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**APPLICATION NUMBER
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Medical Review(s)

N.M

Sotalol pediatric review:

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Refers to IND 3 S 185 *Original*

SEP 18 2000

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HFD-110/CSO/File
HFD-860 JGobburu/JCanal

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Summary:

This submission contains two studies that deal with the pharmacokinetics and pharmacodynamics of sotalol in neonates, infants, pre-school and school-aged children. The sponsor has previously submitted an uncontrolled database that consisted of a total of 78 patients, of which 57 had supraventricular arrhythmias at the time of treatment. In addition, several publications have also been submitted on the use of sotalol in a pediatric aged population. The number of patients included in these publications is 197 patients ranging in age from birth to 24 years. The total number of patients for which sotalol exposure is available is 334 patients. Neither the pharmacokinetic or pharmacodynamic studies reviewed in this submission, nor the pediatric database submitted with the supplement for atrial fibrillation nor the literature studies are controlled. Those enrolled frequently had arrhythmias for which sotalol has not yet been approved. None of the outcomes can, therefore, be interpreted with respect to establishing either the safety or the efficacy of sotalol in the pediatric population. Consequently, no indication for use of sotalol in children should be given.

Two studies were performed and the results of these studies form the essence of this submission. These studies allow some credible statements to be incorporated into the labeling about the kinetics of sotalol in a wide age range of pediatric patients as well as the dynamic effect of sotalol in altering heart rate and repolarization in these children. These studies served as the basis for granting pediatric exclusivity extension to sotalol.

This review was written having read the excellent biopharmaceutical review written by Dr. Joga Gobburu. This review is to a large extent in agreement with his conclusions. Labeling recommendations are appended to the end of this review.

With respect to the kinetics of sotalol, the two studies that were submitted and the kinetic results contained in these studies appear to be consistent with each other. Study 98173 was a single dose study of 30 mg/M² sotalol in neonates (age < 1 month), infants (1-24 months), preschool children (2-6 years) and school-aged children (7-12 years). A total of 33 children were enrolled. Study 98217 was a multiple dose study of 3 dose levels of sotalol 10, 30 and 70 mg/M² given Q 8 hour to neonates, infants, pre-school and school-aged children for a total of three doses at each dose level (a total of 9 doses). A total of 25 patients were enrolled. The children enrolled in these studies generally had histories of supraventricular arrhythmias.

The results of both study suggest that the peak concentration of sotalol when dosed on a per M² basis, appears to be higher in neonates than in school aged children. With respect to the single dose measurements, peak concentrations are approximately 28% higher and AUC 84% higher for neonates than for school-aged children (7-12 years old). The AUC for those in the next youngest group infants (>1-24 months old) was 24% higher than the 7-12 year old cohort.

The results from the multi-dose study are generally consistent with the single dose study. Here too, neonates, the youngest group (< 1 month) had higher peak concentrations

(2 hours post at each dose level) ranged from 36-41% higher than those of school aged children and AUCs ranging from 48-61% higher than the school aged children at the three dose levels. In comparing infants to school aged children the 2-hour post last dose level were 12-37% higher than the school aged children. AUCs for infants compared to school aged children in the multidose study, however, were essentially the same.

These two studies taken together suggest that older children can be dosed on a mg/M^2 basis with fairly predictable plasma concentrations. Neonates and infants are less comfortably dosed on this basis. Neonates clearly differ from older children, but at some age range or some parameter related to age, the kinetics of sotalol in infants approach those of school aged children. Some but not all of the deviant kinetics of neonates and infants are likely attributable to the diminished renal handling of sotalol in young children. The sponsor suggest a cut-off of 0.33 M^2 as a dividing line between those that should be dosed on a per M^2 basis and those aged children for which concentrations deviate. This reviewer agrees with Dr. Gobburu's conclusion that since renal function is not fully matured to between 1-2 years old, a cut off of 2 years seems most appropriate age cut off for reproducible concentrations can be realized when dosed on a mg/M^2 basis. Caution should, therefore, be exercised in the dosing of pediatric patients who are less than 2 years old, with judicious use of ECGs prior to increasing any dose and to steady state.

There is no empirical information as to how to dose sotalol in pediatric patients who have diminished renal function. Caution should be exercised in any dosing recommendations to such patients.

With respect to the dynamic effect of sotalol, ECG measurements were specifically captured by the multiple dose study. No ECGs were captured with the single dose study. Two parameters were analyzed at each timed ECG; R-R intervals and QT interval.

R-R intervals at rest reflect heart rate. To some extent resting heart rate is dependent on circulating catecholamines. A decrease in heart rate (increase in R-R intervals) is produced by the beta blocking effect of sotalol. Since heart rate is age dependent, any unified model for pediatric patients must correct for the different baseline resting heart rates. Dr. Gobburu modeled the % change in heart rate versus concentrations of sotalol. An Emax model was constructed (see equation 2 of this review). The maximal effect on resting heart rate was 16%. The EC50 is approximately 790 ng/ml.

Sotalol also has Vaughn-Williams Class III anti-arrhythmic activity. Dr. Gobburu modeled the corrected QT interval (QTc-Bazett's correction) versus concentration. The data was best fit by a linear model. For each 1000-ng/ml increase in concentration the QTc should increase approximately 15.8 msec (see equation 1 of this review).

The effects of sotalol at a given serum concentration appear similar but may not be equivalent to that of adults. The sum of available Dr. Gobburu analyzed the available data. Across study comparisons of results, however, are fraught with uncertainty. The best that can be said is that the concentration related dynamic effects of sotalol in children are roughly similar to those of adults.

Not reviewed by this reviewer but included in the biopharm review is a technical report on the reproducibility and stability data for the extemporaneous formulation of sotalol. The procedure for formulating a liquid preparation of sotalol is useful information and should be included within labeling.

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Study #1. Protocol 98173

Title of Study: Pharmacokinetics of Sotalol in a Pediatric Population with Ventricular and Supraventricular Tachyarrhythmias

Investigator and sites: The investigator, sites and the number enrolled/site are listed in Table 1.1

Table 1.1 Investigator, sites and number enrolled at each study site.

Center 01 Dianne Atkins, MD University of Iowa Iowa City, IA n=1	Center 02 Lee Beerman, MD Children's Hospital Pittsburgh, PA n=2	Center 03 David Chan, MD Children's Hospital Columbus, OH n=0	Center 04 Macdonald Dick, MD University of Michigan Hospital Ann Arbor, MI n=2
Center 05 Michael R. Epstein, MD Children's Hospital Cincinnati, OH n=2	Center 06 Christopher Erickson, MD Arkansas Children's Hospital Little Rock, AR n=3	Center 07 Frank A. Fish, MD Vanderbilt University Nashville, TN n=0	Center 08 Steven Fishberger, MD St. Joseph's Children's Hospital Paterson, NJ n=0
Center 09 Steven Fishberger Mount Sinai School of Medicine New York, NY n=0	Center 10 Richard Friedman Texas Children's Hospital Houston, Tx n=0	Center 12 J Edward Hulse Children's Mercy Hospital Kansas City, MO n=2	Center 13 Ronald J Kanter Duke University Medical Center Durham NC n=1
Center 14 Peter Karpawich Children's Hospital of Michigan Detroit MI N=4	Center 16 Robert Pass Columbia Presbyterian Medical Center New York, NY n=0	Center 17 Bertrand Ross Children's Hospital of the King's Daughter Norfolk, VA n=0	Center 18 J Philip Saul, MD Children's Heart Center of South Carolina Charleston, SC n=5
Center 19 Michael Shaffer, MD The Children's Hospital Denver, CO n=7	Center 20 William Scott, MD University of Texas Southwestern Medical Center Dallas, Tx n=0	Center 22 Margaret J Strieper, DO The Children's Heart Center Atlanta, GA n=0	Center 23 Ronn Tanel, MD Children's Hospital of Philadelphia Philadelphia, PA n=1
Center 24 John Friedman Children's Hospital Boston, MA n=3	Center 26 George F Van Hare, MD Stanford University School of Medicine Palo Alto, CA n=0	Center 27 Frank Zimmerman St. Louis Children's Hospital St Louis, MO n=1	Center 28 Parvin Dorostkar, MD University Hospital of Cleveland Cleveland, OH n=0
n=34			

Formulation: The formulation of sotalol was extemporaneously compounded. Five intact Betapace tablets (120 mg = 600 mg) were added to 120 ml of commercially obtained simple syrup (contained 0.1% sodium benzoate) in a six ounce amber bottle. The bottle was shaken and the tablets allowed to hydrate for > 2 hours (or overnight). The tablets are shaken intermittently until the tablets disintegrated. The formulating was completed when a dispersion the syrup contained a fine dispersion of particles. The final concentration of the formulation was 5 mg/ml.

Protocol:

Inclusion Criteria: Pediatric patients between the age of birth and twelve years suffering from VT or SVT requiring therapy were eligible to enroll. Subjects may be in normal sinus rhythm at the time of enrollment. Patients who are scheduled for ablation may be enrolled. The procedure for ablation may start after the 22-hour blood sample. For those who are to undergo ablation, Propofol cannot be used. No concomitant drugs related to the ablation procedure can be given within 8 hours prior to the 36-hour time point.

Exclusion Criteria: The protocol excluded patients who had either concomitant cardiovascular conditions or other medical conditions that preclude use of beta-blockers or would result in an ambiguous interpretation of safety. Specifically excluded are patients with:

- Other organ system malfunction
- History of asthma
- Weight < 2 Kg
- Bradycardia: age \leq 1 month < 80 BPM; age > 1-24 months < 75 BPM;
age > 2-4 years < 70 BPM; age > 4-6 < 65 BPM age > 6-12 < 60 BPM
- Systolic hypotension: age \leq 1 month < 55 mm Hg age > 1-24 months < 60 mm Hg
age 2-4 years < 80 mm Hg age > 4-6 years < 80 mm Hg > 6-12 years < 90 mm Hg
- Creatinine clearance < 80% of normal for age estimated by the formula
(0.55 x height in cm) / (serum creatinine concentration in mg/dl).
- CHF NYHA Class III-IV
- Uncorrected hypokalemia, hypomagnesemia or hypocalcemia
- Anemia
- Beta-blocker anti-arrhythmic therapy (can be enrolled after 2 half-live washout); digoxin and adenosine, however are allowed
- Medications which prolong the QT interval.
- QTc at baseline > 500 msec^{-1/2} during previous Class III anti-arrhythmic drug therapy
- If appropriate a negative pregnancy test
- IV amiodarone within 3 days.

The study proposed to enroll 20 patients per group in the following four age groups
1) neonates = < 1 month; 2) infants = > 1 month-24 months; 3) pre-school aged children > 2-< 7 years; 4) school-aged children > 7-12 years.

Each subject was to receive a single dose of 30-mg/M² body surface area. Body surface area was calculated by the formula of Mosteller:

$$BSA (M^2) = \sqrt{[Ht (cm) \times BW (Kg)]/3600}$$

Primary End Point: The primary end point of the study is pharmacokinetic measurements: The specific parameters to be measured include: C_{max}, T_{max}, AUC (0-t_{last}), t_{1/2λz}, AUC, CL/f and V/f.

