 72hr after oral dosing. Venous blood samples were withdrawn into heparinised containers at pre-dose, at 30, 45, 60 and 75 minutes after commencement of the infusion, at 90 minutes (termination of the infusion), and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48 and 72hr aftercompletion of the infusion.
Urine was collected into polythene containers during the 24hr preceding dosing, during 0-12, 12-24hr and thereafter over 24hr periods up to 7 days after dosing. Faeces were collected into separate pre-weighed polythene bags 24 hours prior to dosing, during 0-24hr and thereafter over 24hr periods up to 7 days after dosing. Samples were to be frozen and stored at -20°C until analyzed.

Assay Performance

DATA ANALYSIS: AUC, Cmax, Tmax, $T_{1/2}$, %Dose excreted were calculated.

RESULTS: The results obtained from the study are summarized in Tables 1-4 and Figures 1-3.

TABLE I

THE EXCRETION OF RADIOACTIVITY BY HUMAN SUBJECTS FOLLOWING THE ADMINISTRATION OF A SINGLE ORAL DOSE OF [^{14}C]-UK-68,798

Results are expressed as % dose administered

Time (hours)	Subject Number			Mean ± SD
	1	2	3	
Urine				
0 – 12				45.74 ± 3.12
12 – 24				21.02 ± 1.69
24 – 48				8.59 ± 1.59
48 – 72				1.42 ± 0.09
72 – 96				0.35 ± 0.19
96 – 120				0.23 ± 0.05
120 – 144				0.12
144 – 168				0.07
Total in urine				77.53 ± 2.98
Faeces†				
0 – 24				-
*24 – 48				-
48 – 72				3.10 ± 2.32
72 – 96				0.40 ± 0.56
96 – 120				0.11 ± 0.18
120 – 144				0.04 ± 0.06
144 – 168				-
Total in faeces	14.59	5.66	9.57	10.27 ± 4.01
Total recovery	93.39	80.79	89.73	87.80 ± 6.42

TABLE 2

THE EXCRETION OF RADIOACTIVITY BY HUMAN SUBJECTS FOLLOWING THE ADMINISTRATION OF A SINGLE INTRAVENOUS DOSE OF $I^{14}C$]-UK-68,798

Results are expressed as % dose administered

Time (hours)	Subject Number			Mean ± SD
	4	6	9	
Urine				
0 - 12*				51.03 ± 5.97
12 - 24				17.58 ± 1.42
24 - 48				9.37 ± 2.08
48 - 72				1.16 ± 0.66
72 - 96				0.49 ± 0.43
96 - 120				0.26 ± 0.20
120 - 144				0.10
144 - 168				0.05
Total in urine				80.04 ± 3.59
Faeces†				
0 - 24*				0.08 ± 0.07
24 - 48				0.57 ± 0.60
48 - 72				0.75 ± 0.92
72 - 96				0.30 ± 0.26
96 - 120				0.28 ± 0.29
120 - 144				0.09 ± 0.14
144 - 168				0.17 ± 0.20
Total in faeces				2.23 ± 1.48
Total recovery				82.27 ± 2.17

* - Times are in hours after the completion of the infusion. No urine or faeces were voided during the 90 minute infusion.

SD - Standard deviation
NS - No sample
ND - Not detected

Table 3. Pkarmacokinetics of Dofetilide

Parameter	Oral[1]		Intravenous[1]	
	Dofetilide	Radioactivity	Dofetilide	Radioactivity
Cmax (ng/ml)	1.65 ± 0.6	2.2 ± 0.9	2.98 ± 0.9	3.4 ± 1.0
Tmax (h)	2.3 ± 1.5	1.3 ± 0.6	1.3 ± 0.3	1.4 ± 0.1
AUC(0-24) (ng h/ml)	17.5 ± 3.2	24.9 ± 4.1	21.2 ± 4.5	27.3 ± 4.8
T1/2 (h)	8.0 ± 2.0	7.2 ± 0.6	7.7 ± 0.6	7.8 ± 0.8
Excretion of radioactivity (% dose)				
Urine 0-168 hours	77.53 ± 2.98		80.04 ± 3.59	
Faeces 0-144 hours	10.27 ± 4.01		2.23 ± 1.48	
Total Recovery	87.80 ± 6.42		82.27 ± 2.17	

[1] Mean ± standard deviation

Table 4.

RADIOACTIVITY PROFILES IN 0-24 HOUR URINE SAMPLES FROM HUMAN SUBJECTS FOLLOWING SINGLE ORAL OR INTRAVENOUS DOSES OF 0.5MG [^{14}C]-UK-68,798

Metabolite and Retention Time	Identity by hplc retention time	% radioactivity in 0-24 hour urine							
		p.o.			Mean p.o.	i.v.			Mean i.v.
		Subject 1	Subject 2	Subject 3		Subject 4	Subject 5	Subject 9	
M1 18° 53'	?								1.0
M2 24° 15'	UK-80,725								3.1
M3 33° 19'	UK-69,502								1.8
M4 39° 05'	UK-116,856								2.2
M5 49° 22'	UK-71,385								3.5
UK-68,798 44° 55'	UK-68,798								83.6

Figure 1

Mean plasma concentrations of UK-68,798 and total radioactivity following single iv doses (0.5 mg).

