Table 11. Deaths (ITT)

	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)**
Deaths	232	208	42	27	36
%	43%	40%	22%	15%	19%
Rate per 100 person-years	26.2	24.2	20.2	13.2	18.2
Relative risk	1.06	–	1.12	0.75	–
CI	(0.88, 1.28)		(0.67, 1.86)	(0.43, 1.34)	
p-value	0.54		0.63	0.27	

Medical Officer's Note: Duration of follow-up could potentially account for differences in mortality between studies.

Combined Endpoint of PCP or Death

Within each study, there were no significant differences among treatment groups for the combined endpoint of PCP or death (Table 12).

Table 12. PCP or Death (ITT)

	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)**
Events	281	275	70	52	56
%	52%	53%	37%	30%	30%
Rate per 100 person-years	36.0	37.2	38.4	29.1	31.2
Relative risk	0.95	–	1.21	0.94	–
CI	(0.80, 1.12)		(0.81, 1.80)	(0.61, 1.46)	
p-value	0.51		0.30	0.76	

Efficacy Endpoints Occurring While Receiving Therapy

In both studies, patients continued to be followed after they discontinued originally assigned study drug. Primary efficacy analyses were conducted using the intent-to-treat principle and included all endpoints that occurred during the study. Although this methodology helps to minimize bias, endpoints that occur a substantial time after stopping a particular treatment have questionable importance for the evaluation of the efficacy of that therapy. Clinically, for a drug that is administered for chronic prophylaxis, it is important to know how effective the drug is while it is being taken.

In both studies, patients who had a PCP event often discontinued study medication shortly before their actual diagnosis of PCP. A strict on-therapy definition would not capture these clinically relevant cases. Therefore, "as-treated" analyses were conducted with event cut-off points of the last day of therapy or the last day of therapy plus windows of 15, 30, and 45 days. Results are presented in Table 13.

Table 13. Confirmed or Presumed/Probable PCP Occurring On-Therapy* as Percent of Total PCP (As-treated analysis)

	Last Day of Therapy Plus:			
	0 Days	15 Days	30 Days	45 Days
Study 115-211				
Atovaquone 1500 mg/d	48[a]	64	66	68
Dapsone	54	68	73	74
TOTAL	**51**	**66**	**69**	**71**
Study 115-213				
Atovaquone 750 mg/d	32	92	94	96
Atovaquone 1500 mg/d	31	74	80	80
Aerosolized Pentamidine#	16	48	94	94
TOTAL	**27**	**74**	**89**	**90**

*These numbers refer not to the last day of dosing but to the last day of therapy.
#For the AP arm, on-therapy included the 30 days following the dose.
[a]Values are percent of total PCP events that occurred within the indicated time period.

By 30 days after discontinuation of treatment, 69% of PCP episodes had been diagnosed in study 115-211 and 89% of PCP episodes had been diagnosed in study 115-213. It is likely that most of these episodes of PCP began prior to study medication discontinuation.

Medical Officer's Note: The lower percentage of PCP events in study 115-211 is consistent with the longer duration of follow-up (24 months) than in study 115-213 (11.3 months). Extending the window from 30 to 45 days had a minimal impact on the percentage of the total endpoints that were diagnosed within the window period. These results illustrate two things: 1) for a medication that is dosed monthly, such as aerosolized pentamidine, an event is more likely to occur off therapy(this is > 30 days off treatment), and 2) in the intent-to-treat analysis, the 1500 mg atovaquone group in each study contains a lower percentage of clinically-relevant PCP events. In other words, the longer one is off originally assigned treatment, it is less likely that the occurrence of the PCP was due to the effectiveness of the drug. Thus, as seen from Table 13, 20 to 30% of the PCP events that occurred in the1500 mg atovaquone group may not be "clinically" relevant in the intent-to-treat analysis. Therefore, a window of 30 days was applied in an as-treated analysis to include any PCP events that were diagnosed within 30 days of medication discontinuation (Table 14).

