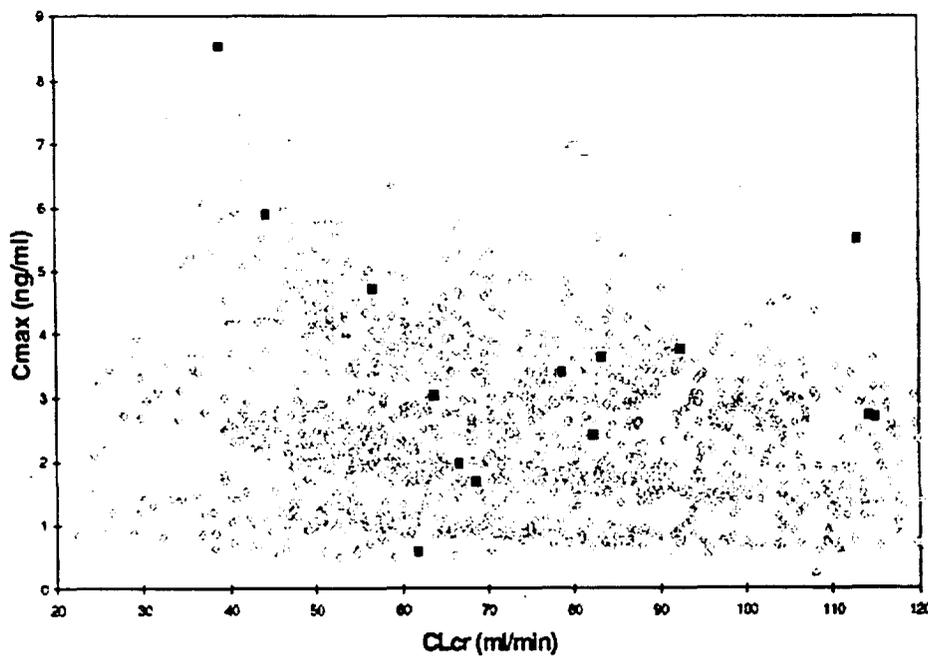
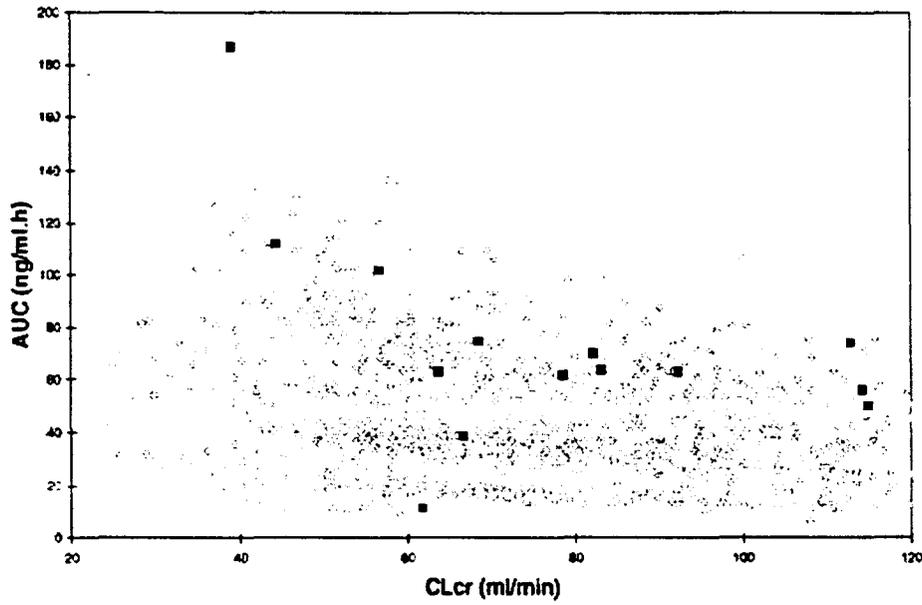


Figure 1 Incidence of Torsades de Pointes (black) in a Phase III population of 1445 patients (grey): a) Daily AUC and b) Cmax vs creatinine clearance



Most of the TdP occurred with AUC values $< 80 \text{ ng}\cdot\text{ml}^{-1}\cdot\text{h}$ and half occurred with C_{max} 3 ng/ml or less. The discussion below relates AUC and C_{max} values to efficacy. According to the figures, the risk of TdP is independent of AUC and C_{max} .

Conversion to SR

Data were available for 205 placebo and 557 patients randomized to dofetilide. The pharmacological conversion rates increased from 1.5% on placebo to 9%, 29% and 56%, for AUC $< 40 \text{ ng}\cdot\text{ml}^{-1}\cdot\text{h}$, 40 to $80 \text{ ng}\cdot\text{ml}^{-1}\cdot\text{h}$ and $> 80 \text{ ng}\cdot\text{ml}^{-1}\cdot\text{h}$, respectively.

Maintenance of sinus rhythm (SR) at 6 months : combined analysis of studies 345 and 120

The combined analysis of 669 patients (including 179 randomized to placebo) from study 115-345 and 115-120. The percentage maintained in SR increased from 25% on placebo to a maximum response of 53% for the AUC range of 40-60 $\text{ng}\cdot\text{ml}^{-1}\cdot\text{h}$.

Pause dependent polymorphic VT

Protocol 115-113 was a double-blind, parallel group study with patients who had a history of spontaneous and/or inducible VT or VF and an implantable cardioverter defibrillator device (ICD) with the capacity to store intracardiac electrograms of events triggering device therapy. A total of 174 patients were randomized to either dofetilide 500 mcg bid (n=87) or placebo (n=87) and followed for 12 months.

The study failed in its primary objective of demonstrating that dofetilide compared to placebo prevented the recurrence of VT or VF and there were 6 patients with reports of TdP in the dofetilide group compared to 0 in the placebo group. An analysis of the intracardiac ECGs identified 15 additional dofetilide patients with "pause dependent polymorphic VT" and after a re-review of the CRFs, it was determined that there was 1 additional case¹ of TdP which resulted in a protocol defined TdP event rate of 8.0% (7/87) for dofetilide. The event rates for "pause dependent polymorphic VT" for dofetilide and placebo patients were 17.2% (15/87) and 5.7% (5/87), respectively.

	dofetilide n=87	placebo n=87
cases of intracardiac ECG identified "pause dependent polymorphic VT"	15 (17.2)	5 (5.7)
number of the above cases resulting in shocks or pacing	11	3
number of the above cases resolving spontaneously	4	2

It is difficult to determine the significance of "pause dependent polymorphic VT" but it occurred more often in the dofetilide group and resulted in more actions being taken (shocking and pacing).

¹There was 1 report of TdP in a placebo patient. The patient (#115-113-670-1273) was actually undergoing amiodarone loading at the time of the event.

Reports of proarrhythmia

The table below shows details for the 10 patients who received oral dofetilide in a SVA study and experienced a proarrhythmia that met the criteria according to the sponsor's consultants. All were discontinued from study drug, most were symptomatic and many degenerated into VF. Most of the events were terminated by an action, such as DC cardioversion or precordial blow.

Patient number	age/race/ sex	total daily dose (mcg)/ duration (d)	comedications	QT/QTc msec	comments
115-120x-568-0485	38/w/m	1000/3	coumadin, digoxin, vasotec, lasix, magnesium, K-Dur, restoril and sodium chloride.	baseline: 373/412 after 4th dose: 417/386 1 minute post event: 388/522	Normal labs including CrCl at screen. EF < 25 %. Developed TdP followed by VF about 1 hour after 5th dose. He was given direct current shock at 200 joules and went into an atrial fibrillation with frequent ectopy for which he was given Magnesium 2 grams IV push. He was transferred to the coronary care unit where he spontaneously converted to normal sinus rhythm.
115-120x-5002- 1032	66/w/f	500/1 downtitrated to 250/1	digoxin, atenolol, allopurinol, tamoxifen, calcium, geritol, lecithin, garlic, demadex, vitamin E, synthroid, coumadin, potassium supplement, theragram M.	Baseline: 308/407 after 1st dose: 363/489 during next day QT: 480-520.	CrCl 62, history of hypothyroid. Developed >15% increase QTc after 1st dose. Decreased dose to 250 mcg. QT was elevated next day. Received 125 mcg dose and developed TdP followed by VF 2.5 hrs later. The subject was defibrillated with a single shock of 330 joules. She was transferred to the intensive care unit. Serum K ⁺ 3.8
115-311/311A- 0022-0070	74/w/f	750/2	digoxin, nicoumalone	baseline: 280/443 after 1 day:480/565	Noraml labs. After 3rd dose developed 8 min run of TdP followed by VF with collapse, but was successfully resuscitated.
115-320-0043-0037	64/w/m	500/1 dose	warfarin, digoxin, nitroglycerin, glibenclamide, quinine (for leg cramps).	baseline QT: 532	Normal labs. Developed TdP about 7 hrs later after 1st 500 dose which was terminated by a blow to the chest (precordial blow).
115-320-0043-0040	80/w/f	1500/2	warfarin, naproxen, heparin, propranolol and digoxin	baseline QT: 448 ranged between 392 and 436.	Developed TdP on 2nd day of dosing. The event lasted 18 seconds (60 beats) and was self- terminating.
115-320-0054-0003	64/w/f	1000/1	digoxin, warfarin, captopril	baseline QT:320 max QT on drug: 520	Developed TdP on 2nd day of dosing. The event lasted 60 seconds and was terminated by DC cardioversion (x2) and intravenous magnesium and atropine.

Proarrhythmia

115-345-0039-0334	73/w/f	1000/3	diamicon, digoxin, captopril, isorbide mononitrate, acenocoumarol, cisapride, glicazide and metformine hydrochloride	not given	1 hour after dose on day 3, patient had frequent runs (up to 30 sec) of TdP over total of 2 hours.
115-345-0103-0937	61/w/f	1000/3	acemocoumanol, enalapril, bumetanide, digoxin, simvastatin.	not given	After 3 days of dosing and discharged from hospital, patient became unresponsive with uncontrolled movements. VF was diagnosed and she was defibrillated, hospitalised and treated with lignocaine. She experienced further events the following day: a possible case of TdP which was terminated with DC cardioversion; self terminating VF; and a further case of VT, VF and TdP which were terminated with a precordial blow. After sinus rhythm was restored, she experienced VT, VF, and TdP again, and sinus rhythm was restored by DC cardioversion and a precordial blow.
115-345-0238-0128	69/w/f	1000/2	isoptin	not given	2 episodes of symptomatic (dizziness) TdP that resolved spontaneously
115-311/311A-0012-0097	63/w/m	750/22	none	baseline: 340/390. Day 3: 500/443 Day 23: 428/410	On day 22, suffered episode of VF requiring resuscitation. Question of latent abnormality of impulse formation/conduction.