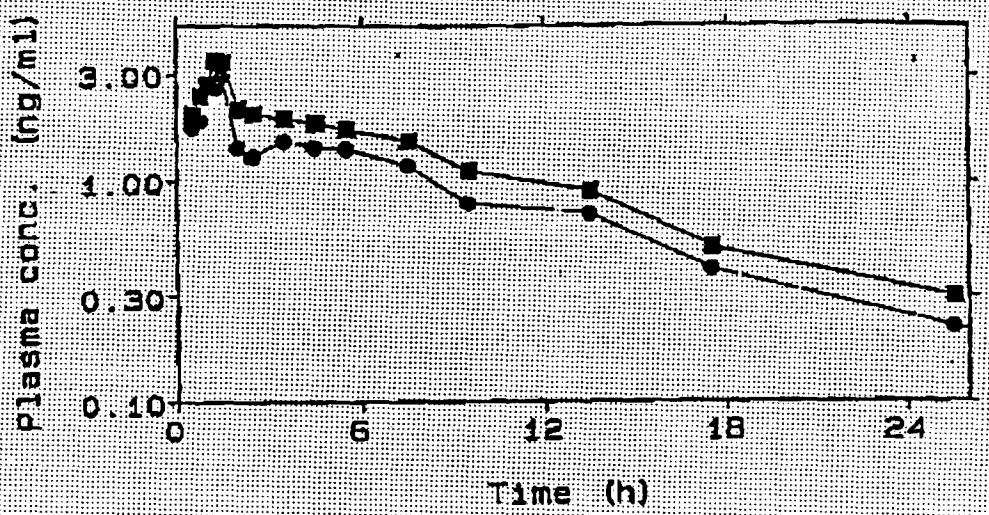


Figure 2

Mean plasma concentrations of UK-68,798 and total radioactivity following single po doses (0.5mg).