In study 115-211, the as-treated analysis demonstrated a trend for a lower rate of PCP in patients treated with atovaquone compared to patients treated with dapsone. While on originally assigned treatment or within 30 days of discontinuation, 15% of the patients assigned atovaquone and 19% assigned dapsone developed PCP. Results from the as-treated analysis were similar to those from the intent-to-treat analysis.

In study 115-213, the as-treated analysis showed very similar rates of PCP in patients treated with aerosolized pentamidine or high-dose atovaquone, and a trend towards higher rates of PCP in patients treated with low-dose atovaquone. Results from the as-treated analysis showed less difference between high-dose atovaquone and aerosolized pentamidine than was suggested by the intent-to-treat analysis.

Table 14. Confirmed or Presumed/Probable PCP Within 30 Days of Last Dose (As-Treated Analysis)

	Study 115-211		Study 115-213		
	Atovaquone 1500 mg/d (n=527)	**Dapsone 100 mg/d (n=510)**	**Atovaquone 750 mg/d (n=188)**	**Atovaquone 1500 mg/d (n=172)**	**Aerosolized Pentamidine (n=169)**
PCP events	80	98	44	31	29
%	15%	19%	23%	18%	17%
Rate per 100 person-years	16.5	20.5	29.5	22.4	18.6
Relative risk	0.77	–	1.47	1.14	–
CI	(0.57, 1.04)		(0.86, 2.50)	(0.63, 2.06)	
p-value	0.08		0.11	0.62	

As was done in the ITT analysis, the above analysis was repeated excluding those patients who received pyrimethamine and folinic acid in addition to dapsone for study 115-211. Again, the results are similar to those seen when all patients who received dapsone were analyzed (Table 15).

Table 15. Confirmed or Presumed/Probable PCP (As-Treated Analysis) Using Patients who received only Dapsone- Study 115-211

	Atovaquone 1500 mg/d (n=527)	**Dapsone 100 mg/d (n=453)**
PCP events	80	87
%	15%	19%
Relative Risk	0.76	
95% CI	(0.56, 1.03)	
p-value	0.0777	

Confirmed Episodes of PCP

Investigators were encouraged to obtain confirmation of all episodes of PCP. Two hundred four of 257 (79%) PCP endpoints in study 115-211 and 86 of 117 (74%) PCP endpoints in study 115-213 were confirmed. Results of intent-to-treat analyses and as-treated analyses of confirmed PCP endpoints are presented in Table 16 and 17, respectively.

Table 16. Confirmed PCP (ITT)

	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	93	111	30	35	21
%	17%	21%	16%	20%	11%
Rate per 100 person-years	11.6	14.6	15.9	19.4	11.4
Relative risk	0.76	–	1.32	1.74	–
CI	(0.58, 1.001)		(0.70, 2.50)	(0.93, 3.25)	
p-value	0.05		0.33	0.04	

Table 17. Confirmed PCP Within 30 Days of Last Dose (As-Treated 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=172)**	**Aerosolized Pentamidine (n=169)**
PCP events	NA[a]	NA	28	28	19
%			15%	16%	11%
Rate per 100 person-years			18.6	20.2	12.2
Relative risk	NA	–	1.40	1.59	–
CI			(0.72, 2.74)	(0.81, 3.11)	
p-value			0.25	0.12	

[a] NA = not analyzed.

In study 115-211, there was a strong trend (p=0.05) towards a lower rate of confirmed PCP in patients treated with atovaquone compared to patients treated with dapsone. These results are consistent with the results for all PCP endpoints (confirmed and probable) in this study.

In study 115-213, there was a strong trend (p=0.04)in the ITT analysis towards a higher rate of confirmed PCP in patients treated with high-dose atovaquone compared to patients treated with aerosolized pentamidine. The applicant suggests that this result must be viewed with caution, however, because in both the intent-to-treat and as-treated analyses of all PCP endpoints (confirmed and presumed), comparisons between low-dose atovaquone and high-dose atovaquone were in favor of high-dose atovaquone.

Statistical Reviewer's Note: The above mentioned p-values need to be interpreted with caution. Confirmed PCP is a secondary endpoint.. Additionally, the p-values for study 115-213 should be compared to an alpha level of 0.025 at the most.

