- Toxicokinetics: Values are mean±SD; n=5[n1].

Dose	5 mg/kg/day	10 mg/kg/day	50 mg/kg/day
C_{max} (ng/ml)	58±16	155±48	796±154
$AUC_{0\text{-}24h}$ (ng*h/ml)	730	1950	9980

***Note:* '[n1]', each group was split into 2 subgroups a and b; blood from each subgroup was sampled at 8 hourly intervals, but sampling from a and b was staggered by 4 hours. Therefore n=5 for each time point.**

Discussion

Testicular atrophy increased in severity with duration of treatment. Since no atrophy was seen in the mid dose group, grade-4 lesions seen in one low dose animal is probably not treatment related. This conclusion is further supported by the sponsor's statement that they have occasionally seen grades 3&4 testicular lesions in control rats in six month and one month studies.

Plasma levels of FSH did not show treatment related s-s changes, and therefore did not prove to be a suitable marker for testicular atrophy. 5 months' recovery period, after dosing for 3 months, did not reduce the incidence of testicular atrophy of grade >2. The sponsor postulates that a smaller difference in mean testicular wts of control and treated animals at end of recovery period than at end of 3 months' treatment period is suggestive of some recovery. However, suggestive results are only useful for further testing in conclusive studies. This study did not establish reversibility of atrophy.

§3: Subchronic & Chronic Toxicity Studies in Dog

Two week oral study (Beagle; study # 86128; study site, sponsor's labs, Ambois, France)

2/sex/group in treatment groups L and H; 1/sex in the control group (C); treatment groups L and H received 2 mg/kg/day and 10 mg/kg/day dofetilide respectively administered in capsules; C received placebo capsules. Animals were observed daily pre-dose and post-dose for clinical signs; body wts were recorded pre-treatment, on day 1, and every 4 days thereafter; EKGs and systolic blood pressure were recorded pre-treatment, and before dosing and ≈ 2 hours post-dose on days 6, and 14; hematology and clinical chemistry were done pre-treatment and on days 1 and 15; toxicokinetics was done 3 and 7 hours post dose on day-1; on day-2, pre-dose, and on day-9, pre-dose and 1, 3, and 7 hours post dose. At sacrifice, complete necropsy and histopathology were done only in the two treatment groups.

Results

- Clinical signs & mortality: The two males in the high dose group exhibited aggressive behavior 1-2 hours post-dose on day-1 of treatment only. There was no mortality.
- Body wt: There were no treatment related adverse effects on body wt.
- EKG: *PQ intervals:* One low dose male (M11) showed first degree heart block on day-6 before dosing, and on day-13 before and after dosing; one high dose male (M22) showed second degree heart block (with Wenkebach phenomenon) before dosing on day-13. *QT interval:* Low dose: QT intervals before dosing were not > than pre-treatment values; after dosing, ΔQTs on day-6 were .02, .03, 0, and .01 sec; on day-13, ΔQTs were .02, .02, .02, and .03 sec. High dose: QT intervals before dosing on day-6 were .01, .01, .04, and .02 sec > than pre-treatment values; QT intervals before dosing on day-13 were not > than pre-dosing intervals on day-6. After dosing ΔQTs were 0, 0, and -.02 sec on day-6, and -.01, -.01, 0, and 0 sec. *Sinus arrhythmia and/or sinus pause:* 1 low dose (m) and 3 high dose animals (2m+1f) showed marked sinus arrhythmia before and after dosing on both days. However, all 3 high dose animals exhibited this finding before dosing, but only 2 exhibited this finding after dosing.

  Comments: QT intervals did not increase in the high dose group, but increased slightly in the low dose group. This result in unexplainable. The sponsor does not mention this curious finding.
- There were no adverse treatment related hematological, clinical chemistry, necropsy, or histological findings.

- Toxicokinetics:

	Low dose		High dose	
	Day-1	Day-9	Day-1	Day-9
C_{max} (ng/ml)	473-839; 630±79	442-827; 614±80	2376-2911; 2676±128	3554-3974; 3679±99
C_{24h} (ng/ml)	nd	nd	42-207; 88±40	43-97; 66±16
AUC_{0-7h} (ng*h/ml)	2594-2894; 2734±70	1911-2764; 2487±198	11386-16226; 14196±1114	17811-22727; ±20374±1027
T_{max} (hr)	1, 1, 1,3hr	1,3,1,3hr	3, 1,1,3hr	1,1,3,1hr

Note: Values are range; mean±SE; males and females are combined; 'nd', is below limit of detection (10ng/ml).

One Month Oral Toxicity Study in the Dog (Beagle; study # 87014; study site, sponsor's labs in Ambois, France).

9-10 ½ months old; 3/sex/group; treatment groups L, M, and H received 0.5, 2, and 10 mg/kg/day dofetilide, respectively, by gavage; control (C) group received vehicle; all animals received the same volume of fluid on a ml/kg basis. Pre-treatment values of all parameters described below were determined. Body wts were recorded weekly; EKG and systolic pressure were measured 2 hours post-dose, during weeks 1 and 4; hematology and clinical chemistry were done during weeks 2 and 4; urine was examined only at the end of treatment. Complete necropsy and histopathology were done at study end. Plasma drug levels were determined on day-11 of the study.

Results

- Clinical signs & mortality: *High dose:* One male and one female showed the following signs during the first 2 days of treatment: motor incoordination in the male and prone position, tremors, pedal movements and excessive salivation in the female; sporadic salivation was observed throughout the study in 5/6 dogs. There was no mortality in any group.
- Body wts: Neither group mean±SD nor individual wts are in the submission; there are graphs of individual wts and mean wts that indicate some decrease in wt over time. The sponsor states that decrease in wt of treated groups were somewhat greater than those of control groups.
- EKG: *QT:* In 3 pretreatment EKGs, QT values changed by ≤ 0.02 sec. Incidences of ΔQTs >0.02 sec (vs the last pretreatment values), 2 hours post dose at weeks 1 and 4 are shown below; numbers within ( ) are range; mean of ΔQTs:

	1 week	4 weeks
C	1/6 (0.06)	1/6 (0.04)
L	3/6 (0.03-0.05; 0.04)	3/6 (0.04)
M	5/6 (0.03-0.05; 0.04)	2/6 (0.03-0.05; 0.4)
H	3/6 (0.04-0.05; 0.043)	3/6 (0.04-0.09; 0.06)

Sinus arrhythmia: Incidences of marked sinus arrhythmia increased during treatment in all treatment groups, but the increase was not dose related. *PQ:* First degree heart block (PQ >0.15 sec) occurred in two low dose, and one mid dose animals. *Second degree heart block* during week-1was seen in one mid dose animal. *PVCs* were seen in one low dose and one mid dose animal.

- Hematology: (*Comments:* Only mean (no SE or SD) and individual values of hematology parameters are provided). There did not seem to be any treatment related adverse effects on any hematology parameter.
- Clinical chemistry: There were no treatment related adverse effects on any parameter.
- Urinalyses: There were no treatment related adverse effects.
- Organ wts: There were no treatment related adverse effects on organ wts.
- Histopathology: *High dose:* Epididymis: Cellular debris in the lumen in epididymal heads was seen in all 3 males (5 heads examined; debris seen in all 5). *Comments:* 4 epididymal heads from 2 control animals, and 2 heads from one low dose animal could be examined, but no histopathological changes were seen in any of these. Coronary artery: Focal periarteritis was seen in one high dose animal.

- Toxicokinetics: Values (range; mean±SE) of various parameters are shown below; values did not seem to differ with gender (L, males>females; M, females>males; H, ≈), therefore males and females are combined.

	0.5 mg/kg/day (n=6)	2 mg/kg/day (n=6)	10 mg/kg/day (n=6)
C_{max} (ng/ml)	92-182; 128±15.2	718-1260; 963±91.7	5524-6800; 6070±230.1
C_{24h} (ng/ml)	nd	10-16; 13.5±0.92	139-229; 195±13.7
AUC_{0-7hr} (μg*h/ml)	0.363-0.777; 0.563±0.062	3.688-5.181; 4.365±0.246	27.259-35.472; 30.627±1.338
t_{max} (hr)	1 (5); 3	1 (6)	1 (5); 3

Note: 'nd' is below detection limit (< 5 ng/ml); for t_{max} number within ( ) after a value is the number of animals which had that value of t_{max}.

Six Month Oral Study in Dog (Beagle; study # 88081; study site, sponsor's labs in Ambois, France). 8-9 months old; 4/sex/group; treatment groups L, M, and H received 0.25, 2, and 10 mg/kg/day dofetilide, respectively, by gavage; control (C) group received vehicle. *Note:* High dose group received 5 mg/kg/day for 4 days, and 10 mg/kg/day thereafter. Rest of the methodology was the same as in the one month study, except that EKG, hematology, and clinical chemistry were done every 2 months, and toxicokinetics was done at the end of the study.

Results

- Clinical signs & mortality: *High dose:* 2/8 dogs displayed sedation and salivation during the first 3 weeks of treatment; the signs lasted 0.5-6 hours post dose.
- Body wts: There was no treatment related adverse effect on body wt.
- EKG: *QT:* In 3 pre-treatment EKGs, QT values changed by ≤ 0.03 sec. Incidences of ΔQTs >0.03 sec (v the last pretreatment values), 2 hours post dose at months 1, 3, and 5 are shown below; numbers within ( ) are 'range; mean' of ΔQTs in sec.

	1 month	3 months	5 months
C	0/8	0/8	0/8
L	5/8 (.04-.07; .052)	3/8 (.05-.06; .057)	3/8 (.06-.07; .067)
M	4/8 (.04-.06; .05)	2/8 (.06-.08; .07)	4/8 (.04-.08; .055)
H	5/8 (.04-.06; .046)	2/8 (.04-.05; .045)	3/8 (.05-.07; .06)

PQ: In 4 low dose, 4 mid dose, and 2 high dose animals 1st degree heart block was seen on 1-3 occasions 2 hours post dose. *Second degree AV block* was seen in 1/8, 3/8, and 4/8 C, L, and M groups respectively. *PVCs* were observed in 2/8 mid dose dogs. Marked *Sinus arrhythmia/sinus pause* was seen in 1, 6, 6, and 4 C, L, M, and H groups respectively (animals that exhibited this feature before start of treatment are excluded).

- Hematology: There were no treatment related adverse effects on any hematology parameter.
- Clinical chemistry: In one mid dose and two high dose animals, blood urea increased more than in any control animal during the study; maximum ↑ in C, 21 mg/dL; in mid-dose, 27 mg/dL[1]; in high dose, 24[1] and 33 mg/dL). *Note:* '[1]', these increases are small and probably not biologically significant.
- Urinalyses: There were no treatment related abnormal findings.
- Organ wts: *Testes:* Both testes in 2 high dose, one/both in 2 mid dose, and one each in 3 low dose males were smaller than the smallest control group testes. Smallest testicular wts in control, and testicular wts in the treated animals referred to above are shown below.

	Control	High dose		Mid dose		Low dose		
	M3	M31	M32	M21	M24	M12	M13	M14
Left testis (gm)	6.09	4.44	4.91	5.61	5.17	5.93	(6.66)	(6.59)
Right testis (gm)	6.21	4.8	4.85	5.48	(6.5)	(6.32)	5.98	5.64

Note: Testes' wts within ( ) are wts not smaller than testes' wts of m3.

- Histopathology: Testes & epididymis: *High dose:* m31: Bilateral moderate (grade-3) atrophy of testes, and abnormal content in both epididymides. m32: Bilateral mild (grade-2) atrophy of testes, and

multi-focal mineral deposits and abnormal content in both epididymides. *Mid dose:* m24: Minimal (grade-1) atrophy in a few tubules in the left testes, and both epididymis heads showed focal retention of contents. M22: Minimal focal mineral deposits in epididymis. M23: Minimal focal mineral deposits in the right epididymis. *Low dose:* m12: Minimal (grade-1) atrophy of one testis. M11: Focal retention of contents in the left epididymis.

- Toxicokinetics: Values (range; mean±SE) of various parameters are shown below;

	0.25 mg/kg/day		2 mg/kg/day		10 mg/kg/day	
	Males (n=4)	Females (n=4)	Males (n=4)	Females (n=4)	Males (n=4)	Females (n=4)
C_{max} (μg/ml)	0.03-0.1;. 058±.016	0.06-0.09;. 0.07±.0.007	0.67-1.0; 0.867±.08	0.77-0.87; 0.815±0.021	4.0-6.15; 5.428±0.513	5.56-8.2; 6.688±0.615
C_{24h} (μg/ml)	nd	nd	.01 (4)	.01 (3); .02	.07-.09;.083	.11-.16; .143
AUC_{0-7hr} (μg*h/ml)	0.09-0.2; 0.15±0.029	0.12-0.21; 0.153±0.21	2.48-2.55; 2.518±0.019	2.32-2.74; 2.605±0.096	14.59-22.88; 19.3±1.96	23.79-27.31; 25.48±0.728
t_{max} (hr)	1 (4)	1 (4)	1 (4)	1 (4)	1 (4)	1 (3), 2

Note: 'nd' is below detection limit (< 5 ng/ml); for t_{max} number within ( ) after a value is the number of animals which had that value of t_{max}.

Discussion: The sponsor states that the minimal testicular atrophy seen in one mid dose and one low dose male is most probably incidental and not treatment related. The rationale given is that more severe testicular lesions than those seen in 2 high dose dogs in this study have been seen with very low incidence in dogs in that lab. However, the severity of lesions is dose related, and the lesions occurred in dogs with the smallest testes. Therefore, it cannot be stated with certainty that 2 mg/kg/day is the NOAED.

12 Month Oral Study in the Dog (Beagle; study # 93021; study site, sponsor's labs in Ambois, France). 9-10 month old; 4/sex/group; treatment groups low (L), medium (M), and high (H) received 0.1, 1, and 10 mg/kg/day dofetilide, respectively, in capsules; control (C) group received placebo capsules. *Note:* High dose group received 5 mg/kg/day for 4 days, and 10 mg/kg/day thereafter. Rest of the methodology was the same as in the six month study, except that EKG, hematology, and clinical chemistry were done at 2 weeks/3months, and 6, 8, 10, and 12 months, and toxicokinetics was done at 8 ½ months.

Results

- Mortality: There were 2 deaths at mid dose; one dog (m22) was found dead on day-22 before dosing; the other (m23) was found dead on day-168, 4 ½ hours after dosing. These animals had exhibited no clinical signs prior to death.
- Clinical signs: *High dose:* 5/8 dogs had increased salivation, that appeared 1-5 hours post dose but was not seen next day; the sign lasted through the first six months.
- Body wts: Body wts (in kg) are shown below. Values are mean±SE; '↓', % decrease v C (if ≥5%).