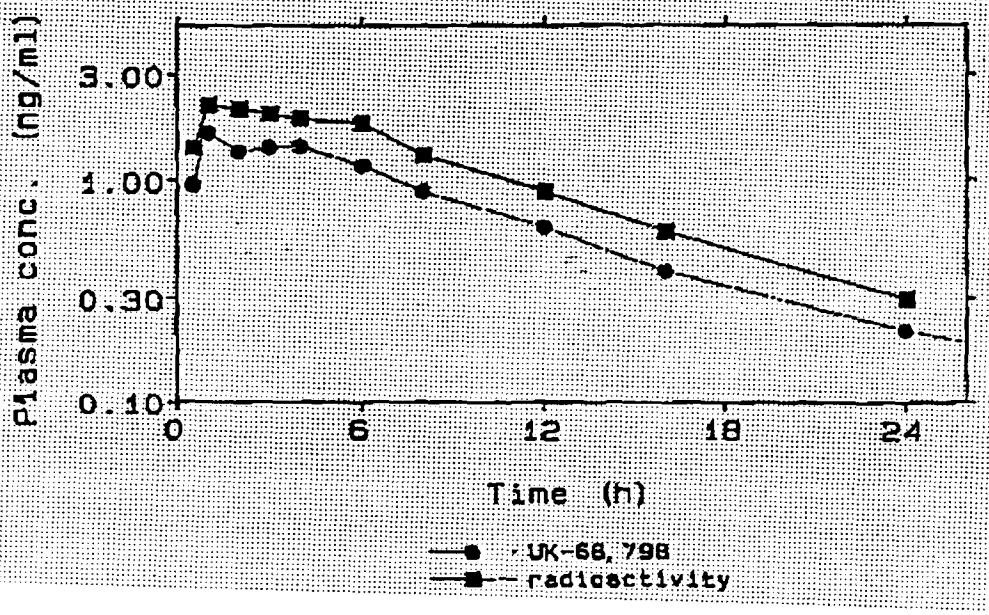


Figure 3

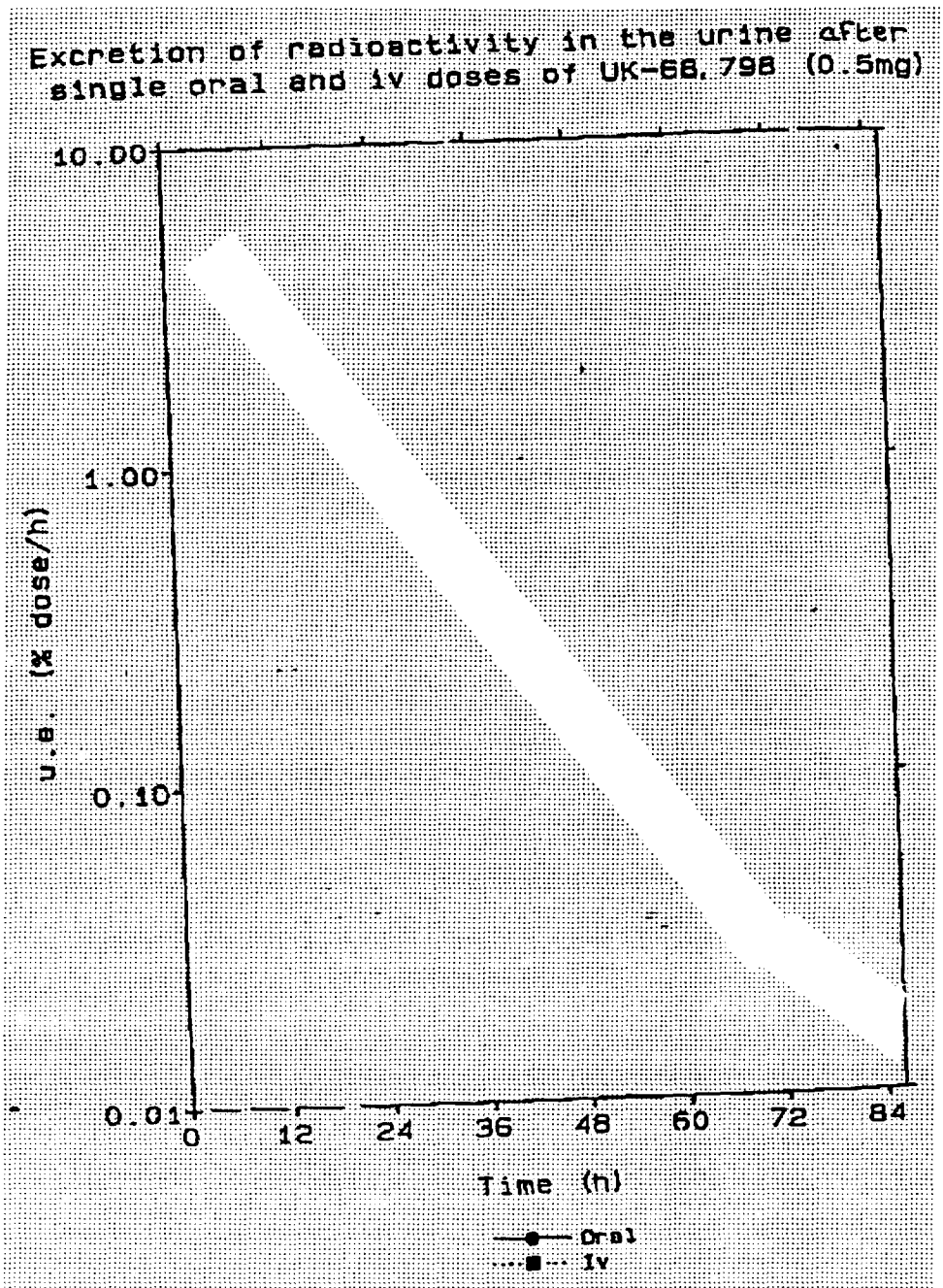
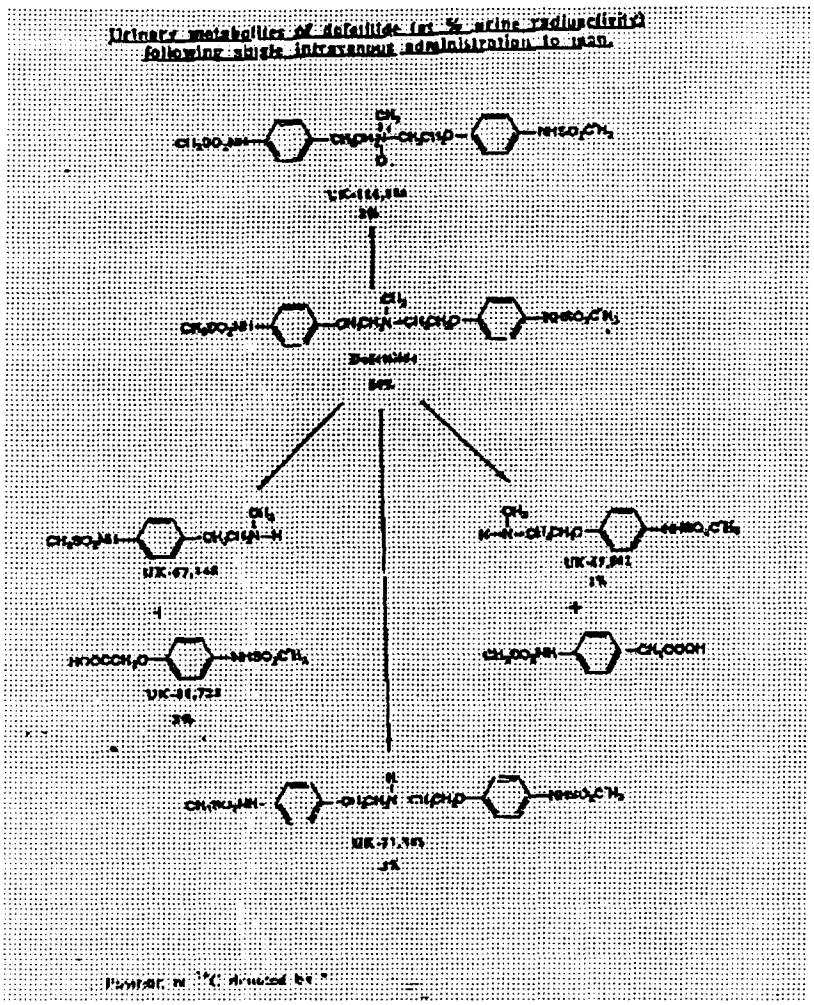

Excretion of radioactivity in the urine after single oral and iv doses of UK-68,798 (0.5mg)
10.00
1.00
0.10
0.01
u.e. (% dose/h)
0
12
24
36
48
60
72
84
Time (h)
Oral
Iv

Figure 4.



CONCLUSIONS:

Radioactivity concentrations (as ng equivalents /ml) in plasma were approximately % higher than the concentration of dofetilide throughout the study, and showed similar concentration time profiles. Comparison of the AUC(0-24) values for dofetilide and radioactivity concentrations indicates that dofetilide accounts for 70% and 78% of total radioactivity following oral and intravenous doses, respectively. The remaining plasma radioactivity most likely constitutes numerous metabolites at concentrations below the limit of detection. Comparison of mean AUC(0-24) values for dofetilide after oral and intravenous routes of administration showed that the mean bioavailability of dofetilide is 83%.

