

Drug Toxicity and Grading

Toxicities were graded according to severity as listed in the toxicity table for grading adverse experiences in the *CPCRA Data Collection Handbook*. Patients were closely monitored for signs and symptoms of study drug toxicity. Laboratory results that indicated toxicity were verified as soon as possible. For all toxicities that required the study therapy to be temporarily or permanently discontinued, relevant clinical and laboratory tests were repeated, as needed, until there was final resolution or stabilization of the toxicity.

The clinician evaluated all toxicities requiring the interruption of study drug to determine whether switchover was needed. All patients were followed until completion of the study.

If a patient's therapy was interrupted for toxicity management, the clinician evaluated the toxicity to determine whether it was being caused by the study drug. Guidelines were used for managing toxicities that were thought to be related to the study drugs. The actual management of toxicities was left to the treating clinician's discretion.

Atovaquone

If a patient developed a toxicity thought to be related to atovaquone, the clinician could do one of the following after resolution of the toxicity:

- Rechallenge at the original dose (1500 mg/day).
- Rechallenge at 750 mg/day then escalate the dose to 1500 mg/day. [The reduced dose must not have been used for longer than 21 days. The patient should have been rechallenged at the originally assigned dose unless doing so was contraindicated in the clinician's opinion. If, on rechallenge, the patient was unable to tolerate the original dose, he/she was switched (if a switch had not already occurred) to the dapsone arm.]
- Switch to the dapsone arm (if a switch had not already occurred).

Dapsone

Patients intolerant of dapsone could not remain in the study on pyrimethamine alone. If a patient developed a toxicity thought to be related to dapsone, the clinician could do one of the following after resolution of the toxicity:

- Rechallenge at the original dose (100 mg/day).
- Rechallenge at 50 mg/day (with 2 tablets of 25 mg each). [The patient could be maintained on the reduced dose or have the dose escalated to 100 mg/day. If the patient was unable to tolerate the 50 mg/day dose, the patient was switched (if a switch had not already occurred) to the atovaquone arm.]
- Switch to the atovaquone arm (if a switch had not already occurred).

Pyrimethamine and Folinic Acid

- Clinicians, at their discretion, could increase the dose of folinic acid being taken by patients receiving dapsone and pyrimethamine to 15 mg/day if they developed grade 2 hematologic toxicity (i.e., thrombocytopenia, neutropenia, anemia) attributed to pyrimethamine. These patients were provided with bottles of 24 tablets in addition to the blister-strips.

- Patients found to be intolerant of, or to have a history of intolerance of, pyrimethamine and/or folic acid continued to receive dapsone and could not receive atovaquone concomitantly.

Switchover

If the patient met any of the criteria below, the clinician switched him/her to the alternate study arm.

- Development of a toxicity that, in the clinician's opinion, warranted the discontinuation of the current study drug.
- Development of PCP and the physician believed that it was in the patient's best interest to switchover.

If the patient reached one of the above switchpoints after having received both study medications, study therapy was discontinued. The patient's physician treated the patient with the prophylactic regimen of his or her choice. However, the patient continued to be followed until study closure.

If the patient was *Toxoplasma* seropositive and was switched from atovaquone to dapsone, and was not known to have a CD4+ cell count of $< 100 \text{ cells/mm}^3$, it was recommended that a CD4+ cell count be obtained to determine if pyrimethamine and folic acid should be added. If the patient's count was $< 100 \text{ cells/mm}^3$ it was recommended that the patient's count be monitored every 4 to 8 months to determine when, or if, the other study drugs should be added.

Adverse Experiences

The CPCRA adverse experience reporting system was developed to ensure timely and accurate reporting of adverse experiences in order to monitor patient safety, comply with FDA regulations, and disseminate information to investigators working with the study drug. All adverse experiences encountered during the course of this study were recorded on standard case report forms according to procedures described in the *CPCRA Data Collection Handbook*. Any life-threatening event or death that occurred on study drug was reported immediately to the CPCRA Statistical Center. The Statistical Center requested additional information based on the severity and nature of the adverse experience. The Statistical Center was responsible for reporting the information to the Pharmaceutical and Regulatory Affairs Branch (PRAB) of the Division of AIDS, NIAID. PRAB was responsible for all reports to the FDA. Local IRBs were informed by unit personnel of any serious or life-threatening adverse experiences as early as possible.

Criteria for Discontinuation of Study Medication

Certain events or conditions required temporary or permanent discontinuation of the study drug. Patients who experienced these events or conditions, however, were still "on study" and were followed until completion of the study. Any patient whose study medication was temporarily discontinued, regardless of the length of time it is suspended, was restarted on study medication as soon as possible.

Guidelines for Permanent Discontinuation of All Study Medication

Below are guidelines for permanent discontinuation of all study therapy:

- The patient developed a toxicity severe enough, in the clinician's judgment, to warrant permanent discontinuation of the current study therapy, but the patient was unable, in the clinician's judgment, to switch to the other study drug.
- The patient developed toxoplasmosis.
- The patient reached a switchpoint but had exhausted switchover alternatives.
- The patient refused further therapy.
- It was the primary physician's judgment that it was no longer in the patient's best interest to continue study therapy.
- Termination of the study.