	Males			
	C	L	M	H
-7 days	11.3±0.23	11.3±0.31	11.25±0.2	11.28±0.6;
2 months	11.2±0.23	10.98±0.46	11.17±0.28	10.65±0.35; ↓5%
4 months	11.88±0.31	11.28±0.61; ↓5%	11.77±0.33	10.88±0.49; ↓8%
6 months	12.83±0.48	12.28±0.73; ↓7%	12.1±0.5, ↓6%	11.53±0.63; ↓10%
8 months	13.2±0.51	12.23±0.69; ↓5%	11.8±0.1; ↓11%	11.4±0.45*; ↓14%
10 months	13.18±0.75	12.45±0.53; ↓5%	11.95±0.45; ↓9%	11.45±0.43; ↓13%
12 months	13.78±0.1	13.0±0.57; ↓6%	12.1±0.2***; ↓12%	11.58±0.53**; ↓16%

Note: '*', p<0.05; '**', p<0.01; '***', p<0.001 v C at the same time point (s-rev)

	Females			
	C	L	M	H
-7 days	8.93±0.0	8.9±0.21	8.93±0.25	8.83±0.05
2 months	9.0±0.62	8.7±0.33;	8.9±0.18	8.6±0.32; ↓4%
4 months	9.53±0.52	9.25±0.35	9.4±0.19	8.88±0.48; ↓7%
6 months	10.83±0.79	10.53±0.59	10.08±0.44; ↓7%	9.53±0.59; ↓12%
8 months	10.48±1.09	10.53±0.59	9.98±0.4; ↓5%	9.35±0.64; ↓11%
10 months	10.78±1.11	10.83±0.71	10.45±0.42	9.58±0.6; ↓11%
12 months	11.05±1.13	11.1±0.76	10.1±0.54; ↓9%	9.83±0.56; ↓11%

- EKG: *QT:* ΔQT (vs pre-treatment values) did not seem to be any > in mid dose than in low dose group. In the high dose group QT values pre-dose were ≈ post-dose values in low and mid dose groups, and did not seem to increase further, 2 hours post dose. *AV block:* 3 mid (includes one mid dose early death), and 3 high dose animals had intermittent first and/or second degree blocks; 1, 5, and 5 low, mid (includes both early deaths), and high dose animals respectively had intermittent bundle branch blocks (BBBs). *PVCs:* 2 mid, and 3 high dose animals had occasional PVCs/ 'premature junctional contractions'. *Sinus arrhythmia/sinus pauses:* Incidence and frequency of this sign were increased in all treatment groups.
- Hematology: There were no treatment related adverse effects on any hematology parameter.
- Clinical chemistry: *High dose:* In one high dose male (m33), triglycerides and serum bilirubin increased progressively. Triglycerides: Pre-treatment, 39 mg/dL; 6 months, 62 mg/dL; one year, 88 mg/dL (highest value in C, 38 mg/dL at 10 months). Bilirubin: Pre-treatment, 0.1 mg/dL; 6 months, 0.25 mg/dL; 12 months, 0.33 mg/dL (highest value in C, 0.22 mg/dL at 12 months).
- Urinalyses: There were no treatment related adverse findings.
- Organ wts: In two mid dose (early deaths), and two high dose males, testes were lighter than the lightest organ in control (wts of testes ≤ lightest control testes are shown in the table below. *Note:* Wts given are of both testes combined in each animal; no reason is given for not providing individual testicular wts).
- Pathology: There were no treatment related gross lesions.
- Histopathology: Incidences of testicular atrophy, and abnormal epididymal findings (the only treatment related lesions seen) are shown below.

	Incidence	Unilateral /Bilateral	Severity	Description of lesions	Wt (gm)
C: (m2)	1/4	Unilateral	Mild	Focal atrophy (a few tubules affected)	13.32
L: (m12)	1/4	Unilateral	Minimal	Focal atrophy (one tubule affected)	
M: (m21)	3/4	Unilateral	Minimal	A few tubules affected.	
(m22; died d-22)		Bilateral	Mild	Focal atrophy	12.28; ↓8%
m23; died d-168)		Bilateral	Mild	Multi-focal	11.24; ↓16%
H: (m31)	4/4	Bilateral	Moderate	Multi-focal; epididymides, abnormal content	11.22; ↓16%
(m32)		Bilateral	Moderate	Multi-focal; epididymides, abnormal content	
(m33)		Bilateral	Moderate	Multi-focal; epididymides, abnormal content and multi-focal spermatic granulomas,	10.16; ↓21%
(m34)		Unilateral	Minimal	Focal atrophy	

Note: '↓', % by which these organs were smaller than the smallest control (m2).

Comments: Incidence and severity of testicular atrophy seems to be dose relatedly increased in mid and high dose animals.

- Toxicokinetics:

	0.1 mg/kg/day		1 mg/kg/day		10 mg/kg/day	
	Males (n=4)	Females (n=4)	Males (n=2)	Females (n=4)	Males (n=4)	Females (n=4)
C_{max} (μg/ml)	0.02-0.03; 0.0225±0.0025	0.02-0.05; 0.03±0.007	0.39-0.42; 0.405±0.015	0.0.29-0.57; 0.39±0.063	3.5-6.39; 5.39±0.748	2.67-6.88; 4.518±0.926
C_{24h} (μg/ml)	nd	nd	nd	nd	0.08-0.19	0.07-0.27
AUC_{1-7hr} (μg*h/ml)	0.05-0.13; 0.095±0.019	0.05-0.18[3] 0.113±0.038	1.38-1.43; 1.405±0.025	1.35-1.75; 1.54±0.095	20.5-32.72; 25.835±2.65	15.52-32.64; 22.925±3.63
t_{max} (hr)	1 (3), 1	1 (2), 3 (2)	1 (2)	1 (3), 3	1, 3 (3)	3 (4)

Note: 'nd' is below detection limit (< 10 ng/ml); '[3]', calculated for n=3; for t_{max} number within ( ) after a value is the number of animals which had that value of t_{max}.

Discussion: The two deaths in mid-dose animals occurred on days 22 and 168; neither animal had exhibited any unusual signs before death, and there were no findings at necropsy that could account for their deaths. Moreover, there were no deaths in the high-dose group, in which C_{max} was ≈ 10 times that in the mid-dose group, and AUC was > 15 times that in the mid dose group. In the six month study also, there were no deaths in the 10 and 2 mg/kg/day groups. The sponsor postulates that these animals may have died from dofetilide induced PVT, as their QTs on 1/3 pre-treatment EKGs were > than those of any other animal on any pre-treatment EKG, and this may have predisposed them to PVT. But the only occasion when their EKGs were recorded post-dose, their ΔQTs were not the highest; and during the treatment period, some other animals had QTs > the highest recorded in these two. However, QTs and ΔQTs post dose in individual animals fluctuated, and it is possible that these animals died from PVT.

§4: Reproduction Toxicology

Fertility Study in Rat (oral) ([redacted]COBS-VAF-CD(SD)BR(France); protocol, 89074; study site, sponsor's labs in France).

One control (C) and three treatment groups; 12 males & 24 females/group; treatment groups low L, M, and H received 0.05, 0.25, and 1 mg/kg/day dofetilide respectively, by gavage; control group received vehicle. Males were treated for 98 days before mating and throughout the mating period; females were treated for 14 days before mating, and through the mating period, gestation, and lactation. Half the mated females were sacrificed 20 days post mating, and assessed for fertility, embryotoxicity, and teratogenicity. The other half were allowed to litter. 20 day sacrifice: All fetuses were examined for external abnormalities; half the fetuses in each litter were examined for skeletal abnormalities and the other half for visceral abnormalities.

Results

Dams

- Mortality & Clinical signs: There was no mortality or any drug related clinical signs in either sex.
- Body wts: There were no s-s differences between the body wts of different groups on day 20 of gestation, and days 1, 7, 14, and 21 of lactation.
- Reproduction parameters: Table below shows the results.

	C	L	M	H
Mating rate	14/24 (58.3%)	20/24 (83.3%)	21/24 (87.5%)	20/24 (83.3)
Pregnancy rate	13/14 (92.9%)	14/20 (70.0%)	16/21 (76.2%)	20/20 (100%)
20 days sacrifice	n=7	n=7	n=9	n=10
Corpora lutea	17.86±1.57	20.3±2.63	17.8±2.11	18.0±1.76
Implantation sites	17.29±1.8	20.14±2.73	16.78±4.41	17.6±2.22
Pre-implantation loss **# with loss/ # pregnant**	4/125 (3.2%) 3/7 (42.9%)	1/142 (0.7 1/7 (14.3%)	9/160 (5.6%) 2/9 (22.2%)	4/180 (2.2%) 3/10 (33.3%)
No of viable fetuses	15.71±2.93	19.14±3.24	16±4.21	15.7±2.5
Post-implantation loss **# with loss/ # pregnant**	11/121 (9%) 4/7 (57.1%)	7/141 (5%) 5/7 (71.4%)	7/151 (4.6%) 5/9 (55.6%)	19/176 (10.8%) 10/10 (100%)
Post lactation sacrifice	n=6	n=7	n=7	n=10
Gestation Length (Days)	21.3±0.5	21.1±0.7	21.4±0.5	21.7±0.5[n1]
Implantation sites	19.5±2.1	20.0±2.2	17.4±2.2	14.5±5.5
No of live pups[n2]	18.8±1.7(96%)	18.3±2.5(91.5%)	16.1±1.5(92.6)	13.3±5.7(91.7%)
No of dead pups	0	1/129 (0.8%)	3/116 (2.6%)	0
Post implantation loss **# with loss/# pregnant**	4/117 (3.4%) 2/6 (33.3%)	12/140 (8.6%) 5/7 (71.4%).	9/122 (7.4%) 6/7 (85.7%)	12/145 (8.3%) 5/10 (50%)
All pregnant females	13	14	16	20
Post implantation loss[n3] **# with loss/# pregnant**	15/238 (6.3%) 6/13 (46.2%)	19/281 (6.8%) 10/14 (71.4%)	16/273 (5.9%) 11/16 (68.8%)	31/321 (9.7%) 15/20 (75%)

Note: Non integer values are mean±SD. '[n1]', Mean gestation length was calculated from 9 dams in this group (one dam that is reported as having a gestation length of 15 days is excluded.). '[n2]', Numbers within ( ) are live pups as % of implantation sites. '[n3]', Post implantation loss as % of implantation sites, C v H, p=0.101; as % of dams with post implantation loss, C v H, p=0.095; combining all treated dams, C v T, p=0.078.

Comments: Smaller litter size in high dose dams allowed to litter is due to a smaller number of implantation sites. This may be a chance finding, since pre-implantation loss in the 20 day sacrifice was not increased in high dose dams.

Fetuses/pups

Table below shows fetal/pup parameters. 'C.' in row 7 stands for cerebral; 'f.' in row 20 stands for fissures.

	C	L	M	H
20 day sacrifice	N=7	N=7	N=9	N=10
Fetal wt (m)	3.94±0.31	3.57±0.28	3.71±0.48	3.94±0.75
Fetal wt (f)	3.67±0.36	3.47±0.25	3.51±0.48	3.75±0.79
Fetal malformations (litter incidences except [n2], which is fetal incidence)				
Skeletal [n1]	3/7	3/7	0/9	7/10
Unossified 5th metacarpal[n2]	26/55	36/68	53/72**	60/78**
Visceral[n3]	3/7 (42.9%)	2/7	6/9 (67%)	8/10 (80%)
Dilated C. ventricles[n4*]	0/7	0/7	1/9	4/10
Skeletal + Visceral[n5]	5/7 (71%)	4/7	6/9 (67%)	10/10 (100%)
Post Lactation sacrifice	n=6	n=7	n=7	n=10
Fetal wt, day-1 (m)	6.57±0.57	6.35±0.43	6.66±0.26	6.59±0.70(n=9)
Fetal wt, day-1 (f)	6.09±0.42	6.00±0.43	6.21±0.32	6.21±0.56(n=10)
Fetal wt day-21 (m)	33.47±2.92	35.95±4.16	39.61±4.65	40.92±11.68
Fetal wt day-21 (f)	30.55±1.85	34.11±2.64	37.66±4.53	38.15±10.61
24 hour survival	113/113 (100%)	128/128 (100%0	113/113 (100%)	133/133 (100%)
4 day survival	113/113 (100%)	126/128 (98.4%)	112/113 (99.1%)	129/133 (97%)
21 day survival	108/113 (95.6%)	120/128 (93.8%)	108/113(95.6%)	124/133 (96.1%)
Righting reflex (d-6)	55/113 (48.7%)	54/124(43.5%)	55/110 (50.0%)	77/128(60.2%)
Grasping reflex (d-6)	49/113 (43.4%)	55/124 (44.4%)	49/110 (44.5%)	80/128 (62.5%)
Incisors present (d-11)	81/110 (73.6%)	83/121 (68.6%)	82/108 (75.9%)	95/126 (75.4%)
Palpebral f. open (d-15)	46/110 (41.8%)	75/120 (62.5%)	63/108 (58.3%)	69/125 (55.2%)

Note:. '**', $p \leq 0.01$. Non integer values are mean±SD. '[n1]', C v H, p=0.268; '[n2]', litter incidence is not available; '[n3]', exact trend test for all visceral, C, M, H, p=0.099; '[n4*]', exact trend test for dilated cerebral ventricles (C. in table) C, M, and H, p=0.033; '[n5]', Skeletal + visceral, C v H, p=0.154 (Fishers exact tests, s-rev).

Nature of abnormalities: Skeletal abnormalities: Asymmetrical sternaebrae; deformed vertebral bodies; deformed/ unossified arches; delayed ossification of 5th metacarpal. Visceral abnormalities: Dilatation of ureters and renal pelves, and dilatation of cerebral ventricles (in 1 and 4 litters in mid and high dose animals respectively); this finding is s-s (p=0.033, see 'Note, '[n4*]' above).

F1

Two males (one low dose and one high dose) died before mating. The high dose animal had hemorrhagic areas in the lungs. One mid dose and two high dose females were sacrificed before mating, as no male was allocated to them.

