Table 14

DISTRIBUTION BY SVT TYPE OF PATIENTS
RANDOMIZED TO ESMOLOL

Variable	"All Patients" N	"All Patients" %	"Efficacy Patients" N	"Efficacy Patients" %	Efficacy Ineligible Patients N	Efficacy Ineligible Patients %
A-FIB	46	72	40	75	6	55
A-FL	12	19	9	17	3	27
PSVT	1	2	0	0	1	9
AAT	3	5	3	6	0	0
ST	2	3	1	2	1	9

Table 15

DISTRIBUTION BY SVT TYPE OF PATIENTS
RANDOMIZED TO PROPRANOLOL

Variable	"All Patients" N	"All Patients" %	"Efficacy Patients" N	"Efficacy Patients" %	Efficacy Ineligible Patients N	Efficacy Ineligible Patients %
A-FIB	53	84	48	84	5	83
A-FL	9	14	8	14	1	17
ST	1	2	1	2	0	0

The distribution of "efficacy patients" by gender, race, type of SVT, primary diagnosis and post operative status was not significantly different among the two treatment groups with respect to treatment centers (see Tables 16, 16A, 17 and 17A). Analysis of Tables 18 and 19 show significant differences between centers for systolic and diastolic blood pressures: the esmolol "efficacy patients" at each center had significantly higher prestudy systolic and diastolic pressures than the propranolol "efficacy patients".

Table 18

PRESTUDY CLINICAL DATA OF "EFFICACY PATIENTS" RANDOMIZED TO ESMOLOL BY CENTER

Investigator (Center #)	N	Heart Rate (bpm)	Systolic Blood** Pressure (mm Hg)	Diastolic Blood** Pressure (mm Hg)
Waldo (06)	6	151.8±15.8	121.7±18.4	76.0±8.8
Horowitz (08)	14	147.7±17.0	112.9±13.3	72.7±9.3
Singh (09)	10	145.3±17.7	132.0±24.3	76.2±8.9
Swerdlow (15)	12	146.3±17.7	129.3±17.3	83.3±11.8
Others*	11	146.1±12.7	137.0±29.4	82.2±11.9

Values represent mean ± S.D.

* Pooled data from centers #1, 2, 5, 7, 10, 12, 13, 14.

Investigators #3, 4, 11, 16, 17, 18 did not enter any patient in the study.

** Significantly different between centers

Table 19

PRESTUDY CLINICAL DATA OF "EFFICACY PATIENTS" RANDOMIZED TO PROPRANOLOL BY CENTER

Investigator (Center #)	N	Heart Rate (bpm)	Systolic Blood** Pressure (mm Hg)	Diastolic Blood** Pressure (mm Hg)
Waldo (06)	7	145.3±7.1	112.0±9.2	71.1±4.3
Horowitz (08)	14	152.6±17.2	110.9±7.6	67.9±6.4
Singh (09)	15	146.3±26.0	121.6±14.6	74.5±9.2
Swerdlow (15)	9	139.8±10.7	120.7±21.6	79.0±14.7
Others*	12	144.2±17.0	121.0±18.3	75.7±13.5

Values represent mean ± S.D.

* Pooled data from centers #1, 2, 5, 7, 10, 12, 13, 14.

Investigators #3, 4, 11, 16, 17, 18 did not enter any patient in the study.

** Significantly different between centers

According to the sponsor "there is no significant interaction of treatment assignment with center for any of the demographic or prestudy clinical data." The significant differences across centers were similar for both treatment groups among the "efficacy patients". Overall, the randomization schedule appears to have resulted in a similar distribution of the patients in the two treatment groups with respect to demographic data, type of SVT, primary diagnosis, and prestudy heart rate.

II Efficacy Results

The therapeutic responses among "all patients" and "efficacy patients" treated with esmolol and propranolol are summarized in Tables 27, 28, 28A, 29, 34, 35, 35A, 38, 40A, 40B, 41, 41A, 42, 42A, Figures 2-5.

a. Therapeutic Endpoints

The key efficacy variable (primary endpoint) in this study was heart rate (ventricular rate). Further, the primary objective of the study was to compare the esmolol and propranolol groups with respect to the therapeutic response criteria, (A - 20% or greater reduction in heart rate from baseline, B - heart rate less than 100 bpm or conversion to NSR). Secondary objectives were to study the dosages required for therapeutic response and to study the amounts of additional heart rate reduction for successive dose increases.

b. Specific Results

In general, the sponsor's claim regarding esmolol efficacy in terms of the predefined response criteria and the direct comparison with propranolol appear valid.

i) Analysis by Treatment Group

The main finding of the study was that the therapeutic response rates were nearly identical for esmolol (72%) (36/50) and propranolol (69%) (38/55) and that the heart rate reductions for esmolol compared favorably with the heart rate reductions for propranolol both during titration and maintenance. Significant additional heart rate reductions and response were obtained with esmolol titration up to 200 mcg/kg/min. The relative therapeutic response rate above 200 mcg/kg/min was numerically less than the response rate at 200 mcg/kg/min or lower dosages.

Table 27

THERAPEUTIC RESPONSE AMONG "EFFICACY PATIENTS" DURING THE ESMOLOL AND PROPRANOLOL TITRATION PERIOD, BY DOSAGE

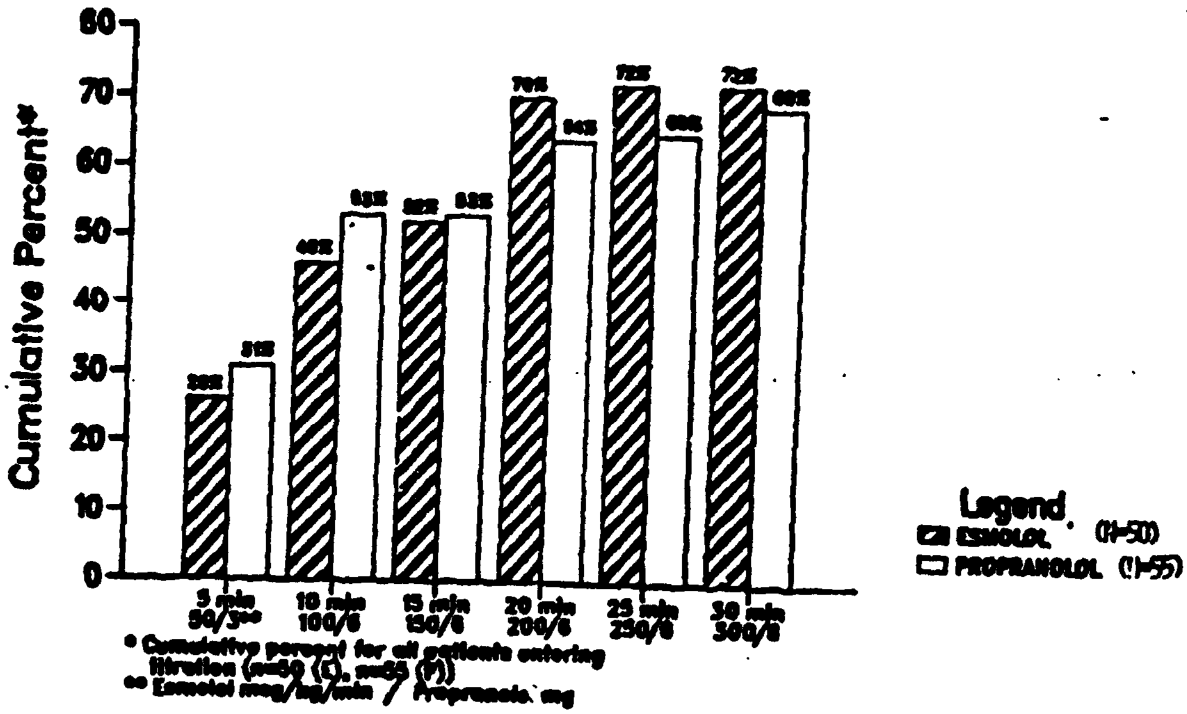
	Esmolol				Propranolol			
Time (min)	Dosage (mcg/kg/min)	Response n/N	Relative Percent(1)	Cumulative Percent(2)	Total Dose (mg)	Response n/N	Relative Percent(1)	Cumulative Percent(2)
5	50	13/50	26%	26%	3	17/55	31%	31%
10	100	10/37	27%	46%	6	12/38	32%	53%
15	150	3/27	11%	52%	6	0/25	0%	53%
20	200	9/23	39%	70%	6	6/25	24%	64%
25	250	1/13	8%	72%	6	1/15	7%	65%
[illegible]	300	0/11	0%	72%	6	2/14	14%	69%

(1) Relative = Number of responders/number of "efficacy patients" at each titration dose.

(2) Cumulative = Number of responders at that dose or a lower dose/number of "efficacy patients" (50 for esmolol, 55 for propranolol).

FIGURE 5

PERCENTAGE OF "EFFICACY PATIENTS" ACHIEVING THERAPEUTIC RESPONSE DURING THE ESMOLOL OR PROPRANOLOL TITRATION PERIOD, BY DOSAGE



There is a discrepancy in these tables regarding the number of efficacy patients tabulated for the propranolol group (Table 25 states 57-4=53 efficacy patients) vs N=55 patients included in the efficacy analysis (Table 35A). This discrepancy however does not appear to affect the overall results. The therapeutic responses among "all patients" and "efficacy patients" treated with both drugs are shown in Table 35A.

Table 39A

THERAPEUTIC RESPONSE AMONG "ALL PATIENTS" AND "EFFICACY PATIENTS" TREATED WITH ESMOLOL AND PROPRANOLOL

FACTOR	ESMOLOL				PROPRANOLOL			
	"EFFICACY PATIENTS" (N=50)		"ALL PATIENTS" (N=64)		"EFFICACY PATIENTS" (N=55)		"ALL PATIENTS" (N=63)	
Response Criteria								
≥20% Reduction	32/50	(64%)	32/64	(50%)	38/55	(69%)	38/63	(60%)
HR <100 bpm	16/50	(32%)	16/64	(25%)	19/55	(34%)	19/63	(30%)
Conversion to NSR	7/50	(14%)	9/64	(14%)	9/55	(16%)	9/63	(14%)
Total Responders*	36/50	(72%)	43/64	(67%)	38/55	(69%)	42/63	(67%)
Type of SVT								
A-FIB	28/38	(74%)	34/46	(74%)	34/46	(74%)	38/53	(72%)
Other	10/12	(83%)	9/18	(50%)	4/9	(44%)	4/10	(40%)
Gender								
Male	22/31	(71%)	28/43	(65%)	23/35	(66%)	25/38	(66%)
Female	14/19	(74%	15/21	(71%)	15/20	(75%)	17/25	(68%)
Age								
≥65 yrs	20/26	(77%)	23/34	(68%)	16/22	(73%)	18/27	(67%)
<65 yrs	16/24	(67%)	20/30	(67%)	22/33	(67%)	24/36	(67%)
Conc. Meds								
Digoxin	22/26	(84%)	26/35	(74%)	21/28	(75%)	24/31	(77%)
No Digoxin	14/24	(58%)	17/29	(59%)	17/27	(63%)	18/32	(56%)

*Some responders achieved more than one response criterion.

When categorized by the three response criteria, the response rates for the esmolol and propranolol "efficacy patients" were not significantly different. When all patients (esmolol N=64 and propranolol N=63) were included in the efficacy assessment of total responders, similar overall results were obtained (esmolol 43/64 [67%] vs propranolol 42/63 [67%]). The average dosage of esmolol in therapeutic responders among the "efficacy patients" was 115.3 ± 10.7 mcg/kg/min or 84.4 ± 0.8 mg/min.

ii) Analysis by Dose-Response

The dose response relationship of "efficacy patients" achieving therapeutic response during the esmolol or propranolol titration period is summarized in Table 27 and Figure 5. Thus, 35 of the 50 esmolol "efficacy patients" (70%) responded at or before 200 mcg/kg/min dosage.

iii) Analysis by Baseline Parameters

The average baseline heart rate was similar in esmolol responders and nonresponders (Table 28A).

Table 28A

SUMMARY OF BASELINE CLINICAL AND PRESTUDY DEMOGRAPHIC DATA VS THERAPEUTIC RESPONSE AMONG "EFFICACY PATIENTS"

	ESMOLOL		PROPRANOLOL	
	Responders (N=36)	Non-Responders (N=14)	Responders (N=38)	Non-Responders (N=17)
Baseline Heart Rate (bpm)	147.9±3.6	145.1±3.9	140.7±2.4	154.6±4.9
Baseline Systolic Blood Pressure (mm Hg)	125.9±4.0*	118.4±5.2	118.0±1.7*	109.2±2.3
Baseline Diastolic Blood Pressure (mm Hg)	76.4±1.8	78.4±2.7	74.2±1.3	73.0±2.2
Age (yrs)	65.6±1.9	62.2±2.4	62.4±1.6	62.2±2.4
Weight (kg)	73.3±2.5	73.1±4.1	76.1±2.5	78.0±4.2

* Significantly greater than non-responders in each treatment group.

In contrast, among propranolol patients the baseline heart rate was higher in nonresponders (155 bpm) than responders (141 bpm). Further, in comparing the responders between the two treatment groups, the baseline heart rate (and systolic blood pressure) was higher in the esmolol group (148 bpm) than in the propranolol group (141 bpm). However, it is not clear what effect if any this difference should or would have on therapeutic response. This could theoretically give an advantage to esmolol since fewer patients would need to reach 100 bpm but would still be a responder based on the 20% reduction criteria. It could reflect mean differences in catechol levels or adrenergic activity in the two treatment groups which conceivably might bear on sensitivity or threshold response to beta blockade. In both treatment groups, more patients who were concurrently on digoxin achieved therapeutic response than patients who didn't receive digoxin (Table 35A).

iv) Analysis By Other Variables

Therapeutic response rate within each treatment group did not significantly differ with respect to age, gender, type of SVT, primary diagnosis (i.e., coronary artery disease) and post operative status of the patients (Tables 28, 35A).

Table 28

THERAPEUTIC RESPONSE BY AGE, GENDER, TYPE OF SVT, PRIMARY DIAGNOSIS AND POSTOPERATIVE PATIENT STATUS AMONG "EFFICACY PATIENTS" TREATED WITH ESMOLOL OR PROPRANOLOL

Variable	Esmolol R/E	Propranolol R/E
Age		
≥ 65 yrs	20/26 (77%)	16/22 (73%)
< 65 yrs	16/24 (67%)	22/33 (67%)
Gender		
Males	22/31 (71%)	23/35 (66%)
Females	14/19 (74%)	15/20 (75%)
Type of SVT		
A-FIB	28/38 (74%)	34/46 (74%)
A-FL	6/8 (75%)	3/8 (38%)
ST	1/1 (100%)	1/1 (100%)
AAT	1/3 (33%)	0
Primary Diagnosis		
CAD	9/15 (60%)	12/18 (67%)
Valve Disease	5/6 (83%)	6/8 (75%)
Other	18/24 (75%)	18/26 (69%)
NR	4/5 (80%)	2/3 (67%)
Postoperative		
Yes	19/26 (73%)	19/28 (68%)
No	14/21 (67%)	19/27 (70%)
NR	3/3 (100%)	0

R/E = Number of therapeutic responders/number of "efficacy patients"

NR = Not recorded

Numbers in parentheses represent percent response

Among the "efficacy patients" who entered the maintenance period (esmolol n=30, propranolol n=36) there was no statistical difference in sustained therapeutic response in the two groups (esmolol 20/30 [67%] vs propranolol 21/36 [58%]).

vi) Analysis During Follow-Up

Analysis of heart rate during the follow up period was performed only for esmolol patients since the followup times were actually 10 and 20 minute post infusion but were various times post infusion for propranolol. Within 20 minutes after discontinuation of esmolol, heart rate returned to approximately 80% of the baseline among responders (compared to 68% of baseline heart rate at the end of infusion) indicating that esmolol's effects were reversible. While there were still significant effects on heart rate and clinical safety variables at 20 minutes post infusion, these effects were less than at the end of the infusion. For the reasons indicated above similar analysis for the propranolol group was not done. Thus it is not clear what the basis is for the sponsor's claim in the expanded overview summary that the propranolol effects lasted longer. The sponsor states in this section "in contrast, 4 hours and 20 minutes after discontinuation of propranolol, heart rate remained the same as at the end of the propranolol injection (at the end of propranolol 74.5% of baseline heart rate; during follow up; 76.3% of baseline heart rate), indicating that propranolol effects lasted longer".

vii) Analysis by Center

Primary efficacy analysis pooled data from the various treatment centers. Therapeutic response rates were also analyzed among the different study centers. These were as follows:

Center #	Treatment	
	Esmolol R/E (%)	Propranolol R/E (%)
6	5/6 (83%)	5/7 (71%)
8	9/14 (64%)	7/14 (50%)
9	6/9 (67%)	9/13 (69%)
15	9/11 (82%)	6/9 (67%)
Others	7/10 (70%)	11/12 (92%)
Total	36/50 (72%)	38/55 (69%)

R/E = Number of responders/Number of "Efficacy Patients"

Although there were variations in response rates across study centers in both treatment groups, the sponsor claims that these differences were not significant. No specific treatment by center interaction for response rates was seen.

III Safety Results

A. Clinical Safety Variables: SBP, DBP, MAP, RPP, RR; Table 51. Review of clinical safety data support the general assessment made in the synopsis that "esmolol patients had greater decreases in systolic, diastolic and mean arterial pressure and greater reductions in rate pressure product at the end of titration and throughout the maintenance than patients on propranolol." Analysis of the follow up period (10 and 20 minutes following the end of esmolol infusion) tend to support the sponsor's claim of a progressive recovery from the reduction in all these clinical variables after stopping the esmolol. In contrast among propranolol treated patients, the reduction in these variables during the follow up period was the same as at the end of the maintenance period.

