APPENDIX I TABLE 7.1
DOFETILIDE PROTOCOL 203
BLOOD PRESSURE. MEAN CHANGES FROM BASELINE

SUPINE DIASTOLIC BP (mmHg)

		DAY 1							DAY 10					
		TIME POST-DOSE (h)							TIME POST-DOSE (h)					
		PRE-DOSE	BASEL-INE	1	2	4	8	12	BASEL-INE	1	2	4	8	12
TREATMENT														
Dofetilide 100 mcg BD	MEAN	71.06	72.28	2.72	-3.78	-1.39	-3.94	0.72	-0.31	-0.38	4.69	-3.19	-3.56	3.38
	S.E.	3.78	4.35	2.06	2.00	2.25	2.03	1.81	2.13	2.64	3.98	3.99	4.90	4.39
	N	9	9	9	9	9	9	9	8	8	8	8	8	8
Dofetilide 200 mcg OD	MEAN	69.81	62.63	1.75	1.19	3.00	-0.69	4.31	10.06	3.00	9.69	4.63	7.19	6.25
	S.E.	3.89	4.33	3.81	3.35	2.34	3.28	2.24	3.95	2.66	2.51	2.41	2.88	4.02
	N	8	8	8	8	8	8	8	8	8	8	8	8	8
Dofetilide 200 mcg BD	MEAN	71.94	71.39	1.17	-5.28	-2.39	-0.22	-2.28	2.19	0.88	1.06	-3.63	-0.19	3.63
	S.E.	4.59	3.74	2.46	1.55	2.08	2.17	2.75	3.41	1.58	2.65	2.65	4.00	2.08
	N	9	9	9	9	9	9	9	8	8	8	8	8	8
Dofetilide 400 mcg BD	MEAN	69.00	75.56	-6.69	-9.13	-12.88	-12.06	-3.44	-8.00	-5.07	-7.14	-7.50	0.57	-5.57
	S.E.	3.34	1.97	2.67	2.82	1.59	2.23	3.75	3.42	2.32	2.12	2.88	3.73	3.85
	N	8	8	8	8	8	8	8	7	7	7	7	7	7
Double Blind Placebo	MEAN	68.27	70.88	-1.65	-3.89	-3.67	-2.94	-2.09	2.58	0.53	0.39	-0.89	-2.52	-0.38
	S.E.	1.76	1.79	1.50	1.10	1.26	1.10	1.34	1.39	1.54	1.40	1.55	1.77	1.62
	N	33	33	33	33	33	33	33	33	33	33	33	33	33

D: 22NOV95
T: 22NOV95(21:45)

Source: Appendix V Table 12

APPENDIX I TABLE 7.1
DOFETILIDE PROTOCOL 203
BLOOD PRESSURE, MEAN CHANGES FROM BASELINE

SUPINE SYSTOLIC BP (mmHg)

		DAY 1							DAY 10					
		TIME POST-DOSE (h)							TIME POST-DOSE (h)					
		PRE-DOSE	BASEL-INE	1	2	4	8	12	BASEL-INE	1	2	4	8	12
TREATMENT														
Dofetilide 100 mcg BD	MEAN	120.33	121.61	4.11	5.50	1.00	-3.78	4.89	-4.81	-0.13	12.13	2.31	-3.13	7.56
	S.E.	3.33	3.77	3.09	2.57	4.20	3.26	2.62	4.83	5.17	5.01	3.64	8.87	5.44
	N	9	9	9	9	9	9	9	8	8	8	8	8	8
Dofetilide 200 mcg OD	MEAN	120.63	111.75	2.81	6.56	7.81	3.38	13.81	11.44	2.06	16.69	6.81	11.25	17.44
	S.E.	3.65	3.33	3.92	2.16	2.47	2.94	3.28	3.03	3.51	3.77	1.80	4.34	3.63
	N	8	8	8	8	8	8	8	8	8	8	8	8	8
Dofetilide 200 mcg BD	MEAN	120.89	121.89	-0.39	4.00	1.44	-2.33	2.11	5.25	-0.19	7.75	3.13	7.00	10.06
	S.E.	4.89	3.38	2.81	1.30	4.10	2.60	4.80	2.88	3.35	4.18	3.48	5.60	2.17
	N	9	9	9	9	9	9	9	8	8	8	8	8	8
Dofetilide 400 mcg BD	MEAN	115.00	118.69	5.38	5.00	-1.94	-1.50	10.25	-3.79	-4.21	7.93	4.14	13.71	8.79
	S.E.	3.78	3.03	2.24	2.93	2.88	3.05	3.84	3.18	3.94	2.33	3.04	5.89	3.34
	N	8	8	8	8	8	8	8	7	7	7	7	7	7
Double Blind Placebo	MEAN	120.00	121.52	-1.61	2.61	1.21	-1.20	3.76	2.30	-1.32	6.45	2.50	-0.35	6.24
	S.E.	1.48	2.32	2.05	1.83	1.97	1.95	1.75	2.59	2.26	2.59	2.06	2.56	2.56
	N	33	33	33	33	33	33	33	33	33	33	33	33	33

D: 22NOV95
T: 22NOV95(21:45)

Source: Appendix V Table 12

1.3 QT Dispersion and Rate Dependency

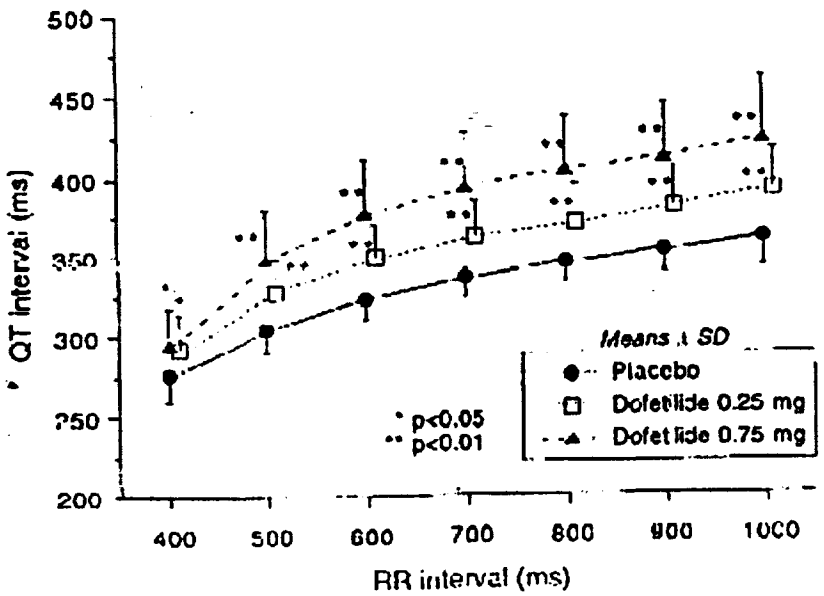
Studies 115-206, 115-218, 115-231, 115-252, and 115-232 evaluated the effect of dofetilide on the prolongation of repolarization at various paced cycle rates.

Study 250: (A double-blind, placebo-controlled, 3 way cross-over study on the effect of dofetilide on ventricular repolarization in young healthy male volunteers: rate dependency of QT prolongation and QT dispersion) was designed to determine the effect of dofetilide on the QT interval and QT dispersion at different heart rates and to determine the effect of heart rate on the QT interval-plasma concentration relationship.

The study measured QT interval prolongation and dispersion at different dofetilide plasma concentrations in 14 healthy male subjects. Physiological stress tests were performed to induce a wide range of heart rates (between 60 and 150 bpm, i.e. RR interval between 1000 and 400 msec) after repeated administration of dofetilide (250 and 750 mcg bid) or placebo bid. Following 7 doses of dofetilide, the subjects were monitored by 12-lead ECG for the QT response during an exercise test performed 2 hours after the last dose. One investigator, blinded to study treatment, manually measured all QT intervals via a computer-linked digitizing pad according to fixed criteria. QT dispersion was measured at rest and during exercise from each of the 12 leads and was defined as the difference between the maximum and minimum QT interval from one set of 12-lead ECG recordings.

QT intervals measured 2 hours after dosing (peak effect) during exercise of different intensities for dofetilide 250 mcg and 750 mcg and placebo are shown below.

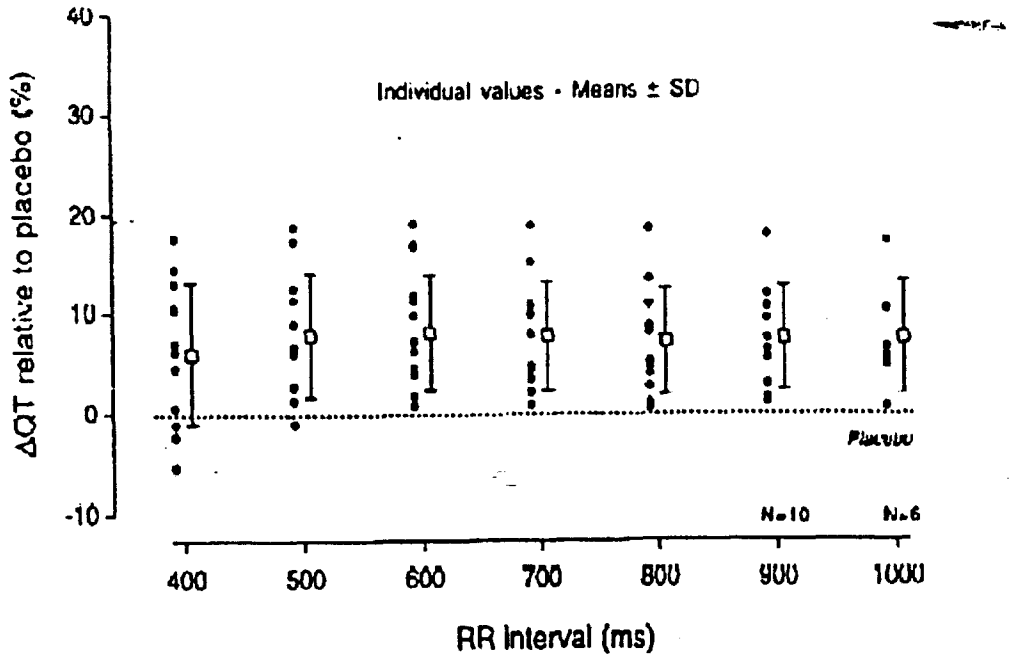
Figure 1B
QT Prolongation 2 Hours After Administration, Day 4



QT intervals increased with all treatment groups and the increases were larger with longer RR intervals. The QT increases observed with the dofetilide groups were always significantly greater compared to placebo regardless of the RR interval.