- Reproduction parameters

	C	L	M	H
No of littering females	4/ 4 (100%)	7/7 (100%)	6/6 (100%))	7/7 (100%)
Gestation length (days)	21.0	21.43±0.54	21.8±0.45	22±063 (n=6)[n1]
No of implants	16.75±0.96	16.14±4.18	18.17±0.98	15.3±1.03(n=6)[n2]
No of viable pups	16.25±0.96	15.86±4.06	17±1.27	14.5±2.43 (n=6)
No of dead pups	0/65	0/111	7/109 (6%)	1/87 (1.1%)
Litters with dead pups	0/4	0/7	3/6	1/6
Resorptions	2/67 (3%)	2/113	0/109	4/92 (4.34%)
Resorptions (L)	2/4	2/7	0/6	2/7

Note: Non integral values are mean±SD. '[n1]', Gestation length of one dam was not known. '[n2]', One dam had only two implants and viable fetuses, and is excluded from all measurements.

- Pups F2

	C (n=4)	L (n=7)	M (n=6)	H (n=7)
24 hour survival	100%	100%	101/102(99%);1L	86/89(96.6%); 1L
4 day survival	63/65 (96.9%); 2L	109/111(98.2 %);1L	83/102 (81.4%)**; 4L	76/89 (85.4%)*; 4L^{n1}
Wt day-1 (m)	5.92±0.01 (n=4)	6.23±0.64 (n=7)	6.33±0.53 (n=6)	6.58±0.83 (n=7)
Wt day-1 (f)	5.67±0.23 (n=4)	5.96±0.61 (n=7)	6.00±0.55 (n=6)	6.26±0.5 (n=7)
Wt day-4 (m)	7.27±0.97 (n=4)	7.6±1.99 (n=7)	7.96±1.64 (n=5)^{n2}	8.62±2.33 (n=6)
Wt day-4 (f)	7.34±0.96 (n=4)	7.39±1.67 (n=7)	7.76±1.64 (n=6)	8.29±1.79 (n=6)

Note: Values are mean±SD. '*', p≤ 0.05; '**', p ≤ 0.01. #L indicates number of litters that lost pups. '^{n1}', One litter lost all 7 pups between days 2 and 4. Survival on day 4 in mid and high dose groups was s-s reduced compared to the control group (Fishers exact test, s-rev). '^{n2}', in one litter all 4 male pups died.

Malformations: There were no external malformations.

Comments

- Dams F0: There were no adverse effects on fertility or any reproductive parameters at any dose. The NOAED for this segment of the study is, therefore, 1 mg/kg/day. Estimated C_{max} and AUC at this dose would be ≈ 50 ng/ml and 200 ng*h/ml (C_{max} by extrapolation from toxicokinetics on p 53; AUC by extrapolation from toxicokinetics on p 40).
- F1 (fetuses): There was an increased litter incidence (s-ns) of dilated cerebral ventricles in high dose fetuses (lack of statistical significance may be due to a small sample size), and s-s increased fetal incidence of delayed ossification of metacarpals in high and mid dose fetuses. F2 (pups): The cause of excessive mortality in one litter each of mid and high dose groups is stated by the sponsor as probably due to hypogalactia in one female each in these groups. It is difficult to see how this can be considered non-treatment related as the sponsor does. A theoretical explanation may be an adverse effect in utero on the F1 dams. The NOAED for F1 fetuses and F2 pups is, therefore 0.05 mg/kg/day. Estimated C_{max} and AUC at this dose would be ≈ 2.5 ng/ml and 10 ng*h/ml.

Fetotoxicity Study in Rat (segment II) ([redacted]xCOBS-VAF-CD(SD)BR; protocol 88152; study site, sponsor's labs in France).

20 inseminated female rats/group; three treatment and one control (C) group; treatment groups L, M, and H received 0.5, 1, and 2 mg/kg/day dofetilide respectively (by gavage); control group received equal volume/kg of vehicle; treatment was given on days 6-15 post-insemination (p.i.). A satellite group of 5 inseminated females received 2 mg/kg /day dofetilide on days 6-15, and were used for toxicokinetics. Hysterectomies were done on day-20 p.i.; all fetuses were examined for external and buccal abnormalities; half of each litter was examined for visceral abnormalities, and the other half for skeletal abnormalities. Doses in this study were selected based on a preliminary study in which complete resorptions occurred at 5 mg/kg/day, and the mean number of viable fetuses was decreased at 2.5 mg/kg/day.

Results

Dams

- Clinical signs & mortality: There were no abnormal signs or mortality in any group.
- Body wts: There were no differences between body wts of different groups up to day-12. Body wts (mean±sd) from day 12-20 are shown below.

	Day 12	Day 16	Day 18	Day 20
Control (n=19)	285.8±10.57	313.2±11.34	339.9±12.00	368±13.53 (Δ 82)
Low dose (n=20)	280.01±14.76	308.6±15.17	335.2±15.85	364.3±17.02
Mid Dose (n=20)	283.3±14.4	311.0±16.74)	335.8±18.75	361.8±21.47
High Dose (n=20)	286.3±15.89	311.7±18.13	332.4±21.33	352.4±28.48*, ↓4%; (Δ66; ↓20%))

Note: '*', p=0.036 (t-test, s-rev).

- Reproductive parameters are shown in the table below.

	C (n=19)	L (n=20)	M (n=20)	H (n=20)
Viable fetuses	14.58±1.57	14.45±1.76	13.95±3.1	11.4±3.84**
Post implantation loss	14/291 (4.8%)	18/307 (5.9%)	20/299 (6.7%)	72/300 (24%)***
Post implantation loss, L	10/19 (52.6%),	9/20 (45%),	10/20 (50%)	18/20 (90%)*

Note: '*', p≤0.05; '**', p≤0.01; '***', p≤0.001. S-s of post implantation loss was tested, using Fishers' exact test , and that of mean number of viable fetuses, using t-test (s-rev).

Fetuses

Table below shows fetal wts and litter incidences of various abnormalities. Numbers within ( ) are fetal incidences within each litter. Litter incidences of delayed ossification are not in the submission.

	C (n=19)	L (n=20)	M (n=20)	H (n=20)
Fetal wt (gm; m)	3.51±0.26	3.59±0.25	3.52±0.26	2.85±0.31***
Fetal wt (gm; f)	3.4±0.22	3.39±0.32	3.35±0.3	2.69±0.29***
External abnormalities[n1]	0/19	1/20	1/20	8/20**
Umbilical hernia		1 (1)		
Astomia			1 (1)	
Cleft palate				6** (1,1,1,4,1,4)
Syndactyly				1 (2)
Adactyly				2 (1;1)
Coelosomia				1 (1)
Protruding tongue				1 (1)
Tail agenesis				1 (1)
Deformed skull				1 (1)
Skeletal abnormalities[n1]	17/19	12/20	19/20	20/20
Deformed vertebrae	13/19	10/20	16/20	19/20*
Rudimentary/wavy rib/ribs	7/19	3/20	6/20	1/20
Asymmetrical sternaebrae	3/19	5/20	1/20	13/20**
Adactyly/absent metacarpals	0/19	0/20	0/20	3/20[n2]
Syndactyly	0/19	0/20	0/20	1/20[n2]
Pelvic bone/s absent	0/19	0/20	0/20	1/20
Visceral abnormalities				
Dilatation of cerebral ventricles	2/19; 4/138	2/20; 5/145	3/20; 3/139	14/20***; 34/115***
Atrophy of thyroid	0	0	0	1/20; 1/115
Levocardia[n3]	0	0	0	7/20**; 7/115
Hydroureters & hydronephroses	0	0	4/20; 4/139	6/20*; 7/115
Thinning of left diaphragm	0	0	0	1/20; 2/115

Note: '*', p≤0.05; '**', p≤0.01; '***', p≤0.001 (all s-rev). '[n1]', some litters had more than one type of abnormality. For visceral abnormalities, incidences are listed as 'L; F'. '[n2]', in one litter, one fetus had adactyly and another, syndactyly. '[n3]', Normal position of the heart, but transposition of other viscera.

Delayed ossification of skull & vertebrae, and non-ossification of 5th metacarpus and pubic bones occurred in all groups. However, litter incidences of these findings are not in the submission. The sponsor states that the incidence (probably fetal) of non-ossification of 5th metacarpus was s-s increased in mid and high dose groups ($p<0.01$), and incidences of marked delay in ossification of vertebrae and skull, and non ossification of pubic bones were s-s ($p<0.001$) increased in the high dose group.

Toxicokinetics

(For toxicokinetics, blood was sampled at one, two, and three hours post dose; dams were then killed and dofetilide concentrations in amniotic fluid and fetal homogenates were determined.)

Dams: C_{max}, 101±1.85 ng/ml (mean±SE; n=5); t_{max}, 1-2 hours. *Amniotic fluid:* 30±3 ng/ml; *fetal homogenates*: 43± 32 ng/gm wet wt .

Comments

Dams: There was no treatment related maternal toxicity. ≈ 4% lower mean body wt on day 20 in the high dose group could have been due to smaller litter size and lower mean fetal wts. Fetuses: *At the high dose* , there was embryolethality, reduced fetal wt, and increased incidences of external, skeletal, and visceral abnormalities. According to the sponsor, non ossification/marked delay in ossification of various bones (see above) was s-s increased in mid and high dose groups. 0.5 mg/kg/day was thus the NOAED for fetuses. Estimated C_{max} and AUC at this dose are ≈ 6 times and 1.3 times respectively the maximum likely parameters in man (AUC is taken from six month gavage study in the rat).

Peri and Post Natal Development Study in the Rat ([redacted]COBS-VAF-CD(SD)BR; protocol, 89115; study site, sponsor's labs in France).

20 inseminated rats/group; 3 treatment groups and one control group (C); treatment groups L, M, and H received 0.05, 0.25, and 1 mg/kg/day dofetilide respectively (by gavage) from day-15 p.i. to day-20 post partum (pp); control group received vehicle.

Results

Dams

- Clinical signs: There were no abnormal clinical signs in any group.
- Body wt: In the high dose group, body wt was 2-4% lower than in Control group from day 7-21 PP, but the decrease was s-s only on one occasion.
- Reproduction parameters are shown below.

	C (n=20)	L (n=20)	M (n=20)	H (n=19)
Length of gestation (days)	21.1±0.31	21.2±0.41	21.3±0.44	21.2±0.42
Viable pups at birth	304/305 (99.7%)	308/310 (99.4%)	315/318 (99.1%)	284/285 (99.6%)
Viable pups/litter	15.2±1.7	15.4±2.2	15.8±2.4	14.9±3.5
Litters with dead pups	1/20	2/20	3/20	1/19
Loss in-utero	13/318 (4%)	20/330 (6.1%)	11/329 (3.3%)	19/304 (6.3%)
Litters with in-utero loss	10/20	10/20	9/20	9/19

Pups

Table below shows various pup parameters.

	C (n=20)	L (n=20)	M (n=20)	H (n=19)
24 hour survival	100%	100%	100%	100%
4 day survival **Litters with pup deaths**	299/304 (98.4%) 3/20	100%	314/315 (99.7%) 1/20	100%
4-21 day survival **Litters with pup deaths**	291/299 (97%) 2/20 (4/20)[n1]	300/308 (97.4%) 6/20	304/314 (96.8%) 7/20	276/284 (97.2%) 4/19
wt day-1 (m) (g)	6.43±0.61	6.59±0.57	6.7±0.6	6.57±0.789
wt day-1 (f) (g)	6.11±0.54	6.32±0.5	6.24±0.61	6.18±0.77
wt day-4 (m) (g)	9.05±0.94	9.33±1.03	9.28±1.18	9.51±1.52
wt day-4 (f) (g)	8.62±0.95	8.97±1.04	8.61±1.12	8.97±1.59

Pup parameters (Continued from previous page)

	C (n=20)	L (n=20)	M (n=20)	H (n=19)
wt day-21 (m) (g)	38.5±2.91	38.2±5.63	37.37±7.00	38.69±7.64
wt day-21 (f) (g)	36.71.43±3.38	36.62≤5.38	34.93±6.62	37.43±8.09
Righting reflex present[n2]	245/295 (83.1%)	275/305 (90.2%)	267/308 (86.7%)	254/283 (89.8%)
Grasping reflex present[n2]	265/295 (89.8%)	258/305(84.6%)*	239/308 (77.6%)***	228/283(80.6%)***
Incisors present[n2]	238/292 (81.5%)	217/301 (72.1%)**	248/305 (81.3%)	239/280 (85.4%)
Palpebral fissures open[n2]	154/292 (52.7%)	2028301 (67.1%)	168/304 (55.3%)	149/279 (53.4%)

Note: '[n1]', Between days 1 and 21, pups in 4 control litters died; of the two litters that lost pups between days 4 and 21, one had also lost pups between days 1 and 4. '[n2]', Righting reflex and grasping reflex were tested on day 6; presence of incisors was checked on day 11, and opening of palpebral fissures was observed on day 15.

Comments: Number of fetuses in which grasping reflex was present on the test day was s-s lower in all treatment groups (Chisqr test, pair wise, s-rev), and the trend for decrease in proportions positive for the test was s-s (One sided chisqr trend, s-rev). A s-s lower number of pups in the low dose group had incisors present on the day tested, but this finding is not dose related.

Discussion: There was no treatment related adverse effect on any of the reproduction parameters. Except for a s-s decrease in the proportion of pups with positive grasping reflex in all treated groups, there were no dose related adverse effects on any pup parameters. The segment-I study did not show any adverse effect on development, even a numerical s-ns delay in development. Moreover, the sponsor has presented data from control groups from 3 other studies, and the lowest % of pups that had a positive grasping reflex was 73.4%. Therefore, this may be a false positive result in the present study. 1 mg/kg/day, therefore is the NOAED. At this dose, mean C_{max} and AUC are ≈ 13 and 2.7 times the respective maximum likely human parameters.

Fetotoxicity Study in Mouse ([redacted]COBS-VAF-CD1(ICR)BR; study site, sponsor's labs in France; Protocol # 88154).

20 inseminated females/group; one control (C) and 3 treatment groups; treatment groups L, M, and H received 0.5, 2, and 5 mg/kg/day dofetilide respectively from days 6-13 post insemination by gavage; control group received vehicle. Hysterectomy was done on day 18 p.i. Rest of the methodology was the same as in the rat study. Doses in this study were selected based on a preliminary study in which 0.5, 2, and 10 mg/kg/day doses were tested. 10 mg/kg/day in that study caused complete resorptions.

Results

Dams

- There were no treatment related clinical signs or deaths.
- Body wts: Body wt of high dose dams is not given, as there were total litter resorptions in all 16 pregnant dams in this group. Mean wt of dams in mid dose group was slightly lower than that of control group on days 14 and 18 (lower by 1.5% and 4.7% respectively), but the differences were s-ns (s-rev).
- Reproduction parameters are shown in the table below.