Appendix IV, tables 1A, 1B, 2A, 2B

4.0 Deaths, serious safety, and withdrawals for adverse events

4.1 All deaths

The number of dofetilide deaths in the dofetilide program as of September 15, 1997 includes 47 who died either on dofetilide or within 7 days of stopping the drug and 47 who died after being off drug for more than 7 days. The table below includes all patients who received oral therapy (excluding DIAMOND patients) as well as short term intravenous therapy.

Deaths	
	dofetilide n=2748 [^]
died on therapy or \leq 7 days of stopping therapy	47+ (1.7)
died >7 days of stopping therapy	47 (1.7)
total deaths	94 (3.4)

+includes one death with missing dates of death or drug stop and #115-109-505-0001.
Table pg 150 ISS

There were few deaths during the studies with the intravenous studies. These are shown below by treatment group with phases I/II/III studies combined.

Deaths in studies with intravenous formulation				
	placebo controlled trials		active controlled trials	
	dofetilide n=720	placebo n=476	dofetilide n=411	active control n=216
deaths \leq 7 days [^]	1	1	1	0
deaths >7 days	9	3	3	1

Deaths grouped by indication

The tables below show the number of deaths by study indication, timing of death, and treatment groups. (All tables come from fax dated 11-25-98).

Deaths in SVA studies--oral formulation			
	placebo controlled trials		active control n=235
	dofetilide n=1346	placebo n=677	
deaths \leq 7 days [^]	11 (0.8)	2 (0.3)	0
deaths >7 days	11	9	0

[^]of stopping treatment

Compared to placebo patients, a higher percentage of dofetilide patients in the SVA placebo controlled trials died either on drug or within 7 days of stopping drug. There were no deaths in the active controlled trials.

Deaths in VA studies--oral formulation

	placebo controlled trials		active controlled trials		uncontrolled
	dofetilide n=102	placebo n=101	dofetilide n=296	active control n=250	dofetilide n=210
deaths \leq 7 days [^]	2 (2.0)	2 (2.0)	8 (2.7)	4 (1.6)	23
deaths >7 days	3	7	6	2	14

The deaths occurring on drug or within 7 days of stopping drug were similar for dofetilide and placebo in the placebo controlled trials. In the active controlled trials, there were more deaths on dofetilide compared to the active control.

Deaths in clin pharm studies--oral formulation

	placebo controlled trials		active controlled trials	
	dofetilide n=304	placebo n=258	dofetilide n=503	active control n=38
deaths \leq 7 days [^]	1	0	0	0
deaths >7 days	1	0	0	0

There were only 2 deaths in the clinical pharmacology studies.

Death classifications

A cardiology consultant was used to classified all deaths on dofetilide. Of the deaths that occurred while patients were on dofetilide or within 7 days of stopping dofetilide, 32 (67%) were classified as sudden cardiac; arrhythmic or presumed arrhythmic (SUCD). There were 14 deaths in the supraventricular arrhythmia studies (9 SUCD and 5 other) and 33 in the ventricular tachycardia studies (24 SUCD and 9 other). The majority of dofetilide deaths were classified as SUCD.

Of the 5 deaths on placebo, 1 was the result of head trauma (VT study); 1 was sudden death, arrhythmic (VT study); 1 was sudden death, presumed arrhythmic in the setting of acute heart failure (SVA study), 1 sudden death, arrhythmic (SVA study); and 1 was sudden, presumed MI (SVA). Few patients died while on placebo.

For the comparators, there were 3 deaths on sotalol: cardiogenic shock, coronary heart disease, and acute cardiovascular insufficiency, and 1 death on amiodarone: sudden unexpected cardiac death (appendix III tables 4 and 10).

Deaths on oral dofetilide are shown below.

Deaths on dofetilide or within 7 days of discontinuation

Patient number	age/race/ sex	total daily (dose mcg) /duration (d)	comedications	comments
115-105-514-0004 Phase I: VT and low EF	44/w/male	750/3. Died 5 days off drug	Medications at screening included cimetidine ^A , digoxin, glipizide, aspirin, colace, lasix, insulin, nitroglycerin, and heparin	sudden death, arrhythmic (VF) unable to be resuscitated. Had atrial ectopy day after study completion and started amiodarone. Died 5 days after completing study. Autopsy showed extensive CAD with recent MI.
115-108B-527-0002 VT	77/w/male	1500/1255	amitriptyline, enalapril, aspirin, potassium, furosemide and isosorbide dinitrate	sudden death, arrhythmic (VF) unable to be resuscitated. History of ischemic CM and MI.
115-109-505-0001 HCM and VT/VF	56/w/male	125mg/518	none	sudden death, arrhythmic. Collapsed and was unable to be resuscitated. Had long history of CM and sustained VT.
115-109-505-0006 HCM and VT/VF	57/w/male	750/253	none	sudden death, arrhythmic. Unable to be resuscitated. History of mitral regurg and hypertrophic CM with PVCs and VT.
115-109-505-0004 HCM and VT/VF	47/w/female	1130/437	conjugated estrogen replacement therapy and aspirin	sudden death, arrhythmic. History of obstructive hypertrophic CM, sustained VT, angina, venous thrombus.
115-113-506-1109 VT	71/w/male	1000/4	isosorbide dinitrate, digoxin, quinapril, glyburide, furosemide, warfarin, and metoprolol	sudden death, arrhythmic (VF), unable to be resuscitated. History of ischemic heart disease with 5 previous MIs, heart failure with LVEF 15%.
115-113-598-1069 VT	51/w/female	1000/14. Died 5 days off drug; died on ethmozine	insulin, warfarin, digoxin, lisinopril, indapamide, bumetanide, potassium chloride, and estrogen	sudden death, arrhythmic (VF). Discontinued from dofetilide 5 days prior to death because of episodes of PMVT degenerating into VF. History of dilated CM and pulmonary HTN.
115-113B-552-0203 VT	62/w/male	250/214	digoxin, aspirin, metoprolol tartrate, furosemide, omeprazole, diltiazem HCl, potassium, magnesium chloride, lisinopril and paroxetine	CVA

Deaths

115-119-634-673 AF/AFI/pSVT	77/w/female	250/254	theophylline, prednisone, atrovent, ventolin, serevent albuterol, nifedipine, synthroid, furosemide, nitroglycerin, isordil, potassium, darvoset, percocet, methadone, acetaminophen, primidone, diazepam, amoxicillin, ranitidine, estratest HS, estracecream, baza cream, betoptic, pilopine 4% gel, megestrol, dulcolax suppository, milk of magnesia, lactulose, mylanta ES, Tums ES and sustacal supplement drink	sudden death, arrhythmic (VF), asystole, respiratory failure. History of COPD, asthma, previous MI
115-119A-506-0111 AF/AFI/pSVT	70/w/male	1000/790	hydrochlorothiazide, acetaminophen, codeine, chemotherapy (unspecified), multivitamin, magnesium chloride, potassium, gyburide, doxazosin, albuterol, atrovent, prochlorperazine (prohibited by protocol)	recurrent colon cancer
115-120-512-0077 AF/AFI	69/b/male	1000/9	digoxin, lasix, K-lor powder, warfarin	sudden death, arrhythmic. History of dilated CM, CHF, alcohol abuse. No autopsy.
115-120-512-0328 AF/AFI	63/b/male	250/211	aspirin, allopurinol, colchicine, vasotec, isosorbide mononitrate, warfarin, potassium elixir, lasix, zaroxolyn, vancomycin, zantac, metronidazole, apresoline	complete bowel infarction. Dofetilide dose had been lowered because of ↓ QTc.

Deaths

115-120-572-0102 AF/AFI	66/b/female	1000/13	isordil, captopril, lasix, lovastatin, enteric ASA, estrogen, NPH humulin insulin, triamcinolone inhaler, albuterol inhaler, coumadin, amoxicillin, ipratropium bromide inhaler, prednisone, digoxin, and potassium supplement	sudden death, arrhythmic. History of MI X 4, CHF with EF 20-25%, asthma.
115-120-661-0445 AF/AFI	78/w/female	62.5/6	nitropaste, nitroglycerin sublingual, isosorbide, demadex, K-dur, and ambien	AMI. History of severe atherosclerotic heart disease., heart failure
115-120A-528-0188 AF/AFI	77/w/male	1000/572	allopurinol, zestril, furosemide, digoxin and aspirin	sudden death, presumed arrhythmic. History of MI, CAD, CHF.
115-120A-572-0314 AF/AFI	62/b/male	2000/428	enteric-coated aspirin, doxazosin, furosemide, captopril, and ranitidine	sudden death, presumed arrhythmic. Recent complaints of angina. History of CHF, HTN.
115-120X-512-0501 AF/AFI	77/w/male	250/239	lasix, corgard, captopril, NPH insulin, nitroglycerin patch, macrodantin, colace, oxybutynin, aspirin, nitroglycerin sublingual, restoril, trilisate	sudden death, presumed arrhythmic. Complained of chest pain about 2 weeks prior to death. History of MI x 5, CAD, CHF.
115-308-0011-0006 VT	73/w/male	1500/4. Died 7 days off drug	procainamide, quinidine and digoxin started the day after his final dose of dofetilide	cardiac failure. 6 days after receiving drug, patient underwent ablation of accessory VT pathway and died 1 day later of acute heart failure resulting from post surgery infarction
115-308-0031-0005 VT	66/w/male	2000/6	bezafibrate, digitoxin, hydrochlorothiazide/tiamteren, isosorbide mononitrate, and nifedipine	sudden death, presumed arrhythmic. History of CAD, MI, reduced LV function, peripheral occlusive disease, VT.
115-308-0031-0008 VT	55/w/female	2000/12. Died 7 days after drug discontinued	ACE inhibitor, aspirin, omeprazole, potassium sparing diuretics and potassium before with additional imipenem/cilastatin and lignocaine	bradycardia. Discontinued drug because of hospitalized for TdP/recurrent VT on day 12. Died 7 days later. History of dilated CM, sustained VT, impaired LV function

Deaths

115-331-0011-0078 VT	72/w/female	1000/134	metoprolol and acenocoumarol	sudden death, probable arrhythmic. No autopsy. History of suspected CM.
115-331-0044-0024 VT	47/w/male	500/190	lisinopril	sudden death, arrhythmic (VT degenerated into VF). Had previous episodes of VT abolished by ICD. History of dilated CM and recurrent VT.
115-333-0076-0148 VT	64/w/female	500/279. Died 7 days off drug	diltiazem, isosorbide mononitrate, digoxin, enalapril, aspirin, ranitidine, nitroglycerin and amitriptyline/medaze pam)	cardiogenic shock status post MI. Discontinued from drug for acute pulmonary edema resulting from CHF secondary to AMI. History of ischemic heart disease and previous MI
115-334A-0311-0039 VT	76/w/male	500/420	captopril, aspirin and nitroglycerin	sudden death, arrhythmic. History of ischemic heart disease, MI, hypertension, sick sinus syndrome.
115-335-034-0066 VT	67/w/male	1000/143	Digoxin, captopril, Famotidine, Fluimucil (acetylcysteine) and aquaphor tablets (Xipamide).	lung cancer diagnosed during study. History of dilated CM, heart failure, COPD.
115-335-129-0110 VT	53/w/female	1000/8	bromhexine, captopril, furosemide, digoxin, potassium and aminophylline.	sudden death, presumed arrhythmic. Complaints of fever before death. Died at home with no autopsy. History of dilated CM, CHF, chronic bronchitis, asthma, duodenal ulcer.
115-335-285-0169 VT	65/w/female	1000/4	ethyl biscoumacetate), amiloride/hydrochlor othiazide, digoxin and enalapril.	sudden death, arrhythmic. Decreased drug to 500 mcg because of prolonged QT and died that day. Autopsy ruled out MI, pulmonary embolism. History of myocarditis, atrial fib, cardiac insufficiency
115-345-0012-0351 AF/AFI	62/w/female	1000/5	insulin and digoxin	sudden death, presumed arrhythmic. Vomited repeatedly day of death. History of afib, hypertension, poorly controlled diabetes. Unremarkable autopsy.
115-365-327-0273 pAF/pAFI	71/w/female	500/1 dose	aspirin, sotalol, furosemide, isosorbide mononitrate, isosorbide dinitrate, digoxin, quinidine and asparcam (aspartic acid)	CVA. Shortly after first dose, patient vomited, developed hemiplegia, and later became comatose. History of ischemic heart disease, CHF.

