CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-386

Medical Review(s)

Division of Cardio-Renal Drug Products
Medical Officer's Review

NDA 19-386
Brevibloc (esmolol)

Reviewer
Ronald Lieberman, M.D.

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MEDICAL OFFICER'S REVIEW

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Section I Clinical Pharmacology

A. Summary Tables of Clinical Pharmacology Studies (Tables A, B_1, B_2 and C)

The following tables summarize the principal clinical studies (phase 1 and phase 2) submitted by the sponsor concerning the clinical pharmacology of esmolol.

5.3.5. SAFETY STUDIES
II Intravenous

INVESTIGATOR / SITE	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	STUDY DESIGN	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Schmolle, H., M.D. [illegible] Institute Ottokrom, East Germany Volume 3.2	8052-01-01	6 Subjects	"First-in-man" randomized, single blind tolerance study in normal male subjects using "down leader" sequential dosing procedure over 5-day period.	From 10 to 650 mcg/kg/min I.V. for four one hour each dose -- sequential administration.	Blood chemistry, hematology, urinalysis, heart rate, blood pressure, respiration rate. Objective and subjective ADR observations. Blood levels of drug and metabolite.	Well tolerated up to 650 mcg/kg/min with regard to ADR's, hemodynamic stability and normality of lab parameters. Initial pharmacokinetic data obtained. ADR's: fatigue, headache, rhinitis, facial flushing, diarrhea, anemia. The anemia was not drug related.
Schmolle, H., M.D. [illegible] Institute Ottokrom, East Germany Volume 3.3 (Medical) Volume 3.4 (Statistical)	8052-01-02	6 Subjects	Single blind, tolerance study in normal male subjects using increasing doses over three day period with beta-blockade assessed by isoproterenol challenge (HR increase of 30 bpm).	50, 150 and 300 mcg/kg/min I.V. for two hours on each of the three days.	Same as Study 8052-01-01 plus blood levels of esmolol.	Well tolerated at all doses with regard to ADR and normality of lab parameters. Esmolol blocked in dose-dependent manner, the increases in HR and SBP and the decreases in DBP induced by isoproterenol. Steady state levels of esmolol achieved within 30 min. Pharmacokinetics: elimination half-life = 9.19 min. Urinary excretion: approx. 3% of total dose excreted in 24 hours (88% as metabolite + 1.9% as esmolol. Ethanol blood levels were all well below toxic levels.
Schmolle, H., M.D. [illegible] Institute Ottokrom, East Germany Volume 3.5	8052-01-03	11 Subjects	Single blind, tolerance study in normal male subjects using increasing infusion periods (from 6 to 48 hours) of a 150 mcg/kg/min dose. Beta-blockade assessed by isoproterenol challenge (HR increase of 30 bpm).	Infusion of 150 mcg/kg/min for 6 hours (1), 12 hours (1), 24 hours (2), 36 hours (2) and 48 hours (6).	Same as Study 8052-01-01.	Well tolerated up to 48 hours in all subjects. Rapid onset of beta-blockade which disappeared within 10 min after end of infusion. ADR's similar to previous studies. Two instances of anemia were not drug related. Pharmacokinetics were determined.

BREVIBLOC® (esmolol HCl) INJECTION (NDA 19-336)
SUMMARY TABLE - CLINICAL STUDIES

E.1.a. SAFETY STUDIES
III) Venous and Perivascular Irritation

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	STUDY DESIGN	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Arnold, J., M.D. Quincy Research Center Kansas City, MO	0052-00-12	19 Subjects	Open label, single blind study in normal male volunteers to evaluate venous and perivascular effects of esmolol (10 mg/mL concentration) when infused for up to 72 hours at dose of 300 mcg/kg/min dose.	Following stepwise titration from 50 mcg/kg/min to 300 mcg/kg/min over 30 min period, 300 mcg/kg/min dose was infused for 24, 48, or 72 hours (3 groups) infusion solution: 10 mg/mL esmolol HCl.	Vital signs [HR, SBP, DBP and RR measured at frequent intervals; blood chemistry, hematology, urinalysis;] creatinine clearance; evaluation of subjective complaints; examination of infusion site at periodic intervals during infusion.	All 6 subjects in Group I completed 24 hour infusion; 4 of 5 in Group II completed 48 hours; 2 of 8 in Group III completed 72 hour infusion. Seven subjects terminated from study due to either systemic adverse reactions (6) or venous irritation (1); infusion site reactions included: pain (11), swelling (8), soreness (6), itching (5), burning (4), erythema (3), redness (2), induration (1). Systemic ADR's: headache (11), dizziness (6), nausea (6), skin discoloration (3), taste perversion (4), chest pain (2). No clinically significant changes in HR, SBP, DBP, laboratory tests, ECG, creatinine clearance, or nurse evaluations were noted.
Smith, H. Eugene, M.D. Quincy Research Center Kansas City, MO	0052-03-24	6 Subjects	Double blind, randomized, placebo controlled study in normal male volunteers to evaluate venous and perivascular effects of esmolol (20 mg/mL) or placebo when infused for 48 hours at dose of 300 mcg/kg/min.	Following 24 hour infusion of D5W, subjects titrated from 50 to 300 mcg/kg/min at 5 min intervals with a 1 min 500 mcg/kg/min loading dose then infused with 300 mcg/kg/min for 48 hours. Infusion solution: 20 mg/mL esmolol HCl.	Same as Study 0052-00-12.	None of the three subjects on esmolol completed the 48 hour infusion due to adverse effects (burning, pain, swelling, erythema, induration, skin rash, itching and paresthesia) at infusion site. Systemic effects: headache, dizziness, syncope, tinnitus, asthenia, paresis, dyspepsia, rash. Due to occurrence of adverse effects, study was terminated prematurely (only 4 of 16 subjects were entered).

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BREVIBLOC® (esmolol HCl) INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

E.1.a. SAFETY STUDIES
(i) Venous and Perivascular Irritation

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	STUDY DESIGN	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Williams, Roger, M.D. University of California San Francisco, CA	8852-CD-46	9 Subjects	Single blind, baseline placebo controlled study in 9 normal male subjects to evaluate venous and perivascular effects of esmolol (20 mg/mL) when infused for 24-48 hours at dose of 300 mcg/kg/min.	Group A: Following 24 hour infusion of PBS, subjects titrated from 50 to 200 mcg/kg/min at 5 min intervals with 1 min loading dose of 500 mcg/kg/min, then infused for 24 hours at a dose of 200 mcg/kg/min. Group B: Same as Group A, except esmolol infusion (300 mcg/kg/min) continued for additional 24 hours.	Same as Study 8852-CD-12.	Group A: One subject completed the 24 hour infusion, other 2 subjects required change of infusion site due to infusion site reactions. Group B: None of the 6 subjects completed the 48 hour infusion -- all terminated due to adverse reactions of infusion site after infusion periods ranging from 22 to 31 hours. ADR's same as observed in Study 8852-CD-24 except phlebitis and thrombosis of vein in 5 of 9 subjects at follow-up.

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(ii) Safety Study in Mild Asthmatics

Shepperd, Dean, M.D. San Francisco General Hospital San Francisco, CA	8852-CD-24	10 Patients	Double blind, randomized, placebo-controlled, crossover study in mild asthmatic patient volunteers to assess the effect of Brevibloc® on airway function and responses to dry-air induced bronchoconstriction and isoproterenol-induced bronchodilation. Six of the ten were also studied with propranolol as active comparison control.	Brevibloc®: Titration from 100 to 300 mcg/kg/min for 5 min each with 1.5 min 500 mcg/kg/min loading dose, then 300 mcg/kg/min for 30 min. Propranolol: 1 to 3 mg in 1 mg increments.	Pulmonary function tests, plethysmography, blood chemistry, hematology, urinalysis; vital signs (HR and BP).	Brevibloc® caused slight but significant effects on bronchomotor responsiveness to dry air and isoproterenol. Propranolol produced more profound effects in 3 of 6 patients tested (marked symptomatic bronchoconstriction and increase in specific airway resistance in 2 of the 6. Brevibloc® may offer advantages over propranolol in asthmatic patients who require I.V. beta-blocker.

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BREVIBLOC® (esmolol HCl) INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

6.1.6. ABSORPTION, DISTRIBUTION METABOLISM, EXCRETION STUDIES

INVESTIGATOR / CITY	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Manigan, John, M.D. Lincoln, NE Volume 3.9 Volume 3.10	8852-02-09	8 Subjects	A study of the pharmaceutics of Brevibloc® and its major metabolite at 50- to 300 mcg/kg/min of the dose proportionality of the pharmacokinetics; and of the effect of long term administration of Brevibloc® at 150 mcg/kg/min. Appropriate blinding and subject safety protection techniques were employed.	Each subject received Brevibloc® 50, 100, 200, and 300 mcg/kg/min for 6 hours with one week interval between each administration. Each subject subsequently received Brevibloc® 150 mcg/kg/min for 24 hours.	Brevibloc® and metabolite (ASL-8123) levels, total body clearance, steady-state volume of distribution, half-life of disposition, and terminal half-life.	Kinetics were linear and not dose-dependent, for both Brevibloc® and ASL-8123. Brevibloc® was rapidly hydrolyzed at a rate greatly exceeding cardiac output. These doses all were tolerated. ADR's: Light-headedness, nausea, occasional ventricular extrasystole irritation at the injection site with 24 hour infusion.
Rollins, Douglas, M.D. Salt Lake City, UT Volume 3.10	8852-02-10	3 Subjects (Normal volunteers) and 9 patients with renal impairment.	An ongoing study of the pharmacokinetics of Brevibloc® and its major metabolite in patients with renal impairment. Seven normals and two patients have entered the study to date.	Brevibloc® 150 mcg/kg/min for four hours.	Essentially similar to those in Study 8852-02-09.	Have to date; study is ongoing. ADR's: Ill-defined episode of hypotension and tachypnea concurrent with infiltration of the infusion site seven minutes into the study, and unsuccessful attempts to restart the infusion in the contralateral arm.
Rollins, Douglas, M.D. Salt Lake City, UT Volume 3.10	8852-04-90	3 Subjects (Normal volunteers) and 9 patients with hepatic disease.	An ongoing study of the pharmacokinetics of Brevibloc® and its major metabolite in patients with documented hepatic disease. Three normals and five patients have entered the study to date.	Brevibloc® 200 mcg/kg/min for four hours.	Essentially similar to those above.	Have to date; study is ongoing. ADR's: Tenderness at infusion site (1), mild headache (2), hot flash (1).

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[illegible] (morphine sulfate) INJECTION (NDA 19-336)
SUMMARY TABLE - CLINICAL STUDIES

6.1.4. SPECIAL STUDIES - [illegible]

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DOSE, DOSAGE AND DURATION	TEST PROCEDURES FOR SAFETY AND/OR EFFICACY	RESULTS
Leventhal, David, M.D. Philadelphia, PA Volume 3.19 Volume 3.20 Volume 3.21	[illegible]-[illegible]-[illegible]	10 Subjects	An open label determination of pharmacokinetic and pharmacodynamic interactions between Brevibloc® and morphine.	Brevibloc® titrated from 50 mcg/kg/min to 300 mcg/kg/min over 30 min followed by a 3.5 hour infusion of 300 mcg/kg/min. Morphine sulfate 3 mg by slow intravenous injection.	Vital signs, blood levels of study drugs.	Morphine may increase steady-state blood levels of Brevibloc®. ADR's: Brevibloc® alone - headache, lightheadedness, erythema. Morphine alone - nausea, shortness of breath, chest tightness, dizziness, difficulty in micturition, diminished micturition, stomach pain. Combination - dizziness, chest tightness, headache, nausea, shortness of breath, stomach pain, flushing of skin, vomiting, diaphoresis.
Leventhal, David, M.D. Philadelphia, PA Volume 3.22 Volume 3.23	[illegible]-[illegible]-[illegible]	12 Subjects	An open label determination of pharmacokinetic and pharmacodynamic interactions between Brevibloc® and digoxin.	A six-hour Brevibloc® infusion titrated from 50- to 300 mcg/kg/min before and during digoxin therapy titrated to a serum digoxin level of 0.8 to 2.0 ng/ml.	Vital signs, P-R interval, and blood levels of study drugs.	Pharmacokinetics of Brevibloc® and its major metabolite are unchanged by digoxin administration. Brevibloc® may increase digoxin serum levels. ADR's: mild headache (4), mild headache and nausea (1), mild nausea (1), moderate headache and photosensitivity (1).
Leventhal, David, M.D. Philadelphia, PA Volume 3.23	[illegible]-[illegible]-[illegible]	10 Subjects	An open label determination of pharmacokinetic interactions between Brevibloc® and warfarin.	A six-hour Brevibloc® infusion titrated from 50 mcg/kg/min up to 300 mcg/kg/min before and during warfarin titrated to a prothrombin time of 1.5 - 2.5 times control value.	Prothrombin times, blood levels of study drugs and ASL-8123.	Clinical phase complete, but blood samples not analyzed to date. ADR's: Headache (2), nausea (1).

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11.

[illegible] (esmolol HCl) INJECTION USP 10-100
SUMMARY TABLE - CLINICAL STUDIES

E.1.d. SPECIAL STUDIES: DRUG INTERACTIONS

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Hurley, V., M.D., Ph.D. Milwaukee, Wisconsin Volume 3.24	[illegible]	10 Patients	An open-label non-randomized, placebo-controlled parallel study of the effect of Brevibloc® on heart rate and blood pressure increases related to endotracheal intubation, and on the duration of succinylcholine induced neuromuscular blockade, in patients anesthetized with thiopental.	Brevibloc® 500 mcg/kg/min 4 minutes followed by Brevibloc® 300 mcg/kg/min for 6 min. Anesthesia induced at minute 3 with thiopental 4 mg/kg. The balance of the preoperative and peri-induction medications were standard for the institution.	Heart rate and blood pressure determinations, continuous muscular twitch measurements.	Brevibloc® produced a modest, statistically significant increase in the duration of succinylcholine-induced neuromuscular blockade. Brevibloc® was effective in blunting the increase in rate-pressure product following endotracheal intubation. ADRs: None reported.

[illegible]
111.

[illegible] INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

I.1.c. SPECIAL STUDIES: GLAUCOMA

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Tremer, Ivan Ren Ulm, West Germany Volume 3.25	8053-82-11	18 Subjects	A single-blind, randomized placebo controlled study of the effects of topical Betaxolol® on intraocular pressure.	Single drop administration of Betaxolol® ophthalmic solutions in concentrations ranging from 0.5% to 5.0% with placebo instillation to the contralateral eye.	Intraocular pressure (IOP) determinations by Goldman applanation, heart rate, blood pressure, respirations.	Single doses of Betaxolol® 3.0% and 5.0% produced significant reductions in IOP over 12 hours. ADR's: Mild local irritation effects.
Tremer, Ivan Ren Ulm, West Germany Volume 3.26	8053-82-19	16 Subjects	A double-blind, randomized placebo controlled study of the effects of topical Betaxolol® 3% ophthalmic solution, administered twice daily for three days.	Single drop administration of Betaxolol® 3% twice daily for three days, with placebo instillation to the to the contralateral eye.	Same as Study 8053-82-11	This formulation was well tolerated and effective in lowering IOP over a 24-hour period. ADR's: None reported.