Table 51

SUMMARY OF CLINICAL VARIABLES DURING TITRATION PERIOD OF PATIENTS TREATED WITH ESMOLOL OR PROPRANOLOL

		Baseline	Titration 5 Min	Titration 10 Min	Titration 15 Min	Titration 20 Min	Titration 25 Min	Titration 30 Min	Highest Titration Dosage
SBP	Esm[a]	123.7±2.0	116.6±3.0	113.3±2.0	109.1±2.0	108.1±2.3	108.7±3.2	104.3±3.3	107.7±2.7
(mm Hg)	Prop[b]	119.3±3.4	112.4±3.0	110.7±2.0	110.7±2.3	110.6±2.5	110.3±3.4	108.7±3.4	111.7±2.0
Δ SBP	Esm		-6.9±1.3**	-10.3±1.3**	-14.8±2.2**	-16.3±2.2**	-15.0±3.4**	-17.4±2.3**	-15.8±2.0**
(mm Hg)	Prop		-3.9±1.0**	-4.3±1.3**	-5.5±1.0**	-4.0±1.3**	-3.6±2.0	-5.2±1.9**	-4.3±1.2**
DBP	Esm	76.8±1.3	75.3±1.4	73.8±1.3	71.3±1.7	70.3±1.7	70.0±2.4	70.0±2.2	71.0±1.3
(mm Hg)	Prop	73.8±1.2	74.3±1.4	72.4±1.3	72.9±2.1	72.9±2.3	74.0±2.4	72.3±2.3	71.6±1.4
Δ DBP	Esm		-1.7±0.9	-2.9±0.9**	-4.3±1.3**	-4.9±1.3**	-5.9±2.1**	-6.0±2.0**	-5.9±1.2**
(mm Hg)	Prop		-0.2±0.8	-2.2±1.2	-2.3±1.0**	-2.0±1.3	0.0±1.3	-2.2±1.9	-2.0±1.0**
MAP	Esm	92.4±1.6	89.3±1.7	87.0±1.8	85.9±1.9	82.4±1.8	82.5±2.4	82.1±2.4	83.3±1.6
(mm Hg)	Prop	87.7±1.2	87.0±1.4	85.2±1.6	85.3±2.1	85.3±2.2	86.2±2.3	84.4±2.4	84.9±1.3
Δ MAP	Esm		-3.2±0.6**	-5.3±0.9**	-7.3±1.3**	-8.6±1.4**	-8.9±2.3**	-10.3±1.8**	-9.1±1.3**
(mm Hg)	Prop		-1.4±0.7**	-3.3±1.1**	-3.4±1.2**	-3.0±1.2**	-1.8±1.2	-3.9±1.8**	-3.2±0.9**
	Esm	16.8±0.4	14.3±0.4	13.8±0.4	13.4±0.4	12.7±0.4	12.0±0.3	12.6±0.3	12.0±0.4
R P P	Prop	16.0±0.3	14.0±0.4	13.7±0.4	14.0±0.5	13.7±0.5	14.1±0.8	13.6±0.7	12.3±0.4
R P P	Esm		10.6±1.0**	23.1±1.6**	23.1±2.1**	28.9±2.3	27.1±3.4**	27.7±2.9**	32.0±2.0**
Decrease (%)	Prop		17.4±1.0**	19.7±1.0**	17.0±1.9**	19.9±2.2**	18.1±3.4**	28.7±2.0**	28.7±1.9**
Sample	Esm	63	62	53	44	41	27	21	62
Size[c]	Prop	62	63	50	43	39	23	23	61

Esm = Esmolol; Prop = Propranolol

a Esmolol Dose Schedule: 50 ug/kg/min-5 min; 100 ug/kg/min-10 min; 150 ug/kg/min-15 min; 200 mcg/kg/min-20 min; 250 mcg/kg/min-25 min; 300 mcg/kg/min-30 min.

b Propranolol Dose Schedule: 1 mg-1 min; 1 mg-2 min; 1 mg-3 min; 1 mg-4 min; 1 mg-7 min; and 1 mg-8 min.

** Indicates significant change from baseline (p≤0.05).

c Sample size variation at each time period reflects either absence of the data in some patients or patients completing the titration period at various times (i.e. 5 to 30 minutes).

RPP = Rate Pressure Product (Heart Rate x SBP/1000)

Values are given as average ± SEM

8. Adverse Effects: Tabulation of adverse effects observed during the study is summarized in the following tables: 45, 49, 50. Safety was a.sessed in the 127 "all patients" treated with esmolol (N=64) and with propranolol (N=63) during the study. 29 patients treated with esmolol (45%) and 11 patients treated with propranolol (18%) were reported to have adverse effects. 41% (26/64) of esmolol patients and 10% (6/63) of propranolol patients developed cardiovascular adverse effects (Table 45).

Table 45

SUMMARY OF ADVERSE EFFECTS, BY BODY SYSTEM IN PATIENTS TREATED WITH ESMOLOL OR PROPRANOLOL

Body System	Type of Reaction	Number of Patients Esmolol	Propranolol
Cardiovascular	Symptomatic Hypotension	4	1
	Asymptomatic Hypotension	19	3
	Premature Ventricular Contraction	1	0
	Increased Congestive Heart Failure	0	1
	Bradycardia	0	2
	Dyspnea	1	0
	Diaphoresis	4	0
	Subtotal*	26	6
Central Nervous System	Dizziness	1	0
	Weakness	1	0
	Headache	0	1
	Subtotal*	2	1
Gastrointestinal	Nausea	0	4
	Vomiting	0	1
	Taste Perversion	0	1
	Subtotal*	0	4
Respiratory	Rales	1	0
	Cyanosis	0	1
	Shortness of Breath	0	1
	Subtotal*	1	1
Miscellaneous	Burning at IV site	1	0
	Injection Site Inflammation	1	0
	Injection Site Erythema	1	0
	IV infiltration	2	0
	Subtotal*	5	0

* Some patients experienced more than one of the above adverse reactions

The most frequently reported adverse effects in the esmolol group was hypotension in 23 patients. Four of 23 were symptomatic with esmolol vs 1/4 with propranolol. Criteria hypotension (as defined by systolic pressure or diastolic pressure less than 90/50 mm Hg) was seen in 27 esmolol patients (includes 16 reported patients) and in 10 propranolol patients (includes 3 reported patients). Thus a total of 34 esmolol patients and 11 propranolol patients developed hypotension. Thus 53% (34/64) of esmolol treated patients developed hypotension. In the majority of patients, onset of hypotension occurred during the titration period although there appear to be no clear relationship to esmolol dosage and hypotension (Table 49).

Table 49

INCIDENCE OF REPORTED HYPOTENSION BY ACC CRITERIA
VS ESMOLOL DOSAGE

Esmolol Dosage at Onset (mcg/kg/min)	Patients Who First Developed Hypotension (by ACC Criteria) at the Respective Dosages (N=27*)		
	Titration	Maintenance	Total
50	2	2	4
100	0	1	1
150	3	1	4
200	2	2	4
250	1	2	3
300	1	7	8
500+	1	0	1
200 or Lower	7	6	13
250,300 or 500+	3	9	12
All Dosages	10	15	25*

* Remaining two patients (#1505, 1512) developed hypotension within the first 10 minutes after discontinuation of esmolol infusion.
\+ 500 mcg/kg/min was infused only during one minute intervals as a loading dose. See Appendix IX, Protocol.

The majority of the hypotensive patients in the esmolol group were postoperative 25/34 and were greater than 65 years of age (18/34). In the propranolol group the distribution of hypotensive patients by these two categories was 5/11 postoperative and 6/11 (greater than or equal to 65 years). There was also a difference in the incidence of hypotension with respect to the treatment center (Table 50).

Table 50

FREQUENCY OF REPORTED HYPOTENSION AND
CRITERIA HYPOTENSION BY CENTER*

	Esmolol				
	Mean Baseline Clinical Variables			Investigator Reported Hypotension	ACC Criteria# Hypotension
	HR (bpm)	SBP (mm Hg)	DBP (mm Hg)		
Center 6	155	115	76	7/8 (88%)	4/8 (50%)
Center 8	145	115	71	8/15 (53%)	6/15 (40%)
Center 9	144	129	78	1/13 (8%)	2/13 (15%)
Center 15	140	124	83	1/12 (8%)	5/12 (42%)
Other	150	132	77	6/16 (38%)	10/16 (62%)
Total	147+	124+	77+	23/64 (36%)	27/64 (42%)

	Propranolol				
	Mean Baseline Clinical Variables			Investigator Reported Hypotension	ACC Criteria# Hypotension
	HR (bpm)	SBP (mm Hg)	DBP (mm Hg)		
Center 6	147	112	67	0/9 (0%)	1/9 (11%)
Center 8	149	110	68	1/14 (7%)	0/14 (0%)
Center 9	146	120	76	0/15 (0%)	1/15 (7%)
Center 15	141	116	81	1/11 (9%)	4/11 (36%)
Other	142	119	76	2/14 (14%)	3/14 (21%)
Total	145+	115+	74+	4/63 (6%)	9/63 (14%)

* Ratios are number of cases/number of patients who received drug.

\# Criteria hypotension is SBP <90 mm Hg or DBP <50 mm Hg.

\+ Mean of all the centers

Relative differences among certain centers with respect to key clinical variables may be related to differences in patient samples from center to center. In addition, there appeared to be a significant inverse relationship between the occurrence of investigator reported hypotension and the use of digoxin as a concurrent medication (see Table).

Hypotension Reported by the Investigator	Esmolol Without Digoxin	Patients With Digoxin	Propranolol Without Digoxin	Patients With Digoxin
Yes	16 (55%)	7 (20%)	4 (12%)	0
No	13 (45%)	28 (80%)	28 (88%)	31 (100%)
Total	29	35	32	31

This latter finding lends support to the hypothesis that one mechanism of the hypotension associated with esmolol is related to the negative inotropic effect observed with beta blockade. This is further supported by the clinical data that some patients in the study develop rales and shortness of breath with dyspnea (probably indicative of congestive heart failure).

C. Dropouts/Terminations

(See Tables 20 and 22 for summary of "all patients" at each study phase.)

Tables 21 (esmolol) and 23 (propranolol) summarize the reasons for the discontinuation of patients assigned to either treatment group. A total of 32 esmolol-treated patients (including 12 nonresponders) and 28 propranolol-treated patients (including 12 nonresponders) were discontinued from the study. Analysis of the data indicates that a similar number of "all patients" in both groups entered the maintenance period [N=37 (B) N=39 (P)] and a similar number completed the maintenance period [N=26 (B), N=30 (P)]. However, a major difference relates to the reasons for patient termination from the study (especially for terminations during the maintenance period). Approximately 45% (7/16) of the esmolol terminations were related to hypotension whereas 41% (7/17) of the propranolol terminations were related to recurrence of SVT (as opposed to only 2/17 for esmolol). Therefore, hypotension was a major factor for esmolol treated patients.

Analysis of Tables 21 and 23 further reveals that overall of the 64 patients treated with esmolol, 15 patients were terminated prematurely from the study due to hypotension.

Table 21

REASONS FOR DISCONTINUATION FROM THE STUDY
OF PATIENTS RANDOMIZED TO ESMOLOL

Patient #	Period of Discontinuation		Reason for Discontinuation
502	Titration	2.5 mins	Hypotension
504	Maintenance	120 mins	Recurrence of SVT and hypotension
602	Maintenance	160 mins	Hypotension
603	Titration	20 mins	No therapeutic response and hypotension
610	Titration	5 mins	Hypotension
611	Maintenance	200 mins	Hypotension
614	Maintenance	90 mins	Recurrence of SVT
616	Maintenance	80 mins	Hypotension
618	Titration	20 mins	Rhythm changed from A-FIB to A-FL and hypotension
701	Maintenance	100 mins	Patient request
705	Titration	25 mins	Patient request
802	Maintenance	9 mins	Recurrence of SVT
804	Maintenance	16 mins	Investigator not satisfied with heart rate reduction
806	Maintenance	120 mins	Recurrence of SVT
812	Titration	30 mins	No therapeutic response
814	Maintenance	27 mins	No therapeutic response and hypotension
816	Maintenance	40 mins	No therapeutic response and hypotension
818	Maintenance	40 mins	No therapeutic response and hypotension

Table 21 (Continued)

REASONS FOR DISCONTINUATION FROM THE STUDY OF PATIENTS RANDOMIZED TO ESMOLOL

Patient #	Period of Discontinuation		Reason for Discontinuation
820	Maintenance	24 mins	No therapeutic response and hypotension
828	Titration	30 mins	Investigator not satisfied with therapeutic response
829	Titration	30 mins	Investigator not satisfied with heart rate reduction
913	Titration	30 mins	No therapeutic response
926	Titration	30 mins	No therapeutic response
929	Titration	30 mins	No therapeutic response
1202	Maintenance	120 mins	No therapeutic response
1307	Titration	15 mins	Hypotension
1407	Titration	25 mins	Hypotension
1505*	Maintenance	11 mins	Investigator not satisfied with heart rate reduction
1506	Maintenance	20 mins	Hypotension
1512	Titration	30 mins	No therapeutic response
1526	Maintenance	80 mins	Patient request
1528	Titration	30 mins	No therapeutic response

* Although this patient entered the maintenance period, clinical observations were not obtained prior to discontinuation. This patient had the last observations taken at the end of the dose titration period.

Table 23

REASONS FOR DISCONTINUATION OF THE STUDY OF PATIENTS RANDOMIZED TO PROPRANOLOL

Patient #	Period of Discontinuation		Reason for Discontinuation
102	Titration	20 mins	No therapeutic response
501	Maintenance	140 mins	Recurrence of SVT
604	Maintenance	140 mins	2 ampuls of drug accidentally broken
606	Maintenance	55 mins	No therapeutic response
609	Maintenance	20 mins	Recurrence of SVT
703	Maintenance	30 mins	Increasing congestive heart failure
805	Maintenance	100 mins	Investigator not satisfied with heart rate reduction
813	Maintenance	10 mins	No therapeutic response
815	Maintenance	20 mins	No therapeutic response
817	Maintenance	160 mins	Recurrence of SVT
819	Maintenance	20 mins	No therapeutic response
822	Maintenance	20 mins	Shortness of breath and cyanosis
827	Titration	30 mins	No therapeutic response
903	Titration	30 mins	No therapeutic response

Table 23 (Continued)

REASONS FOR DISCONTINUATION OF THE STUDY OF PATIENTS RANDOMIZED TO PROPRANOLOL

Patient #	Period of Discontinuation		Reason for Discontinuation
909	Titration	10 mins	No therapeutic response and nausea
921	Maintenance	40 mins	No therapeutic response
930	Titration	30 mins	No therapeutic response
1203	Titration	25 mins	Sinus bradycardia
1303	Maintenance	200 mins	Recurrence of SVT
1305	Titration	30 mins	Investigator not satisfied with heart rate reduction
1309	Maintenance	140 mins	Recurrence of SVT
1511	Maintenance	200 mins	Nausea/vomiting and headache
1513	Titration	30 mins	Patient request
1514	Titration	30 mins	No therapeutic response
1519	Titration	20 mins	Hypotension and nausea
1523	Titration	30 mins	No therapeutic response
1527	Maintenance	120 mins	Recurrence of SVT
1529	Maintenance	25 mins	Recurrence of SVT

Of the 63 patients treated with propranolol 6 patients were terminated prematurely from the study due to the following adverse effects.

Patient #	Adverse Effect
703	Progressive congestive heart failure
822	Shortness of breath, cyanosis
909	Nausea
1203	Bradycardia, hypotension
1511	Nausea, vomiting, headache
1519	Nausea, hypotension

D. Deaths

One patient treated with esmolol (#1506) and one patient treated with propranolol (#1527) died within 12 hours after D/C of study drugs.

E. Other Side Effects and Relationship to Dose

Five of the 64 esmolol patients developed infusion site reactions during the study. However, none of the patients were discontinued from the study and all reactions were resolved by change of IV site. The occurrence of adverse effects was more frequent in patients receiving esmolol at doses $\geq$ 200 mcg/kg/min than in patients with doses < 200 mcg/kg/min. The distribution of adverse effects by dose is as follows:

50	mcg/kg/min ---	6
100	" ---	1
150	" ---	6
200	" ---	11
250	" ---	5
300	" ---	4
500	" ---	1

Since the sample size is quite small, a clear dose relationship cannot be established from this data.

Review of Supportive Evidence (Partially Controlled Trials) of Efficacy for Brevibloc In SVT:

i - 8052-83-23/30/36 (Study 1)

ii - 8052-83-31 (Study 2)

iii - 8052-83-33 (Other Trial)

A. Overview

Two multicenter trials were conducted to examine the safety and effectiveness of esmolol in the treatment of SVT. These studies were baseline controlled and, based on the very small placebo response rate found in the controlled trial reported in the previous section (study 8052-82-05), provide additional evidence of efficacy in a relatively large number of patients. Both of the above studies shared certain basic common features regarding: (1) esmolol dosage and titration schedule, (2) primary entrance criteria and patient selection (HR greater than or equal to 100 bpm in hospitalized patients with persistent SVT), (3) primary endpoint (15% or greater reduction from the average baseline HR or conversion to NSR) and (4) similar maintenance titration (6-24 hours). The major differences in these studies revolved around the number of patients enrolled - 160 (study 1) vs 49 (study 2). In addition, study 2 also evaluated transfer from esmolol to an alternative antiarrhythmic agent. Similar overall therapeutic response rates were observed in these studies during the (a) titration period: 79% (116/147) for study 1 and

81% (29/36) for study 2; (b) maintenance period: 60% (60/99) for study 1 and 75% (21/28) for study 2. Furthermore, in both studies a dose response relationship was observed with increasing doses of esmolol i.e., 74% and 79% of "efficacy patients" responded at or below the 200 mcg/kg min dosage. In addition, preliminary data from study 2 (the trial is still ongoing) suggest that the majority of the SVT patients, whose HR was controlled by esmolol alone, were successfully transferred to other alternate antiarrhythmic agents without clinically significant loss of therapeutic response. A similar pattern and incidence of ADE and premature terminations due to ADE was noted in the two studies: cardiovascular ADE - 51% (study 1) and 48% (study 2) and terminations - 21% (study 1) and 25% (study 2). In general, the overall therapeutic results of these two studies appear consistent with the findings of the two pivotal studies and hence serve to reinforce the overall conclusions re safety and efficacy of esmolol in patients with SVT.

B. Specific Results

(i) Study 1 8052-83-23/30/36

Study Design

This was a multicenter baseline controlled trial involving 22 investigators.

Study 1 includes three protocols. The basic protocol (study 8052-83-23) was followed by 22 investigators. Another investigator followed 8052-83-30 and another followed 8052-83-36. These two protocols added the evaluation of hemodynamic effects of esmolol and one (8052-83-30) studied patients who were on a stable dose of a conventional beta blocking agent. The results of these 3 protocols are incorporated in a single study report (volumes 3.46, page 1).

Study Objectives and Patient Selection Criteria

The objectives of this open label baseline controlled study were: to determine the safety and efficacy of I.V. esmolol administered through a large peripheral vein in the treatment of persistent SVT in hospitalized patients when infused for periods up to 24 hours. The primary entrance criteria was an average heart rate of 100 or more beats per minute (bpm) during a 30 minute baseline period.