Medical Officer's Note: Also, since confirmation of PCP was not a requirement, there was the potential for differences among treatment groups with regard to the diligence with which confirmation was pursued, and the results indicate a potential bias may exist with regard to confirmed endpoints. In study 115-213, 90% of the PCP endpoints in the

high-dose atovaquone group were confirmed while in the low-dose atovaquone and aerosolized pentamidine groups only 64% and 68%, respectively, were confirmed. This difference in percentages in confirmed endpoints is the strongest reason for looking at the comparison between high-dose atovaquone and other groups with caution. Unfortunately, data on attempts at confirmation of a PCP event were not captured in this study. However, when confirmed PCP endpoints that occurred on therapy or within 30 days of discontinuation were analyzed using the as-treated methodology, the difference between High-Dose and AP was not significant (p=0.12).

Subgroup Analysis by Prior PCP History

Reviewers' Note: Primary and secondary prophylaxis patients were expected to have different levels of risk for development of PCP. Therefore, patients were stratified at entry based on their history of PCP. For Study 115-213, the strata, last PCP within 6 months and last episode more than 6 months, were combined and considered as secondary prophylaxis. The studies were not powered to detect treatment differences within strata. However, descriptive statements can be made.

The incidence of PCP in the primary prophylaxis group was 20% in study 115-211 and 13% in study 115-213 (Table 18). As expected, the incidence of PCP was higher in the secondary prophylaxis group (37% in study 115-211 and 33% in study 115-213). There were no significant differences among treatment arms, and the relative risks in each subgroup were consistent with the relative risks in the entire population.

Table 18. Endpoint Comparison by PCP History: PCP (ITT)

	Study 115-211		Study 115-213		
	Atovaquone 1500 mg/d	**Dapsone 100 mg/d**	**Atovaquone 750 mg/d**	**Atovaquone 1500 mg/d**	**Aerosolized Pentamidine**
Primary Prophylaxis					
PCP events/N	67/382	81/377	15/109	16/102	10/107
%	18%	21%	14%	16%	9%
Rate per 100 person-years	11.2	14.1	12.7	13.7	8.8
Relative risk	0.80	–	1.46	1.57	–
CI	(0.58, 1.10)		(0.58, 3.64)	(0.64, 3.89)	
p-value	0.17		0.35	0.26	
Secondary Prophylaxis					
PCP events/N	55/154	54/144	32/79	23/73	21/79
%	36%	38%	41%	32%	27%
Rate per 100 person-years	29.9	34.1	49.5	36.8	31.9
Relative risk	0.87	–	1.39	1.11	–
CI	(0.60, 1.27)		(0.74, 2.61)	(0.56, 2.20)	
p-value	0.47		0.24	0.74	

Mortality in the primary and secondary prophylaxis groups was 36% and 57%, respectively, in study 115-211 and 13% and 27%, respectively, in study 115-213 (Table 19). There were no significant differences among treatment arms.

Medical Officer's Note: The higher mortality rates in study 115-211 are consistent with the longer duration of follow-up in that study. Median CD4 lymphocyte counts were similar in the two studies.

Table 19. Endpoint Comparison by PCP History: Mortality

	Study 115-211		Study 115-213		
	Atovaquone 1500 mg/d	**Dapsone 100 mg/d**	**Atovaquone 750 mg/d**	**Atovaquone 1500 mg/d**	**Aerosolized Pentamidine**
Primary Prophylaxis					
Deaths/N	150/382	121/377	19/109	8/102	15/107
%	39%	32%	17%	8%	14%
Rate per 100 person-years	23.2	18.6	15.0	6.3	12.6
Relative risk	1.24	–	1.19	0.50	–
CI	(0.98, 1.58)		(0.55, 2.58)	(0.19, 1.34)	
p-value	0.07		0.62	0.11	
Secondary Prophylaxis					
Deaths/N	82/154	87/144	23/79	19/73	21/79
%	53%	60%	29%	26%	27%
Rate per 100 person-years	34.3	41.3	28.1	24.8	26.6
Relative risk	0.82	–	1.07	0.95	–
CI	(0.61, 1.11)		(0.54, 2.10)	(0.46, 1.93)	
p-value	0.20		0.83	0.86	