The mean percentage of dosed radioactivity recovered in the urine was 80% following IV administration and 78% following oral administration. Only a small proportion of dofetilide was recovered in the faeces (2% and 10% after IV and oral administration, respectively) i.e most orally administered dofetilide is absorbed from the gastrointestinal tract. Analysis of the 0-24hr urine samples indicated that unchanged dofetilide made up the majority of radioactivity present in the urine (mean 83%), representing 66% of the

administered dofetilide. Five polar metabolites were detected in the urine, four of which were identified. The metabolite profiles were similar for both routes of administration. No single metabolite accounted for more than 3.5% or less than 1% of urine radioactivity in any individual. The two most lipophilic of these metabolites were the N-oxide and the N-desmethyl forms of dofetilide. Two other components were the carboxylic acid and secondary amine metabolites resulting from N-dealkylation type metabolism of dofetilide around the basic nitrogen. Since these metabolites have a minimal presence in plasma, they are not expected to contribute to the therapeutic or side effect profile of the compound.

IN VITRO METABOLIC STUDIES

PROTOCOL NUMBER: DM/004/95

STUDY DATES: February 1995 to June 1995

INVESTIGATOR AND LOCATION:

OBJECTIVE: To characterize the in vitro metabolism of dofetilide in human liver microsomes

PROCEDURES: Three aspects of in vitro metabolism of dofetilide were studied.

RESULTS: Tables 1 & 2 and Figures 1 -3 summarize the results of the study.

Table 1.

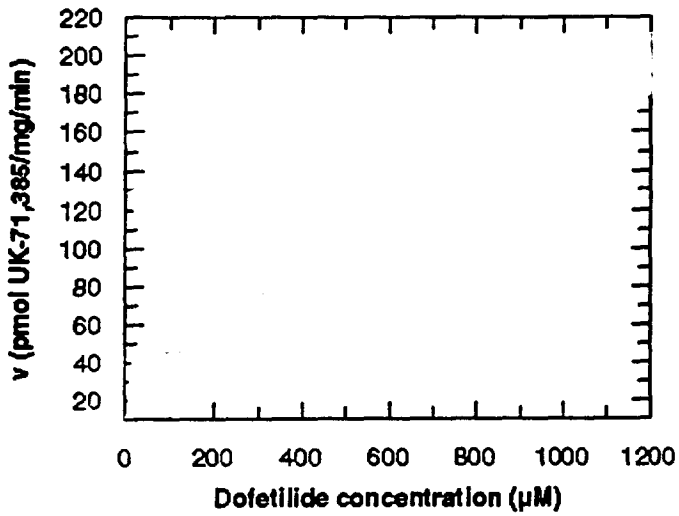
KINETIC DATA FOR DOFETILIDE N-DEMETHYLATION IN THREE HUMAN LIVER MICROSOME PREPARATIONS.

Human liver microsomes	Km (μM)	Vmax (pmol/mg/min)	Relative CYP3A4 activity
HM13	525	49	1
HM8	704	163	1.6
HM6	742	313	3.6
Mean	657±116	175±108	-

Correlation of UK-71,385 formation and P450 isoform activities

P450 Isoform	500μM Dofetilide Correlation Coefficient
CYP1A2	0.699
CYP2C9	0.358
CYP2D6	0.537
CYP2E1	0.395
CYP3A4	0.903

Figure 1:
MICHAELIS-MENTEN (A) AND EDIE-HOFSTEE (B) PLOTS FOR RATES OF DOFETILIDE N-DEMETHYLATION IN HUMAN LIVER MICROSOMES.
A)



B)

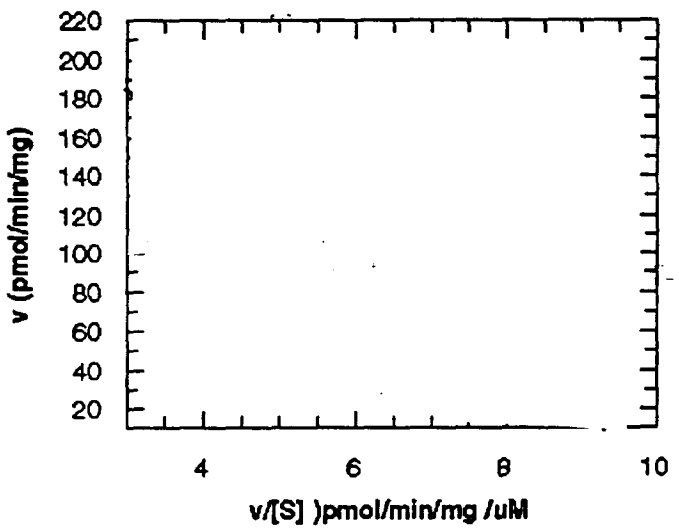


Figure 2:

EFFECT OF SPECIFIC CYTOCHROME P450 INHIBITORS AND ACTIVATORS ON THE N-DEMETHYLATION OF DOFETILIDE BY HUMAN LIVER MICROSOMES