Dosages

Patients enrolled in the study were randomized to one of two arms:

Arm I –

Dapsone 100 mg P.O. daily
 (It was recommended strongly that patients randomized to the dapsone arm, who had CD4+ counts below 100 cells/mm³, and who were toxoplasmosis seropositive, receive 50 mg of pyrimethamine and 15 mg of folinic acid per week. Patients with prior or anticipated intolerance of pyrimethamine who were randomized to the dapsone arm could continue on dapsone alone.

Arm II –

Atovaquone 1500 mg P.O. daily

Measurements and Evaluations

Screening

The following was documented prior to patient enrollment:

Any time prior to enrollment:

- Working diagnosis of HIV infection
- History of intolerance of trimethoprim and/or sulfonamides
- CD4+ cell count of < 200 cells/mm³ or < 15 percent of the total lymphocyte
- G6PD status

Baseline Assessments

The baseline assessments listed below were completed before the patient enrolled.

Any time prior to enrollment:

- Documented *Toxoplasma* serology

Within 3 months prior to enrollment (screening CD4+ cell count could be used as baseline measure if it was within 3 months prior to enrollment):

- CD4+ cell count

Within 30 days prior to enrollment:

- A baseline targeted history and clinical evaluation was performed in accordance with standard CPCRA procedures. Information on any antiretroviral therapy, anti-PCP therapy, rifampin, rifabutin, or macrolides (clarithromycin/azithromycin) the patient was receiving was recorded.
- Complete blood count with differential and platelet count.
- Liver function tests (AST or SGOT, total bilirubin).

Within 14 days prior to randomization or at randomization:

- Documentation of pregnancy status (collected by patient report or pregnancy test).

Once it was determined that the patient met the eligibility criteria, details of the study were discussed with the patient. The patient (or parent or legal guardian for minors) was asked to read and sign an institutional review board (IRB)-approved consent form.

Study Endpoints

Primary Endpoint

The primary endpoint of this study was occurrence/recurrence of morphologically or histologically proven PCP or probable PCP. A confirmed diagnosis of PCP required histologic or cytologic evidence of *P. carinii* organisms on bronchoalveolar lavage (BAL), lung biopsy or sputum (induced or non-induced). Probable PCP was diagnosed when there was (1) a history of either dyspnea on exertion or a non-productive cough, and (2) evidence of diffuse bilateral pulmonary disease on either chest X-ray or gallium scan, or abnormal arterial blood gases, and (3) absence of another diagnosis, such as bacterial pneumonia or tuberculosis, capable of explaining the syndrome. The clinician made every effort to confirm the diagnosis of PCP by obtaining specimens from bronchoalveolar lavage (BAL), biopsy, or sputum identification of *P. carinii* by standard staining techniques. In the event that such confirmation was not possible, an episode could be classified as probable PCP according to the definition provided in the *Clinical Events Handbook*.

Secondary Endpoints

1. Study drug intolerance/toxicity sufficient to warrant permanent discontinuation of assigned therapy.
2. The combined endpoint of PCP, extrapulmonary pneumocystosis, or death.
3. Development of confirmed or probable toxoplasmosis.
4. Death.

Data Management and Analysis

Primary Analysis

Analysis of the primary outcome, development of PCP, was evaluated by a test of the hypothesis that the two arms of the study have equal distributions of time to outcome using the stratified log rank statistic, stratified by baseline PCP status.

The date of randomization was used to determine the time to event or censoring in order to ensure an unbiased measurement. For the primary analysis, individuals were analyzed according to their randomly assigned group membership, regardless of the actual therapies received (intent-to-treat). Death, loss to follow-up, and event-free survival to the closing date were the only censoring mechanisms.

Secondary Analyses

Secondary analyses compared the rates of mortality, toxicity, toxoplasmosis, and the combined rate of PCP, extrapulmonary pneumocystosis or death in the same way as the primary analysis (except that death was not a censoring event in the mortality analyses).

Additional analyses for the primary and secondary endpoints considered subgroups based on prior PCP status, baseline prophylaxis and endpoints that occurred during, or within 30 days of discontinuation of assigned therapy.

Interim Analyses

Data monitoring included the analysis of the primary and secondary outcomes to permit assessment of possible highly significant treatment effects and, additionally, the potential for any future significant treatment effects. Standard CPCRA practice uses the Lan-DeMets method to account for increased Type I error from examining the data before the designed study end. Data monitoring was done at 6-month intervals. Following their review in February of 1997, they determined that study objectives had been achieved and recommended stopping the study.

Statistical Reviewer's Note: A detailed description of the interim analysis plan was not included in the submission. However, with the Lan-DeMets method, the significance level for the final results is at or approximately 0.05.

Data Collection and Monitoring

Study data were collected on standardized case report forms developed by the CPCRA Statistical Center. It was assumed that most data would be collected during patient visits to health care providers. In some instances, it was necessary to obtain and abstract hospital records for which written permission from the patient was generally required. Study data and case report forms were made available to the FDA and to CPCRA site monitoring personnel.