Description of the protocol:

The schedule of events is shown in Table 1.2.

Table 1.2 Procedures:

Procedure	Screening	Day 1 Hour [±]										Day 2 Hour [±]			Post
		0	0.5	1	2	3	5	8	12	16	22	36			
Dosing		X													
Enter Site	X														
PK		X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG, Physical Exam, laboratory	X														X
HR/ Blood Pressure	X	X			X										X
Telemetry		X	----->								End				

Patients are not permitted to have xanthine-containing food or beverages from 48-hours prior to dosing.

Of note, no on-treatment ECGs for each patient was available for defining the effect of a single dose of sotalol on repolarization or heart rate.

Results:

A total of 34 patients enrolled into the study and received a single dose of Betapace at a dose of 30 mg/M².

Demographics: The demographics (Table 1.3) as well as the underlying cardiac diseases (Table 1.4) and previous treatments (Table 1.5) are shown:

Table 1.3 Demographics

Parameter		< 1 month	> 1-24 months	>2-<7 years	7-12 years	All Patients
Age (months)	N	2	8	6	17	33
	Mean	0.2	10.3	56.1	114.2	71.5
	Min-Max	0.2-0.2	1.6-18.3	34.1-83.1	86.6-146.2	0.2-146.2
Sex	Male	2	4	3	8	17
	Female	0	4	3	9	16
Race	Caucasian	2	5	6	14	27
	Black	0	3	0	1	4
	Hispanic	0	0	0	2	2
Height (cm)	N	2	8	6	17	33
	Mean	53.1	72.5	104.5	134	108.8
	Min-Max	52.1-54.0	52-86	92.5-123	114-164	52-164
Weight (Kg)	N	2	8	6	17	33
	Mean	3.6	8.0	17.2	31.1	21.3
	Min-Max	2.8-4.5	3.8-12.2	14.2-24.7	20.2-54.4	2.8-54.4
BSA (M ²)	N	2	8	6	17	33
	Mean	0.23	0.4	0.7	1.07	0.79
	Min-Max					
Creatinine Clearance (ml/min/1.73 M ²)	N	2	8	0	17	33
	Mean	54	106	141	136	124
	Min-Max					

Table 1.4 Baseline arrhythmias- Patients can be counted more than once.

Parameter	< 1 month	> 1-24 months	>2-<7 years	7-12 years	All Patients
Baseline Arrhythmia	PSVT (2) Other Ht Dis Structural (1)	PSVT (7) Accessory Path (5) Aflutter (1) WPW (3) Chaotic A. Tachy (1) VT (1) Cong Heart Dis (3) L Vent Dysf (1) CHF (3) Prior Ht Surgery (2) Prior Cardiovers. (3) Pharmacologic (3)	PSVT (4) Accessory Path (1) A flutter (1) WPW (2) Ectopic A Tachy (1) Cong Heart Dis (1) Prior Ht Surgery (1) Prior Cardiovers. (4) Pharmacologic (3) Paced (1) Dir Current (2) Planned Ablation (3)	PSVT (13) A-V node reentry (1) Access Path (6) A flutter (3) A Fib (1) WPW (3) VT (2) Cong Heart Dis (3) L Vent Dys (2) CHF (3) Other Str Heat Dis (2) Prior Ht Surgery (3) Prior Cardiovers. (7) Pharmacologic (5) Paced (2) Dir Current (3) Planned Ablation (10)	PSVT (26) A-V node reentry (1) Access Path (6) A flutter (5) A Fib (1) WPW (8) Ectopic A Tachy (1) Chaotic A. Tachy (1) VT (3) L Vent Dys (3) Cong Heart Dis (7) Other Struct Heat Dis (3) CHF (6) Prior Ht Surgery (6) Prior Cardiovers. (16) Pharmacologic (13) Paced (3) Dir Current (5) Planned Ablation (13)

Table 1.5 Medications

Parameter		< 1 month	> 1-24 months	>2-<7 years	7-12 years	
Medication	Baseline	2	8	4	10	
	Post Tx	1	3	1	7	
Adenosine	Baseline	2	0	1	0	0
	post-Tx	0	0	0	1	3
Amiodarone	Baseline	0	0	0	1	0
	post-Tx	0	0	0	0	0
Beta Blocker	Baseline	0	7	4	6	6
	post-Tx	0	0	0	0	0
Ca Chanel Block	Baseline	0	0	0	0	2
	post-Tx	0	0	0	0	1
Digoxin	Baseline	1	3	2	5	5
	post-Tx	1	3	0	0	3
Procainamide	Baseline	0	1	1	1	1
	post-Tx	0	0	0	0	0
Propofanone	Baseline	0	0	1	0	0
	post-Tx	0	0	0	0	0

Six of those who received sotalol had been treated with sotalol till immediately prior to the study. Since these patients previously tolerated sotalol, adverse events are less likely to be observed in that fraction of the cohort.

Outcomes:

The outcomes for these subjects are shown Table 1.6. One patient between in the 1-24 month age range had no data available.

Table 1.6 Outcomes

	< 1 month	> 1-24 months	>2-<7 years	7-12 years	Total
Received Drug	2	9	6	17	34
Discontinued prematurely	0	1	0	0	1
Withdrew Consent	0	1	0	0	0
Loss to follow-up or death	0	0	0	0	0
All bloods obtained	1	8	6	16	31

Pharmacokinetics

The concentration time effect for the various age groups is shown in Figure 1.1 and the parameters tabulated (from sponsor's page 93) as Table 1.7. The two subjects in the youngest group (< 1month) have higher concentrations (C_{max} and AUC). The concentration among those in the 1-24 month age group appears higher than the two older groups.

Figure 1.1

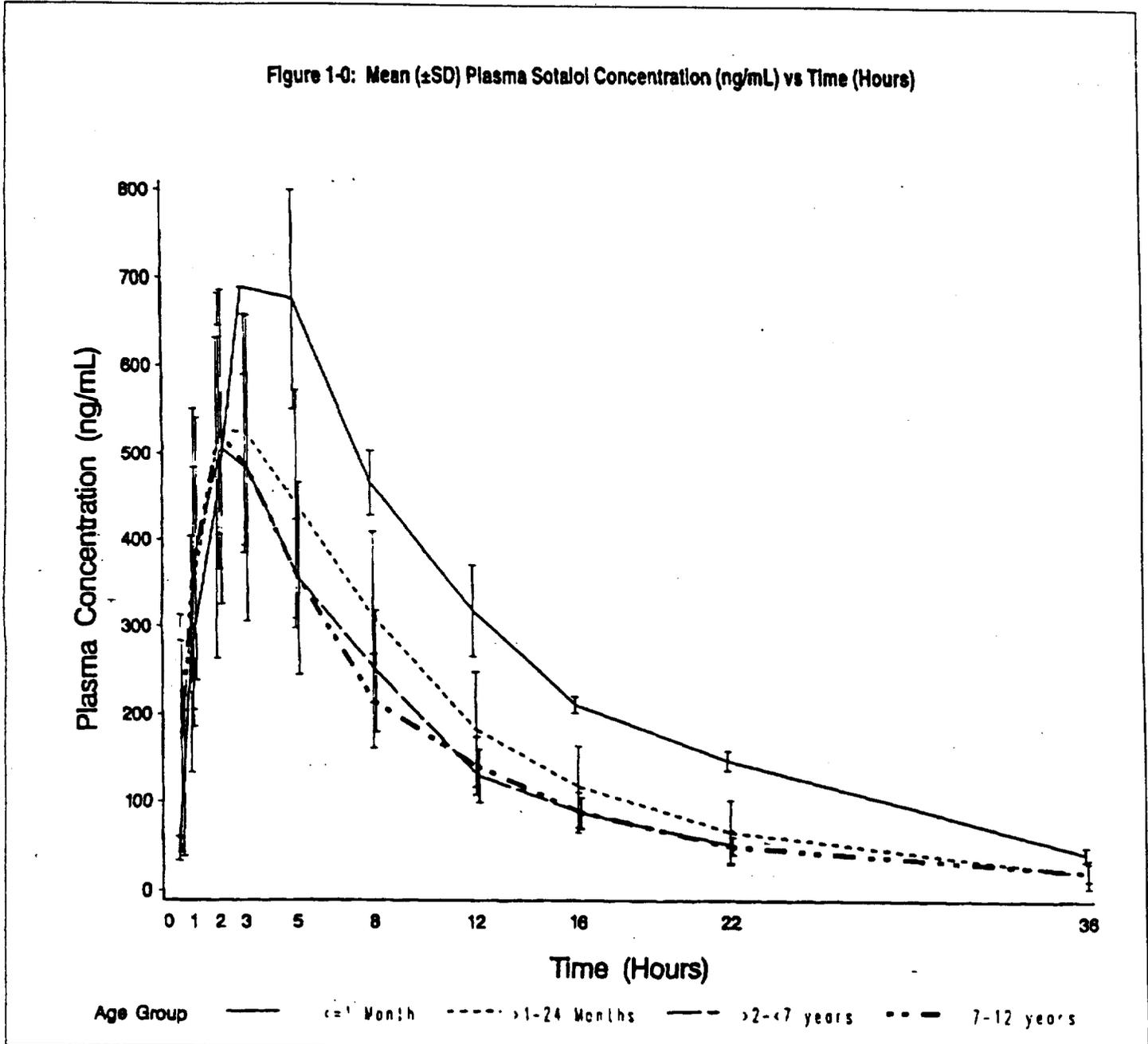


Table 1.7

Parameter		< 1 month	> 1 -24 months	> 2-<7 years	7-12 years
C _{max} (ng/ml)	N	2	8	6	17
	mean	726.21	585	528	569
	Min-Max				
T _{max} (hr)	N	2	8	6	17
	mean	4.0	2.5	2.33	2.77
	Min-Max				
AUC 0-Tlast hr*ng/ml	N	2	8	6	17
	mean	8980	5919	4919	4817
	Min-Max				
AUC 0-∞ hr*ng/ml	N	2	8	6	17
	mean	94992	6162	5220	5154
	Min-Max				
λ _z (hr ⁻¹)	N	2	8	6	17
	mean	0.08	0.1	0.08	0.08
	Min-Max				
t _{1/2λz}	N	2	8	6	17
	mean	8.4	7.37	9.11	9.22
	Min-Max				
Vλ _z /f	N	2	8	6	17
	mean	7.79	19.6	49.9	76.45
	Min-Max				
Weight (Kg)	N	2	8	6	17
	Mean	3.6	8.0	17.2	31.1
	Min-Max				
Cl/f (ml/min)	N	2	8	6	17
	mean	10.7	19.6	49.9	76.5
	Min-Max				

The two subjects in the < 1 month age group appear to have higher C_{max} and AUC as well as the lowest clearance than the other groups. For the small number of the youngest patients, the volume of distribution/unit weight was somewhat lower than the other groups (2.16 versus 2.45-3.19). In addition to youngest age groups, these two groups also have the lowest BSA and creatinine clearances.