	C (n=15)	L (n=13)	M (n=14)	H (n=16)
Viable fetuses (mean±SD)	11.13±4.05	11.08±3.57	9.14±3.72	0
Post implantation loss	19/186 (10.2%)	13/157 (8.2%)	55/183 (30.1%)***	189/189 (100%)****
Post implantation loss (L)	9/15 (60%)	8/13 (61.5%)	14/14 (100%)**	16/16 (100%)**

Note: '*', p≤0.05;'*', p≤0.01; '***, p≤0.001; Fishers' exact tests (s-rev); '****', p≤0.0001, Chisquare test, s-rev.

Comments: Two dams in the low dose group littered before planned sacrifice and are not included in the calculations. Since early littering did not occur in the mid dose group, this finding is probably not treatment related.

Fetuses

Various parameters are shown in the table below.

	C (n=15)	L (n=13)	M (n=14)
Fetal wt (gm; m) (mean±SD)	1.45±0.13	1.44±0.11	1.33±0.11**
Fetal wt (gm; f) (mean±SD)	1.44±0.14	1.41±0.13	1.26±0.1***
External abnormalities	1/15	0/13	2/14
Cleft palate	1/15 (1)	0	0
Short fingers	0	0	1/14 (1)
Agenesis of a finger	0	0	1/14 (1)
Skeletal abnormalities: L; F	10/15; 13/83(16%)	7/13; 9/71(13%)	13/14; 52/65(80%)****
Unossified calcaneum/s: L; F	5/15; 7/83 (8.3%)	4/13; 5/71 (7%)	9/14; 25/65 (38.5%)***
Sternebral abnormalities: L; F	5/15; 6/83 (7.2%)	4/13; 4/71 (5.6%)	8/14; 15/65 (23.1%)**
Vertebral abnormalities: L	0/15	0/13	13/14****
Visceral abnormalities: L; F	2/15	0	3/14
Thoracic hemorrhage:	1/15; 1/84 (1.2%)	0	0
Thinning of diaphragm	0	0	1/14; 1/63 (1.6%)
Liver hemorrhage	0	0	1/14; 1/63 (1.6%)
Kidney agenesis[nl]	0	0	1/14; 1/63 (1.6%)
Testes agenesis	1/15;1/84 (1.2%)	0	0
Testicular atrophy	0	0	1/14; 1/63 (1.6%)

Note: 'L'is litter; 'F' is fetal. '*', p≤0.05; '**', p≤0.01; '***', p≤0.001; '****', p≤0.0001.(t-test for continuos variables; Fishers' exact test for %s, s-rev). '[nl]', sponsor's listing of abnormalities by litters does not mention agenesis of kidney; therefore, it is not possible to determine whether 3 or 4 litters in the mid dose group had visceral abnormalities.

Vertebral abnormalities were of several types: unossified, divided, rudimentary, fused, scoliosis (when more than one contiguous vertebra was affected), or deformed in other ways. *Comments:* Litter incidence of vertebral abnormalities is highly s-s increased in the mid dose group. Visceral abnormalities are probably not treatment related; they seem to be isolated random occurrences.

Toxicokinetics: A satellite group of 10 inseminated females was dosed with 5 mg/kg/day dofetilide from post insemination days 6-13. On day 13, plasma dofetilide levels were determined at one hour post dose and 3 hour post dose. None of these females were pregnant. Plasma dofetilide levels were:

One hour (n=5)	3 hours (n=5)
246±37 ng/ml	55±10 ng/ml

t ½, estimated from 1 and 3 hour mean values, is 0.93 hours. Using this value of t ½, plasma levels would be above detection limit of 10 ng/ml for ≈ 5 hours. Estimated AUC would be 467 ng*h/ml.

Discussion: There was no maternal toxicity at any of the doses tested. 5 mg/kg/day killed all embryos in all dams. 2 mg/kg/day was embryolethal and was associated with s-s increases in the following skeletal abnormalities: a) Vertebral abnormalities. b) Litter incidences of unossified calcaneum and sternebral abnormalities were increased but were s-ns; but the fetal incidences were s-s. Estimated C_{max} and AUC at this dose would be ≈ 25 and 2.5 times, respectively, the maximum likely human parameters. The fetal NOAED is 0.5 mg/kg/day. At this dose, estimated C_{max} and AUC would be ≈ 6 and 0.6 times, respectively the maximum likely human values (*Note:* C_{max} and AUC at different doses in the mouse are estimated, assuming linear pharmacokinetics).

§5 : Genotoxicity & Clastogenicity

Ames test (Study # 95-68-82; study site, sponsor's labs in Japan).

Salmonella typhimurium strains TA 1535, TA 1537, TA 98, and TA 100, and E. Coli strain WP2 uvra were used for testing the mutagenic potential of dofetilide. The bacterial strains were tested in the presence and absence of a metabolic activating system (S9 fraction prepared from livers of male SD rats after 4 i/p injections of phenobarbital and one injection of 5, 6 brenzoflavone). Appropriate negative and positive controls were used. Two tests were conducted, and duplicate plates were prepared for each test condition in each test. The sponsor's criterion for mutagenicity is doubling of the negative control mutant frequency; this seems reasonable.

Results: Table below shows the numbers of revertant colonies (average of counts from the two plates) for each test condition in the two tests (n1, n2)

Concentrations (μg/plate)	TA 1535	TA 1537	TA 98	TA 100	WP2 uvra
Without S9					
Neg Control (DMSO)	**10, 16**	**9, 8**	**22, 20**	**87, 92**	**19, 18**
9AA (80)		**1412, 1067**			
ENNG (5, 3, 2)[n1]	**276, 275,**			**568, 666**	**281, 185**
4NQO (0.2)			**153, 176**		
Dofetilide (1, 39.1)	11, 18	7, 7	19, 19	72, 88	21, 21
Dofetilide (5, 78.1)	15, 15	7, 6	18, 17	76, 86	14, 22
Dofetilide (10, 56)	14, 11	7, 6	21, 22	74, 102	17, 17
Dofetilide (50, 313)	12, 10	8, 6	19, 15	69, 96	16, 17
Dofetilide (100, 625)	12, 13	7, 8	23, 22	73, 90	21, 13
Dofetilide (500, 1250)	13, 15	7, 7	26, 22	61, 96	22, 15
Dofetilide (1000, 2500)	11, 15	9, 6	29, 19	80, 100	20, 16
Dofetilide (5000)	10, 12	5, 7	23, 19	78, 94	19, 17
With S9					
Neg Control (DMSO)	**13, 12**	**13, 9**	**40, 31**	**93, 92**	**21, 27**
2AA (2,2,0.5,1,10)[n1]	**324, 345**	**254, 296**	**401, 459**	**798, 1150**	**403, 370**
Dofetilide (1, 39.1)	112, 2	16, 7	26, 20	87, 93	32, 21
Dofetilide (5, 78.1)	15, 16	14, 5	38, 25	83, 99	23, 21
Dofetilide (10, 156)	15, 12	12, 6	34, 28	83, 99	22, 25
Dofetilide (50, 313)	16, 13	11, 8	35, 29	81, 92	22, 16
Dofetilide (100, 625)	12, 10	9, 5	31, 30	78, 101	19, 28
Dofetilide (500, 1250)	12, 14	9, 8	29, 30	91, 88	18, 18
Dofetilide (1000, 2500)	15, 14	13, 7	40, 27	84, 90	23, 15
Dofetilide (5000)	16, 15	11, 6	28, 24	93, 101	22, 16

Note: '[n1], when different concentrations of a positive control are used for different strains, the positive control concentrations are for the strains as listed from left to right. For each strain and condition, the first value is for test #1. Different concentrations of dofetilide were used in the two tests, but the upper limit was 5mg/plate in both.

Comments: Dofetilide was not mutagenic to the 5 bacterial strains tested either in the presence or absence of S9.

Mammalian Cell Gene Mutation Assay (Mouse Lymphoma L5178Y, TK +/- cells) (Study # 87-642-01; study site, sponsor's labs in Groton, Connecticut).

The cells, suspended in culture medium with and without S9 (liver S9 fraction from untreated male CD rats was used for metabolic activation) were incubated at 37°C for 3 hours in the presence of different test substances; the cells were then washed with culture medium and incubated for 48 hours for mutant expression. Test substances were different concentrations of dofetilide, and positive and negative controls; the cultures were then plated with and without 4 μg/ml trifluorothymidine (for mutant selection, and for viability determination respectively), and incubated for 7-12 days at 37°C.

Results: Table below shows growth, cloning efficiency (CE) and mutant frequency in different test conditions.

Test substance	Concentration (• g/ml)	Growth (% of control)		Absolute CE (colonies/plate) ?[nl]		Mutant Frequency (per 10^6 cells)	
		-S9	+S9	-S9	+S9	-S9	+S9
Control-1		100	100	107	121	11	12
Control-2		100	100	112 (110)	115 (118)	**13**	**18**
Dofetilide	1104	0	--	--	--	--	--
	920	1	**14**	16 (14.5%)	**89 (75%)**	25	**17**
	767	**20**	31	**94 (85.5%)**	106 (89.8%)	**13**	17
	639	45	49	100 (90.9%)	104 (88%)	18	17
	532	41	59	102 (92.7%)	105 (89%)	14	11
	444	80	69	117 (106%)	118 (100%)	17	16
	370	75	69	99 (90%)	112 (94.9%)	17	8
	308	79	76	121 (110%)	112 (94.9%)	11	13
EMS (for –S9)	621	**37**		**72 (65.5%)**		**478**	
	62	**102**		**108 (98.2%)**		**57**	
3MCA(for +S9)	5.37		**33**		**113 (95.8%)**		**89**
	2.69		**56**		**101 (85.6%)**		**83**

Note: '[nl], the sponsor has labeled this column as %, which obviously is wrong. These values must be number of colonies/plate. Taking the mean of the two control values (number within ( ) in the control-2 row) as 100%, I have calculated the CE as % of control, and these %s are shown within ( ) after each colony count.. EMS is ethyl methane sulphonate; 3 MCA is 3-methyl cholanthrene. Values for the highest usable dofetilide concentrations, for the positive controls, and the higher of the two values for mutant frequencies for negative controls are highlighted in bold font.

Discussion

The study is badly presented, and has the following flaws: a) There is no mention of number of plates/test condition for mutant growth; therefore, one does not know what the single values for mutant frequencies in each test condition represent (values from single plates (inappropriately conducted test), or mean values from an unknown number of plates). b) The criteria for positive and negative results are not provided. c) The test must be repeated at least once to confirm the results, but the sponsor has provided results from only one test. d) Usually S9 fraction for metabolic activation prepared from livers of aroclor induced rats is used. The sponsor has used S9 from non-induced rat livers, and has not provided any rationale for doing so.

For this test, the highest concentration of the test substance should be such that no more than 90% of cells are killed, and CE at the time of plating for mutation should not be low. Based on these criteria, 920 μg/ml dofetilide in the presence of metabolic activation, and 767 μg/ml in the absence of metabolic activation are the highest usable concentrations (CE at these concentrations was 75% and 85% respectively of the control value). Mutant frequencies at these concentrations are not greater than the higher of the two control values. Assuming that mutant frequencies are means of some number of plates, the results of this test show dofetilide to lack mutagenic potential with or without metabolic activation.

Clastogenicity Test Using Cultured Human Lymphocytes (Study # 87-642-01; study site, sponsor's labs in Groton, Connecticut).

2-4 cultures were used for each test condition; test substances were several concentrations of dofetilide up to 100 μg/ml, and negative and positive controls. Tests were done in the absence and presence of S9 fraction from rat liver; positive control in the absence of metabolic activation was mitomycin-C 0.05 μg/ml, and in the presence of metabolic activation, cyclophosphamide 300 μg/ml. (*Note:* There is no mention as to whether S9 fraction was obtained from induced or non-induced rats.) For the test with no metabolic activation, the cells were incubated with various test substances for 24 hours at 37°C, with colecemid 0.02 μg/ml added during the final 3 hours of incubation. For metabolic activation studies, cells were incubated with various test substances in the presence of S9 from one hour, washed, and incubated for further 23 hours, with colcemid added for the final 3 hours of incubation. Slides were then prepared for examination for chromosomal abnormalities; 100 metaphase figures were analyzed for each test condition, and frequency of mitosis was determined from examination of 1000 cells on each slide.

Results are shown in the tables below.

Without Metabolic Activation

Test substance	No. Cells	Chromatid Breaks	Chromosome Breaks	Rearrange-ments	Multiple Breaks	Abnormal Cells %	Mitotic Index %
Negative Control	100	0	0	0	0	0	9.4
	100	0	0	0	0	0	13.0
	100	5	0	0	0	3.0 [nl]	7.0
	100	2	0	0	0	2.0	5.2
Pooled	400	7	0	0	0	**1.2**	**8.8**
Mitomycin 0.05 μg/ml	50	27	5	12	2	44.0[nl]	6.1
	50	16	8	17	1	46.0[nl]	6.3
	50	14	8	6	0	30.0[nl]	2.8
	50	8	8	10	1	32.0[nl]	3.7
Pooled	200	65	29	47	4	**38.0[nl]*****	**4.7**
Dofetilide 75 μg/ml	100	1	2	0	0	3.0	12.2
	100	0	1	0	0	1.0	7.6
Pooled	200	1	3	0	0	2.0	9.9
Dofetilide 100 μg/ml	100	2	1	0	0	3.0	12.9
	100	2	1	0	0	3.0	9.0
Pooled	200	4	2	0	0	3.0	10.9
Dofetilide 200 μg/ml	100	100	1	0	0	1.0	7.9
	100	100	1	0	0	1.0	9.8
	100	100	3	0	0	3.0	3.5
	100	100	0	0	0	0.0	3.4
Pooled	400	400	5	0	0	1.2	6.1
Dofetilide 225 μg/ml	100	100	2	0	0	2	1.7
	100	100	0	0	0	0	1.7
Pooled	200	200	2	0	0	**1.0**	**1.7**

Note: Concentrations of dofetilide in the range 250-1000 μg/ml inhibited mitosis completely. '[nl]', some cells had more than one type of chromosomal abnormality. % of abnormal cells in this case is < than the sum of cells with different types of abnormalities. '***', $p < 0.001$ (Fishers' exact test, s-rev)

With Metabolic Activation

Test substance	No Cells	Chromatid Breaks	Chromosome Breaks	Rearrangements	Multiple Breaks	Abnormal Cells %	Mitotic Index %
Negative Control	100	0	0	0	0	0.0	11.5
	100	0	0	0	0	0.0	12.6
Pooled	200	0	0	0	0	0.0	**12.0**
Cyclophosphamide	50	12	12	10	3	36^{nl}	8.1
300 μg/ml	50	14	6	10	1	34^{nl}	10.2
Pooled	100	26	18	20	4	**35^{nl***}**	**9.1**
Dofetilide	100	1	0	0	0	1.0	7.7
100 μg/ml	100	1	0	2	0	2.0^{nl}	7.8
Pooled	200	2	0	2	0	1.5	7.7
Dofetilide	100	2	0	0	0	2.0	7.8
200 μg/ml	100	0	0	0	0	0.0	11.8
Pooled	200	2	0	0	0	1.0	9.8
Dofetilide	100	3	0	0	0	3.0	8.4
300 μg/ml	100	1	0	0	0	1.0	12.7
Pooled	200	4	0	0	0	**2.0**	**10.5**

Note: Concentrations of dofetilide ≥ 500 μg/ml are stated to have induced complete mitotic inhibition (no mitosis). '[nl]', some cells had more than one type of chromosomal abnormality. % of abnormal cells in this case is < than the sum of cells with different types of abnormalities. '[***]', $p<0.001$ (Fishers' exact test, s-rev).