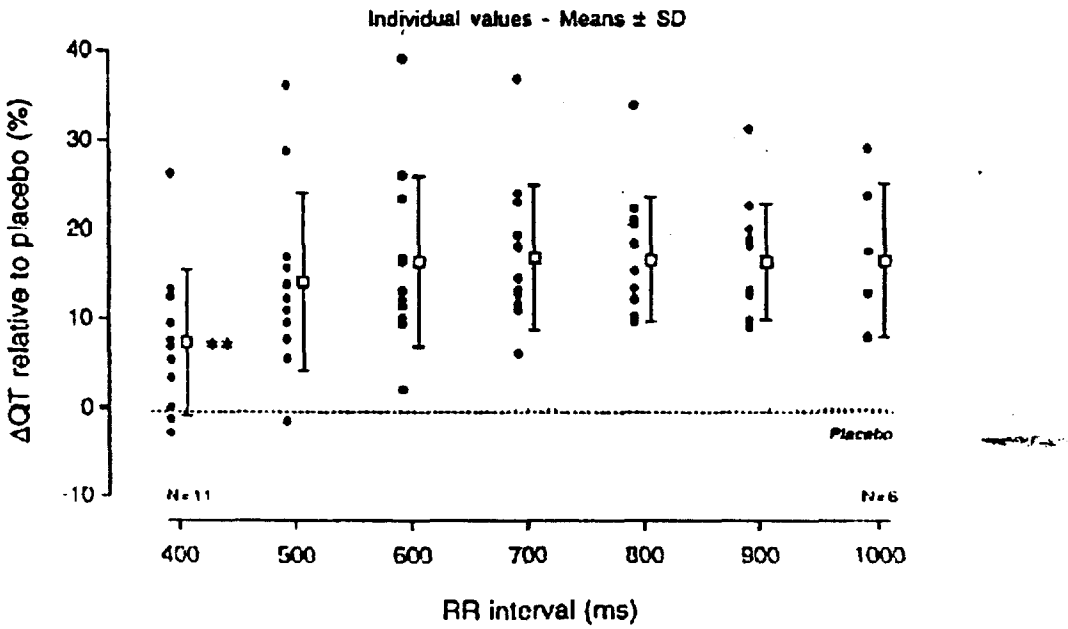
The figures below show the QT variation at different RR intervals for the dofetilide 250 and 750 mcg doses relative to placebo at peak concentration. The figure displays individual values, the mean value, and the SD.

Figure 2A
QT Variation 2 Hours After Administration, Day 4
Dofetilide 250mcg / Placebo



The mean changes relative to placebo for the QT interval for the 250 mcg doses were roughly 10% regardless of RR interval; some individual changes were around 20%.

Figure 2B
QT Variation 2 Hours After Administration, Day 4
Dofetilide 750mcg / Placebo

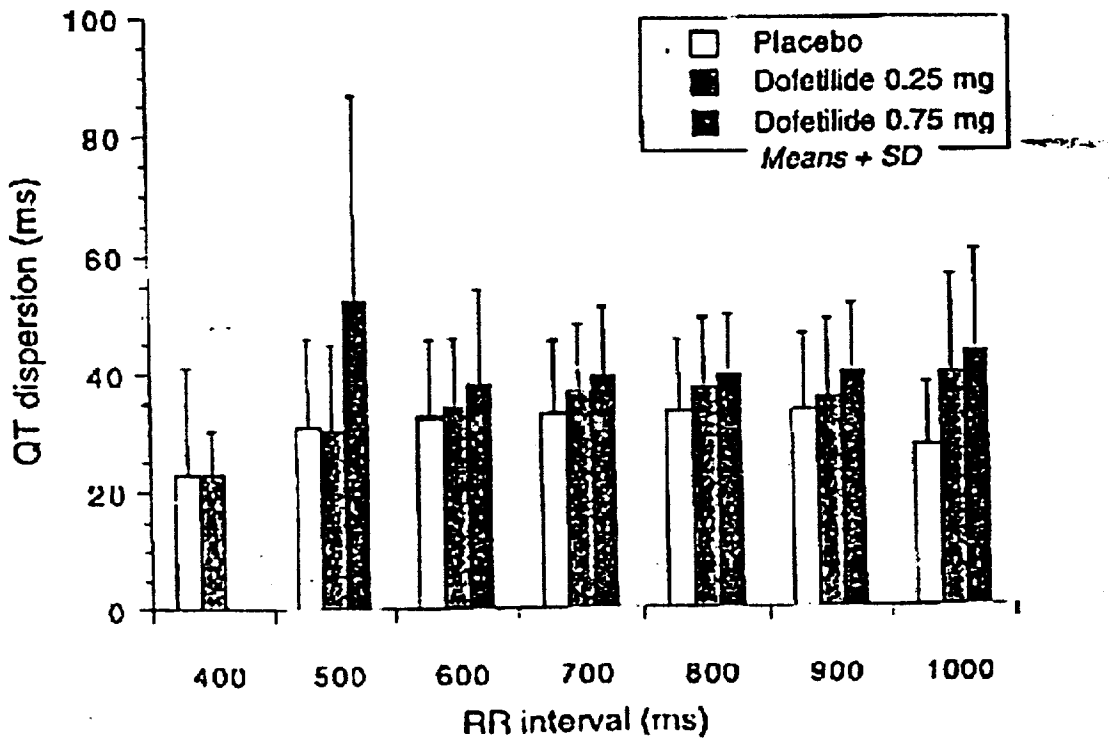


The means and the variation in the QT at peak drug concentration were much higher for the 750 mcg dose compared to the 250 mcg dose. For the higher dose group, the mean QT changes relative to placebo were about 10-20% with individual changes as high as 40%.

QT dispersion (defined as the difference between the maximum and minimum QT interval from one set of 12-lead ECG recordings) was measured at rest and during exercise from each of the 12 leads according to the method of Day et al (1991)[1]. The figure below shows the QT interval dispersion at peak drug concentration for the 3 treatment groups at the different RR intervals.

[1]Day CP et al. European Heart Journal 1991; 12: 423-427

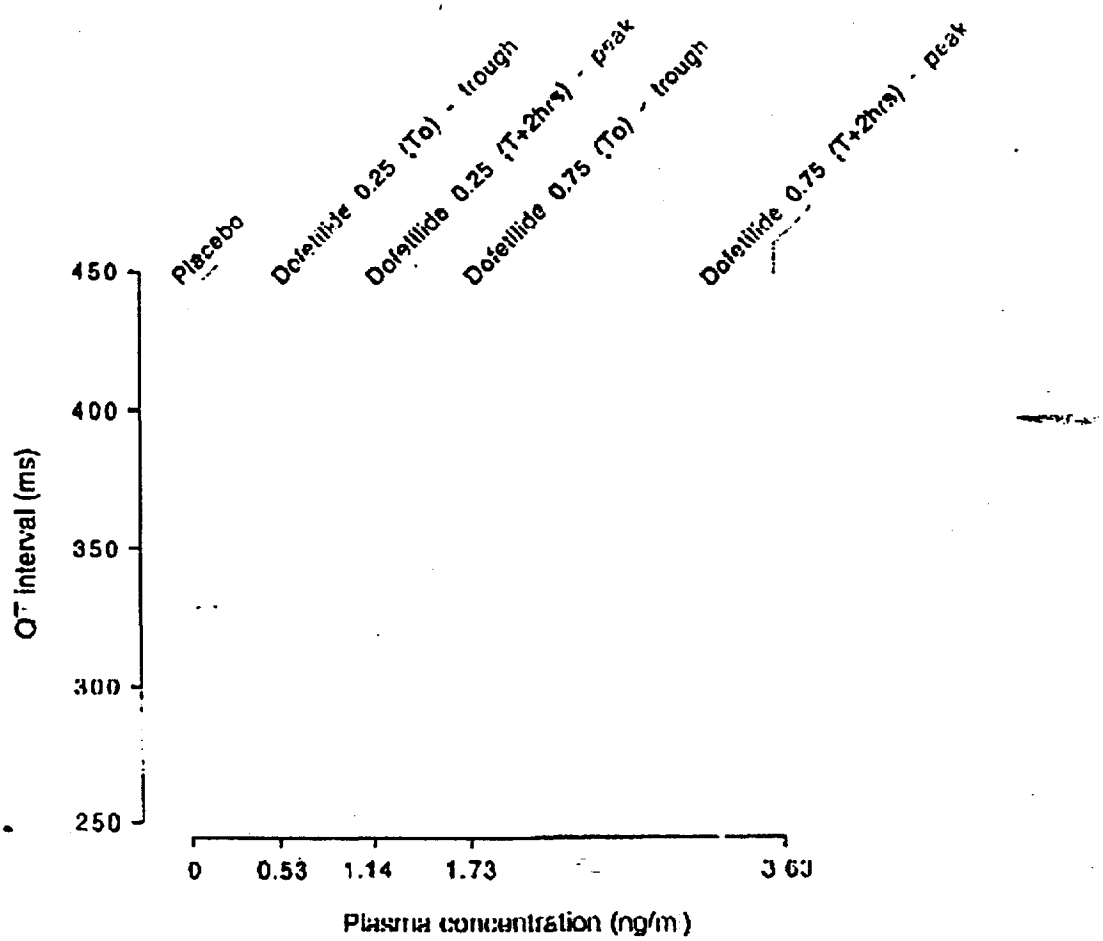
Figure 3B
QT Interval Dispersion 2 Hours After Administration, Day 4



QT dispersion was similar in all 3 dose groups and not related to heart rate.