At a minimum, all items referenced in the protocol as being relevant to the research study were recorded in the patient's research record in accordance with standard CPCRA procedures. In addition, all items specifically required by the protocol were recorded on case report forms. Items that were recommended but not required by the protocol may or may not have been recorded on case report forms.

Informed Consent

Study was conducted in accordance with the principal of the Declaration of Helsinki. This protocol received the approval of each participating site's IRB prior to implementation. All participants signed an informed consent form. The confidentiality of all study participants was protected in accordance with standard CPCRA procedures.

III. A Randomized, Open-Label Trial of High Dose Atovaquone vs Low Dose Atovaquone vs Aerosolized Pentamidine for Prophylaxis of *Pneumocystis Carinii* Pneumonia in Patients with HIV Infection who are Intolerant of TMP/SMX

Study 115-213

1. OBJECTIVE

- To assess whether high-dose or low-dose atovaquone suspension is more effective than aerosolized pentamidine (AP) for the prophylaxis of *Pneumocystis carinii* pneumonia in high-risk HIV-infected patients.
- To compare the safety of chronic administration of high-dose or low-dose atovaquone suspension with the safety of AP in patients with advanced HIV disease.
- If high-dose and low-dose atovaquone are demonstrated to be superior to AP, to compare the safety and efficacy of high-dose versus low-dose atovaquone.
- To determine the relationship between steady-state atovaquone plasma concentrations and its effectiveness for PCP prophylaxis.

2. STUDY DESIGN

General Description

This was a multi-center, randomized, open-label comparative trial of atovaquone suspension and aerosolized pentamidine for prophylaxis of *Pneumocystis carinii* pneumonia in HIV-infected patients in Canada and the US.

3. MATERIALS AND METHODS

- Patient Selection

Investigators and Study Centers

<u>Site No.</u>	<u>Investigator</u>	<u>Study Center</u>
01	Charles Chan, MD	Toronto, Ontario, Canada
02	Julio Montaner, MD	Toronto, Ontario, Canada
03	J. Gill, MD	Vancouver, BC, Canada
04	W.F. Schlech III, MD	Calgary, Alberta, Canada
05	I. Fong, MD	Halifax, Nova Scotia, Canada
06	A. Rachlis, MD	Toronto, Ontario, Canada
07	I. Salit, MD	Toronto, Ontario, Canada
08	W. Cameron, MD	Toronto, Ontario, Canada
09	J. Falutz, MD	Ottawa, Ontario, Canada
10	P. Rene, MD	Montreal, Quebec, Canada
11	E. Toma, MD	Montreal, Quebec, Canada
12	A. Martel, MD	Montreal, Quebec, Canada
	S. Trotter, MD	St. Foy, Quebec, Canada
13	G. Frechette, MD	Montreal, Quebec, Canada
	E. Lefebvre, MD	Montreal, Quebec, Canada
14	I. Mackie, MD	London, Ontario, Canada
	J. Gilmour, MD	London, Ontario, Canada

15	P.M. Ford, MD	Kingston, Ontario, Canada
16	F. Smail, MD	Hamilton, Ontario, Canada
17	S. Choudhri, MD	Winnipeg, Manitoba, Canada
18	I. Bowmer, MD	St. John's, Newfoundland, Canada
31	Michael Dohn, MD	Cincinnati, Ohio
32	Ramon Torres, MD	New York, New York
33	Daniel Seekins, MD	Tampa, Florida*
34	C. Jeffrey Goodgame, MD	Maitland, Florida
35	Bisher Akil, MD	Los Angeles, California
36	David Hardy, MD	Los Angeles, California
	Margrit Carlson, MD	
37	Gifford Leoung, MD	San Francisco, California
38	John Turner, MD	Philadelphia, Pennsylvania
39	Gary Morey, MD	Coral Gables, Florida
40	Cal Cohen, MD	Brookline, Massachusetts
41	Carol Brosgart, MD	Berkeley, California
42	David Wheeler, MD	Baltimore, Maryland
43	Patricia Kloser, MD	Newark, New Jersey
44	Stephen Follansbee, MD	San Francisco, California
45	Robert Murphy, MD	Chicago, Illinois
46	Jared Spotkov, MD	Harbor City, California
47	Joel Raskin, MD	Los Angeles, California
48	Karen Tashima, MD	Providence, Rhode Island
49	Stephen Green, MD	Hampton, Virginia
51	Charles van der Horst, MD	Chapel Hill, North Carolina

**Exclusion of Data from Site 33*

Medical Officer's Note: During routine monitoring at one site (Site 33), the monitor discovered two randomization envelopes that had apparently been prematurely opened and resealed. The investigator was informed of this. He subsequently suspended further enrollment pending an investigation. The results of the investigation were that a former staff member had opened randomization envelopes prematurely, but the contents remained known only to the staff member. The FDA was notified of the violation and further enrollment at the site was permanently discontinued. Following discussions with FDA, it was agreed that data from this site would not be included in any analyses. Data listings for Site 33 are not included in this package, but are, per the Applicant, available if requested.

This information was forwarded to DSI. Patient numbers by study site are presented in Appendix I.

Entry Criteria

Medical Officer's Note: The italicized sections below are additional inclusion and exclusion criteria of the Applicant to protocol 211.