Patient Numbers - "All", "Efficacy", "Exclusions"

162 patients were entered into the study. Of these, 2 patients were assigned patient numbers but never received esmolol. Thus 160 patients received esmolol in the study. These patients are refered to as "all patients". The protocol was adhered to in 147 of the 160 "all patients" and these patients were classified as "efficacy patients". 13 patients were not included in the efficacy patients group. The reasons for

excluding these patients were: administration of concurrent medications which might affect the efficacy and safety of esmolol (3 patients), baseline heart rate less than 100 bpm (4 patients), deviation from the dose titration schedule (5 patients), and entrance criteria deviation (1 patient). Thus the data from the remaining 147 patients were included in the analysis of therapeutic response. Safety assessment was based on the analysis of the data from 160 "all patients"; however partial laboratory data from 19 patients were excluded from safety analysis. Reasons for exclusions were either samples were hemolyzed and/or followup samples were collected 24 hours after the discontinuation of esmolol.

Treatment Plan and Response Criteria

Following completion of a 30 minute baseline period during which the stability of the patient's SVT was assessed, esmolol was administered in a 5 to 105 minute dose titration period (the length of the dose titration period was increased from 90 minutes to 105 minutes by protocol amendment dated March 14, 1984).

Brevibloc was titrated according to the following schedule:

First Titration	500 mcg/kg/min for 0.5 minutes 25 mcg/kg/min for 4.5 minutes*
Second Titration	500 mcg/kg/min for 0.5 minutes 50 mcg/kg/min for 4.5 minutes*
Third Titration	500 mcg/kg/min for 1.0 minutes 100 mcg/kg/min for 4.0 minutes*
Fourth Titration	500 mcg/kg/min for 1.0 minutes 150 mcg/kg/min for 4.0 minutes*
Fifth Titration	500 mcg/kg/min for 1.0 minutes 200 mcg/kg/min for 4.0 minutes*
Sixth Titration	500 mcg/kg/min for 1.0 minutes 250 mcg/kg/min for 4.0 minutes*
Seventh Titration	500 mcg/kg/min for 1.0 minutes 300 mcg/kg/min for 4.0 minutes*

* The maintenance infusion period of each titration dose could be extended up to 14 minutes.

Response Criteria

The titration procedure was continued for each patient until achievement of a specified therapeutic response, i.e., 15% or greater reduction from the average baseline heart rate or conversion to normal sinus rhythm. If a significant adverse effect occurred, the dose of esmolol was reduced or discontinued. If the patient exhibited a therapeutic response during the esmolol dose titration period, the patient was entered into a 24 hour maintenance period, during which esmolol was administered at the dosage at which the response was achieved. All patients who received esmolol regardless of whether or not they completed the titration or maintenance periods were entered into a 30 minute follow up period following discontinuation of esmolol.

Efficacy Results

The sponsor summarizes the efficacy data for this study as follows "the drug was found to be effective (either a greater than or equal to 15% reduction in heart rate or a conversion to NSR) at a dose as low as 25 mcg/kg/min." The overall therapeutic response rate was 79%, similar to that observed in the two well controlled studies. The average effective dosage among responders was 97.2 mcg/kg/min. In 18% of the patients, SVT was converted to NSR. Therapeutic response rates were similar among patients with ages less than 65 years and greater than 65 years; and between postoperative and nonpostoperative patients. Reversal of heart rate reduction after discontinuation of esmolol had no relationship to the length of infusion. Therapeutic response was similar among patients with atrial fibrillation, atrial flutter or sinus tachycardia.

Safety Results

113 patients were reported by the investigators to have developed an adverse effect. The most frequently reported adverse effect pertained to the cardiovascular system. 51% (81/160) of the patients exhibited cardiovascular related adverse effects. A total of 33 patients (21%) were terminated from the study prematurely due to adverse effects. 24 of the 159 patients (15%) who received esmolol via peripheral vein, developed infusion site reactions during the study. None of these patients were terminated from the study and all reactions resolved after the I.V. site was changed or after the infusion was discontinued. No relationship was observed between gender, age or type of SVT and the occurrence of adverse effects. No relationship between the length of duration of the esmolol infusion and the occurrence of adverse effects were seen. A list of reported adverse effects are shown in the Table below.

Table

LISTING OF ADVERSE EFFECTS BY BODY SYSTEM

Body System	Adverse Effect	Number of Patients*
Cardiovascular	Hypotension	70
	Diaphoresis	16
	Peripheral ischemia	3
	Narrowed pulse pressure	2
	Recurrence of supraventricular tachycardia	2
	Cardiac dyspnea	2
	Pallor	2
	Flushing	2
	Chest pain	1
	Angina	1
	Bradycardia	1
	Ventricular arrhythmia	1
	Increased pulmonary artery pressure	1
	Pulmonary edema	1
	Subtotal	8[illegible]
Central Nervous System	Somnolence	11
	Agitation	7
	Headache	6
	Dizziness	6
	Confusion	5
	Fatigue	3
	Paresthesia	2
	Asthenia	2
	Depression	2
	Abnormal thinking	1
	Anxiety	1
	Anorexia	1
	Subtotal	39
Gastrointestinal	Nausea	20
	Vomiting	3
	Dry mouth	3
	Abdominal discomfort	2
	Dyspepsia	1
	Constipation[a]	1
	Subtotal	26

Table (Continued)

LISTING OF ADVERSE EFFECTS BY BODY SYSTEM

Body System	Adverse Effect	Number of Patients*
Respiratory	Dyspnea and Cheyne Stokes respirations	1
	Bronchospasm	1
	Rales	1
	Rhonchi	1
	Wheezing	1
	Nasal congestion	1
	Pharyngitis	1
	Increased pleural effusion and atelectasis	1
	Common cold	1
	Pleural Pain	1
	Subtotal	8
Genitourinary	Urinary retention	3
	Subtotal	3
Special Senses	Speech disorder	1
	Abnormal vision	1
	Subtotal	2
General	Mid-scapular pain	1
Skin	IV induration	7
	IV inflammation	8
	Ecchymosis of IV site	1
	Edema at IV site	1
	Erythema	1
	Skin discoloration (blue palm)	1
	Enlarged macular area (axilla)[a]	1
	IV Infiltration	7
	Subtotal	24

[a] Began prior to the start of the esmolol infusion.

* Some patients exhibited more than one adverse effect and therefore were listed more than once.

Symptomatic hypotension developed in 21 patients and asymptomatic hypotension developed in an additional 49 patients. Thus a total of 70 patients developed hypotension during the study. The following data reproduced from the overview summary characterizes the hypotension observed in the study.

1. Of the 70 patients who developed hypotension (symptomatic or asymptomatic), 29 patients had the onset during the dose titration period and 33 had onset during the maintenance period. The remaining eight patients had onset of hypotension during either the pre or postinfusion periods.

2. The average dose of Brevibloc at the onset of hypotension (139.7±11.5 mcg/kg/min) was higher than the average dose of Brevibloc at which therapeutic response occurred (106.4±9.5 mcg/kg/min).

3. More postoperative patients (50/100 or 50%) than non-postoperative patients (20/60 or 33%) developed hypotension and the average dose of Brevibloc at which hypotension occurred was lower in postoperative patients (123.3±10.7 mcg/kg/min) than in non-postoperative patients (204.2±21.6 mcg/kg/min).

4. The average dose of Brevibloc at which hypotension occurred was similar for patients <65 years and ≥65 years of age (146.2±13.3 vs 146.4±19.4 mcg/kg/min).

5. An inverse relationship between the average base line SBP and DBP and the frequency of hypotension was seen.

6. The majority of patients with hypotension (61 out of 70) had received medications concurrently with Brevibloc which could lower blood pressure.

7. In a total of 21 patients, the Brevibloc infusion was discontinued due to the development of hypotension. The majority of these patients (15/21) received medications concurrently with Brévibloc which could lower blood pressure.

8. Of the 62 patients with onset of hypotension during the Brevibloc infusion, hypotension resolved in 36 patients while the infusion of Brevibloc continued. Of the remaining 26 patients, hypotension resolved after discontinuation of Brevibloc and in the majority of these patients (21/26) resolution occurred within 30 minutes after discontinuation.

b. Clinical Safety Variables

Statistically significant dose dependent reductions in SBP, DBP, MAP, and RPP in the titration and maintenance periods were obtained. In most of these variables, significant reversal to the baseline level was observed within 60 minutes after discontinuation of esmolol.

c. Disease States Associated with Increase Risk in Treatment with Beta Blockers

Forty of the sixty-one patients with disease states associated with increased risks from beta blockers, developed adverse effects. 11 of the 40 patients were terminated from the study due to adverse effects. The majority of the 61 patients tolerated treatment with esmolol.

d. Renal Disease

Of the 8 patients who entered the study with possible renal impairment, 4 patients developed adverse effects and one patient was dropped due to adverse effects. However, the investigators did not definitely attribute the relationship of the adverse effects to esmolol in any of these patients.

e. Hemodynamic Data

Four patients entered into the study had hemodynamic data collected. All four patients were evaluated within 3 days after coronary artery by-pass surgery and all were therapeutic responders to esmolol. 3 of the 4 had a prior history of myocardial infarction. The major hemodynamic findings were (1) significant reduction in heart rate and decreases in SBP; (2) decreases in cardiac output and cardiac index largely due to a reduction in heart rate; (3) decreased stroke work index; (4) small increases in systemic vascular resistance secondary to reduced cardiac output and systolic arterial pressure and (5) increased pulmonary arterial resistance.

Conclusion:

According to the sponsor in most of the patients with hypotension, resolution occurred within 30 minutes after discontinuation of esmolol. esmolol was generally well tolerated in patients with disease states which placed them at risk from treatment with beta blocking agents. No clinically significant trend was seen among changes in laboratory variables.

(ii) Study 2 (8052-83-31)

Study Design

This was a multicenter open label baseline controlled trial involving 10 investigtors. The design was similar to that of the previous trial but included transfering patients whose SVT was controlled on esmolol to an alternative antiarrhythmic agent. This study remains in progress (so this represents an interim report).

Study Objectives

To determine the feasibility of transfering patients with supraventricular tachycardia whose heart rate was controlled by an infusion of esmolol to an alternate antiarrhythmic agent without a clinically significant loss in therapeutic response.

Patient Selection Criteria

Same as previous study.

Treatment Plan and Response Criteria

Same as previous study (See Study 8052-83-23).

Alternate Drug Treatment

Following successful completion of the esmolol maintenance period, the patient entered the alternate drug therapy part. The first dose of the alternate antiarrhythmic agent chosen by the investigator for the patient was administered at time 0 of the alternate drug therapy. The dose of esmolol was adjusted, as indicated in the protocol, based on the pharmacokinetics of esmolol and each of the alternate antiarrhythmic agents (see Guidelines for alternate drug therapy). Following the second dose of the alternate antiarrhythmic agent, esmolol was continued for a period of time suggested in the protocol and was then discontinued.

Patient Numbers - "All", "Efficacy", "Exclusions"

49 patients were entered into the study. Investigators adhered to the protocol in 36 of these patients and these were classified as "efficacy patients." 13 patients were not included in the efficacy patients group. The reasons for excluding these patients were "administration of concomitant medications which might effect the efficacy and safety of esmolol (2 patients), sinus tachycardia possibly due to administration of theophylline (3 patients), dose schedule deviations during the titration period (4 patients), and dosage deviations during the titration period (4 patients). Thus the data from the remaining 36 patients were used in the analysis of therapeutic response. Safety assessment was based on analysis of the data from 49 "all patients". Since the study is still ongoing this is an interm report of a total of 49 patients.

Efficacy Results

According to the summary provided by the sponsor "esmolol was found to be effective (either a greater than or equal to 15% reduction in heart rate or a conversion to NSR) in a dosage range of 25 to 150 mcg/kg/min in the treatment of patients with SVT. The overall therapeutic response rate was 78%. The average effective dose among these responders was 61.8 mcg/kg/min. In 14% of the patients, SVT was converted to NSR. The number of patients who were successfully transfered from esmolol to other alternate antiarrhythmic agents was as follows: oral verapamil-1/2 (50%); oral or I.V. digoxin-7/12 (58%); oral propranolol-8/11 (73%); oral metoprolol-2/3 (67%); oral quinidine-1/1 (100%); oral digoxin plus oral quinidine-0/2 (0%); oral digoxin plus oral verapamil-1/1 (100%); and oral digoxin plus oral metoprolol-0/1 (0%) (this patient did not complete the study due to the investigator's concern over a low heart rate). According to the sponsor, the data obtained from these patients revealed that the majority of the SVT patients, whose heart rate was controlled by esmolol alone, were successfully transferred to other alternate antiarrhythmic agents without clinically significant loss of therapeutic response. The recommended dosage schedule for transition from I.V. esmolol to an alternate antiarrhythmic agent is provided in the accompanying figure.

Recommended Schedule For Transition From
Esmolol to an Alternate Antiarrhythmic Agent*

Verapamil (N=1)		Propranolol (N=8)		Quinidine (N=1)		Digoxin			
						Oral (N=3)		IV (N=4)	
Dose* Of Esmolol	Verapamil	Dose* Of Esmolol	Propranolol	Dose* Of Esmolol	Quinidine	Dose* Of Esmolol	Digoxin	Dose* Of Esmolol	Digoxin (N=8)
200	80 mg q.8h	25-200	10-20 mg q.4h-q.6h	50	200 mg q.2h	50-300	0.125-0.5 mg q.6h	25-150	0.125-0.5 mg q.6h

- Dose range of esmolol (mcg/kg/min) at the end of the maintenance period on which the patient(s) maintained therapeutic response.
- The dosage of Brevibloc should be reduced as follows:

1. Within the first hour following the first dose of the alternative agent, reduce the Brevibloc infusion rate to one-half (50%).
2. Following the second dose of the alternative agent, monitor the patient's response and if satisfactory, control is maintained for the first hour", discontinue the Brevibloc infusion.

Safety Results

Safety was assessed in the 49 "all patients" treated with esmolol. 27 patients were reported by the investigators to have adverse effects. The most frequently reported adverse effect pertained to the cardiovascular system. 48% (24/49) of the patients developed cardiovascular related adverse effects. All reported adverse effects are shown in the table below.

Table 31

Adverse Effects by Body System

Body System	Adverse Effect	
Cardiovascular	Hypotension	24
	Diaphoresis	4
	Chest pain	1
	Abnormal ECG	1
	Heart block	1
	Syncope	1
	Number of Patients	24
Central Nervous System	Headache	2
	Confusion	3
	Fatigue	1
	Dizziness	2
	Number of Patients	7
Gastrointestinal	Nausea	3
	Vomiting	1
	Abnormal pain	1
	Constipation	1
	Number of Patients	4
Respiratory	Wheezing	1
	Number of Patients	1
Miscellaneous	Abnormal Vision	1
	Rigors	1
	Fever	1
	Injection Site	2
	Number of Patients	2
ALL	TOTAL	27*

* Some patients had more than one adverse effect and were therefore counted twice.

Twelve patients were discontinued prematurely from the study due to the development of adverse effects. In 6 of these patients, adverse effects were attributed to esmolol. No dose dependent relationship was seen in the development of adverse effects. The frequency of occurrence of adverse effects was similar in patients less than 65 years of age (28%) and in patients greater than 65 years of age (26%). More nonpostoperative patients (64%) than post operative patients (46%) developed adverse effects. Of the 24 patients with hypotension, 16 patients developed hypotension during the esmolol titration or maintenance period. Of the remaining 8 patients, 6 patients developed hypotension during the alternative drug therapy period and 2 patients had hypotension prior to the start of the esmolol infusion. Among patients who developed hypotension, esmolol dosage data revealed no dose dependent relationship. In the majority of the patients, hypotension resolved either during the study while esmolol infusion was still going, or within 20 minutes after discontinuation of esmolol. Among the patients (n=19) in the study with diseased states associated with increased risk from treatment with beta blockers, 12 patients developed adverse effects. Four of these patients were terminated from the study due to the development of adverse effects. No clinically significant trend was seen among changes in laboratory variables.

Other Trials (8052-83-33)

One additional open pilot study was undertaken to examine the safety and effects of esmolol in patients with myocardial infarction or unstable angina pectoris who in the judgement of the treating physician and the investigators would benefit from a reduction in heart rate. This study was intended to evaluate the effects of esmolol in these patients using Swan-Ganz hemodynamic monitoring and continuous Holter monitoring to assess ST segment changes and changes in incidence, frequency and characterization of arrhythmias (study 8052-83-33).

Study 8052-83-33

Number of Patients

19 patients entered and completed the study. All 19 patients received esmolol and were analyzed for changes from baseline in hemodynamic parameters during esmolol infusion and in the post infusion period. Four patients did not have invasive Swan-Ganz monitoring performed. Safety analysis was based on data from all 19 patients.

Treatment Plan

Following a baseline controlled period, esmolol was infused in a step wise fashion from 50 mcg/kg/min to 300 mcg/kg/min (50 mcg/kg/min increments): each dose was given for 4-14 minutes with each increase in dose preceeded by a loading dose of 500 mcg/kg/min for 1 minute.

Response Criteria

Heart rate, blood pressure, respiration rate and hemodynamic measurements including cardiac index and pulmonary artery catheter measurements were obtained during baseline, after each dose titration period, during maintenance and the follow up period.

Study Population

7 of the 19 patients entered into this study had unstable angina and 12 patients had myocardial infarction.

Pharmacodynamic Results

Each dose of esmolol tended to produce a progressive decrease in heart rate, systolic blood pressure, mean arterial pressure and rate pressure product suggesting a dose response effect for these variables. A decrease in heart rate occurred for all patients within the first 5 minutes (50 mcg/kg/min dosage) of study drug infusion and peak effect was achieved between the doses of 150 and 200 mcg/kg/min. Most variables returned to baseline 30 minutes after termination of esmolol infusion. Pulmonary capillary wedge pressure results indicated that the filling pressure of the left ventricular was essential unchanged during esmolol infusion. In addition, cardiac index decreased by the end of titration but returned to baseline by the end of maintenance and showed no changes post infusion. Reductions in systemic vascular resistance continued throughout the titration and maintenance period but returned to baseline by 30 minutes post infusion. (This is at variance with the results reported in the Pharmacodynamic section re studies 14 and 25.)