The relationship between dofetilide concentration (peak and trough) and QT interval at different heart rates is shown below.

Effect of dofetilide or QT interval at Steady State



The higher QT intervals were associated with higher dofetilide doses and plasma concentrations. For each plasma concentration, the QT interval tended to be longer with longer RR intervals.

In conclusion, dofetilide increased QT interval duration but not QT dispersion in a dose and concentration related manner. There were individual variations in the amount of QT prolongation, particularly with the higher dose.

1.4 Monophasic action potential

Dofetilide's effect on the atrial and ventricular MAP durations were measured in 5 studies using various doses, formulations, and cycle lengths. The studies are briefly described below.

Study 115-218 was a randomized, double-blind, placebo-controlled parallel group study in 18 subjects randomly receiving either (3.0+1.5) mcg/kg dofetilide, (6.0+3.0) mcg/kg dofetilide or placebo steady-state intravenous infusions.
Study 115-231 was an open single dose study that utilized a dofetilide steady-state intravenous infusion (4.0+2.0) mcg/kg in 10 subjects.
Study 115-105 was a multicenter, randomized, double-blind study of orally administered dofetilide or placebo in subjects with non-sustained or sustained VT and impaired left ventricular function (20%<LVEF<30%).
Study 115-252 was an open study of nine subjects receiving 6mcg/kg constant rate infusion of dofetilide over 10 minutes.
Study 115-322 was a randomized, double-blind, placebo-controlled, parallel group study of 12 subjects receiving 8mcg/kg constant rate infusion of dofetilide or placebo in a 2:1 randomization.

Measurements were made in the high right atrium, the right ventricular apex, and/or the right ventricular outflow tract. The changes from baseline of the MAP duration observed in these trials are shown below.

Table 2 Summary of Change from Baseline (msec) of Monophasic Action Potential Duration at Various Doses, Positions in the Heart and Cycle Lengths.

Site Protocol	Dose	Site Cycle length	HRA	RVA	RVOT
115-218	(3+1.5)mcg/kg (N=6)	500		35.0 **	25.8 *
ss inf	(6+3)mcg/kg (N=6)	500		40.0 **	33.3 *
	placebo (N=6)	500		-1.7	4.2
	(3+1.5)mcg/kg	800		25.0	38.3 *
	(6+3)mcg/kg	800		48.3 **	45.8 *
	placebo	800		2.5	-5.0
115-231	(4+2)mcg/kg (N=10)	500	49.2	34.9	27.2
ss inf		600	59.3	51.5	53.8
115-105	250mcg tid (N=8)	500		44.43	
oral	500mcg tid (N=9)	500		62.80	
	placebo tid (N=8)	500		10.50	
115-252	6mcg/kg (N=9)	SR	34.00	61.67	
inf		300	-	-	
		400	38.13	35.50	
		500	42.50	45.56	
		600	50.00	44.44	
		700	50.00	53.33	
115-322	8mcg/kg (N=8)	700	82.9 **	73.6 **	
inf	placebo (N=4)	700	-1.3	-10.0	

HRA = high right atrium; RVA = right ventricular apex; RVOT = right ventricular outflow tract

* $p \leq 0.01$; ** $p \leq 0.05$ compared to placebo

The results show that dofetilide, compared to placebo when placebo was present, prolongs the MAP duration in both atria and ventricles. The effect was greater with larger doses of dofetilide and the changes in the atria tended to be larger than the change in the ventricles. The changes in the MAP durations tended to be longer with higher cycle lengths (slower heart rates).

1.5 Effective refractory period

Dofetilide's effect on the atrial and ventricular EFP was measured in 7 studies using various doses, formulations, and cycle lengths. The studies include those described in the previous section (1.4) and the following:

Study 115-206 was a randomized, double-blind, placebo-controlled study in 2 phases using steady-state intravenous infusions consisting of a loading infusion of 15 minutes followed immediately by a maintenance infusion of 45 minutes. In the first phase of 9 subjects, the 2 treatments were dofetilide (3.0+1.5)mcg/kg or placebo in a 2:1 randomization; in the second phase of 9 subjects, the dofetilide dose was(5.0+2.5)mcg/kg, again in a 2:1 randomization.

Study 115-232 was a randomized, double-blind, placebo-controlled study of (5.0+2.5) mcg/kg dofetilide steady-state intravenous infusion versus placebo in a 2:1 randomization of 18 subjects.

The changes from baseline of the ERP duration (msec) from these trials are shown below.

Table 3 Summary of Change from Baseline (msec) of Atrial and Ventricular Effective Refractory Periods at various doses and cycle lengths.

Protocol	Dose	Site Cycle length	HRA AERP	RVA VERP
115-206	(3+1.5)mcg/kg (N=6)	450	26.0 *	36.0 **
ss inf	(5+2.5)mcg/kg (N=6)	450	48.3 *	36.7 **
	placebo (N=6)	450	4.0	-4.0
	(3+1.5)mcg/kg	600	22.0 **	34.0 *
	(5+2.5)mcg/kg	600	40.0 *	38.0 *
	placebo	600	0	8.0
115-218	(3+1.5)mcg/kg (N=6)	500		30.0
ss inf	(6+3)mcg/kg (N=6)	500		41.7
	placebo (N=6)	500		3.3
	(3+1.5)mcg/kg	800		34.0
	(6+3)mcg/kg	800		51.7
	placebo	800		0.0
115-231	(4+2)mcg/kg (N=10)	500		23.6
ss inf		600		32.6
115-232	(5.0+2.5)mcg/kg (N=12)	450	28.6	26.4
ss inf	placebo (N=6)	450	7.5	-4.0
	(5.0+2.5)mcg/kg	600	33.8	36.4
	placebo	600	-2.0	10.0
115-105	250mcg tid (N=8)	500		10.00
oral	500mcg tid (N=9)	500		23.33
	placebo tid (N=8)	500		-16.25
115-252	6mcg/kg	NSR	38.33	40.00
inf		300	-	20.00
		400	26.25	31.11
		500	31.11	33.33
		600	30.00	31.11
		700	34.29	43.33
115-322	8mcg/kg (N=8)	700	61.3 **	48.8 **
	placebo (N=4)	700	12.5	7.5

HRA = high right atrium; RVA = right ventricular apex; RVOT = right ventricular outflow tract; NSR = normal sinus rhythm

* $p \leq 0.01$; ** $p \leq 0.05$ compared to placebo

Compared to placebo, dofetilide increased the ERP in both the atrium and ventricle in a dose related fashion and the changes are larger with longer pacing cycles. There is a tendency for the ERP to be

increased more in the atrium than in the ventricle only at higher dofetilide doses.

Study 115-206 (a double-blind, placebo controlled, acute evaluation of the electrophysiological effects of dofetilide and placebo in subjects with stable angina pectoris: an intravenous study) was designed to assess the safety and tolerance of single intravenous doses of dofetilide in patients with stable angina pectoris, and to determine the effect of dofetilide on resting and paced cardiac electrophysiological parameters. Patients received 3 mcg/kg loading plus 1.5 mcg/kg maintenance infusion, or 5 mcg/kg loading plus 2.5 mcg/kg maintenance infusion, or placebo. The loading infusion was given over 15 minutes and it was followed by a 45 minute maintenance infusion.

Resting electrophysiological parameters: RR (time between the two consecutive R waves), AH (represents atrio-ventricular nodal conduction time), HV (His-Purkinje system conduction time), PA (intra-atrial conduction time), QRS (depolarization of intra-ventricular septum), QT, QTc intervals and sinus cycle length parameters were measured immediately before dosing and 15 minutes following the end of the loading infusion. Paced electrophysiological parameters were also measured at the same time points, and also included atrial, A-V nodal, ventricular and His-Purkinje effective (ERP) and functional refractory periods (FRP), sinus node recovery time and corrected sinus node recovery time[2].

Parameters including ERP assessed in the AV node and His-Purkinje system, paced sinus node recovery time, and corrected sinus node recovery time are briefly summarized below. Tables showing the full results follow the discuss of this study.

Means (msec) ± SE 30 minutes post dose

	dofetilide 3+1.5 mcg/kg (n=6)		dofetilide 5+2.5 mcg/kg (n=6)		placebo (n=6)	
parameter	cycle length 450 msec	cycle length 600 msec	cycle length 450 msec	cycle length 600 msec	cycle length 450 msec	cycle length 600 msec
AV node ERP	27 ±12	23 ±8	22 ±20	21 ±14	5 ±7	12 ±10
His-Purkinje ERP	7 ±8	22 ±9	27 ±11	38 ±10	-7 ±5	-7 ±9
sinus node recovery time	41 ±51	-30 ±57	38 ±65	23 ±96	-105 ±61	-54 ±72
corrected sinus node recovery time	26 ±36	-53 ±49	-32 ±53	-48 ±74	-116 ±76	-49 ±76

Compared to placebo, dofetilide prolongs mean AV node and His-Purkinje ERP but has no effect on sinus node recovery time.

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[2]Corrected by subtracting the spontaneous sinus node cycle length (prior to pacing) from the sinus recovery time.