BREVIBLOC® (esmolol HCl) INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

E.2 [illegible]

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DOSE SCHEDULE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Schlepper, Martin Bad Nauheim, West Germany Volume 3.27	[illegible]	5 Patients	Placebo controlled pilot study of the effect of Brevibloc® on heart rate in patients with atrial fibrillation during mild to moderate exercise, with concurrent assessment of Brevibloc® blood levels.	Thirty-minute placebo infusion followed by a 120 min infusion of Brevibloc®, including a dose titration phase; and a final 30 minute placebo infusion. Doses of Brevibloc ranged from 50- to 300 mcg/kg/min.	Heart rate, sitting systolic and diastolic blood pressure, pulmonary capillary wedge pressures recorded before, during, and after placebo and Brevibloc® infusions, and before and during bicycle exercise.	Data were not analyzed due to small study population. ADR's: None reported.
Strickfaldt, A. Munich, West Germany Volume 3.27	[illegible]	12 Patients	Single blind, placebo controlled determination of efficacy and safety of Brevibloc® infusion for control of heart rate in patients with supra-ventricular tachycardia.	Thirty minute placebo infusion followed by 20.5 minute infusion of Brevibloc® at 50, 100, 150, and 200 mcg/kg/min. Each Brevibloc® infusion preceded by a 0.5 min loading dose of 500 mcg/kg/min. Placebo infusion for 30 min at conclusion of study.	Heart rate, systolic and diastolic blood pressure, drug and drug metabolite level studies.	Heart rate, systolic blood pressure, as well as double product, all showed significant decrease following Brevibloc®, when compared to placebo, generally greater with increasing doses. No conversions to NSR. A good correlation between reduction in heart rate and Brevibloc® blood levels was demonstrated. ADR's: Moderate hypotension, dizziness, diaphoresis, drowsiness.

[illegible] Injection (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

U.S. Open Nursing: Anesthesia

Investigator / Institution	Study Number	Number of Subjects/ Patients	Description	Drug Dosage and Duration	Test Parameters for Safety and/or Efficacy	Results
Raven, Joseph D., M.D. Birmingham, AL	8053-CS-21	42 Patients	Open label pilot study to evaluate the effect of Brevibloc® on heart rate and blood pressure increase resulting from endotracheal intubation of anesthetized patients. [Part of three-site, multicenter study.]	Patients were non-randomly assigned to: 1) placebo; 2) Brevibloc® 100 mcg/kg/min; 3) Brevibloc® 200 mcg/kg/min; 4) Brevibloc® 300 mcg/kg/min; infusions were for seven min, with intubation after min 3. Brevibloc® loading dose were 500 mcg/kg/min for one min (100 mcg/kg/min dose), two min (200 mcg/kg/min dose), or three min (300 mcg/kg/min dose).	Heart rate and blood pressure, for all patients. Hemodynamic measurements for 25 patients.	Brevibloc® attenuated the effects of intubation: increases in heart rate, systolic blood pressure, and rate-pressure product. ADR's: hypotension in one patient, attributed to other causes by investigator.
Volume 3.28						
Zelgowski, Elmer, M.D. Chicago, IL	8053-CS-44	48 Patients	Open label, non-randomized study to compare effects of three dosing levels of Brevibloc® and placebo on heart rate and blood pressure increases resulting from endotracheal intubation. [Part of three-site, multicenter study.]	Patients were assigned to one of four treatment groups essentially the same as those in the previous study.	Heart rate and blood pressure, rate-pressure product, and plasma catecholamine levels.	Brevibloc®, at all dosing levels, was more effective than placebo in attenuating increases in rate-pressure product following endotracheal intubation. Brevibloc® at 200- and 300 mcg/kg/min, was more effective than Brevibloc® at 100 mcg/kg/min and than placebo attenuating the increase in systolic blood pressure following endotracheal intubation. ADR's: None reported.
Volume 3.29						
Reid, Martin, M.D. Miami, FL	8053-CS-43	48 Patients	Open label, non-randomized study to compare effects of three dosing levels of Brevibloc® and placebo on heart rate and blood pressure increases resulting from endotracheal intubation. [Part of a three-site, multicenter study.]	Patients were assigned to one of four treatment groups essentially the same as those in the previous studies.	Same as the previous study.	Results essentially the same as those of the other two sites. ADR's: One transient occurrence of brady-cardia.
Volume 3.30 (Medical) **Volume 3.31** (Statistical)						

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Table C

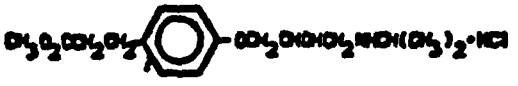
Study #	Medical Procedure	Prior or Conurrent Medications
8052-82-13	Routine diagnostic electrophysiology testing	Bupivicaine, heparin, diazepam*
8052-82-14	Cardiac catheterization invasive hemodynamics	Nitroglycerin or isosorbide dinitrate*
8052-82-15	Non-invasive hemodynamics	Nifedipine*, nitroglycerin*
8052-82-21	Anesthesia - coronary revascularization	Diazepam, morphine, scopolamine, pancuronium, nitrous oxide, nitroglycerin*, fentanyl, enflurane*
8052-83-25	Anesthesia - coronary revascularization	Diazepam, morphine, scopolamine, fentanyl or pancuronium
8052-83-44	Anesthesia - endotracheal intubation - non-cardiac surgery	Hydroxyzime, meperidine, glycopyrrolate, thiopental, nitrous oxide, succinylcholine
8052-83-45	Anesthesia - endotracheal intubation - non-cardiac surgery	Diazepam, meperidine, glycopyrrolate, ketamine, enflurane, succinylcholine

* Not all but a significant portion of the patients received this medication

B. Chemical Structural Formula

1. Formula and Description

Chemical structure:



Empirical Formula: $C_{16}H_{25}NO_4Cl$

Molecular Weight: 331.8

Description: White to off-white, free flowing, crystalline powder, very soluble in water, freely soluble in alcohol.

Chemical Name: Methyl 3-[4-[2-hydroxy-3-(isopropylamino)propoxy] phenyl]propionate hydrochloride.

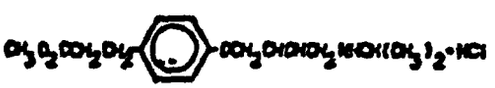
Code numbers:

Descriptive Name: Esmolol hydrochloride (USAN, 1983)

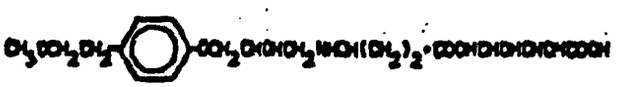
Tradename: Brevibloc®

2. Relationship to Related Drugs

Esmolol hydrochloride is chemically related to beta-blockers of the phenoxypropanolamine class. In particular, it is closely related to the commercially available beta-blocker, metoprolol tartrate, as shown below:



esmolol hydrochloride



metoprolol tartrate

In contrast to these other beta-blockers, however, esmolol has an enzymatically labile ester function incorporated into its chemical structure. This allows rapid metabolism of esmolol and is responsible for its short plasma half-life of less than 10 minutes in man. Because of the enzymatic lability of the ester function, esmolol is only used by intravenous administration. Esmolol hydrochloride, like the majority of commercially available beta-blockers, is a racemic mixture.

Pharmacologically, esmolol hydrochloride is related to other beta-adrenergic receptor blocking agents, specifically to cardioselective beta-blockers such as metoprolol. However, in contrast to esmolol, these beta-blockers have long plasma half-lives in the range of 3 to 24 hours.

3. Description of Dosage Form and Quantitative Composition

Brevibloc® injection is a sterile, non-pyrogenic solution for intravenous infusion, supplied in 10 mL Type I glass ampuls in two strengths: 1.0 g/10 mL (100 mg/mL) and 2.5 g/10 mL (250 mg/mL). The two strengths are identical in composition with respect to both active and inactive ingredients and differ only with respect to concentration as shown below:

	1 gram 100 mg/mL 10 mL ampul	2.5 gram 250 mg/mL 10 mL ampul
Active Ingredient		
Esmolol Hydrochloride	1.0 g	2.5 g
Inactive Ingredients		
Sodium Acetate, USP	68.0 mg	170.0 mg
Glacial Acetic Acid, USP	0.0286 mL	0.0715 mL
Propylene Glycol, USP	1.0 mL	2.5 mL
Alcohol, USP	1.0 mL	2.5 mL
Sodium Hydroxide, NF	as needed to adjust pH to 3.5-5.5	
Hydrochloric Acid, NF	as needed to adjust pH to 3.5-5.5	
Water for Injection, USP	q.s. to 10 mL	q.s. to 10 mL

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Section II - Review of Clinical Efficacy Trials

I. Clinical Purpose: Brevibloc (esmolol hydrochloride) is proposed for the treatment of (1) supraventricular tachycardia (SVT) and for (2) the management of perioperative tachycardia and hypertension.

II. Efficacy Data: The following studies are submitted as principal evidence (pivotal studies) and supportive evidence in support of the sponsor's claim for clinical efficacy (Table D Summary Tables - Clinical Efficacy Trials).

Table

BREVIBLOC® (esmolol HCl) INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

Controlled Trials: SVT

INVESTIGATOR/ INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Multicenter Study 18 Investigators Volumes 3.32 & 3.33 Volumes 3.34, 3.35 & 3.36 Volumes 3.60 - 3.64	8052-81-04 (Medical) (Statistical) (Patient Case Reports)	127 Patients	A randomized, double-blind parallel comparison of the effects of Breviblоc® and propranolol in patients with supraventricular tachycardia in an 18-site multicenter trial.	Breviblоc® titrated in increasing doses from 50 mcg/kg/min to 300 mcg/kg/min or propranolol 3 to 6 mg by repeat bolus injections, to a therapeutic end point.	The therapeutic success end points were: 1) 20% or greater reduction in heart rate from average baseline, or 2) reduction in heart rate to less than 100 bpm, or 3) conversion to NSR.	Thirty-six of 50 patients receiving Breviblоc® (72% and 38 of 55 patients receiving propranolol (69%) achieved therapeutic success. ADR's: The most frequently reported ADR's were related to the cardiovascular system with 29 patients treated with Breviblоc® and 11 patients treated with propranolol experiencing ADR's overall.
Multicenter Study 9 Investigators Volume 3.37 Volume 3.38 & 3.39 Volumes 3.65 - 3.68	8052-81-05 (Medical) (Statistical) (Patient Case Reports)	71 Patients	A randomized, double-blind cross-over comparison of the effects of Breviblоc® and placebo in patients with supraventricular tachycardia in a nine-site multicenter trial.	Breviblоc® titrated in increasing doses from 50 to mcg/kg/min to 300 mcg/kg/min to a therapeutic end point, for a maximum of 30 min.	The therapeutic success end points were: 1) 20% or greater reduction in heart rate from overall baseline, or 2) reduction in heart rate to less than 100 bpm, or 3) conversion to NSR.	Thirty-nine of 61 patients receiving Breviblоc (64%) achieved therapeutic success vs. three of 39 patients receiving placebo (8%). ADR's: Hypotension, and diaphoresis, other less frequent CNS, GI and miscellaneous effects.

BREVIBLOC® (esmolol HCl) INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

E.4. PARTIALLY CONTROLLED STUDIES : SVT

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Multicenter Study 24 Investigators	8052-85-29/30/36	162 Patients	An open-label, multicenter, base line control study of the effect of Brevibloc® in patients with supra-ventricular tachycardia.	Brevibloc® titrated from 25 mcg/kg/min to 300 mcg/kg/min, with appropriate loading doses, for a maximum of 24 hours, infused through a large peripheral vein.	Therapeutic response was defined as 1) 15% or greater reduction in heart rate from base line average or 2) conversion to NSR.	Brevibloc® was safe and effective in treating patients with supra-ventricular tachycardias. ADR's: 113 patients experienced adverse effects, most frequently pertaining to the cardiovascular system and infusion site reactions. ADR's in 24 patients were "definitely" attributed to Brevibloc® by the investigators.
Volumes 3.46 thru 3.51						
Volumes 3.56-3.57	(FD-1639)					
Volumes 3.79-3.80	(Patient Case Reports - Dropouts)					
Multicenter Study Ten Investigators	8052-85-31	49 Patients	An open-label, multicenter, base line controlled evaluation of the effect of Brevibloc® in patients with supraventricular tachyrhythmias, with evaluation of transition from Brevibloc® to an alternate antiarrhythmic agent. This Study is ongoing.	Brevibloc® titrated from 25 mcg/kg/min to 300 mcg/kg/min with appropriate loading doses. Brevibloc® maintenance infusion at level of therapeutic effect for 6 to 10 hours. Then Brevibloc® titrated downward following initiation of alternate antiarrhythmic agent.	Therapeutic end points for Brevibloc therapy were: 1) 15% or greater reduction in heart rate from base line average or 2) conversion to NSR.	Brevibloc® was safe and effective in treatment of this patient population. The majority of patients responding to Brevibloc® remained adequately controlled during transition to alternate therapy. ADR's: Cardiovascular system effects were most frequently observed (24 patients). Therapy in 12 patients was prematurely discontinued due to ADR's.
Volume 3.52						
Volume 3.58	(FD-1639)					
Volume 3.81	(Patient Case Report -. Dropouts)					

BREVIBLOC® (esmolol HCl) INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

E.4. PARTIALLY CONTROLLED STUDIES

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Elmer, Robert, M.D., Ph.D.	8052-05-33	19 Patients	Open label pilot study of effect of Brevibloc® infusion on heart rate, hemodynamics, and cardiac rhythm in patients with myocardial infarction or or unstable angina.	Brevibloc® infusion was titrated from 50 mcg/kg/min to a maximum of 300 mcg/kg/min in 50 mcg/kg/min increments, with a loading dose preceding each increment. Dosing intervals were 4 to 10 min, with maximum infusion duration of 24 hours at the investigator's option.	Heart rate, blood pressure, respiration rate, and hemodynamic measurements.	Brevibloc® produced a rapid reduction in heart rate and was hemodynamically safe when infused for periods of up to 24 hours. AER's: There were relatively frequent instances of hypotension (10/19), but blood pressure usually was adequately controlled and peak reductions in heart rate maintained by reducing Brevibloc® dosage. Single or infrequent incidents of reduced cardiac output, oliguria, nausea and vomiting in conjunction with hypotension, nausea alone in conjunction with hypotension, increased capillary wedge pressure.

Volume 3.53

Volume 3.58 (FD-1639)

Volume 3.81 (Patient Case Reports - Dropouts)

BREVIBLOC® (esmolol HCl) INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

E.9. CONTROLLED CLINICAL TRIALS: ANESTHESIA

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Multicenter Study Six Investigators Volume 3.40 (Medical) Volume 3.41 (Statistical) Volume 3.69 - 3.72 (Patient Case Reports)	8052-84-91A	112 Patients	A randomized, double-blind, parallel, placebo-controlled evaluation of the effect of Brevibloc® on increases in heart rate and blood pressure observed during endotracheal intubation in patients anesthetized with thiopental. A six-site Multicenter Study.	Brevibloc® loading dose of 500 mcg/kg/min for four min, followed by Brevibloc® maintenance dose of 300 mcg/kg/min for eight min; or placebo.	Heart rate and blood pressure recordings at periodic intervals throughout the preinduction through postintubation period.	Brevibloc® significantly blunted increases in heart rate and systolic blood pressure resulting from the stimulus of endotracheal intubation, compared to placebo. ADR's: One patient receiving placebo exhibited itching at injection site and wheezing following intubation.
Multicenter Study Four Investigators Volume 3.42 (Medical) Volume 3.43 (Statistical) Volume 3.73 - 3.75 (Patient Case Reports)	8052-84-91B	73 Patients	A double-blind, randomized, parallel, placebo-controlled evaluation of the effect of Brevibloc® in controlling increases in heart rate and blood pressure during endotracheal intubation in patients induced with thiopental.	Brevibloc® 500 mcg/kg/min for 4 min, followed by Brevibloc® 300 mcg/kg/min for 11 min, with induction at minute 10.	Heart rate and blood pressure determinations at appropriate intervals.	Brevibloc® was effective in blunting increases in heart rate, systolic- and mean arterial blood pressures, and rate-pressure product following endotracheal intubation. ADR's: None reported.
Multicenter Study Seven Investigators Volume 3.44 (Medical) Volume 3.45 (Statistical) Volume 3.76-3.78 (Patient Case Reports)	8052-83-49	74 Patients	A double-blind, randomized parallel, placebo-controlled evaluation of the effect of Brevibloc® in controlling heart rate and blood pressure increases during endotracheal intubation, in patients undergoing carotid endarterectomy.	Same as in Study 8052-84-91B, above, with induction at minute 5.	Heart rate and blood pressure determinations at appropriate intervals.	Brevibloc® was effective in blunting increases in heart rate; systolic-, diastolic-, and mean arterial blood pressure; and rate-pressure product following endotracheal intubation. Brevibloc® also prevented clinically significant increases in heart rate and systolic blood pressure following intubation when compared to placebo. ADR's: Essentially identical in both groups, mainly related to the cardiovascular system.