Safety Results

Ten episodes of hypotension were reported in this study, but blood pressure was usually adequately controlled (SBP greater than 90 mm Hg), and peak reductions in heart rate were maintained by reducing the esmolol dosage. In these cases, heart rate and blood pressure returned to control values within 30 minutes of stopping the study drug infusion. Other adverse effects included decreased cardiac output, oliguria, nausea and vomiting in association with hypotension, and increased pulmonary capillary wedge pressure. According to the sponsor, esmolol caused a rapid reduction in heart rate and was hemodynamically safe in these patients with ischemic heart disease for periods up to 24 hours. However, the decrease in both cardiac output and SVR (and hypotension) is of concern (see analysis of Study 25 Pharmacodynamics).

Overall Results and Conclusions of Brevibloc Efficacy and Safety for Each Claim (Indication)

A. Supraventricular Tachycardia

(1) Efficacy

In controlled and partially controlled SVT clinical trials (studies 8052-81-04, 8052-81-05, 8052-83-23/30/36 and 8052-83-31), a dosage-effect response relationship was found (as shown in the table below) over the ranges of less than or equal to 50 mcg/kg/min to 200 mcg/kg/min with small additional benefit derived from dosages of 200 and 300 mcg/kg/min. Overall the esmolol response rate was 74% with 71% responding at dosages of 200 mcg/kg/min or less.

Therapeutic Responders by Dosage

Dosage (mcg/kg/min)	Study Number 8052-				Responders	
	81-04	81-05	81-23	81-31	Total	Cummulative %
≤ 50	13	21	54	15	103	35%
100	10	7	31	10	58	55%
150	3	7	18	1	29	65%
200	9	2	8	1	20	71%
250	1	1	4	1	7	74%
≥ 300	0	1	1	0	2	74%
TOTAL	36	39	116	28	219	
N (Efficacy)	50	61	147	36	294	
% Responders	72%	64%	79%	78%	74%	

Esmolol in the dose ranged described was found to be either as effective as propranolol or significantly better than placebo in two well controlled clinical trials. Thus the sponsor's claim regarding the benefit and efficacy of esmolol is supported by these studies.

Addendum to Overall Results and Conclusions

In response to our request for a more detailed summary of esmolol responders who converted from SVT to NSR, the sponsor has submitted new tables of efficacy patients from the two well controlled trials (04 and 05) and the two partially controlled trials (see appendix 2B). These results support the fact that only a minority of SVT patients treated with esmolol (6-14%) can be expected to convert to NSR during the initial titration period. The data that some additional conversions to NSR also occur (during maintenance must be viewed with caution since the maintenance period was relatively extended (up to 24 hours) in the two partially controlled trials.

Recommendation

Based on the evidence discussed above, esmolol can be recommended for approval for treatment of SVT.

(ii) Safety

In these studies, adverse reactions were relatively common but were often related to the pharmacology of esmolol and their occurrence were frequently confounded by the hemodynamic instability of the patients or the use of other drugs concomitartly which are known to effect hemodynamic variables. Evaluation of the adverse effects reported in these clinical trials showed no clear correlation with the dosage of esmolol. Analysis of total ADE showed fairly consistant incidences across dosages. The tables below illustrate the incidence of ADE as a function of dose and the number of patients discontinued from treatment for ADE by dosage.

SVT Adverse Effect Incidences by Dosage

Dosage (mcg/kg/min)	Study Number 8052- 81-04	81-05	81-23	81-31	Total
≤ 50	6	4	33	24	67
100	1	2	42	11	56
150	6	0	43	9	58
200	11	5	30	2	48
250	5	4	12	3	26
≥ 300	5	10	18	2	35
Total Incidences	34	25	178	53	290
N (All Patients)	64	71	160	49	344

SVT Patients Discontinued for ADEs by Dosage

Dosage (mcg/kg/min)	Study Number 8052- 81-04	81-05	81-23	81-31	Total	% of All Patients
≤ 50	1	2	3	5	11	3.1%
100	0	1	8	2	11	3.1%
150	3	0	5	3	11	3.1%
200	3	1	7	1	12	3.4%
250	3	1	6	0	10	2.9%
≥ 300	5	1	4	1	11	3.1%
Total Patients	15	6	33	12	66	
N (All Patients)	64	71	160	49	344	
% of N	23%	8%	21%	24%	19%	

Although these tables show no clear relationship of dose with ADE and/or withdrawals, the number of patients subjected to higher dosages is considerably less (since over 70% responded at dosages of 200 mcg/kg/min or less). Accordingly, the sponsor recommends a usual effective dose range of 50-200 mcg/kg/min. Reported ADE in decreasing order by body system include cardiovascular, central nervous system, gastrointestinal, skin (I.V. inflammation and induration), genitourinary and special senses. [However, the sponsor has not summarized ADE by body system for the entire cohort of patients.] Esmolol was generally associated with a significant incidence of ADE which were predominately cardiovascular (hypotension and diaphoresis). In one well controlled study, (04) over 50% (34/64) of esmolol treated patients developed hypotension and a significant number of esmolol treated patients had to be terminated prematurely from the study due to hypotension (15/64). In the single largest trial reported by the sponsor involving 160 patients (study 81-23) which was an open label baseline controlled trial, 44% (70/160) of esmolol treated patients developed hypotension and 21% (33/160) were terminated from the study prematurely due to ADE. After cardiovascular (hypotension) ADE, the next most frequent ADE pertains to the CNS (somnolence, agitation, headache, dizziness, confusion). The overall incidence of CNS ADE was almost 25% (39/160) in study 8052-81-23. Furthermore there has been 1 case report [redacted] documenting a grand mal seizure in an 89 year old male with mild congestive heart failure and atrial fibrillation (heart rate of 120) treated with esmolol. Additional case reports of adverse reactions in patients with CAD including transient sinus arrest and hypotension associated with cardiac arrest have been described. Moreover, it is important to note that in most cases, ADE (hypotension) including those which prompted withdrawal from studies, resolve quickly either spontaneous, by lowering the dosage, or by discontinuing the drug. The prompt resolution of most ADE is further supported by the significant improvement within 20 to 30 minutes in clinical safety variables following discontinuation of esmolol infusion (studies 04 and 05). Finally, the sponsor's recommendation that final infusion concentrations greater than 10 mg/ml should be avoided is reasonable based on the drug's irritation potential.

Addendum to Overall Summary Safety

In response to our request for a comprehensive summary of ADE by body system, the sponsor has submitted new tables which attempt to quantify the ADE for both the SVT and Anesthesia trials. (See Appendix 2C.) Review of these tables reveal several important shortcomings. First, the ADE listed are those reported by the investigators. In several studies (04 and 05) the actual incidence was shown to be substantially higher when the sponsor reviewed the data for criteria hypotension. In study 8052-81-05, application of this principle resulted in a doubling of the reported incidence of hypotension. Thus, the true incidence of ADE (especially re hypotension) is probably much higher than the numbers reported in these tables. Second, the sponsor continues to overlook at least three other cases of myocardial ischemia (patient numbers 602, 613, and 617) in study 49. Two additional patients (#619 and 624) are more difficult to classify since they appeared to have evidence of ischemia prestudy and esmolol did not prevent perioperative ischemia. Case #619 may also have had ischemic changes sinus ST segment upsloping was noted. Since the patient numbers are so small (N=32 for esmolol and N=30 for placebo) it is not fair to conclude that there is no difference in the incidence of ischemia in the two treatment groups: esmolol - 4/32; Placebo - 0/30. It is probably more correct to conclude that the data is not capable of showing the true size of the difference if one is truly there. Nevertheless, this data raises the issue of possible serious ADE associated with esmolol in this patient population (CAD).

4. Review of Pivotal Studies

Second Indication

B. Perioperative Tachycardia and Hypertension:

Overview of Principal Evidence

The sponsor's claim for esmolol's safety and efficacy (effectiveness in attenuating tachycardia and hypertension during endotracheal intubation) is based on the results of three randomized, parallel, placebo controlled multicenter trials. These three trials shared some common features in terms of basic design, esmolol dosage, endpoint determination and analysis. The studies varied primarily in their patient populations. The first study (8052-84-51A) enrolled patients classified as ASA I or II while the second study (8052-84-51B) was limited to patients with ASA classification III and IV (see table below re this physical status classification).

AMERICAN SOCIETY OF ANESTHESIOLOGISTS' PHYSICAL STATUS CLASSIFICATION[1]

Class 1. The patient has no organic, physiologic, biochemical or psychiatric disturbance. The pathologic process for which operation is to be performed is localized and does not entail a systemic disturbance. Examples: a fit patient with inguinal hernia; fibroid uterus in an otherwise healthy woman.

Class 2. Mild to moderate systemic disturbance caused either by the condition to be treated surgically or by other pathophysiologic processes. Examples: non- or only slightly limiting organic heart disease, mild diabetes, essential hypertension, or anemia. Some might choose to list the extremes of age here, either the neonate or the octogenarian, even though no discernible systemic disease is present. Extreme obesity and chronic bronchitis may be included in this category.

Class 3. Severe systemic disturbance or disease from whatever cause, even though it may not be possible to define the degree of disability with finality. Examples: severely limiting organic heart disease; severe diabetes with vascular complications; moderate to severe degrees of pulmonary insufficiency; angina pectoris or healed myocardial infarction.

Class 4. Indicative of the patient with severe systemic disorders that are already life-threatening, not always correctable by operation. Examples: patients with organic heart disease showing marked signs of cardiac insufficiency, persistent anginal syndrome, or active myocarditis; advanced degrees of pulmonary, hepatic, renal, or endocrine insufficiency.

Class 5. The moribund patient who has little chance of survival but is submitted to operation in desperation. Examples: the burst abdominal aneurysm with profound shock; major cerebral trauma with rapidly increasing intracranial pressure; massive pulmonary embolus. Most of these patients require operation as a resuscitative measure with little if any anesthesia.

[1] Dripps, RD, Eckenhoff, JE, Vandam, LD: Introduction to Anesthesia: The Principles of Safe Practice. W. B. Saunders, Philadelphia, PA, 6th Edition, pp 17 and 18, 1982.

The third study (8052-84-49) included only patients undergoing carotid endarterectomy. Individual differences among these studies re duration of esmolol dosage, timing and dose of thiopental induction and the general anesthetic agent (halothane vs isoflurane) are summarized below.

Study	Duration of esmolol Infusion	Dose and Time of Thiopental Induction	General Anesthetic
51A	12 minutes	4 mg/kg-minute 5	Halothane (0-1.6% inspired)
51B	15 minutes	5 mg/kg-minute 10	Halothane (0-1.6% inspired)
49	12 minutes	6 mg/kg-minute 5	Isoflurane (0-6% inspired)

In general, the overall therapeutic results in these three trials were very similar. Compared to placebo, esmolol significantly attenuated the increases in HR and SBP (primary efficacy variables) during the stimulus of endotracheal intubation. Also, the increases in MAP and RPP (secondary efficacy variables) were significantly lower in esmolol-treated patients. Comparative responses in the primary efficacy variables are summarized below.

Study	Average Maximum (Mean) Increase In HR (bpm)	SBP (mmHg)
49	BREV 8	2
	PBO 24	45
51A	BREV 23	26
	PBO 38	40
51B	BREV 8	19
	PBO 24	46

However, (as discussed below under the individual studies) a serious note of caution must be sounded in interpreting these encouraging results since the sponsor has arbitrarily excluded in a systematic way part of the efficacy data from the majority of esmolol treated patients. The net effect is to leave intact for analysis only a single study point (maximum change observed in HR and SBP after intubation) and exclude all other relevant study points. Although the overall incidence of ADE reported by the sponsor in these trials was low, several important safety issues were raised. First, the partial exclusion of efficacy and clinical safety data probably means that the actual incidence of cardiovascular ADE (hypotension) may be understated. Second, the association of EKG documented myocardia ischemia and esmolol treatment in the carotid artery study (Study 49) is of particular concern. The impact and implications of this exclusion process in terms of assessing efficacy and clinical safety are also further discussed below.

Medical Reviewer's Note

A further point of clarification concerns trials 51A and 51B. Originally, this multicenter trial involved only ASA class I or II patients. However, as this trial progressed several important protocol changes were made (amendment number 4 dated June 14, 1984) which altered both the design of the study and the types of patients enrolled. These included (a) changing the length of the infusion period from 12 to 15 minutes; (b) changing the patient population from ASA I or II to ASA III or IV; (c) beginning anesthesia induction at minute 10 vs minute 5; of the infusion; (d) increasing the thiopental induction dose from 4 to 5 mg/kg; and (e) allowing a choice of preopertive meds (i.e., diazepam, morphine or glycopyrrolate. As a result of these changes, the sponsor decided to analyze the data as two separate studies, i.e., patients studied up until amendment IV are denoted as being in study #8052-84-51A, and patients studied after this amendment are denoted as being in study #8052-84-51B. [Because of this change in the handling of the data which was originally a single multicenter trial, the data from 51A and 51B should be referred to our Biostatistical section to see if there is a difference if the trials are analyzed separately or combined and also to help decide as to the appropriateness of separating these studies.]

Addendum to Medical Reviewer's Note

In response to our request re the rationale for separate statistical analysis for Studies 51A and 51B, the sponsor has submitted the following explanation.

RATIONALE FOR SEPARATE STATISTICAL ANALYSIS
FOR STUDIES 8052-84-51A AND 8052-84-51B

1. ANESTHESIOLOGY CONSULTANTS SUGGESTED A STUDY PLAN WHICH SEPARATED ASA I & II PATIENTS FROM ASA III & IV PATIENTS.

2. APPROXIMATELY 70-80 ASA I & II PATIENTS STUDIED WITH NO SAFETY PROBLEMS.

3. SWITCHED 3 OF THE 5 STUDY CENTERS FROM ASA I & II STUDY PATIENTS TO ASA III & IV STUDY PATIENTS.

RATIONALE FOR SEPARATE STATISTICAL ANALYSIS FOR STUDIES 8052-84-51A AND 8052-84-51B

(CONTINUED)

	ASA I & II		ASA III & IV	
	DATE		DATE	
CENTER	START	STOP	START	STOP
01	6/6/84	8/13/84	------------	
03	4/23/84	7/16/84	7/18/84	9/27/84
04	5/23/84	7/11/84	7/24/84	10/2/84
05	4/3/84	6/14/84	------------	
06	5/31/84	6/6/84	7/6/84	9/20/84

Based on discussions with biostatistics and since each of these studies showed statistically significant differences in the two treatment groups, it is reasonable to allow the sponsor's analysis to stand.

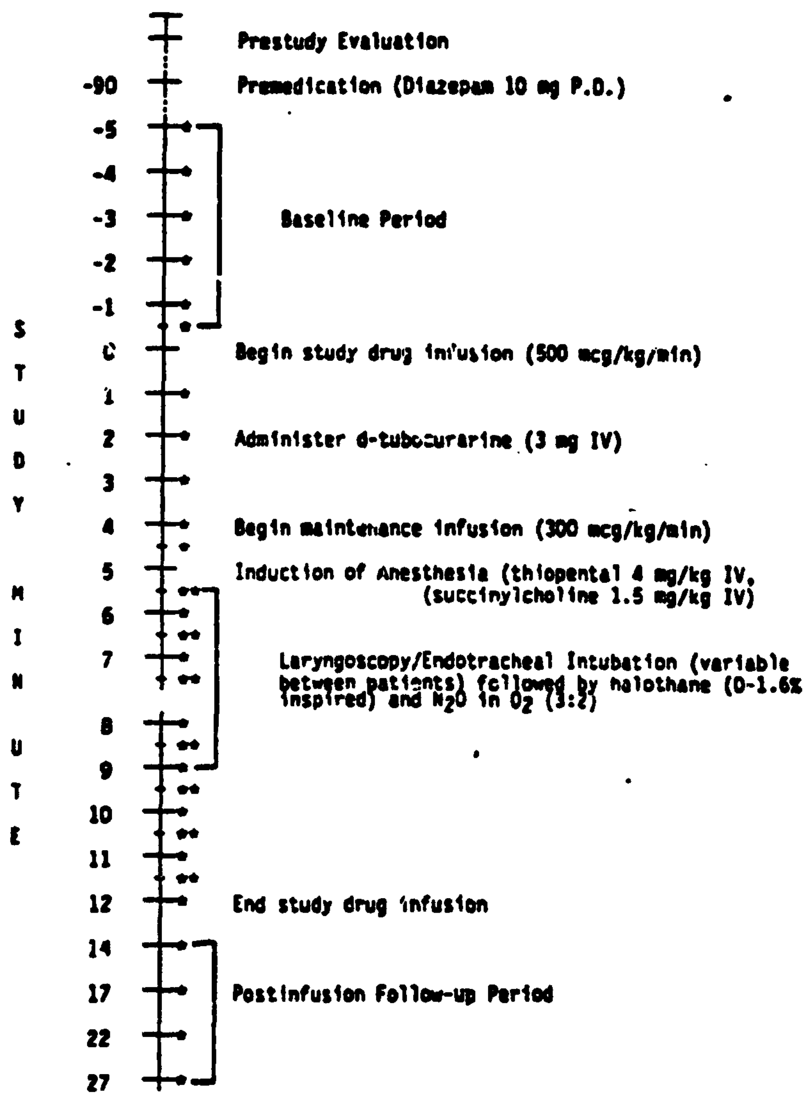
Specific Results

Since the above three studies were basically similar in terms of study design, objectives, treatment plan as well as safety and efficacy evaluation, the following comments serve to describe their common features.

1) Study Objective For All Three Studies: The objective of these studies was to evaluate the effect of esmolol (esmolol-300 mcg/kg/min) vs placebo on increases in heart rate and blood pressure observed during endotracheal intubation in patients induced with thiopental.

2) Study Design and Treatment Plan For All Three Studies: These studies were randomized, double-blind, parallel, placebo controlled, multicenter trials. A schematic representation of the typical study design is provided in the Figure below.

FIGURE 2.1: Protocol Schematic



ECG monitored continuously from baseline through follow-up. 30-second ECG tracings obtained every minute from time of induction to end of infusion.

* Collection of heart rate and blood pressure
** Collection of heart rate only

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The study consisted of the following periods: (a) prestudy evaluation period; (b) 5 minute baseline period; (c) esmolol/placebo infusion period; (d) post infusion follow-up period. Briefly, after administration of appropriate preoperative medications and following a 5 minute preinfusion baseline period, an infusion of esmolol or placebo was started and continued for a 12 minute period (or 15 minutes see study #51B). The study drug dosage was administered according to the following schedule: 500 mcg/kg/min for 4 minutes, followed by 300 mcg/kg/min for 8 minutes (or 11 minutes see study #51B). The infusion rate of both esmolol and placebo was based on the assumption that esmolol was present in both solutions.