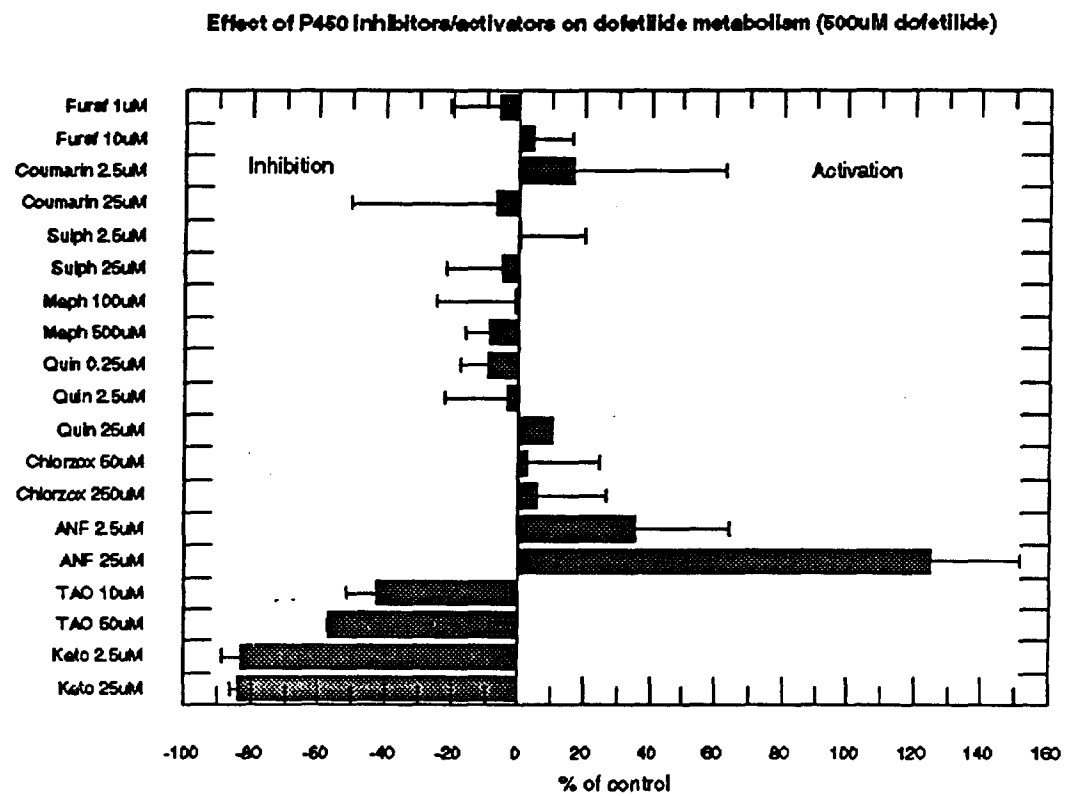
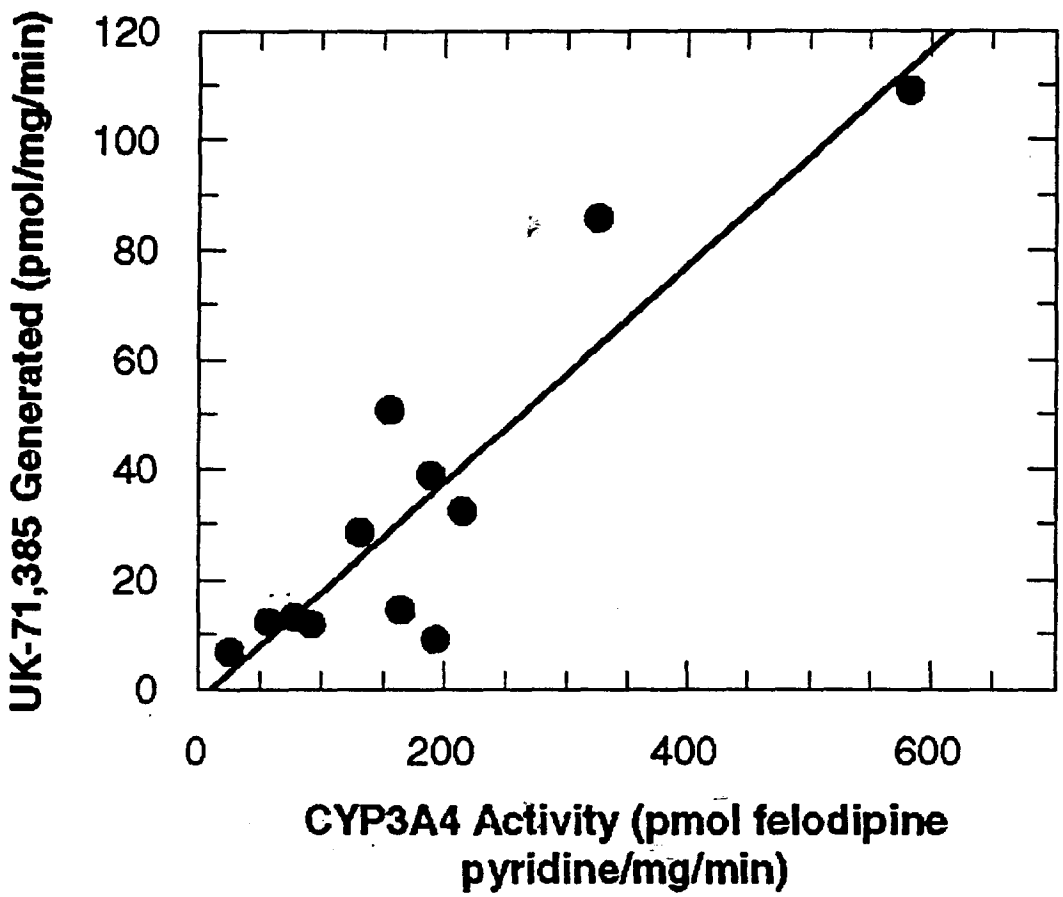


Figure 3:

Figure 3:
CORRELATION BETWEEN RATE OF DOFETILIDE N-DEMETHYLATION AND CYP3A4 ACTIVITY ACROSS A BANK OF HUMAN LIVER MICROSOMES



CONCLUSIONS: The results show that:

1. The major metabolic route of dofetilide is N-demethylation to UK-71385 and this pathway is characterized by a Km value of 657+/-116uM and a mean Vmax of 175+/- pmol/mg/min.