TABLE 6.1.11
DOFETILIDE PROTOCOL 206
MEAN AV-NODE ERP - INTENTION-TO-TREAT

Treatment Group	Planned/Nominal Time Post Dose		Cycle Length (msec) 450: AV Node ERP (msec)	450: Change from Baseline	600: AV Node ERP (msec)	600: Change from Baseline
Dofetilide (3+1.5 mcg/kg)	Baseline	Mean	276.7		281.7	
		S.E.	23.2		19.6	
		N	6	0	6	0
	30 mins post-dose	Mean	303.3	26.7	305.0	23.3
		S.E.	18.6	11.7	17.3	8.4
		N	6	6	6	6
Dofetilide (5+2.5 mcg/kg)	Baseline	Mean	300.0		289.2	
		S.E.	18.1		12.8	
		N	6	0	6	0
	30 mins post-dose	Mean	321.7	21.7	310.0	20.8
		S.E.	11.4	19.7	9.7	13.9
		N	6	6	6	6
Double Blind Placebo	Baseline	Mean	275.0		285.0	
		S.E.	10.6		10.6	
		N	6	0	6	0
	30 mins post-dose	Mean	280.0	5.0	296.7	11.7
		S.E.	10.0	6.7	16.5	9.8
		N	6	6	6	6

D: 29APR96
T: 29APR96(16:23)

Source: Appendix IV Table 2.1

TABLE 6.1.13
DOFETILIDE PROTOCOL 206
MEAN HIS-PURKINJE ERP - INTENTION-TO-TREAT

Treatment Group	Planned/Nominal Time Post Dose		Cycle Length (msec) 450 His-Purkinje ERP (msec)	450 Change from Baseline	600 His-Purkinje ERP (msec)	600 Change from Baseline
Dofetilide (3+1.5 mcg/kg)	Baseline	Mean	375.0		378.3	
		S.E.	19.8		22.1	
		N	6	0	6	0
	30 mins post-dose	Mean	381.7	6.7	408.0	22.0
		S.E.	16.4	8.4	19.8	9.2
		N	6	6	5	5
Dofetilide (5+2.5 mcg/kg)	Baseline	Mean	383.3		390.0	
		S.E.	14.5		13.2	
		N	6	0	6	0
	30 mins post-dose	Mean	410.0	26.7	428.3	38.3
		S.E.	8.2	10.9	10.8	10.1
		N	6	6	6	6
Double Blind Placebo	Baseline	Mean	388.3		394.2	
		S.E.	18.5		13.4	
		N	6	0	6	0
	30 mins post-dose	Mean	381.7	-6.7	386.7	-7.5
		S.E.	16.6	4.9	14.1	9.1
		N	6	6	6	6

D: 29APR96
T: 29APR96(16:23)

Source: Appendix IV Table 2.1

TABLE 6.1.15
DOFETILIDE PROTOCOL 206
MEAN VENTRICULAR ERP - INTENTION-TO-TREAT

Treatment Group	Planned/Nominal Time Post Dose		Cycle Length (msec) 450 Ventricular ERP (msec)	450 Change from Baseline	600 Ventricular ERP (msec)	600 Change from Baseline
Dofetilide (3+1.5 mcg/kg)	Baseline	Mean	221.7		235.0	
		S.E.	10.8		10.6	
		N	6	0	6	0
	30 mins post-dose	Mean	256.7	35.0	268.3	33.3
		S.E.	8.4	5.6	7.9	3.3
		N	6	6	6	6
Dofetilide (5+2.5 mcg/kg)	Baseline	Mean	225.0		238.3	
		S.E.	8.5		7.9	
		N	6	0	6	0
	30 mins post-dose	Mean	261.7	36.7	275.0	36.7
		S.E.	10.1	5.6	11.2	6.7
		N	6	6	6	6
Double Blind Placebo	Baseline	Mean	233.3		236.7	
		S.E.	15.8		7.6	
		N	6	0	6	0
	30 mins post-dose	Mean	231.7	-1.7	245.0	8.3
		S.E.	4.8	13.3	5.6	4.0
		N	6	6	6	6

D: 29APR96
T: 29APR96(16:23)

Source: Appendix IV Table 2.1

TABLE 6.3.4
DOFETILIDE PROTOCOL 206
MEAN SINUS NODE RECOVERY TIME - INTENTION-TO-TREAT

Treatment Group	Planned/Nominal Time Post Dose		Cycle Length (msec) 450 SNRT (msec)	450 Change from Baseline	600 SNRT (msec)	600 Change from Baseline
Dofetilide (3+1.5 mcg/kg)	Baseline	Mean	936.7		985.0	
		S.E.	84.6		127.4	
		N	6	0	6	0
	30 mins post-dose	Mean	977.5	40.8	955.0	-30.0
		S.E.	95.7	50.5	96.4	57.1
		N	6	6	6	6
Dofetilide (5+2.5 mcg/kg)	Baseline	Mean	1061.7		1069.2	
		S.E.	57.2		55.4	
		N	6	0	6	0
	30 mins post-dose	Mean	1100.0	38.3	1091.7	22.5
		S.E.	103.7	65.4	115.9	95.9
		N	6	6	6	6
Double Blind Placebo	Baseline	Mean	1178.3		1099.2	
		S.E.	104.0		85.5	
		N	6	0	6	0
	30 mins post-dose	Mean	1073.3	-105.0	1045.0	-54.2
		S.E.	78.3	60.8	84.3	71.9
		N	6	6	6	6

D: 07DEC95 - 16MAY96
T: 16MAY96(14:30)

Source: Appendix IV Table 2.3

TABLE 6.3.5
DOFETILIDE PROTOCOL 206
MEAN CORRECTED SINUS NODE RECOVERY TIME - INTENTION-TO-TREAT

Treatment Group	Planned/Nominal Time Post Dose		Cycle Length (msec) 450 CSNRT (msec)	450 Change from Baseline	600 CSNRT (msec)	600 Change from Baseline
Dofetilide (3+1.5 mcg/kg)	Baseline	Mean	180.8		237.5	
		S.E.	41.1		73.4	
		N	6	0	6	0
	30 mins post-dose	Mean	206.7	25.8	184.2	-53.3
		S.E.	52.7	36.1	50.5	48.9
		N	6	6	6	6
Dofetilide (5+2.5 mcg/kg)	Baseline	Mean	292.5		300.0	
		S.E.	28.7		44.4	
		N	6	0	6	0
	30 mins post-dose	Mean	260.8	-31.7	252.5	-47.5
		S.E.	47.8	52.7	61.2	73.9
		N	6	6	6	6
Double Blind Placebo	Baseline	Mean	371.3		292.2	
		S.E.	77.0		61.5	
		N	6	0	6	0
	30 mins post-dose	Mean	255.0	-116.3	243.3	-48.8
		S.E.	63.2	76.2	74.1	75.7
		N	6	6	6	6

D: 07DEC95 - 16MAY96
T: 16MAY96(14:30)

Source: Appendix IV Table 2.3

TABLE 6.2.4
DOFETILIDE PROTOCOL 206
MEAN ATRIAL CONDUCTION TIME - INTENTION-TO-TREAT

Treatment Group	Planned/Nominal Time Post Dose		PA Interval (msec)	Change from Baseline
Dofetilide (3+1.5 mcg/kg)	Baseline	Mean	24.2	
		S.E.	4.4	
		N	6	0
	30 mins post-dose	Mean	25.0	0.8
		S.E.	6.7	4.7
		N	6	6
Dofetilide (5+2.5 mcg/kg)	Baseline	Mean	24.2	
		S.E.	6.1	
		N	6	0
	30 mins post-dose	Mean	28.3	4.2
		S.E.	5.6	10.8
		N	6	6
Double Blind Placebo	Baseline	Mean	22.0	
		S.E.	3.7	
		N	5	0
	30 mins post-dose	Mean	25.0	6.0
		S.E.	5.2	8.3
		N	6	5

D: 07DEC95 - 29APR96
T: 29APR96(16:45)

Source: Appendix IV Table 2.2

TABLE 6.2.5
DOFETILIDE PROTOCOL 206
MEAN AV-NODE TO HIS CONDUCTION TIME - INTENTION-TO-TREAT

Treatment Group	Planned/Nominal Time Post Dose		AVN-H Interval (msec)	Change from Baseline
Dofetilide (3+1.5 mcg/kg)	Baseline	Mean	80.0	
		S.E.	6.3	
		N	6	0
	30 mins post-dose	Mean	76.7	-3.3
		S.E.	6.8	3.6
		N	6	6
Dofetilide (5+2.5 mcg/kg)	Baseline	Mean	84.2	
		S.E.	10.5	
		N	6	0
	30 mins post-dose	Mean	93.3	9.2
		S.E.	14.6	7.4
		N	6	6
Double Blind Placebo	Baseline	Mean	93.3	
		S.E.	9.5	
		N	6	0
	30 mins post-dose	Mean	94.0	2.0
		S.E.	9.3	3.4
		N	5	5

D: 07DEC95 - 29APR96
T: 29APR96(16:45)

Source: Appendix IV Table 2.2

TABLE 6.2.6
DOFETILIDE PROTOCOL 206
MEAN HIS-VENTRICLE CONDUCTION TIME - INTENTION-TO-TREAT

Treatment Group	Planned/Nominal Time Post Dose		H-V Interval (msec)	Change from Baseline
Dofetilide (3+1.5 mcg/kg)	Baseline	Mean	51.7	
		S.E.	1.7	
		N	6	0
	30 mins post-dose	Mean	49.2	-2.5
		S.E.	4.2	3.6
		N	6	6
Dofetilide (5+2.5 mcg/kg)	Baseline	Mean	54.2	
		S.E.	2.7	
		N	6	0
	30 mins post-dose	Mean	54.2	0.0
		S.E.	3.7	2.2
		N	6	6
Double Blind Placebo	Baseline	Mean	50.0	
		S.E.	3.4	
		N	6	0
	30 mins post-dose	Mean	48.0	-1.0
		S.E.	3.7	2.4
		N	5	5

D: 07DEC95 - 29APR96
T: 29APR96(16:45)

Source: Appendix IV Table 2.2

TABLE 6.3.6
DOFETILIDE PROTOCOL 206
MEAN SINUS CYCLE LENGTH - INTENTION-TO-TREAT

Treatment Group	Planned/Nominal Time Post Dose		Sinus CL (msec)	Change from Baseline
Dofetilide (3+1.5 mcg/kg)	Baseline	Mean	747.5	
		S.E.	55.6	
		N	6	0
	30 mins post-dose	Mean	770.8	23.3
		S.E.	52.3	10.6
		N	6	6
Dofetilide (5+2.5 mcg/kg)	Baseline	Mean	769.2	
		S.E.	34.8	
		N	6	0
	30 mins post-dose	Mean	839.2	70.0
		S.E.	77.6	49.5
		N	6	6
Double Blind Placebo	Baseline	Mean	807.0	
		S.E.	51.3	
		N	6	0
	30 mins post-dose	Mean	818.3	11.3
		S.E.	49.7	26.7
		N	6	6

D: 07DEC95 - 16MAY96
T: 16MAY96(14:30)

Source: Appendix IV Table 2.3

1.6 Conduction time

Results for conduction times (atrial, AV node to His, and His to ventricle) and sinus cycle length from protocol 115-206 are shown below.