3) Efficacy and Safety Assessment for All Three Studies: Efficacy was defined as the attenuation of increases in heart rate and blood pressure during and immediately following endotracheal intubation by esmolol when compared to placebo. The primary efficacy variables were heart rate (HR) and systolic blood pressure (SBP). The secondary variables evaluated were diastolic blood pressure (DBP), mean arterial pressure (MAP) and rate pressure product (RPP). A schedule of study observations is presented in the Table below.

Table 2

SCHEDULE OF OBSERVATIONS

	Prestudy Evaluation Period	Five-minute Baseline Period					Esmolol/Placebo Infusion Period (Induction* at 5; Intubation 5–9)													Postinfusion Follow-up Period			
time* (minutes)		-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	14	17	22**	27**
Informed Consent	x																						
Medical History	x																						
Physical Examination	x																						
12-Lead ECG	x																						
Heart Rate+		x	x	x	x	x	x	x	x	x	x	XX	XX	XX	XX	X x	X x	X X	X	x	x	x	x
Blood Pressure+		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
10-30 sec. ECG Strip												x	x	x	x	x	x	x	x				

* As related to start of study drug infusion.

\+ Heart rate was recorded every 30 seconds and the blood pressure every minute from time of induction (i.e., minute five of infusion) to the end of infusion (i.e., minute 12).

** Heart rate and blood pressure measurements scheduled for 10 and 15 minutes postinfusion were not mandatory (per protocol amendment).

The primary purpose of analysis was to compare the maximum change observed between the esmolol and placebo group with respect to these primary and secondary variables.

4) Safety Assessment - Adverse Effects: All patients were closely monitored throughout the study to detect the occurence of adverse effects. The nature and extent of the evaluation was similar to the previously described SVT studies.

5) Data Management and Statistical Methodology: All statistical analysis were performed using version 4.07 of the SAS. The results of statistical tests were assessed using the 0.05 level of significance. Two sided paired t-tests were used for testing significance of changes in efficacy parameters within each treatment group.

6) Patient Selection for Studies 51A and 51B: Patients were selected for these studies according to the following entrance criteria.

5.1 Inclusion Criteria

a. Either males or non-pregnant females (as confirmed by a negative pregnancy test just prior to entry into the study), 21 years of age or older.

b. Patients were those scheduled for general anesthesia prior to noncardiac surgery. They were classified as either American Society of Anesthesiologists' (ASA) physical status I or II. (Appendix I provides the ASA physical status definitions).*

c. All patients signed an informed consent form prior to study participation.

5.2 Exclusion Criteria

a. Females who were pregnant.

b. Atrial fibrillation or flutter.

c. AV conduction block greater than first degree.

d. Myocardial infarction within six months prior to the study.

e. Any cardiac condition which significantly reduced the interpretability of the hemodynamic variables recorded during the study, such as ventricular arrhythmias requiring drug therapy and sick sinus syndrome.

f. Systolic blood pressure less than 100 mm Hg or diastolic less than 50 mm Hg.

g. Severe renal or hepatic failure.

h. History of bronchospasm or bronchial asthma that precluded therapy with a beta-adrenergic blocking drug.

i. History of drug allergy or idiosyncracy to beta-adrenergic blocking drugs.

j. Those patients whose last oral or IV dose of any of the following medications was received within four half-lives of time of anesthesia induction:

Propranolol	Pindolol
Metoprolol	Timolol
Atenolol	Verapamil
Nadolol	Diltiazem

Other oral or intravenous cardiovascular medications (e.g., digoxin, quinidine, procainamide) could be continued provided their doses permitted blood drug levels to remain at steady-state throughout the study period.

k. Patients who had received adrenergic-augmenting drugs (including monoamine oxidase inhibitors) or adrenergic-depleting drugs (i.e. reserpine or guanethidine) during the six week period prior to entry into the study.

l. Experimental drug administration within the previous two weeks, or proportionately longer if the drug had a long half-life.

Specific Results for Study No. 8052-84-51A

Investigators and Institutions/Study 51A: All investigators were board certified anesthesiologists. Of the 6 centers selected to participate in this study, 5 contributed 9 or more patients. The other center (center 2: Mayo Clinic) withdrew. For a complete listing of investigators, institutions and number of patients enrolled at each center see Table 1.

Table 1

LIST OF INVESTIGATORS AND
NUMBER OF PATIENTS ENROLLED

CENTER NUMBER	INVESTIGATOR AND INSTITUTION	NUMBER OF PATIENTS ENROLLED
1	Philip Liu, M.D. Brigham and Women's Hospital Boston, Massachusetts	32
2	Christopher Sill, M.D. Mayo Clinic Rochester, Minnesota	0
3	Fred Brindle, M.D. Jackson Memorial Hospital Miami, Florida	35
4	Simon Gelman, M.D. University of Alabama, Birmingham Birmingham, Alabama	20
5	Theodore Stanley, M.D. University of Texas Health Center at Houston Houston, Texas	16
6	Martin I. Gold, M.D. Veterans Administration Medical Center Miami, Florida	9

<u>Number of Patients for Study 51A-"All", "Efficacy", "Dropouts", "Exclusions"</u>: 112 patients were entered into this multicenter study and were randomized to either esmolol or placebo. These were referred to as "all patients". Of these 112 patients, 101 were classified as "efficacy patients" (N=50 for esmolol and N=51 for placebo). Derivation of "all patients" and "efficacy patients" in the study are summarized in Table 5.

Table 5

DERIVATION OF "ALL PATIENTS" AND

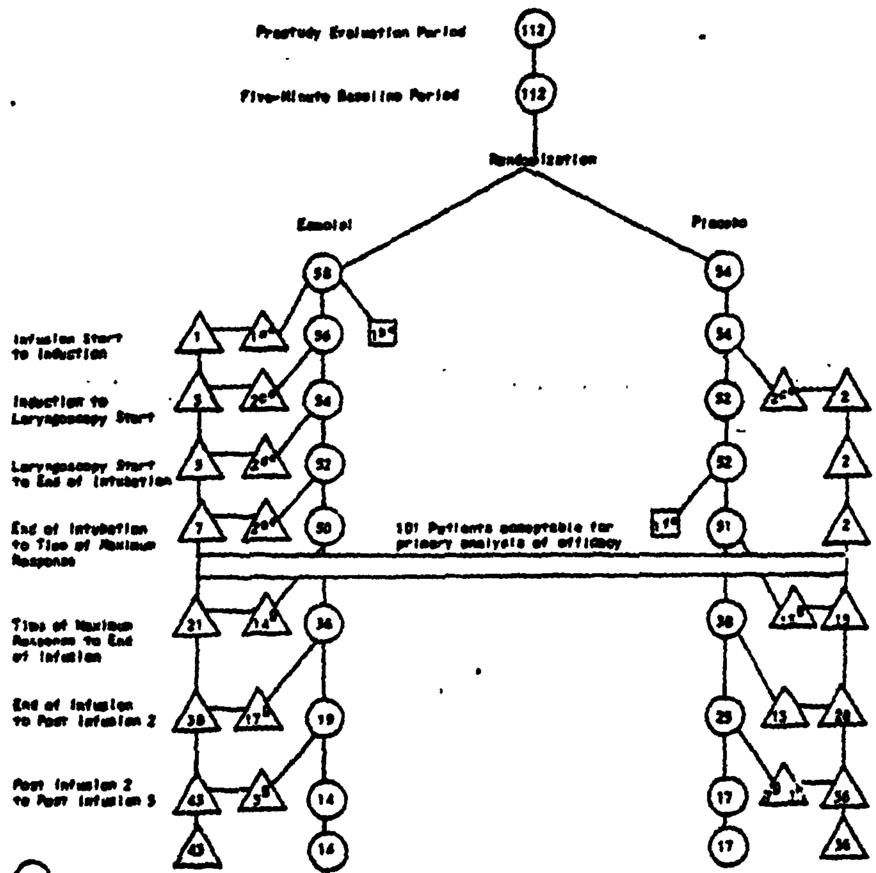
"EFFICACY PATIENTS" IN THE STUDY

"All Patients"	112	58	Esmolol
		54	Placebo
Excluded from efficacy analysis	11	(#113, 118, 129, 301, 408, 506, 510, 607)	Esmolol
		(#104, 116, 509)	Placebo
"Efficacy Patients"	101	50	Esmolol
		51	Placebo

A summary of "all patients" at each phase of the study is given in Table 6.

TABLE 6

SUMMARY OF "ALL PATIENTS"
AT EACH PHASE OF THE STUDY



Eligible for efficacy analysis

Study not completed (ineligible for efficacy analysis)

Ineligible for efficacy analysis; outside columns indicate cumulative total excluding patients who did not complete study.

a 200 mcg/kg/min infusion (Patient #301)
b Infusion terminated due to technical difficulties (Patient #310)
c Thiopental dose >5.5 mg/kg [Patients #113, 118(E); Patients #104, 116(P)]
d Multiple intubations (Patients #120, 607)
e Enflurane anesthetic (Patients #408, 506)
f Infusion terminated due to adverse effect (Patient #309)
g Changes in halothane (% inspired)
h Data not retrievable
i Ineligible for all efficacy analyses

The reasons for the exclusions from the efficacy analysis is summarized for each patient in Table 7.

Table 7

LIST OF PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

PATIENT NUMBER	TREATMENT	DEMOGRAPHIC DATA SEX	AGE (yrs)	WEIGHT (kg)	BASELINE DATA HEART RATE (bpm)	BLOOD PRESSURE SBP(mmHg)	DBP	REASON FOR EXCLUSION FROM EFFICACY ANALYSIS
104	Placebo	F	43	50	63	126	75	Received incorrect dose of induction agent. (7.5 mg/kg thiopental administered.)*
113	Esmolol	F	41	62	59	110	66	Received incorrect dose of induction agent. (5.8 mg/kg thiopental administered.)*
116	Placebo	M	24	75	100	140	84	Received incorrect dose of induction agent. (8.1 mg/kg thiopental administered in three divided doses over a two-minute period.)
118	Esmolol	F	25	58	71	111	71	Received incorrect dose of induction agent. (5.9 mg/kg thiopental administered in two divided doses over a 40-second period.)*
120	Esmolol	F	41	66	80	137	85	Patient was intubated twice during infusion period.
301	Esmolol	F	36	100	86	127	72	Patient was administered a 200 mcg/kg/min maintenance infusion of esmolol. Although this was correct at the time, the protocol was later amended back to the original dose of 300 mcg/kg/min. Thus, this data could not be used.
400	Esmolol	F	57	75	94	150	93	Received incorrect inhalation agent. (Enflurane administered instead of of Halothane.)
506	Esmolol	M	34	110	60	140	69	Received incorrect inhalation agent. (Enflurane administered instead of Halothane.)
509	Placebo	F	19	50	70	134	82	Patient did not complete the study (Infusion terminated at minute 7 due to adverse effects).
510	Esmolol	M	31	75	64	147	72	Patient did not complete the study. (Infusion terminated at minute 4 due to technical problems.)
607	Esmolol	M	48	85	67	181	98	Intubation was attempted 3-4 times over an eight-minute period during infusion.

* Protocol specified thiopental dose 4 mg/kg. Acceptable upper limit 5.5 mg/kg.

Eleven "all patients" were not included in the "efficacy patients" group for the following reasons: incorrect esmolol dosage (1 patient), deviations from dose allowed for anesthesia induction (4 patients), difficult intubation requiring several attempts (2 patients), deviations from the prescribed anesthesia (2 patients), did not complete study (2 patients). Analysis of the effect of esmolol and placebo on heart rate, blood pressure and other efficacy variables was performed on 101 "efficacy patients" as well as on "all patients". Safety was based on the data from all 112 patients.

Study Results: (51A)

I Baseline Demographics and Comparability of Treatment Groups:

Baseline demographic and clinical characteristics were similar for both treatment groups (see Tables 8B, 10 and 13). As is evident from Table 13, although there was a significant (p less than 0.05) difference at baseline for heart rate and diastolic blood pressure among the 5 centers, nevertheless there were no statistically significant differences between the pooled treatment groups at baseline with respect to any of the 5 efficacy variables.

Table 8B

SUMMARY OF DEMOGRAPHIC DATA BY CENTER*, EFFICACY ELIGIBLE, EFFICACY INELIGIBLE AND "ALL PATIENTS"

GROUP	ASA PHYSICAL STATUS**		SEX**		RACE**			
	I	II	M	F	CAUC	BLACK	ORNTL	OTHER
Center 1	21	11	3	29	23	4	1	4
Center 3	15	20	3	32	17	18	0	0
Center 4	9	11	7	13	17	3	0	0
Center 5	14	2	10	6	4	9	0	3
Center 6	1	8	9	0	9	0	0	0
Eligible+	52	49	28	73	64	30	1	6
Ineligible++	8	3	4	7	6	4	0	1
"All Patients"	60	52	32	80	70	34	1	7

* Center 2 did not enter any patients.
** Indicates significant difference among the centers ($p < 0.001$).
\+ Patients eligible for efficacy analysis.
\++ Patients ineligible for efficacy analysis.

Table 10

Summary of Demographic and Prestudy Clinical Data, by Treatment Group for "All Patients"

Variable	Treatment[*]	Mean	± S.D.	Min	Max	N
Age (years)	Esmolol	39.4	12.3	19.0	69.0	58
	Placebo	40.3	15.0	19.0	83.0	54
Height (cm)[a]	Esmolol	168.3	8.2	150.0	193.0	58
	Placebo	165.8	9.1	147.5	185.4	52
Weight (kg)	Esmolol	72.2	14.0	49.0	110.0	58
	Placebo	69.3	15.0	49.5	110.0	54
BSA (m2)[a]	Esmolol	1.8	0.2	1.5	2.4	58
	Placebo	1.8	0.2	1.4	2.2	52
Heart Rate[b] (bpm)	Esmolol	76.9	12.9	56.0	108.0	45
	Placebo	76.0	14.3	54.0	139.0	47
SBP (mm Hg)	Esmolol	122.6	16.6	92.0	170.0	58
	Placebo	122.1	16.4	90.0	170.0	54
DBP (mm Hg)[c]	Esmolol	75.9	9.1	60.0	95.0	58
	Placebo	75.6	10.1	51.0	100.0	53

a Height and body surface area were not obtained from Patients #407 and 413.
b Prestudy 12-Lead ECG was not obtained for 20 patients; however 4 of these 20 patients did have heart rate measurements taken.
c Diastolic blood pressure measurement was not obtained for Patient #107.
* No significant differences between the esmolol and placebo treatment groups were detected ($p \geq 0.05$).

Table 13

Summary of Baseline Observations for "Efficacy Patients", by Center and Treatment Group

Center[a]	Group	HR, bpm Mean	± SEM	SBP, mm Hg Mean	± SEM	DBP, mm Hg Mean	± SEM	MAP, mm Hg Mean	± SEM	RPP Mean	± SEM	N
1	Esmolol	75.0	3.2	132.8	4.7	78.7	3.0	98.8	3.5	10.0	0.5	15
	Placebo	83.9	5.1	130.8	6.3	78.5	3.4	95.9	4.3	10.9	0.8	12
	Pooled	79.0	3.0	131.9	3.7	78.6	2.2	96.4	2.7	10.4	0.5	27
3	Esmolol	78.0	3.2	130.9	4.1	83.3	3.2	99.2	3.4	10.3	0.6	18
	Placebo	73.7	2.8	125.7	4.1	76.3	2.5	92.8	2.9	9.3	0.5	16
	Pooled	75.7	2.1	128.2	2.9	79.6	2.1	95.8	2.3	9.7	0.4	34
4	Esmolol	67.5	3.3	131.0	5.3	76.4	2.8	94.6	3.0	8.9	0.6	9
	Placebo	77.4	4.0	129.6	3.5	79.1	2.4	95.9	2.8	10.0	0.5	10
	Pooled	72.7	2.8	130.3	3.0	77.8	1.7	95.3	1.9	9.5	0.4	19
5	Esmolol	69.8	6.8	124.0	6.5	65.3	4.1	84.9	4.3	8.6	0.9	6
	Placebo	62.4	2.4	125.4	3.1	72.2	4.0	89.9	3.6	7.8	0.4	7
	Pooled	65.7	3.4	124.7	3.3	69.0	2.9	87.6	2.6	8.2	0.5	13
6	Esmolol	73.5	11.1	144.7	10.9	83.2	5.1	103.7	6.8	10.9	2.1	4
	Placebo	67.0	2.7	136.3	6.4	76.5	5.8	96.5	5.5	9.1	0.4	4
	Pooled	70.2	5.4	140.5	6.1	79.9	3.8	100.1	4.3	10.0	1.0	8
Group												
Pooled	Esmolol	73.9	1.9	131.8	2.4	78.5	1.7	98.3	1.8	9.8	0.3	50
	Placebo	74.7	2.0	128.5	2.2	78.8	1.4	94.0	1.6	9.6	0.3	51
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		

a Significant differences among the centers for HR (Centers 1 and 5) and DBP (Centers 5 and 6) were detected ($p<0.05$).
b N.S. indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$).

II Efficacy Results: (51A) (First Pivotal Study)

A. Analysis and Comment

The interpretation of the therapeutic results observed in this clinical trial is somewhat obfuscated and confused due to the sponsor's partial exclusion of efficacy data. As previously mentioned (see section on number of patients), 101 of the original 112 patients entered into the study were eligible for "efficacy analysis." Although the reasons provided in Table 7 for the exclusion of 11 patients (8 in the esmolol group and 3 in the placebo group) do not seem entirely appropriate in all instances (particularly patient number 129, 301, 509, 510, 607), nevertheless these exclusions probably do not affect the overall results obtained. However, a serious and potentially more questionable action was the sponsor's decision to exclude partial data from 69 patients for efficacy analysis due to "changes in the inspired halothane dose (that the sponsor claims "affected the interpretability of data collected subsequent to the intervention." The justification for the sponsor's decision is futher clouded by the sponsor's own statement that "changing the inspired dose of halothane was not a study conduct or protocol deviation but was done "because of the hemodynamic effects produced by halothane." Thus 69/101 "efficacy patients" had heart rate and blood pressure data excluded subsequent to a change from the initial inspired dose of halothane during maintenance anthesia. As can be deduced by Table 6, this means that all phases of the study (and study data points therein) beyond the end of intubation to the time of maximum response are significantly affected and probably renders evaluation and interpretation of treatment differences at these particular study points uninterpretable. This applies particularly to the results obtained at 2 minutes and 5 minutes post infusion in which the number of patients used in the efficacy analysis is very small. Hence, although efficacy parameters were to be determined at 2, 5, 10 and 15 minutes post infusion, due to the exclusion of 69 patients (as mentioned above), the timing of the skin incision and protocol amendments (the 10 and 15 minute timepoints were later amended to be optional) only the 2 and 5 minute times were considered for analysis by the sponsor. However, the primary study efficacy variable (maximum change observed in heart rate and systolic blood pressure during and after endotracheal intubation) can still be discerned from the available data. Moreover, in accord with the sponsor's presentation of the data in terms of 101 patients acceptable for primary analysis of efficacy, up to the time of maximum response after intubation, there appears to be sufficient patient numbers to warrant further analysis.