Discussion

In the test without metabolic activation, the highest concentration of dofetilide used inhibited mitosis by more than 50% and; thus, met the criterion of an appropriate test. In the presence of S9, the highest concentration of dofetilide used inhibited mitosis by a very small amount and, thus, was not high enough. There was no reason for omitting dofetilide concentrations in the range 325-475 μg/ml in the test with metabolic activation.

Therefore, dofetilide was shown not to have the potential for clastogenicity in the absence of metabolic activation, but in the presence of metabolic activator, high enough concentrations of dofetilide were not used, and there is no evidence to state that in the presence of a metabolic activator, dofetilide is not a clastogen.

/S/

Pritam Gill-Kumar, M.D.

Nov. 16, 1998

Editorial revision Jan 5, 1999

cc: HFD 110/Original NDA
HFD 110/CSO
HFD 345
HFD 110/P. Gill-Kumar
HFD 110/Shaw Chen
HFD 110/C. Resnick 1-5-99

NDA # 20931

Attachment I

D-Rweden

FEB 10 1999

NDA # 20931

Addendum to Pharm/Tox Review

Studies Reviewed: Genotoxicity studies submitted under IND correspondence dt. Jan 25, '99.

Reviewer: P. Gill-Kumar, M.D.
Review dt: Feb 8, '99

Note: This submission contains two genetic toxicology studies. Both studies are stamped 'Draft'. According to Dr. C. Resnick, he had told the sponsor that they can submit the studies before the data is audited by the quality control unit of the sponsor/lab, and that the stamp 'Draft' simply indicates that the data has not been audited yet. Both studies are stated to have been conducted in accordance with the GLP regulations of the agency. In the text below, s-s and s-ns stand for statistically significant and statistically not significant respectively; s-rev stands for statistical tests done by this reviewer. Statistical results mentioned without a qualifier are tests done by the sponsor.

In-vitro Clastogenicity Test using Cultured Human Lymphocytes (Study # 98-642-02; study site, sponsor's labs in Connecticut)

The study was conducted in the presence of the metabolic activating system A study without the metabolic activating system has already been reviewed. A preliminary cytotoxicity test was conducted using several concentrations of dofetilide and exposing the cultures to for 3 hours at 37°C, followed by 21-hour incubation in fresh culture medium. In the definitive assay, two replicate cultures were used for each test condition, and 100 cells in metaphase were analyzed from each culture, with the exception of positive control (cyclophosphamide). In cultures exposed to positive control, 50 cells in each culture were analyzed.

In the preliminary cytotoxicity assay, at 500 μg/ml concentration (the highest concentration used) cell growth was reduced by 23%, but there was no reduction of mitotic index. Based on these results, 400-2600 μg/ml concentrations of dofetilide were tested in the definitive assay. Slides from cultures exposed to dofetilide concentrations 400, 749, and 1170 μg/ml were scored for chromosomal damage.

Results:

Table below shows incidences of various chromosomal abnormalities

Concentration μg/ml	Mitotic Index (%)	Polyploidy	Gaps		Other Abnormalities			No. abnormal cells[a]	p value (Fishers' exact test; one sided)
			Ct	Cs	Ct break	Cs break	B & R		
DMSO	21.6	1	1	0	1	0	0	1	
DMSO	19	0	0	0	0	0	0	0	
Dof 400	18.3	3	1	0	2	0	0	1*	0.500
Dof 400	16.7	2	1	1	2	0	0	1*	
Dof 749[P]	16.6	2	2	0	0			0	0.500
Dof 749[P]	15.5	3	3	0	2			2	
Dof 1170[P]	8.3	1	1	1	3	0	0	3	0.186
Dof 1170[P]	11.0	1	0	1	1	0	0	1	
Cyclph 10	9.9	0	8	0	18	1	3	16*	≤0.001
Cyclph 10	10.3	0	5	1	15	5	7	19*	

Note: 'Dof' is dofetilide; 'Cyclph' is cyclophosphamide; Numbers after treatment names are concentrations; 'Ct' is chromatid; 'Cs' is chromosome; 'B & R' is breaks and rejoining. '[P]', indicates presence of a precipitate. '*', some cells had more than one abnormality. '[a]', gaps and polyploidy have not been counted as abnormalities by the sponsor. Statistical tests were done on combined values for both cultures for a test condition.

Comments:

≈ 50% reduction in mitotic index at the highest drug concentration indicates that the test was conducted at appropriate drug concentrations. The numerical increase in polyploidy at 400 and 749 μg/ml dofetilide concentrations is probably not drug related, since the number of cells with polyploidy at the highest concentration is < than that at these two concentrations, and is ≈ the number in the negative control. The sponsor states that if a substantial number of polyploidal cells in cultures exposed to the drug are noted, then a more definitive polyploidy index is obtained by scoring 1000 metaphase cells/culture for polyploidy.

As can be seen from the table above, there is no s-s treatment related increase in chromosomal abnormalities in this test. Dofetilide was therefore not found to be clastogenic in this test.

In-vivo Mouse micronucleus assay (study # 98642-04; study site, sponsor's labs in Connecticut)

6 CD-1 mice/sex/group were weighed and then administered 3 daily doses of test substances. Dofetilide (500, 1000, and 2000 mg/kg/day) and the vehicle (0.5% methylcellulose) were administered by gavage, and mitomycin (positive control) 0.5 mg/kg/day was administered by i/p injection. The animals were weighed and then sacrificed, 24 hours after the last dose, and bone marrow slides were prepared from 5/sex/group. In each slide, 1000 erythrocytes were examined for determining the % of polychromatic erythrocytes (PCEs); and 2000 PCEs were examined for determining the % of micronucleated polychromatic erythrocytes (MNPs).

Results

- In high dose males, there was decreased activity. Two high dose females had to be sacrificed on day-3 as they exhibited whole body tremors, ptosis, prostration, and dehydration. Other high dose females had decreased activity.
- Table below shows the results from bone marrow slides. Values are mean±SD; all p values are from tests done by this reviewer.

Treatment	Males (n=5/group)			Females(n=5, 5, 5, 4/3, 5)		
μg/kg/day	% wt gain	% PCEs	% MNPs	% wt gain	% PCEs	% MNPs
Methylcellulose	1.2±4.7	59.5±2.2	0.10±0.08	-1±1.9	51.7±6.6	0.04±0.04
Dofetilide 500	-2.0±4.1	49.3±5.6	0.08±0.06	-2.9±5.2	45.5±4.6	0.04±0.07
Dofetilide 1000	-7.8±0.8	55.5±8.1	0.11±0.07	-6.3±2.6	48.7±4.6	0.07±0.04 p=0.135)
Dofetilide 2000	-12.0±3.6 **p<0.001**	41.9±5.6 **p<0.001**	0.12±0.08 p=0.35	-15.6±8.9 **p=0.024**	32.2±19.4 [n1] p=0.07	0.15±0.09 [n1] 0.11±0.10[n2] **p=0.045** [n1] p=0.117 [n2]
Mitomycin 0.5	2.1±2.2	51.9±11.0 p=0.102	1.38±0.40 **p<0.0001**	-0.4±3.3	47±7.9 p=0.168	1.16±0.39 **p=0.006**

Note: s-s, p values (comparisons to values in vehicle control; one tailed t-tests; s-rev,) are shown in bold and are underlined. '[n1]', in one female, only 97 (instead of 2000) PCEs are reported to have been counted for determining the % of MNPs (0/97); %MNP value for this animal is excluded, and n=3. '[n2]', value from the animal mentioned above is included, and n=4.

Comments

The highest dose induced severe clinical signs, necessitating sacrifice of 2/6 females. At this dose, wt gain was s-s reduced in both sexes, and % of PCEs was s-s reduced in high dose males, indicating bone marrow toxicity. The test therefore has been conducted using an appropriate high dose. In males, % of MNPs is not s-s different from that in negative control. In females, excluding the value in one animal in which only 97 PCEs are reported as counted for determining %MNPs (the sponsor

offers no explanation for including this value), there is a s-s increase in MNPs. At the next lower dose (1000 μg/kg/day) % of MNPs is not s-s different from that in negative control. Therefore, dofetilide at the highest non lethal dose, was not clastogenic.

Recommendations for Labeling:

Page 14 of sponsor's proposed labeling (attachment III to the original review): Under the heading of **'Carcinogenesis, Mutagenesis, Impairment of Fertility:'** the following text should replace the crossed out text marked '|' on the left side and '*I*' on the right side. "mouse bone marrow in-vivo test for clastogenicity; and human lymphocytes in-vitro test for clastogenicity."

/S/

Pritam Gill-Kumar, M.D.

Feb 8, 1999.

cc: HFD 110/Original NDA
HFD 110/CSO
HFD 345
HFD 110/P. Gill-Kumar
HFD 110/Charles Resnick

D. Roeder

JAN 22 1999

DIVISION OF CARIDO-RENAL DRUG PRODUCTS
REVIEW OF CLINICAL PHARMACOLOGY

NDA #20,931
Drug Name: Dofetilide (Tikosyn™)
Sponsor: Pfizer, Inc.
Medical reviewer: Maryann Gordon, MD
Completion date: 1-22-99

/S/ / /
MD

cc
Orig.
HFD 110
HFD 110/D Roeder/M Gordon

Pharmacodynamics

Summary

The sponsor has conducted a total of 74 clinical pharmacology studies. These studies evaluated the pharmacokinetics, pharmacodynamics, the PK/PD relationship, the bioavailability, bioequivalency, interaction with food and drugs, safety and toleration of dofetilide in normal healthy volunteers (primarily if not exclusively male) as well as in special patient populations. This review pertains only to the pharmacodynamics of dofetilide.

Of the 74 studies, 10 (115-010, 115-208, 115-217, 115-220, 115-222, 115-227, 115-237, 115-238, 115-240 and 115-243) were considered by the sponsor to not provide useful information on the pharmacological profile of dofetilide capsules and were labeled non-relevant, but the safety summaries were included. Of these 10, 5 (115-220, 115-227, 115-237, 115-238, 115-240,) evaluate several slow release preparations or the transdermal patches. None of these formulations are to be developed commercially. The results of study 115-010 were thrown out because "inexplicably high plasma dofetilide concentrations were noted in baseline plasma samples and there were many sampling-time deviations which rendered the data non-evaluable." Study 115-208 was terminated following recruitment of only 2 subjects. Study 115-217 evaluated the PK and PD of intravenous dofetilide in patients but, following the decision not to pursue the intravenous formulation of dofetilide, the results were considered to be not relevant. Study 115-222 was designed to evaluate the effects of age on dofetilide pharmacokinetics, but failed to recruit elderly subjects.

Dofetilide acts by blocking the cardiac K+ channels (predominantly Ikr) which increases cardiac action potential duration (reflected by QT prolongation) and refractoriness.

Dofetilide consistently and significantly lengthens the QT/QTc interval[1] in a dose related manner with maximum increases occurring around 2 hours after dosing and returning to baseline at the end 12 hours. There are indications that there are greater variations of QT/QTc prolongation with higher doses. Dofetilide did not increase QT dispersion. Dofetilide lowers heart rate by approximately 6 bpm, but this effect was not seen in all studies. Dofetilide has no obvious effect on the PR interval or QRS width or blood pressure.

Dofetilide prolongs monophasic action potential and increases effective refractory period in the atria, ventricles, AV node, and His-Purkinje system. Dofetilide does not have an effect on sinus node recovery time or conduction times (atrial, AV node to His, and His to ventricle). Patients with conduction abnormalities and/or sinus node dysfunction had similar results.

There is no convincing evidence that dofetilide has an effect on execise other than by its ability to keep patients in sinus rhythm. There is no convincing evidence that dofetilide has an adverse effect on cardiac function or the defibrillation threshold.

[1]Determinations of the QT interval tended to be made from lead V2; determination of the QTc interval was made using Bazett's Formula: $QTc=QT(1000/RR)^{1/2}=QT(HR/60)^{1/2}$, where RR is the time in msec between the two preceding R waves and HR is the heart rate.

1.1 QT/QTc prolongation

Five studies (115-201, 115-202, 115-203, 115-204 and 115-205) evaluated the effects of increasing doses of dofetilide on QT/QTc intervals in normal male volunteers.
-studies 115-201 and 115-202 evaluated the PK and PD of single oral doses of dofetilide,
-study 115-203 evaluated multiple oral dose regimens,
-study 115-204 evaluated single intravenous doses.

The dose range to be covered initially was 1 mcg/kg to 320 mcg/kg (70 mcg to 22400 mcg for an average 70 kg adult). Because of safety concerns, the protocols were amended to study dose ranges of 1 mcg/kg to 15 mcg/kg and then amended again to limit the maximum dose to 10 mcg/kg. Study 115-201 was terminated early because of poor recruitment.