Means (msec) ± SE 30 minutes post dose

	dofetilide 3+1.5 mcg/kg (n=6)	dofetilide 5+2.5 mcg/kg (n=6)	placebo (n=6)
atrial conduction time	1 ±5	4 ±11	6 ±8
AV node to His	-3 ±4	9 ±7	2 ±3
His-ventricle	-3 ±4	0 ±2	-1 ±2
sinus cycle length	23 ±11	70 ±50	11 ±27

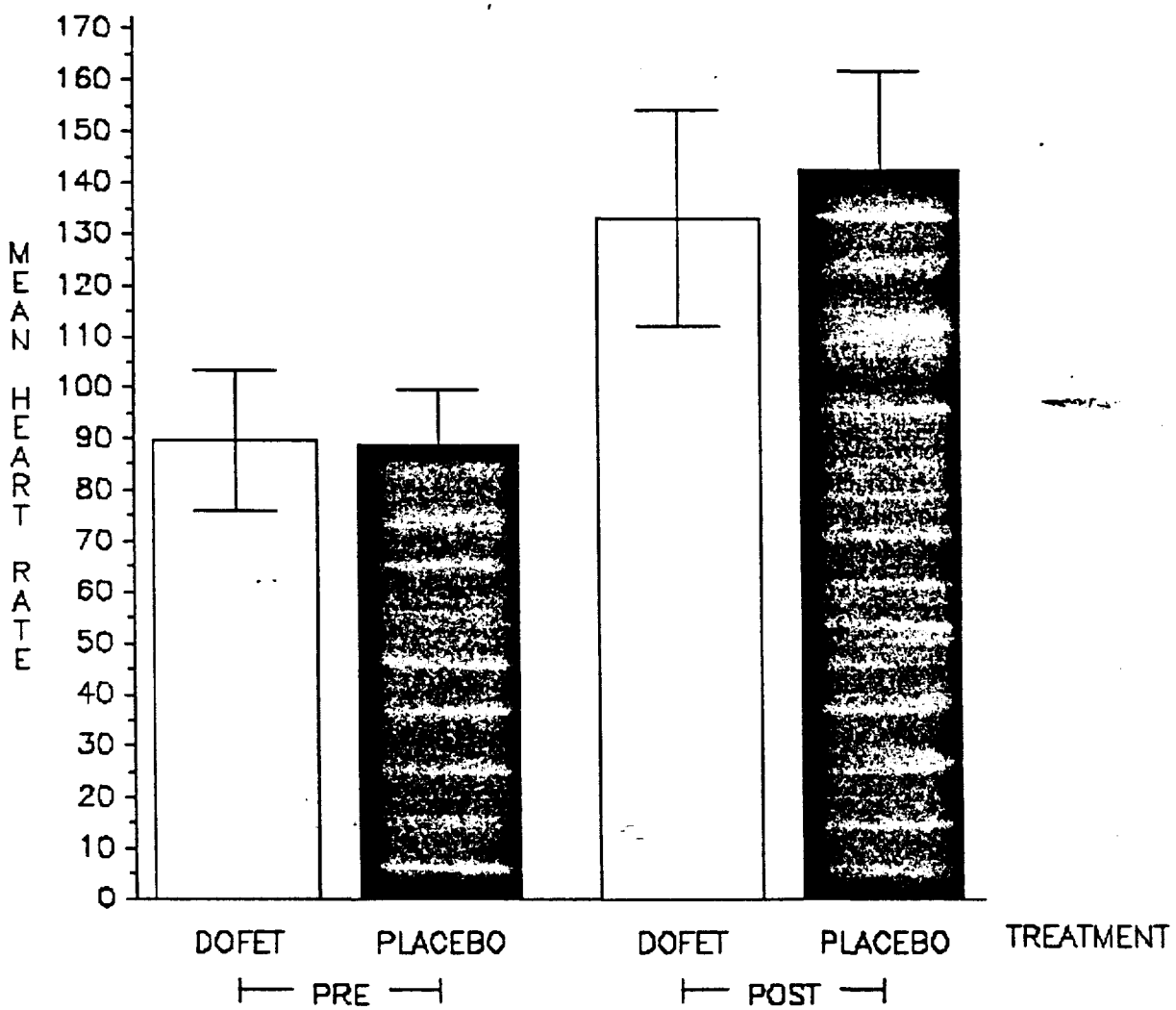
Dofetilide appears to have no effect on these parameters.

1.7 Exercise tolerance

Study 115-313 (a double-blind, placebo-controlled, crossover study to investigate the efficacy of dofetilide on exercise tolerance of patients with well-controlled chronic atrial fibrillation) was designed to investigate the potential of dofetilide 500 mcg bid to increase exercise tolerance in patients with well-controlled chronic atrial fibrillation (AF). Maximal exercise tolerance, assessed by exercise duration and ventilation and heart rate responses (STEEP protocol), was measured at baseline and at intervals throughout the study. The sample size was 14; 2 patients were excluded from efficacy analysis because they converted to sinus rhythm while taking dofetilide.

Patients on placebo walked longer (adjusted mean difference between total exercise time was 30.14 sec) compared to the patients on dofetilide but the difference was not statistically significant. There was no difference between dofetilide and placebo treatment in anaerobic threshold, VO2max or VO2max per unit weight. Heart rates at baseline and at endpoint are shown below.

FIGURE 1
DOFETILIDE PROTOCOL 313
HISTOGRAM OF MEAN HEART RATE BEFORE/AFTER EXERCISE



Heart rate was similar between dofetilide and placebo at the end of treatment (89.8 bpm for both groups). However, the pre- to post-exercise heart rate changes were larger for the placebo group (52.7± 6.2bpm) compared to dofetilide (39.2 ± 6.7 bpm).

Exercise Substudy 115-120X (effects of conversion to sinus rhythm on exercise tolerance in patients with chronic atrial fibrillation: a substudy of protocol 120) was designed to evaluate in a subset of patients, changes in exercise tolerance that occurred after cardioversion to normal sinus rhythm. The main study was randomized, double-blind, placebo-controlled, with parallel groups. Hospitalized patients were given dofetilide 125mcg, 250 mcg, 500 mcg or placebo bid. Those who did not convert pharmacologically after 5 doses were electrically converted. Patients who remained in NSR for 24 hours entered a 12 month evaluation of maintenance of NSR, and, for patients in 120X, evaluation of exercise tolerance.

Patients in the substudy performed a standardized Naughton multistage exercise test on a treadmill. The exercise test was performed twice during the run-in phase (while the subject was still in AF), 1-3 days post cardioversion, Day 30, Day 60 and at completion of Study 120 or relapse to AF, whichever came first. The second test, performed 5-9 days before hospitalization, was the baseline test. A total of 56 patients who were able to perform treadmill exercise tests participated in an exercise substudy.

Analysis of the exercise data was conducted after a natural log transformation of all data. The sponsor stated that "the log transformation allowed exercise duration to be expressed in terms of percentage change from baseline while reducing the impact of extreme values and stabilizing the variance among groups. After analysis the log transformed summary statistics were converted back for presentation." The mean (seconds) and the percent change from baseline (based on geometric means) with se of % change for various visits (baseline (in AF/AFl), post cardioversion (CV; in NSR), Day 30 (in NSR), Day 60 (in NSR), at completion of study (in NSR), and at relapse to AF/AFl are shown in the table on the following page.

TABLE 6.18
DOFETILIDE PROTOCOL 120
TOTAL EXERCISE DURATION - CHANGE FROM BASELINE FOR ALL SUBJECTS
EXERCISE SUBSTUDY SUBJECTS

Exercise Test Subject* Visit Grouping	N	Mean Exercise Duration (seconds)** Baseline	Change***	% Change from Baseline	SE of % Change
Training (AF/AFl)	46	539.0	609.8	-70.8	
Baseline (AF/AFl)	56	656.0	656.0		
Post CV (NSR)	29	556.3	530.9	25.4	4.8	5.8
Day 30 (NSR)	20	634.5	533.1	101.4	19.0	8.2
Day 60 (NSR)	18	724.4	569.9	154.5	27.1	11.0
Completion (NSR)	14	730.9	592.8	138.1	23.3	15.5
Relapse (AF/AFl)	14	543.4	521.3	22.1	4.2	15.4

D: 01AUG1997 - 05SEP1997
T: 06SEP97(03:56)

Source: Appendix IV Table 8

* Visits with scheduled exercise tests
** Based on geometric means
*** Difference from baseline to the assessment timepoint

The results show that the patients who converted to sinus rhythm had, at all times tested, an increase in mean exercise duration from baseline (5% for the 29 patients post cardioversion, 19 % for the 20 patients in NSR at 30 days, and 27% for the 18 patients in NSR at 60 days). The mean increase in exercise duration for the 14 patients who completed the 12 month study in sinus rhythm was 23%; for the 14 subjects who relapsed to AF/AFl had an increase of 4% over their baseline. Although the number of patients is small, these results indicate that patients probably have a greater tolerance for exercise when they are in sinus rhythm and those who relapse into AF lose their tolerance for exercise.