The sponsor's summary for each claim is reproduced in Appendix 2A (see Overall Expanded summary pages 169-173).

III Background/Rationale

A. SVT

Beta-adrenoceptor-blocking drugs have been established as one of the standard therapies for SVT.[1-5] The effect of beta blockers on automaticity and A-V conduction velocity forms the basis for their use in the treatment of supraventricular tachyarrhythmias (SVT).[6,7] SVT includes atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia (PSVT), supraventricular tachycardia associated with Wolff-Parkinson-White (WPW) syndrome, automatic atrial tachycardia and sinus tachycardia. Although beta blockers are effective in the management of SVT, there may be a degree of risk involved in their use since these arrhythmias can be associated with or indeed caused by cardiac failure. If cardiac failure is undiagnosed or sympathetically compensated, then induction of beta blockade can produce serious adverse hemodynamic effects. Moreover, at the time of therapy with beta blockers, the presence or absence of cardiac failure and the degree of sympathetic compensation is often not known and thus, the hemodynamic effects of beta blockade are difficult to predict. Conventional beta adrenergic blocking agents have long half lives, ranging from approximately 4 to 24 hours, which complicate the treatment of adverse effects that may develop. Esmolol, has a very short half life (approximately 9 minutes in man, permitting in theory rapid modification or reversal of beta blockade if adverse cardiac effects related to beta blockade occur. In addition, esmolol can be titrated rapidly in patients to achieve a desired level of beta blockade. Esmolol, an ultrashort acting beta adrenergic receptor blocker has recently been introduced for use in critical care situations.[8,9] Esmolol, has been used in the treatment of acute onset supraventricular arrhythmias predominantly following cardiac surgery.[10,11,12] Thus esmolol might be useful in these settings if it allows rapid titration of therapy and rapid recovery from drug effect upon discontinuation.

B. Use of Esmolol in the Management of Perioperative Tachycardia and Hypertension

Esmolol is also proposed for the management of perioperative tachycardia and hypertension elicited by endotracheal intubation and other surgical stimuli in patients under general anesthesia.[13,14,15] The catecholamine mediated reflex hypertension and tachycardia that occurs during intubation and surgery can be attenuated by beta adrenergic blockade.[16] Clinically significant increases in the rate pressure product during endotracheal intubation in patients with coronary artery disease may be especially undesirable. Cases of enhanced myocardial ischemia and infarction in CABG patients following perioperative tachycardias have been documented with electrocardiographic and hemodynamic evidence.[17,18] Slogoff and Keats have demonstrated an association between perioperative tachycardia, myocardial ischemia and postoperative myocardial infarction in CABG patients.[19] While episodes of perioperative tachycardia and hypertension can be relatively brief, there is some experimental data in dogs that even intermittent brief periods of

myocardial ischemia have an accumulative effect and can therefore lead to myocardial dysfunction and necrosis.[20] Therefore, it is reasonable to attempt to limit perioperative tachycardia and hypertension associated with the induction of anesthesia.

However, it is not clear from the available evidence whether one can equate blunting of this adrenergic mediated response (tachycardia and hypertension) with prevention of myocardial ischemia/infarction and clinical benefit. To date, there have been no well controlled prospective randomized clinical trials with IV beta blockers which have directly answered this question. Until there is objective evidence of patient benefit from this intervention, the utility of beta blockade in this setting is conjectural. Hence, the theoretical benefit to patients with CAD must be weighed against the risks presented by a potent IV beta blocker such as hypotension, bradycardia and depression of left ventricular function.

Clinical studies have suggested that perioperative tachycardia and hypertension can be prevented or significantly reduced by intravenous administration of beta blockers.[21,22] The use of currently available beta blockers with long elimination half lives (example propranolol) in this setting, however is associated with a risk of cardiac failure especially in patients with coronary artery disease.[23] Recently esmolol has been used in the perioperative setting to control heart rate and blood pressure rises during intubation.[24,25,26] Since esmolol has a biological half life of approximately 9 minutes, this drug may be extremely useful in this situation in that it would provide rapid titration of therapy and rapid recovery from the drug effect upon discontinuation.

C. References

1. Stock JP, Dale N: Beta-adrenergic receptor blockade in cardiac arrhythmia. B Med J 2: 1230-1233, 1963.

2. Rowlands DJ, Howitt G, Markman P: Propranolol in disturbances in cardiac rhythm. B Jed J 1: 891-894, 1965.

3. Harrison DC, Griffin JR, Flene TJ: Effects of beta-adrenergic blockade with propranolol in patients with arrhythmia. N Engl J Med 723: 410-415, 1965.

4. Besterman EMM, Friedlander DH: Clinical experiences with propranolol. Post-Grad Med J 41: 526-535, 1965.

5. Schamroth L: Immediate effects of propranolol on various cardiac arrhythmias. Am J Cardiol 18: 438-443, 1966.

6. Friskman, WS, Silverman, R: Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 2. Physiologic and metabolic effects. Am Heart J 97:797-807, 1979.

7. Singh, BN, Jewitt, DE: B-adrenergic receptor blocking drugs in cardiac arrhythmias. Drugs 7:426-461, 1974.

8. Byrd RC, Sung RJ, Mark J, Newlands J, Parmley, W: Safety and Efficacy of Esmolol (ASL-8052: An Ultrashort-Acting Beta-Adrenergic Blocking Agent) For Control of ventricular Rate in Supraventricular Tachycardias. J-Am Coll Card 3:394-399, 1984.

9. Angaran D, Fitzpatrick P, Gray R, Hochman J, Kaplan K, Lester R, Schwartz M, Turlapaty P: Antiarrhythmic Efficacy and Safety of Esmolol-An Ultra Short Acting Beta-Blocker Clin Res 1984; 3248A.

10. Gray R, Bateman T, Czer L, Conklin C, Matloff J: Esmolol - A New Ultra Short Acting Beta Blocking Agent for Rapid Control of Heart Rate in Postoperative Supraventricular Tachycarrhythmias. Circulation 70(4), Part II, 1984.

11. Das G, Barr C, Ferris J: Management of supraventricular tachycardia with esmolol hydrochloride. Clinical Pharmacology and Therapeutics 37(2): 189, 1985.

12. Morganroth J, Singh J, Swerdlow C: Safety and efficacy of esmolol vs propranolol in patients with supraventricular tachycardia. J Am Coll of CArdiol 5(2): 438, 1985.

13. King, BD, Harris, LC, Greifenstein, FE: Reflex circulatory response to direct laryngoscopy and tracheal intubation performed during general anesthesia. Anesthesiology 12:556-566, 1951.

14. Prys-Roberts, C, Green LT, Melache, R, Foex, P: Studies of anesthesia in relation to hypertension. II:Hemodynamic consequences of induction and endotracheal intubation. Brit J Anesthesia 43:531-547, 1971.

15. Tomori, Z, Widdicombe, JC: Muscular bronchometer and cardiovascular reflexes ilicited by mechanical stimulation of the respiratory tract. J Physiol 200:25-49, 1969.

16. Menkaus PG, Reves JG, Alvis JM, et al.: Attenuation of Heart RAte Response to Intubation by a New Beta-Adrenergic Blocking Drug, Esmolol. Anesthesiology 71(3A):A20, 1984.

17. Giles, RW, Berger, HJ, Barash, PG, Tarabadkar, S, Marx, PG, Hammond, GL, Geha, AS, Laks, H, Zaret, BL: Continuous monitoring of left ventricular performance with the computerized nuclear probe during larynogoscopy and intubation before coronary artery bypass surgery. Am J Cardiol 50:735-741, 1982.

18. Geft, JL, Fishbein, MC, Ninomeya, K, Hashida, J, Chaux, E, Yano, J, Y-Rit, J, Genov, T, Shell, W, Ganz, W: Intermittent brief periods of ischemia have a cumulative effect and may cause myocardial necrosis. Circulation 66:1150-1153, 1982.

19. Slogoff, S, Keats, AS: Does Perioperative Myocardial Ischemia Lead to Postoperative Myocardial Infarction? Anesthesiology 62:107-114, 1985.

20. Roy, WL, Edelist, G., Gilbert, B: Myocardial ischemia during non-cardiac surgical procedures with coronary artery disease. Anesthesiology 51:393-397, 1979.

21. Coleman, AJ, Jordon, C: Cardiovascular responses to anesthesia: Influence of beta-adrenorecptor blocakde with metoprolol. Anesthesia 35:975-978, 1980.

22. Safwat, AM, Reltan, JA, Misle, GR, Hurley, EG: Use of propranolol to control rate-pressure product during cardiac anesthesia. Anes Ann 60:732-735, 1981.

23. Viljoen, JF. Estafanous, FG, Kellner, GA: Propranolol and cardiac surgery. J Thorac Cardiovas Surg 64:826-830, 1972.

24. Gold MI, Brown MS, Selem JS: The Effect of Esmolol on Hemodynamics After Ketamine Induction and Intubation. Circulation II 61(3A):A19, 1984.

25. Menkhaus P, Reves J, Kissin I, et al: Cardiovascualr effects of esmolol in anesthetized humans. Anesth. Analg. 64:327-334, 1985.

26. Reves, JG, Flezzam P. Perioperative Use of Esmolol. Amer J Cardiol (In Press)

IV. Review of Pivotal Studies:

First Indication

(A) SVT

Overview of Principal Evidence (Pivotal Studies) and Supportive Evidence (Partially Controlled Trials) of Brevibloc for SVT

(a) Pivotal Studies (8052-81-04 and 8052-81-05)

Both of these studies were multicenter randomized controlled trials which used the same esmolol treatment schedule, response and patient selection criteria. In general, the overall therapeutic results were similar in the active drug controlled (04) and the placebo controlled trial (05). Among the esmolol-treated patients in these two trials-the comparative response rates were 64% (05) and 72% (04). Both trials demonstrated a similar dose response relationship with the majority of patients responding at a esmolol dosage of 200 mcg/kg/min or less: 61% (05) and 70% (04). The major therapeutic endpoint in these studies was control of ventricular response (HR). Although the relative incidence of adverse drug effects (ADE) was higher in 04, the overall spectra and nature of the ADE was very similar with a predominance of cardiovascular side effects (hypotension). Therefore these two well controlled studies support the sponsor's claim that esmolol is a safe and effective agent for the treatment of SVT.

(b) Partially Controlled Trials [8052-83-23/30/36 (Study 1) and 8052-83-31 (Study 2)]

Both of these studies utilized a similar esmolol dosage and titration schedule, response and patient entrance criteria. The patient entrance criteria (HR greater than or equal to 100 bpm) and primary efficacy endpoint (15% or greater reduction in HR) differed from the two pivotal studies: (entrance criteria HR greater than or equal to 120 bpm; endpoint 20% or greater reduction in HR). Overall therapeutic response rates (during the titration period) were: 79% (116/147) for study 1 and 81% (29/36) for study 2. Both studies demonstrated a similar dose response relationship with a majority of the patients responding at or below the 200 mcg/kg/min dosage (74% and 79%). Furthermore, a similar pattern and incidence of ADE and premature terminations due to ADE was noted in the two studies. Thus, these two studies tend to reinforce and support the overall findings of the two well controlled multicenter trials (pivotal studies).

Specific Results

Two multicenter, randomized, controlled studies were conducted to establish the safety and efficacy of esmolol in the treatment of SVT. These studies are reviewed in this section. One of the studies was placebo controlled (8052-81-05) and the other study was actively controlled with propranolol (8052-81-04). Both of these trials shared common features re esmolol dosage and titration schedule, patient selection criteria and efficacy assessment (primary endpoint).

1st Pivotal Study

1. Study 8052-81-05 (Placebo controlled)

Study Objective: The objective of the study was to evaluate the efficacy and safety of esmolol vs placebo in the treatment of patients with persistent supraventricular tachyarrhythmia (SVT). Treatment efficacy was determined by reduction in ventricular rate or conversion of SVT to NSR.

Investigators and Institutions: All investigators were board certified cardiologists. For a complete listing of investigators, institutions and the number of patients enrolled at each center (see Table 1 below). One investigator (center 09:Gopal Das, M.D.) conducted the study at two centers both in Fargo, ND. The study was conducted from June 1982 through March 1984, and was monitored by the staff of the medical department at American Critical Care. The number of patients entered in the study varied considerably among the centers (from 0 at center 6 to 20 at center 2). In four centers, six or fewer patients were entered (center 3: 6 patients, center 5: 3 patients, center 7: 5 patients, and center 8: 1 patient). Due to the small sample size in each of these four centers, the data from the 15 patients studied in centers 3, 5, 7 and 8 were pooled.

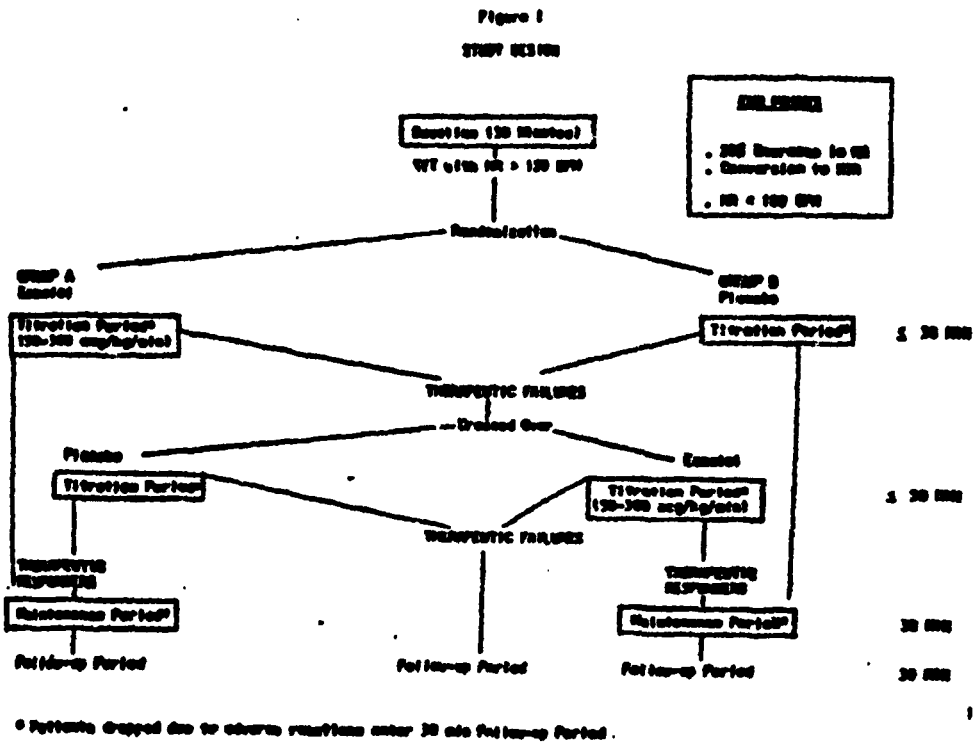
Table 1

LIST OF INVESTIGATORS AND NUMBER OF PATIENTS AT EACH CENTER

CENTER NUMBER	INVESTIGATOR AND INSTITUTION	NUMBER OF PATIENTS ENROLLED	NUMBER OF PATIENTS TREATED
01	David Williams, M.D. Rhode Island Hospital Providence, Rhode Island	12	12
02	Ruey Sung, M.D. San Francisco General Hospital San Francisco,California	21	20
03*	Gary Wilner, M.D. Evanston Hospital Evanston, Illinois	7	7
04	John Schroeder, M.D. Stanford University Med. Center Stanford, California	9	8
05*	Sol Rajfer, M.D. University of Chicago Med. Center Chicago, Illinois	3	3
06	Jonas Brachfeld, M.D. Rancocas Valley Hospital Willingboro, New Jersey	0	0
07*	Robert Engler, M.D. Veterans Administration Hospital San Diego, California	5	4
08*	Robert Zoole, M.D. Veterans Administration Hospital Tampa, Florida	2	1
*09	Gopal Das, M.D. Veterans Admin. Hospital (09A) and St. John's Hospital (09B) Fargo, North Dakota	17	16

* Data from these centers were pooled.