Inclusion

- A. HIV infection documented by standard methods, *Patients who had previously tested positive for HIV were not required to repeat these tests. However, documentation of these previous tests was required.*
- B. A previous episode of PCP (histologically confirmed or presumed), or documented CD4 lymphocyte count of $<200 \text{ cells/mm}^3$ ($<0.20 \times 10^9 \text{ c/L}$) or constitutional symptoms such as thrush or unexplained fever $>100^\circ\text{F}$ (37.8°C) for >2 weeks.

- C. Demonstrated prior intolerance to T/S or other trimethoprim or sulfa-containing regimens.
- D. 13 years or older.
- E. *Clinical Laboratory Criteria*
 - Serum creatinine <227 mmol/L (<2.5 mg/dL).
 - Serum amylase <2 x upper limit of normal.
 - Absolute neutrophil count >0.75 x 10⁹/L (750 /mm³).
 - Platelet count >80 x 10⁹/L (80,000 /mm³).
 - Hemoglobin >80 gm/L (8.0 gm/dL) (patients could be transfused to this level prior to entry).
 - SGPT (ALT) <5 times upper limits of normal.
- F. Normal chest X-ray or chest X-ray without signs of active PCP.
- G. Willing and able to give informed consent.
- H. Pregnant women could be enrolled in this trial at the discretion of the investigator and after the patient had given informed consent.

Exclusion

- A. Life expectancy of less than 6 months.
- B. Patients receiving systemic neoplastic chemotherapy for Kaposi's Sarcoma, lymphoma, other active malignancies or other diseases which may confound the safety and efficacy assessments of this trial.
- C. End of therapy for acute episode of PCP <30 days prior to randomization, or current or suspected diagnosis of active PCP.
- D. Significant psychosis, emotional disorder, or active substance abuse such that the patient would not be compliant with the study protocol.
- E. Concurrent use of medication likely to have anti-pneumocystis effect, e.g., atovaquone, dapson, trimethoprim, pyrimethamine, trimetrexate other DHFR inhibitors, sulfadiazine, sulfamethoxazole, other sulfonamides, primaquine, clindamycin, sulfonyleureas, or pentamidine.
- F. Severe chronic diarrhea (e.g., > 5 stools/day) which may negatively influence the absorption of an oral medication.
- G. Unable to take medication orally, or unwilling or unable, to take study medication with food.
- H. Prior history of severe or intractable intolerance to atovaquone (566C80, atovaquone) or AP.
- I. Patients receiving treatment with rifampin.
- J. Patients who had experienced hypoglycemia, pancreatitis, arrhythmias, or severe hypotension associated with any form of pentamidine.
- K. Previous enrollment in this protocol.
- L. Use of another investigational therapeutic agent, except drugs which are available via Treatment INDs or other expanded access programs.

Medical Officer's Note: The inclusion and exclusion criteria are acceptable.

Stratification

Patients were stratified according to PCP history at the time of randomization as follows:

- prior episode of PCP (Group A or B);
 - Patients with a history of PCP were further stratified according to the date from completion of therapy for the acute episode to the date of randomization:
 - <6 months (Group A)
 - >6 months (Group B).
- no prior episode of PCP with $CD_4 < 200 /mm^3$ or constitutional symptoms such as thrush or unexplained fever $>100^\circ F (37.8^\circ C)$ for >2 weeks (Group C).

Reviewers' Note: When this is compared to the Study 115- 211, the criteria was "prior or no prior event". At randomization, Study 115-211 also stratified by Toxoplasma serology results.

Randomization

After stratification, the patients were randomized in a 1:1:1 ratio, to receive either:

- A. 750 mg (5 mL) atovaquone suspension orally once daily with food
- B. 1500 mg (10 mL) atovaquone suspension orally once daily with food
- C. 300 mg pentamidine isethionate inhaled once every 4 weeks.

Patient Management

Diagnosis of PCP

Medical Officer's Note: Please refer to Study 115- 211 for further details.

Concomitant Medications

Medical Officer's Note: Please refer to the inclusion and exclusion criteria for further details.

Pregnancy

Medical Officer's Note: Pregnant patients were allowed in the study and a patient who became pregnant was allowed to continue in the study at the discretion of the investigator. The patient may have been temporarily discontinued from study medication, at the discretion of the investigator, during certain periods of the pregnancy and post-partum period, including the first trimester and the period from the 38th week of pregnancy through delivery or through the second post-partum month if the patient breastfed. If a pregnant patient was enrolled or, if at any time a patient became pregnant, she was to be given an informed consent detailing the risk and benefits of treatment in this protocol for a pregnant patient.

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Measurements and Evaluations

Screen Assessments

- Entry Criteria: A targeted clinical exam and medical history.
- Chest Radiograph: Posteroanterior and lateral views within 14 days prior to randomization.
- HIV Serology: ELISA and Western Blot tests were performed for all patients who had not previously tested positive for HIV antibody. Documentation of prior positive test was required.
- CD4+ Cell Count: Absolute and percent CD4+, and total lymphocyte count within 14 days prior to randomization.
- Hematology Tests: Hemoglobin, platelet count, WBC count and neutrophil count within 14 days prior to randomization.
- Clinical Chemistries: Creatinine, SGPT (ALT), sodium, potassium, glucose, amylase within 14 days prior to randomization.
- Pregnancy Test: For all females of childbearing potential within 14 days prior to randomization.

Baseline Assessments

Performed between screening and time of study entry and treatment initiation (Week 0).

- Physical Exam and Medical History: Complete physical exam (including Karnofsky score), medical history (including history of PCP and experience with PCP prophylaxis agents).
- Toxoplasma Antibody Test: Qualitative assessment of *Toxoplasma* antibody in serum. This test was not required for patients with a prior positive test. Documentation of prior positive test was required.
- Clinic Visit: Weight and height were obtained.
- Hematology Tests: Hemoglobin, platelet count, WBC count and neutrophil count unless within 7 days of screening visit.
- Clinical Chemistries: Creatinine, SGPT (ALT), sodium, potassium, glucose, amylase unless within 7 days of screening visit.

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Assessments During Therapy

- Drug Dispensing: Every 4 weeks beginning at week 0.
- Physical Exam: Complete physical examination (including Karnofsky score) to be performed at week 24.
- Clinic Visit: Weight and plasma sample for atovaquone levels (atovaquone patients only) were obtained at weeks 4, 12 and every 12 weeks thereafter.
- CD4+ Cell Count: Absolute and percent CD4+, and total lymphocyte count were performed every 24 weeks and at time of PCP occurrence.
- Hematology Tests: Hemoglobin, platelet count, WBC count and neutrophil count at weeks 4, 12 and every 12 weeks to study end.
- Clinical Chemistries: Creatinine, SGPT (ALT), sodium, potassium, glucose, amylase at weeks 4, 12 and every 12 weeks to study end.

Assessments at End of Therapy and at Week 12 Post-Treatment

- Physical Exam: Complete physical exam (including Karnofsky score) was performed at end of treatment only. Not required if an exam had been performed within 4 weeks.
- Clinic Visit: Weight and plasma samples for atovaquone levels (atovaquone patients only) (at end of therapy only).
- CD4+ Cell Count: Absolute and percent CD4+, and total lymphocyte count (end of therapy only; not required if performed within 4 weeks).
- Hematology Tests: Hemoglobin, platelet count, WBC count and neutrophil count.
- Clinical Chemistries: Creatinine, SGPT (ALT), sodium, potassium, glucose, amylase.

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Assessments After Cross-Over to Alternate Study Medication or Restart of Original Study Medication

<u>Drug Dispensing:</u>	Every 4 weeks.
<u>Clinic Visit:</u>	Weight and plasma samples for atovaquone levels (atovaquone patients only) were obtained at post cross-over weeks 4, 12 and every 12 weeks thereafter. Physical Exam was done every 12 weeks after post cross-over Week 12.
<u>Hematology Tests:</u>	Hemoglobin, platelet count, WBC count and neutrophil count at post cross-over weeks 4 and 12.
<u>Clinical Chemistries Tests:</u>	Creatinine, SGPT (ALT), sodium, potassium, glucose, amylase at post cross-over weeks 4 and 12.
<u>Adverse Events/Death:</u>	All adverse events were recorded through week 12 post cross-over. Serious adverse events and deaths were recorded to the end of the study.

Assessments for Patients Who Discontinue Study Medication, Remain on Study and Do Not Crossover

<u>Complete Physical Exam:</u>	Every 12 weeks.
<u>Serious Adverse Events:</u>	Until end of study
<u>Survival:</u>	Until end of study

Adverse Events

Medical Officer's Note: Signs and symptoms associated with HIV disease and its complications were not considered adverse events for the purposes of this study. These events were recorded on the HIV-Associated Conditions/Infections pages of the CRF.

Management of Adverse Events in the Study

Premature Discontinuation of Study Medication

Medical Officer's Note: All patients who prematurely discontinued study medication were monitored for 12 weeks per protocol. Thereafter, they had physical exams every 12 weeks and were monitored for SAEs, acute episodes of PCP and survival until the end of the study.

Data Management and Analysis

Sample Size

The primary objective of this study was the comparison of the safety and efficacy of high-dose atovaquone (1500 mg daily) and low-dose atovaquone (750 mg daily) with the standard anti-pneumocystis prophylaxis agent AP. The sample-size estimation is directed toward these parallel comparisons. If the high-dose of atovaquone and the low-dose of

atovaquone were significantly better than AP, comparison of the low-dose of atovaquone vs. the high-dose of atovaquone was to be explored. This restriction maintained an overall Type I error of approximately 0.05 (0.025 for each primary comparison).

The 18-month risk of developing PCP for patients receiving AP was estimated at 17.2%. This estimate was based on a 28% risk for patients receiving secondary prophylaxis following an episode of PCP and a 10% risk for patients receiving primary prophylaxis. With an estimated enrollment ratio of 40:60 for secondary and primary prophylaxis patients, a 17.2% breakthrough for AP patients in 18 months was predicted.

The endpoint chosen for the purpose of sample size estimation was the time to PCP breakthrough. A statistically significant fifty percent reduction in the proportion of patients with a PCP breakthrough required a minimum of 110 events (PCP breakthroughs). In estimating the sample size required to detect this difference between treatment groups, proportional hazard functions were assumed. Based on 15-month accrual and 18-month follow-up periods, 272 patients were needed in each of the three treatment groups. This sample size would provide 80 percent power at the 0.025 level and would allow for a thirty percent dropout. Accrual of patients was to continue until either 816 patients had been randomized and received study medication or until 110 events had occurred. Follow-up was to continue until 18 months had passed from the completion of the accrual period or until 110 events had occurred.

Reviewers' Note: 117 PCP events had occurred at the time the study was discontinued.

Study Endpoints

Reviewers' Note: Primary and Secondary endpoints were the same as in Study 115-211, as were the definitions of efficacy endpoints which were confirmed PCP and presumed PCP. Extrapulmonary Pneumocystis Infection was defined in the protocol as the demonstration of Pneumocystis organisms by histological techniques in tissue biopsy samples obtained from a site other than lung, in conjunction with local clinical symptoms of the infection. A presumptive diagnosis of extrapulmonary pneumocystosis was not considered a study endpoint.

Statistical Analysis

Data Analysis

Patients were stratified into three groups, based on their history of PCP, and then randomized to receive 1500 mg atovaquone once daily, 750 mg atovaquone once daily, or aerosolized pentamidine once every 4 weeks. The stratification resulted in a balanced patient population in the treatment groups. In order to avoid a compromised randomization, a minimum of twenty patients should have been enrolled by each study site. However, only 8 of 35 sites enrolled at least 20 patients.

Reviewers' Note: There were relatively few subjects in strata A and B (prior PCP <6 months or prior PCP > 6 months). Although the Applicant states that subjects in strata A and B were combined and prior PCP status (primary prophylaxis or secondary prophylaxis) was the only stratification variable used for statistical analyses, the analyses were stratified using the 3 strata. Only the subgroup analysis by PCP history combined strata A and B to form the primary prophylaxis group.

The distribution of the time to PCP breakthrough is estimated using the Kaplan-Meier product-limit survival method. Treatment differences are assessed using the log rank test with adjustments for baseline PCP history. A similar analysis for safety compares survival and PCP-free survival differences.

Reviewers' Note: This study was designed and powered to detect a 50% difference in the rate of PCP incidence between either high or low dose atovaquone and aerosolized pentamidine. If high dose atovaquone was significantly better than aerosolized pentamidine, comparisons between the low and high atovaquone doses would be explored. This, however, did not occur.

Intent to Treat Analysis

Reviewers' Note: In order to preserve the full advantages of the randomized design and to minimize the introduction of bias into the treatment comparison, primary analyses were performed using the intention to treat rule, i.e., statistical analyses included all members of a randomized group who met the entry criteria, irrespective of early failure, study medication withdrawal, or medication compliance.

Protocol Amendments

The protocol was amended twice.

Amendment 1

- increased the enrollment from 615 to 816 patients in order to shorten the follow-up time from 78 weeks to 44 weeks.
- changed the percentage of secondary prophylaxis patients from a minimum of 80% to a minimum of 85%.
- required a physical exam every 12 weeks after permanent discontinuation of original study medication.
- changed the criteria for secondary prophylaxis from prior 'confirmed' episode of PCP to 'confirmed or presumed' prior episode.

Amendment 2

- changed the duration of the study from '44 weeks beyond the last patient enrollment to '88 weeks beyond the last patient enrollment or until 110 episodes of PCP have occurred'. Duration of follow-up was extended to reflect a lower incidence rate that would result from enrollment of a higher percentage of primary prophylaxis patients.
- removed the statement about the enrollment target ratio of secondary to primary prophylaxis patients.

IV. INTEGRATED SUMMARY OF EFFICACY AND SAFETY

1. RESULTS:

Reviewers' Note: For Study 211, all cases were reviewed. No patient changes were made. Given that no patient changes were made in protocol 211, a 10% random patient selection of the data in protocol 213 was reviewed. No patient changes were made in the random selection of patients in protocol 213. Therefore, the Applicant's data was accepted.

Demographics

Reviewers' Note: In both studies, patients were predominantly white (63-80%) males (86-94% within each treatment group) with a mean age of 38 years (Table 6). They had advanced HIV disease, with a median CD4 count of 52-65/mm³ and a median Karnofsky score of 90. Toxoplasma serology tests were positive in 16% of patients in study 115-211 and 9% of patients in study 115-213. At enrollment, dapsone was being used for PCP prophylaxis by approximately 50% of patients in study 115-211, while aerosolized pentamidine was being used for PCP prophylaxis by approximately 50% of patients in study 115-213. Less than 3% of patients were using atovaquone for prophylaxis in both studies. Most patients in both studies were candidates for primary prophylaxis, with 28% and 42% of patients in studies 115-211 and 115-213, respectively, having a history of prior PCP. Baseline demographic characteristics were well balanced among treatment groups within each study.

Table 6. Baseline Values of Demographic Characteristics by Treatment Group

	Study 115-211		Study 115-213		
	Atovaquone 1500 mg/d (n=536)	Dapsone 100 mg/d (n=521)	Atovaquone 750 mg/d (n=188)	Atovaquone 1500 mg/d (n=175)	Aerosolized Pentamidine (n=186)
Mean age (yr)	38	38	37	37	36
Gender (% male)	89	86	91	90	94
Race/ethnicity (%)					
White	66	63	80	79	79
Black	21	23	9	11	10
Latino/Hispanic	12	12	—	—	—
Asian	—	—	5	2	2
Other	2	2	6	6	9
Median CD4 count (cells/mm ³)	55	65	52	55	60
Karnofsky score (median)	90	90	90	90	90
Toxoplasma seropositive (%)	16	16	10	7	9
PCP prophylaxis at baseline (%)	74	72			
Dapsone (%)	53	50	18	18	18
Aerosolized pentamidine (%)	19	21	50	51	50
Atovaquone (%)	3	2	2	1	2
Prior PCP (%)	29	28	42	44	42

Medical Officer's Note: 50% of patients were on AP at study entry. As a result, patients who were subsequently enrolled on AP may have been more likely to succeed in terms of efficacy and toxicity.

Patient Accountability

Both studies were of long duration (30-36 months) and most patients discontinued therapy before the end of the study. In study 115-211, 77% and 81% of patients in the atovaquone and dapsone arms, respectively, stopped their initially assigned therapy prematurely, principally for adverse events, inadequate response or death. In study 115-213, 69-70% of patients in the atovaquone arms and 63% of patients in the aerosolized pentamidine arm stopped their initially assigned therapy prematurely, principally for adverse events, inadequate response or withdrawn consent (Table 10).

In study 115-211, the median duration of follow-up was 24 months and 21% of patients completed the study. In study 115-213, the median duration of follow-up was 11.3 months and 41% of patients completed the study. The reasons for premature discontinuation from study are summarized in Table 7.

Table 7. Disposition of Patients

	Study 115-211		Study 115-213		
	Atovaquone 1500 mg/d (n=536)	Dapsone 100 mg/d (n=521)	Atovaquone 750 mg/d (n=188)	Atovaquone 1500 mg/d (n=175)	Aerosolized Pentamidine (n=186)
Premature discontinuation of therapy	81 ^a	77	69	71	63
Adverse event	25	26	19	24	8
Death	11	13	4	2	5
Inadequate response	18	20	21	15	15
Consent withdrawn	13	7	15	18	22
Lost to follow-up	3	2	6	6	8
Protocol violation/other	10	10	4	7	6
Premature discontinuation from study ^b	-	-	59	59	59
Adverse event	-	-	10	11	5
Death	-	-	13	8	12
Inadequate response	-	-	4	3	3
Consent withdrawn	-	-	19	20	25
Lost to follow-up	-	-	10	11	11
Protocol violation/other	-	-	4	6	4

^a Values are percentages of patients enrolled in each group.

^b Reasons for premature discontinuation from study were not collected in study 115-211.

Reviewers' Note: In study 213, the principal reason for premature discontinuation of dosing in the low-dose atovaquone group was inadequate response to therapy (21%); in the high-dose atovaquone group, adverse event (24%); in the AP group, withdrawal of

consent (22%). These three categories accounted for approximately 77% of the dosing discontinuations in all three groups.

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Duration of Therapy

In study 115-211, the median duration of initially assigned therapy was 6.6 months but varied significantly depending on whether patients were taking dapsone at the time of enrollment into the study. For patients taking dapsone at enrollment, the median duration of therapy with dapsone was 10.2 months, while for patients taking neither dapsone nor atovaquone at enrollment the median duration of therapy with dapsone was 3.0 months. The most likely explanation for this difference is that patients who were taking dapsone at enrollment were pre-selected to be able to tolerate dapsone. Thus the duration of therapy in patients taking neither dapsone nor atovaquone at enrollment is more likely to reflect the results in a population of patients newly intolerant to TMP/SMX.

In contrast to the large difference in duration of therapy with dapsone depending on prior dapsone experience, the median duration of therapy with atovaquone was similar for patients who were or were not taking dapsone at enrollment (Table 8).

In study 115-213, the median duration of treatment with low-dose and high-dose atovaquone was 6.2 and 6.0 months, respectively, and the median duration of treatment with aerosolized pentamidine was 7.8 months.

Reviewers' Note: The duration of therapy was calculated based on 28 days after the last dose for the aerosolized pentamidine group, but was based on the last day of therapy for the atovaquone and dapsone groups.

Table 8. Duration of Assigned Therapy

	Study 115-211		Study 115-213		
	Atovaquone 1500 mg/d (n=536)	Dapsone 100 mg/d (n=521)	Atovaquone 750 mg/d (n=188)	Atovaquone 1500 mg/d (n=175)	Aerosolized Pentamidine (n=186)
All enrolled patients	6.7 ^a	6.5	6.2	6.0	7.8
Patients taking dapsone at enrollment	5.9	10.2	-	-	-
Patients taking neither study drug at enrollment	7.5	3.0	-	-	-

^a Values are median duration of therapy in months. For aerosolized pentamidine, duration of therapy was calculated based on 28 days after the last dose of study drug.