1.8 Patients with conduction abnormalities/sinus node dysfunction

Study 115-232 (the influence of intravenous dofetilide on basic invasive electrophysiological parameters in patients with conduction anomalies and/or sinus node disturbances) was designed to assess, in a double-blind, placebo-controlled manner, the effect of dofetilide on basic electrocardiographic and electrophysiologic parameters in patients with conduction anomalies and/or disturbances in sinus node function, referred for a routine electrophysiological investigation.

Eighteen patients were randomized to either 5 mcg/kg loading over 15 minutes plus 2.5 mcg/kg maintenance infusion over 45 minutes of dofetilide, or placebo. Primary diagnoses of patients in the dofetilide treatment group included AV block (4), left bundle branch block (3), right bundle branch block (5), hemiblock anterior (1) and left anterior hemiblock (1). One patient had AV block, LBB block, RBB block and left anterior hemiblock and another patient had hemiblock anterior and LBB block. All patients in the placebo group had a primary diagnosis of AV block.

Electrophysiological parameters, conduction parameters, and effect on sinus node were measured prior to the start of the loading infusion and during the maintenance infusion. Refractoriness (effective refractory period (ERP) in atria, AV node, His-Purkinje system and ventricles) was discussed in section 1.4 and is not repeated here.

Conduction parameters

The table below shows the mean change from baseline at 15 minutes post dose.

Mean change from baseline (msec)±SE

parameter	dofetilide 5+2.5 mcg/kg (n=12)	placebo (n=6)
PA-interval	-6 ±3	0 ±6
AH-interval	-3 ±3	-7 ±14
HV-interval	6 ±3	7 ±7
Wenkebach point	2 ±8	20 ±28

Compared to placebo, dofetilide did not affect conduction time in these patients.

Electrophysiological parameters

The table blow shows the mean change from baseline at 15 minutes post dose for selected parameters.

Mean change from baseline (msec)±SE

parameter	dofetilide 5+2.5 mcg/kg (n=12)	placebo (n=6)
PR interval	9 ±7	10 ±8
QRS interval	1 ±1	1 ±4

Compared to placebo, dofetilide did not affect these electrophysiological parameters.

The results of the sinus node recovery times are shown below.

Mean change from baseline (msec)±SE

	dofetilide 5+2.5 mcg/kg (n=11+)		placebo (n=4^)	
parameter	cycle length 450 msec	cycle length 600 msec	cycle length 450 msec	cycle length 600 msec
sinus node recovery time	16 ±46	-98 ±80	40 ±115	-68 ±92
corrected sinus node recovery time	43 ±58	107 ±112	-63 ±28	49 ±75

+n varies from 10-12
^n varies from 3-5

The changes from baseline seen in the dofetilide group are similar to those in the placebo group for the sinus node recovery time. Dofetilide seems to increase corrected sinus node recovery time compared to placebo but the variability in both groups is large.

The changes in mean cycle length are shown below.

Mean change from baseline (msec) ±SE

	dofetilide 5+2.5 mcg/kg (n=12)	placebo (n=6)
sinus cycle length	-26±54	-18±30

Compared to placebo, dofetilide did not change sinus cycle length.

There were no serious adverse events or withdrawals resulting from adverse events. Dofetilide seemed to be well tolerated in this population of patients with conduction abnormalities.

TABLE 6.1
DOFETILIDE PROTOCOL 232
SINUS NODES RECOVERY TIMES SUMMARY
MEAN BASELINE AND MEAN CHANGE FROM BASELINE

			PACED CYCLE LENGTH			
			450 (msec)		600 (msec)	
			Time Post Dose		Time Post Dose	
			Baseline	15 (mins)	Baseline	15 (mins)
SNRT (msec)	Dofetilide 5+2.5mcg/kg	MEAN	1125.0	15.5	1225.0	-98.2
		SE	55.72	46.11	69.59	80.34
		N	10	10	12	11
	Double Blind Placebo	MEAN	1270.0	40.0	1272.0	-68.0
		SE	249.06	114.60	173.74	92.22
		N	4	4	5	5
CSNRT (msec)	Dofetilide 5+2.5mcg/kg	MEAN	170.4	43.3	244.8	106.6
		SE	30.44	57.50	43.72	112.27
		N	9	8	11	8
	Double Blind Placebo	MEAN	427.5	-63.3	405.0	48.8
		SE	171.63	28.48	167.21	74.56
		N	4	3	4	4

D: 19NOV96
T: 19NOV96(12:19)

Source: Appendix IV Table 2.1

TABLE 6.2
DOFETILIDE PROTOCOL 232
CONDUCTION TIMES SUMMARY
MEAN BASELINE AND MEAN CHANGE FROM BASELINE

			Time Post Dose	
			Baseline	15 (mins)
PA-Interval (msec)	Dofetilide 5+2.5mcg/kg	MEAN	37.6	-5.9
		SE	4.28	3.04
		N	12	12
	Double Blind Placebo	MEAN	31.7	0.0
		SE	4.59	5.92
		N	6	6
AH-Interval (msec)	Dofetilide 5+2.5mcg/kg	MEAN	103.4	-3.4
		SE	9.15	3.44
		N	12	12
	Double Blind Placebo	MEAN	208.3	-6.7
		SE	30.60	13.58
		N	6	6

D: 19NOV96
T: 19NOV96(12:30)

Source: Appendix IV Table 2.2

TABLE 6.2
DOFETILIDE PROTOCOL 232
CONDUCTION TIMES SUMMARY
MEAN BASELINE AND MEAN CHANGE FROM BASELINE

			Time Post Dose	
			Baseline	15 (mins)
HV-Interval (msec)	Dofetilide 5+2.5mcg/kg	MEAN	59.6	6.3
		SE	5.05	3.43
		N	12	12
	Double Blind Placebo	MEAN	57.5	6.7
		SE	7.93	7.49
		N	6	6
QRS-Interval (msec)	Dofetilide 5+2.5mcg/kg	MEAN	107.1	0.8
		SE	6.29	1.49
		N	12	12
	Double Blind Placebo	MEAN	96.7	0.8
		SE	8.43	3.75
		N	6	6

D: 19NOV96
T: 19NOV96(12:30)

Source: Appendix IV Table 2.2

TABLE 6.2
DOFETILIDE PROTOCOL 232
CONDUCTION TIMES SUMMARY
MEAN BASELINE AND MEAN CHANGE FROM BASELINE

			Time Post Dose	
			Baseline	15 (mins)
PR-Interval (msec)	Dofetilide 5+2.5mcg/kg	MEAN	188.5	8.6
		SE	11.40	7.35
		N	12	12
	Double Blind Placebo	MEAN	283.3	10.0
		SE	31.69	8.16
		N	6	6
Wenckebach point (msec)	Dofetilide 5+2.5mcg/kg	MEAN	418.3	1.6
		SE	29.77	7.54
		N	12	11
	Double Blind Placebo	MEAN	535.0	20.0
		SE	40.31	28.40
		N	6	6

D: 19NOV96
T: 19NOV96(12:30)

Source: Appendix IV Table 2.2

The plots of Kaplan-Meier estimates of the survival probabilities for female and male rats are given in Figures 1 and 2, respectively. The result of the homogeneity test and dose-mortality trend test for comparing five groups of survival distributions (Two Controls, Low, Medium and High) are given in Table 1. The results of pairwise comparisons among those groups are given in Table A-1 in Appendix.

Table 1

P-values of tests for positive linear trend in mortality in the rats

	Test	P-value	
		Female	Male
Homogeneity	Cox	0.7341	0.4796
	Kruskal-Wallis	0.6916	0.4966
Dose-mortality trend	Cox	0.8676	0.2954
	Kruskal-Wallis	0.9169	0.2583

For both female and male rats, the differences in survival among the five groups were not statistically significant, and there were no significant dose-mortality trends. In the following tumor analysis, the two control groups were combined since they were not statistically significantly different.

2.4 Tumor Data Analysis

In the tumor data analysis, the tumors were classified as either fatal (lethal) or non-fatal (non-lethal) type. In the analysis for a selected tumor, the significance of dose-tumor positive linear trend was the primary interest. Using the method of Peto et al (1980), the death-rate method for fatal tumors and prevalence method for non-fatal tumors were applied. The p-values of these tests were evaluated by an exact permutation method. For tumors that caused deaths for some, but not all rats, a combined test was performed. The combined test used the Z-statistic which was assumed to follow a standard normal distribution. This test was referred to as the asymptotic test in the following context. The details of these tests can be found in Lin et. al. (1994). To adjust p-values for the effect of multiple testing, a rule proposed by the Division of Biometrics, CDER/FDA was used in the review. This rule says that in order to keep the false-positive rate at the nominal level of approximately 0.1, tumor types with a spontaneous tumor rate of $\leq$ 1% (rare tumor) should be tested at a 0.025 significance level, otherwise (common tumor) a 0.005 significance level should be used.

The p-values of the tested tumor types for female and male rats are given in Tables A-2 and A-3, respectively. The time intervals used were 0-64, 65-80, 81-93, 94-103 weeks and

terminal sacrifice. Note that the reviewer's decision on significance of trend for tumors that were either fatal or non-fatal to all rats (MSFLG=s) relied on the p-values of exact permutation tests. For other tumors (MSFLG=m), the p-values of asymptotic tests were used.

There were no statistically significant positive linear trends detected for both female and male rats.

3. The Mouse Study

The Sponsor's Analysis

3.1 Design

Two separate experiments, one in female and one in male mice, were conducted. In these experiments, mice were fed with dofetilide at concentrations to average daily intake of 2, 6, or 20 mg/kg. Two control groups received unsupplemented diet. Each group consisted of 50 mice/sex. All animals were observed daily for mortality. They were observed for clinical signs and weighted once a week. Histopathological examinations were carried out on a wide range of tissues recovered from animals found dead during the study, sacrificed as moribund or at the scheduled sacrifice.