B. Specific Results

Therefore in light of this background, the sponsor has opted to present the efficacy results with respect to the primary study endpoints (HR SBP) and the secondary endpoints (DBP MAP RPP).

i) Analysis by Treatment Group

Tables 11/25, 12/26 and 14 provide the mean and standard error for the 5 efficacy variables at each of the main study periods for the 101 "efficacy patients" and 112 "all patients".

Table 11

Heart Rate and Systolic Blood Pressure with Changes from Baseline, by Period, for "Efficacy Patients" Treated with Esmolol or Placebo[a]

		BASELINE			PREINDUCTION			PREINTUBATION			MAXIMUM			POST INF 2			POST INF 5		
		Mean ± SEM		N	Mean ± SEM		N	Mean ± SEM		N[b]	Mean ± SEM		N	Mean ± SEM		N	Mean ± SEM		N
	Group																		
(bpm)	Esmolol	73.9	1.9	50	68.8	1.5	50	80.5	1.8	46	97.1	1.9	50	81.3	3.8	19	80.6	4.4	14
	Placebo	74.7	2.0	51	77.4	2.4	51	88.9	2.2	49	112.3	2.2	51	91.7	2.5	25	89.9	4.2	17
Change	Esmolol				-5.1#	1.0	50	6.6#	1.9	46	23.3	2.3	50	7.9	2.5	19	6.4	2.9	14
	Placebo				2.7#	1.1	51	13.8#	1.6	49	37.5	2.2	51	15.6#	3.4	25	13.2	5.0	17
parison of Change[c]		N.S.			P>E**			P>E*			P>E**			N.S.			N.S.		
(mmHg)	Esmolol	131.8	2.4	50	127.0	2.3	50	124.8	2.8	43	157.9	3.0	50	110.9	4.3	19	103.5	5.5	14
	Placebo	128.5	2.2	51	128.3	2.3	51	121.9	2.3	48	168.7	3.4	51	118.8	2.7	25	113.8	2.9	17
Change	Esmolol				-4.8#	0.9	50	-6.9#	2.2	43	26.2	2.5	50	-19.7#	8.0	19	-26.9#	8.5	14
	Placebo				-0.2	1.0	51	-6.4#	2.0	48	40.2	2.5	51	-11.7#	2.4	25	-19.2#	4.1	17
parison of Change[c]		N.S.			P>E*			N.T.			P>E**			N.S.			N.S.		

Indicates significant change from baseline (p<0.05). Maximum change from baseline was not tested for significance.
Significant center by treatment interaction was detected for SBP at the preintubation period (p<0.05).
Preintubation heart rates were not determined in Patients #101, 115, 511, and 513 in the esmolol group and in Patients #504 and 508 in the placebo group. In addition to these patients, SBP was not measured i. Patients #154, 160 and 310 in the esmolol group and in Patient #126 in the placebo group.
N.S. indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * p<0.05, ** p<0.01
N.T. Not tested because of significant center by treatment interaction.

TABLE 25

Heart Rate and Systolic Blood Pressure with Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo[a]

		BASELINE			PREINDUCTION			PREINTUBATION			MAXIMUM			POST INF 2			POST INF 5		
		MEAN ± SEM		N	MEAN ± SEM		N	MEAN ± SEM		N	MEAN ± SEM		N	MEAN ± SEM		N	MEAN ± SEM		N
	Group																		
(bpm)	Esmolol	73.9	1.8	58	69.7	1.6	57[c]	81.5	1.9	53[c]	97.2	[illegible]	[illegible]	75.8	1.7	57[c]	72.8	1.7	56[c]
	Placebo	74.9	1.9	54	77.8	2.4	54	88.8	2.1	52	113.1	[illegible]	[illegible]	86.8	1.9	53	82.0	2.2	51
Change	Esmolol				-4.4[#]	1.2	57	[illegible][#]	1.9	53	23.1	2.1	57	1.7	2.0	57	-1.6	1.9	56
	Placebo				2.9[#]	1.1	54	13.5[#]	1.6	52	38.1	2.1	53	11.8[#]	2.1	53	6.6[#]	2.4	51
...mparison of Change[b]		N.S.			P>E**			P>E*			P>E**			P>E**			P>E*		
...P (mm Hg)	Esmolol	132.3	2.2	58	127.4	2.2	57	126.5	2.8	49	160.4	2.8	57	107.1	3.1	57	100.4	2.7	56
	Placebo	128.7	2.1	54	128.4	2.2	54	122.5	2.2	51	167.8	3.3	53	116.7	2.0	53	107.6	2.2	50
...P Change	Esmolol				-4.7[#]	0.9	57	-6.0[#]	2.0	49	28.3	2.2	57	-24.9[#]	3.3	57	-31.8[#]	3.2	56
	Placebo				-0.4	1.0	54	-6.1[#]	1.9	51	39.1	2.5	53	-12.0[#]	1.7	53	-20.1[#]	2.1	50
...mparison of Change[b]		N.S.			P>E**			N.T.			P>E**			P>E*			P>E*		

Indicates significant change from baseline (p<0.05). Maximum change from baseline was not tested for significance.
Significant center by treatment interactions were found for both DBP and MAP at the preintubation period (p<0.05).
N.S. Indicates no significant difference between the esmolol and placebo treatment groups (p≥0.05).
P = Placebo, E = Esmolol 300 mcg/kg/min, * p<0.05, ** p<0.01
N.T. Not tested because of significant center by treatment interactions.
Data not available for all patients.

Table 12

Diastolic Blood Pressure, Mean Arterial Blood Pressure, and Rate-Pressure Product with Changes from Baseline, by Period, for "Efficacy Patients" Treated with Esmolol or Placebo[a]

		BASELINE			PREINDUCTION			PREINTUBATION			MAXIMUM			POST INF 2			POST INF 5		
	Group	Mean ± SEM		N	Mean ± SEM		N	Mean ± SEM		N[b]	Mean ± SEM		N	Mean ± SEM		N	Mean ± SEM		N
DBP (mmHg)	Esmolol	78.5	1.7	50	77.3	2.0	50	81.2	2.7	43	111.0	2.6	50	67.8	4.3	19	62.5	4.7	14
	Placebo	76.8	1.4	51	76.0	1.4	51	75.1	1.9	48	114.2	2.5	51	71.6	2.6	25	73.5	2.9	17
DBP Change	Esmolol				-1.3	0.9	50	2.9	2.7	43	32.5	2.0	50	-10.2#	3.3	19	-15.6#	4.8	14
	Placebo				-0.8	1.2	51	-1.7	1.6	48	37.4	2.0	51	-7.9#	2.3	25	-8.0#	3.6	17
Comparison of Change[c]		N.S.			N.S.			N.T.			N.S.			N.S.			N.S.		
MAP (mmHg)	Esmolol	96.3	1.8	50	93.9	2.0	50	95.7	2.6	43	125.9	2.6	50	82.2	4.1	19	76.2	4.8	14
	Placebo	94.0	1.6	51	93.4	1.5	51	90.7	1.9	48	131.2	2.7	51	87.3	2.5	25	86.9	2.7	17
MAP Change	Esmolol				-2.4#	0.7	50	-0.3	2.4	43	29.6	2.0	50	-13.4#	4.0	19	-19.4#	5.9	14
	Placebo				-0.6	0.9	51	-3.3#	1.5	48	37.2	2.1	51	-9.2#	2.1	25	-11.7#	3.4	17
Comparison of Change[c]		N.S.			N.S.			N.T.			P>E*			N.S.			N.S.		
RPP	Esmolol	9.8	0.3	50	8.8	0.3	50	10.0	0.3	43	14.3	0.5	50	9.2	0.7	19	8.5	0.8	14
	Placebo	9.6	0.3	51	9.9	0.3	51	10.8	0.3	48	18.0	0.6	51	10.8	0.3	25	10.3	0.7	17
RPP Change	Esmolol				-1.0#	0.2	50	0.2	0.4	43	4.5	0.4	50	-0.5#	0.6	19	-1.2#	0.8	14
	Placebo				0.3	0.2	51	1.2#	0.3	48	8.4	0.5	51	0.9	0.5	25	0.1	0.9	17
Comparison of Change[c]		N.S.			P>E**			N.S.			P>E**			N.S.			N.S.		

Indicates significant change from baseline (p<0.05). Maximum change from baseline was not tested for significance.
Significant center by treatment interactions were found for both DBP and MAP at the preintubation period (p<0.05).
Preintubation blood pressure was not determined in Patients #101, 115, 154, 160, 310, 511, and 513 in the esmolol group and Patients #126, 504 and 508 in the placebo group.
N.S. Indicates no significant difference between the esmolol and placebo treatment groups (p≥0.05).
P = Placebo, E = Esmolol 300 mcg/kg/min, * p<0.05, ** p<0.01
N.T. Not tested because of significant center by treatment interactions.

TABLE 26

Diastolic Blood Pressure, Mean Arterial Blood Pressure, and Rate-Pressure Product with Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo[a]

		BASELINE			PREINDUCTION			PREINTUBATION			MAXIMUM			POST INF 2			POST INF 5		
		MEAN	± SEM	N	MEAN	± SEM	N	MEAN	± SEM	N	MEAN	± SEM	N	MEAN	± SEM	N	MEAN	± SEM	N
	Group																		
(mm Hg)	Esmolol	78.5	1.6	58	77.3	1.8	57[c]	81.3	2.7	49[c]	112.7	2.6	57[c]	68.2	2.9	57[c]	62.8	2.1	56[c]
	Placebo	77.0	1.4	54	75.7	[illegible]	54	74.7	1.8	51	113.3	2.5	53	69.5	1.7	53	66.1	1.8	50
Change	Esmolol				[illegible]	0.8	57	2.8	2.5	49	34.1	1.9	57	-10.4#	2.5	57	-16.2#	1.8	56
	Placebo				-1.2	1.2	54	-2.4	1.6	51	36.4	2.0	53	-7.4#	1.4	53	-10.7#	1.6	50
parison of Change[b]		N.S.			N.S.			N.T.			N.S.			N.S.			N.S.		
(mm Hg)	Esmolol	96.4	1.7	58	94.0	1.9	57	96.4	2.6	49	127.8	2.6	57	81.2	2.9	57	75.2	2.2	56
	Placebo	94.2	1.5	54	93.3	1.4	54	90.6	1.8	51	130.2	2.7	53	85.2	1.7	53	79.9	1.8	[illegible]
Change	Esmolol				-2.4#	0.7	57	-0.1	2.2	49	31.4	1.9	57	-15.2#	2.6	57	-21.4#	2.2	56
	Placebo				-1.0	0.9	54	-3.6#	1.5	51	36.1	2.1	53	-9.0#	1.3	53	-13.8#	1.6	50
parison of Change[b]		N.S.			N.S.			N.T.			N.S.			N.S.			N.S.		
P	Esmolol	9.8	0.3	58	8.9	0.3	57	10.2	0.3	49	14.6	0.5	57	8.2	0.4	57	7.4	0.3	56
	Placebo	9.6	0.3	54	10.0	0.3	54	10.9	0.3	51	17.9	0.6	53	10.1	0.3	53	9.0	0.4	50
P Change	Esmolol				-0.9#	0.2	57	0.3	0.3	49	4.7	0.4	57	-1.6#	0.4	57	-2.5#	0.4	56
	Placebo				0.3	0.2	54	1.2#	0.3	51	8.3	0.5	53	0.5	0.3	53	-0.7	0.4	50
mparison of Change[b]		N.S.			P>E**			N.S.			P>E**			P>E**			P>E**		

Indicates significant change from baseline ($p<0.05$). Maximum change from baseline was not tested for significance.
Significant center by treatment interactions were found for both DBP and MAP at the preintubation period ($p<0.05$).
N.S. Indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$
N.T. Not tested because of significant center by treatment interactions.
Data not available for all patients.

TABLE 14

Maximum Change from Baseline for "Efficacy Patients"

		HR CHANGE (bpm)		SBP CHANGE (mm Hg)		DBP CHANGE (mm Hg)		MAP CHANGE (mm Hg)		RPP CHANGE (mm Hg)		
		MEAN ± SEM		MEAN ± SEM		MEAN ± SEM		MEAN ± SEM		MEAN ± SEM		N
Center[a]	Group											
1	Esmolol	21.1	5.5	17.6	5.6	29.1	3.8	23.6	4.2	2.9	0.8	15
	Placebo	33.6	5.2	41.0	4.5	37.3	3.6	36.8	4.0	8.3	1.2	12
3	Esmolol	21.5	3.6	33.9	3.5	34.4	3.3	33.9	3.1	5.6	0.8	16
	Placebo	33.8	3.3	38.7	4.9	31.1	3.8	33.2	4.1	7.7	0.8	18
4	Esmolol	24.5	3.3	31.1	5.0	30.2	3.7	29.8	3.7	5.1	0.6	9
	Placebo	47.2	5.2	43.2	6.1	46.3	3.6	44.6	3.8	10.3	1.2	10
5	Esmolol	28.4	4.6	19.3	5.2	33.7	2.6	28.7	2.3	4.4	1.2	6
	Placebo	43.6	4.9	40.5	4.1	45.4	2.5	42.4	2.1	8.9	1.1	7
6	Esmolol	28.3	10.8	28.5	8.6	40.5	12.9	35.7	11.5	5.1	2.2	4
	Placebo	31.3	2.7	36.9	10.9	30.2	5.8	28.4	8.8	6.7	1.4	4
	Group											
Pooled	Esmolol	23.3	2.3	26.2	2.5	32.5	2.0	29.6	2.0	4.5	0.4	50
	Placebo	37.5	2.2	40.2	2.5	37.4	2.0	37.2	2.1	8.4	0.5	51
	Comparison[b]	P>E**		P>E**		N.S.		P>E*		P>E**		

a No significant differences among the centers were detected ($p \geq 0.05$).
b N.S. indicates no significant difference between the esmolol and placebo treatment groups ($p \geq 0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

The data is also graphically displayed in Figures 2, 3 (HR), 4, 5 (SBP), 6, 7 (DBP), 8, 9 (MAP), 10, 11 (RPP). In these tables "BASELINE" represents an average of the 6 values collected before starting the infusion, "PREINDUCTION" represents minute 5 (in almost all cases) of infusion which is just prior to induction, "PREINTUBATION" represents the measurements immediately prior to laryngoscopy and intubation, and "MAXIMUM" denotes the maximum values within the period starting at laryngoscopy and continuing to the end of infusion. "POST INFUSION II" represents the value at 2 minutes after discontinuing the infusion, "POST INFUSION V" represents the value at 5 minutes after discontinuing the infusion.

(a) Primary Efficacy Variables (HR, SBP): According to the sponsor, esmolol significantly blunted the increases in HR (Figures 2 and 3) and SBP (Figure 4 and 5) compared to placebo during the stimulus of endotracheal intubation (p less than 0.01). As stated in the overview summary "the average maximum heart rate increase in placebo treated patients was 38 bpm as opposed to an average increase of 23 bpm in patients treated with esmolol. The average maximum systolic blood pressure increase in the placebo group was 40 mm Hg, while an average increase of 26 mm Hg was observed in the esmolol group.

FIGURE 2

Heart Rate
(mean ± standard error)

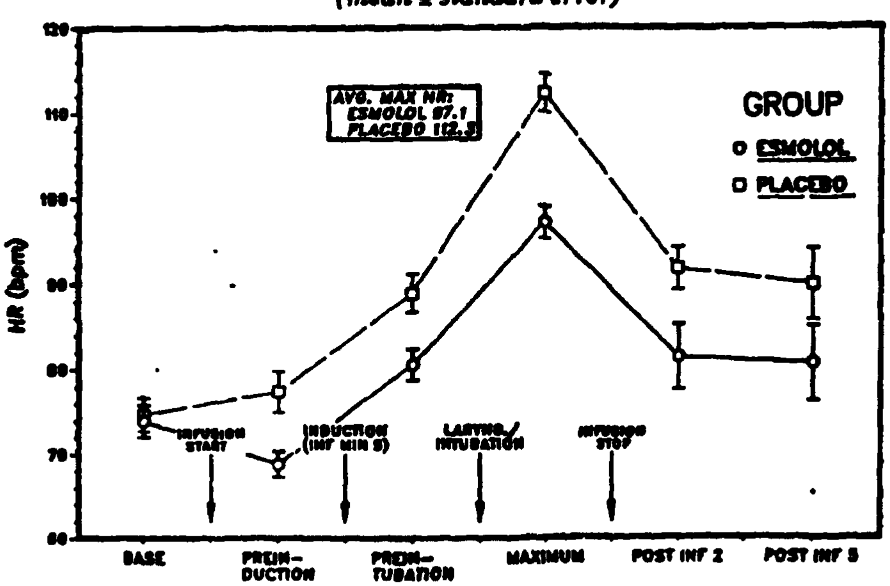
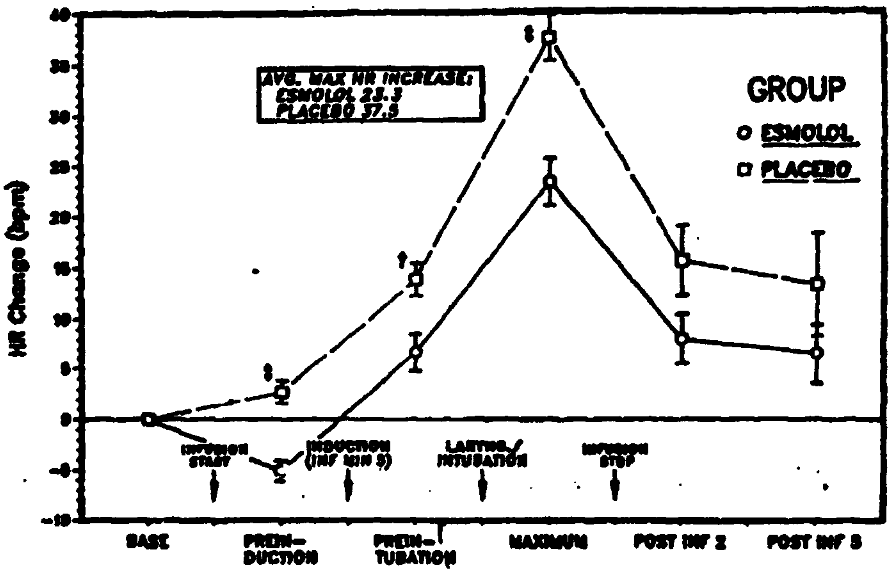


FIGURE 3

Heart Rate Changes from Baseline
(mean ± standard error)



† Significant difference between esmolol and placebo with respect to change from baseline ($p<0.05$).
‡ $p<0.01$.

FIGURE 4

Systolic Blood Pressure
(mean ± standard error)

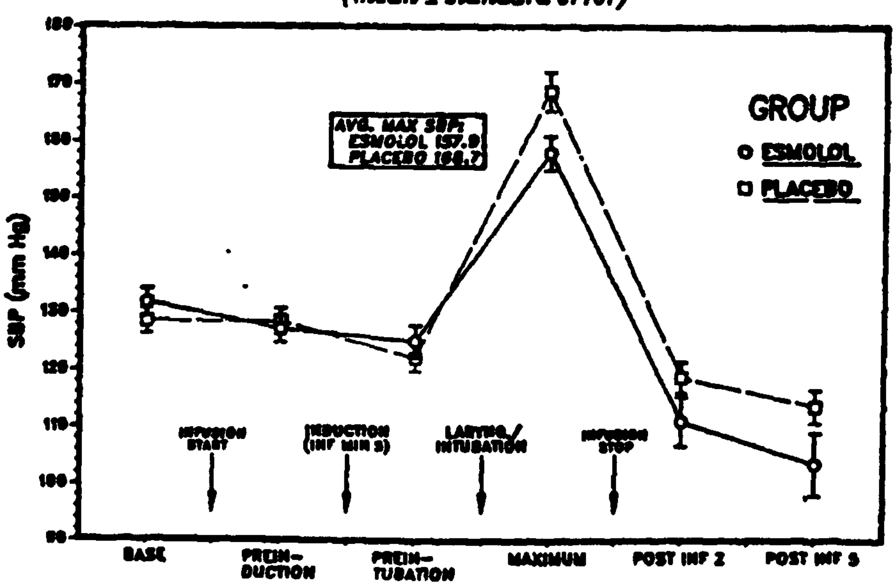
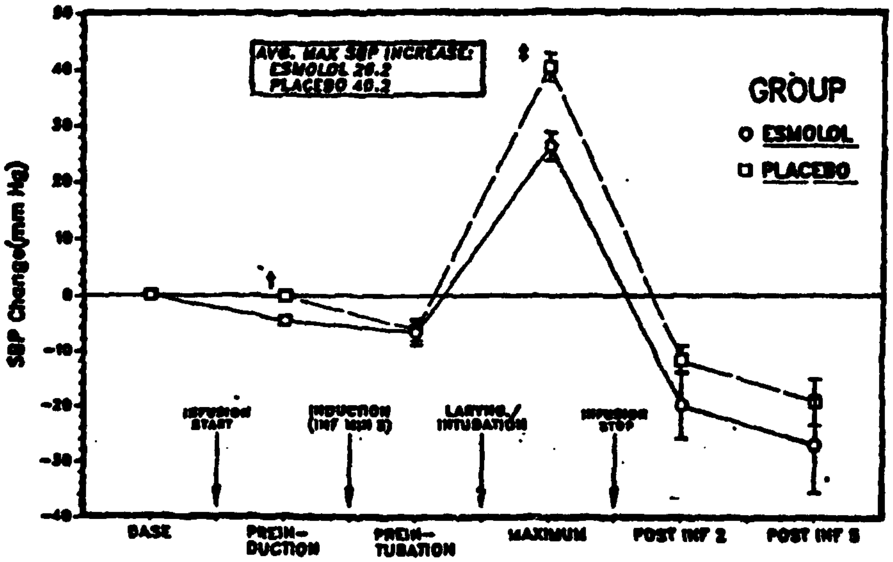


FIGURE 5

Systolic Blood Pressure Changes from Baseline
(mean ± standard error)



† Significant difference between esmolol and placebo with respect to change from baseline (p<0.05).
‡ p<0.01.

(b) Secondary Efficacy Variables (RPP, MAP, DBP): Analysis of both RPP (Figures 10 and 11) and MAP (Figures 8 and 9) showed that both variables exhibited "significantly greater increases in the placebo group than in the esmolol group." There was no significant difference between the two study groups for DBP with respect to maximum changes from baseline. However, the sponsors claim that by 2 minutes post infusion the heart rate had returned to baseline is not correct. In fact, even by 5 minutes post infusion the heart rate had not returned to baseline in the esmolol treated group. (80.6 bpm vs 73.9 bpm) Similarly, at the 5 minute post infusion time point, the SBP (especially SBP in the esmolol group was significantly below the baseline [p less than 0.05]).

FIGURE 8

Mean Arterial Blood Pressure
(mean ± standard error)

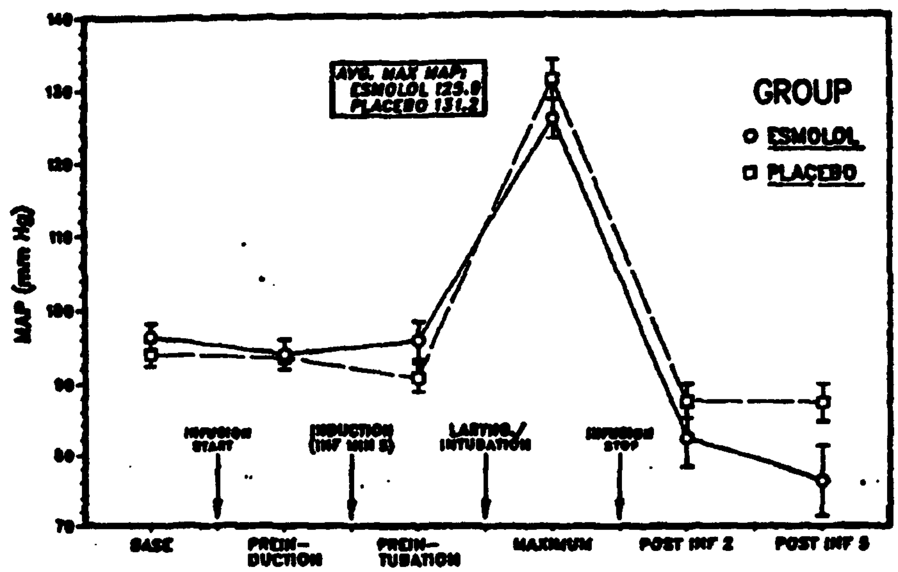
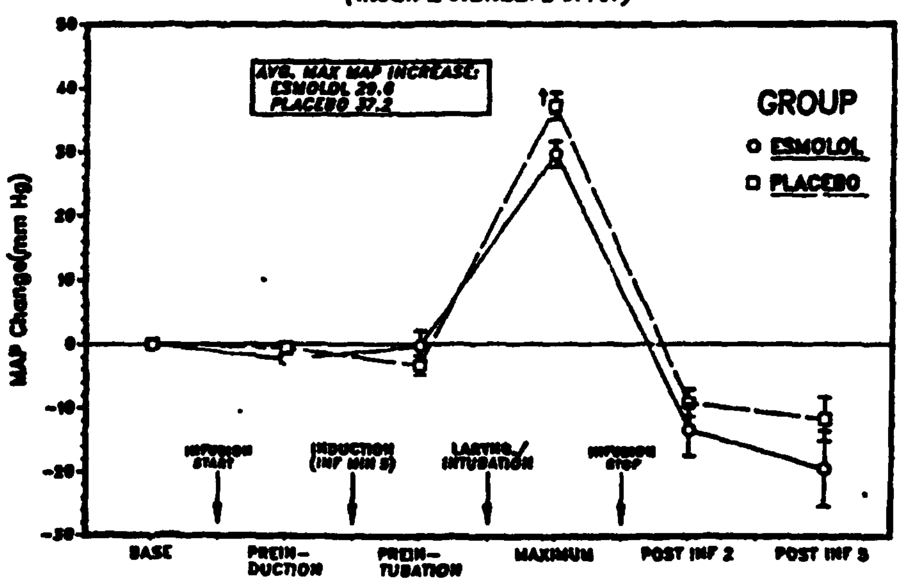


FIGURE 9

Mean Arterial Pressure Changes from Baseline
(mean ± standard error)



† Significant difference between esmolol and placebo with respect to change from baseline (p<0.05).

FIGURE 10

Rate–Pressure Product
(mean ± standard error)

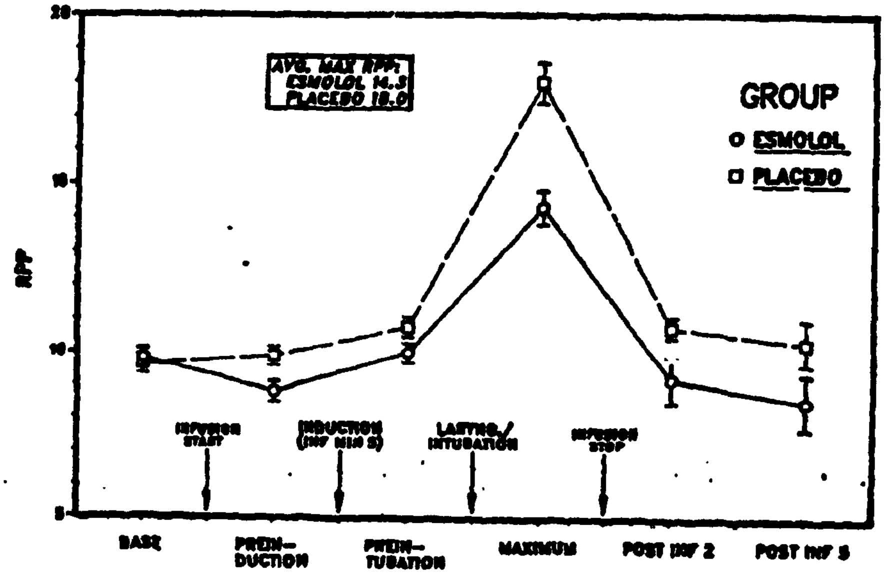
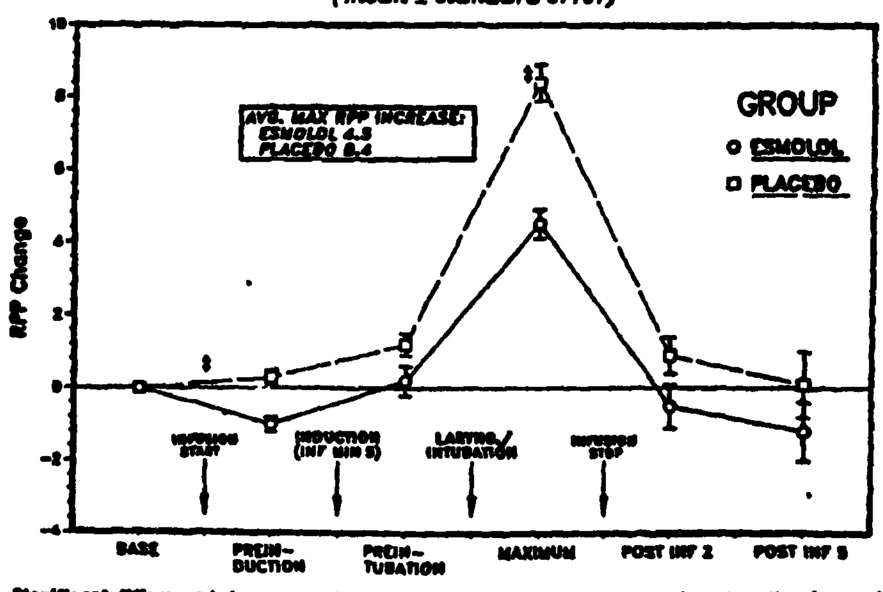


FIGURE 11

Rate–Pressure Product Changes from Baseline
(mean ± standard error)



‡ Significant difference between esmolol and placebo with respect to change from baseline (p<0.01).

(c) Clinically Significant Increases in Heart Rate and Systolic Blood Pressure: (Table 15) The actual benefit to patients and impact on clinical outcome should ultimately be the criteria upon which to judge efficacy of any therapeutic modality. So it is of interest that the sponsor has attempted to extrapolate the results of beta blockade (blunting of HR and SBP which esmolol clearly produces) to potential clinical benefit. This analysis is based on the premise (which is probably valid) that adverse perturbation of the balance between myocardial oxygen demand vs supply in patients with CAD are related to the maximum values of heart rate and SBP (and hence RPP) attained by a patient following intubation (for further details see section on background/rationale). The following analysis is based on the sponsor's arbitrary criteria for clinically significant levels: (heart rate greater than or equal to 100 bpm and SBP greater than or equal to 180 mm Hg). According to the sponsor, "there was a significantly larger number of patients who demonstrated HR greater than 100 bpm in the placebo group (42/51, 82%) than in the esmolol treated group (17/50, 34%, p less than 0.01). There was a larger number of patients with SBP greater than 180 in the placebo group (16/51, 31%) than in the esmolol group (8/50, 16%), however, this difference was not statistically significant. There was a significantly greater number of placebo patients (44/51, 86%) who demonstrated either a HR greater than or equal to 100 or a SBP greater than or equal to 180 as compared to the esmolol group (21/50, 42%, p less than 0.01). In addition, there was a significantly larger number of placebo patients (14/51, 27%) who demonstrated a maximum HR greater than 100 and a SBP greater than 180 as compared to the esmolol group (4/50, 8%, p less than or equal to 0.01).

TABLE 15

Clinically Significant Heart Rate (bpm) and Systolic Blood Pressure (mm Hg)

Center[a]	Group	HR≥100	SBP≥180	HR≥100 AND SBP≥180	HR≥100 OR SBP≥180	N
1	Esmolol	4	1	0	5	15
	Placebo	9	3	3	9	12
3	Esmolol	6	6	3	7	16
	Placebo	16	8	5	17	18
4	Esmolol	2	1	0	3	9
	Placebo	10	4	4	10	10
5	Esmolol	2	0	0	2	8
	Placebo	6	1	1	6	7
6	Esmolol	3	2	1	4	4
	Placebo	1	2	1	2	4
	Group					
Pooled	Esmolol	17	8	4	21	50
	Placebo	47	16	14	44	51
	Comparison[b]	P>E**	N.S.	P>E**	P>E**	

a No significant differences among the centers were detected (p≥0.05).

b N.S. indicates no significant difference between the esmolol and placebo treatment groups (p≥0.05)

P = Placebo, E = Esmolol 300 mcg/kg/min. * p<0.05. ** p<0.01

d) Analysis of Maximum Changes From Baseline by Center

The primary efficacy analyses pooled the data from the five treatment centers. However, if the treatment groups are analyzed by center, different results are observed. In this case, only HR, MAP and RPP attain statistical significance in 3 of the 5 centers. For SBP, only in two centers (HS) did the two treatment groups significantly differ (Table 23).

Table 23

Maximum Change from Baseline for "Efficacy Patients" by Center and Treatment

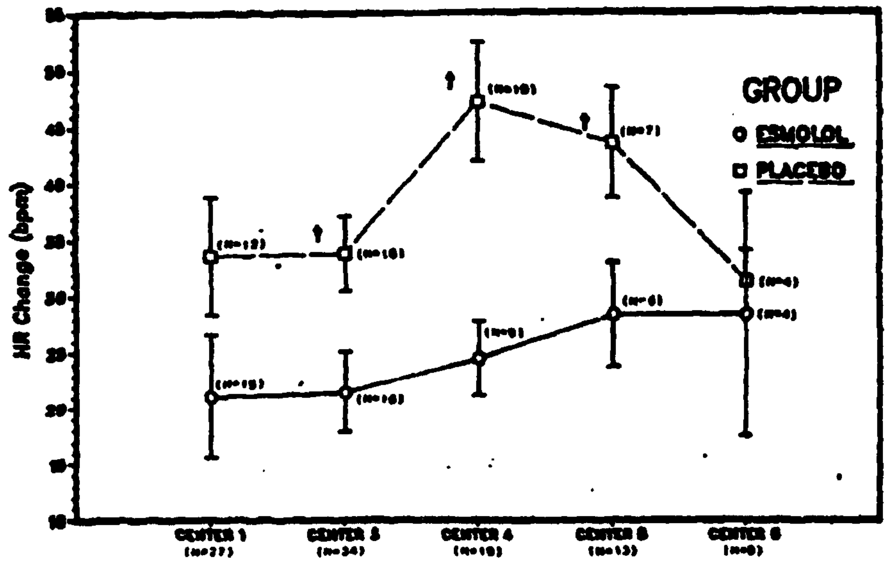
Center	Group	HR Change (bpm) Mean	± SEM	SBP Change (mm Hg) Mean	± SEM	DBP Change (mm Hg) Mean	± SEM	MAP Change (mm Hg) Mean	± SEM	RPP Change Mean	± SEM	N
1	Esmolol	21.1	5.8	17.8	5.6	29.1	3.0	23.8	4.2	2.9	0.8	15
	Placebo	33.8	5.2	41.0*	4.5	37.3	3.6	38.8*	4.0	8.3*	1.2	12
3	Esmolol	21.9	3.0	33.9	3.5	34.4	3.3	32.9	3.1	5.6	0.8	16
	Placebo	33.8*	3.3	38.7	4.9	31.1	3.8	33.2	4.1	7.7	0.8	18
4	Esmolol	24.9	3.3	31.1	5.0	30.2	3.7	28.8	3.7	3.1	0.8	9
	Placebo	47.2*	5.2	43.7	6.1	46.3*	3.0	44.0*	3.0	10.3*	1.2	10
5	Esmolol	28.4	4.8	19.3	5.2	33.7	2.6	28.7	2.3	4.4	1.2	8
	Placebo	43.6*	4.9	40.5*	4.1	45.4*	2.5	42.4*	2.1	8.9*	1.1	7
6	Esmolol	28.3	10.8	28.5	8.8	40.5	12.9	35.7	11.5	5.1	2.2	4
	Placebo	31.3	7.7	36.9	10.9	30.2	5.8	28.4	8.8	6.7	1.4	4

* Indicates significant difference between the esmolol and placebo treatment group ($p<0.05$).

Figures 12 and 13 provide center by center illustrations for the primary efficacy variables (HR, SBP).

FIGURE 12

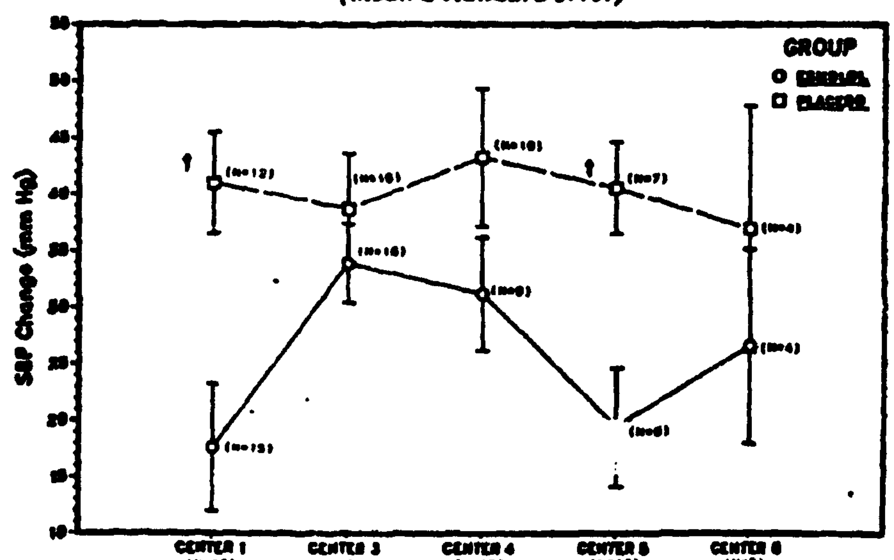
Maximum Heart Rate Changes from Baseline, by Center
(mean ± standard error)



† *Significant difference between esmolol and placebo treatment groups(p<0.05).*

FIGURE 13

Maximum Systolic Blood Pressure Changes from Baseline, by Center
(mean ± standard error)



† *Significant difference between esmolol and placebo treatment groups(p<0.05).*

Comment: Although the above mentioned clinical parameters (see section c) were classified by the sponsor as secondary efficacy variables in terms of the study objectives, they may be quite relevant from the standpoint of trying to assess the potential benefit that beta blockade (with an ultrashort acting beta blocker) might have on either improving clinical outcome or preventing the occurrence of undesirable events related to induction of anesthesia and endotracheal intubation in the general patient population or special patient subsets (i.e., CAD). Such an analysis of clinical outcome ideally should be based on objective criteria of morbidity associated with endotracheal intubation and general anesthesia or particular events associated with or aggrevated by general anesthesia such as myocardial ischemia. The problem with this study (and the other two studies that follow) is that they only address the issue of whether the agent (esmolol) effectuates beta blockade and not the crucial issue of its overall impact on surgical/clinical outcome. Therefore, our ultimate assessment of whether these studies actually demonstrate "safety and efficacy" will hinge upon our criteria of "efficacy" and our ability to extrapolate in a reasonable and logical manner from the achievement of beta blockade to the actual benefit patients might derive from such an effect during endotracheal intubation and general anesthesia and subsequent surgery.

III Safety Results: (51A)

(a) Adverse Effects: According to the sponsor, only 1 of the 112 patients entered into the study exhibited an adverse effect: patient 509 who received a placebo infusion, exhibited both itching at the injection site and wheezing following intubation. The itching continued for approximately 3 minutes until the patient was asleep. The infusion was discontinued when the wheezing occurred. The wheezing continued at a mild degree throughout surgery.

(b) Other Noted Effects: The sponsor further reports that "4 patients (#302, #305, #318, #515) exhibited findings which although not considered to be adverse effects, were noted by the investigators. These effects included patient #302 (esmolol treated) and #305 (placebo treated) mild hypertension post infusion period, patient #318 (esmolol treated) coughing episode immediately after administration of thiopental and succinylcholine, patient #505 (esmolol treated) feeling "drunk and very weak" immediately prior to induction. Although none of the above were attributed to esmolol, it is possible that these reactions were related to esmolol itself.

(c) Patients With Diseases at Risk for Beta Blockers: Of 112 patients receiving esmolol or placebo, 8 patients (#108, #115, #303, #306, #312, #322, #416 and #606) had concurrent disease states (reactive airway disease, diabetes mellitus and hepatic insufficiency) which are known to be at increased risk with beta blockers. However, only one patient (#115-diabetes mellitus) received esmolol. These numbers are clearly too small to allow any conclusion regarding safety.

(d) EKG Findings

The incidence and severity of EKG abnormalities during the study reported by the sponsor did not appear to differ significantly between esmolol vs placebo i.e. 28 patients (12 esmolol treated and 16 placebo treated).

(e) Deaths

None were reported.

Comments: Due to the exclusion of partial data from 69 efficacy patients, the ability to analyze and evaluate clinical safety variables (MAP, DBP, RPP) is significantly hampered. Thus it is not possible to interpret these parameters during successive observation periods during the study. It appears from the data presented that in order to achieve significant reductions in the primary efficacy variables HR and SBP, a significant reduction in SBP (as detected during the 2 and 5 minute post infusion period) from the baseline was necessary. With insufficient data available to analyze these parameters at the 10 and 15 minute post infusion time points (probably the most important in assessing recovery from esmolol), we cannot assess safety from the standpoint of prompt and complete recovery from beta blockade. This is disappointing since one of the potential advantages of esmolol should be short duration of action and quick reversal after discontinuation of the infusion. Further, there is no information provided re: the two treatment groups in terms of clinical outcome (results and response to surgery). This same problem pervades the other two trials as well (51A and 49).

REVIEW OF PIVOTAL STUDIES continued

(b) Perioperative Tachycardia and Hypertension

Study No. 8052-84-51B (Second Pivotal Study)

Overview

As previously indicated under discussion of study no. 8052-84-51A, the original clinical trial under the aegis of 8052-84-51 has been arbitrarily divided by the sponsor into two entities: 51A and 51B. These could be construed as part A and part B of one multicenter trial. Since the results reported under 51B represent patients enrolled by the same investigators and same institutions as in 51A (centers 1 and 2 did not participate in phase B and center 5 did not enter any patients) and the decision to separate this multicenter trial for the purpose of NDA submission was made post hoc, concerns over the validity of this action are raised. Therefore it will be useful to obtain consultation from our biostatistical group and analyze the data from part A and part B individually and combined. The relative differences between part A and part B have been delineated in the previous section. For specific details regarding study objectives, design, treatment plan, efficacy and safety assessment as well as statistical methodology see appropriate sections under study 8052-84-51A (since these features are essentially unchanged).

The findings of 51B will be discussed in this section. In general, the results reported under part B are very similar to the therapeutic responses reported in part A. Similar to 51A, esmolol significantly blunted the increases in heart rate and systolic blood pressure (primary efficacy variables) when compared to placebo during endotracheal intubation (p less than 0.01). Analysis of secondary efficacy variables (MAP and RPP) revealed similar findings to that of HR and SBP. Moreover, a similar pattern was observed in terms of esmolol showing a decided advantage over placebo in controlling clinically significant increases in HR and SBP. In addition the sponsor has treated the efficacy analysis similarly in that a majority of the "efficacy patients" (50/63) had part of their efficacy data excluded because of changes in the inspired dose of halothane (and because one patient received a second dose of thiopental post infusion). Thus similar limitations are again imposed in terms of the ability to evaluate efficacy variables during successive phases of the study period. Again patient numbers are too small especially at the important 2 and 5 minute post infusion study periods to be able to statistically assess the data presented. Furthermore with the requirement for observations at 10 and 15 minutes post infusion modified to optional, no information at these time intervals are presented. In addition it is worth noting that there are a number of calculation errors in Tables 11 and 12 regarding the HR changes and SBP changes recorded at post infusion2 and 5 minutes which further impair any analysis. (The sponsor explains these apparent errors due to the fact that the actual means used to compute the data come from only the few patients selected for efficacy assessment at these timepoints and not the baseline values in the table for the esmolol groups as a whole.)

Specific Results: For details of study objectives, design, treatment plan and efficacy assessment see study 51A.

Investigators and Institutions: Of the 5 centers who contributed patients to phase A, four continued onto phase B. For a complete listing of investigators, institutions and the number of patients enrolled at each center see Table 1.

Table 1

LIST OF INVESTIGATORS AND
NUMBER OF PATIENTS ENROLLED

CENTER NUMBER*	INVESTIGATOR AND INSTITUTION	NUMBER OF PATIENTS ENROLLED
3	Fred Brindle, M.D. Jackson Memorial Hospital Miami, Florida	6
4	Simon Gelman, M.D. University of Alabama, Birmingham Birmingham, Alabama	36
5	Theodore Stanley, M.D. University of Texas Health Center at Houston Houston, Texas	0
6	Martin I. Gold, M.D. Veterans Administration Medical Center Miami, Florida	31

* Center #1 did not agree to go on to phase B of the study. Center #2 withdrew from study participation prior to phase A of the study.

Patient Selection: Patients were selected as in 51A except only patients classified as either ASA physical status 3 or 4 were eligible instead of ASA 1 or 2.

Treatment Plan: As a result of amendment 4 (June 14, 1984) the following modifications to the original treatment were made:

(1) Length of esmolol infusion was increased from 12 to 15 minutes,

(2) Anesthesia induction at minute 10 instead of minute 5 of the infusion.

(3) Increase in the thiopental induction dose from 4 mg/kg to 5 mg/kg and

(4) Allowing a choice of preoperative medications including diazepam, morphine, or glycopyrrolate.

Number of Patients - "All", "Efficacy", "Exclusions" and "Dropouts": 73 patients who entered into this multicenter study were randomized to either esmolol or placebo. Of these 73 "all patients", 63 were classified as "efficacy patients" (n=32 for esmolol and n=31 for placebo). The derivation of "all patients" and "efficacy patients" is shown in Table 5.

Table 5

DERIVATION OF "ALL PATIENTS" AND

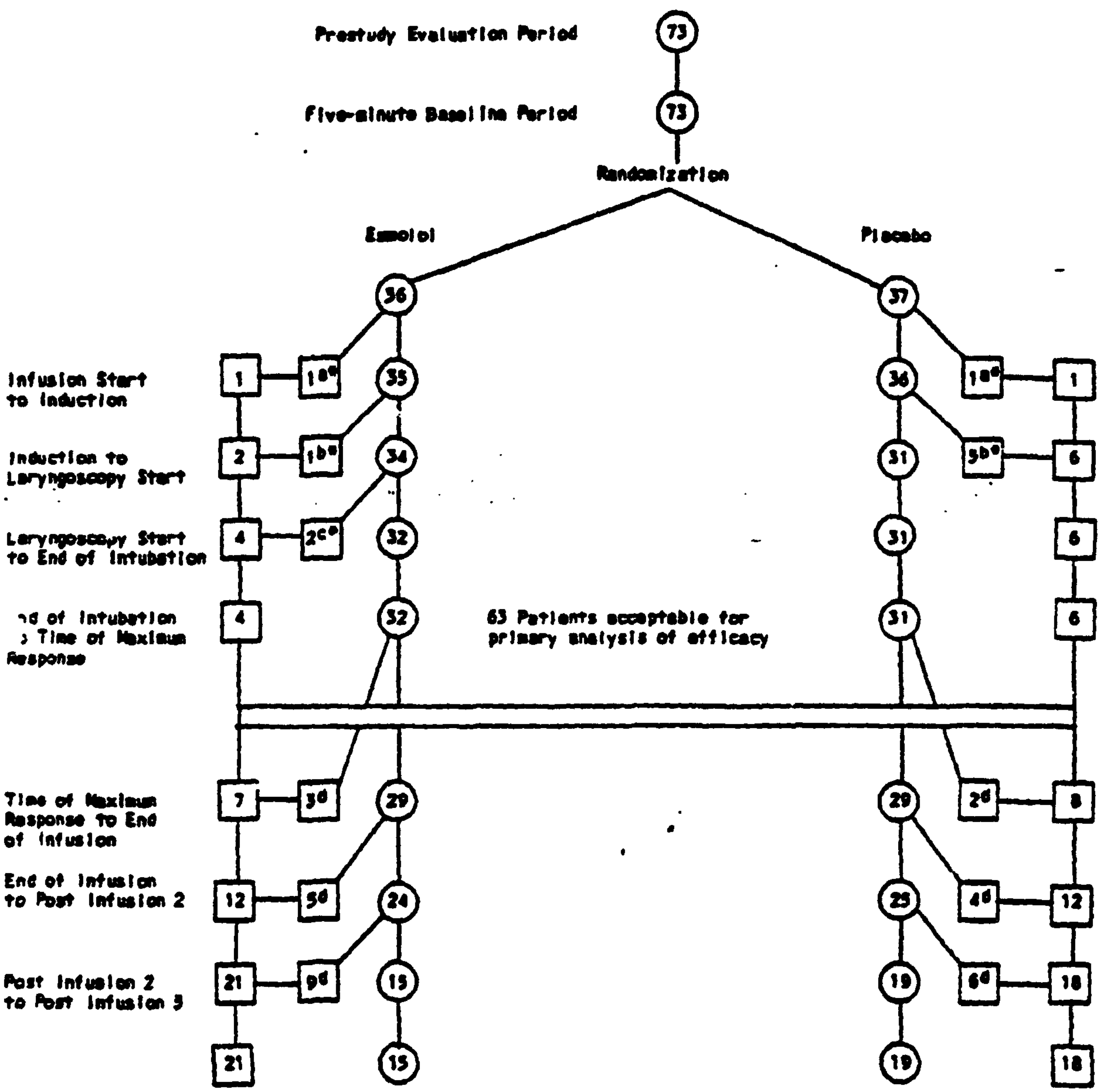
"EFFICACY PATIENTS" IN THE STUDY

"All Patients"	73	36	Esmolol
		37	Placebo
Excluded from efficacy analysis	10	(#337, 435, 610, 617)	Esmolol
		(#343, 434, 612, 613, 627, 633)	Placebo
"Efficacy Patients"	63	32	Esmolol
		31	Placebo

A summary of "all patients" by study period is provided in Table 6.

Table 6

SUMMARY OF "ALL PATIENTS" AT EACH PHASE OF THE STUDY



○ Eligible for efficacy analysis

□ Ineligible for efficacy analysis; outside columns indicate cumulative totals.

a Patients #434(P) and 435(E) received Regroton <6 weeks before entering the study
b Patients #343(P), 612(P), 613(P), 617(E), 627(P), and 633(P) received thiopental dose >5.5 mg/kg
c Patients #337(E), and 610(E) experienced multiple intubations. Patient #343 also experienced multiple intubations; however, this patient was already excluded from efficacy analysis due to an excessive thiopental dose.
d Changes in halothane (% inspired)
e Ineligible for all efficacy analyses

Data from 10 patients were excluded from efficacy analysis (see Table 7 for reasons for exclusion) on account of the following: received unacceptable prior or concurrent medications (2 patients), deviations from dose allowed for anesthesia induction (6 patients), difficult intubation requiring several attempts (2 patients). As a whole these exclusions seem to be reasonable and probably don't affect the overall results.

Table 7

LIST OF PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

PATIENT NUMBER	TREATMENT	DEMOGRAPHIC DATA			BASELINE DATA			REASON FOR EXCLUSION FROM EFFICACY ANALYSIS
		SEX	AGE (yrs)	WEIGHT (kg)	HEART RATE (bpm)	BLOOD PRESSURE SBP (mmHg)	DBP	
337	Esmolol	M	77	59	80	137	83	Intubation was attempted four times over a three-minute period during and after infusion.
343	Placebo	F	58	59	82	147	93	Received incorrect dose of induction agent. (6.7 mg/kg thiopental administered in two divided doses over a four-minute period.)*
434	Placebo	F	59	108	70	117	48	Received a reserpine-containing adrenergic-depleting drug (Regroton) within the six week period prior to the study.
435	Esmolol	F	70	82	81	118	61	Received a reserpine-containing adrenergic-depleting drug (Regroton) within the six week period prior to the study.
610	Esmolol	M	74	70	54	147	87	Multiple intubation attempts during and after infusion.
612	Placebo	M	37	90	88	116	72	Received incorrect dose of induction agent. (5.8 mg/kg thiopental administered.)*
613	Placebo	M	64	90	84	165	98	Received incorrect dose of induction agent. (2.5 mg/kg thiopental administered.)*
617	Esmolol	M	66	60	74	142	96	Received incorrect dose of induction agent. (5.8 mg/kg thiopental administered.)*
627	Placebo	M	44	85	90	125	79	Received incorrect dose of induction agent. (6.3 mg/kg thiopental administered in two divided doses over a one-minute period.)*
633	Placebo	M	39	66	51	139	85	Received incorrect dose of induction agent. (7.8 mg/kg thiopental administered in two divided doses over a one-minute period.)*

* Protocol specified thiopental dose 5 mg/kg. Acceptable upper limit 5.5 mg/kg.

Study Results

Ia Baseline Demographics and Comparability of Treatment Groups: Baseline demographic and clinical characteristics (including key efficacy variables) were similar for both treatment groups (Tables 10 and 13).

Table 10

Summary of Demographic and Prestudy Clinical Data, by Treatment Group for "All Patients"

Variable	Treatment[c]	Mean	± S.D.	Min	Max	N
Age (years)	Esmolol	60.3	12.4	22.0	89.0	38
	Placebo	57.1	13.0	29.0	81.0	37
Height (cm)[a]	Esmolol	170.6	7.9	155.0	185.0	36
	Placebo	170.5	11.2	142.2	190.0	35
Weight (kg)	Esmolol	75.1	16.5	50.0	120.0	38
	Placebo	76.0	17.2	44.5	110.0	37
BSA (m2)[a]	Esmolol	1.9	0.2	1.5	2.4	36
	Placebo	1.9	0.2	1.4	2.1	35
Heart Rate[b] (bpm)	Esmolol	80.1	17.0	52.0	134.0	38
	Placebo	76.9	12.9	53.0	98.0	36
SBP (mm Hg)	Esmolol	131.5	16.1	110.0	170.0	38
	Placebo	133.0	20.4	100.0	200.0	37
DBP (mm Hg)	Esmolol	80.2	11.6	60.0	100.0	38
	Placebo	83.1	12.2	66.0	110.0	37
Resp (/min)	Esmolol	17.2	3.3	14.0	24.0	38
	Placebo	16.6	3.2	12.0	24.0	37
Temp (°C)	Esmolol	36.8	0.5	36.1	38.3	38
	Placebo	36.7	0.5	35.6	37.7	37

a Height and body surface area were not obtained from Patients #436 and 453.
b Prestudy heart rate was not obtained for Patient #[illegible].
c No significant differences between the esmolol and placebo treatment groups were detected ($p \geq 0.05$).