2. Generation of UK-71,385 is primarily mediated by CYP3A4. A high correlation was seen between the CYP3A4 activities of the 12 livers and UK-71,385 generation from dofetilide. Correlation with the other isoforms were weaker (CYP1A2 > CYP2D6 > CYP2E1 > CYP2C9).

3. THE SPONSOR STATES: Since the Km values are 150 fold higher than the concentrations expected therapeutically, metabolism based drug interactions are unlikely. Km is higher than most CYP3A4 substrates. PREVIOUSLY IT HAS BEEN SHOWN THAT DOFETILIDE IS UNLIKELY TO EXHIBIT ANY CLINICALLY RELEVANT DRUG INTERACTIONS BECAUSE OF ITS WEAK INTERACTIONS WITH CYP450s

BIOAVAILABILITY / BIOEQUIVALENCE STUDY
STUDY 115-014 VOLUMES: 1.25 & 2.18

INVESTIGATOR AND LOCATION:

STUDY DATE: March 18 to April 24, 1996.

OBJECTIVES:
To determine the bioequivalence of two 500mcg research capsule formulations of dofetilide.

FORMULATIONS:
500mcg dofetilide research capsule formulation (FID #0964, Lot No. 503-19-G1)
500mcg dofetilide research capsule formulation (FID #QC2061, Lot No. ED-O-104-493)

STUDY DESIGN:
This was an open, randomized, two-period, two-treatment crossover study in twenty healthy subjects (11 male, 9 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 #0964 or FID #QC2061 research capsule 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 and up to 48 hours after each dose of study drug.

ASSAYS:

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

RESULTS: Tables 1-2 and Figures 1-5 summarize the pharmacokinetic pharmacodynamic data obtained from the study.

Table 1. Bioequivalence of the two formulations

Pharmacokinetic Results: Mean Pharmacokinetic Parameters (n=20)

	FID #QC2061	FID #0964	Ratio	90% Confidence Limits
AUC (ng•hr/ml)*	22.47	23.09	97.3%	(92.9%, 102.0%)
Cmax (ng/ml)*	2.01	2.02	99.5%	(91.0%, 108.7%)
			Difference	
Tmax (hr)**	2.7	2.9	-0.2	(-0.8, 0.4)
Kel (/hr)**	0.0915	0.0904	0.0010	(-0.0021, 0.0041)

* Adjusted Geometric Mean ** Adjusted Arithmetic Mean

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Table 2. Gender Analysis of PK Parameters {Mean (CV)}

Parameter	Male Subjects	Female Subjects	All Subjects
FID #0964			
AUC (h*ng/ml)[a]	21.6 (16)	25.1 (24)	23.1 (21)
C_{max} (ng/ml)[a]	1.79 (20)	2.34 (25)	2.02 (26)
T_{max} (h)	2.9 (28)	2.9 (47)	2.9 (37)
Kel (h^{-1})	0.0896 (15)	0.0914 (14)	0.904 (14)
$T_{1/2}$ (h)[b]	7.7	7.6	7.7
FID #QC2061			
AUC (h*ng/ml)	20.1 (15)	25.8 (22)	22.5 (22)
C_{max} (ng/ml)	1.73 (17)	2.41 (22)	2.01 (25)
T_{max} (h)	3.1 (39)	2.2 (50)	2.7 (46)
Kel (h^{-1})	0.0876(12)	0.0962(14)	0.0915(13)
$T_{1/2}$ (h)[b]	7.9	7.2	7.6

[a]Geometric Means
[b]Harmonic Means

Figure 1: Individual Plasma Profiles Following Administration of Formulation FID #0964