Analysis:

The sponsor performed several linear regression analyses with the independent parameters either BSA, age or weight. The correlation is shown in Table 1.8.

Table 1.8. Analysis

	Independent Parameter								
	BSA (M ²)			Weight (kg)			Age (years)		
	Intercept	Slope	R ²	Intercept	Slope	R ²	Intercept	Slope	R ²
	mean (SE) [p-value]	mean (SE) [p-value]		mean (SE) [p-value]	mean (SE) [p-value]		Mean (SE) [p-value]	mean (SE) [p-value]	
C _{max} (ng/ml)	658 (59) [<0.001]	-106 (68) [0.127]	0.073	637 (46) [<0.001]	-2.9 (1.9) [0.1272]	0.073	620 (99) [<0.001]	-7.5 (11.4) [.518]	0.02
AUC (hr*ng/ml)	7549 (557) [<0.001]	-2376 (644) [0.0009]	0.305	6918 (457) [<0.001]	-58.4 918.3) [0.0033]	0.247	5498 (659) [<0.001]	-39.6 (76) [0.61]	0.013
λ _z (hr ⁻¹)	0.097 (0.0) [<0.001]	-0.015 (0.0) [0.14]	0.068	0.095 (0.0) [<0.001]	-0.000 (0.0) [0.104]	0.083	0.085 (0.0) [<0.001]	-0.000 (0.0) [0.771]	0.004
T _{1/2λz} (hr)	6.846 (1.1) [<0.001]	2.342 (1.3) [0.0716]	0.101	7.131 (0.8) [<0.001]	0.074 (0.0) 0.0370	0.133	7.760 (1.9) 0.001	0.174 (0.2) 0.448	0.028
Cl/f (ml/min)	-9.877 (7.2) [0.179]	99.8 (8.3) [<0.001]	0.823	11.72 (6.1) [0.062]	2.68 (0.2) [<0.0001]	0.795	23.47 (16.6) [0.17]	7.69 (1.9)	0.436
Vλ _z /f (L)	-17.4 (10.1) [0.96]	90.1 (11.7) [0.001]	0.655	-0.644 (7.4) [0.931]	2.543 (0.3) [<0.0001]	0.702	7.96 (21.5) [0.715]	7.46 (2.5) [0.0066]	0.302

Of the above, three parameters, dosing by either weight or BSA correlate best with the total data, particularly for the parameters of $V\lambda z/f$ (L) and Cl/f (ml/min) (highest R²). None of the three independent parameters, however, adequately address the results observed in the youngest children.

In young children renal function is immature and the corresponding handling of drugs that are renally excreted might be altered in the younger children. Dr. Gobburu fitted drug clearance to creatinine clearance. There was a statistically significant linear correlation between Cl/F and $CLcr$ ($p < 0.0001$; $R^2 = 0.831$).

ECGs were not evaluated to except prior to and after therapy. No correlation between dose and QTc were therefore available. Safety was monitored during the single dose by telemetry.

Heart rates: Vital signs were measured at baseline and 2 hours (approximately peak). No analysis was performed comparing the effect plasma concentration and percent change in heart rate.

Safety:

Deaths, Dropouts Discontinuations:

There were no deaths in the study. The sponsor notes that 2 patients had serious adverse events during the study. The CRFs for both patients were supplied and reviewed.

Patient #19002, a 10-year old Caucasian female patient aspirated during intubation prior to an ablation procedure. The event resulted in an additional day of hospitalization. A phone conversation between hospital staff and the patient's family, approximately 2-weeks later indicated no ongoing or additional respiratory symptoms were present.

Patient # 05002, a 6-year old Caucasian female experienced a right pleural effusion that occurred after radio-frequency ablation. This patient had a Tetralogy of Fallot repair in 1992. The effusion during this study resulted in an additional day of hospitalization.

Overall adverse events are shown in Table 1.9: Given the small study size and the small exposure to sotalol hydrochloride, the lack of excessive adverse events is not surprising.

Table 1.9 Adverse Events

	< 1 month (n=2)	> 1-24 months (n=9)	>2-<7 years (n=6)	7-12 years (n=17)	All (n=34)
≥ 1 Adverse event	0	3 (33%)	2 (33%)	11 (65%)	16 (47%)
Body as a whole		1 (11%)	0	3 (18%)	4 (12%)
Fever				1 (6%)	2 (6%)
Pain		1 (11%)	0	2 (12%)	2 (6%)
Cardiovascular system	0	0	0	2 (12%)	2 (6%)
Bradycardia				2 (12%)	2 (6%)
Digestive System	0	1 (11%)	0	6 (35%)	7 (21%)
Diarrhea		1 (11%)	0	0	1 (3%)
Nausea		0	0	6 (35%)	6 (18%)
Vomiting		0	0	6 (35%)	6 (18%)
Nervous System	0	0	0	4 (24%)	4 (12%)
Headache				4 (24%)	4 (12%)
Respiratory System	0	0	2 (33%)	1 (6%)	3 (9%)
Pleural effusion			1 (17%)	0	1 (3%)
Aspiration pneumonia			0	1 (6%)	1 (3%)
Sinusitis			1 (17%)	0	1 (3%)
Skin and Appendages	0	1 (11%)	0	0	1 (3%)
Rash		1 (11%)			1 (3%)
Special Senses	0	0	0	2 (12%)	2 (6%)
Conjunctivitis				1 (6%)	1 (3%)
Eye Pain				1 (6%)	1 (3%)

Although the study only administered a single dose and steady state effects were not reached, two patients had bradycardia as an adverse event.

Vital Signs, Physical Examination, ECGs, Laboratory

Vital signs for this group were collected at screening, baseline, 2-hours post dose and at exit. Several patients had changes in vital signs that are of note. This reviewer looked through the sponsor's tabulated data for 2 hour measurements and some measurements that appear notable in this reviewer's opinion are shown below.

Table 1.10 Vital signs of interest.

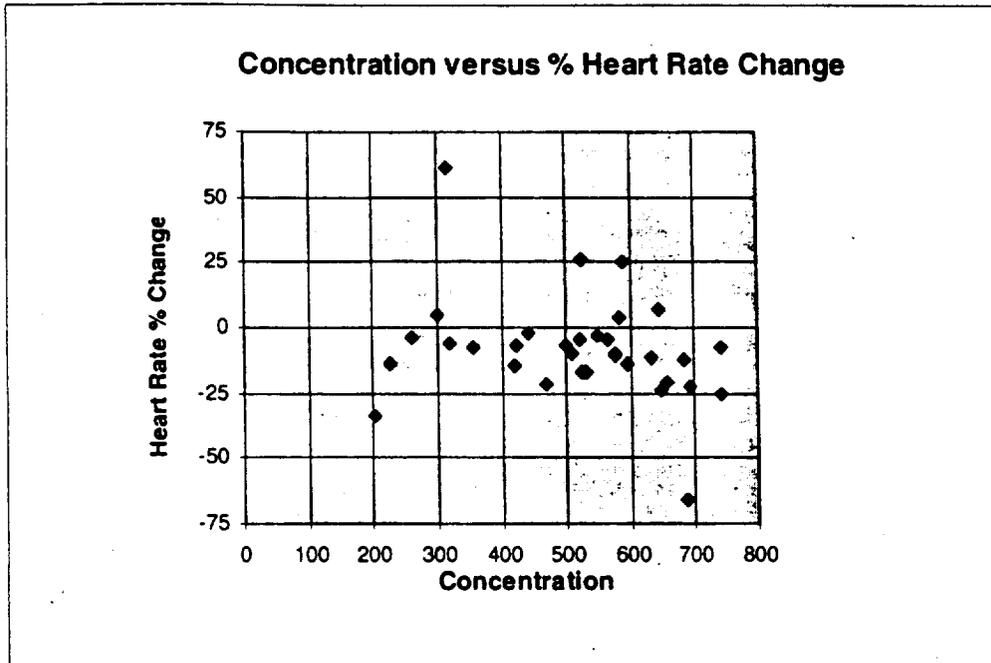
Pt #	Age	Vital Sign	Baseline	2 hour	post	comment
4001	1.0wk	HR	130	210	213	This tachycardia appears to be consistent with an arrhythmia and not normal heart rate for this child. Could also be due to anxiety crying.
		BP	Not stated	57/33	NS	Arterial pressure low relative to screening 96/40
4003	6.9 wk	HR	140	112	125	Heart rate decrease
		BP	104/83	83/38	89/46	Mild drop at 2 hours
4004	18 mo	HR	130	101	107	HR drop
9007	6.7	BP	95/66	109/44	114/50	Drop in Diastolic blood pressure
6002	11.2 y	HR	95	68	70	Drop in Heart rate, post treatment more like two hour value
8003	7.9 y	HR	72	54	70	Bradycardia
9004	8.4 y	BP	124/73	99/55	105/52	Decrease blood pressure
		HR	156	53	79	Bradycardia- This rate appears to be tachycardia at baseline (arrhythmia?) followed by bradycardia

The relationship between heart rate and serum concentration are shown in Figure 1.2. The majority of heart rates were less than those at baseline.

With respect to electrocardiograms, these were only measured at baseline and post-treatment. Three patients had arrhythmias post-treatment Patient #5001 had a loss of pre-excitation pattern following ablation (not surprising). Patient # 6003 had sinus bradycardia. Patient # 19007 had multiple premature atrial contractions that were consistent with the underlying rhythm disorder.

Laboratory: There were eight subjects new post study drops in hemoglobin, not surprising given the blood drawing requirements of the study. Three patients develop elevated white blood counts. One patient had an episode of aspiration (patient # 19002). A second patient had elevated WBC count post anesthesia (# 18005). The third patient # 1001 had no apparent reason for elevated WBC.

Figure 1.2 Concentration versus heart rate effect at Two hours



Conclusion: This was a pharmacokinetic study carried out in a wide age range of children with arrhythmias but with normal renal and hepatic function. A total of 34 patients were enrolled of which 33 had data evaluable for pharmacokinetic measurements. There were only 2 children in the age group of ≤ 1 month, too few to make any definitive conclusion, but the results are suggestive of altered kinetics in this and possibly the next youngest age group compared to school aged children.

There was a reasonable correlation between either BSA or weight and plasma sotalol concentrations. Dr. Gobburu's analysis also suggests that creatinine clearance is an independent of sotalol concentrations.

Dosing for young patients with additional renal dysfunction was not addressed in this study. Although the youngest age group had lower creatinine clearance, commensurate with the immaturity of their renal function, the estimate of their clearancès was 54 ml/min/M². There were only two neonates with this degree of creatinine clearance. Extrapolating the data to patients with more severe renal dysfunction seems unwise. Perhaps the best way to treat little patients with concomitant renal dysfunction is cautiously.

Study# 2. Protocol number 98217

Title of Study: Pharmacokinetics and Pharmacodynamics of Sotalol in a Pediatric Population with Ventricular and Supraventricular Tachyarrhythmias Analyzed by the Traditional 2-stage Approach.