Study Design: The design of this prospective multicenter clinical trial was double-blind, randomized placebo-controlled, partial crossover. Patients who failed to respond to the initial treatment were crossed over and received the second treatment. For a schematic representation of the study design see the figure below.



Treatment Plan and Response Criteria: Following completion of a 30 minute baseline period, during which the stability of the patient's SVT was monitored, an infusion of esmolol or placebo was administered during a 30 minute initial titration period. The study drug dosage was titrated upward (from 50 mcg/Kg/min to 300 mcg/Kg/min) stepwise until a therapeutic response (20% or greater heart rate reduction (HRR), HRR to less than 100 bpm or conversion to NSR) was achieved.

The infusion schedule in the dose titration period was as follows:

500 mcg/kg/min for 1 min - 50 mcg/kg/min for 4 min
500 mcg/kg/min for 1 min - 100 mcg/kg/min for 4 min
500 mcg/kg/min for 1 min - 150 mcg/kg/min for 4 min
500 mcg/kg/min for 1 min - 200 mcg/kg/min for 4 min
*500 mcg/kg/min for 1 min - 250 mcg/kg/min for 4 min
*500 mcg/kg/min for 1 min - 300 mcg/kg/min for 4 min

*The protocol was amended on November 1, 1982 to add two additional doses (250 and 300 mcg/kg/min) to the titration schedule.

Therapeutic failures during the initial titration period were given the alternative drug during a similar crossover titration period. The therapeutic responders from either titration period entered a 30 minute maintenance period. The dosage given during this period was to be the same dosage at which the therapeutic response was exhibited. Following completion of the maintenance period (therapeutic responders) or the crossover titration period (therapeutic failures) a 30 minute follow up period was completed. Thus, the entire study period lasted 2 1/2 hours. Clinical measurements taken during the study consisted of heart rate, blood pressure and respiration rate. Heart rates were taken from one minute ECG strips (lead II). The ECG tracings from all study patients were retained in the case record forms and the heart rate and the type of the SVT was diagnosed from these. However, there were no safety checkpoints predefined such as SBP less than 90 mmHg, DBP less than 50 mmHg or HR less than 50. In view of the relatively high incidence hypotension, such checkpoints are recommended.

For a complete display of the clinical observations made in this study see Table 2.

Table 2

SCHEDULE OF OBSERVATIONS
Esmolol vs Placebo

	Pre Study Evaluation	Baseline	Initial Dose Titration Dose (mcg/kg/min) 50 100 150 200 250 300	Crossover Dose Titration* Dose (mcg/kg/min) 50 100 150 200 250 300	Maintenance	Follow-up
		0 30 min min	5 10 15 20 25 30 min min min min min min	5 10 15 20 25 30 min min min min min min	10 20 30 min min min	10 20 30 min min min
Informed Consent	X					
Medical History	X					
Physical Examination	X					X
Blood Chemistry	X					X
Hematology	X					X
Urinalysis	X					X
1 min ECG		X X	X X X X X X	X 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
Respiration Rate		X X	X X X X X X	X X X X X X	X X X	X X X

* Patients who did not achieve a therapeutic response during initial titration period were entered into the crossover titration.

Patient Selection: Patients were selected for this study according to the following entrance criteria.

Inclusion Criteria:

a. Either males or females (without childbearing potential) of any race from 18 to 75 years of age. Patients over the age of 75 were permitted in the study if, in the opinion of the investigator, study participation would not be detrimental to their health.

b. All study patients were hospitalized with supraventricular tachyrhythmia with a ventricular rate exceeding 120 beats per minute with or without digitalis administration, for which therapy with a beta-adrenergic blocking drug would be considered useful. (The duration of the SVT whether it was acute vs chronic was not specified.)

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

d. The tachyrhythmia had to be continuously present during the 30-minute baseline control period of the study.

Exclusion Criteria:

a. Females of child-bearing potential.

b. All degrees of AV conduction block.

c. Sick sinus syndrome.

d. Hypotension with systolic blood pressure less than 100 mm Hg or diastolic less than 70 mm Hg.

e. Congestive heart failure, New York Heart Association Grades III and IV, unless failure was secondary to a tachyrhythmia treatable with propranolol.

f. Chronic obstructive pulmonary disease of a degree that precluded therapy with beta-adrenergic blocking drugs.

g. Bronchial asthma or patients prone to bronchospasm.

h. Ventricular arrhythmias that required drug therapy.

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

j. Current drug or alcohol abuse.

k. Experimental drug administration within the preceding three months or any previous administration of esmolol.

l. Cardiogenic shock.

m. Patients who received adrenergic-augmenting psychotropic drugs (including MAO inhibitors) or adrenergic-depleting drugs (i.e., resperine) during the six week period prior to entry into the study.

n. Severe hepatic or renal failure (in the judgment of the investigator).

o. Clinically significant electrolyte abnormalities.

p. Cardiac valvular disease of sufficient degree to produce significantly abnormal hemodynamics or intracardiac pressures.

q. Tachyhythmia of extracardiac origin (anemia, infection, etc.). The presence of hyperthyroidism was not an exclusion criterion.

r. All degrees of AV conduction delay except for paroxysmal tachycardia with block associated with digitalis administration.

s. Patients receiving oral cardiovascular medications were to be carefully reviewed prior to their entry into the study. Those patients whose last oral dose of the following medications was received within two half-lives of the study medications were not to be considered for entry into the study.

Calcium Channel Blockers	e.g., verapamil, nifedipine, diltiazem, etc.
Beta Adrenergic Blockers	e.g., propranolol, nadolol, metoprolol, timolol, etc.

t. Any other condition which in the opinion of the investigator endangered the patient.

Efficacy Assessment

The variable evaluated for efficacy in this study was heart rate. The heart rates were measured at the beginning and the end of the baseline period, at five-minute intervals during the drug titration periods, and at ten-minute intervals during the maintenance and follow-up periods.

The analysis of efficacy was based on the achievement of a therapeutic response during the esmolol (or placebo) titration period. Three response criteria were used in this study:

a) 20% or greater reduction from the average baseline heart rate;

b) reduction in ventricular rate to less than 100 bpm;

c) conversion to normal sinus rhythm.

Safety Assessment:

a. Adverse Effects: All patients were closely monitored throughout the study to detect the occurrence of adverse effects. Investigators were particularly vigilant in looking for adverse effects common to beta-blocking drugs such as hypotension and bradycardia.

b. Clinical Safety Variables: The influence of esmolol and placebo on the following clinical safety variables i.e., systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and rate-pressure product (RPP) was determined.

Statistical Methodology:

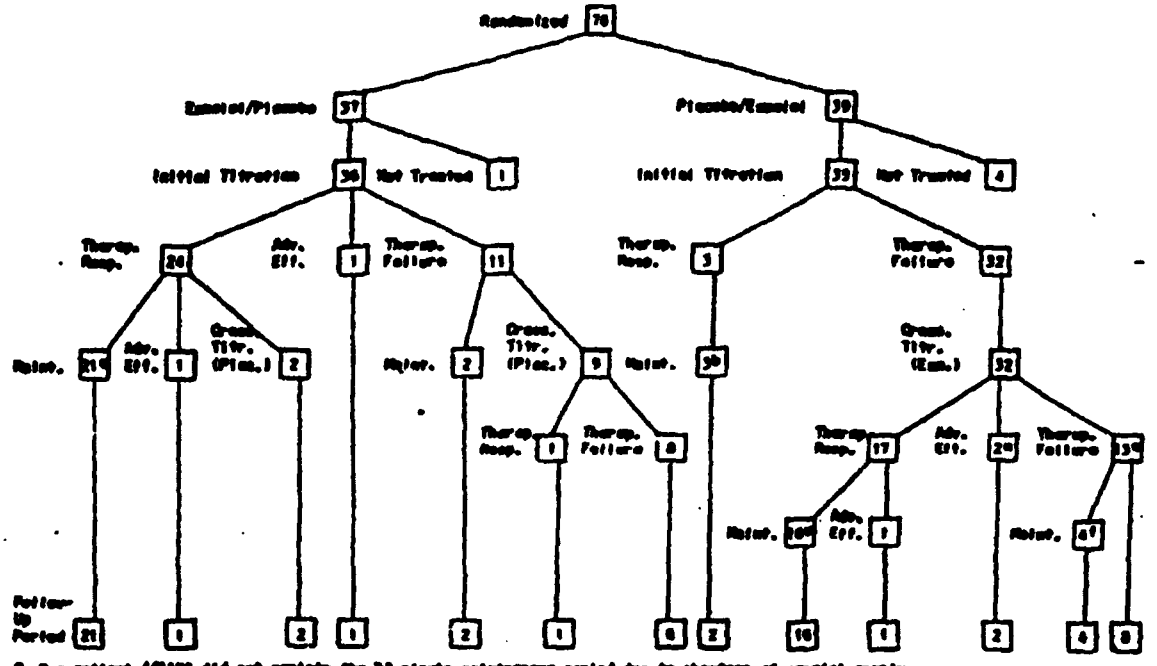
The results of statistical tests were assessed using the 0.05 level of significance. The SAS was also used to prepare data listings, tables of summary statistics, and plots.

Number of Patients ("all", "efficacy", "dropouts, "exclusions" and "terminations":

Tables 16 and 17 (see below) summarize the "all patients" and "efficacy patients" during all phases of the study. The effects of esmolol and placebo were compared in 71 patients (5 patients did not receive the study drug). The patients were categorized into 2 groups, "all patients" (those who received either study medication, n=71) and "efficacy patients" (those who met all protocol requirements, n=63). The derivation of "all patients" and "efficacy patients" are presented in Table 9. A list of the 8 patients excluded from the efficacy analysis and their reasons for exclusion are summarized in Tables 10 and 11. Four of the eight exclusions were due to verapamil administration within 2 half-lives of study entry. The reasons for exclusion of patients from safety analysis are provided in Table 11. Thus protocol deviations (collection of data either too early or too late) led to the disqualification of data from the analysis of safety for 14 patients. Of the 71 "all patients", 10 patients did not complete the study. The period during which the study was terminated and the reason for termination are listed for each of these patients in Table 19. It is worth noting that the occurrence of adverse cardiovascular effects during esmolol titration or maintenance led to premature termination of the study for 6 of these 10 patients (105, 106, 409, 410, 913, 914). Four of these six terminations were related to hypotension. [In addition, four of the 39 esmolol responders did not enter the maintenance period: two were dropped due to adverse effects and two were mistakenly crossed over to the placebo titration period.]

Table 16

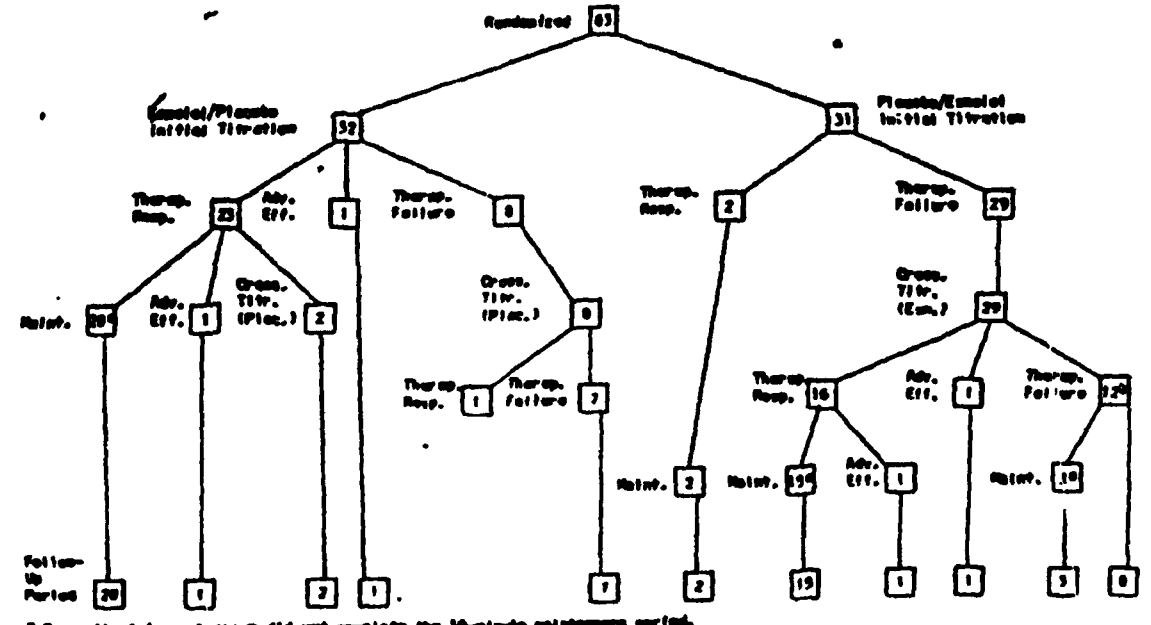
SUMMARY OF PATIENTS AT EACH PHASE OF THE STUDY ("ALL PATIENTS")



a One patient (5/122) did not complete the 30-minute maintenance period due to shortage of exmoist supply
b One patient (5/106) did not enter the follow-up period.
c One patient (5/103) did not complete the 30-minute maintenance period due to adverse effect.
d One patient (5/109) entered the maintenance period for 10 minutes prior to infusion termination.
e One patient (5/210) did not enter the follow-up period.
f One patient (5/203) did not complete the 30-minute maintenance period due to failure to maintain response.

Table 17

SUMMARY OF PATIENTS AT EACH PHASE OF THE STUDY ("EFFICACY PATIENTS")



a One patient in each group did not complete the 30-minute maintenance period.
b One patient did not enter the follow-up period.

Table 9

DERIVATION OF "ALL PATIENTS",
"EFFICACY PATIENTS" IN THE STUDY

"All Patients"	71	36	Esmolol/Placebo
		35	Placebo/Esmolol
Exclusions a. Efficacy	8*	110, 306, 704, 916, 104, 211, 214, 913	(Esmolol/Placebo) (Placebo/Esmolol)
b. Safety	14**	102, 108, 209, 304, 501, 704	(Esmolol/Placebo)
		101, 105, 109, 203, 206, 210, 301, 901	(Placebo/Esmolol)
"Efficacy Patients"	63	32	Esmolol/Placebo
		31	Placebo/Esmolol

* Efficacy data from these 8 patients were excluded from efficacy analysis.
** Part of the safety data from these 14 patients was excluded from safety analysis. Reasons for exclusion -- see Tables 10 and 11.

: 10

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	TYPE OF SVT	REASON FOR EXCLUSION FROM EFFICACY ANALYSIS
104	Placebo/Esmolol	F	85	60	128	155	100	A-flb	Received other treatment during titration period. [Accidental carotid massage resulting in conversion to normal sinus rhythm.]
110*	Esmolol/Placebo	F	83	60	133	137	74	A-flb	Patient had a titration schedule deviation (investigator skipped the 250 mcg/kg/min dose.)
211	Placebo/Esmolol	M	55	66	126	150	110	PSVT	Deviation of entrance criteria. [Patient received Verapamil within 2 half-lives (3.5 hours) of study initiation.]
214*	Placebo/Esmolol	F	64	52	137	148	93	A-flb	Termination from titration period prior to obtaining therapeutic response. [Patient inadvertently classified as a responder and thus transferred to maintenance period...actually achieved 18% reduction on 250 mcg/kg/min dose.]
108*	Esmolol/Placebo	M	86	57	145	120	80	A-flb	Termination from titration period prior to obtaining therapeutic response. [Patient inadvertently classified as a responder and thus transferred to maintenance period...actual-achieved 19% reduction on 100 mcg/kg/min dose.]