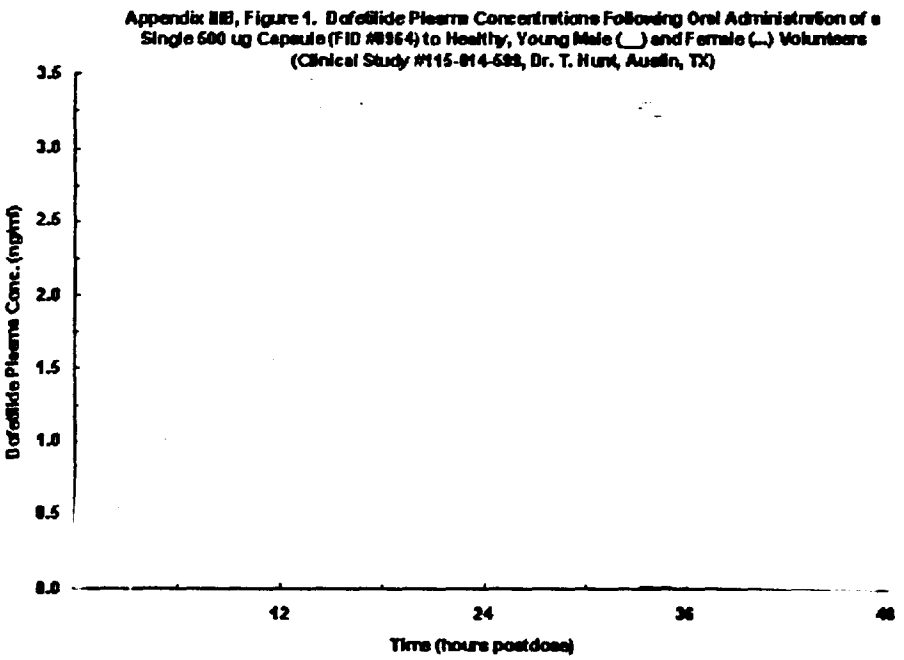


Figure 2: Individual Plasma Profiles Following Administration of Formulation FID #QC2061

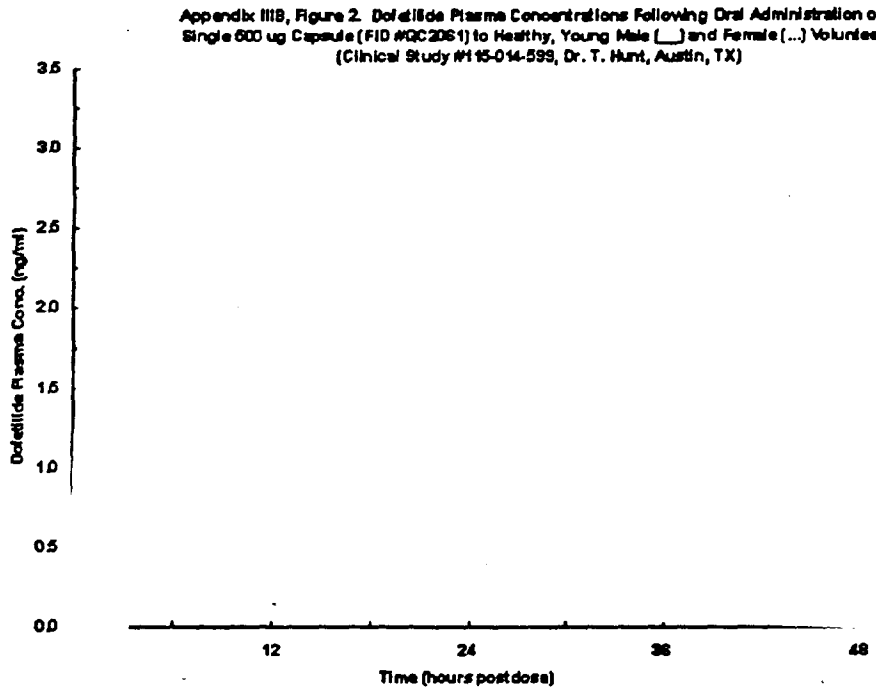


Figure 3: Mean Plasma Profiles Following Administration of Formulation FID #0964

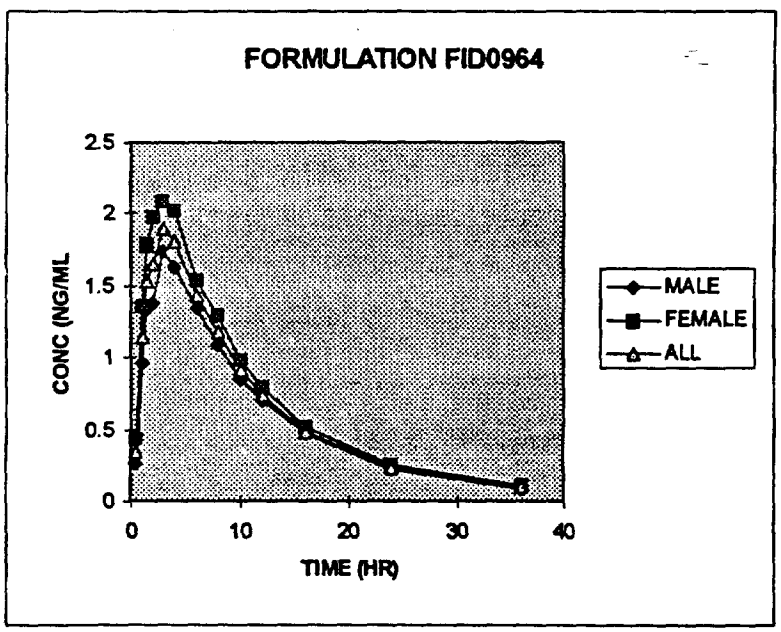


Figure 4: Mean Plasma Profiles Following Administration of Formulation FID #QC2061