Investigator and sites:

There were a total of 21 sites that participated in this study. Only 11 sites however enrolled patients. Twenty percent of those evaluate were derived from study center 47. The primary investigators, their sites and the number of patients enrolled are shown in Table 2.1.

Table 2.1 Investigator and sites:

Center 31 Dianne Atkins, MD University of Iowa Iowa City, IA n=2	Center 32 Lee Beerman, MD Children's Hospital Pittsburgh, PA n=3	Center 33 David Chan, MD Children's Hospital Columbus, OH n=0	Center 34 Macdonald Dick, MD University of Michigan Hospital Ann Arbor, MI n=1
Center 35 Michael R. Epstein, MD Children's Hospital Cincinnati, OH n=2	Center 36 Christopher Erickson, MD Arkansas Children's Hospital Little Rock, AR n=1	Center 37 Frank A. Fish, MD Vanderbilt University Nashville, TN n=2	Center 38 Steven Fishberger, MD St. Joseph's Children's Hospital Paterson, NJ n=0
Center 39 Steven Fishberger Mount Sinai School of Medicine New York, NY n=0	Center 40 Richard Friedman Texas Children's Hospital Houston, Tx n=1	Center 46 Robert Pass Columbia Presbyterian Medical Center New York, NY n=0	Center 47 Bertrand Ross Children's Hospital of the King's Daughter Norfolk, VA n=5
Center 48 J Philip Saul, MD Children's Heart Center of South Carolina Charleston, SC n=4	Center 49 Michael Shaffer, MD The Children's Hospital Denver, CO n=3	Center 50 William Scott, MD University of Texas Southwestern Medical Center Dallas, Tx n=0	Center 52 Margaret J Strieper, DO The Children's Heart Center Atlanta, GA n=0
Center 53 Ronn Tanel, MD Children's Hospital of Philadelphia Philadelphia, PA n=1	Center 54 John Triedman Children's Hospital Boston, MA n=0	Center 56 George F Van Hare, MD Stanford University School of Medicine Palo Alto, CA	Center 57 Frank Zimmerman St. Louis Children's Hospital St Louis, MO
Center 58 Parvin Dorostkar, MD University Hospital of Cleveland Cleveland, OH	Total n=25		

Protocol Dates: No date is supplied on the protocol.
No date is supplied on the statistical methods report.

Formulation: The formulation of sotalol was extemporaneously compounded. Five intact Betapace tablets (120 mg = 600 mg) were added to 120 ml of commercially obtained simple syrup (contained 0.1% sodium benzoate) in a six ounce amber bottle. The bottle was shaken and the tablets allowed to hydrate for > 2 hours (or overnight). The tablets are shaken intermittently until the tablets disintegrated. The formulating was completed the syrup.

contained a fine dispersion of particles. The final concentration of the formulation was 5 mg/ml.

Type of Study: This was an open label study.

Protocol: The study planned to enroll a total of 20 neonates (0-1 month) and 20 infants (1-24 months) with a cardiac arrhythmia (VT or SVT). In addition, 10 children in each of two age groups (2-6 years and 6-12 years) were also to be enrolled. The study, however, was considered complete when 6 neonate and 11 infants had assessable data. Patients were eligible for enrollment if they had VT or SVT which required therapy (the patient in all likelihood did not have arrhythmia at the time of enrollment) and informed consent by the appropriate parent or guardian was obtained.

Exclusion Criteria:

Patients were excluded for concomitant medical conditions or baseline conditions that increased the risk of using a beta-blocker or a drug with Class III antiarrhythmic activity.

Specifically, the patients that were excluded consisted of:

- Patients weighing less than 2 kg
- Patients with asthma
- Bradycardia: age \leq 1 month $<$ 80 BPM; age $>$ 1-24 months $<$ 75 BPM; age $>$ 2-4 years $<$ 70 BPM; age $>$ 4-6 $<$ 65 BPM age $>$ 6-12 $<$ 60 BPM
- Systolic hypotension: Age \leq 1 month $<$ 55 mm Hg age $>$ 1-24 months $<$ 60 mm Hg age 2 $<$ 4 years $<$ 80 mm Hg; age $>$ 4-6 years $<$ 80 mm Hg $>$ 6-12 years $<$ 90 mm Hg
- Creatinine clearance $<$ 80% of normal for age estimated by the formula (0.55 x height in cm) (serum creatinine concentration in mg/dl).
- CHF NYHA Class III-IV
- Uncorrected hypokalemia, hypomagnesemia or hypocalcemia
- Anemia
- Beta-blocker anti-arrhythmic therapy (can be enrolled after 2 half-live washout), however, digoxin and adenosine were allowed.
- Medications which prolong the QT interval.
- QTc at baseline $>$ 500 msec^{-1/2} during previous Class III anti-arrhythmic drug therapy
- If appropriate a negative pregnancy test
- IV amiodarone within 3 days.
- Positive pregnancy test (where applicable).

Each subject is to be hospitalized for the duration of the study. The scheme for the procedures that were scheduled for this study are shown below:

III (ng/ml) . These values were derived from the 8-hour time point.

Fluctuation factor (I-III) $C_{max,ss}/C_{min,ss}$ at dose levels I, II or III.

AUC_{ss}⁺ (I-III) The AUC was estimated from measurements taken between 0.5 to 8 hours after the third dose at all levels.

Cl_f Apparent oral total clearance (ml/min).

AUC_{ss}⁺/Time (I-III) Average concentration during a dose interval at steady state at dose levels I, II or III (ng/ml)

⁺ Reviewer's comment: Although the measurements are referred to as steady state measurements, these measurements are clearly not made long enough at a fixed dose of medication to approach steady state. Assuming a half-life of approximately 9.5 hours for sotalol, the measurements during the third dose at each dose levels reflect 1.6-2.5 half-lives of treatment. As such, these measurements reflect approximately 70-85% of steady state levels or perhaps slightly higher because of the earlier dose levels.

The determination of kinetic measurements, particularly for little ones, is clearly limited by blood drawing limitations. It is not surprising, therefore, that limited kinetic data is available for these children.]

Dynamic Measurements:

The 6-lead ECG was recorded at a rate of 50 mm/sec and a sensitivity of 10 mm/mV. Each center was supplied with the same ECG machine (). The ECGs were shipped to the core laboratory immediately after each participant completed the study. The sequence and patient number was blinded.

Once received at the core laboratory, the cardiologist screened the ECG tracings. Tracings with irregular RR intervals (RR > 10% variability), excessively flat T-waves, or motion artifacts were excluded from analysis. In the situation where there was a potential case of limb lead reversal, the reading was excluded from the QT analysis, but was utilized for R-R analyses.

When the rhythm was other than sinus, unless the rate was regular and the QRS interval was stable the ECG was excluded. If the QRS interval was stable and the R-R interval regular in these tracings with non-sinus rhythms, the RR interval was used for QT correction (what QT was used?).

For patients with pre-excitation the measurements were performed by utilizing the J-T interval, the R-T interval or the earliest notch in the QRS complex. The JT intervals or RT intervals were then transformed to QT measurements by the addition of the non-excited portion of the ECG (these apparently were approximated from age-normalized measurements). The decision as to which of these methods was left to the discretion of the cardiologist. The cardiologist could exclude tracings in which there were marked changes in pre-excitation and consequently in the ventricular depolarization pattern.

All ECGs were quantified by the use of a digitizing pad. Lead II was used for measurements unless sharper T-waves were observed in other of the lead I or III. In situations in which there was a U-wave, the U-wave was excluded. In situations in which there was imperfect resolution of the T and U-waves, a tangent to the steepest portion of the T-wave was constructed. The end of the T-wave was defined as the intersection of this tangent with the isoelectric baseline measurement. In situations where there was marked fusion of the T and U-waves, and the U-wave was large, the tangent to intersect the isoelectric line was constructed through the steepest portion of the T-U complex.

ECG measurements:

The mean QT interval was determined from 5 consecutive sinus beats. Two corrections of repolarization were performed

$$\text{Bazett: } \text{QTcB (msec}^{1/2}) = \text{QT (msec)} / \sqrt{\text{RR (sec)}}$$

$$\text{Fridericia: } \text{QTcB (msec}^{2/3}) = \text{QT (msec)} / \sqrt[3]{\text{RR (sec)}}$$

Definitions: Note the abbreviation (I-III) means I or II or III.

AUEb	Area under the QTc or RR interval time curve measured over a time interval of 7.5 hours during baseline session prior to the first dose of sotalol (msec x h)
AUEss⁺ (I-III)	Area under effect versus time curve at steady state ⁺ measured from 0.5 to 8 hours after the third dose, AUEss ⁺ (QTc), AUEss ⁺ (RR) at dose level I, II or III (msec x h)
ΔAUEss⁺ (I - III)	AUE ss ⁺ (I-III) - AUEb (msec x h)
%ΔAUEss⁺ (I-III)	100 x [AUE ss ⁺ (I-III) - AUEb] / AUE b (%)
AUEss⁺ /Time (I-III)	Average baseline corrected effect on QTc or RR interval during a dose interval at steady state ⁺ at dose levels I, II or III (msec)
ΔAUEss⁺ /Time (I-III)	Average baseline corrected effect on QTc or RR interval during a dose interval at steady state ⁺ at dose levels I, II or III (msec)

E_b	Average QTc or RR interval at baseline computed from AUE _b /7.5, where 7.5 is the time interval in hours during which the ECG intervals were measured (msec)
E_{max,ss*}⁺ (I-III)	Observed maximum QTc (QTc, max ss ⁺ or RR max, ss ⁺) interval at steady state ⁺ at dose levels I, II or III (msec)
E_{max,ss*}⁺ (I-III)	Nominal maximum QTc or RR interval at steady state ⁺ 2 hours after the dose at dose level I, II or III (msec)
E_{min,ss*}⁺ (I-III)	Nominal maximum QTc or RR interval at steady state ⁺ 8 hours after the dose at dose level I, II or III (msec)
Δ E_{max,ss*}⁺ (I-III)	E _{max,ss*} ⁺ (I-III) -E _b (msec)
ΔE_{max,ss*}⁺ (I-III)	E _{max,ss*} ⁺ (I-III) -E _b (msec)
% Δ E_{max,ss*}⁺ (I-III)	100 x [Δ E _{max,ss*} ⁺ (I-III)-E _b]/E _b (%)
% Δ E_{max,ss*}⁺ (I-III)	100 x [Δ E _{max,ss*} ⁺ (I-III)-E _b]/E _b (%)
ΔE_{min,ss*}⁺ (I-III)	E _{min,ss*} ⁺ (I-III)-E _b /E _b (msec)
% ΔE_{min,ss*}⁺ (I-III)	100 x [E _{min,ss*} ⁺ (I-III)-E _b]/E _b (%)
tE_{max,ss*}⁺ (I-III)	Time to observed maximum steady state ⁺ QTc (tQTc _{max,ss*} ⁺) or RR (tRR _{max,ss*} ⁺) interval at dose levels I, II and III (h)

* steady state as defined by sponsor. There is clearly inadequate time for steady state to have been approached (i.e. > 4-5 terminal half-lives). Assuming a half-life of 9.5 hours, the data for the times measured reflect 1.68 to 2.5 half-lives

Results:

A total of 25 patients were enrolled. The specific outcome for the populations are shown in Table 2.3.