* Heart rate of these patients was included in the heart rate analysis

Table 10 (cont.)

LIST OF PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

PATIENT NUMBER	TREATMENT	DEMOGRAPHIC DATA			BASELINE DATA			TYPE OF SVT	REASON FOR EXCLUSION FROM EFFICACY ANALYSIS
		SEX	AGE (Yrs)	WEIGHT (Kg)	HEART RATE (bpm)	BLOOD PRESSURE SBP (mmHg)	DBP		
704	Esmolol/Placebo	M	35	75	150	109	80	A-flb	Deviation of entrance criteria [Patient received verapamil within 2 half-lives (3.4 hrs) of study initiation.]
913	Placebo/Esmolol	M	74	89	180	125	105	A-flb	Deviation of entrance criteria [Patient received verapamil - within 2 half-lives (6.7 hrs) of study initiation.]
916	Esmolol/Placebo	M	76	74	140	173	80	A-flb	Deviation of entrance criteria [Patient received verapamil within 2 half-lives (3.2 hrs) of study initiation.]

Table 11

LIST OF PATIENTS EXCLUDED FROM SAFETY ANALYSIS

PATIENT NUMBER	TREATMENT	DEMOGRAPHIC DATA			BASELINE DATA			TYPE OF SVT	ACTUAL DATA EXCLUDED, AND REASON FOR EXCLUSION, FROM SAFETY ANALYSIS
		SEX	AGE (Yrs)	WEIGHT (Kg)	HEART RATE (bpm)	BLOOD PRESSURE SBP (mmHg)	DBP		
101	Placebo/Esmolol	F	59	100	148	195	83	A-flb	Post-study urinalysis excluded... specimen obtained >24 hours after study.
102	Esmolol/Placebo	F	78	52	139	123	88	A-flb	Pre-study blood chemistry/hematology/ urinalysis excluded...specimen obtained > 7 days prior to study. Post-study urinalysis excluded...specimen obtained > 24 hours after study.
103	Placebo/Esmolol	F	82	52.7	129	110	69	A-flb	Post-study blood chemistry/hematology/ urinalysis excluded...specimen obtained > 24 hours after study.
105	Esmolol/Placebo	F	64	88	122	121	75	A-flb	Post-study urinalysis excluded...specimen obtained > 24 hours after study.
109	Placebo/Esmolol	M	47	90	148	113	81	A-flb	Post-study urinalysis excluded...specimen obtained > 24 hours after study.
203	Placebo/Esmolol	F	49	58.1	128	130	85	A-flb	Post-study urinalysis excluded...specimen obtained > 24 hours after study.
205	Placebo/Esmolol	F	81	48.1	148	105	80	AAT	Pre-study blood chemistry/hematology/ urinalysis excluded...specimen obtained during infusion. Post-study urinalysis excluded...specimen obtained > 24 hours after study.
209	Esmolol/Placebo	M	69	80	134	170	88	A-flb	Pre-study blood chemistry/hematology excluded...specimen obtained during infusion.
210	Placebo/Esmolol	M	66	86	124	174	68	A-flb	Pre-study blood chemistry/ hematology excluded...specimen obtained during infusion.
301	Placebo/Esmolol	F	68	55	160	130	80	A-flb	Pre-study urinalysis excluded...specimen obtained > 7 days prior to study.
306	Esmolol/Placebo	M	75	90	159	150	110	A-fl	Post-study urinalysis excluded...specimen obtained > 24 hours after study.
501	Esmolol/Placebo	F	72	66	149	130	82	A-flb	Pre-study urinalysis excluded...specimen obtained > 7 days prior to study.
704	Esmolol/Placebo	M	35	75	150	109	80	A-flb	Pre-study urinalysis excluded...specimen obtained on day of study, but time unknown.
901	Placebo/Esmolol	M	69	90	128	118	75	AAT	Pre-study urinalysis excluded...specimen obtained during infusion.

Table 18

PATIENTS WHO DID NOT COMPLETE THE STUDY

Patient	Details	Reason
104	Therapeutic responder during the initial titration period (placebo); completed the placebo maintenance period, but did not enter the follow-up period	Investigator's clinical judgment
105	Therapeutic responder during the crossover titration period (esmolol); esmolol maintenance period (200 mcg/kg/min) was discontinued after 10 minutes; follow-up period was completed	Adverse experiences (drop in heart rate, junctional rhythm)
108	Initial titration period (esmolol) terminated at 150 mcg/kg/min; follow-up period was completed	Adverse experiences (hypotension, dyspnea, diaphoresis)
112	Therapeutic responder during the initial titration period (esmolol); esmolol maintenance period ended after 20 minutes; follow-up period was completed	Drug supply ran out (an insufficient supply was mixed by the investigator)
218	Completed initial (placebo) and crossover (esmolol) titration periods without responding, but did not enter the follow-up period	Investigator's clinical judgment
408	Crossover titration period (esmolol) terminated at 50 mcg/kg/min; transferred to maintenance period for 10 minutes; follow-up period was completed	Adverse experiences (increased pulmonary artery pressure, mild sweating)
410	Crossover titration period (esmolol) terminated at 50 mcg/kg/min (subsequent to achievement of therapeutic response); follow-up period was completed	Adverse experience (hypotension)
703	Therapeutic responder during the crossover titration period (placebo); did not enter maintenance period; follow-up period was completed	Investigator failed to classify the patient as a therapeutic responder
813	Crossover titration period (esmolol) terminated at 250 mcg/kg/min; follow-up period was completed	Adverse experiences (hypotension, irritability, diaphoresis)
814	Initial titration period (esmolol) terminated at 300 mcg/kg/min (subsequent to achievement of therapeutic response); follow-up period was completed	Adverse experiences (hypotension, lightheadedness, diaphoresis)

Study Results:

I Baseline Demographics and Comparability of Treatment Groups

A. Analysis by Center

Tables 7, 7A and 8 describe characteristics of the study population by center. Due to the small sample size in four of the centers (centers 3, 5, 7 and 8), the data from these centers were pooled whenever results for the individual centers were provided. The patients ranged in age from 25 to 91 years with a mean of 67 years. 39 (63%) of the 71 patients who were randomized and received study drug treatment were at least 65 years old. 52 (73%) of the patients were males, and 19 (27%) were females. The majority of the patients were Caucasian. The types of SVTs exhibited by the patients were classified and distributed as shown below.

The types of SVTs exhibited by the patients were classified as shown below:

A-FIB	Atrial fibrillation; atrial fibrillation/flutter.
A-FL	Atrial flutter.
PSVT	Paroxysmal supraventricular tachycardia (i.e. paroxysmal atrial tachycardia in the form of reentrant AV nodal tachycardia or paroxysmal junctional (nodal) tachycardia).
WPW	Wolff-Parkinson-White Syndrome with associated tachycardias.
AAT	Automatic atrial tachycardia (i.e. multifocal atrial tachycardia and ectopic atrial tachycardia).
ST	Sinus tachycardia.
Other	SVT not fitting into one of the other six categories.

TYPES OF SVT'S IN THE STUDY POPULATION

TYPE OF SVT	NUMBER OF PATIENTS	(%)
A-FIB *	43	(61)
A-FL	15	(21)
PSVT	3	(4)
WPW	1	(1)
AAT	6	(8)
ST	1	(1)
Other	2*	(3)

* Pt. #307: A-FL/Paroxysmal atrial tachycardia
Pt. #409: Sinus tachycardia/atrial reciprocating tachycardia/AAT

Although the patient distributions by type of SVT did not differ significantly among the centers, the proportions of patients with A-FIB varied considerably (from 47% in the pooled centers to 83% in Center 01). Similarly, more than 1/3 of the patients from Center 04 and from the pooled centers (number 03, 05, 07, 08) had A-FL compared with 0% to 19% of the patients from any of the other centers (Table 7A). There were no statistically significant differences among the centers with respect to the HR, SBP, and DBP (Table 8).

Table 7

CHARACTERIZATION OF STUDY POPULATION BY CENTER

INVESTIGATOR CENTER #	N	SEX MALE	SEX FEMALE	AGE (YRS.) MEAN±S.D.	AGE (YRS.) RANGE	HEIGHT (cm)	WEIGHT (kg)	BSA (m^2)	RACE Caucasian	RACE Black	RACE Oriental
WILLIAMS 01	12	3	9	71.3 ±12.4	47-85	155.8 ±6.0	64.5 ±23.1	1.7 ±0.2	11	0	0
SUNG 02	20	15	5	64.1 ±15.5	25-91	166.8 ±17.7	64.7 ±17.8	1.7 ±0.2	12	4	4
SCHROEDER 04	8	8	0	52.9 ±16.8	28-75	179.7 ±6.7	86.4 ±14.2	2.0 ±0.2	8	0	0
DAS 09	16	14	2	71.4 ± 8.9	58-91	176.2 ±10.3	79.2 ±13.7	1.9 ±0.2	16	0	0
OTHERS*	15	12	3	68.3 ±14.7	35-87	170.5 ±9.3	69.9 ±14.1	1.8 ±0.2	13	2	0

* Others: Pooled data from center #03 (Wilner), 05 (Rajfer), 07 (Engler) and 08 (Zoble). Investigator #06 (Brachfeld) did not enter any patient in the study.

Table 7A

DISTRIBUTION OF STUDY POPULATION BY TYPE OF SVT BY CENTER

Group	Type of SVT A-FIB	A-FL	PSVT	WPW	AAT	ST	Other
Center 1	10	0	1	0	1	0	0
Center 2	13	2	1	1	2	1	0
Center 4	4	3	0	0	0	0	1+
Center 9	9	3	1	0	3	0	0
Others*	7	7	0	0	0	0	1++

* Others: Pooled data from center #03 (Wilner), 05 (Rajfer), 07 (Engler) and 08 (Zoble). Investigator #06 (Brachfeld) did not enter any patient in the study.

\+ Patient #307 classified as "other" — type of SVT was atrial flutter vs paroxysmal atrial tachycardia.

++ Patient #409 classified as "other" — type of SVT was sinus tachycardia vs automatic atrial tachycardia vs atrial reciprocating tachycardia.

Table 8

SUMMARY OF BASELINE CLINICAL DATA BY CENTER

Investigator (Center #)	N	Heart Rate (bpm)	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)	Post-Op+		Diagnostics+		
					yes	no	CAD	valve	other
Williams (01)	12	147.1 ± 31.6	131.8 ± 27.9	82.3 ± 9.9	2	8	2	1	7
Sung (02)	20	137.4 ± 12.0	127.4 ± 20.9	81.8 ± 13.7	4	16	3	2	15
Schroeder (04)	8	144.4 ± 18.4	117.3 ± 17.4	78.8 ± 8.9	2	6	3	0	5
Das (09)	16	138.4 ± 13.9	136.7 ± 22.6	82.8 ± 12.0	0	14	5	1	10
Others*	19	143.1 ± 14.2	125.2 ± 12.0	82.1 ± 12.2	1	13	1	1	13

Values represent mean ± S.D.

* Pooled data from centers 03 (Wilner), 05 (Rajfer), 07 (Engler) and 08 (Zoble). Investigator #06 (Brachfeld) did not enter any patients in the study.

+ Data in this column may not equal (in sum) the number of patients at each center due to missing observations.

B. Analysis by Treatment Group

Tables 14 and 15 below summarize the prestudy demographic and clinical data separately for patients initially treated with esmolol and patients initially treated with placebo. In general, the mean values for the variables presented in the two tables do not differ significantly between the two groups of patients.

Table 14

SUMMARY OF DEMOGRAPHIC AND PRESTUDY CLINICAL DATA, BY INITIAL TREATMENT GROUP (ESMOLOL OR PLACEBO)

Variable*	Initial Treatment	Mean	S.D.	Min	Max	N
Age (years)	Esmolol	66.7	13.8	32.0	91.0	36
	Placebo	66.5	15.4	25.0	91.0	35
Height (cm)[a]	Esmolol	166.7	14.8	134.0	188.0	32
	Placebo	170.4	12.4	137.5	205.7	34
Weight (kg)	Esmolol	73.7	17.6	35.0	114.0	36
	Placebo	69.6	16.5	41.0	108.0	35
BSA (m^2)[a]	Esmolol	1.8	0.3	1.4	2.3	32
	Placebo	1.8	0.2	1.3	2.3	34
Heart Rate (bpm)	Esmolol	140.9	20.2	120.0	235.0	36
	Placebo	141.7	15.8	120.0	180.0	35
Systolic Blood Pressure (mm Hg)	Esmolol	132.5	20.8	104.0	190.0	36
	Placebo	124.7	20.9	98.0	180.0	35
Diastolic Blood Pressure (mm Hg)	Esmolol	83.9	11.2	62.0	110.0	36
	Placebo	79.7	11.9	60.0	110.0	35

[a] Height and body surface area were not obtained from five patients

* There were no statistically significant differences between patients first treated with esmolol and patients first treated with placebo.

... crossover period.

Table 15

SUMMARY OF PATIENTS
BY INITIAL TREATMENT GROUP (ESMOLOL VS. PLACEBO),
BY SEX AND TYPE OF SVT

	Initial Treatment Group	
Variable	Esmolol	Placebo
Type of SVT		
A-Flb	23	20
A-Fl	9	6
PSVT	0	3
WPW	0	1
AAT	3	3
ST	1	0
Other	0	2
Sex Males	27	25
Females	9	10

II Efficacy Results:

Initial Titration Response

A. Analysis by Treatment Group

The therapeutic responses to either esmolol or placebo during the initial or crossover titration period, the esmolol maintenance and follow up period are summarized in Tables 20, 22, 23, and Figure 4. Of the 63 "efficacy patients", 32 received esmolol and 31 received placebo during the initial titration period. Two placebo patients (6%) and 23 esmolol patients (72%) were therapeutic responders during the initial titration period. The percent response in patients treated with esmolol (72%) was significantly greater than the placebo response (6%) (p less than 0.001). Of the 23 responders on esmolol, distribution by the response criteria was as follows:

1. 20% reduction in the heart rate n=22

... the crossover period.

2. heart rate less than 100 bpm n=1

3. Conversion to NSR n=2
(These two patients also had a 20% reduction in the heart rate.)

Table 20

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

Esmolol Dosage mcg/kg/min	No. of Pats.[a]	Responders			Nonresponders		
		No.	%	Cum. %	Titr. Cont.[b]	Adv. Effect[c]	Ther. Failure[d]
50	32	10	31.3	31.3	22	0	0
100	22	4	18.2	43.8	18	0	0
150	18	5	27.8	59.4	12	1	0
200	12	2	16.7	65.6	5	0	5
250	5	1	20.0	68.8	4	0	0
300	4	1[d]	25.0	71.9	0	0	3

[a] Number of patients eligible for the efficacy analysis

[b] Number of patients who continued to the next higher dosage

[c] Number of patients who were terminated due to the occurrence of adverse effects

[d] Patient 914 responded at the 300 mcg/kg/min dosage, but the titration period was then terminated due to the occurrence of adverse effects

The protocol initially allowed a maximum dose of 200 mcg/kg/min of esmolol. The protocol was later on amended to allow 300 mcg/kg/min esmolol. This explains the difference in sample size at 200 mcg/kg/min, 250 mcg/kg/min, and 300 mcg/kg/min.

Combining the results from the initial and crossover titration periods, 61 of the 63 patients eligible for the efficacy analysis were treated with esmolol (32 during the initial titration and 29 during the crossover period). Two patients (#702 and 917) responded to placebo during initial titration and thus were not crossed over to esmolol.