Deaths

115-397-009-0001 pAF	59/w/male	1000/567	enalapril, furosemide and allopurinol	sudden death, presumed arrhythmic. Had episodes of nonsustained VT on Holter monitor during treatment. History of HOCM, gout, previous CVA.
115-397-009-0006 VT	78/female	1000/916	warfarin	CVA. Collapsed at home. History of dilated CM, TIAs.
115-398-011-0002 VT	63/w/male	1000/804	insulin, isorbide dinitrate, captopril, digoxin, simvastatin, and bumetanide	pancreatic carcinoma
115-398-011-0007 AF	74/w/female	1000/609	nicoumalone, enalapril, and amlodipine	CVA. History of angina, HTN, CABG, anemia, impaired renal function. Taking acenocoumarol.
115-398-226-0001 VT	66/w/male	1000/840	ramipril, warfarin, pravastatin, and magnesium	sudden death, probable arrhythmia. No autopsy. History of ischemic heart disease, MI, dilated CM.
115-398-226-0003 VT	67/w/male	500/484	enalapril, digoxin, furosemide, simvastatin, warfarin, nitroglycerin, and allopurinol	sudden death, presumed arrhythmic. History of MI, dilated CM, ischemic heart disease, pulmonary infarction, peripheral vascular disease.
115-398-440-0002 pAF	64/w/female	4000/184	captopril, aspirin, propranolol, glibenclamide, metformin and isosorbide mononitrate	sudden death, presumed arrhythmic. History of angina, CHF, ischemic heart disease, valve insufficiency, LH hypertrophy, diabetes.
115-399-011-0005 VT	64/w/male	4000/555	nicoumalone	sudden death, arrhythmic. History of VT and valvular disease.
115-399-011-0006 VT	60/w/male	4500/446	captopril and nicoumalone	sudden death, arrhythmic. History of heart failure, MI, VF.
115-399-011-0007 VT	60/w/female	1000-6750/185	captopril, furosemide, nicoumalone, triamterene and temazepam	heart failure. Hospitalized for impaired cardiac function and died about 5 days later after unsuccessful resuscitation. History of MI, heart failure with EF 18%, VT, AICD, AF.
115-399-033-0001 VT	67/w/male	500/1805	aspirin, nifedipine and molsidomine	sudden death, presumed arrhythmic. History of CAD, MI.
115-399-033-0006 VT	59/w/female	1000/1875	digoxin, captopril, aspartic acid, fenofibrate, ISMN, phenprocoumon and ISDN	sudden death, presumed arrhythmic. Decreased initial dose from 2000 mcg on day 2 because of QT prolongation. History of CAD, ischemic CM, MI, reduced cardiac function.

Deaths

115-399-034-0003 VT	73/w/female	2000/1634	novodigal, dytide h, lopirin cor, isoket retard, asa 100, zyloric 300, isoptin, and tromcardin forte	sudden death, presumed arrhythmic. Hospitalized for episode of VT. Died at home 1 month later. History of AICD, syncope, AF, MI, hypertension.
115-399-034-0005 VT	65/w/female	3000/258	unknown	sudden death, presumed arrhythmic. History of hypertension, diabetes, ischemic heart disease, MI.
115-399-034-0007 VT	65/w/male	3000/84	flecainide, digoxin, L-thyroxin, captopril and furosemide	cardiac, presumed arrhythmic, cardiogenic shock. Hospitalized for multiple discharges of AICD and signs of LV failure and shock. Died the next day. History of COPD, ischemic CM, MI, and VF.
115-399- 105-0001 VT	54/w/male	2000/9. Died 4 days off drug.	digoxin, amiodarone, glibenclamide, frusemide, enalapril, heparin, potassium, flucloxacillin, magnesium salts, lidocaine, amiloride betaine/potassium, warfarin, diazepam, bumetanide and acetaminophen.	sudden death, presumed arrhythmic. Discontinued drug for lack of effect. Died 4 days later awaiting cardiac transplantation.

^ because of an interaction of dofetilide with cimetidine, concomitant use of cimetidine became an exclusion criteria in later protocols.
appendix III tables 2 and 10

APPEARS THIS WAY
ON ORIGINAL

The 2 deaths that occurred during intravenous dosing with dofetilide are described below.

Deaths with iv dosing

Patient number	age/race/ sex	total daily (mcg)/ duration (d)	comedications	comments
115-302-0011-0027 AF/AfI	75/w/male	8/kg/1 dose (IV). Died 4 days off drug	digoxin and verapamil	pulmonary embolism. Died 4 days after receiving iv dofetilide and 3 days after converting to sinus rhythm. Had been in af for <2 days. History of COPD with recent deterioration of lung function.
115-315-005-0002 VT	63/w/female	313.2/1. Died 7 days off drug	simvastatin, prednisolone, ranitidine, trifluoperazine, salbutamol, becotide and atrovent.	pneumonia and cardiac arrest. Took iv drug for 1 day. Developed pneumonia 3 days later and died short time later.

Appendix III tables 2 and 10

There was 1 patient who died of VT 5 days after receiving intravenous placebo (acute conversion study 115-361).

APPEARS THIS WAY
ON ORIGINAL

4.1.1 Survival analysis

The objective of this meta analysis was to determine the effect of oral dofetilide on overall survival in patients with chronic or paroxysmal AF/AFL with and without paroxysmal supraventricular tachycardia (pSVT) who participated in a randomized double blind, placebo controlled dofetilide study. The authors of the final report were Edward Pritchett, M.D. and William Wilkinson, Ph.D.

The study included all patients in randomized, double-blind, parallel, placebo-controlled dofetilide protocols designed primarily for patients with chronic or paroxysmal AF/AFL or with pSVT who were randomized to either dofetilide or placebo.¹ Patients who received an active control drug were not included.

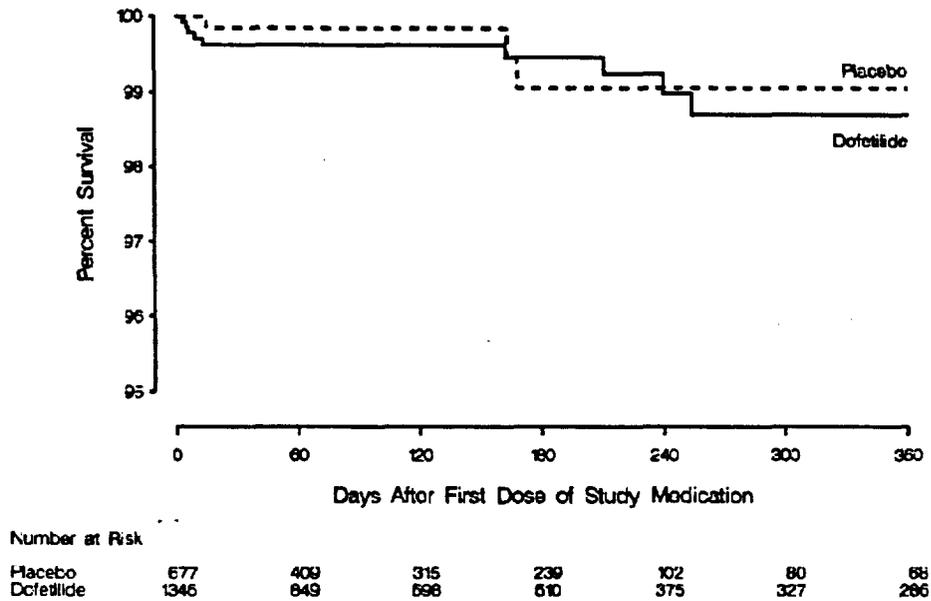
When patients with AF/AFL and patients with pSVT are included in the analysis, the mortality rates are 0.9% (12/1346) for dofetilide and 0.4% (3/677) for placebo. From the proportional hazards model, the estimated hazard ratio for death associated with dofetilide (as compared to placebo) is 1.4; a 95% confidence interval for the hazard ratio is (0.4, 5.1). Adjusted for the potentially confounding effects of primary diagnosis, age, gender and the presence of structural heart disease, the estimated hazard ratio is 1.1 with a 95% confidence interval of (0.3, 4.3). The survival distributions for the two treatment groups are plotted in Figure A; the difference is not significant (log-rank chi-square = 0.26, $p > 0.6$) but the trend favors placebo.

APPEARS THIS WAY
ON ORIGINAL

¹ 8 dofetilide protocols were excluded from the analysis: 111 (enrolled patients with hypertrophic cardiomyopathy or coronary artery disease), 114C, 307, 310 and 364 (not placebo-controlled); 313 (a cross-over trial), 400 and 400X (enrolled patients with congestive heart failure or myocardial infarction).