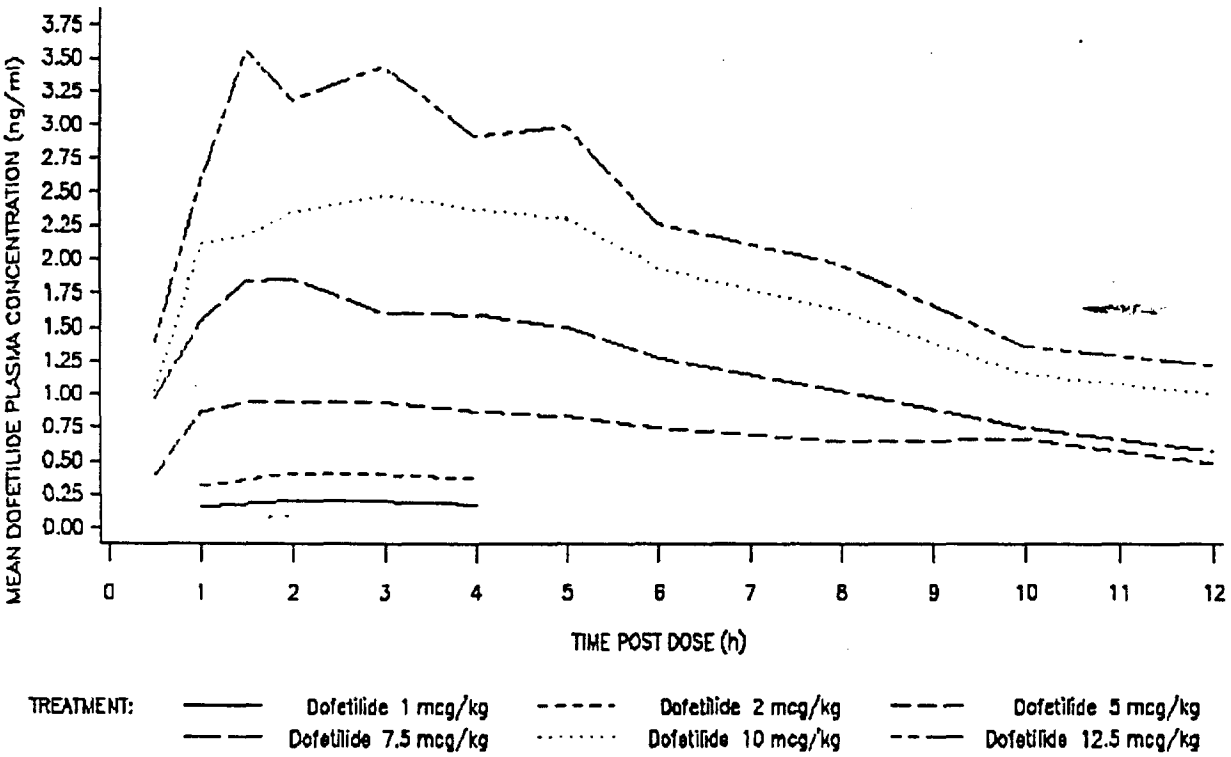
Most studies found that increasing doses of dofetilide predictably increased exposure in a linear fashion. QTc lengthening from baseline that were different from placebo were noted with oral doses starting with 100 mcg and the lengthenings increased with increasing dose. Results are discussed below.

Single dose, oral

Study 115-201 (A double-blind, randomized, placebo controlled, repeated single oral solution dose-ranging crossover study of the safety, tolerance and pharmacokinetics of dofetilide) was designed to evaluate the safety, toleration, and pharmacokinetics of escalating single oral doses of dofetilide in healthy volunteers and to establish the dose of dofetilide required to produce measurable changes in QT interval. All subjects were white males and doses used were 1 (n=4), 2 (n=3), 5 (n=8), 7.5 (n=8), 10 (n=8), and 12.5 (n=4) mcg/kg and placebo (n=12).

Plasma concentration profiles by dose for the first 12 hours are shown below.

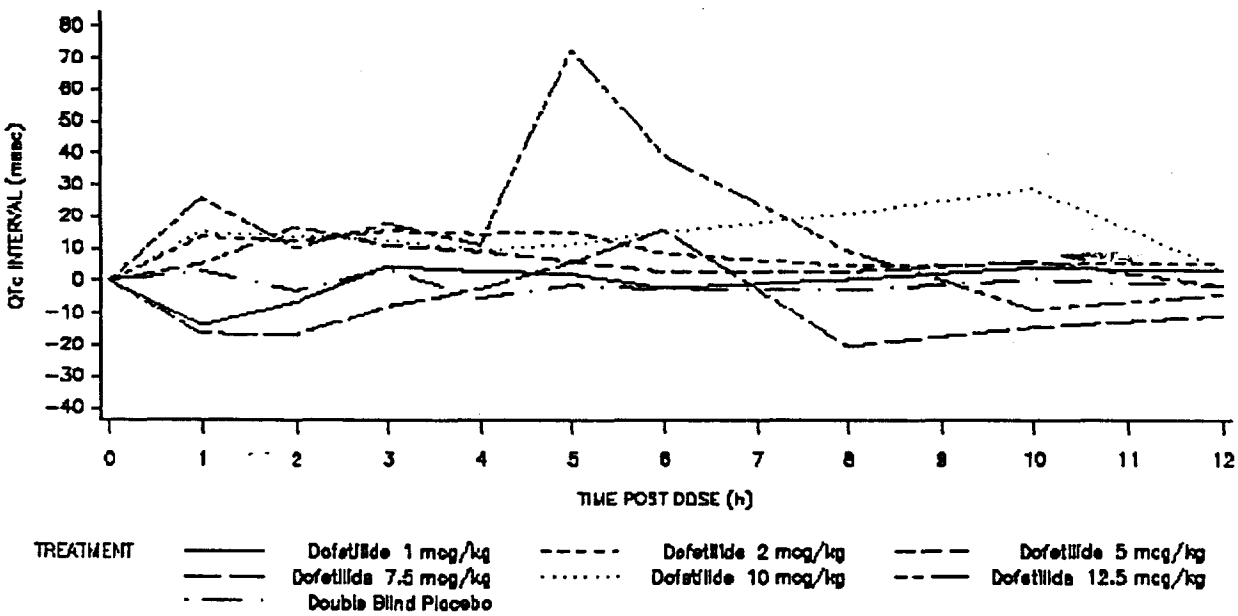
FIGURE 1.1
DOFETILIDE PROTOCOL 201
MEAN DOFETILIDE PLASMA CONCENTRATION UP TO 12 HOURS POST DOSE



Plasma concentrations were linearly related to dose with Cmax occurring about 1-3 hours after dosing.

The figure below shows the mean change from baseline profiles for the QTc intervals by dose.

FIGURE 1.4
DOFETILIDE PROTOCOL 201
QTC INTERVAL, MEAN CHANGES FROM BASELINE

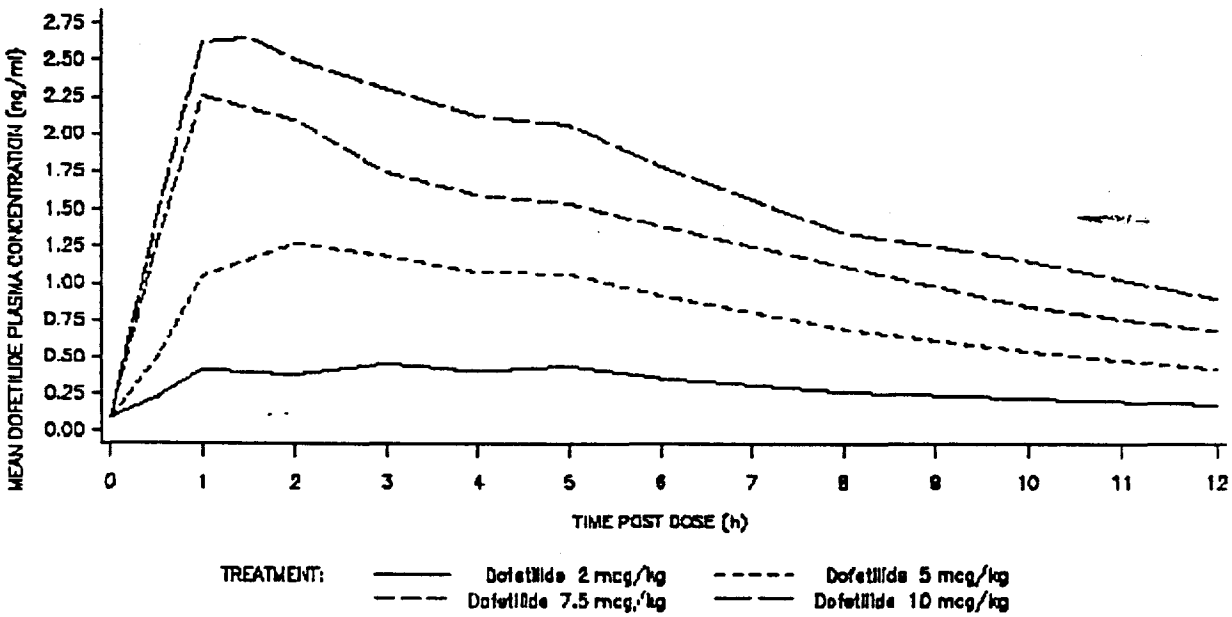


The 12.5 mcg/kg dose produced the largest change from baseline for the QTc interval with a maximum increase of 80 msec at 5 hours. By 8 hours, the QTc had returned to baseline. The second highest dose (10 mcg/kg) produced QTc increases from baseline that were smaller (15 to 30 msec) but the maximum increase occurred at 10 hours. For both doses, the maximum QTc increase did not occur at peak concentration. In this study, there was a poor correlation between plasma concentration and QTc increase which is inconsistent with results from later studies.

Study 115-202 (a single-blind, placebo-controlled, repeated single oral dose-ranging crossover study of the safety, tolerance and pharmacokinetics of dofetilide) was designed to assess the safety and toleration of dofetilide and to establish the dose required to produce measurable changes in the QT interval of the ECG. A total of 12 male subjects were randomized in equal numbers into two groups to receive placebo and 1, 2, 5, 7.5 and 10 mcg/kg dofetilide. Each dose was given on a separate day and each study day was separated by at least 7 days.

The figure below shows the mean plasma concentration by dose for the first 12 hours.

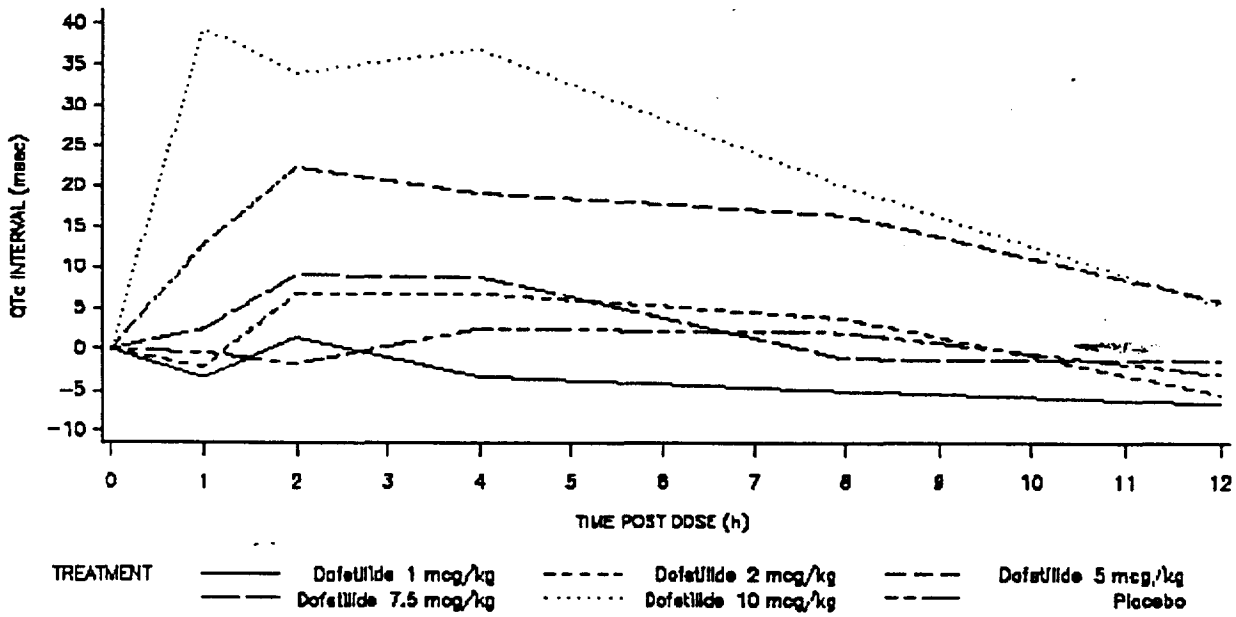
FIGURE 1.1
DOFETILIDE PROTOCOL 202
MEAN DOFETILIDE PLASMA CONCENTRATION UP TO 12 HOURS POST DOSE



There is a direct relationship between dose and plasma concentration. Cmax occurred about 1-2 hours after dose.

The mean increase from baseline for QTc interval over the 12 hour period by dose is shown below.

FIGURE 2
DOFETILIDE PROTOCOL 202
QTC INTERVAL, MEAN CHANGES FROM BASELINE



The 10 mcg/kg dose of dofetilide, at Cmax, produced a mean increase in QTc of 40 msec. The 5 mcg/kg dose produced a 22 msec increase and 7.5 mcg/kg produced about a 9 msec increase from baseline. The maximum mean change in QTc for all doses occurred between 1 and 4 hours after dosing and then decreased rapidly. The mean increase in QTC was about 10 msec for the 10 and 5 mcg/kg doses at hour 12.

Multiple dose, oral

Study 115-203 (a ten-day double-blind multiple dose study in normal male volunteers to compare the safety, toleration and pharmacokinetics of dofetilide with placebo when administered orally in solution) was designed to investigate the pharmacokinetics of four oral dose levels of dofetilide administered for 10 days. At each of the 2 centers, 4 groups of 8 males subjects (4 dofetilide and 4 placebo subjects) were studied. The doses of dofetilide were 100 mcg bid, 200 mcg qd, 200 mcg bid, and 400 mcg bid.

The table below shows the Cmax on days and 10, the ratio, and the mean QTc change from baseline at hour 3 day 1 and hour 3 day 10.

		dofetilide (mcg)			
	placebo	100 bid	200 qd	200 bid	400 bid
Cmax day 1 (ng/ml)	-	0.5	0.83	0.83	1.81
Cmax day 10 (ng/ml)		0.59	0.87	1.19	2.73
Cmax day 10/day 1	-	1.18	1.0	1.4	1.5
Mean QTc+: hour 3 day 1 (msec)	5	-11	19	18	45
Mean QTc+: hour 3 day 10 (msec)	5	1	21	17	39

+mean change from baseline with baseline defined as the last recording obtained prior to the first dose on day 1

Compared to Cmax after a single dose, the Cmax at steady state (reached about day 3) was higher for the bid doses, indicating drug accumulation. Dofetilide doses above 100 mcg increased the QTc from baseline more than placebo with the highest dose causing a 45 msec mean increase. The mean increases in QTc at hour 3 day 10 were about the same as the increases on day 1 even though the drug concentrations were higher.