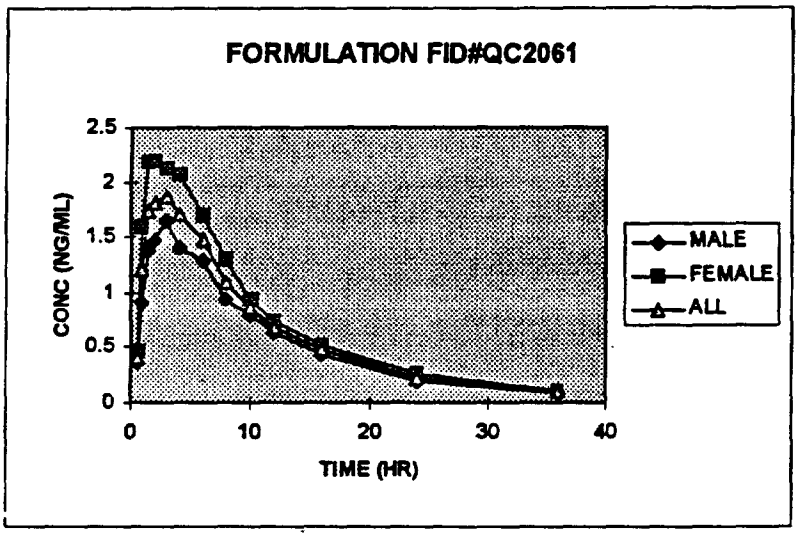
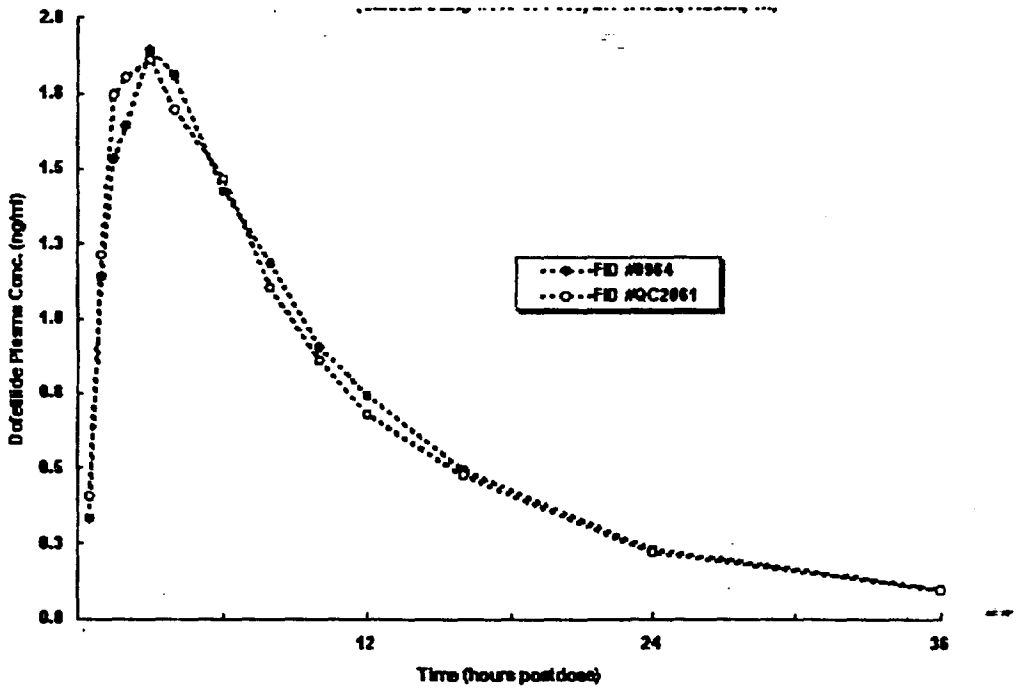


Figure 5. Mean Dofetilide Plasma Profiles Following Oral Administration of the Capsule Formulations



CONCLUSIONS:

The results obtained from the study indicated that:

(1) the two capsule formulations of dofetilide were bioequivalent.

(2) there are gender differences in the pharmacokinetics of dofetilide with females having higher plasma levels than male subjects (about 22% increase in AUC and 35% increase in Cmax for female subjects when compared to male subjects). This difference will reduce when correction is made for weight based on the following data on the weights of the subjects which shows that women received a higher dose on μ/kg basis:

	FID 0964 → FID QC2061		FID QC2061 → FID 0964	
	MALE	FEMALE	MALE	FEMALE
Weight Range (kg)	71 - 90	61-66	66 - 89	57 - 89
Mean Weight (kg)	81	64	73	65
Dose/Weight (μ/kg)	6.2	7.8	6.8	7.7

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DOFETILIDE-ORAL CONTRACEPTIVE INTERACTION STUDY

STUDY 115-236 **VOLUME: 2.51** **PAGES: 1-443**

INVESTIGATOR AND LOCATION:

STUDY DATE: September 1991 - June 1992.

OBJECTIVES:
To investigate the safety and toleration of dofetilide and its influence on plasma oral contraceptive concentrations in healthy women.

FORMULATIONS:
Dofetilide, 500mcg capsules: FID 0964; Lot. 904-05
Dofetilide 250mcg capsules: FID 0963; Lot. 904-04
Identical placebo capsules: FID 0034 Lot No. 748-06
Oral contraceptive tablets: combined 150mcg levonorgestrel/30mcg ethinyloestradiol (Microgynon)

STUDY DESIGN:
This was a double-blind, two-way, placebo-controlled, crossover study conducted in two identical stages. During each stage, randomized subjects received either 750mcg dofetilide, given twice daily, or placebo for 6 days. Each stage of the study was performed in the first half of the subject's normal menstrual cycle. On Day 4 subjects received a single dose of oral contraceptive (300mcg levonorgestrel/60mcg ethinyloestradiol). Blood samples were collected for estimation of plasma levels of levonorgestrel and ethinyloestradiol at the following times on Day 4: pre-dose (time 0) and at 1, 2, 3, 4, 6, 8, 10, 14, 24, 36, 48 and 72 hours post-dose. Blood samples were collected for estimation of plasma levels of dofetilide at the following times on Day 4: baseline dofetilide (time 0) and at 2, 4, 6 and 10 hours after the morning dose.

ASSAYS: