Table 33. Summary of IND Safety Reports Submitted to the FDA from Advanced AIDS Patients Enrolled in Protocols 115-211 and 115-213, by Category of Event

Safety Report Event	Number of Reports	Study
Cancer	5	115-211
Psychotic behavior/psychosis	3	115-211
Pancreatitis	3	115-211
Rash	2	115-211
Hepatitis	2	115-211
Death with unknown cause	2	115-211
Pericardial effusion with tamponade	1	115-211
Maculopathy	1	115-211
Death due to probable congestive heart failure	1	115-211
Vision loss	1	115-211
Death due to dehydration	1	115-211
Death due to cryptococcal meningitis	1	115-211
Increased liver enzyme levels, nausea, vomiting	1	115-213
Erythema multiforme	1	115-213
Pseudomembranous colitis	1	115-213
Abdominal distention	1	115-213
TOTAL	27	

All patients included in the above IND Safety Reports had advanced HIV disease, often with a variety of concurrent medical conditions, and were treated with a variety of concomitant medications. Review of these reports revealed no pattern of toxicity that can be attributed to treatment with atovaquone.

Summary of Deaths

In study 115-211, 440 patients (42%) died during the study. Similar numbers of deaths occurred in the atovaquone group (43%) and dapsone group (40%), with no statistically significant difference between groups (see Table 35). The most common category of death was "miscellaneous" (29% of deaths), and "unknown" was the single largest cause in this category (79 patients). Additional common categories of deaths were respiratory (26%), HIV progression (26%) and cerebral (12%).

In study 115-213, 105 patients (19%) died during the study. The fewest deaths occurred in the high-dose atovaquone group (15%) and the greatest number of deaths occurred in the low-dose atovaquone group (22%). Differences among groups were not statistically significant (see Table 35). The majority of deaths were due to causes in three main areas: respiratory (47%), HIV progression (23%) and cerebral (12%).

PCP was listed as a contributory or principal cause of death for 12% of patients who died in study 115-211 (9% for the atovaquone group and 15% for the dapsone group), and for 18% of patients who died in study 115-213 (26% for the low-dose atovaquone group, 15% for the high-dose atovaquone group and 11% for the aerosolized pentamidine group). These differences were not statistically significant.

Categories of causes of death in the two studies are listed in Table 34.

Table 34. Summary of Cause of Death (Number of Patients)*

Category	Study 115-211			Study 115-213			
	Atovaquone 1500 mg/d n=536	Dapsone 100 mg/d n=521	Total n=1057	Atovaquone 750 mg/d n=188	Atovaquone 1500 mg/d n=175	Aerosolized Pentamidine n=186	Total n=549
Respiratory[a] (PCP)	62 (22)	53 (32)	115 (54)	22 (11)	14 (4)	13 (4)	49 (19)
HIV Progression[b]	61	52	113	12	4	8	24
Cerebral[c]	25	26	51	3	2	8	13
Neoplasm[d]	13	6	19	2	3	2	7
Renal Failure	4	3	7	1	1	1	3
Cardiovascular[e]	2	5	7	0	0	2	2
Miscellaneous[f]	65	63	128	2	3	2	7
Total	232	208	440	42	27	36	105

*Numbers in brackets are percentages. All other numbers are absolute numbers.

[a]Respiratory includes respiratory failure, PCP, pneumonitis/pneumonia, aspiration, pneumothorax, dyspnea, pulmonary Kaposi's sarcoma, pulmonary lymphoma

[b]HIV progression includes wasting/cachexia, candida esophagitis, malnutrition, CMV, MAI, histoplasmosis, HSV

[c]Cerebral includes PML, encephalopathy, meningitis, cerebral hemorrhage, toxoplasmosis, dementia, cerebral lymphoma

[d]Neoplasm includes lymphoma, Kaposi's sarcoma, liver adenocarcinoma, and malignant neoplasm

[e]Cardiovascular includes myocardial infarct, cardiopulmonary arrest, ventriculitis, cardiac arrest

[f]Miscellaneous includes sepsis, septicemia, colitis, dehydration, cellulitis, acidosis, heroin overdose, cirrhosis, hypoglycemia, angiomatosis, hemorrhage, pancreatitis, anemia, liver failure, adrenal insufficiency, pancytopenia, colitis and unknown

Summary of Clinical Laboratory Safety Data

Medical Officer's Note: Clinical laboratory data were collected systematically only in study 115-213.

During this study, hematology (hemoglobin, platelet, white blood cell and neutrophil counts) and biochemistry (sodium, potassium, creatinine, alanine aminotransferase (ALT), glucose and amylase) data were collected at screen and at weeks 4, 12 and every 12 weeks thereafter. Analysis of laboratory data included calculation of median values, median changes from baseline, and Hodges-Lehmann estimates of treatment differences for each parameter. These analyses were performed for the total population and by age, race and gender.

Medical Officer's Note: Baseline laboratory values were comparable among the three treatment groups. Neither atovaquone nor aerosolized pentamidine was associated with a substantial change from baseline values in any measured laboratory parameter, nor were there any significant differences among treatment groups in any measured

laboratory parameter over time. The baseline values and maximum median change from baseline during the first 36 weeks of the study are shown in Table 35.

Table 35. Baseline Values and Changes from Baseline for Laboratory Parameters

Laboratory Parameter	Baseline Value[a]	Maximum Median Change From Baseline (range)[b]		
		Atovaquone 750 mg/d	Atovaquone 1500 mg/d	Aerosolized Pentamidine
Hemoglobin (g/dL)	12.5	(-.05, 0.2)	(-0.2, 0.2)	(-.05, 0.1)
Platelets (x 1000/μL)	181	(-5, 3.5)	(-2.5, 11)	(-9, 4.5)
WBC (x 1000/μL)	3.61	(-0.1, 0.25)	(-0.55, -0.2)	(-0.18, 0.1)
Neutrophils (x 1000/μL)	1.82	(0, 0.06)	(-0.3, -0.1)	(-0.2, 0)
Sodium (mmol/L)	140	(-1, 0)	(0, 0)	(0, 0)
Potassium (mmol/L)	4.2	(0, 0.1)	(-0.1, 0)	(-0.1, 0)
Creatinine (mg/dL)	0.96	(0, 0)	(-0.03, 0)	(0, 0)
ALT (U/L)	36.3	(-2, 2)	(-0.5, 2)	(-1, 1)
Glucose (mg/dL)	87.1	(-1.8, 2)	(-1, 3.6)	(0, 2.7)
Amylase (U/L)	71.3	(-2, -1)	(-5, -1)	(-2, -1)

a Average (mean) of baseline median values for all therapy groups

b Numbers represent the maximum change in the median values and not the absolute values of the laboratory parameter. Since more than two thirds of patients had discontinued assigned therapy by Week 48, only data from week 4 through week 36 are presented.

Although there were no significant changes in laboratory parameters in the populations treated with either drug, a few patients had laboratory abnormalities that were considered serious by the investigator (14 patients) or that contributed to discontinuation of therapy (6 patients). None of the serious laboratory abnormalities in the low-dose atovaquone and aerosolized pentamidine groups were considered to be related to study drug. The single serious laboratory abnormality in the high-dose atovaquone group (elevated liver function tests) was considered to be related to study drug.

Table 36. Laboratory Parameters Noted as Serious (# of Patients)

Parameter	Atovaquone 750 mg/day	Atovaquone 1500 mg/day	Aerosolized Pentamidine
Anemia	4		2
Pancytopenia	1		2
Elevated			
BUN	1		
Creatinine	1		
Bilirubin	1		
LFT		1	1
Hypokalemia	1		1

Laboratory abnormalities were reported as contributing factors to discontinuation of study medication for six patients, including five patients (two in the low-dose atovaquone group and three in the high-dose atovaquone group) with elevated liver function tests.

An age-related analysis dividing the population into two groups based on the median age of 37 years was performed. No clinically significant differences between treatment groups by age or between the two age groups were noted.

Females comprised 8.2% of the population with available clinical laboratory data. Analysis of the median changes from baseline of clinical laboratory data by gender showed no clinically significant differences between treatment groups in the female population or between the female and male populations.

Analysis of the median change from baseline of clinical laboratory data was performed by race (white versus non-white). No clinically significant differences between treatment groups in the non-white population or between the white and non-white populations were noted.

Safety Data from Other Sources

As of 30 November 1997, Glaxo Wellcome Worldwide Product Surveillance and Pharmacovigilance had received 108 spontaneous adverse event reports. Sources of these reports included health care providers, consumers, medical sales representatives, worldwide regulatory agencies, and published literature. The most commonly reported adverse events were in the integumentary (29), hepatobiliary and pancreas (14), blood and lymphatic (14), non-site specific (11), urologic (9), neurologic (8), and gastrointestinal (7) body systems.

Two adults, not participating in clinical trials, each of whom ingested nearly an entire 210 ml bottle (31,500 mg) of MEPRON (atovaquone) Suspension, have been reported to Glaxo Wellcome. One of these patients had no associated adverse events and one had methemoglobinemia that lasted for 1 day. The lack of significant toxicity in these two patients provides further evidence that atovaquone suspension is unlikely to be associated with serious risks.

Summary and Conclusions Regarding Safety

The overall safety profile of atovaquone suspension during chronic administration for prophylaxis of PCP was favorable. Except for rash, which occurred more often in patients treated with atovaquone than in patients treated with aerosolized pentamidine, the overall rate of adverse events was similar in patients treated with atovaquone or aerosolized pentamidine, and there was no evidence of a dose-related increase in the frequency of adverse events in patients treated with atovaquone suspension. Serious adverse events attributable to study drug were uncommon, overall mortality rates were comparable to the comparator drugs and consistent with the mortality experience expected in patients with advanced HIV disease, and clinically important changes in laboratory parameters associated with treatment were rare. As expected, the rate of treatment-limiting adverse events was higher in patients receiving systemic therapy with atovaquone suspension than in patients receiving inhaled therapy with aerosolized pentamidine, with more treatment-limiting events in patients treated with the higher dose of atovaquone suspension. In treatment-naive patients, the rate of treatment-limiting adverse events was lower for patients treated with atovaquone than for patients treated with dapsone.

Taken as a whole, these data provide evidence of the safety of atovaquone suspension for prevention of PCP.

Medical Officer's Note: There was no evidence for an increased incidence of adverse events in patients treated with the higher dose of atovaquone. Among the 25 most common adverse events, which were reported in at least 10% of patients in either atovaquone arm, the rates were generally similar or lower in the high-dose arm compared to the low-dose arm (refer back to Table 32). Similar results were seen for less common adverse events. In addition, serious adverse events possibly attributable to atovaquone were uncommon, with three such events in patients treated with either high-dose or low-dose atovaquone. Clinically important laboratory abnormalities associated with either dose of atovaquone were rare.

V. CONCLUSIONS ON EFFICACY AND SAFETY

A. Tabular Results of Efficacy and Safety

Tabular results of efficacy and safety in the two pivotal studies follow:

Table 37. Comprehensive Efficacy Table for 211 and 213

Event	Study 115-211		Study 115-213		
	Atovaquone 1500 mg/d	Dapsone 100 mg/d	Atovaquone 750 mg/d	Atovaquone 1500 mg/d	Aerosolized Pentamidine
PCP (Intent-to-Treat)	23	26	25	22	17
PCP (As-Treated)	15	19	23	18	17
Death	43	40	22	15	19
PCP or Death	52	53	37	30	30
PCP (Primary Prophylaxis)	18	21	14	16	9
PCP (Secondary Prophylaxis)	36	38	41	32	27
Death (Primary Prophylaxis)	39	32	17	8	14
Death (Secondary Prophylaxis)	53	60	29	26	27
Confirmed PCP (Intent-to-Treat)	17	21	16	20	11
Confirmed PCP (As-Treated)	NA	NA	15	16	11
PCP (Dapsone at Entry)	27	26	NA	NA	NA
PCP (Neither Study Drug at Entry)	17	25	23	18	18
PCP (Pentamidine at Entry)	NA	NA	28	27	16
Death (Dapsone at Entry)	43	43	NA	NA	NA
Death (Neither Study Drug at Entry)	44	37	22	18	15
Death (Pentamidine at Entry)	NA	NA	23	13	24

Table 38. Treatment Limiting Adverse Events for Study 115-211.

Event	Dapsone At Baseline		Neither Dapsone Nor Atovaquone At Baseline	
	Atovaquone (N=285)	Dapsone (N=261)	Atovaquone (N=238)	Dapsone (N=249)
Any Event	28[a]	9	20	43[a]
Rash	6	2	8	16[a]
Nausea	5[a]	0	3	1
Vomiting	3[a]	<1	1	1
Diarrhea	4[a]	0	2	0
Pruritus	<1	0	<1	2
Fever	1	0	0	6[a]
Allergic Reaction	1	1	1	5[a]
Anemia	0	1	0	2

[a] $p<0.05$, Fisher's exact test

Adverse events resulting in discontinuation of original therapy in ≥2% of patients in either therapy group.

Table 39. Treatment Limiting A/E in Protocol 213

Event	Atovaquone 750 mg/day (n = 188)	Atovaquone 1500 mg/day (n = 175)	Aerosolized Pentamidine (n = 186)
Rash	6[a,b]	6[b]	0
Diarrhea	3[b]	4[b]	0
Nausea	3	3[b]	0
Vomiting	3	2	0
Fever	2	2	1
Pneumonia	2	1	1
Pruritis	1	2	0
Liver function abnormality	1	2	0
Anorexia	2	1	0
Bronchospasm	0	0	2
Any treatment-limiting event	16[b]	25[b]	7

B. Conclusions Study 211:

- The study demonstrated that patients assigned prophylaxis with either atovaquone or dapsone had similar rates of confirmed or probable episodes of PCP and survival.
- There was a trend favoring atovaquone over dapsone toward better efficacy for prevention of PCP.
- In a subgroup analysis, a trend favoring the dapsone-assigned group was noted for survival among patients without a history of PCP (primary prophylaxis). These data have to be interpreted cautiously for two reasons:
    1) treatment differences were not significant; and
    2) PCP event rates decreased greatly after study drug discontinuation, and the possible reasons for this include better antiretroviral treatment, use of macrolides for MAC prophylaxis, and underreporting of PCP events after study drug discontinuation. If there is differential underreporting of PCP events by treatment group after study drug discontinuation, some of the subanalyses could be biased. In the subgroups based on dapsone use at baseline, patients stopped one drug significantly sooner than the other, and this could cause a bias in favor of the drug discontinued earlier.
- There were no differences in the rates of adverse events rates necessitating discontinuation of assigned study drug or in the median time on assigned treatment between atovaquone and dapsone.
- The toxicity profile for atovaquone and dapsone are quite distinct, with gastrointestinal symptoms predominating in the atovaquone group and hypersensitivity reactions and anemia in the dapsone group.
- Patient preference was a significantly more frequent cause for study drug discontinuation in patients assigned atovaquone.
- Only treatment limited adverse events were looked at.
- A significant proportion of patients enrolled in the study were receiving dapsone at baseline. Patients taking dapsone at baseline were significantly more likely to stay on

study-assigned dapsone than atovaquone. Those receiving neither drug at baseline were more likely to tolerate atovaquone than dapsone.

- In conclusion, the rates of PCP, survival and tolerance were similar in this study which compared atovaquone to dapsone for the prevention of PCP among patients intolerant to T/S.
- In the subgroup of patients who were on dapsone at baseline, dapsone was better tolerated than atovaquone. Thus, patients on dapsone should continue to receive it.
- In the subgroup of patients not on dapsone at baseline, atovaquone was better tolerated. Thus, for newly identified patients who are intolerant to T/S who have not received dapsone, although atovaquone and dapsone are equally effective in preventing PCP, atovaquone may be a better initial choice based on tolerance.

C. Conclusions on Protocol 213

- There was no statistical difference in the incidence of PCP between either dose of atovaquone and aerosolized pentamidine.
- There was no difference in survival among therapy groups.
- For both survival and prevention of PCP, there was a trend toward better outcome in the High-Dose group compared to the Low-Dose group.
- There was a trend toward better efficacy with aerosolized pentamidine compared to atovaquone for prevention of PCP. This was not statistically significant.
- There was a trend toward better survival with High-Dose compared to Low-Dose and aerosolized pentamidine.
- Treatment-limiting adverse events occurred significantly more frequently in the two atovaquone groups.
- There were no statistically significant differences among therapy groups with regard to time on study medication. The principal reasons for discontinuation of study medication were:
    - Low-Dose - inadequate response
    - High-Dose - adverse event
    - Aerosolized Pentamidine - consent withdrawn

D. Conclusions ACTG277

1. Dosing recommendations are not appropriate, based on the pharmacokinetic data collected in pediatric patients.
2. The doses recommended by the applicant did not result in atovaquone $C_{avg,ss}$ values between 15-25 mcg/mL.
3. No safety and efficacy data has been submitted to date in children. The sample size in each of the three dose/kg categories is low.
4. Explanation as to why a dose of 45 mg/kg is required in the 3-24 months age group has not been provided. Please refer to the pharmacokinetic review for further details regarding ACTG 227.

E. Overall conclusions

- Data in this application demonstrate efficacy at least as good as alternative therapies with a convenient dosing regimen, and safety comparable to alternative therapies. There was a trend favoring atovaquone over dapsone toward better efficacy for prevention for prevention of PCP. There was a trend toward better efficacy with aerosolized pentamidine compared to atovaquone for prevention of PCP.
- The rate of breakthrough PCP was not higher in patients receiving long-term therapy with atovaquone suspension, 1500 mg daily, than in patients receiving dapsone or aerosolized pentamidine.
- Safety overall was acceptable, with low rates of serious adverse events. Thus once daily treatment with atovaquone suspension provides a safe and effective alternative to existing therapies to prevent PCP in patients who are intolerant to TMP/SMX.

Recommendations:

- The drug should be approved but the Applicant's proposed label needs the following modifications:

D. Labeling recommendations

1. Clinical Pharmacology:

A. Microbiology:

- Statement regarding emerging atovaquone resistance

B. Special Populations: Pediatrics

- Accept tabular data from ACTG 227
- Include a statement regarding dosing regimen of the study

2. Indications and Usage:

- Include a comment of median follow-up of studies 115-211 and 213.
- Include a table of the results of studies 115-211 and 115-213.
- Include an explanation of relative risk values in the table.
- Include descriptive statements regarding the ITT analysis and mortality rates.

3. Precautions:

A. Pediatric use:

- Include a comment that safety and effectiveness has not been established in pediatric patients.

B. Geriatric use:

- Accept the Applicant's statement.

4. Adverse Reactions:

- Inclusion of the daily dose into subsequent tables.
- Removal of p-values from the subsequent tables

5. Dosage and Administration:

- Removal of comments regarding pediatric dosing.

Signature Block:

Concur:

/S/

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Division of Biometrics III

/S/

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Distribution List:

cc:NDA 20-500/S-005
HFD-590
HFD-590/ DIVDIR/ MGoldberger
HFD-590/SMO/ RHopkins
HFD-590/MO/RViraraghavan
HFD-590/SCSO/EFrank
HFD-590/CSO/BAtkins
HFD-725
HFD-725/DIVDIR/MHuque
HFD-725/TLStat/NSilliman
HFD-725/ Stat/CDixon

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[31] JID (in press)

VII Appendix 1

List of Investigators, Sites, and Enrollment

CPCRA 034/ACTG277

Investigator	Site	Enrollment
Henry Balfour Jr., MD	Univ. of Minnesota, Minneapolis	63
Ann Collier, MD	Univ. of Washington, Seattle	56
Charles van der Horst, MD	Univ. of North Carolina, Chapel Hill	51
Robert Murphy, MD	Northwestern Univ., Chicago	48
John Leedom, MD	USC, Los Angeles	47
Robert Schooley, MD	Univ. of Colorado, Denver	46
Michael Lederman, MD	Case Western Res. Univ., Cleveland	40
L. Joseph Wheat, MD	Indiana Univ., Indianapolis	40
Douglas Richmond, MD	UCSD, San Diego, CA	36
William Powderly, MD	Wahsington Univ., St. Louis	33
Roberta Luskin-Hawk, MD	St. Joseph's Hosp., Chicago	32
Harvey Friedman, MD	Univ. of Pennsylvania, Philadelphia	31
George Perez, MD	North Jersey CRI, Newark, NJ	30
John Bartlett, MD	Johns Hopkins Univ. Baltimore	28
Princy Kumar, MD	Georgetown Univ., Washington, DC	28
Henry Sacks, MD	Mt. Sinai Med. Cntr., New York, NY	27
Richard Pollard, MD	Univ. of Texas, Galveston, TX	26
Robert Fass, MD	Ohio State Univ., Columbus, OH	24
Thomas Kerkering, MD	Richmond AIDS Consortium, Richmond, VA	23
Ruy Soeiro, MD	Albert Einstein Coll. of Med., NY	21
Lawrence Crane, MD	Wayne State Univ., Detroit	20
Judith Feinberg, MD	Univ. of Cincinnati	20
Ronald Mitsuyasu, MD	UCLA, Los Angeles	19
Mark Jacobson, MD	San Francisco Gen. Hospital	19
C. Lynn Besch, MD	Tulane Univ., New Orleans	17
Louis Saravolatz, MD	Henry Ford Hosp., Detroit	17

List of Investigators, Sites, and Enrollment

Investigator	Site	Enrollment
Elizabeth Cooney, MD	Yale Univ., New Haven, CT	17
Wafaa El-Sadr, MD	Harlem Hospital, NY	16
Margaret Fischl, MD	Univ. of Miami, Miami, FL	16
James Sampson, MD	The Research and Education Group, Portland, OR	15
Richard Reichman, MD	Univ. of Rochester, Rochester, NY	15
Martin Hirsch, MD	Mass. General Hosp., Boston	14
Donald I. Abrams, MD	San Francisco Gen. Hospital	13
Michael Saag, MD	Univ of Alabama, Birmingham	13
Steven Szebenyi, MD	Albany Med. College, Albany, NY	12
Mary Ann South, MD	Meharry Med. College, Nashville, TN	12
Cecilia Shikuma, MD	Univ. of Hawaii	11
Fred Gordin, MD	VAMC, Washington, DC	10
Keith Chirgwin, MD	SUNY, Brooklyn, NY	10
Jay Dobkin, MD	Columbia-Presbyterian, NY	10
Thomas Merigan, Jr., MD	Stanford University	8
Robert Delapenha, MD	Howard Univ., Washington, DC	7
Fred T. Valentine, MD	New York University, NY	4
	Region IV Hemophilia Centers	4
	Region I Hemophilia Centers	3
	Region II/III Hemophilia Centers	2
	Region IX/X Hemophilia Centers	2
Melanie Thompson, MD	AIDS Research Consortium of Atlanta	1

List of Investigators, Sites, and Enrollment

GW213

Investigator	Site	Enrollment
Julio Montaner, MD	St. Paul's Hospital, Vancouver	70
Charles Chan, MD	Wellesley Hospital, Toronto	44
G. Frechette, MD E. Lefebvre, MD	Clinique Actuel, Montreal	33
Gary Morey, MD	CRI of South Florida, Coral Gables	33
Michael Dohn, MD	Univ. of Cinn., Cincinnati	27
A. Martel, MD S. Trottier, MD	C.H. De Laval, Ste. Foy, Quebec	24
C. Jeffrey Goodgame, MD	Goodgame & Assoc., Maitland, FL	21
P. Rene, MD	Royal Victoria Hosp., Montreal	20
Jared Spotkov, MD	Kaiser, Harbor City, CA	19
Stephen Green, MD	Hampton Roads Med Specialists, Hampton, VA	19
A. Rachlis, MD	Sunnybrook Health, Toronto	18
R. Torres, MD	St. Vincent's Hospital, New York	18
J. Gill, MD	Southern Alberta Clinic, Calgary	17
Bisher Akil, MD	ComBAT, Los Angeles	14
W. Cameron, MD	Ottawa General Hosp., Ottawa	13
I. Mackie, MD J. Gilmour, MD	St. Joseph's Health Center, London, Ont	13
John Turner, MD	Philadelphia FIGHT, Philadelphia	13
Joel Ruskin, MD	LA Kaiser, Los Angeles	12
I. Salit, MD	Toronto General, Toronto	11
Gifford Leoung, MD	St. Francis Hospital, San Francisco	11
Robert Murphy, MD	Northwestern Univ., Chicago	11
J. Falutz, MD	Montreal General, Montreal	10
Karen Tashima, MD	Miriam Hospital, Providence, RI	10
E. Toma, MD	Hotel Dieu, Montreal	9
Carol Brosgart, MD	East Bay AIDS Cntr., Berkeley, CA	9
Patricia Kloser, MD	New Jersey Med. School, Newark	8

List of Investigators, Sites, and Enrollment

Investigator	Site	Enrollment
P.M. Ford, MD	Kingston General Hosp., Kingston, Ont	7
David Hardy, MD Margrit Carlson, MD	UCLA, Los Angeles	7
W.F. Schlech, MD	Victoria General Hosp., Halifax, NS	6
I. Fong, MD	St. Michael's Hosp., Toronto	6
David Wheeler, MD	Baltimore TRIALS, Baltimore	6
S. Choudhri, MD	St. Boneface Hospital, Winnipeg	4
Stephen Follansbee, MD	Davies Med. Cntr., San Francisco	3
Charles van der Horst, MD	Univ. North Carolina, Chapel Hill	2
Cal Cohen, MD	CRI of New England, Brookline, MA	1
F. Smaill, MD	McMaster Univ. Med. Cntr., Hamilton, Ont	0
I. Bowmer, MD	Health Sci. Cntr., St. John's, Newfoundland	0