Single dose, intravenous

Study 115-204 (a double-blind, randomized, placebo controlled, repeated single intravenous dose-ranging crossover study of the safety, tolerance, and pharmacokinetics of dofetilide) was designed to assess the safety of intravenous dofetilide, to examine the pharmacokinetic profile, and to establish the dose of intravenous dofetilide required to produce changes in the QT interval of the ECG. Single doses of placebo and dofetilide were given to a total of 12 male subjects over 10 minutes with the interval between doses at least 7 days. One dose of placebo was randomly inserted into the dosing scheme for each subject.

The table below shows the maximum mean change from baseline in QTc intervals (and the range), by dose.

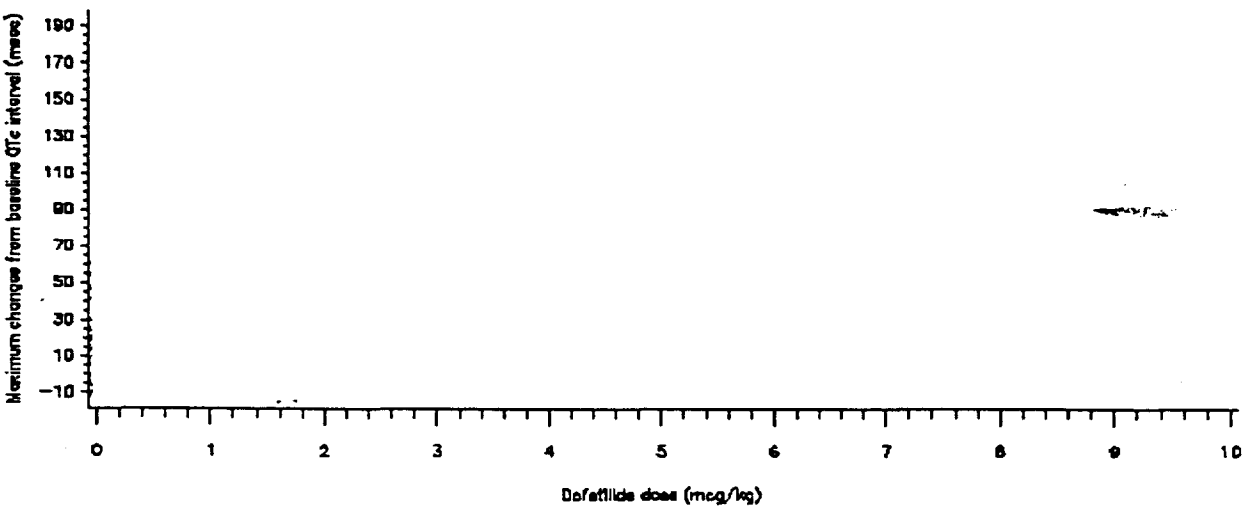
Mean maximum changes from baseline QTc (msec) ± SE and (range)

	dofetilide mcg/kg						
placebo	0.1	0.2	0.5	1	2	5	10
20±16 (-8-45)	27±16 (4-72)	26±6 (13-39)	18±4 (-4-37)	16±10 (2-47)	28±5 (12-47)	52±9 (36-73)	85±30 (42-171)

The mean maximum changes from baseline for QTc were numerically different from placebo for doses 5 mcg/kg and above. The mean change for the 10 mcg/kg dose, minus the placebo change, was 65 msec.

Individual maximum changes from baseline for the QTc interval, by dose, are shown in the figure below.

FIGURE 3.2
DOFETILIDE PROTOCOL 204
MAXIMUM CHANGE FROM BASELINE QTC VERSUS DOSE



There is a linear relationship between dofetilide doses and maximum change from baseline for the QTc. The largest increase from baseline was 170 msec.

1.2 PR interval, QRS width, heart rate, blood pressure

Study 115-202 (a single-blind placebo controlled repeated single oral dose-ranging crossover study of the safety, tolerance and pharmacokinetics of dofetilide) was designed to examine the pharmacokinetic profile of a single dose of dofetilide (see previous section). ECG parameters were also investigated and is the topic of this section. Subjects were randomized in equal numbers into two groups and received placebo and 1, 2, 5, 7.5 and 10 mcg/kg dofetilide. Each dose was given on a separate day and each study day was separated by at least 7 days.

The results of the changes in PR interval, QRS width, heart rate, and blood pressure by dose are shown in the tables on the following pages. There were no changes in the dofetilide group for any of these parameters that were distinct from the changes in the placebo group.

APPENDIX I TABLE 6
DOFETILIDE PROTOCOL 202
ECG. MEAN CHANGES FROM BASELINE

QRS WIDTH (msec)

		TIME POST DOSE (h)						
		BASE-LINE	1	2	4	8	12	24
TREATMENT								
DOFETILIDE 1 mcg/kg ORAL SOLUTION	MEAN	100.73	-2.18	-3.64	-1.88	-3.76	-3.45	-0.73
	S.E.	4.91	1.97	1.96	1.51	1.31	1.01	1.77
	N	11	11	11	11	11	11	11
DOFETILIDE 2 mcg/kg ORAL SOLUTION	MEAN	98.00	1.60	1.60	0.00	1.00	-1.40	2.80
	S.E.	4.18	1.22	1.60	0.91	1.08	1.27	1.69
	N	10	10	10	10	10	10	10
DOFETILIDE 5 mcg/kg ORAL SOLUTION	MEAN	99.60	-1.20	0.20	-0.27	-1.60	-1.60	-1.20
	S.E.	3.84	1.04	1.50	0.97	1.42	1.39	1.34
	N	10	10	10	10	10	10	10
DOFETILIDE 7.5 mcg/kg ORAL SOLUTION	MEAN	103.50	-2.50	-3.75	-1.67	-1.83	-4.00	2.50
	S.E.	5.37	1.50	2.09	1.65	1.64	2.24	4.07
	N	8	8	8	8	8	8	8
DOFETILIDE 10 mcg/kg ORAL SOLUTION	MEAN	101.50	1.50	1.50	0.25	-0.08	-1.75	3.50
	S.E.	4.53	2.92	2.23	2.10	2.62	1.44	3.33
	N	8	8	8	8	8	8	8
PLACEBO	MEAN	96.73	1.45	2.18	1.76	3.03	-0.55	-0.91
	S.E.	5.22	4.12	4.16	4.14	4.58	4.24	3.85
	N	11	11	11	11	11	11	11

D: 31MAY95 - 08JUN95
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Source: Appendix IV Table 1.1

APPENDIX I TABLE 6
DOFETILIDE PROTOCOL 202
ECG, MEAN CHANGES FROM BASELINE

PR INTERVAL (msec)

		TIME POST DOSE (h)						
		BASE-LINE	1	2	4	8	12	24
TREATMENT								
DOFETILIDE 1 mcg/kg ORAL SOLUTION	MEAN	161.09	-2.91	-1.27	-0.73	-6.00	-8.55	-2.55
	S.E.	6.56	2.91	4.53	7.03	4.54	7.05	6.93
	N	11	11	11	11	11	11	11
DOFETILIDE 2 mcg/kg ORAL SOLUTION	MEAN	162.80	-8.00	-5.60	-5.13	-8.40	-6.40	-0.40
	S.E.	4.81	6.23	6.34	5.02	3.65	5.87	2.63
	N	10	10	10	10	10	10	10
DOFETILIDE 5 mcg/kg ORAL SOLUTION	MEAN	163.60	-5.20	-4.40	-0.07	-10.53	-4.60	-7.20
	S.E.	6.81	1.58	6.87	3.66	5.94	4.57	7.75
	N	10	10	10	10	10	10	10
DOFETILIDE 7.5 mcg/kg ORAL SOLUTION	MEAN	167.50	-10.63	-5.75	1.63	-9.17	-5.75	-11.50
	S.E.	6.95	8.87	3.41	3.08	3.36	4.65	8.12
	N	8	8	8	8	8	8	8
DOFETILIDE 10 mcg/kg ORAL SOLUTION	MEAN	166.00	-3.50	-4.25	1.33	-8.67	-8.75	-3.00
	S.E.	8.25	2.67	3.57	3.06	3.92	6.50	4.39
	N	8	8	8	8	8	8	8
PLACEBO	MEAN	162.45	-5.73	-3.36	-0.76	-7.73	-4.27	-1.36
	S.E.	5.30	2.90	2.23	2.84	2.45	3.09	5.11
	N	11	11	11	11	11	11	11

D: 31MAY95 - 08JUN95
T: 08JUN95(15:49)

Source: Appendix IV Table 1.1

APPENDIX I TABLE 7
DOFETILIDE PROTOCOL 202
BLOOD PRESSURE, MEAN CHANGES FROM BASELINE

SUPINE SYSTOLIC BP (mmHg)

		TIME POST DOSE (h)							
		BASELINE	1	2	4	6	8	12	24
TREATMENT									
DOFETILIDE 1 mcg/kg ORAL SOLUTION	MEAN	107.82	0.00	-3.27	-4.00	-0.09	-2.55	0.36	5.64
	S.E.	2.70	2.78	2.15	2.52	1.72	2.19	2.14	2.00
	N	11	11	11	11	11	11	11	11
DOFETILIDE 2 mcg/kg ORAL SOLUTION	MEAN	110.60	1.00	-4.80	-5.20	2.10	-3.20	-0.40	0.00
	S.E.	2.15	2.03	2.29	1.98	3.31	3.50	2.70	2.15
	N	10	10	10	10	10	10	10	10
DOFETILIDE 5 mcg/kg ORAL SOLUTION	MEAN	109.60	-0.80	-1.40	-0.60	5.60	-1.00	5.40	3.70
	S.E.	2.54	2.97	3.04	2.91	2.99	3.45	3.07	3.60
	N	10	10	10	10	10	10	10	10
DOFETILIDE 7.5 mcg/kg ORAL SOLUTION	MEAN	112.25	-6.00	-1.00	-7.50	2.00	-4.75	-0.75	0.75
	S.E.	3.59	3.23	4.34	2.85	2.85	4.17	2.20	2.78
	N	8	8	8	8	8	8	8	8
DOFETILIDE 10 mcg/kg ORAL SOLUTION	MEAN	109.25	-1.50	0.25	-1.50	1.75	-3.00	3.00	6.50
	S.E.	3.89	4.67	3.26	3.89	1.91	4.71	2.70	4.26
	N	8	8	8	8	8	8	8	8
PLACEBO	MEAN	107.18	2.09	1.00	-1.18	4.27	0.27	3.91	3.55
	S.E.	2.30	2.47	2.24	3.14	2.98	2.74	2.46	1.15
	N	11	11	11	11	11	11	11	11

D: 31MAY95
T: 31MAY95(17:51)

Source: Appendix V Table 12

APPENDIX I TABLE 7
DOFETILIDE PROTOCOL 202
BLOOD PRESSURE. MEAN CHANGES FROM BASELINE

SUPINE DIASTOLIC BP (mmHg)

		TIME POST DOSE (h)							
		BASELINE	1	2	4	6	8	12	24
TREATMENT									
DOFETILIDE 1 mcg/kg ORAL SOLUTION	MEAN	61.27	5.09	2.91	3.45	0.73	0.09	5.64	7.64
	S.E.	2.69	1.97	1.73	2.41	2.83	2.18	2.57	2.72
	N	11	11	11	11	11	11	11	11
DOFETILIDE 2 mcg/kg ORAL SOLUTION	MEAN	65.20	-1.70	1.00	-1.00	-1.10	-2.60	2.90	0.40
	S.E.	2.31	4.65	4.71	1.77	4.60	3.35	2.14	2.32
	N	10	10	10	10	10	10	10	10
DOFETILIDE 5 mcg/kg ORAL SOLUTION	MEAN	65.80	1.00	3.00	2.00	1.20	1.40	4.00	-0.50
	S.E.	2.54	3.01	2.60	2.68	2.50	2.98	1.91	3.54
	N	10	10	10	10	10	10	10	10
DOFETILIDE 7.5 mcg/kg ORAL SOLUTION	MEAN	64.75	3.00	1.75	-0.75	2.25	0.25	0.75	2.75
	S.E.	1.73	2.54	3.15	2.90	3.10	3.35	2.51	2.70
	N	8	8	8	8	8	8	8	8
DOFETILIDE 10 mcg/kg ORAL SOLUTION	MEAN	68.25	-2.25	-1.50	3.75	-3.50	-4.75	1.75	0.75
	S.E.	4.01	3.84	4.90	3.49	2.61	4.00	3.86	3.29
	N	8	8	8	8	8	8	8	8
PLACEBO	MEAN	64.18	4.00	6.73	2.91	-2.00	-2.27	6.73	5.91
	S.E.	3.49	2.95	2.31	2.18	3.66	2.70	2.45	3.48
	N	11	11	11	11	11	11	11	11

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Source: Appendix V Table 12

APPENDIX I TABLE 7
DOFETILIDE PROTOCOL 202
BLOOD PRESSURE. MEAN CHANGES FROM BASELINE

STANDING SYSTOLIC BP (mmHg)

		TIME POST DOSE (h)							
		BASELINE	1	2	4	6	8	12	24
TREATMENT									
DOFETILIDE 1 mcg/kg ORAL SOLUTION	MEAN	110.36	-8.73	-6.00	-9.27	-7.45	-3.45	-2.00	-2.18
	S.E.	4.48	2.82	4.39	3.08	4.05	3.81	2.43	2.83
	N	11	11	11	11	11	11	11	11
DOFETILIDE 2 mcg/kg ORAL SOLUTION	MEAN	105.40	5.40	3.20	-1.20	1.20	2.30	1.70	5.20
	S.E.	4.22	3.98	4.26	4.43	5.60	5.55	3.65	3.56
	N	10	10	10	10	10	10	10	10
DOFETILIDE 5 mcg/kg ORAL SOLUTION	MEAN	116.40	-7.40	-8.90	-10.00	-8.00	-10.80	1.00	-4.40
	S.E.	3.95	2.70	3.90	3.98	4.34	4.37	3.45	2.68
	N	10	10	10	10	10	10	10	10
DOFETILIDE 7.5 mcg/kg ORAL SOLUTION	MEAN	111.00	-1.25	-2.50	-8.00	4.50	-6.75	0.00	-2.75
	S.E.	3.09	4.02	2.13	3.00	4.90	4.58	4.80	4.03
	N	8	8	8	8	8	8	8	8
DOFETILIDE 10 mcg/kg ORAL SOLUTION	MEAN	109.50	-0.50	-2.50	-2.25	-5.25	-1.25	4.00	-0.88
	S.E.	5.12	5.22	4.72	4.86	3.96	4.61	4.84	4.63
	N	8	8	8	8	8	8	8	8
PLACEBO	MEAN	107.36	-2.82	-3.73	-4.27	0.82	-3.36	1.55	5.00
	S.E.	3.61	1.79	2.29	3.27	3.19	1.85	3.17	3.14
	N	11	11	11	11	11	11	11	11