3.2 Survival Data Analysis

The sponsor reported no significant differences in mortality between the 2 control groups for either sex. There were no differences in mortality between treated and individual, or combined, control groups. The sponsor provided with two survival curves of Kaplan and Meier type for female and male mice in their report.

3.3 Tumor Data Analysis

The sponsor reported that there were no significant tumor trends detected in the study. Proliferative changes in the rete testis (hyperplasia, adenoma and carcinoma) displayed apparent dose-related increase in treated groups:

Table 2

Carcinoma + adenoma + hyperplasia, rete testis (from table 16, page 99 of the sponsor's report)

Group	Without	With	Expected
Control 1	43	7	9.30
Control 2	42	8	9.52
2 mg/kg	41	9	9.05
6 mg/kg	40	10	9.45
20 mg/kg	37	13	9.68

The Peto analysis yielded a p-value of 0.072.

TABLE 6.3
DOFETILIDE PROTOCOL 232
REFRACTORY PERIODS SUMMARY
MEAN BASELINE AND MEAN CHANGE FROM BASELINE

			PACED CYCLE LENGTH			
			450 (msec)		600 (msec)	
			Time Post Dose		Time Post Dose	
			Baseline	15 (mins)	Baseline	15 (mins)
AFRP (msec)	Dofetilide 5+2.5mcg/kg	MEAN	254.3	58.0	255.0	32.9
		SE	24.96	19.85	16.80	18.22
		N	7	5	8	7
	Double Blind Placebo	MEAN	287.5	22.5	282.5	2.5
		SE	24.96	13.15	19.31	21.75
		N	4	4	4	4
AERP (msec)	Dofetilide 5+2.5mcg/kg	MEAN	238.9	28.6	236.7	33.8
		SE	22.33	24.73	18.26	16.36
		N	9	7	9	8
	Double Blind Placebo	MEAN	225.0	7.5	284.0	-2.0
		SE	2.89	4.79	37.23	14.97
		N	4	4	5	5

D: 19NOV96
T: 19NOV96(12:28)

Source: Appendix IV Table 2.3

TABLE 6.3
DOFETILIDE PROTOCOL 232
REFRACTORY PERIODS SUMMARY
MEAN BASELINE AND MEAN CHANGE FROM BASELINE

			PACED CYCLE LENGTH			
			450 (msec)		600 (msec)	
			Time Post Dose		Time Post Dose	
			Baseline	15 (mins)	Baseline	15 (mins)
AVNFRP (msec)	Dofetilide 5+2.5mcg/kg	MEAN	378.3	-16.7	403.3	13.3
		SE	31.03	12.02	41.33	35.18
		N	6	3	9	6
	Double Blind Placebo	MEAN	500.0	-90.0	492.5	-93.3
		SE	100.00	70.00	51.54	58.40
		N	2	2	4	3
AVNERP (msec)	Dofetilide 5+2.5mcg/kg	MEAN	313.8	0.0	339.0	21.3
		SE	30.88	18.71	39.59	24.67
		N	8	4	10	8
	Double Blind Placebo	MEAN	525.0	-32.5	485.0	-50.0
		SE	76.76	69.93	55.72	65.80
		N	4	4	6	5

D: 19NOV96
T: 19NOV96(12:28)

Source: Appendix IV Table 2.3

TABLE 6.3
DOFETILIDE PROTOCOL 232
REFRACTORY PERIODS SUMMARY
MEAN BASELINE AND MEAN CHANGE FROM BASELINE

			PACED CYCLE LENGTH			
			450 (msec)		600 (msec)	
			Time Post Dose		Time Post Dose	
			Baseline	15 (mins)	Baseline	15 (mins)
VFRP (msec)	Dofetilide 5+2.5mcg/kg	MEAN	250.0	30.0	271.4	40.0
		SE	10.47	6.17	10.33	8.16
		N	7	7	7	7
	Double Blind Placebo	MEAN	273.3	-10.0	275.0	10.0
		SE	13.33	5.77	11.90	7.07
		N	3	3	4	4
VERP (msec)	Dofetilide 5+2.5mcg/kg	MEAN	221.8	26.4	240.0	36.4
		SE	5.85	5.09	7.63	8.12
		N	11	11	11	11
	Double Blind Placebo	MEAN	230.0	-4.0	236.7	10.0
		SE	8.37	5.10	4.94	5.77
		N	5	5	6	6

D: 19NOV96
T: 19NOV96(12:28)

Source: Appendix IV Table 2.3

1.9 Invasive hemodynamic parameters

The effect of dofetilide on hemodynamics was evaluated in 3 studies (115-105, 115-127, 115-207) and each are briefly discussed.

study 115-105 a randomized, double blind, placebo controlled, parallel group, multiple dose oral study which measured cardiac function with right heart catheterization in patients with non-sustained or sustained VT and left ventricular functionless than 30% but more than 20%. Doses of dofetilide were 250 and 500 mcg tid.

Table 7 Summary of Mean Change from Baseline Results from Protocol 115-105

	dofetilide (N=8) 250mcg tid	dofetilide (N=9) 500mcg tid	placebo (N=8)	p-value	
				250mcg tid vs. placebo	500mcg tid vs. placebo
mean pulmonary artery pressure (mmHg)	-2.88	-5.11	-1.00	0.826	0.093
pulmonary artery occluded pressure (mmHg)	-3.13	-2.78	0.63	0.436	0.082
cardiac output (L/min)	0.15	0.44	-0.11	0.569	0.271
cardiac index (L/min/m^2)	0.05	0.17	-0.06	0.480	0.297
stroke volume index (ml/m^2)	2.80	4.47	1.08	0.494	0.207
heart rate (BPM)	-8.13	-0.11	-5.75	0.335	0.352
QT (msec)	44.63	71.50	5.00		
QTc (msec)	41.39	48.46	-0.44		

The mean changes from baseline for the hemodynamic parameters are shown below.

There were no significant difference between either dose of dofetilide and placebo for any of the parameters tested. QT/QTc interval change from baseline was not tested by the sponsor but undoubtedly the difference for both dose groups would have been statistically different from placebo. The effect of 500 mcg tid dofetilide versus placebo on mean pulmonary artery pressure and pulmonary artery occluded pressure approached significance. Cardiac index and stroke volume index were essentially unchanged from baseline.

Study 115-127 a randomized, double blind, placebo controlled, parallel group single intravenous dose study was designed to compared the effects of dofetilide and placebo on left ventricular function, systemic hemodynamics and myocardial oxygen consumption and to correlate the changes in QT/QTc and left ventricular maximum dP/dt with the duration of the electromechanical systole. Study patients were those with mild to moderate CHF and ejection fraction less than 35%. Intravenous amiodarone was included because it is a negative inotrope.

The mean changes from baseline for various hemodynamic parameters and QT/QTC interval are shown below.

Table 5 Summary of Mean Change from Baseline Results from Protocol 115-127

	dofetilide (n=9) 8mcg/kg i.v.	amiodarone (n=6) 5mg/kg i.v.	placebo (n=12)	dofetilide vs. placebo	dofetilide vs. amiodarone
cardiac contractility and relaxation				treatment difference (95% CI)	
peak + dP/dt (mmHg/sec)	-22.583	-229.167	-47.917	13.82 (-69.0, 96.63)	193.9 (92.63, 295.2)
dP/dt normalized for 40 mmHg (/sec)	0.250	-4.000	0.083	-0.17 (-2.40, 2.05)	4.06 (1.36, 6.77)
peak - dP/dt (mmHg/sec)	39.42	126.17	63.75	-22.1 (-81.0, 36.79)	-82.8 (-155, -10.6)
time constant of pressure decay over 80 msec (msec)	1.92	6.33	-0.17	2.25 (-2.22, 6.71)	-4.10 (-9.59, 1.39)
myocardial oxygen consumption (ml/min)	-1.64	-0.22	-1.02		
angiographic parameters				p-value	
LV end diast volume index (ml/m²)	3.95	6.36	-4.10	0.054	0.611
LV end syst. Volume index (ml/m²)	-1.37	7.93	-3.97	0.425	0.028
heart rate (BPM)	-8.08	-7.33	-2.58	0.013	0.463
difference between end diastolic and end systolic volumes				p-value	
cardiac output (L/min)	0.14	-0.66	-0.19	0.394	0.294
cardiac index (L/min/m²)	0.07	-0.37	-0.10	0.390	0.346
stroke volume (ml)	10.17	-2.67	-0.17	0.131	0.151
ejection fraction	2.22	-1.20	-0.07	0.157	0.175
difference between minimum and maximum volumes in the completed cycle				p-value	
cardiac index (L/min/m²)	-0.21	-0.45	-0.42	0.473	0.922
QT interval					
single lead QTc (msec)	82.49	-2.95	-4.46		
QT dispersion (msec)	-2.82	5.50	1.38		

These results in this small study suggest that dofetilide does not depress the myocardium in patients with NYHA Class II/ III CHF and LVEF 35% or less. The changes seen with dofetilide that were significantly different from changes seen with placebo include heart rate (placebo subtracted decrease of 5 bpm) and LV end diastolic volume index (increase of 4 ml/m2 in the dofetilide group compared to decrease of 4 ml/m2 in the placebo group). The changes in the indices of cardiac contractility and myocardial oxygen consumption are similar for all treatment groups and have wide confidence intervals.

There were 2 patients (both in dofetilide group) who were discontinued for ventricular tachycardia: 1 with monomorphic and the other with polymorphic VT.

Study 115-207 an open single intravenous dose study in patients with stable angina pectoris stratified by cardiac function after the baseline measurements (pulmonary artery occluded pressure change with exercise). Patients were given three 10 minute infusions of placebo followed by up to three 10 minute infusions of dofetilide (2.5, 2.5 and 5 mcg/kg), each infusion separated by a period of 12 minutes (protocol amendment omitted the third infusion).The new dosing regimen was two 15 minute infusions of placebo followed by up to two 15 minute infusions of dofetilide (2.5 and 2.5mcg/kg), each infusion separated by a period of 10 minutes. Resting ECG and hemodynamic measurements were made pre-infusion and immediately following each infusion. Exercise recordings (4 minute supine leg exercise test or bicycle exercise) were made pre-infusion and after the final dofetilide infusion.