Sixteen (55%) of the 29 "efficacy patients" (therapeutic failures on placebo) treated with esmolol during the crossover period achieved therapeutic response. Only one (12%) of the eight esmolol failures

Table 22

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

Esmolol Dosage mcg/kg/min	No. of Pats.[a]	Responders			Nonresponders		
		No.	%	Cum. %	Titr. Cont.[b]	Adv. Eff.[c]	Ther. Failure
50	29	11[d]	37.9	37.9	17	1	0
100	17	3	17.6	48.3	14	0	0
150	14	2	14.3	55.2	12	0	0
200	12	0	0.0	55.2	8	0	4
250	8	0	0.0	55.2	8	0	0
300	8	0	0.0	55.2	0	0	8

[a] Number of patients eligible for the efficacy analysis

[b] Number of patients who continued to the next higher dosage

[c] Number of patients who were terminated due to the occurrence of adverse effects

[d] Patient 410 responded at the 50 mcg/kg/min dosage, but the titration period was then terminated due to the occurrence of adverse effects.

Overall Response (Initial and Crossover Titration)

Therefore, combining the results from the initial and crossover titration periods, the response rates in esmolol-treated and placebo-treated patients were 64% (39/61) and 8% (3/39). When the response rates are calculated for "all patients" regardless of whether eligible for efficacy or not, similar results are found: 67% for esmolol, 9% for placebo during the initial titration period; 60% for esmolol, 9% for placebo on the combined periods (p less than 0.001).

Table 23

OVERALL THERAPEUTIC RESPONSE TO ESMOLOL
AMONG "EFFICACY PATIENTS" BY ESMOLOL DOSAGE

Esmolol Dosage mcg/kg/min	No. of Pats.[a]	Responders			Nonresponders		
		No.	%	Cum. %	Titr. Cont.[b]	Adv. Effect[c]	Ther. Failure
50	61	21[d]	34.4	34.4	39	1	0
100	39	7	17.9	45.9	32	0	0
150	32	7	21.9	57.4	24	1	0
200	24	2	8.3	60.7	13	0	9
250	13	1	7.7	62.3	12	0	0
300	12	1[e]	8.3	63.9	0	0	11

[a] Number of patients eligible for the efficacy analysis who received esmolol

[b] Number of patients who continued to the next higher dosage

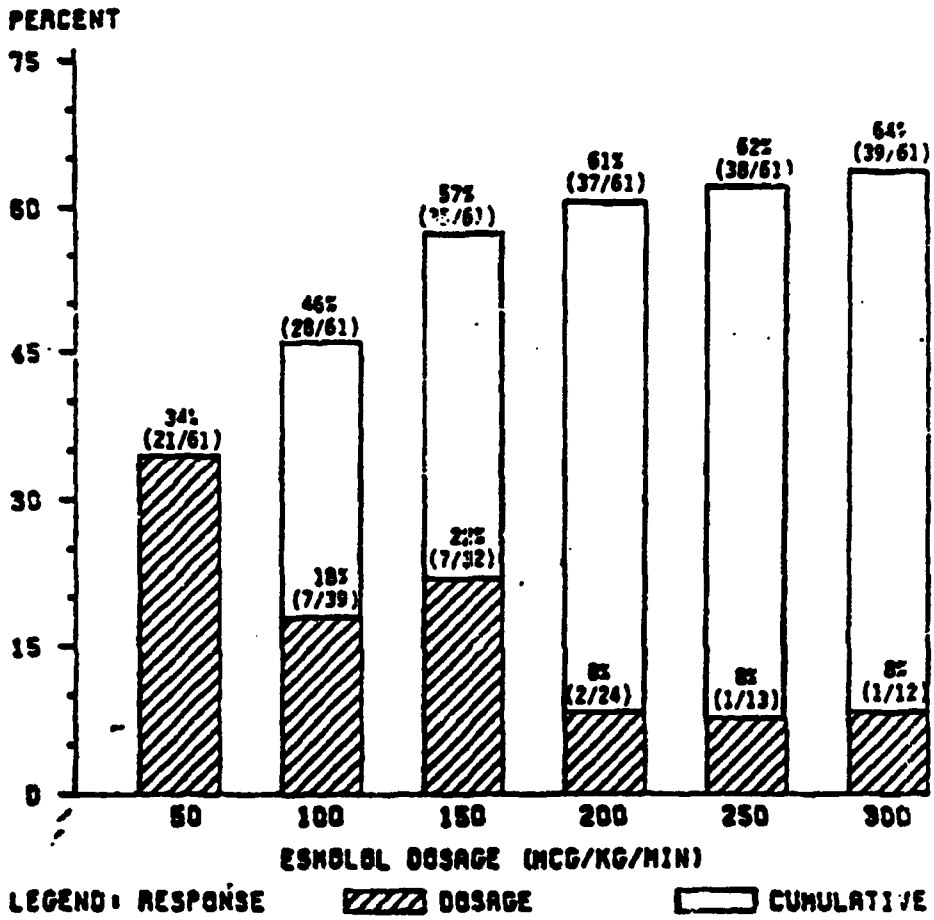
[c] Number of patients who were terminated due to the occurrence of adverse effect

[d] Patient 410 responded at the 50 mcg/kg/min dosage during the crossover titration period, but titration was then terminated due to the occurrence of adverse effects.

[e] Patient 914 responded at the 300 mcg/kg/min dosage during the initial titration period, but titration was then terminated due to the occurrence of adverse effects.

FIGURE 4

PERCENTAGE OF PATIENTS ACHIEVING A THERAPEUTIC RESPONSE DURING THE INITIAL AND CROSSOVER ESMOLOL TITRATION PERIODS, BY ESMOLOL DOSAGE



Dose Response Relationship

The average effective dose of Brevibloc (esmolol) among responders was 97.5 mcg/Kg/min. The average dosage at the end of esmolol titration (optimal dosage) was 195 mcg/Kg/min. Of esmolol-treated patients, 61% (37/61) responded at or before the 200 mcg/Kg/min dose (Table 23). Of those titrated above 200 mcg/Kg/min, only [illegible] (15%) responded. Response rates at these two dose ranges were significantly different (p less than 0.01). Therapeutic response rates in selected patient subgroups are shown in Table 24. The response rates did not differ significantly for any of the variables [illegible] in Table 24.

Table 24

THERAPEUTIC RESPONSE RATES IN SELECTED PATIENT SUBGROUPS AMONG "EFFICACY PATIENTS"

Variable	Category	R/E[a]	%[b]
Age (years)	<65	13/22	59
	65+	26/39	67
Sex	Male	28/45	62
	Female	11/16	69
Type of SVT	A FIB	24/35	69
	A FL	8/14	57
	Other[c]	7/12	58
Diagnosis	CAD	10/11	91
	Valve	5/5	100
	Other	24/43	56
Post-Op	Yes	8/9	89
	No	29/48	60

[a] Number of therapeutic responders(R)/number of patients eligible for the primary analysis of efficacy who received esmolol(E)

[b] Percent response: no statistically significant differences between categories were detected for any of the tabulated variables

[c]

PSVT	0/2
WPW	0/1
AAT	6/6
ST	1/1
A FL/PAT	0/1
ST/AAT	0/1

B. Analysis of Efficacy Results by Center

Primary efficacy analysis pooled the data from the treatment centers. Therapeutic response rates were also analyzed among the different study centers. Therapeutic response among "efficacy patients" on esmolol for each center is provided in Table 24A. As shown, the percent response ranged from 25% in pooled centers (others) to 83% in Center 02. The esmolol response rate in the individual centers was found to be significantly different (p=0.02). Patient data from the pooled centers were reviewed to determine if any factors could be responsible for the low percentage response to esmolol (25%) compared to the remaining 4 individual centers. No significant difference in any of these factors in patient population from pooled centers compared to individual centers was seen. According to the sponsor (which is probably correct) the sample size is too small to make any definitive conclusion from this data.

Table 24A

THERAPEUTIC RESPONSE DURING THE INITIAL AND CROSS-OVER TITRATION PERIOD BY CENTER

Investigator/Center	Esmolol R/E[a]	Esmolol %[b]	Placebo R/E[a]	Placebo %[b]
WILLIAMS/01	6/10	60	0/5	0
SUNG/02	15/18	83	0/9	0
SCHROEDER/04	5/8	62	0/6	0
DAS/09	10/13	77	1/7	14
OTHERS[c]	3/12	25	2/12	17
TOTAL	39/61	64	3/39	8

[a] Number of therapeutic responders(R)/number of patients eligible for the primary analysis of efficacy who received the indicated treatment(E)

[b] Response percentage

[c] Centers 03, 05, 07 and 08

C. Analysis During Maintenance and Follow-up Periods

31 of the 35 esmolol responders who entered the 30 minute maintenance period maintained their therapeutic response and entered the 30 minute follow up period. Six of the 31 patients maintained a therapeutic respone during the entire follow-up period. The other 25 patients escaped response during the follow-up period, 19 (76%) by minute 10.

D. Analysis of Recovery from Brevibloc

The percentage heart rate reduction in esmolol responders at the end of infusion was 27%. During the follow-up period, the percent reductions at 10, 20, 30 minutes were 15%, 11% and 9% respectively, indicating a progressive recovery from esmolol-induced beta blockade, after its discontinuation (Table 33).

Table 33

HEART RATES (BPM) OF EFFICACY PATIENTS DURING FOLLOW-UP PERIOD

Study Period	Esmolol		Placebo
	Responders (N=34)	Nonresponders (N=16)	(N=12)
Baseline	135.3±2.2	145.4±4.4	139.7±4.0
End of Infusion	98.7±2.2	126.8±4.6	124.5±5.1
Follow-up Period 10 Min	115.0±2.9*	135.0±4.9*	128.3±5.5*
20 Min	120.2±2.9*	140.3±5.0**	128.2±5.1*
30 Min	123.6±2.6*	140.8±4.8*	129.4±5.0*

Values represent mean ± SEM.

* Significantly different from the corresponding baseline mean ($p<0.05$) and from the corresponding end of infusion mean ($p<0.05$)

** Significantly different from the end of infusion mean

IV Safety Results:

Safety related results are summarized in Tables 36, 37, 38, 39, 40, 41, 42, 47, 48. Adverse experiences were reported for 16 (23%) of the 71 patients in the study; nearly all adverse experiences occurred during esmolol infusion. Adverse effects by body system are summarized in Table 37.

Table 37

SUMMARY OF ADVERSE EFFECTS, BY BODY SYSTEM

Body System	Adverse Effect	Number of Patients	
		Esmolol	Placebo
Cardiovascular	Hypotension (Symptomatic)	7	1
	Hypotension (asymptomatic)	1	0
	Diaphoresis	7	0
	Paired VPC's	1	0
	Increased VPC's	1	0
	Decreased heart rate	1	0
	Junctional Rhythm	1	0
	Chest Pain	0	1
	Increased pulmonary artery pressure	1	0
	Dyspnea	1	0
	Subtotal	12	1
Central Nervous System	Dizziness	1[a]	1
	Lightheadedness	1	0
	Irritability	1	0
	Paresthesia	1	0
	Headache	0	1[b]
	Subtotal	4	2
Gastrointestinal	Nausea	0	1
Miscellaneous	IV Infiltration	0	1
	Redness at Injection Site	1	0
	Subtotal	1	1
All	Total	13	3

[a] Occurred after completion of the initial titration period (esmolol), but prior to start of the crossover period

[b] Began prior to start of the initial titration period (placebo)

The most frequently observed adverse effect in patients treated with esmolol pertained to the cardiovascular system 17.6% (12/68). Hypotension (9 patients) and diaphoresis (7 patients) were the most frequently experienced adverse effects. Six patients treated with esmolol were terminated from the study due to systemic adverse effects. Hypotension was reported by the investigators in 8 patients treated with esmolol and in 1 patient treated with placebo (Table 38).

Table 38

SUMMARY OF PATIENTS WITH HYPOTENSION (AS INDICATED BY INVESTIGATOR)

Treatment/Study Period	Patient Number	Onset Dosage (mcg/kg/min)	Blood Pressure (SBP/DBP) Baseline (mm Hg)	At the time of onset (mm Hg)
Esmolol				
Titration	106	150	110/80	70/NR
	410	50	108/85	85/52
	704	200	109/80	80/70
	908	300	129/84	96/72
	910*	200	120/69	78/61
	913	200	125/105	60/43
	914	300	118/83	69/54
Maintenance	408	100	113/62	104/56
Placebo				
Titration	703	300	141/81	60/NR

* Asymptomatic

NR: Not recorded

Of these, 7 on esmolol and 1 on placebo were symptomatic (Table 37). In addition to these, 8 patients on esmolol and 1 patient on placebo were found to have criteria hypotension: systolic blood pressure less than 90 mmHg and or diastolic blood pressure less than 50 mmHg during the study period (Table 39).

Table 39

SUMMARY OF PATIENTS WITH HYPOTENSION
(*AS DEFINED BY CRITERION: BP <90/50 MM HG)

Treatment/Study Period	Patient Number	Onset Dosage (mcg/kg/min)	Blood Pressure(SBP/DBP) Baseline (mm Hg)	Blood Pressure(SBP/DBP) At the time of onset (mm Hg)
Esmolol				
Titration	217	300	105/65	86/58
	218	100	102/72	105/44
	302	200	122/90	84/72
	911	150	109/69	84/66
Maintenance	212	250	120/80	88/74
	213	200	113/90	80/60
	215	300	114/75	88/70
	904	150	118/72	85/64
Placebo				
Titration	701	150	110/70	88/70

* Six patients (#106, 410, 704, 910, 913, 914) on esmolol and one patient (#703) on placebo, who were indicated by investigator as having hypotension, also met this criterion.

None of these patients was symptomatic and none was indicated by the investigator as having hypotension. Hence the actual incidence of hypotension was double the rate reported by the investigators. Therefore 16 of the 61 esmolol treated patients experienced hypotension. According to the sponsor, in all cases hypotension was resolved rapidly (within 30 minutes) after discontinuation of esmolol. The patients who exhibited hypotension (Table 40) were (1) younger (age less than 65 years developed more hypotension when compared to patients with age greater than 65 years), (2) had higher baseline heart rates and (3) had lower baseline systolic blood pressure than the nonhypotensive patients.

Table 40

OCCURRENCE OF HYPOTENSION IN SELECTED PATIENT SUBGROUPS

Variable	Category	H/T[a]	%
Age (years)	<65	9/25	36*
	65>	5/42	12
Sex	Male	11/49	22
	Female	3/18	17
Race	Caucasian	9/56	16
	Black	1/6	17
	Oriental	3/4	75
Weight (kg)	<75	5/34	15
	75>	9/33	27
BSA (m^2)[b]	<1.9	4/34	12
	1.9>	8/28	29
Type of SVT	A FIB	8/41	20
	A FL	4/13	31
	Others	2/13	15
Diagnosis	CAD	1/13	8
	Valve	1/5	20
	Other	11/47	23
Post-Op	Yes	1/9	11
	No	12/53	23
Baseline HR (bpm)	<135	4/31	13
	135>	10/36	28
Baseline SBP (mm Hg)	<120	10/27	37*
	120>	4/40	10
Baseline DBP (mm Hg)	<80	6/27	22
	80>	8/40	20
Digoxin	No	3/19	16
	Yes	11/46	23
IV Digoxin	No	12/52	24
	Yes	2/17	12

[a] Number of patients with hypotension as defined by the formal criteria(H)/number of patients who received esmolol(T)
[b] BSA was not obtained from five of the 67 patients.
* Statistically significant difference between categories ($p<0.05$)

N 19386 (2 of 10)

Although the incidence of hypotension was somewhat less frequent at dosages of 200 mcg/Kg/min or less (15%) than at dosages of greater than 200 mcg/Kg/min (21%), the difference was not statistically significant. The relationship between esmolol dose vs adverse effects was examined in this study (Table 37A.