Table 2.3 Outcomes.

Received Drug	25 (100%)
Provided All Scheduled Blood Samples	24 (96%)
Discontinued Prematurely	1 (4%)
Adverse Event	1 (4%)

One patient discontinued for an adverse event.(see Safety)

Demographics: The distribution of patients among the age groups are shown Table 2.4:

Table 2.4 Demographic mean + SD

	Age				Total
	Neonates < 1 month	Infants >1 to < 2 months)	Children >2 to < 7 years	Children > 7 to 12 years	
Total Enrolled	7	9	3	6	25
PK	7	9	3	6	25
PD					
QTc	6	8	3	6	23
RR	6	8	3	5	22
Age months	0.7 + 0.3	9.4 + 7.5	57 + 21	118.5 + 25.0	
Sex M/F	3/5	6/3	2/1	2/4	13/12
Race W/B/H/O	6/1/0/0	7/2/0/0	2/0/1/0	5/0/0/1	20/3/1/1
Body surface Area	0.22 + 0.03	0.41 + 0.10	0.7 + 0.08	1.17 + 0.22	0.58 + 0.39
Height (cm)	51.7 + 3.1	70.7 + 103	103.5 + 9.9	139.1 + 18.3	85.8 + 35.9
Weight(kg)	3.6 + 0.7	8.8 + 3.2	17.1 + 2.4	35.8 + 8.8	14.8 + 13.5
Cl Cr (ml/min/1.73 M ²)	51 + 23	101 + 14	121 + 35	129 + 21	96 + 37

Table 2.5 Baseline History of Arrhythmias

Type of Arrhythmia	Number (%)
Supraventricular Tachycardia	24 (96%)
PSVT	21 (84%)
Accessory Pathway	12 (48%)
WPW Syndrome	9 (36%)
Not WPW syndrome	3 (12%)
AV node entry	0
SA node entry	0
Unknown	9 (36%)
Atrial Flutter	4 (16%)
Atrial Fibrillation	1 (4%)
Ectopic Atria; Tachycardia	0
Chaotic Atrial Tachycardia	1 (4%)
Ventricular Tachycardia	2 (8%)

Patients could have more than one type of arrhythmia
AV= atrioventricular; SA= sinoatrial; PSVT=paroxysmal supraventricular tachycardia; WPW= Wolff-Parkinson-White

Compliance: Two patients vomited or spat up doses. Patient # 31001 vomited immediately after the second dose at the second level. This patient was re-dosed patient # 35001 spit out a portion (estimated by the investigator as 50% of the dose) after the first dose level first dose and was not re-dosed. The values of the first dose levels were excluded.

Patient # 49001, was receiving sotalol at approximately the mid-dose level (53.3 mg/M² q 8 hours) for up to 22 hours prior to the start of the study. The sotalol levels after the first dose level was excessively high, this value was excluded from analysis.

With respect to pharmacodynamic measurements, the following represents the decisions made by the sponsor to include or analyze the ECGs generated during each of the dosing levels. There were to be 24 measurements of RR and QT intervals for each patient (6 measurements at each dose level i.e. baseline, 10 mg/M², 30 mg/M² and 70 mg/M²). The following reflects the decision process of the sponsor in evaluating the various ECGs.

[Reviewer's comments: There were several patients whose ECGs with particular reference to the time of repolarization should have been excluded from the analysis. Any patient with an abnormal depolarization process is likely to have an abnormal repolarization process. The magnitude of the QTc increase in these patients may or may not be similar to those patients with a normal repolarization. I suspect that the analysis was unbiased but because of the small study, there was some impetus to include as much "usable" data as possible. I did not, however, re-analyze the data, excluding these patients.]

Patient 31001: This patient had pre-excitation. The JT interval was measured. The estimated QT interval was defined as the JT interval plus 50 msec.

Patient 31002: Only 12 ECGs received. This patient had marked intraventricular conduction delay (160 msec). The normal QRS for this age was assumed to be 70 msec. For this subject the QT was assumed to be the measured QT minus 90 msec. *[This patient's depolarization process was abnormal and repolarization should be looked at skeptically]*.

Patient 32001: No ECGs evaluated because of sinus node dysfunction with junctional escape beats. *[Variable pre-excitation is also suggestive of variable ventricular depolarization and repolarization]*.

Patient 32002: Tracings with variable pre-excitation so that JT was measured, and QT calculated by adding 50 msec to JT interval.

Patient 32003: Only 19 RR and 24 QT intervals were recorded. Patient had stable intraventricular conduction delay (110 msec) in all tracings. The normal QRS interval in this age is 75 msec. The QT for this subject was computed as the measured QRS duration (110 msec) minus the normal QRS duration. Only one baseline value was available for assessing RR intervals. *[Again abnormal depolarization pattern and consequently abnormal repolarization]*.

Patient 34001: One tracing had QT measurement could not be measured due to baseline artifact. In one other time point only 2 complexes were available.

Patient 35001: No values ascertained because of quasi-incessant ventricular tachycardia.

Patient 35002: All measurements available.

Patient 36001: Three tracings were excluded either because of wandering baseline. One tracing showed TU fusion.

Patient 37001: Only 10 QT measurements were considered as valid due to rounded T waves with TU fusion or wandering baseline.

Patient 37002: More than one ECG machines were used during the course of the study.

Patient 40001: Patient had variable pre-excitation. QT was estimated as JT plus 40 msec. (duration of non-pre-excitation QRS). *[Variable pre-excitation suggests variable ventricular depolarization and consequently repolarization.]*

Patient 47001: Only 22 of the QT intervals were available. The two excluded measurements had T-wave morphology and baseline artifacts that precluded accurate measurements.

Patient 47002: In this patient with pre-excitation, the QT interval was determined by the addition of 20 msec from the RT interval (the estimated time of QR duration).

Patient 47003: Several of the tracings done on a machine other than that supplied by the sponsor.

Patient 47004: Occasional complexes not valid because of variable RR intervals, but all data points measured.

Patient 47005: All OK

Patient 48001: ECG collected but no values generated due to irregular R-R intervals, atrial fibrillation, chaotic atrial rhythm and ectopic complexes.

Patient 48002: Only 20 of 24 QT measurements generated because of marked change in QRS morphology or change in T-wave morphology. Three of the missing values were from baseline.

Patient 48003: Only 18 of the QT intervals obtained. Missing QTs interval measurements because of altered QRS morphology and axis probably due to pre-excitation pattern. For those QT intervals measured, the QT interval was measured from the first notch in the R wave to end of T-wave. All high dose QT intervals were excluded.

Patient 48004: Only 16 of the QT intervals generated. For 5 ECGs there was excessive baseline artifact. For 3 tracings, there was an apparent limb reversal. Only two ECGs (4 and 8 hours) reflecting the highest dose were available.

Patient 49001: Only 20 R-R intervals and 17 of the QT intervals were generated. Three tracings were unusable for either QT or RR intervals due to SVT. Four additional QT measurements could not be made because of limb reversal and lead disconnection.

Patient 49002: One QT-interval missing because of poor quality. QT measured from early notch in QRS where the delta wave meets the QRS.

Patient 49003: Only 11 of the QT intervals that were generated were analyzed because of excessively flat T-waves (12 tracings) and one tracing with non-readable data.

Patient 53001: 2 R-R intervals and 1 QT interval missing. One tracing was completely missing. One additional tracing shows a regular ectopic atrial rhythm that does not reflect sinus rhythm.

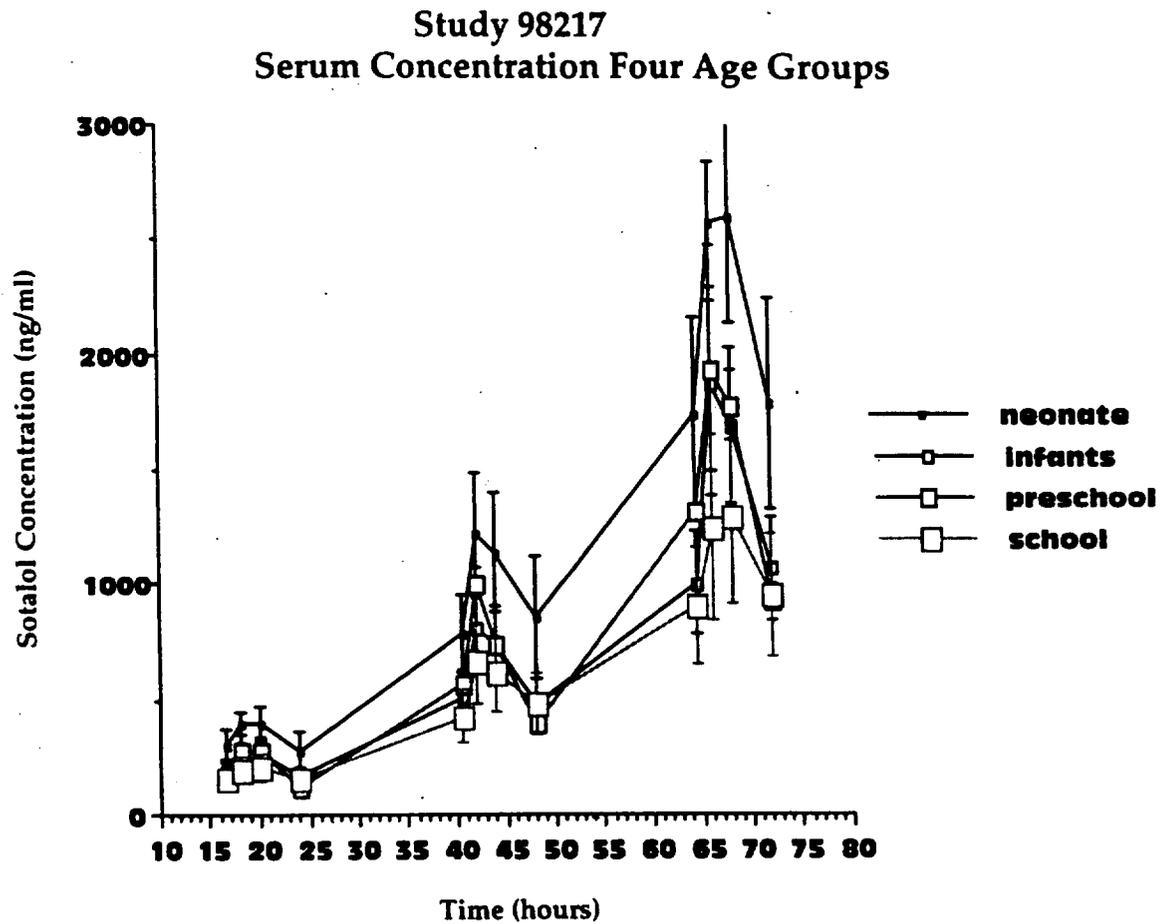
Discontinuations:

One patient (# 31002) discontinued the study for increasing sinus node dysfunction (see description under SAFETY).

Pharmacokinetics:

The concentration time curves for the three dose levels of sotalol are shown in Figure 2.1. Neonates had higher concentration than the other three groups. In general, the groups ordered per age. The number of subjects in the preschool group was small (n=1-3/ value at each measurement point) and consequently, the values for this group are not known with confidence. Infants (n=6-8/value per point) and school age children (n=6/value per point). The sponsor did not analyze the specific pharmacokinetic parameters by age.

Figure 2.2 (Mean \pm SEM)



Pharmacokinetic constants:

Table 2.6 The pharmacokinetic measurements based on dose level

		Dose Level		
		10 mg/M2	30 mg/M2	70 mg/M2
C _{max,ss+} (ng/ml)	N	23	22	22
	Mean ± SD	331 ± 101	986 ± 440	2203 ± 636
	Min-max			
C _{min,ss+} (ng/ml)	N	22	24	24
	Mean ± SD	186 ± 130	546 ± 432	1256 ± 752
	Min-max			
AUC _{ss} + (hr*ng/ml)	N	23	24	24
	Mean ± SD	1973 ± 868	5948 ± 3029	13277 5292
	Min-max			
Fluctuation Index	N	22	22	22
	Mean ± SD	2.03 ± 0.52	2.13 ± 0.8	1.94 ± 0.58
	Min-max			
T _{max}	N	23	24	24
	Mean ± SD	2.43 ± 0.84	2.5 ± 0.88	2.58 ± 0.92
	Min-max			

+ss -there is inadequate exposure to be at steady state.

The peak, trough and AUC values are dose-proportional. With an eight hour dosing regimen, fluctuation index is approximately 2. There is substantial overlap in parameters (see max-min) among patients treated with different doses.

Per sponsor, the clearance of sotalol is well correlated with either BSA or creatinine clearance. The sponsor tabulated the correlation constants and these are shown in Table 2.7.

Table 2.7 Correlations of sotalol clearance with BSA and Creatinine Clearance

		Sotalol Clearance/F (ml/min)		
		10 mg/M2	30 mg/m2	70 mg/M2
BSA (m2)	R	0.959	0.969	0.906
	p-value	<0.0001	<0.0001	<0.0001
Creatinine Clearance	R	0.935	0.918	0.912
	p-value	<0.001	<0.0001	<0.0001

The scatter plots for AUC versus BSA, Creatinine clearance or Age are shown in Figures 2.3, 2.4 and 2.5, respectively. Deviations at each of the dose levels are most obvious at the smallest BSA, the youngest age and the lowest creatinine clearance.

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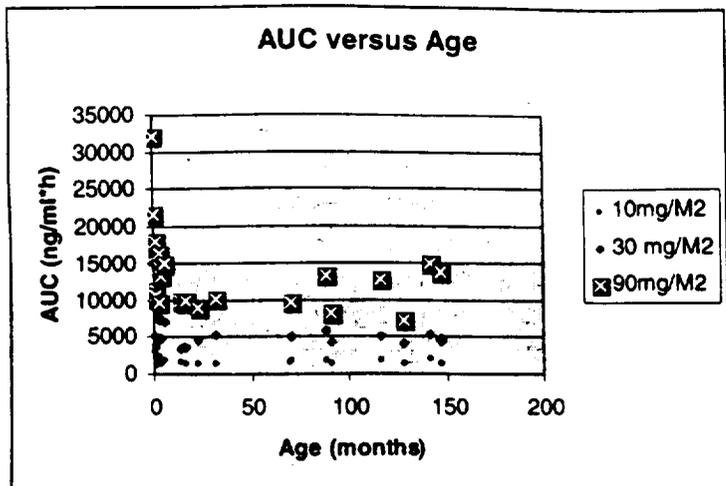


Figure 2.3 BSA versus AUC

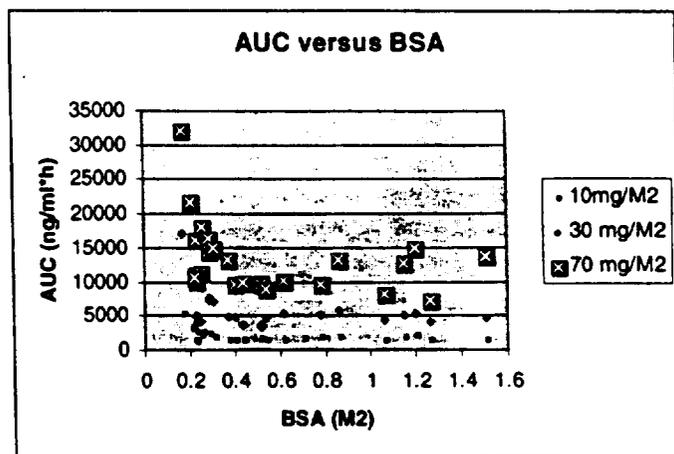


Figure 2.4 AUC versus Age

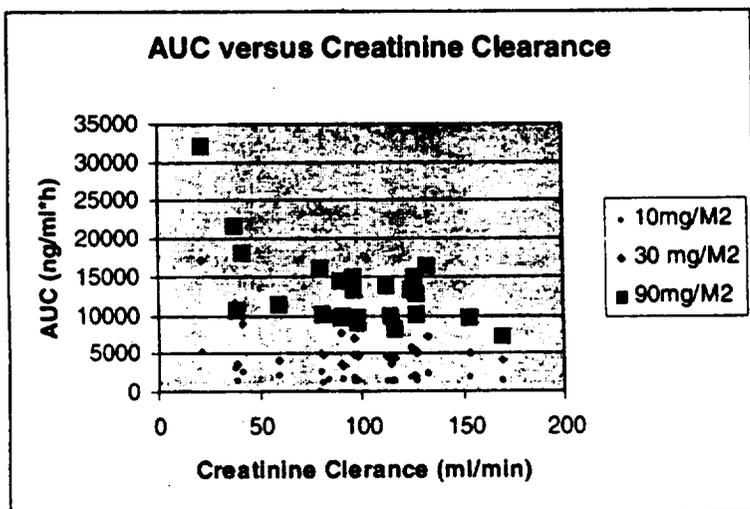


Figure 2.5 AUC versus Creatinine clearance

Pharmacodynamics:

Baseline measurements: The baseline measurements for the different age groups during the time interval of observation are shown in Table 2.8 for QTcB and RR intervals

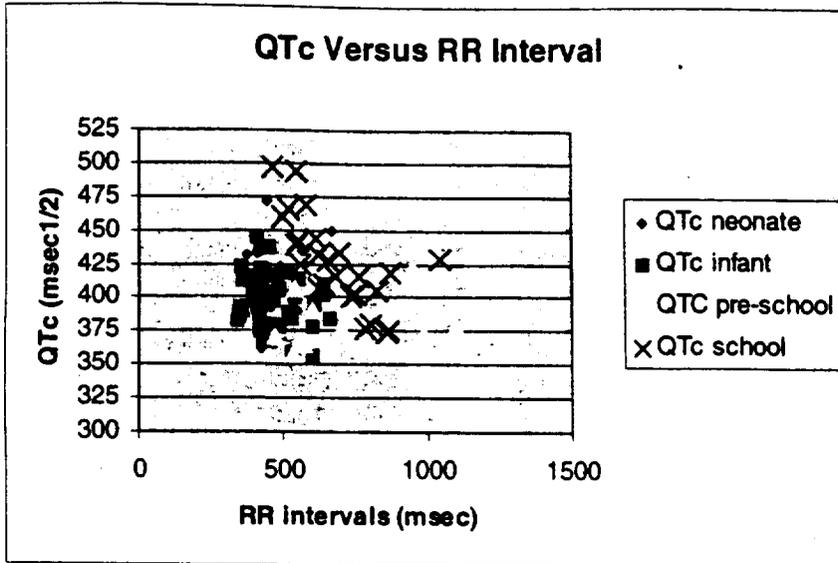
Table 2.8 QTcB and RR intervals at baseline (mean + SD)

	Age range				
	Neonates < 1 month	Infants >1 to < 2 months)	Children >2 to < 7 years	Children > 7 to 12 years	
QTcB	-7.5 h	N=4 403 ± 21.9	N=5 404 ± 20.5	N=2 410 ± 4.5	N=6 422 ± 26.5
	-6.5 h	N=4 400 ± 20.2	N=4 394 ± 17.1	N=3 378 ± 30.7	N=6 425 ± 14.7
	-6.0	N=5 417 ± 25.3	N=6 394 ± 15.7	N=3 395 ± 36.2	N=6 425 ± 40.7
	-5.0	N=4 416 ± 14.5	N=8 405 ± 18.9	N=3 377 ± 12.7	N=6 402 ± 35.9
	-4.0	N=4 414 ± 41.5	N=7 398 ± 24.1	N=3 400 ± 31.1	N=6 427 ± 20.9
	0	N=5 402 ± 28.3	N=8 400 ± 27.0	N=3 359 ± 22.6	N=8 400 ± 27.0
RR	-7.5 h	N=6 455 ± 80	N=7 454 ± 54	N=2 722 ± 263	N=5 768 ± 217
	-6.5 h	N=6 441 ± 81	N=7 487 ± 80	N=3 735 ± 187	N=4 623 ± 57
	-6.0	N=6 459 ± 104	N=7 471 ± 83	N=3 703 ± 231	N=4 631 ± 151
	-5.0	N=6 463 ± 75	N=8 471 ± 91	N=3 714 ± 242	N=4 756 ± 164
	-4.0	N=6 472 ± 32	N=8 472 ± 86	N=3 811 ± 121	N=4 686 ± 162
	0	N=6 423 ± 46	N=8 450 ± 114	N=2 836 ± 369	N=4 618 ± 104

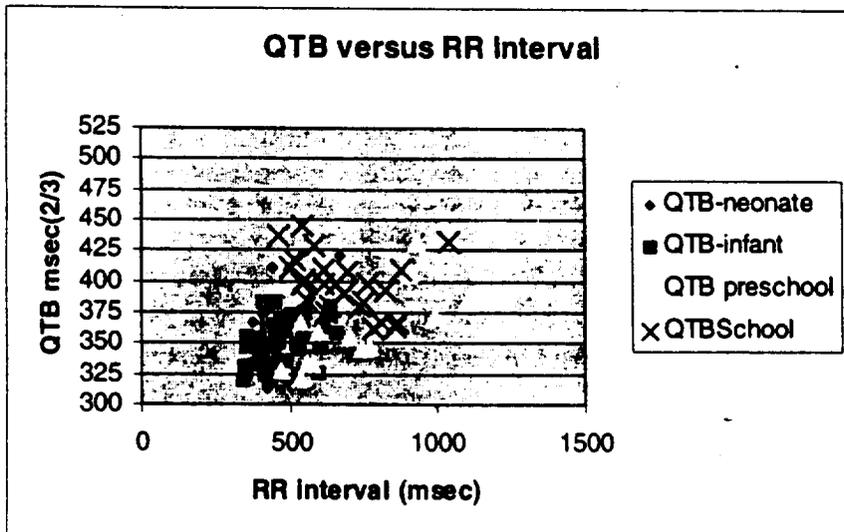
The study analyzed the effect on repolarization both by the Bazett and Fridericia correction of QT for heart rate. The difference is that the Bazett correction normalizes QT by the square root of the RR interval, the Fridericia normalized for the cube root of the RR interval. The relationship between the corrected QT intervals by the two methods and R-R intervals for baseline measurements are shown Figure 2.3. This graph contains multiple data points for each subject (between 0-6 points based on number of baseline measurements). The scatter of values for the Bazett correction has virtually no slope. The correction by the Fridericia formula slope upward as the RR interval increases. Since those with the smallest R-R intervals are the youngest children (with the most rapid heart rates), if one assumes that all aged children should have the same corrected QT interval, the Bazett's correction appears the most appropriate.