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Source: Appendix V Table 12

APPENDIX I TABLE 7
DOFETILIDE PROTOCOL 202
BLOOD PRESSURE, MEAN CHANGES FROM BASELINE

STANDING DIASTOLIC BP (mmHg)

		TIME POST DOSE (h)							
		BASELINE	1	2	4	6	8	12	24
TREATMENT									
DOFETILIDE 1 mcg/kg ORAL SOLUTION	MEAN	72.73	1.27	3.45	4.36	2.18	4.73	4.36	1.09
	S.E.	2.98	2.23	2.02	2.07	2.42	1.97	2.47	3.36
	N	11	11	11	11	11	11	11	11
DOFETILIDE 2 mcg/kg ORAL SOLUTION	MEAN	77.00	0.40	1.50	-2.40	-3.40	-2.60	-2.40	-4.20
	S.E.	2.91	2.45	3.67	3.24	3.41	4.02	2.81	3.51
	N	10	10	10	10	10	10	10	10
DOFETILIDE 5 mcg/kg ORAL SOLUTION	MEAN	77.00	-4.20	1.90	-2.80	-1.40	0.80	1.60	-4.00
	S.E.	2.48	2.16	2.67	1.98	1.40	2.11	1.86	2.23
	N	10	10	10	10	10	10	10	10
DOFETILIDE 7.5 mcg/kg ORAL SOLUTION	MEAN	77.00	-1.75	1.38	-3.75	-3.00	-4.50	1.75	-4.25
	S.E.	4.52	3.77	4.40	3.03	4.99	3.94	2.28	4.95
	N	8	8	8	8	8	8	8	8
DOFETILIDE 10 mcg/kg ORAL SOLUTION	MEAN	77.50	-0.50	-0.50	1.25	-7.63	-2.75	-1.38	-1.00
	S.E.	4.03	3.44	3.58	1.85	2.78	3.07	3.21	4.55
	N	8	8	8	8	8	8	8	8
PLACEBO	MEAN	76.27	-3.36	-2.64	1.18	-2.55	-1.00	-2.45	-1.09
	S.E.	3.56	2.63	2.58	1.91	2.34	2.69	2.55	3.16
	N	11	11	11	11	11	11	11	11

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T: 31MAY95(17:51)

Source: Appendix V Table 12

APPENDIX I TABLE 6
DOFETILIDE PROTOCOL 202
ECG, MEAN CHANGES FROM BASELINE

HEART RATE (bpm)

		TIME POST DOSE (h)						
		BASE-LINE	1	2	4	8	12	24
TREATMENT								
DOFETILIDE 1 mcg/kg ORAL SOLUTION	MEAN	59.09	-8.36	-9.73	-6.44	-2.80	-3.50	-5.91
	S.E.	2.62	1.52	1.40	1.11	1.39	1.32	1.73
	N	11	11	11	11	11	11	11
DOFETILIDE 2 mcg/kg ORAL SOLUTION	MEAN	62.90	-12.30	-9.80	-6.08	-4.23	-6.55	-4.40
	S.E.	3.46	1.65	1.90	1.70	2.64	2.49	2.18
	N	10	10	10	10	10	10	10
DOFETILIDE 5 mcg/kg ORAL SOLUTION	MEAN	61.40	-8.60	-10.75	-7.23	-4.87	-5.75	-3.70
	S.E.	2.66	2.32	1.94	2.56	2.24	2.47	2.41
	N	10	10	10	10	10	10	10
DOFETILIDE 7.5 mcg/kg ORAL SOLUTION	MEAN	61.63	-12.38	-7.75	-7.94	-6.06	-4.50	-5.25
	S.E.	3.35	1.65	1.75	1.17	0.95	1.93	1.18
	N	8	8	8	8	8	8	8
DOFETILIDE 10 mcg/kg ORAL SOLUTION	MEAN	57.50	-8.00	-7.94	-5.04	-0.85	-2.38	0.63
	S.E.	3.00	1.72	1.33	0.43	1.08	1.40	2.20
	N	8	8	8	8	8	8	8
PLACEBO	MEAN	64.82	-13.36	-13.50	-10.24	-8.67	-9.82	-8.45
	S.E.	2.53	1.69	2.17	2.25	2.16	2.13	2.41
	N	11	11	11	11	11	11	11

D: 31MAY95 - 08JUN95
T: 08JUN95(15:49)

Source: Appendix IV Table 1.1

Study 115-203 (a ten-day double-blind multiple dose study in normal male volunteers to compare the safety, toleration and pharmacokinetics of dofetilide with placebo when administered orally in solution) was designed to investigate the pharmacokinetics of four oral dose levels of dofetilide administered for 10 days. At each of the 2 centers, 4 groups of 8 males subjects (4 dofetilide and 4 placebo subjects) were studied. The doses of dofetilide were 100 mcg bid, 200 mcg qd, 200 mcg bid, and 400 mcg bid.

The results of the changes in PR interval, QRS width, heart rate and blood pressure by dose are shown in the tables on the following pages. As with the single oral dose study, dofetilide, at the doses used, did not have an obvious effect on any of these parameters.

APPENDIX I TABLE 6
DOFETILIDE PROTOCOL 203
MEAN CHANGES FROM BASELINE FOR ECG PARAMETERS ON DAYS 1 AND 10

PR INTERVAL (msec)

		DAY 1				DAY 10			
		TIME POST-DOSE (h)				TIME POST-DOSE (h)			
		BASEL-INE	3	6	12	BASEL-INE	3	6	12
TREATMENT									
Dofetilide 100 mcg BD	MEAN	160.00	-9.00	-10.56	-8.56	4.00	1.75	-2.63	4.75
	S.E.	8.93	4.69	5.60	9.83	4.35	6.00	3.45	2.13
	N	9	9	9	9	8	8	8	8
Dofetilide 200 mcg OD	MEAN	146.25	2.75	-4.75	-4.63	-2.13	0.25	-0.88	-0.88
	S.E.	7.42	3.52	1.93	2.63	2.09	3.10	2.41	3.18
	N	8	8	8	8	8	8	8	8
Dofetilide 200 mcg BD	MEAN	149.78	3.89	1.78	-0.44	13.29	2.43	-1.29	1.86
	S.E.	7.53	5.26	7.07	6.09	8.13	6.76	6.98	7.92
	N	9	9	9	9	7	7	7	7
Dofetilide 400 mcg BD	MEAN	147.00	0.25	0.13	-0.50	6.00	3.57	-0.71	-1.57
	S.E.	5.12	6.83	2.82	3.89	3.79	4.93	4.56	5.58
	N	8	8	8	8	7	7	7	7
Double Blind Placebo	MEAN	154.58	-3.70	-4.39	-4.91	0.91	-2.69	-5.69	-2.22
	S.E.	3.24	1.99	1.44	1.46	1.76	2.11	1.87	1.61
	N	33	33	33	33	32	32	32	32

D: 22NOV95
T: 22NOV95(21:44)

Source: Appendix IV Table 1.1

APPENDIX I TABLE 6
DOFETILIDE PROTOCOL 203
MEAN CHANGES FROM BASELINE FOR ECG PARAMETERS ON DAYS 1 AND 10

QRS WIDTH (msec)

		DAY 1				DAY 10			
		TIME POST-DOSE (h)				TIME POST-DOSE (h)			
		BASELINE	3	6	12	BASELINE	3	6	12
TREATMENT									
Dofetilide 100 mcg BD	MEAN	96.11	-1.33	-3.00	-1.00	-2.50	-1.25	-5.50	-2.88
	S.E.	3.36	1.55	2.62	3.63	2.88	3.63	3.43	2.63
	N	9	9	9	9	8	8	8	8
Dofetilide 200 mcg OD	MEAN	95.50	-0.38	0.13	0.00	-0.25	1.13	-1.25	1.38
	S.E.	3.40	1.10	0.95	1.32	1.28	1.54	0.67	1.40
	N	8	8	8	8	8	8	8	8
Dofetilide 200 mcg BD	MEAN	93.44	-0.56	-3.00	-0.56	-1.29	1.00	0.00	2.00
	S.E.	3.18	2.01	1.92	2.82	2.80	3.61	2.75	3.83
	N	9	9	9	9	7	7	7	7
Dofetilide 400 mcg BD	MEAN	91.25	4.38	-2.13	1.00	4.00	3.14	-2.86	-1.00
	S.E.	4.16	3.16	2.01	0.87	3.87	3.94	2.86	1.70
	N	8	8	8	8	7	7	7	7
Double Blind Placebo	MEAN	93.55	0.52	0.09	0.88	0.59	1.16	-1.00	1.34
	S.E.	1.76	0.93	0.73	1.02	0.76	0.91	0.85	0.97
	N	33	33	33	33	32	32	32	32

D: 22NOV95
T: 22NOV95(21:44)

Source: Appendix IV Table 1.1

APPENDIX I TABLE 6
DOFETILIDE PROTOCOL 203
MEAN CHANGES FROM BASELINE FOR ECG PARAMETERS ON DAYS 1 AND 10

HEART RATE (bpm)

		DAY 1				DAY 10			
		TIME POST-DOSE (h)				TIME POST-DOSE (h)			
		BASEL-INE	3	6	12	BASEL-INE	3	6	12
TREATMENT									
Dofetilide 100 mcg BD	MEAN	65.33	-6.89	-3.33	-7.22	-7.69	1.38	0.38	3.38
	S.E.	4.76	6.25	6.03	5.47	5.67	6.51	5.35	6.10
	N	9	9	9	9	8	8	8	8
Dofetilide 200 mcg OD	MEAN	62.63	-0.88	0.25	4.13	-7.06	4.13	1.63	0.63
	S.E.	4.18	6.68	5.32	5.72	6.10	6.37	5.95	6.83
	N	8	8	8	8	8	8	8	8
Dofetilide 200 mcg BD	MEAN	63.00	1.89	-0.44	5.00	-6.36	1.43	9.57	4.43
	S.E.	3.84	3.16	2.60	4.54	2.98	4.12	5.04	3.95
	N	9	9	9	9	7	7	7	7
Dofetilide 400 mcg BD	MEAN	57.38	3.50	5.75	4.50	1.14	6.00	11.14	10.43
	S.E.	2.94	2.46	3.16	2.73	3.20	2.38	4.69	3.01
	N	8	8	8	8	7	7	7	7
Double Blind Placebo	MEAN	58.61	3.09	2.12	0.88	-2.03	8.13	7.31	6.81
	S.E.	1.66	1.84	1.69	1.97	1.56	1.82	1.85	2.37
	N	33	33	33	33	32	32	32	32

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Source: Appendix IV Table 1.1

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

STANDING 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	73.72	81.83	0.17	-7.61	-5.39	-7.06	-5.50	-5.25	-4.25	-3.56	-9.50	-11.44	-4.00
	S.E.	2.75	4.55	1.48	2.33	2.07	2.38	2.46	2.69	2.35	2.31	3.62	5.71	5.20
	N	9	9	9	9	9	9	9	8	8	8	8	8	8
Dofetilide 200 mcg OD	MEAN	72.38	72.13	5.13	-6.38	-3.63	0.38	-0.31	5.44	2.75	7.25	-0.06	3.75	3.19
	S.E.	3.29	2.55	1.21	4.17	2.36	4.18	2.50	3.60	1.83	2.17	1.46	2.96	1.34
	N	8	8	8	8	8	8	8	8	8	8	8	8	8
Dofetilide 200 mcg BD	MEAN	70.33	75.06	-2.06	-2.28	-5.06	-2.17	-7.00	-0.50	-3.88	-3.25	1.81	-4.25	-0.63
	S.E.	2.91	3.57	2.66	1.52	1.58	2.40	1.09	3.65	3.90	3.32	2.52	2.38	3.28
	N	9	9	9	9	9	9	9	8	8	8	8	8	8
Dofetilide 400 mcg BD	MEAN	75.56	78.31	-5.13	-0.44	-8.06	-6.38	-0.69	-5.14	3.14	-6.07	-7.43	-2.07	-5.14
	S.E.	3.06	3.78	3.14	2.91	4.27	3.36	5.39	3.86	3.34	4.31	2.53	5.09	4.26
	N	8	8	8	8	8	8	8	7	7	7	7	7	7
Double Blind Placebo	MEAN	74.86	74.11	1.97	-0.48	-2.91	-2.97	0.59	2.35	0.12	2.85	0.65	-1.36	0.85
	S.E.	1.64	2.30	1.40	1.73	1.90	1.82	2.02	1.94	2.01	1.98	2.07	1.96	2.05
	N	33	33	32	33	33	33	33	33	33	33	33	33	33

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T: 22NOV95(21:45)

Source: Appendix V Table 12

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

STANDING 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	118.72	124.61	2.00	0.78	1.06	-9.56	1.11	-4.69	-4.19	1.31	-8.56	-3.56	2.50
	S.E.	3.13	3.62	2.94	3.36	5.67	4.44	4.74	5.85	4.44	4.98	5.88	8.88	7.37
	N	9	9	9	9	9	9	9	8	8	8	8	8	8
Dofetilide 200 mcg OD	MEAN	117.13	119.00	4.38	-3.13	-1.75	3.63	7.44	10.13	1.25	14.00	2.31	6.88	8.94
	S.E.	4.93	4.50	3.38	3.68	4.28	2.56	4.47	6.29	4.04	5.19	3.32	7.47	2.85
	N	8	8	8	8	8	8	8	8	8	8	8	8	8
Dofetilide 200 mcg BD	MEAN	115.11	121.00	-0.83	8.00	-0.17	-4.44	4.94	-1.63	-7.38	4.25	4.06	-0.25	8.31
	S.E.	4.10	3.37	2.77	3.26	2.60	4.11	2.82	6.56	5.43	4.71	5.61	6.68	5.69
	N	9	9	9	9	9	9	9	8	8	8	8	8	8
Dofetilide 400 mcg BD	MEAN	119.31	119.81	4.06	5.06	3.88	-2.94	7.06	4.29	6.71	6.00	6.57	16.93	11.79
	S.E.	5.39	3.56	5.06	3.72	6.02	5.07	5.80	2.99	4.25	4.91	5.57	4.39	4.12
	N	8	8	8	8	8	8	8	7	7	7	7	7	7
Double Blind Placebo	MEAN	123.00	121.70	-1.38	6.26	2.21	-1.20	5.67	0.85	-0.41	6.91	2.02	0.47	7.35
	S.E.	1.69	2.24	2.29	3.16	2.57	2.70	2.85	2.37	2.27	2.76	3.26	2.51	2.80
	N	33	33	32	33	33	33	33	33	33	33	33	33	33

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Source: Appendix V Table 12