Table 37A
Esmolol Dose vs ADE

Body System/ Symptom	Dose of Esmolol (mcg/kg/min)						
	50	100	150	200	250	300	500
Cardiovascular							
Hypotension							
Symtomatic	1	1	0	1	1	2	1
Asymptomatic	0	0	0	1	0	0	0
Diaphoresis	1	1	0	0	2	2	1
Dyspnea	0	0	0	0	0	0	1
Increased Pulmonary Artery Pressure	1	0	0	0	0	0	0
Paired PVC's	0	0	0	0	0	0	1
Increased PVC'S	0	0	0	0	0	0	0
Decreased Heart Rate	0	0	0	1	0	0	0
Junctional Rhythm	0	0	0	1	0	0	0
CNS							
Dizziness	0	0	0	0	0	1	0
Irritability	0	0	0	0	1	0	0
Light Headedness	0	0	0	0	0	1	0
Miscellaneous							
Infusion Site Reaction	0	0	0	1	0	0	0

Hypotension, diaphoresis and CNS adverse effects appear to occur more frequently at higher doses of esmolol (greater than 200). Since the sample size is very small, a definite conclusion regarding a dose relationship cannot be drawn from this data. In addition, patients with disease states (n=28), which are at risk for treatment with beta blockers, such as COPD, bronchitis, asthma, CHF, recent MI, or AV conduction block were treated with esmolol. Of these, 3 patients were terminated from the study due to adverse effects.

Finally, no significant trend was seen among lab parameters with clinically significant changes from prestudy to post study. No association between maximum esmolol dosage and the occurrence of laboratory parameter changes was seen.

2nd Pivotal Study

Study No. 8052-81-04 "Safety and Efficacy of Esmolol vs Propranolol in the Treatment of SVT.

Investigators and Institutions: Multicenter Study; 18 investigators. See Table 1 for list of investigators and number of patients enrolled.

TABLE 1

LIST OF INVESTIGATORS AND NUMBER OF PATIENTS ENROLLED

Center Number	Investigator and Institution	Number of Patients
1	John Allen, M.D. White Memorial Hospital Los Angeles, California	1
2	Onkar Narula, M.D. International Hospital Miami, Florida	2
3	Bert Wong, M.D. University of Kansas Medical Center Kansas City, Kansas	0
4	Peter Steele, M.D. Mercy Hospital Denver, Colorado	0
5	Jonathan Abrams, M.D. University of New Mexico (OSA) Albuquerque, New Mexico Veterans Admin. Hospital (OSB) Albuquerque, New Mexico	5
6	Albert Waldo, M.D. University of Alabama Birmingham, Alabama	17
7	Bramah Singh, M.D. Wadsworth VA Medical Center Los Angeles, California	3
8	Leonard N. Horowitz, M.D. Hahnemann Hospital Philadelphia, Pennsylvania	29
9	Jang B. Singh, M.D. St. Vincent Hospital Worcester, Massachusetts	28

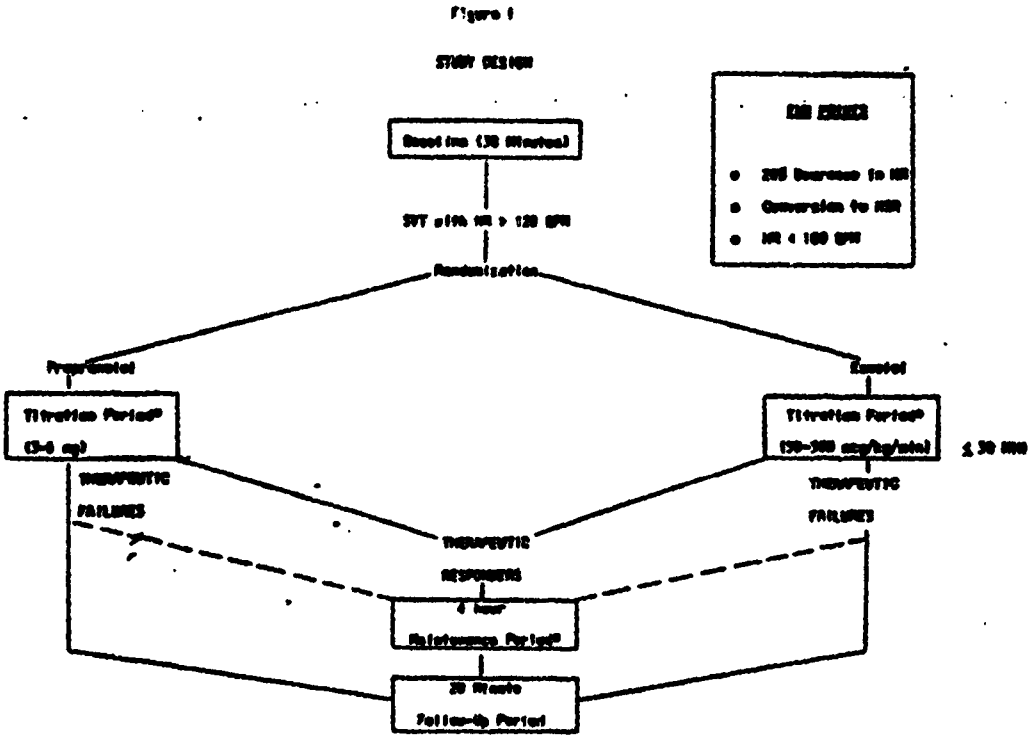
TABLE 1 (Continued)

LIST OF INVESTIGATORS AND NUMBER OF PATIENTS ENROLLED

Center Number	Investigator and Institution	Number of Patients
10	Robert DiBianco, M.D. Washington Adventist Hosp. (10A) Tacoma Park, Maryland Veterans Admin. Med. Ctr. (10B) Washington, D.C.	4
11	Juan Aranda, M.D. V.A. Hospital Medical Center San Juan, Puerto Rico	0
12	Kul Chadda, M.D. Long Island Jewish Hillside Memorial Hospital Long Island, New York	2
13	Jeffrey Anderson, M.D. LDS Hospital (13A) Salt Lake City, Utah University of Utah Med. Ctr.(13B) Salt Lake City, Utah	9
14	Laurence Favrot, M.D. Sharp Memorial Hospital (14A) San Diego, California Sharp Cabrillo Hospital (14B) San Diego, California	4
15	Charles Swerdlow, M.D. Deaconess Hospital (15A) Spokane, Washington Sacred Heart Medical Center (15B) Spokane, Washington	23
16	M. Sridharan, M.D. Eastern Virginia Medical Center Hampton, Virginia	0
17	Garrett Lee, M.D. Cedars South Miami, Florida	0
18	Hugos Cuadros, M.D. Christ Hospital Oak Lawn, Illinois	0

Study Objective: The objective of the study was to compare the efficacy and safety of IV esmolol with that of IV propranolol in the treatment of hospitalized patients with persistent SVT. The primary entrance criterian was an average ventricular heart rate exceeding 120 beats per minute during a 30 minute baseline control period. Treatment efficacy was evidenced by either conversion to normal sinus rhythm (NSR) or by predefined reduction in ventricular rate.

Study Design and Treatment Plan: The study was a randomized, double-blind parallel group trial. A schematic representation of the study design is provided in Figure 1.



- - - - Therapeutic failures could also enter maintenance period based on the clinical judgment of investigator.

* Patients dropped due to adverse effects after 20 minute Follow-Up Period

The study consisted of four periods: a 30 minute baseline period, a 30 minute dose titration period, a 4 hour maintenance period, a 20 minute follow up period. To qualify to receive study medication, the average of the four baseline heart rates (taken at 0, 10, 20, and 30 minutes) had to exceed 120 bpm. Briefly, the treatment consisted of IV esmolol dose titration from 50-300 mcg/kg/min or titration of 3 to 6 mg of IV propranolol with titration ending when the patient achieved therapeutic response or the highest dose had been given. Patients who achieved therapeutic response during titration were entered into a four hour maintenance period during which esmolol was continued at the same rate at which response was observed, but no additional propranolol was given. Esmolol (or placebo) infusion and propranolol (or placebo) injections were initiated simultaneously. The dose titration schedule for esmolol was (the same as in study 05) as follows:

Brevibloc

500 mcg/kg/min for 1 min - 50 mcg/kg/min for 4 min
500 mcg/kg/min for 1 min - 100 mcg/kg/min for 4 min
500 mcg/kg/min for 1 min - 150 mcg/kg/min for 4 min
500 mcg/kg/min for 1 min - 200 mcg/kg/min for 4 min
500 mcg/kg/min for 1 min - 250 mcg/kg/min for 4 min
500 mcg/kg/min for 1 min - 300 mcg/kg/min for 4 min

The dosage titration schedule for propranolol was as follows:

Propranolol

1 mg/min	0-1 min
1 mg/min	1-2 min
1 mg/min	2-3 min
0 (placebo)	3-4 min
0 (placebo)	4-5 min
1 mg/min	5-6 min
1 mg/min	6-7 min
1 mg/min	7-8 min
0 (placebo)	8-30 min

Thus 3 mg of propranolol were injected during the first 5 minutes of the titration period and; provided if therapeutic response was not observed at minute 5 of titration, an additional 3 mg of propranolol was injected during the second 5 minutes of the titration period. The maximum dose of propranolol (6 mg) was not exceeded. Both study drugs were administered intravenously through a large peripheral vein; however esmolol was given by continuous infusion whereas propranolol was given by bolus injection. Because of these differing methods of intravenous administration, the study was blinded by means of a double placebo technique. That is, patients receiving active esmolol infusion simultaneously received placebo injections, and those receiving active propranolol injections, received a placebo infusion.

For patients randomized to propranolol, a placebo solution was infused during the maintenance period to keep the double-blind design of the study.

Study Details

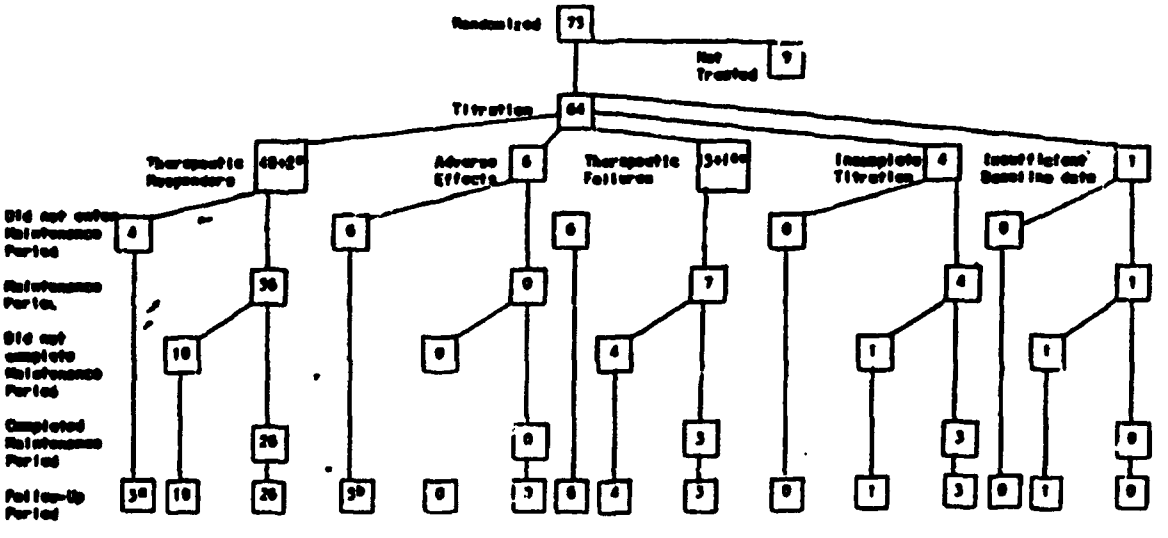
For details of the method of patient selection (inclusion and exclusion criteria) efficacy and safety assessment and data management and statistical methodology see appropriate sections under study 8052-81-05 (as these parameters are essential unchanged). The schedule of study observations is summarized in Table 2 (see study 05).

Number of Patients - "All," "Efficacy," "Drop-outs" "Exclusions"

The effects of esmolol and propranolol were compared in 127 patients (9 patients on esmolol and 7 patients on propranolol were assigned patient numbers but never received the study drug). The patients were categorized into 2 groups: "All patients" (total 127); those who received either study medication (esmolol N=64; Propranolol N=63) and "efficacy patients" (total 110); those who met all protocol requirements, esmolol N=63; Propranolol N=57. A summary of "all patients" at each phase of the study for both treatment groups is provided in Tables 20, 20A 22, and 22A.

Table 20

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



* Two patients (8010, 8101) were also included under adverse effects.

** One patient (8003) was also included under adverse effects.

a One patient (8703) did not enter follow-up period.

b One patient (8603) did not enter follow-up period.

Table 20A

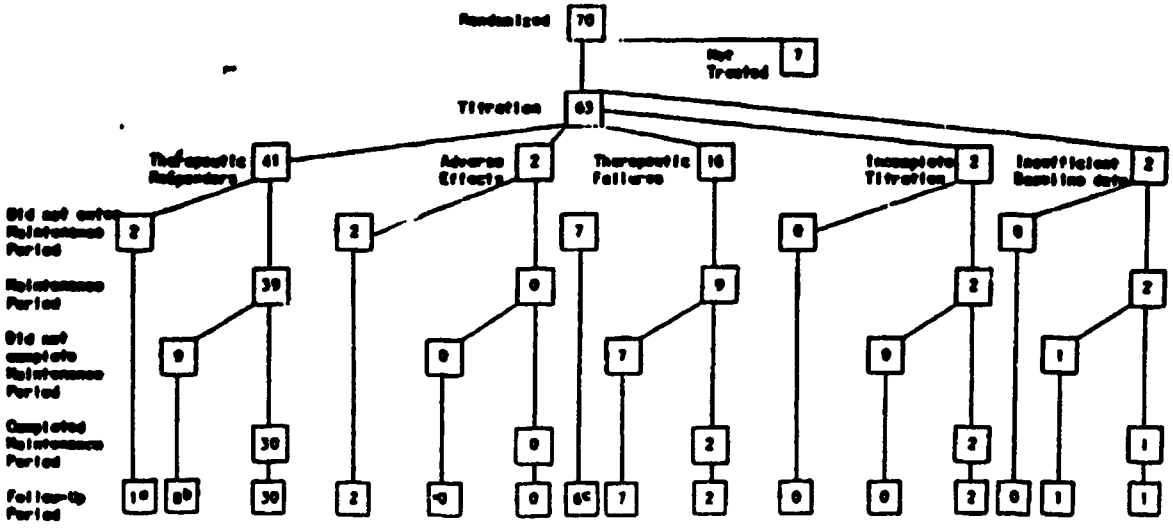
STUDY OUTCOME OF "ALL PATIENTS"
DURING THE ESMOLOL TITRATION PERIOD

Study Outcome	Patient Numbers
Achieved Therapeutic Response (N=42)	#201, 203, 504, 602, 505, 610, 611, 614, 616, 618, 705, 712, 804, 806, 808, 809, 821, 823, 825, 828, 829, 901, 904, 910, 911, 920, 924, 934, 1001, 1003, 1302, 1306, 1404, 1502, 1505, 1506, 1510, 1516, 1518, 1520, 1524, 1526
Dropped Due to Adverse Effects (N=6)	#502, 603*, 610**, 618**, 1307, 1407
Therapeutic Failures (N=14)	#603, 812, 814, 816, 818, 913, 915, 926, 929, 932, 1202, 1301, 1512, 1528
Incomplete Titration (N=4)	#820, 905, 1006, 1503
Insufficient Baseline Data (N=1)	#701

* Also a therapeutic failure
** Also achieved therapeutic response

Table 22

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



* One patient (#1203) did not enter follow-up period.

b One patient (#909) did not enter follow-up period.

c One patient (#1102) did not enter follow-up period.