The pharmacodynamic effects of sotalol during these studies are taken from Dr Gobburu's review. There are several conclusions with respect to the description of the hemodynamics of sotalol. Two parameters were analyzed. The first was repolarization., because of the more constant baseline measurements when Bazett's correction when compared to Fridericia's correction, Bazett's correction was used by Dr. Gobburu.

Figure 2.3 (a) QTc and 2.3 (b) QTb versus RR intervals



2.3 (b) Correction via Fridericia



The second parameter, the R-R interval, which was measured is a reflection of heart rate (the sponsor collected R-R intervals (heart rate can be calculated by multiplying by 60 the reciprocal of the R-R interval) from the ECGs. Since, however, heart rate (and consequently R-R interval) is markedly age dependent, the % change in this parameter appears to be the most appropriate method of normalizing these R-R intervals across all age ranges. The dose related effects are shown in Table 2.9 below for maximum, and minimum effect for sotalol at the different doses.

Table 2.9 Effect on pharmacodynamic parameters.

Parameter↓		Dose (mg/M ²) given Q 8 H								
		10			30			70		
ΔQTcB max	N	21	21	20	RR max,ss	N	20	20	20	
	Mean	23	36	55		Mean	10.85	48.5	58.3	
	SD	16	16	29		SD	88.7	75.1	61.2	
ΔQTcB max ▲	N	18	17	16						
	Mean	24.0	37.6	52.9						
	SD	17.2	15.5	30.0						
%ΔQTcB max,ss*	N	21	21	20	%ΔRR max,ss*	N	20	20	20	
	Mean	6	9	14		Mean	18	23	25	
	SD	4	4	7		SD	12	16	15	
t QTcB max,ss*	N	22	22	21	TRRmax,ss*	N	21	21	21	
	Mean	3.7	2.9	3.2		Mean	2.2	3.3	3.0	
	SD	2.8	2.2	2.5		SD	2.3	3.0	2.3	
t QTcB max,ss* ▲	N	18	18	17						
	Mean	3.7	2.8	2.4						
	SD	2.9	2.1	1.8						
%Δ QTcB min,ss	N	20	20	19	%ΔRR min,ss	N	20	20	20	
	Mean	1	2	5		Mean	1	7	9	
	SD	7	5	7		SD	12	14	15	
%ΔAUEss (QTcB)	N	20	19	18	%ΔAUEss (RR)	N	20	19	20	
	Mean	1	4	7		Mean	4	8	12	
	SD	5	4	5		SD	8	10	13	

▲ Excludes subjects 32002, 32001, 32003, 40001 those with unusual repolarization and repolarization

With respect to measurements reflecting repolarization, both ΔQTcB,max,ss* %ΔQTcB,max,ss* (which approximates peak effect on corrected QT intervals at the last dose of each dose level and the corresponding percent change, respectively), increased as the dose increased. All doses clearly appear different than baseline (average of all six timed measurements at baseline were collapsed as the baseline measurement). The time to maximum effect is between 2.9 to 3.7 hours. At 8 hours (i.e. min value), only the highest dose level clearly differed from baseline. Integrating the effect over the eight-hour dosing regimen [%ΔAUEss (QTcB)], there appeared to be a dose proportional increase in effect over the range 10 to 70 mg/M². The overall % increase in %ΔAUEss (QTcB) only differed from baseline measurements for the highest dose and trended that way for the middle dose.

Excluding the 4 patients (# 32001, 32001, 32003 and 40001), who had abnormal depolarization patterns but were nevertheless included in the sponsor's analysis, had little effect on the magnitude of effect for QTcB but did shorten the time to maximum QTcB for the highest dose (from 3.2 to 2.4 hours).

With respect to R-R intervals, there was a dose related effect in the % change from baseline in peak effect. All doses are clearly different than baseline. At trough, only the high dose group appears to differ from baseline. The time to maximal effect in RR intervals

was between 2.2 to 3.0 hours. Although the time to maximum effect was approximately the same as that of the QTc (Table 2.8) and peak concentrations (see Table 2.6), there was sufficient spread of values that some delay cannot be excluded.

Dr. Gobburu fit the entirety of the data for the QTc versus concentration. For QTc, the best-fit equation shows a linear relationship between QTc and sotalol concentration. There was no benefit in the fit by the use of a model that included an effect compartment. The intercept for QTcB was 405 msec^{1/2}. The slope of this function was 0.0158 msec^{1/2}/ng/ml. The highest concentration measured was 4792 ng/ml in a 0.6 week female child. Based on this measurement, the calculated QTc for this infant would be 480 msec^{1/2}, or an increase of approximately 75 msec^{1/2}. For this rather small database, this is a rather large effect. (If one corrects for the less than sufficient time to reach steady state, the smallest child could be expected to have concentration at steady state around 6200 ng/ml. This would result in an increase of QTc of approximately 95 msec^{1/2} at steady state.)

$$QTc = 405 + 0.0158 [C] \quad (\text{equation 1})$$

Where QTc is in sec^{1/2} and [C]= concentration is in ng/ml

With respect to RR interval, Dr. Gubburu actually modeled heart rate. The data was best fit to E max model. Since the baseline heart rate is dependent on patients post-natal age or weight, the model contains term for weight. The equation is as follows:

$$HR = 96 (WT/20)^{0.25} * \frac{(1 - 0.16[C])}{790 + [C]} \quad (\text{equation 2})$$

Where HR is heart rate in BPM; WT is weight in Kg; Emax is fraction of maximum response and is =0.16; [C] is concentration in ng/ml.

The maximal effect on heart rate was 16% of the baseline heart rate. Baseline heart rate is weight dependent (weight and age or weight and BSA are metrics that are age-dependent). It should be noted that [C] is dependent on dose in mg/M2 and weight/age/BSA or creatinine clearance.

Safety:

Deaths:

There were no deaths in this study

Dropout

One patient (# 31002) discontinued the study for increasing sinus node dysfunction. This was a 5 year 9 month year old Hispanic female with a history of teratology of fallot repair at the age of 2 years 6 months and a further correction 22 months later. The child had residual pulmonary artery insufficiency, right ventricular enlargement, left pulmonary artery branch stenosis and pulmonary valve stenosis. The patient received all three doses of sotalol. ECGs were all collected (based on the presence of coded numbers affixed to the ECGs) but only ECGs after the first two doses were supplied. I have reviewed the submitted CRF but the heart rate associated with the sinus node dysfunction was not stated.

Adverse events:

The adverse events are shown in Table 2.10:

Table 2.10 Adverse events

Body system or Event	N=25	
One or more adverse event	11 (44%)	
Body as a whole	3 (12%)	
Accidental injury		1 (4%)
Fever		2 (8%)
Abdominal Pain		1 (4%)
Cardiovascular System	7(8%)	
Sinus Bradycardia		1 (4%)
Electrocardiogram abnormal		1 (4%)
Chest pain		1 (4%)
QT-interval prolonged		3 (12%)
Vasodilation		1 (4%)
Digestive System	3 (112%)	
Diarrhea		1 (4%)
Nausea		1 (4%)
Vomiting		2 (8%)
Metabolic and Nutritional Disorders	2 (8%)	
Healing abnormal		1 (4%)
SGOT increased		1 (4%)
SGPT increased		1(4%)
Nervous System	3 (12%)	
Dizziness		1 (4%)
Headache		3 (12%)
Respiratory System	1 (4%)	
Upper respiratory infection		1 (4%)

Laboratory:

Laboratory measurements were performed pre and post study. Many of the children had decreases in measurements of red blood cell mass, not inconsistent with phlebotomy. One patient (#patient 35001) sustained an elevation in liver function during the study.

Table 2.11 Number of patients with abnormality/ total number normal baseline observations-Chemistry

Ca	PO4	Glu	BUN	Cr	Tprot	Alb	Bili	SGOT	SGPT	GGT	Na+	K+	Cl-	HCO3	Mg++
0/23	1/14	1/18	3/17	0/20	4/18	5/17	0/16	3/20	2/17	2/20	2/20	4/18	1/16	1/20	0/21

Table 2.12 Laboratory values for LFTs patient 35001

	Normal Range	Baseline 28 June 99	Post-study 2 July 99	Repeat 8 July 99	5 week post 9 Aug 99
SGOT	20-60	50	139	80	48
SGPT	5-45	24	185	135	15

One patient # 35002 had a post study elevation in SGOT (post=93 versus baseline = 37). The SGPT, however was low post study =3. No further values were supplied. Three patients had increases in K+ levels. Patient 36001 baseline and post therapy values were 4.1 to 5.5; patient 32002 from 4.4 to 5.7 and patient 35002 from 4.1 to 5.5.

Table 2.13 Number of patients with abnormality/ total number of normal baseline observations-Hematology urine selected parameters

Hgb	Hct	RBC	WBC	Plt		Urine WBC	Urine RBC
2/14	3/13	3/12	1/19	1/15		2/17	0/16

Vital signs: Vital signs were collected baseline and post study. No listings of blood pressures were available. (The sponsor says such measurements are listed in Appendix 16.4 listing 10. No such listing was available).

Heart rates, however were available by the analysis of ECGs.

ECGs. The primary end point of the study was the dynamic effects of sotalol on ECG parameters. ECGs were measured at baseline (6 measurements over an 8 hour period) and after the third dose at each dose level.

Heart rates:

With respect to heart rate, one patient discontinued due to excessive sinus pauses. This patient #31002 had a heart rate of 55 at the 8 hour baseline measurement. After the 10 mg/m² dose the heart rate ranged from 60-70. This patient was on digoxin.

One additional patient #32003, a 12.2-year old Caucasian female had a single baseline RR interval available, corresponding to a heart rate of 56. Heart rates for this patient were less than 60 after all doses. At the highest dose the 2 hour-post dose measurement the heart rate was 35 (RR interval = 1708). At 4 hours post dose, the heart rate was 41. At the time of the bradycardia, this patient was not taking digoxin or other medications that might alter heart rate.

Patient # 47004 had a heart rate of 60 after the 30-mg dose and 54 after the highest dose level.