FIGURE A

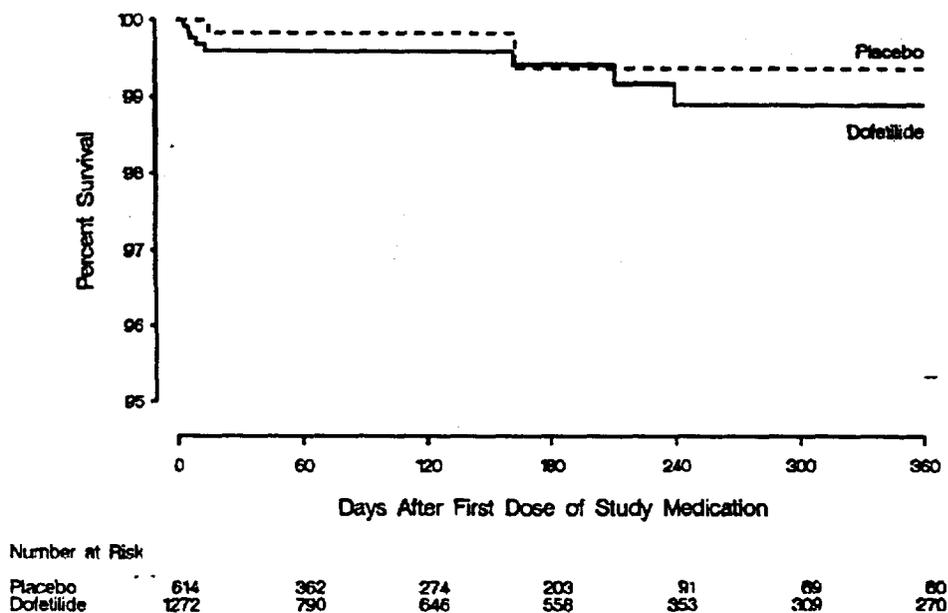
COMPARISON OF SURVIVAL DISTRIBUTIONS (INCLUDING PATIENTS WITH pSVT)



When patients with pSVT are excluded from the analysis, the mortality rates are 0.9% (11/1272) for dofetilide and 0.3% (2/614) for placebo. From the proportional hazards model, the estimated hazard ratio for death associated with dofetilide (as compared to placebo) is 1.9; a 95% confidence interval for the hazard ratio is (0.4, 8.6). Adjusted for the potentially confounding effects of primary diagnosis, age, gender and the presence of structural heart disease, the estimated hazard ratio is 1.4 with a 95% confidence interval of (0.3, 6.9). The survival distributions for the two treatment groups are plotted in Figure B; the difference is not significant (log-rank chi-square = 0.65, $p > 0.4$) but the trend favors placebo.

FIGURE B

COMPARISON OF SURVIVAL DISTRIBUTIONS (EXCLUDING PATIENTS WITH pSVT)



The results of the quinidine meta-analysis² conducted by Coplen, et.al., in 1990, found the pooled odds ratio of dying on quinidine compared to the control group to be 2.98 (95%CI: 1.1-8.3). A recent mortality trial³ with bidisomide compared to placebo in patients with AF/AFI or pSVT (prepared by AFIB investigators, 1997) was prematurely discontinued with a hazard ratio (bidisomide:placebo) for the primary mortality analysis of 2.82 (95% CI:0.76, 10.45). Results for both of these agents are not much different from the results for dofetilide and, based on the data in the NDA, it is not possible to conclude that dofetilide is safer than these other antiarrhythmics.

²Coplen SE; AntmanEM; BerlinJA; Hewitt P; ChalmersTC:Circulation. 1990 Oct; 82(4):1106

³The Atrial Fibrillation Investigation with Bidisomide (AFIB) Investigators: Circulation. 1997 Oct 21; 96(8):2625

4.1.2 DIAMOND AF/AFL substudy

The objective of the substudy was to evaluate the potential for dofetilide to restore sinus rhythm (SR) in an AF/AFL population with reduced left ventricular function and its ability to maintain SR over a 12 month period in subjects in whom SR had been restored by either dofetilide or DC cardioversion. The substudy was also to evaluate the impact of dofetilide on morbidity and mortality. This review is only evaluating the mortality results.

The sponsor claims that the substudy was flawed primarily because only a third of the eligible patients were enrolled and recruitment was allowed over the period of hospitalization, i.e. after the start of study drug. These findings led the sponsor to the conclusion that this substudy was flawed in design and conduct and consequently none of the data (including mortality) can be used.

The total number of subjects in DIAMOND who presented with AF/AFL at baseline was 506, representing 17% of the overall population. Each of the centers in DIAMOND was approached to participate in the substudy, but contrary to expectations, several declined (for reasons that were not discussed in the NDA), thereby reducing the eligible population with baseline AF/AFL from 506 subjects in 37 centers to 401 subjects in 25 centers. Only 178 patients were enrolled with 97 in the dofetilide group and 81 in the placebo group, representing 49.5% and 39.5%, respectively, of the available treatment populations. Of the patients recruited, 34% were recruited after the start of the study treatment.

The baseline characteristics and concomitant medications were balanced for the 2 treatment groups. The deaths are shown below.

Number and (percent) of patients		
deaths	dofetilide n=97	placebo n=81
at 12 months	24 (25)	14 (17)
during observation period	34 (35)	21 (26)

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The mortality rate for this subpopulation was not significantly different for the 2 treatment groups (p=0.6326).

4.2 Serious adverse events

The sponsor states that the serious adverse event data, including deaths, have been compiled from all completed and ongoing Phase I, II, and III trials conducted in the United States and outside the United States in the clinical program. The cutoff dates for inclusion in the NDA serious adverse event database was September 15 1997. In the dofetilide clinical program, subjects who reached a study endpoint (recurrence of their index arrhythmia) were frequently hospitalized to terminate the arrhythmia or initiate alternate therapy. These hospitalizations are included in the total listings of serious adverse events.

The sponsor reported serious adverse events on a case-by-case basis. A case is considered a single event or a series of events not separated in time occurring in a single subject. Therefore, a single subject reporting serious adverse events at different time points would be counted as multiple cases. In addition, cases could be comprised of both serious and non serious events, as all events occurring at the time of the report were captured, not only those considered serious.

All trials

The serious adverse event cases entered into the database as of September 15, 1997, include:

- 919 cases for those who received dofetilide (total number of dofetilide patients is 2748),
 - 350 cases for those who received placebo (total number of placebo patients is 1036), and
 - 123 cases for those who received an active comparator (total number of comparator patients is 534).
- (H.6.2.1, H.6.2.10). Patient numbers as of 9-15-97 were obtained from table on page 140 ISS.

The table below shows the serious events reported by at least 5 dofetilide patients.

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ON ORIGINAL

Number and (percent[^]) of patients

	dofetilide n=2748	placebo n=1036	comparator n=534
number of cases	919 (33.4)	350 (33.8)	123 (23.0)
application site complications, etc	10	2	1
body as a whole	37	7	7
death incl. sudden	15 (0.5)	2 (0.2)	2 (0.4)
cardiovascular, general	101	45	15
cardiac failure+	61	25	12
syncope	27	10	1
nervous system	27	4	3
dizziness	15 (0.5)	1 (0.1)	0
GI system	43	19	5
GI hemorrhage	7	2	0
nausea	7 (0.3)	0	0
heart rhythm/rate#	382	183	48
VF	29 (1.1)	5 (0.5)	2 (0.4)
VT	159 (5.8)	43 (4.2)	7 (1.3)
ventricular arrhythmia	8 (0.3)	0	3 (0.6)
AICD discharge-arrhythmia unknown	7 (0.3)	0	0
AV block	5	5	2
arrhythmia	10	2	2
bradycardia	10	5	10
cardiac arrest	7	5	2
QT increased	8	1	1
Liver/biliary	13	4	3
SGOT/SGPT increase	6	0	2
metabolic/nutritional	15	4	1
dehydration	6	1	0
myo/endo/pericardial	87	36	3
angina	33 (1.2)	6 (0.6)	3 (0.6)

Serious adverse events

chest pain	28	14	0
myocardial infarction	20	10	0
neoplasms	47	6	2
basal cell	14 (0.6)	0	0
carcinoma nos	11	2	0
pulmonary carcinoma	6	1	1
procedures	188	63	26
platelet/bleeding/clotting	16	2	3
hematoma	5	1	0
psychiatric	5	2	0
reproductive, male	5	0	0
prostatic disorder	5	0	0
respiratory	56	24	10
dyspnea	7	3	0
pneumonia incl lobar	20	8	2
pulmonary edema	5	2	3
urinary system	22	8	3
UTI	10 (0.4)	1 (0.1)	0
vascular, extra cardiac	36	18	6
cerebrovascular disorder	25	9	2

^the percent of patients may be incorrect because the sponsor states it is unable to provide correct number of patients with events; this reviewer acknowledges that there is a margin of error but the percents represent a "good guess" in the absence of additional information.

+includes left cardiac failure, worsening heart failure

#atrial arrhythmia, atrial fibrillation, and supraventricular tachycardia are not included

H.6.8.1

The serious adverse events that occurred more often in the dofetilide group compared to the placebo group include death, dizziness, nausea, AICD discharge, ventricular arrhythmia, VF, VT, angina, and basal cell carcinoma. The reasons for the excessive reporting of angina is unclear.

Supraventricular arrhythmia

Selected serious events are shown below for these studies (n=1331), by actual dose received.

Number and (percent) of patients

	dofetilide mcg bid			
	<250 n=375	250 n=497	500 n=426	>500 n=33
any serious event	117 (31.2)	148 (29.8)	85 (20.0)	7 (21.2)
VT	3 (0.8)	8 (1.6)	7 (1.6)	3 (9.1)
VF	2 (0.5)	1 (0.2)	3 (0.7)	2 (6.1)
syncope	0	3 (0.6)	1 (0.2)	1 (3.0)
death incl. sudden	1 (0.3)	0	3 (0.7)	0
angina incl. aggravated	1 (0.3)	5 (1.0)	6 (1.4)	0

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VT, VF, and syncope appear to be dose related, and it is reasonable to conclude that there would have been excessive deaths in the >500 mcg bid dosing category had the sponsor not terminated this dosing arm. Angina and its relationship to dofetilide is less clear.

4.3 Study withdrawals

This section focuses upon the incidence of study withdrawal because of a safety reason. This included withdrawals for death, an adverse event classified as either a) a treatment emergent adverse events (TESS) or b) an objective adverse event (defined by the sponsor as ECG changes including atrial arrhythmias, sinus bradycardia, and TdP or laboratory test abnormalities including abnormal LFTs,) laboratory abnormality, and QT/QTc prolongations (referred to by the sponsor as special safety test).

There was some lack of consistency in the different safety tables submitted by the sponsor and this is explained in part by the following statement:

“In the Discontinuations from Study table the number of subjects who discontinue due to adverse events is the number of subjects who have a final status, as assigned by the investigator, which indicates a discontinuation due to adverse events. In the Summary of Adverse Event tables, the number of subjects who discontinue due to adverse events is the number of subjects who have at least one adverse event for which the action taken, as recorded by the investigator, was discontinuation of study medication. The numbers in these two summary tables may differ if for example the investigator records an adverse event with an outcome of study drug discontinued but on the discontinuation page records the main reason for discontinuation as some other reason e.g. lack of efficacy, laboratory abnormality or special safety test finding.”

All phase II/III trials

The number and percent of patients who were enrolled into the relevant and other Phase II/III trials and withdrew for any reason are shown below.

Number and (percent) of patients

	placebo controlled trials		active/uncontrolled trials	
	dofetilide n=1479	placebo n=778	dofetilide n=462	active comparator [^] n=496
total withdrawals	709 (47.9)	405 (52.1)	197 (42.6)	180 (36.3)
all safety*	453 (30.6)	224 (28.9)	133 (28.8)	118 (23.8)
protocol violation	12 (0.8)	7 (0.9)	2 (0.4)	5 (1.0)
lost to follow up	6 (0.4)	1 (0.1)	0	3 (0.6)
other+	87 (5.9)	44 (5.7)	26 (5.6)	4 (0.8)
did not meet randomization criteria	15 (1.0)	24 (3.1)	0	0
withdrew consent	31 (2.1)	20 (2.6)	11 (2.4)	14 (2.8)
lack of effect	345 (23.3)	232 (29.8)	84 (18.2)	89 (17.9)
Dose reduced or temporarily discontinued#	73 (4.9)	20 (2.6)	23 (5.0)	20 (4.0)

[^]includes quinidine, propafanone, sotalol, amiodarone (counted 464 patients)

*includes H.6.6.10a objective adverse events

+dofetilide patients only: failed to achieve/did not remain in NS (60), physician decision (14), safety (8), patient moved out of town (6), study terminated by sponsor (4), low creatinine clearance (4), site administrative reasons (2), patient wished to withdraw (2), received heart transplant (2), noncompliance (2), and 1 each for investigator error, ethics committee stopped trial, not further specified, study had ended, dosing interval deemed to be ineffective, approval not given for chronic phase (submission 5-5-98)

#H.6.2.10

H.6.1.10 (fax 7-21-98 states that patients "discontinuing from a study due to an arrhythmia that was not a protocol endpoint or due to lack of efficacy are counted in these discontinuation tables in the Adverse event category. These adverse events have not been further analyzed in the ISS. . . .")

The percents of patients who withdrew from a study are similar across treatment groups, but, excluding the active comparator group, more patients in dofetilide tended to withdraw for safety and more placebo patients tended to withdraw for lack of effect. About twice as many dofetilide patients had to have a dose reduction or temporary discontinuation compared to placebo patients.

The table below shows just the patients who withdrew for selected safety reasons.

Number and (percent) of patients

	placebo controlled trials		active/uncontrolled trials	
	dofetilide n=1479	placebo n=778	dofetilide n=462	active comparator [^] n=496
death	12 (0.8)	2 (0.3)	22 (4.8)	4 (0.8)
adverse event (TESS)	132 (8.9)	71 (9.1)	41 (8.9)	45 (9.1)
objective adverse event+	240 (16.2)	147 (18.9)	59 (12.8)	53 (10.7)
lab abnormality	11 (0.7)	3 (0.4)	4 (0.9)	12 (2.4)
QT/QTc prolongation	58 (3.9)	1 (0.1)	7 (1.5)	4 (0.8)

[^]includes quinidine, propafanone, sotalol, amiodarone (counted 464 patients)

+H.6.6.10a

H.6.1.10

While the rate of drop outs for TESS, objective adverse events, and laboratory abnormalities were higher in the placebo patients, there were more deaths in the dofetilide patients, particularly in the active/uncontrolled trials.

Selected TESS and objective adverse events that resulted in discontinuation in at least 5 dofetilide patients who participated in a placebo controlled trial are shown below.

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Number and (percent) of patients

adverse event leading to withdrawal	placebo controlled trials			active/uncontrolled trials	
	dofetilide n=1479	placebo n=778	placebo subtracted %	dofetilide n=462	active comparator n=496
any discontinuation for TESS	111 (7.5)	77 (9.9)	-2.4	23 (5.0)	43 (8.7)
any discontinuation for objective event [^]	240 (16.2)	147 (18.9)	-2.7	59 (12.8)	53 (10.7)
body as a whole	27 (1.8)	11 (1.4)	0.4	3 (0.6)	9 (1.8)
asthenia	8 (0.5)	4 (0.5)	0	1 (0.2)	5 (1.0)
chest pain ⁺⁺	7 (0.5)	1 (0.1)	0.4	0	0
cardiovascular excluding objective arrhythmias	53 (3.6)	42 (5.4)	-1.8	16 (3.5)	22 (4.4)
palpitations	11 (0.7)	11 (1.4)	-0.7	1 (0.2)	3 (0.6)
bradycardia	5 (0.3)	3 (0.4)	-0.1	1 (0.2)	4 (0.8)
syncope	7 (0.5)	6 (0.8)	-0.3	3 (0.6)	1 (0.2)
heart failure ⁺	9 (0.6)	7 (0.9)	-0.3	2 (0.4)	3 (0.6)
Selected ventricular arrhythmias[^]					
VF	6 (0.4)	2 (0.3)	0.1	4 (0.9)	2 (0.4)
VT ^{^^}	64 (4.3)	34 (4.4)	-0.1	48 (10.4)	6 (1.2)
digestive	17 (1.1)	9 (1.2)	-0.1	2 (0.4)	8 (1.6)
nausea	8 (0.5)	2 (0.3)	0.2	2 (0.4)	4 (0.8)
nervous	19 (1.3)	11 (1.4)	-0.1	2 (0.4)	3 (0.6)
dizziness	9 (0.6)	2 (0.3)	0.3	2 (0.4)	2 (0.4)
respiratory	14 (0.9)	11 (1.4)	-0.5	3 (0.6)	11 (2.2)
dyspnea	8 (0.5)	3 (0.4)	0.1	1 (0.2)	7 (1.4)

[^]H.6.6.10a

+includes worsening heart failure, congestive heart failure, left ventricular failure

++includes substernal chest pain

^{^^}includes TdP per sponsor

H.6.6.10

There is surprisingly little difference in the drop out rates for any of these events between

dofetilide and placebo in the placebo controlled trials. However, in the active/uncontrolled trials, the drop out rate for VT was 10.4% in the dofetilide group, 2.4 times the rate seen in the dofetilide patients who participated in a placebo controlled trial. The corresponding VT drop out rate for the active control group was 1.2%.

Supraventricular arrhythmias

The number and percent of patients who were enrolled into the relevant supraventricular arrhythmia studies and withdrew prematurely are shown below by treatment group.

Number and (percent) of patients

	placebo controlled trials			active comparator n=235 –
	dofetilide n=1331	placebo n=672	placebo subtracted %	
total withdrawals	616 (46.3)	357 (53.1)	-6.8	136 (57.9)
all safety	165 (12.4)	54 (15.1)	-2.7	39 (16.6)
protocol violation	14 (1.1)	7 (1.0)	0.1	3 (1.3)
lost to follow up	5 (0.4)	1 (0.1)	0.3	0
other+	78 (5.9)	37 (5.5)	0.4	2 (0.9)
did not meet randomization criteria	14 (1.1)	24 (3.6)	-2.5	0
withdrew consent	26 (2.0)	16 (2.4)	-0.4	8 (3.4)
lack of effect	314 (23.6)	218 (32.4)	-8.8	84 (35.7)

+majority of these withdrawals were the result of not converting/not remaining in NSR

H.6.1.6

Overall, more placebo patients withdrew than dofetilide patients.

The table below shows the patients who withdrew for safety reasons.

Number and (percent) of patients

	placebo controlled trials		% placebo subtracted	active comparator n=235
	dofetilide n=1331	placebo n=672		
death	8 (0.6)	1 (0.1)	0.5	0
adverse event (TESS)	94 (7.1)	49 (7.3)	-0.2	30 (12.8)
objective adverse event+	189 (14.2)	117 (17.4)	-3.2	38 (16.2)
lab abnormality	10 (0.8)	3 (0.4)	0.4	5 (2.1)
QT/QTc prolongation	52 (3.9)	1 (0.1)	3.8	4 (1.7)

+H.6.6.6A

H.6.1.6

The rates of death and drop outs for QT/QTc prolongation and lab abnormalities were higher in the dofetilide patients.

TESS and selected objective adverse events that resulted in discontinuation in at least 5 dofetilide patients who participated in a placebo controlled trial are shown below.

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Number and (percent) of patients			
adverse event leading to withdrawal	dofetilide n=1331	placebo n=672	placebo subtracted %
any discontinuation for TESS	93 (7.0)	55 (8.2)	-1.2
any discontinuation for objective event [^]	189 (14.2)	117 (17.4)	-3.2
body as a whole	25 (1.9)	9 (1.3)	0.6
asthenia	8 (0.6)	4 (0.6)	0
chest pain ⁺⁺	6 (0.5)	1 (0.1)	0.4
cardiovascular excluding objective arrhythmias	42 (3.2)	31 (4.6)	-1.4
palpitations	11 (0.8)	12 (1.8)	-1.0
bradycardia	5 (0.4)	3 (0.4)	0
syncope	6 (0.5)	2 (0.3)	0.2
heart failure ⁺	6 (0.5)	5 (0.7)	-0.2
Selected ventricular arrhythmias[^]			
VF	4 (0.3)	1 (0.1)	0.2
VT ^{^^}	25 (1.9)	8 (1.2)	0.7
digestive	14 (1.1)	8 (1.2)	-0.1
nausea	8 (0.6)	2 (0.3)	0.3
nervous	15 (1.1)	5 (0.7)	0.4
dizziness	6 (0.5)	2 (0.3)	0.2
respiratory	12 (0.9)	6 (0.9)	0
dyspnea	7 (0.5)	2 (0.3)	0.2

[^]H.6.6.6A

⁺includes worsening heart failure, congestive heart failure, left ventricular failure

⁺⁺includes substernal chest pain

^{^^}includes TdP per sponsor

H.6.6.6

Overall, more placebo patients dropped out for TESS and objective adverse events but more dofetilide patients died and/or had VF or VT, although the VT rate for the dofetilide patients is surprisingly low.

Dose response

The table below shows patients who dropped out for safety reasons, by actual dose received in the relevant supraventricular studies (n=1331). Of the 705 patients randomized to 500 mcg bid (H.2.1.5), only 426 (60.4%) were on that dose at discontinuation, indicating that many patients could not tolerate 500 mcg bid for a variety of reasons. N.B. Doses higher than 500 mcg bid were discontinued from development because of excess ventricular arrhythmias. Therefore, the number of patients who received this dose is small (n=33).

Number and (percent) of patients

	dofetilide (mcg bid)				placebo n=672
	<250 n=375	250 n=497	500 n=426	>500 n=33	
any reason	209 (55.7)	219 (44.1)	172 (40.4)	33 (48.5)	357 (53.1)
death	3 (0.8)	2 (0.4)	3 (0.7)	0	1 (0.1)
adverse event (TESS)	28 (7.5)	32 (6.4)	31 (7.3)	3 (9.1)	49 (7.3)
objective adverse event+	58 (15.5)	77 (15.5)	49 (11.5)	5 (15.2)	117 (17.4)
lab abnormality	1 (0.3)	1 (0.2)	8 (1.9)	0	3 (0.4)
QT/QTc prolongation	19 (5.1)	18 (3.6)	11 (2.6)	4 (12.1)	1 (0.1)

+Table 14 submission 7-10-98

Table 6 submission 7-10-98

It is surprising that the incidence rate for drop outs because of QT/QTc prolongation was inversely related to dose except for the >500 mcg bid group.

The table below shows incidence rates for selected adverse events, by dose. The >500 mcg group has been eliminated because there were so few patients. However, for this dose, the VF and VT rates were 3% and 9.1%, respectively, 6 and 4.3 times higher than the rates for the next highest dofetilide dose.

	Number and (percent) of patients			placebo n=672
	dofetilide (mcg bid)			
adverse event leading to withdrawal	<250 n=375	250 n=497	500 n=426	
any discontinuation for TESS	33 (8.8)	33 (6.6)	26 (6.1)	55 (8.2)
any discontinuation for objective event [^]	58 (15.5)	77 (15.5)	49 (11.5)	117 (17.4)
body as a whole	9 (2.4)	8 (1.6)	8 (1.9)	9 (1.3)
asthenia	3 (0.8)	1 (0.2)	4 (0.9)	4 (0.6)
chest pain ⁺⁺	2 (0.5)	4 (0.8)	0	1 (0.1)
cardiovascular excluding objective arrhythmias	17 (4.5)	18 (3.6)	6 (1.4)	31 (4.6)
palpitations	6 (1.6)	3 (0.6)	2 (0.5)	12 (1.8)
bradycardia	3 (0.8)	1 (0.2)	1 (0.2)	3 (0.4)
syncope	1 (0.3)	4 (0.8)	0	2 (0.3)
heart failure ⁺	4 (1.1)	2 (0.4)	0	5 (0.7)
Selected ventricular arrhythmias[^]				
VF	0	1 (0.2)	2 (0.5)	1 (0.1)
VT	7 (1.9)	6 (1.2)	9 (2.1)	8 (1.2)
digestive	3 (0.8)	4 (0.8)	7 (1.6)	8 (1.2)
nausea	2 (0.5)	1 (0.2)	5 (1.2)	2 (0.3)
nervous	4 (1.1)	4 (0.8)	7 (1.6)	5 (0.7)
dizziness	1 (0.3)	2 (0.4)	3 (0.7)	2 (0.3)
respiratory	5 (1.3)	4 (0.8)	3 (0.7)	6 (0.9)
dyspnea	3 (0.8)	3 (0.6)	1 (0.2)	2 (0.3)

+includes worsening heart failure, congestive heart failure, left ventricular failure

++includes substernal chest pain

[^]Table 14

Table 13

Overall, patients discontinued use of dofetilide primarily for ventricular tachycardia and/or ventricular fibrillation and QT/QTc prolongation. Drop out rates for these events in patients receiving doses above 500 mcg bid were exceedingly high.

5.0 Adverse events

Adverse events included events involving adverse drug reactions, illness with onset during the study, exacerbation of pre-existing illness. All treatment emergent adverse events (TESS) occurring either during study drug treatment or within 7 days after the end of treatment are summarized. An event was defined as treatment-emergent if it first occurred during the treatment period, or, if it occurred prior to the treatment period, its severity increased during the treatment period. The investigator's terminology for each adverse event was classified by involved body system using the assigned preferred term of the COSTART dictionary.

A subject with multiple adverse events was counted only once in the total for number of subjects with adverse events. A subject with multiple events within a body system was counted only once in the total for number of subjects with adverse events within that body system. An adverse event which occurred more than once for the same subject was counted only once in the total for that adverse event and in the total for number of adverse events.

Events referred to as adverse objective test findings (e.g. ECG changes or laboratory test abnormalities) were to be reported as adverse events only if they led to a temporary or permanent change in dose. Objective test findings are summarized separately from adverse events (section 5.2).

Proarrhythmic events are discussed in detail in section 4.0.

5.1 TESS

Placebo controlled trials

The table below shows the number, percent, and percent placebo subtracted (for dofetilide) and placebo patients who participated in placebo controlled trials (SVA, ventricular, other indications) and reported an adverse event. The last column displays the incidence rate for the same events reported by dofetilide patients in the active/no control studies. **NOTE:** while the table shows total events by body systems, it includes only those individual events that were reported by more than 2% of dofetilide patients and were reported more frequently by dofetilide patients compared to placebo patients.

Number and (percent) of patients

TESS	placebo controlled trials			active/no control
	dofetilide n=1418	placebo n=759	placebo subtracted %	dofetilide n=358
any report	856 (60.4)	427 (56.3)	4.1	122 (34.1)
body as a whole	512 (36.1)	232 (30.6)	5.5	41 (11.5)
chest pain	137 (9.7)	54 (7.1)	2.6	16 (4.5)
flu syndrome	48 (3.4)	13 (1.7)	1.7	0
headache	147 (10.4)	66 (8.7)	1.7	10 (2.8)

Adverse events

	accidental injury	40 (2.8)	9 (1.2)	1.6	0
	application site complications	37 (2.6)	12 (1.6)	1.0	1 (0.3)
	back pain	43 (3.0)	15 (2.0)	1.0	3 (0.8)
	procedure	48 (3.4)	18 (2.4)	1.0	3 (0.8)
	pain	31 (2.2)	13 (1.7)	0.5	1 (0.3)
	abdominal pain	41 (2.9)	19 (2.5)	0.4	1 (0.3)
cardiovascular		314 (22.1)	158 (20.8)	1.3	61 (17.0)
	hypertension	52 (3.7)	25 (3.3)	0.4	6 (1.7)
	angina pectoris	31 (2.2)	16 (2.1)	0.1	5 (1.4)
digestive		213 (15.0)	110 (14.5)	0.5	20 (5.6)
	nausea	71 (5.0)	29 (3.8)	1.2	7 (2.0)
	diarrhea	43 (3.0)	16 (2.1)	0.9	-3 (0.8)
endocrine		3 (0.2)	2 (0.3)	-0.1	0
heme/lymph		12 (0.8)	4 (0.5)	0.3	0
metabolic/nutritional		61 (4.3)	40 (5.3)	-1.0	2 (0.6)
musculoskeletal		115 (8.1)	45 (5.9)	2.2	3 (0.8)
nervous		265 (18.7)	133 (17.5)	1.2	28 (7.8)
	dizziness	113 (8.0)	51 (6.7)	1.3	18 (5.0)
	insomnia	51 (3.6)	24 (3.2)	0.4	2 (0.6)
respiratory		255 (18.0)	131 (17.3)	0.7	32 (8.9)
	respiratory tract infection	94 (6.6)	36 (4.7)	1.9	3 (0.8)
	dyspnea	87 (6.7)	44 (5.8)	0.9	11 (3.1)
skin and appendages		133 (9.4)	53 (7.0)	2.4	12 (3.4)
	rash	38 (2.7)	15 (2.0)	0.7	4 (1.1)
	sweating	31 (2.2)	16 (2.1)	0.1	3 (0.8)
special senses		74 (5.2)	27 (3.6)	1.6	1 (0.3)
urogenital		74 (5.2)	41 (5.4)	-0.2	7 (2.0)
	urinary tract infection	32 (2.3)	15 (2.0)	0.3	4 (1.1)

H.6.4.2

The placebo subtracted incidence rate for adverse events reported for all placebo controlled trials was 4.1%. The largest differences for dofetilide and placebo occurred for chest pain, respiratory tract infection, flu syndrome, and headache.

Intercurrent illnesses

Certain protocols¹ collected some events as intercurrent illnesses and listed them separately from adverse events. All other studies collected intercurrent illnesses as adverse events. The table below outlines the "intercurrent illnesses" that occurred in at least 4 dofetilide patients and reported more often compared to the placebo patients.

event	dofetilide n=738+	placebo n=175
any event	95 (12.9)	16 (9.1)
atrial fib	19 (2.6)	2 (1.1)
respiratory tract disorder	11 (1.5)	0
hypokalemia	9 (1.2)	0
headache	7 (0.9)	0
syncope [^]	6 (0.8)	1(0.6)
device complication	5 (0.7)	0
accidental injury	4 (0.5)	0

¹+combines dofetilide placebo trials and active/no control trials

[^]includes syncope and collapse

H.6.2.11

Only respiratory tract disorder (see previous section) and hypokalemia stand out (reported more by placebo patients in table H.6.4.2a). In addition, there was 1 report of liver damage and 1 report of liver function abnormal.

Supraventricular arrhythmia

The table below shows the number, percent, and percent placebo subtracted for dofetilide and placebo patients who participated in a placebo controlled SVA trials and reported an adverse event. NOTE: while the table shows total events by body systems, it includes only those individual events that were reported by more than 1% of dofetilide patients and were reported more frequently in dofetilide patients compared to placebo patients.

¹ Protocols 102, 107, 109, 201, 202, 203, 205, 206, 209, 210, 211, 214, 216, 217, 218, 220, 221, 222, 223, 224, 228, 229, 238, 301, 302, 303,304, 305, 306, 308, 310 and 311

Number and (percent) of patients

adverse event	dofetilide n=1331	placebo n=672	placebo subtracted %
any report	797 (59.9)	363 (54.0)	5.9
body as a whole	475 (35.7)	196 (29.2)	6.5
chest pain	128 (9.6)	45 (6.7)	2.9
flu syndrome	47 (3.5)	11 (1.6)	1.9
accidental injury	39 (2.9)	8 (1.2)	1.7
headache	142 (10.7)	61 (9.1)	1.6
procedure	42 (3.2)	15 (2.2)	1.0
back pain	41 (3.1)	14 (2.1)	1.0
application site complications	30 (2.3)	10 (1.5)	0.8
abdominal pain	37 (2.8)	16 (2.4)	0.4
pain	28 (2.1)	12 (1.8)	0.3
cardiovascular	288 (21.6)	124 (18.5)	3.1
hypertension	52 (3.9)	23 (3.4)	0.5
bradycardia	25 (1.9)	10 (1.5)	0.4
angina pectoris	29 (2.2)	13 (1.9)	0.3
digestive	193 (14.5)	92 (13.7)	0.8
nausea	62 (4.7)	26 (3.9)	0.8
diarrhea	36 (2.7)	14 (2.1)	0.6
endocrine	3 (0.2)	2 (0.3)	-0.1
heme/lymph	11 (0.8)	4 (0.6)	0.2
metabolic/nutritional	54 (4.1)	32 (4.8)	-0.7
edema@	46 (3.5)	20 (3.0)	0.5
musculoskeletal	110 (8.3)	38 (5.7)	2.6
arthritis	19 (1.4)	4 (0.6)	0.8
leg cramps	15 (1.1)	3 (0.4)	0.7
nervous	244 (18.3)	109 (16.2)	2.1
dizziness	102 (7.7)	42 (6.3)	1.4
somnolence	14 (1.1)	2 (0.3)	0.8
depression	14 (1.1)	5 (0.7)	0.4

Adverse events

	insomnia	49 (3.7)	22 (3.3)	0.4
respiratory		233 (17.5)	105 (15.6)	1.9
	respiratory tract infection	87 (6.5)	32 (4.8)	1.7
	dyspnea	83 (6.2)	32 (4.8)	1.4
	cough increase	27 (2.0)	9 (1.3)	0.7
skin and appendages		122 (9.2)	40 (6.0)	3.2
	rash	34 (2.6)	14 (2.1)	0.5
	sweating	30 (2.3)	13 (1.9)	0.4
special senses		71 (5.3)	22 (3.3)	2.0
	abnormal vision	21 (1.6)	8 (1.2)	0.4
urogenital		72 (5.4)	34 (5.1)	0.3
	urinary tract infection	32 (2.4)	13 (1.9)	0.5*

*includes peripheral edema
H.6.4.6

The placebo subtracted rates for individual events were highest for chest pain, flu syndrome, accidental injury, respiratory tract infection, dizziness, and dyspnea but all except for chest pain were <2%.

5.2 Objective Adverse Events

Placebo controlled trials

Events were classified as objective if tests such as ECG changes or laboratory test abnormalities were reported and they led to a temporary or permanent change in dose.

The table below shows the number, percent, and percent placebo subtracted for dofetilide and placebo patients who participated in placebo controlled trials, regardless of indication, and had an objective adverse event. NOTE: while the table shows total events for all body systems, it includes only those individual events that usually cause concern, such as anemia, LFT abnormalities, etc.

Number and (percent) of patients

objective adverse event	dofetilide n=1418	placebo n=759	placebo subtracted %
any report	434 [^] (30.6)	264 (34.8)	-4.2
body as a whole	8 (0.6)	1 (0.1)	0.5
cardiovascular	377[^] (26.6)	246 (32.4)	-5.8
	TdP [^]	0	1.1
	AV block+	3 (0.4)	0.7
	sinus bradycardia	6 (0.8)	0.4

Adverse events

	ventricular arrhythmia	7 (0.5)	3 (0.4)	0.1
	ventricular fibrillation	8 (0.6)	4 (0.5)	0.1
	ventricular tachycardia	80 (5.6)	49 (6.5)	-0.9
digestive		9 (0.6)	5 (0.7)	-0.1
	GGT increase	1 (0.1)	0	0.1
	LFTs abnormal	8 (0.6)	5 (0.7)	-0.1
heme/lymph		14 (1.0)	8 (1.1)	-0.1
	leukopenia	1 (0.1)	0	0.1
	marrow depression	1 (0.1)	0	0.1
	anemia	4 (0.3)	4 (0.5)	-0.2
	thrombocytopenia	2 (0.1)	2 (0.3)	-0.2
metabolic/nutritional		35 (2.5)	22 (2.9)	-0.4
	Alk phos increase	1 (0.1)	0	0.1
	SGOT increase	3 (0.2)	1 (0.1)	0.1
	SGPT increase	5 (0.4)	2 (0.3)	0.1
	bilirubinemia	0	0	0
	creatinine increase	1 (0.1)	1 (0.1)	0
	LDH increase	0	0	0
urogenital		12 (0.8)	3 (0.4)	0.4
	creatinine clearance decrease	10 (0.7)	1 (0.1)	0.6
	kidney function abnormal	1 (0.1)	1 (0.1)	0

*includes patients from H.6.11.2.1

+includes first, second degree block, and heart block
H.6.4.2a

Dofetilide is similar to placebo except for cardiac rate/rhythm disturbances and decreasing creatinine clearance.

Supraventricular arrhythmia

The table below shows the number, percent, and percent placebo subtracted of dofetilide and placebo SVA patients who participated in placebo controlled trials and had an objective adverse event. NOTE: while the table shows total events for all body systems, it includes only those individual events that usually cause concern, such as anemia, LFT abnormalities, etc.

Adverse events

Number and (percent) of patients

objective adverse event	dofetilide n=1331	placebo n=672	placebo subtracted %
any report	381[^] (28.6)	216 (32.1)	-3.5
body as a whole	8 (0.6)	1 (0.1)	0.5
cardiovascular	327[^] (24.6)	200 (29.8)	-5.2
ventricular tachycardia	44 (3.3)	16 (2.4)	0.9
TdP [^]	10 (0.8)	0	0.8
AV block+	14 (1.1)	3 (0.4)	0.7
sinus bradycardia	17 (1.3)	5 (0.7)	0.6
ventricular fibrillation	5 (0.4)	1 (0.1)	0.3
ventricular arrhythmia	7 (0.5)	3 (0.4)	0.1
digestive	9 (0.7)	5 (0.7)	0
GGT increase	1 (0.1)	0	0.1
LFTs abnormal	8 (0.6)	5 (0.7)	-0.1
heme/lymph	13 (1.0)	3 (0.4)	0.6
anemia	3 (0.2)	1 (0.1)	0.1
leukopenia	1 (0.1)	0	0.1
marrow depression	1 (0.1)	0	0.1
thrombocytopenia	2 (0.2)	1 (0.1)	0.1
metabolic/nutritional	32 (2.4)	15 (2.2)	0.2
Alk phos increase	1 (0.1)	0	0.1
bilirubinemia	0	0	0
creatinine increase	0	1 (0.1)	-0.1
LDH increase	0	0	0
SGOT increase	3 (0.2)	1 (0.1)	0.1
SGPT increase	5 (0.4)	2 (0.3)	0.1
urogenital	12 (0.9)	3 (0.4)	0.5
creatinine clearance decrease	10 (0.8)	1 (0.1)	0.7
kidney function abnormal	1 (0.1)	1 (0.1)	0

[^]includes events from H.6.11.5.1

+includes first, second degree block, and heart block
H.6.4.6a

Dofetilide is similar to placebo except for cardiac rate/rhythm disturbances and decreasing creatinine clearance.

5.3 Randomized dose response

Placebo controlled trials

The table below shows events by randomized dose, all indications.

Number and (percent) of patients

TESS-body systems	dofetilide (mcg)			
	<250 bid n=217	250 bid n=392	500 bid n=1058	>500 bid n=51
body as a whole	89 (41.0)	156 (39.8)	291 (27.5)	5 (9.8)
cardiovascular	52 (24.0)	99 (25.3)	198 (18.7)	- 6 (11.8)
digestive	26 (12.0)	65 (16.6)	138 (13.0)	0
endocrine	0	2 (0.5)	1 (0.1)	0
heme/lymphatic	1 (0.5)	2 (0.5)	9 (0.9)	0
metabolic/nutritional	6 (2.8)	23 (5.9)	34 (3.2)	0
musculoskeletal	21 (9.7)	41 (10.5)	54 (5.1)	2 (3.9)
nervous	36 (16.6)	80 (20.4)	162 (15.3)	1 (2.0)
respiratory	35 (16.1)	84 (21.4)	159 (15.0)	1 (2.0)
skin/appendages	22 (10.1)	44 (11.2)	74 (7.0)	0
special senses	8 (3.7)	26 (6.6)	41 (3.9)	0
urogenital	9 (4.1)	29 (7.4)	41 (3.9)	0

H.6.4.5

It is difficult to determine if there are adverse events that are dose related because so few study patients received doses above 500 mcg bid. The sponsor stopped all trials with higher doses because there was excessive reporting of ventricular arrhythmias in patients who received 750 mcg bid.

Supraventricular arrhythmia

The table below shows the results of reporting of adverse events, objective adverse events, serious adverse events, discontinuations for safety, and dose adjustments for safety, by total daily randomized dose in the placebo controlled trials.

Number and (percent) of patients

	dofetilide (mcg)				placebo
	<250 bid n=217	250 bid n=384	500 bid n=697	>500 bid n=33	n=672
at least 1 event	131 (60.4)	243 (63.3)	413 (59.3)	10 (30.3)	368 (54.8)
At least 1 objective event	58 (26.7)	136 (35.4)	172 (24.7)	5 (15.2)	216 (32.1)
Serious event	52 (24.0)	88 (22.9)	148 (21.2)	6 (18.2)	158 (23.5)
Discontinued for safety	60 (27.6)	91 (23.7)	125 (17.9)	6 (18.2)	172 (25.6)
Dose adjustment for safety	8 (3.7)	11 (2.9)	36 (5.2)	0	15 (2.2)

H.6.2.6, H.6.2.9

The table below shows selected adverse events reported by at least 2% of the dofetilide patients randomized to 500 mcg bid in the SVA trials and reported more often by these patients than the placebo patients.

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	Percent of patients		
	placebo controlled trials		
	dofetilide 500 mcg bid n=697	placebo n=622	placebo subtracted
any event	59.3	52.6	6.7
dyspnea	6.0	3.5	2.5
chest pain	8.0	5.8	2.2
flu syndrome	3.4	1.6	1.8
dizziness	7.5	5.9	1.6
accidental injury	2.7	1.3	1.4
angina pectoris	2.6	1.6	1.0
procedure	3.2	2.3	0.9
headache	10.5	9.6	0.9
diarrhea	3.0	2.1	0.9
nausea	4.6	3.7	0.9
urinary tract infection	3.0	2.1	0.9
abdominal pain	2.9	2.1	0.8
back pain	2.7	1.9	0.8
respiratory tract infection	5.3	4.8	0.5
pain	2.2	1.9	0.3
hypertension	3.7	3.5	0.2
edema/peripheral	3.2	3.1	0.1
arthralgia	3.3	3.1	0.2

H.6.4.7B

The reporting rates for events in the dofetilide group that were at least 1% higher than in the placebo group were: dyspnea, chest pain, flu syndrome, dizziness, accidental injury, and angina.

6.0 Laboratory safety

The following parameters were not discussed by the sponsor in the NDA integrated summary of safety: urinalysis, inorganic phosphorus, uric acid, albumin and globulin levels.

The laboratories routinely collected in clinical trials included
 -alkaline phosphatase, SGOT, SGPT, glucose, cholesterol, triglycerides, sodium, potassium, chloride, calcium, magnesium, inorganic phosphorus, uric acid, BUN, creatinine, total protein, albumin, globulin, total bilirubin, and random glucose;
 -hemoglobin, hematocrit, MCV, MCH, MCHC, RBC and platelet count; total WBC and differential count;
 -urinalysis using BM-Test-5L stick for pH, protein, glucose, ketones, and blood.

6.1 Discontinuations for laboratory abnormalities

The table below shows the number of patients who discontinued treatment because of a laboratory abnormality in *all* Phase II/III studies.