Table 22A

STUDY OUTCOME OF "ALL PATIENTS"
DURING THE PROPRANOLOL TITRATION PERIOD

Study Outcome	Patient Numbers
Achieved Therapeutic Response (N=41)	#501, 503, 601, 607, 609, 612, 813, 615, 617, 801, 803, 807, 817, 822, 824, 826, 902, 906, 908, 912, 917, 923, 925, 927, 931, 1005, 1203, 1303, 1304, 1305, 1308, 1309, 1403, 1408, 1501, 1504, 1509, 1511, 1522, 1527, 1529
Dropped Due to Adverse Effects (N=2)	#909, 1519
Therapeutic Failures (N=16)	#102, 604, 606, 805, 811, 813, 815, 819, 827, 830, 903, 921, 930, 1513, 1514, 1523
Incomplete Titration (N=2)	#916, 919
Insufficient Baseline Data (N=2)	#505, 703

Seventeen "all patients", 11 in the esmolol group and 6 in the propranolol group were not included in the efficacy analysis. Derivation of "all patients", "efficacy patients" for both esmolol and propranolol treated groups are provided in Tables 4 and 5.

Table 4

DERIVATION OF "ALL PATIENTS", "EFFICACY PATIENTS"
IN THE STUDY: ESMOLOL

"All Patients"		64	
Exclusions	a. Efficacy*	11	(#502, 605, 616, 701, 802, 913, 929, 934, 1006, 1302, 1404)
	b. Safety**	10	(#602, 603, 605, 616, 808, 816, 1003, 1306, 1407, 1512)
"Efficacy Patients"		53	

* Efficacy data from these 11 patients were excluded from efficacy analysis. Reasons for exclusion appear in Table 6.

** Part of the safety data from these 10 patients was excluded from safety analysis. Reasons for exclusion appear in Table 8.

Table 5

DERIVATION OF "ALL PATIENTS", "EFFICACY PATIENTS"
IN THE STUDY: PROPRANOLOL

"All Patients"		63	
Exclusions	a. Efficacy*	6	(#505, 609, 613, 703 1504, 1523)
	b. Safety**	17	(#102, 501, 505, 604, 607, 609, 613, 615, 807, 815, 819, 903, 916, 925, 1203, 1305, 1308)
"Efficacy Patients"		57	

* Efficacy data from these 6 patients were excluded from efficacy analysis. Reasons for exclusion appear in Table 7.

** Part of the safety data from these 17 patients was excluded from safety analysis. Reasons for exclusion appear in Table 9.

The reason for the exclusions from the efficacy analysis is summarized for each patient in Table 6 and 7.

Table 6
DETAILS OF ESMOLOL PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

PATIENT NUMBER	DEMOGRAPHIC DATA			BASELINE DATA			TYPE OF SVT	REASON FOR EXCLUSION FROM EFFICACY ANALYSIS
	GENDER	AGE (Yrs)	WEIGHT (Kg)	HEART RATE (bpm)	BLOOD PRESSURE SBP (mm Hg)	DBP (mm Hg)		
302	M	39	70	148	110	74	ST	Study conduct deviation. Titration stopped at 2.3 minutes due to hypotension. Steady state drug levels were not reached prior to discontinuation.
603	M	61	72	132	99	69	A-FIB	Study conduct deviation. Baseline cardiac rhythm discovered to have been sinus at minute 5 of esmolol titration.
616	M	62	69	197	110	84	A-FIB	Entrance criteria deviation. Patient received IV verapamil within 2 half-lives (approximately 3.7 hours) of entry into the study.
.708	M	28	114	NR	NR	NR	A-FIB	Study conduct deviation. Baseline measurements not obtained.
802	M	69	70	148	144	74	A-FIB	Study conduct deviation. Conversion to normal sinus rhythm. Patient entered immediately into maintenance period.
913	M	68	69	149	112	70	A-FL	Entrance criteria deviation. Patient received IV propranolol within 2 half-lives (approximately 9.9 hours) of entry into the study.
929	M	71	82	160	123	63	A-FL	Entrance criteria deviation. Patient received oral propranolol within 2 half-lives (3.9 hours) of entry into the study.
934	F	67	52	135	137	99	A-FIB	Entrance criteria deviation. Patient received IV verapamil within 2 half-lives (7.25 hours) of entry into the study.
1008	M	38	86	136	109	70	PSVT	Entrance criteria deviation. Patient received IV verapamil within 2 half-lives (3.8 hours) of entry into the study.
1302	M	74	99	127	138	99	A-FL	Entrance criteria deviation. Patient received oral preparation containing reserpine 12.25 hours before entry into the study.
1404	M	60	91	177	115	73	A-FIB	Entrance criteria deviation. Patient received IV verapamil within 2 half-lives (8 hours) of entry into the study.

NR = not retrievable

Table 7

DETAILS OF PROPRANOLOL PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

PATIENT NUMBER	DEMOGRAPHIC DATA			BASELINE DATA			TYPE OF SVT	REASON FOR EXCLUSION FROM EFFICACY ANALYSIS
	GENDER	AGE (Yrs)	WEIGHT (Kg)	HEART RATE (bpm)	BLOOD PRESSURE SBP (mm Hg)	BLOOD PRESSURE DBP (mm Hg)		
509	F	60	79	150	132	88	A-FIB	Study conduct deviation. No heart rates obtained at baseline 10, 20, and 30 minutes (Only one baseline measurement obtained.)
609	M	52	79	165	106	61	A-FIB	Entrance criteria deviation. Patient received IV verapamil within 2 half-lives (approximately 5.3 hours) of entry into the study.
615	F	74	65	153	114	63	A-FIB	Entrance criteria deviation. Patient received IV verapamil within 2 half-lives (5.3 hours) of entry into the study.
705	M	67	65	NR	NR	NR	A-FL	Study conduct deviation. Baseline measurements were not obtained.
1504	M	79	69	153	101	69	A-FIB	Study conduct deviation. Study drug (propranolol) boluses given much later than called for by study (study minutes 60 and 72 for last two boluses).
1523	F	70	70	122	144	107	A-FIB	Entrance criteria deviation. Patient received oral medical within 2 half-lives (19.5 hours) of entry into the study.

NR = not retrievable

In addition, 3 "efficacy patients" from the esmolol and 2 "efficacy patients" from the propranolol group were excluded from the analysis of therapeutic response due to:

1. The titration period was stopped prior to achieving therapeutic response (4 patients) and 2) interrupted titration period due to I.V. infiltration (1 patient). Since both treatment groups are equally affected by these exclusions, they probably won't change the overall results. Therefore 105 "efficacy patients" (esmolol, N=50; propranolol N=55) were analyzed for therapeutic response. For analysis of heart rate changes, data from the total 110 "efficacy patients" were used. Safety assessment was based on analysis of the data from 127 "all patients" though partial data from 27 patients (esmolol N=10; propranolol N=17) were excluded from safety analysis. The reasons for the exclusion from the safety analysis is summarized in Tables 8 and 9.

Table 8

DETAILS OF ENROLLED PATIENTS EXCLUDED FROM SAFETY ANALYSIS

PATIENT NUMBER	DEMOGRAPHIC DATA			BASELINE DATA			TYPE OF SPT	ACTUAL DATA EXCLUDED, AND REASON FOR EXCLUSION FROM SAFETY ANALYSIS
	GENDER	AGE (Yrs)	WEIGHT (kg)	HEART RATE (bpm)	SBP (mm Hg) Blood Pressure	DBP (mm Hg)		
002	M	58	88	191	127	78	A-PIB	Pretreatment urinalysis excluded because urine specimen collection time is not retrievable.
005	F	71	61	199	148	92	ART	Pre- and pretreatment urinalysis excluded because urine specimen was obtained 8 days prior to the study and more than 24 hours after the end of the study, respectively.
009	M	61	72	152	99	69	A-PIB	Pretreatment blood chemistry, hematology and urinalysis excluded because specimens obtained > 24 hours after end of study.
010	M	62	80	157	118	84	A-PIB	Pretreatment blood chemistry and hematology excluded because specimen collection time is not retrievable.
008	F	64	69	127	102	68	A-PIB	Pretreatment urinalysis excluded because urine specimen obtained 10 days prior to the study.
016	F	66	97	137	113	69	A-PIB	Pretreatment urinalysis excluded because urine specimen obtained 12 days prior to the study.
1005	F	59	71	120	193	101	A-PIB	Pretreatment blood chemistry, hematology and urinalysis excluded because specimens obtained > 24 hours after end of study.
1308	M	66	80	104	123	68	A-PIB	Pretreatment blood chemistry, hematology, and urinalysis excluded because specimens collected during cuvelet infusion.
1407	F	73	90	100	127	87	A-PIB	Pretreatment blood chemistry and hematology excluded because specimen collected > 24 hours after the end of study.
1512	F	57	66	126	101	66	A-PIB	Pretreatment blood chemistry and hematology excluded because specimen collected during cuvelet infusion.

Table 9

DETAILS OF PROPRANOLOL PATIENTS EXCLUDED FROM SAFETY ANALYSIS

PATIENT NUMBER	DEMOGRAPHIC DATA			BASELINE DATA			TYPE OF SPT	ACTUAL DATA EXCLUDED, AND REASON FOR EXCLUSION FROM SAFETY ANALYSIS
	GENDER	AGE (Yrs)	WEIGHT (Kg)	HEART RATE (bpm)	SBP Blood Pressure (mm Hg)	DBP (mm Hg)		
102	M	62	89	136	104	71	A-PL	Predrug blood chemistry excluded because specimen collected more than 1 week prior to the study. Hematology and urinalysis excluded because specimens collected during the infusion period.
301	F	50	70	133	105	75	A-P1B	Predrug urinalysis excluded because specimen obtained 8 days prior to the study.
305	F	60	79	150	132	88	A-P1B	Predrug blood chemistry, hematology, and urinalysis excluded because specimen collection times are not retrievable. Postdrug blood chemistry, hematology, and urinalysis excluded because specimens collected >24 hours after the end of study.
606	M	69	88	147	99	62	A-P1B	Postdrug urinalysis excluded because specimen obtained 2 days after the study.
607	M	52	91	137	102	68	A-P1B	Predrug blood chemistry, hematology, and urinalysis excluded because blood specimens obtained during infusion and urine specimen obtained > 7 days before study.
609	M	52	70	165	108	81	A-P1B	Pre- and postdrug blood chemistry, hematology, and urinalysis excluded because specimen collection times are not retrievable.
613	F	74	68	153	114	63	A-P1B	Predrug hematology excluded because specimen collected during the infusion period.
615	F	91	69	150	125	77	A-P1B	Predrug blood chemistry and hematology excluded because specimen collection times are not retrievable.
807	M	60	88	143	109	62	A-P1B	Predrug urinalysis excluded because specimen obtained 10 days before the study.

Table 9 (Continued)

DETAILS OF PREMATURELY DISCONTINUED PATIENTS EXCLUDED FROM SAFETY ANALYSIS

PATIENT NUMBER	DEMOGRAPHIC DATA			BASELINE DATA			TYPE OF DIS	ACTUAL DATA EXCLUDED, AND REASON FOR EXCLUSION FROM SAFETY ANALYSIS
	GENDER	AGE (Yrs)	WEIGHT (Kg)	HEART RATE (bpm)	SBP (Blood Pressure) (mm Hg)	DBP (mm Hg)		
819	F	55	60	136	102	61	A-FIB	Prestudy urinalysis excluded because specimen obtained > 7 days prior to the study.
819	M	50	105	104	108	67	A-FIB	Prestudy urinalysis excluded because specimen obtained 14 days prior to the study.
905	M	64	80	100	139	90	A-FIB	Poststudy blood chemistry and hematology excluded because specimens obtained > 24 hours after the end of study.
916	F	74	65	103	110	65	A-FIB	Prestudy blood chemistry and hematology excluded because specimen collection times are not retrievable.
923	F	67	55	132	117	75	A-FIB	Poststudy hematology and urinalysis excluded because specimens obtained > 24 hours after the end of study.
1203	M	57	80	129	110	70	A-FIB	Pre- and poststudy hematology and urinalysis and poststudy blood chemistry excluded because specimen collection times are not retrievable. Prestudy blood chemistry excluded because specimen obtained more than 1 week prior to the study.
1309	M	61	68	104	112	74	A-FIB	Poststudy blood chemistry and hematology excluded because specimens obtained > 24 hours after the end of study.
1308	F	52	70	121	109	72	A-FIB	Poststudy blood chemistry, hematology, and urinalysis excluded because specimens obtained > 24 hours after the end of study.

Study Results:

I Baseline Demographics and Comparability of Treatment Groups

Tables 12 and 13 below describe the prestudy clinical data of "all patients" and "efficacy patients" treated with esmolol and propranolol respectively. There was no significant difference in heart rate and systolic blood pressure between the two treatment groups.

Table 12

PRESTUDY CLINICAL DATA OF PATIENTS RANDOMIZED TO ESMOLOL

Variable	"ALL PATIENTS" N	Mean	S.D.	Range	"EFFICACY PATIENTS" N	Mean	S.D.	Range	"EFFICACY-EVALUABLE PATIENTS" N	Mean	S.D.	Range
Heart Rate (bpm)	64	147.5	14.7	120.0-180.0	53	147.1	15.9	120.0-180.0	11	148.5	7.5	135.0-160.0
Systolic Blood Pressure (mm Hg)	64	123.9	21.2	90.0-190.0	53	126.2	22.2	90.0-190.0	11	113.0	11.2	102.0-140.0
Diastolic Blood Pressure (mm Hg)	64	77.1	19.9	47.0-110.0	53	78.1	19.9	60.0-110.0	11	72.4	10.4	47.0-90.0
Primary Diagnosis	64*				53**				11*			
CAD	19				16				3			
Valve	7				6				1			
Other	38				22				9			
Post-op/ Non Post-op	64*				53**				11*			
Post-op	34				27				7			
Non Post-op	29				25				2			

* Data from eight patients on primary diagnosis (0201, 203, 502, 701, 709, 901, 1503, 15201) and from five patients in post-op category (0201, 203, 502, 701, 703) were not available.

** Data from six patients on primary diagnosis (0201, 203, 705, 901, 1503, 15201) and from three patients in post-op category (0201, 203, 709) were not available.

* Data from two patients on primary diagnosis and post-op category (0502, 701) were not available.

Table 13

PRETREAT CLINICAL DATA OF PATIENTS RANDOMIZED TO PROPAFENONE

	"ALL PATIENTS"				"EFFICACY PATIENTS"				"EFFICACY-INELIGIBLE PATIENTS"			
Variable	N	Mean	S.D.	Range	N	Mean	S.D.	Range	N	Mean	S.D.	Range
Heart Rate (bpm)	63	168.8	17.8	119.0-214.0	57	168.2	18.3	119.0-214.0	6	143.3	13.4	124.0-156.0
Systolic Blood Pressure (mm Hg)	63	118.8	16.8	91.0-166.0	57	117.3	15.2	91.0-164.0	6	122.7	25.3	98.0-166.0
Diastolic Blood Pressure (mm Hg)	63	74.3	12.1	50.0-120.0	57	73.4	10.7	50.0-110.0	6	83.2	21.1	60.0-120.0
Primary Diagnosis	63*				57**				6*			
CAD	19				18				1			
Valve	10				8				2			
Other	30				28				2			
Post-op/ Non post-op	63*				57				6*			
Post-op	31				28				3			
Non post-op	31				29				2			

* Data from four patients on primary diagnosis (#501, 705, 1311, 1914) and from one patient in post-op category (#705) were not available.

** Data from three patients (#501, 1311, 1914) were not available.

* Data from one patient on primary diagnosis and post-op category (#705) were not available.

The distribution of patients by SVT type in both treatment groups is provided in Tables 14 and 15 respectively. No significant difference in the distribution by type of SVT was seen between the two treatment groups.