The results of hemodynamic parameters recorded at rest are shown below by treatment group and patient type.

Table 6 Summary of Resting Mean Results from Protocol 115-207

	no cardiac dysfunction		mild cardiac dysfunction	
resting means	control	dofetilide	control	dofetilide
mean systemic arterial pressure (mmHg)	103	103	99	100
HR (BPM)	67	63 *	66	62 *
mean pulmonary arterial pressure (mmHg)	14.8	14.6	21.0	18.6 *
pulmonary artery occluded pressure (mmHg)	6.6	6.5	11.5	10.1 *
cardiac output (L/min)	6.4	5.8 *	5.9	5.5
LV end diastolic pressure (mmHg)	7.0	7.6	16.0	12.0
stroke volume (ml/beat)	98	93	89	89
stroke work (g/beat)	129	123	105	108
mean difference between before and after exercise	before dofetilide infusion	after dofetilide infusion	before dofetilide infusion	after dofetilide infusion
mean systemic arterial pressure	28	13	10	17
HR	30	25	35	32
mean pulmonary arterial pressure	11.3	10.4	17.0	18.4
pulmonary artery occluded pressure	7.6	5.0	14.0	12.4
cardiac output	3.6	5.6	2.9	3.9
LV end diastolic pressure	4.5	2.0	7.3	8.7
stroke volume	20	25	-5	4
stroke work	72	39	-16	12

* p<0.05

Heart rate was significantly lower in both patient groups who received dofetilide (by 4 bpm) compared to the control groups. Mean pulmonary arterial pressure and pulmonary artery occluded pressure were also significantly different from control, but only in patients with mild cardiac dysfunction. Cardiac

output was lower in the dofetilide patients who did not have cardiac dysfunction but similar to control in patients with mild dysfunction. Post-dofetilide exercise hemodynamics were not statistically significantly different from preinfusion exercise hemodynamics.

There is no evidence that dofetilide has a negative inotropic effect in patients regardless of their left ventricular ejection fraction.

2.0 Defibrillation threshold

Study 115-110 (A pilot open-label evaluation of the effects of intravenously administered dofetilide on defibrillation energy requirements in patients undergoing implantation of the implantable cardioverter defibrillator) studied doses of 3.5mcg/kg loading infusion and 0.06mcg/kg/min maintenance infusion (total dose 6.5mcg/kg) or 3.5mcg/kg loading infusion and 0.12mcg/kg/min maintenance infusion (total dose 9.0mcg/kg). The loading infusion was 15 minutes and the maximum maintenance infusion was 45 minutes.

Minimum defibrillation energy requirements and VF cycle length were determined after induction of VF at baseline and 10-15 minutes after the start of the maintenance infusion with dofetilide. The mean changes of defibrillation energy for the 16 patients are shown below. (21 patients were randomized, 20 were able to be induced into VF, and an additional 4 patients were excluded from "ITT." There were 8 patients per dose group).

TABLE 6.2
DOFETILIDE PROTOCOL 110
DEFIBRILLATION ENERGY ANALYSIS RESULTS (INTENT TO TREAT)

MEAN CHANGE OF DEFIBRILLATION ENERGY (joules)	STANDARD ERROR (joules)	NUMBER OF SUBJECTS ANALYSED	95% C.I. FOR TREATMENT DIFFERENCE LOWER LIMIT (joules)	UPPER LIMIT (joules)	VALUE OF T STATISTIC	2-TAILED P-VALUE
-3.89	1.30	16	-6.65	-1.13	3.00	0.009

The defibrillation energy requirements for patients receiving dofetilide were statistically significantly lower (by about 4 joules) compared to the pre-dofetilide baseline. Two subjects who received dofetilide 9.0mcg/kg were discontinued during maintenance infusion because of non-sustained polymorphic VT.

KIDEC

DEC 15 1998

REVIEW OF CLINICAL PHARMACOLOGY

NDA#: 20-931
Drug: Dofetilide
Sponsor: Pfizer
Reviewer: Knud Knudsen, MD /S/
Date of review: 12/8/1998

Dofetilide is a class III antiarrhythmic drug which, if approved, will be promoted for use in supraventricular arrhythmia(1).

Basic Electrophysiology:
Dofetilide prolongs the action potential duration (APD) of cardiac muscle cells, thereby prolonging the effective refractory period (ERP) of the cell(2,3). There is compelling evidence that Dofetilide has no effect on sodium channels, calcium channels, or on the steady state potassium conduction; it blocks only the time dependent potassium channels (I_{Kr}), responsible for the early repolarisation of the cell. Unlike Sotalol. it is therefore described as a 'pure' class III antiarrhythmic drug. The magnitude of the effect depends on extracellular potassium concentration. Low $[K^+]_{out}$ reduces the blocking effect.(4,5)

One single cell electrophysiology study suggests that in doses that are orders of magnitude higher than those that affect the I_{Kr} channels, dofetilide may block K_{ATP} channels(6). Further, one animal study (7) has shown that premedication with dofetilide significantly reduces VF in experimental ischemia of the heart. In this sense dofetilide may resemble glybenclimide and could theoretically have an effect on glucose metabolism. There is no clinical evidence that this is the case.

The time dependent potassium channels are not uniformly present in all cells and all organs. Thus atrial cells are more sensitive to the drug effect han are ventricular cells, and both differ from the Purkinje cells. Single cells from guinea pig papillary muscle are highly sensitive, while the drug has no effect on similar cells from the rat (2). There is no evidence, that we know of, to suggest that dofetilide has an effect on cells from any other organ system

In single cell electrophysiology tests, dofetilide has no effect on the maximum depolarization potential, nor on the value of the resting potential. As with other class III drugs, early reactivation *i.e.* a new depolarisation, can be elicited before the potential has returned to resting levels. There is a negative use dependence, and at slow pacing the action potential is distorted. Indeed, if sodium channels can be reactivated before the ATP-driven pumps have restored electrolyte equilibrium to the cell, the consequences for the heart may be unpredictable.

Pharmacodynamic Consequences:

Extrapolation from single cell activity suggests that Dofetilide may be a potent antiarrhythmic agent,(8), but also that it may share with other ClassIII agents a pro-arrhythmic propensity. Only clinical trials can provide answers. On the one hand, premature contractions of a cell may be caused by reentrant stimuli from surrounding cells that march to a different drummer. In that case prolongation of ERP might cancel the vicious cycle that is one cause of tachycardia, arrhythmia and fibrillation. On the other hand, the fact that cells do not have a uniform reaction to the drug may itself lead to a breakdown of the orderly operation of the heart.

EKG studies show that dofetilide has no effect on conduction time or maximum depolarisation voltage. This is consistent with the single cell electrophysiology findings. There is a dose dependent prolongation of the QT_c interval, again, consistent with the prolongation of ERP of the single cell.

Dofetilide: Dose vs Change from Baseline QTc; Oral doses

Study #	Dose	ΔQTc			
115-202	1 µg/kg	1.4 ± 4.06			
	2 µg/kg	6.7 ± 6.41			
	5 µg/kg	22.35 ± 5.05			
	7.5 µg/kg	9.02 ± 6.08			
	10 µg/kg	34.04 ± 17.18			
		ΔQTc		Δ AUEC	
		Day 1	**Day 10**	**Day 1**	**Day 10**
115-203	100 µg/kg	-6.01	2.18	-131.53	-93.15
center 1	200 µg/kg	28.58	24.17	174.18	141.34
center 2	200 µg/kg	18.55	41.6	107.09	203.05
	400 µg/kg	58.91	53.41	368.95	418.09
	Placebo	14.68	14.77	56.45	37.86

The main clinical concern will be whether the prolonged QT interval predisposes to *Torsade de Pointes.* The sponsor argues that clinical trials show no dispersion of the QT_c prolongation, and that therefore *TdP* is unlikely. While the premise may be true, the conclusion is *not* supported by current consensus. As recent as in June this year '*Circulation*' had a paper and an editorial claiming that there is no correlation between dispersion and *TdP* (9,10). The articles also pointed to the great uncertainties in defining the QT interval. During the clinical pharmacology trials of dofetilide *TdP* did occur, and it is my understanding that it also emerged as a serious issue during the clinical development.

Programmed electrical stimulation (PES), (protocols 115-304, 115-305, and 115-310; abstracts enclosed) performed on patients with Atrio-Ventricular Nodal Re-entrant Tachycardia (AVRT) found a trend to increasing QT and QT_c with dose but no strong correlation. There was a relation, however, between inducibility of AVRT and dose that showed a short-term effect of treatment. A long term extension of the study suggested a lasting benefit. However, in the long term extension of the trial, non-responders seemed to benefit as well as responders (protocol 115-310) and the

authors question the prognostic value of PES. These were open label studies but EKG records ought to be impartial and relatively immune from patient and investigator bias.

The sponsor presents a daunting list of clinical trials to investigate ADME and PK/PD in normal subjects and in patients with different health problems. In this section the bulk of the material is concerned with pharmacokinetics, reviewed by Dr. Fadiran. The short answers are that there is a close correlation between dose and blood levels, and between blood levels and QT duration. Blood levels must be closely monitored. The drug is almost completely absorbed, has no active metabolites, and is excreted mainly in the urine. Cimetidine interferes with excretion. Blood levels depend on dose, on kidney function and on coadministration with Cimetidine.

Dofetilide has non-significant negative chronotropic and positive inotropic effects. There is no demonstrated effect on organs other than the heart. On the heart itself, prolongation of the QT_c interval is the only measurable pharmacodynamic effect. Safety issues, of which the main is the correlation between dose, QT_c,*TdP* and arrhythmias, are reviewed by Dr. Gordon

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