QT intervals: QT intervals were prolonged upon therapy with sotalol. There were two patients who had a greater than 50 msec increase in QTcB at the 10 mg dose when compared to baseline (There were, however, two patients who had a decrease by 50 msec at the 10 mg/m² dose). There were 5 patients who had a greater than 50 msec increase at the mid dose level with none having a drop of > 50 msec. At the highest dose, there were 11 patients who had at least one QTcB increase of > 50 msec of the 20 patients with at least one measurement after this dose. The largest increase was 109 msec at two hours post dose for patient # 47001.

Other ECG abnormalities are listed in Table 2.13:

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Table 2.14 ECG abnormalities at screening and post-treatment

37001	0.02 y/o F/W	Screening Post	-Right atrial enlargement, non-specific T wave abnormality QTc 470 msec -NSR, possible RVH, nonspecific T wave abnormality, prolonged QTc
49003	0.2 y/o F/W	Screening post	-
48001	0.2 y/o M/B	Screening Post	-left axis deviation -Chaotic atrial tachycardia with intermittent aberrant ventricular beats -RAD
47003	1.1 y/o M/B	Screening Post	-
35001	1.25 y/o M/W	Screening Post	-Incessant VT (RBBB; superior axis) with VA dissociation and intermittent conducted sinus beats. Sinus CL 420 msec. QT (on conducted beats) 240 ms; QTc > 370 msec -Right atrial enlargement and nonspecific T wave changes, resolution of VT
3002	1.9y/o M/W	Screening Post	-Sinus rhythm with low voltage P-waves in I, mild first degree AV block Q-wave in Vi c/w corrected transposition. No pre-excitation -NSR, WPW syndrome, pre-excitation, QTc mildly prolonged, Normal axis, Baseline no pre-excitation due to flecainide
31002	5.8 y/o F/H	Screening Post	-CRBBB (QRS duration =0.22) QT interval =0.42 -CRBBB HR=64, QT=0.43. QRS duration 0.18
35002	7.3 y/o F/W	Screening Post	-Borderline Sinus tachycardia followed by Sinus slowing Right Atrial enlargement. Qtc=0.43; nonspecific T-wave Changes -Right Atrial enlargement, QTc 480. Increase from baseline, non-specific T wave changes, sinus Tachycardia resolved
32001	7.6 y/o M/Other	Screening Post	-Junctional rhythm -none
32003	12.2 y/o F/W	Screening Post	-Sinus bradycardia, RBBB, Normal QTc -

Conclusions: This was a modest sized study in which pediatric patients received incremental sotalol doses. There were 25 patients who were enrolled of which 24 completed the three dose levels as well as the three doses in each level. Of these 25 patients, 7 were neonates (< 1 month), 9 were infants (> 1-24 months), 3 were pre-school aged children (2-6 years old) and 6 were school aged children (7 to 12 years old).

All patients were treated with the same dosing scheme, three doses of sotalol at each of the following doses 10, 30 and 70 mg/M² administered Q 8 H (between 30-210 mg/M²/day). The intent was to reach steady state and to define the pharmacodynamic effects at steady state. Since the half-life of sotalol is approximately 9.5 hours, the measurements that were collected between the second and third dose were 16-24 hours are only approximately 1^{3/4} - 2^{1/2} half-lives of treatment (far less than the usual 4-5 half-lives that defines steady state).

With respect to metrics of sotalol exposure, when dosed on a mg/M² regimen, there were deviations from constancy at the youngest age, the lowest creatinine clearance or the smallest BSA in that these patients had much greater concentrations of sotalol than predicted.

With respect to the dynamic effects of sotalol, Dr. Gobburu analyzed the data as a whole for both QT intervals as well as heart rate dependence. The corrected QTc interval by the method of Bazett for the population as a whole appears to be less dependent on baseline heart rate (60/RR-interval) than when corrected by the method of Fridericia. The change in QTc is approximately linear with concentration of sotalol.

Heart rate at baseline is age dependent. The % change of resting heart rate versus concentration is best fit by an Emax model. Maximal effect on resting heart rate was 16%.

The concentration at which half maximal heart rate was observed was approximately 790 ng/ml.

Since study 98217 was of relatively short duration (subjects received 3 dose levels of sotalol three times daily for a total exposure of three days) the majority of the safety concerns reflect excessive anticipated hemodynamic effect. One patient discontinued due to excessive sinus node dysfunction. A second patient had heart rates down to the mid-thirties but did not discontinue. QT intervals and particularly when corrected for heart rate, were on occasions excessively prolonged. The longest increase in QT intervals was 109 msec^{1/2}. Four of the 20 patients (20%) with evaluable ECGs after the highest dose, had QTc measurements of > 500 msec^{1/2}.

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Publications: The sponsor submits four studies on the use of sotalol in pediatrics. In addition, there was an uncontrolled data base in pediatric and adolescent patients that was reviewed in conjunction with the supplemental NDA for the use of Betapace In the treatment of atrial fibrillation/atrial flutter. The exposure to pediatric patients in these uncontrolled data bases is far greater than in the clinical trial

1. Beaufort-Krol, GCM; Bink-Boelkens, MTE. "Effectiveness of sotalol for atrial flutter I children after surgery for congenital heart disease". Am J Cardiol 1997; 79:92-4.

Study summary: This was an uncontrolled study that involved 15 pediatric patients with atrial flutter as a consequence of repair of underlying congenital heart disease. Thirteen of these fifteen patients were enrolled in atrial fibrillation at the time of enrollment, two patients were converted prior to enrollment. The initial dose regimen was 3-4 mg/kg/day with an increase of 2 mg/kg/day to a maximum dose of 8mg/kg/day. The children were followed for a mean of 2.2 ± 1.6 years). There were no torsades or proarrhythmic events during this study. Heart rates in children without pacemakers decreased from 108 ± 44 to 90 ± 30 BPM (it is not stated when relative to dose or start of treatment these measurements were made). One patient had a pacemaker inserted during the course of the study (this child had left isomerism with and a total cavopulmonary connection).

2. Maragnes, P; Tipple, M and Fournier A; " Effectiveness of Oral Sotalol for Treatment of Pediatric Arrhythmias". Am J Cardiol 1992, 69: 751-754.

Study Summary: This was an uncontrolled, open-label observational study carried out in two hospitals. A total of 66 patients between the ages of 9 days to 24 years (obviously not all pediatric patients) were exposed to sotalol for a duration of between 2 days to 5 years (mean 13.3 ± 14.3 months). The total daily dose of sotalol ranged from 40-350 mg/M2 divided BID. The paper notes one subject who received 350 mg/M2 had an episode of syncope. Two patients had excessive bradycardia (38 and 40 BPM) , one required a pacemaker. QT intervals apparently were not prolonged (the timing of these measurements was not stated, the ECG intervals apparently were not corrected for heart rate).

3. Pfammatter, JP; Paul, T, Lehmann, C and Kallfelz, HC; "Efficacy and Proarrhythmia of Oral Sotalol in Pediatric patients" J Amer Coll Cardiol. 1995; 26: 1000-7.

Study Summary: This was an uncontrolled observational study. A total of 71 pediatric patients (mean age 7.3 ± 5.8 years; range 0.1 to 19.9 years) were treated with sotalol at a starting dose of 2 mg/kg divided into three equal doses. The majority of these patients had some form of reentrant arrhythmia (WPW=17 patients; AVNRT= 7 patients; concealed accessory pathway =16 patients, permanent junctional reciprocating tachycardia=1 patient). The dose was increased at 1-2 mg/kg at three-day intervals. Initiation and up-titration was performed under constant monitoring in hospital. The duration of treatment was not stated. There were seven subjects who had adverse rhythm events on sotalol. One patient a 1.3-year old had multiple episodes of syncope, diagnosed as torsades de pointes after one year of treatment. One patient with AVNRT had nonsustained monomorphic VT after 2 days of sotalol. Two patients had high grade AV block in one of these patients a pacemaker was

inserted. One patient had a SA block with bradycardia < 50 BPM. One patient had monomorphic ventricular bigeminy and couplets. One patient had Wenckebach second degree heart block with ventricular bigeminy. Two additional patients discontinued one due to dizziness and one due to fatigue. Three patients had transient increases in ventricular ectopy that resolved while on continued sotalol treatment.

4. Tanel, RE; Walsh, EP; Lulu, JA; Saul, JP;" Sotalol for Refractory Arrhythmias in Pediatric and Young Adult Patients: Initial Efficacy and Long-term Outcome" Am Heart J; 1995 130, 791-7.

Study Summary: This was an observational database in which 45 pediatric patients with either supraventricular or ventricular arrhythmias that were treated with sotalol. The patients ranged in age from one week to 26 years (mean 8.1 ± 7.8 years). The sotalol dosage ranged from 40-270 mg/M² day (mean 116 mg/M²). For the majority of the patients, the dosage was divided BID; the rest Q 8 H. Seven patients whose dose was changed from BID to TID were changed because of arrhythmia recurrence at the end of the dosing interval. Ten patients had adverse events, of which four patients withdrew. One patient died during therapy. There were two patients with proarrhythmic events. Other adverse events included headache (n=1); dizziness (n=1), abdominal pain (n=3); fatigue (n=1), depression (n=1), bradycardia (n=2), ventricular dysfunction (n=1), and proarrhythmia (n=2).

Additional Information.

Study 03 titled "Oral Sotalol Hydrochloride for Control of Supraventricular and Ventricular Arrhythmias in Children and Adolescents" was reviewed by Dr. U in the supplemental NDA for Betapace use in the treatment of supraventricular arrhythmias. There were 78 patients ranging from birth to 20 years old who were enrolled into this study. Of these patients 58 had supraventricular arrhythmias. These patients had arrhythmias (either supraventricular or ventricular) that were refractory to other treatments. Those patients > 6 months old were initially treated with doses at 40 mg/M² divided Q12 hours. The dose was titrated upward to an effective dose (not stated what "effective" means) to a maximum dose of 180 mg/M²/day or 320 mg/day unless approval was obtained from the clinical study director. For infants < 6 months old the initial dose were 15 mg/M² BID.

The duration of treatment for these patients is unclear from the study review. There were three sudden deaths among the 57 patients with supraventricular arrhythmias. In addition, one patient had a torsades de pointes event as well as VFib. Other serious adverse events included lack of efficacy (2 patients); asthma (1 patients), palpitation (1 patient) headache (1 patient), depression (1 patient), convulsion (1 patient) prolonged QT interval (1 patient).

Labeling Comments:

The following labeling comments are my suggestions. They have taken into account Dr. Gobburu's comments. The pages refer to the sponsor's pages.

On page 00190 the inclusion labeled as (1) and on page 191 labeled as (2) should both be removed and incorporated into a separate section labeled as pediatric Clinical Pharmacology. This section should be added right before the section labeled as "Clinical Actions"

Pediatric Clinical Pharmacology (add to page 191).

Draft

On page 192 labeled as (3)

Pharmacokinetics

Pediatrics:

1 pages redacted from this section of
the approval package consisted of draft labeling

Page 204 labeled as (7) is acceptable

Page 204 labeled as (8) is acceptable.

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Appendix 1 Sponsor's Labeling

16 pages redacted from this section of
the approval package consisted of draft labeling