	Number and (percent) of patients		
	dofetilide		placebo n=778
	placebo controlled trials n=1479	active/uncontrolled trials~ n=462	
discontinued for lab abnormalities	11 (0.7)	4 (0.9)	3 (0.4)

H.6.1.10

The 15 dofetilide patients listed in the above table are described below.

Dofetilide patients			
patient ID	sex/age	dose/duration	comment±
liver function			
335-01280085	F/52	500 mcg bid/ 137 days	mildly elevated liver function tests (SGOT 1.7x, SGPT 1.4x) and urea (1.4x). No other reported events.
119-05860327	F/74	250 mcg bid/ 5 days	elevated alk phos (1.2x) and GGT (3x) at screening. Both were still elevated after 5 days of dofetilide treatment: alk phos (1.5x) and GGT (5.3x). 3 weeks after drug was discontinued, GGT remained mildly elevated. No other reported events.
119-06350045	F/31	375 mcg bid/ 32 days	elevated alk phos (1.2x), LDH (1.1x), SGOT (2x), SGPT (3x) beginning on study day 1 through day 32. SGOT and SGPT remained mildly elevated 10 weeks after discontinuing drug. Headache was reported on day 32
310-00450003*		750 mcg bid/ 32 days	elevated SGOT, SGPT and creatinine kinase (CK)
320-00430034	M/67	500 mcg bid/ 4 days	elevated alk phos, SGOT, total bilirubin, urea, and serum creatinine at baseline. First day of dofetilide treatment SGPT increased (1.8x). Patient was withdrawn when baseline values became known. Other reported events were bradycardia, hypertension, short runs of VT.

365-04050403	M/71	500 mcg bid/ 94 days	mildly (>2x) elevated SGOT and SGPT at baseline. Slightly enlarged liver on echo. Enzymes continued to increase (SGOT 12x, SGPT 5x); total bilirubin increased (2.6x) and serum albumin slightly decreased. Values repeated about 2 weeks after drug discontinuation were lower. Other reported events were nausea and hypomagnesemia.
Kidney function			
333-03430025	F/75	500 mcg bid/ 596 days	low creatinine clearance per protocol. No other reported events.
372-01520105	F/73	500 mcg bid/ 32 days	decreased creatinine clearance per protocol amendment. Other reported event was dyspnea.
372-01540022	F/74	500 mcg bid/ 27 days	decreased creatinine clearance per protocol amendment.
Miscellaneous			
109-05050008	F/45	250 mcg tid/ 743 days	potassium < 4.0 mEq/l. Other events include headaches, photosensitivity reaction, worsening heart failure
345-00220362	F/59	250 mcg bid/ 3 days	potassium <3.5 mEq/l. No other reported events.
345-00430601	M/52	500 mcg bid/ 380 days	thrombocytosis. Elevated baseline platelet count (1.9x) which essentially did not change during dofetilide treatment. Etiology unknown, no other reported events.
345-02340145	F/73	500 mcg bid/ 278 days	elevated eosinophil count (4.6x), etiology unknown. Other reported events were asthenia and dizziness.
345-02830513	F/50	500 mcg bid/ 3 days	elevated INR (warfarin temporarily discontinued). Other reported events were vomiting and insomnia.
345-03710476	M/60	125 mcg bid/ 124+ days	elevated CK (1.4x) which remained above normal 3 months after drug was discontinued. Other reported events were pruritus and UTI.

^numbers in parentheses are times upper limit of normal

+study report states 86 days

*patient does not appear in appendix II Table 6
appendix II Table 6

Of the 15 dofetilide withdrawals for lab abnormalities shown in the above table, 6 were for mild liver enzyme changes, 3 were for low creatinine clearance (per protocol amendment), 2 were for low potassium, and the remaining 4 were for thrombocytosis, eosinophilia, elevated INR, and elevated CK. The 3 placebo patients withdrew for elevated LFTs. There is no evidence that a pattern of laboratory abnormalities is emerging.

Clinical pharmacology

The following table displays dropouts for laboratory abnormalities in the clinical pharmacology studies.

Subjects who withdrew in clinical pharmacology studies

subject ID	sex/age	dose/duration	comment+
310-00450003	M/22	750 mcg bid/ 28 days	decreased testosterone (<0.8x) and increased CK (>2x)

203-00010001	M/25	100 mcg bid/ 3 days	increased CK (>2x), increased SGOT (>3x)
221-00010004	M/26	750 mcg qd/ 1 day	increased CK, increased lymphocytes

Appendix II Table 2

6.2 Means and mean changes from baseline

The sponsor determined means and mean changes from baseline for selected hematology, liver function, and renal function and electrolytes. As stated in the NDA:

The analysis of clinical laboratory abnormalities includes clinical laboratory tests performed during treatment and up to 7 days after the end of treatment. Lag times (7 days, or the duration of the washout period in crossover studies with washout < 7 days) were included in the determination. In order to be included in the summary of clinical laboratory data, a subject must have had at least one post-baseline value obtained during this period. Baseline was defined as the last value prior to dosing with active or randomized therapy. The final value was defined as the last observation recorded before the end of active or randomized therapy regardless of when that took place.

The criteria for clinically significant laboratory abnormalities do not take into account the subject's baseline values. Thus, abnormalities included in these analyses may have been present at baseline. The mean change from baseline was calculated using the maximum increase or decrease from baseline for each subject during treatment including lag time as described above. If maximum increase = maximum decrease, then the maximum increase was used. Thus, the change from baseline was the maximum change from baseline, not the difference between baseline and end of treatment.

In addition to means and mean changes from baseline, the sponsor identified patients who had what was defined by the sponsor as clinically significant laboratory abnormalities.

6.2.1 Hematology

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

Hematology values

parameter	dofetilide in placebo controlled trials n=1418			placebo n=759		
	no. evaluable patients	baseline mean	mean change from baseline±SEM	no. evaluable patients	baseline mean	mean change from baseline±SEM
hematocrit (%) males	731	44.56	-0.65±0.18	396	43.97	-0.18±0.23
hematocrit (%) females	306	41.16	-0.67±0.26	176	41.79	-0.79±0.45
hemoglobin (g/dl) males	811	14.85	-0.21±0.05	437	14.75	-0.05±0.06
hemoglobin (g/dl) females	366	13.54	-0.22±0.07	204	13.67	-0.21±0.11
platelets (10 ³ /mm ³)	1170	218.57	-0.77±1.68	633	220.05	8.88±3.26
WBC (10 ³ /mm ³)	1162	6.99	0.11±0.07	632	6.95	0.29±0.10
neutrophils (%)	1098	61.67	1.01±0.42	584	61.26	1.05±0.54

H.6.16.2

The tables below shows the number and percent of patients in Phase II/III placebo controlled trials who had a mildly to moderately (first table) and those with a severely (second table) abnormal hematology parameter.

Mild to moderate clinically significant abnormalities

parameter	criteria for clinically significant change from baseline-mild to moderate	dofetilide in placebo controlled trials n=1300		placebo n=700	
		number evaluable	number and (percent) abnormal	number evaluable	number and (percent) abnormal
hematocrit (%) males	20-60% decrease	805	22 ⁺ (2.7)	425	4 (0.9)
hematocrit (%) females	20-60% decrease	333	6 (1.8)	188	6 (3.2)
hemoglobin (g/dl) males	20-60% decrease	889	22 ⁺ (2.5)	472	3 (0.6)
hemoglobin (g/dl) females	20-60% decrease	396	7 (1.8)	219	8 (3.7)
platelets (10 ³ /mm ³)	50-75	1286	10 (0.8)	687	5 (0.7)
WBC (10 ³ /mm ³)	1.5-2.5	1283	3 (0.2)	688	2 (0.3)
neutrophils+ (%)	<0.5 x LLN	1136	4 (0.4)	617	1 (0.2)

⁺20 were mild abnormalities (20-40% decrease); 1 abnormality is missing see table H.6.12.2

+ H.6.12.2, H.6.13.9

Severe clinically significant abnormalities					
parameter	criteria for clinically significant change from baseline-severe	dofetilide in placebo controlled trials n=1300		placebo n=687	
		number evaluable	number and (percent) abnormal	number evaluable	number and (percent) abnormal
hematocrit (%) males	>60% decrease	805	0	425	1 (0.2)
hematocrit (%) females	>60% decrease	333	0	188	0
hemoglobin (g/dl) males	>60% decrease	889	0	472	0
hemoglobin (g/dl) females	>60% decrease	396	0	219	0
platelets (10 ³ /mm ³)	<50	1286	5 (0.4)	687	1 (0.1)
WBC (10 ³ /mm ³)	<1.5	1283	2 (0.2)	688	1 (0.1)

H.6.13.9

More dofetilide males reported mild to moderate abnormal Hb/Hct compared to their placebo counterparts but the reverse was true for females. Somewhat more dofetilide patients had platelet counts less than 50,000 compared to placebo patients. Overall, no trends are evident.

6.2.2 Liver Function Tests

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

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Means

parameter	dofetilide in placebo controlled trials n=1418			placebo n=759		
	no. evaluable patients	baseline mean	mean change from baseline±SEM	no. evaluable patients	baseline mean	mean change from baseline±SEM
SGPT (IU/L)	1204	24.99	4.46±1.08	652	27.95	2.15±1.43
SGOT (IU/L)	1202	23.31	3.99±0.92	652	25.66	1.82±1.31
alk phos (IU/L)	1203	99.86	0.52±0.81	653	90.44	-1.26±1.02
GGT (IU/L)	324	37.12	4.49±3.35	219	40.40	-2.26±2.54
LDH (IU/L)	327	159.41	7.33±3.64	223	168.12	-6.20±7.01
t. bili (mg/dl)	1203	0.75	-0.02±0.01	652	0.74	0.01±0.01

H.6.16.2

Although most of these parameters showed mean increases from baseline for the dofetilide group compared to placebo, the changes were small. The tables below show the number and percent of patients in Phase II/III placebo controlled trials who had a mildly, a moderately, or a severely abnormal SGOT, SGPT, or total bilirubin.

Clinically significant abnormalities

	SGOT		SGPT		t bilirubin	
	dofetilide n=1296	placebo n=696	dofetilide n=1297	placebo n=694	dofetilide n=1294	placebo n=693
mild: 1-3 x ULN	143 (11.0)	71 (10.2)	175 (13.5)	88 (12.7)	126 (9.7)	56 (8.1)
moderate: 3-5 x ULN	9 (0.7)	8 (1.1)	12 (0.9)	9 (1.3)	1 (0.1)	0
severe: >5 x ULN	5 (0.4)	4 (0.6)	6 (0.5)	5 (0.7)	0	0

H.6.14.9

Reported abnormalities were similar for the 2 treatment groups.

Dose response

There is a dose-dependent increase in the mean maximum change from baseline for LFTs. This is shown in the table below, by randomized dose.