Efficacy:

Statistical Reviewer's Note: In the following analyses, relative risks from the Cox proportional hazards model stratified by history of PCP at baseline are compared to Dapsone (Study 115-211) or AP (Study 115-213). Values <1 favor Atovaquone and values >1 favor the comparator. P-values are from the log rank test stratified by PCP history. Due to multiple comparisons in Study 115-213, the p-values should be compared

to an alpha level of 0.025. Thus, 95% confidence intervals about the relative risk are reported for study 115-211 and 97.5% confidence intervals are reported for Study 115-213. The PCP history strata are no prior/prior PCP for Study 115-211 and no prior PCP, prior PCP within 6 months, and PCP more than 6 months prior for Study 115-213. Even though Study 115-211 was randomized by *Toxoplasma* serology results, the analyses presented by the applicant were not stratified by this variable. Reviewer performed analyses stratified by *Toxoplasma* serology could not be performed using the datasets that were received. Rate per 100 person years is calculated as the number of events divided by the total person time in years followed. It can be interpreted as the number of incidences seen given 100 persons are followed for a year. Both studies were designed to detect a 50% reduction in the rate of PCP incidence for atovaquone versus the comparator.

Primary Efficacy Parameter: PCP

In both studies, the primary efficacy endpoint was the occurrence of confirmed or presumed/probable PCP. In intent-to-treat analyses, there were no significant differences among treatment groups in either study in the relative risk of PCP (Table 9).

Table 9. Confirmed or Presumed/Probable PCP (Intent-to-Treat Analysis)

	Study 115-211		Study 115-213		
	Atovaquone 1500 mg/d (n=536)	Dapsone 100 mg/d (n=521)	Atovaquone 750 mg/d (n=188)	Atovaquone 1500 mg/d (n=175)	Aerosolized Pentamidine (n=186)
PCP events	122	135	47	39	31
%	23%	26%	25%	22%	17%
Rate per 100 person-years	15.7	18.4	25.8	21.8	17.3
Relative risk	0.83	-	1.41	1.26	-
CI	(0.65, 1.06)		(0.84, 2.37)	(0.73, 2.17)	
p-value	0.13		0.14	0.34	

Reviewers' Note: In study 115-213, the relative risk values for both Low-Dose and High-Dose groups favor AP, but the 97.5% confidence intervals include 1 and the differences are not significant.

In patients randomized to treatment with 1500 mg atovaquone daily, the rate of PCP per 100 person-years was higher in study 115-213 (21.8) than in study 115-211 (15.7). This probably reflects the higher proportion of patients receiving secondary prophylaxis in study 115-213, since a prior episode of PCP is known to increase the rate of subsequent PCP.

There were no statistically significant treatment differences in the PCP event curves as assessed by the log rank test. Examination of the Kaplan-Meier curves showed a crossing of the treatment event curves at or about 100 to 120 days in study 115-213. Prior to 120 days, the low dose and high dose atovaquone curves were higher (more patients PCP free) than the aerosolized pentamidine curve. Following 120 days, the aerosolized pentamidine curve was higher than the two atovaquone curves.

Further examination of the data showed that within the first 120 days followed there was a similar number of PCP events (19 in the low dose atovaquone arm, 16 in the

high dose atovaquone arm, and 17 in the aerosolized pentamidine arm) but the number of censored observations differed greatly (20 in the low dose atovaquone arm, 13 in the high dose atovaquone arm, and 32 in the aerosolized pentamidine arm). Censoring is defined as the actual time until event is not observed. In the context of this study, censored individuals are those patients who for a reason stopped original treatment and no data is available after that point in time. In the AP arm, the primary reason for stopping original treatment were: consent withdrawn, followed by AE/toxicity and lost to follow-up.

Following 120 days, the number of censored observations was similar (121 in the low dose atovaquone arm and 123 in both the high dose atovaquone arm and the aerosolized pentamidine arm) and the number of PCP events differed somewhat (28 in the low dose atovaquone arm, 23 in the high dose atovaquone arm, and 14 in the aerosolized pentamidine arm).

In study 115-211, patients randomized to the dapsone arm who had CD4+ counts < 100 cells/mm³ and who were toxoplasmosis positive could also receive pyrimethamine and folinic acid. A total of 58 patients received pyrimethamine and folinic acid in addition to dapsone. Due to a suspected PCP prophylaxis effect of the pyrimethamine, the above analysis was repeated using those patients who received only dapsone. The results, presented in Table 10, are similar to the results seen when all patients randomized to receive dapsone were used in the analysis.

Table 10. Confirmed or Presumed/Probable PCP (Intent-to-Treat Analysis) Using Patients who received only Dapsone- Study 115-211

	Atovaquone 1500 mg/d (n=536)	Dapsone 100 mg/d (n=463)
PCP events	122	121
%	23%	26%
Relative Risk	0.81	-
95% CI	(0.63, 1.05)	-
p-value	0.1089	-

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Mortality

As expected in studies of long duration in patients with advanced HIV disease, overall mortality was high. In study 115-211, with a median duration of follow-up of 24 months, 42% of patients died during the study. In study 115-213, with a median duration of follow-up of 11.3 months, 19% of patients died during the study. Within each study, there were no significant differences in mortality among treatment groups (Table 11)