Subgroup Analysis by Baseline Prophylaxis

In study 115-211, 3% of patients were receiving atovaquone and 52% of patients were receiving dapsone at the time of enrollment into the study. Intolerance to either of the study drugs was an exclusion criterion, and thus patients receiving one of these drugs for PCP prophylaxis at enrollment had been pre-selected as being able to tolerate this therapy. This is supported by the observation that the median duration of treatment with dapsone was much longer in patients taking dapsone at enrollment (10.2 months) than in patients who were taking neither dapsone nor atovaquone at enrollment (3.0 months). Although failure of prophylaxis with one of the study drugs was not an exclusion criterion, prophylaxis is often changed when patients develop PCP while on a given prophylactic agent.

Medical Officer's Note: Use of one of the study drugs at enrollment might also pre-select for patients who had not failed prophylaxis with that drug, and efficacy analyses that included such patients might be biased.

As seen in Table 20, if dapsone was given prior to study entry, PCP events occurred with increased incidence as compared with no baseline dapsone or atovaquone given for those in the atovaquone arm. In the subgroup of patients who were taking dapsone at enrollment, PCP endpoints occurred with similar frequency in patients randomized to receive either dapsone or atovaquone. However, in patients receiving neither dapsone nor atovaquone at baseline, significantly fewer patients randomized to atovaquone developed PCP.

There were no significant differences in mortality between treatment arms within the subgroups of patients who were taking dapsone at enrollment or taking neither study drug at enrollment (Table 20).

Table 20. Endpoint Comparison by Prior Prophylaxis with Dapsone (Study 115-211)

	PCP (ITT)		PCP (As-treated)		Deaths	
	Atovaquone 1500 mg/d	Dapsone 100mg/d	Atovaquone 1500 mg/d	Dapsone 100mg/d	Atovaquone 1500 mg/d	Dapsone 100mg/d
Dapsone at Entry						
Events/N % Rate per 100 person-years	76/285 27% 18.5	68/261 26% 19.5	47/279 17% 18.7	63/254 25% 22.4	123/285 43% 25.7	112/261 43% 26.7
Relative Risk (95% CI) p-value	0.95 (0.69, 1.31) 0.74	–	0.80 (0.55, 1.17) 0.25	–	0.95 (0.74, 1.23) 0.70	–
Neither Dapsone nor Atovaquone at Entry						
Events/N % Rate per 100 person-years	41/238 17% 11.7	63/249 25% 17.0	29/235 12% 13.1	32/246 13% 17.2	105/238 44% 27.3	91/249 37% 21.5
Relative Risk (95% CI) p-value	0.67 (0.45, 0.99) 0.04	–	0.71 (0.43, 1.18) 0.19	–	1.25 (0.94, 1.66) 0.12	–

Medical Officer's Note: The results in patients taking neither dapsone nor atovaquone at enrollment are probably more representative of the results that would be expected in patients newly intolerant to TMP/SMX. The number of patients taking atovaquone at enrollment was too small for meaningful analysis of that subgroup.

Similar analyses were performed for study 115-213, in which 50% of patients were receiving aerosolized pentamidine and 2% of patients were taking atovaquone at the time of enrollment into the study. There were no significant differences among treatment arms for either PCP endpoints or mortality within the subgroups of patients who were taking aerosolized pentamidine at enrollment or were taking neither study drug at enrollment. However, there was a trend suggesting more effective prophylaxis with aerosolized pentamidine in patients who were taking aerosolized pentamidine at enrollment (Table 21). This is consistent with the hypothesis that patients taking aerosolized pentamidine at enrollment were pre-selected for a good efficacy outcome compared to treatment-naive patients. This was not the case for mortality, where there was a survival trend in favor of the high-dose atovaquone group in patients taking aerosolized pentamidine at enrollment.

Table 21. Endpoint Comparison by Prior Prophylaxis with Aerosolized Pentamidine (Study 115-213)

	PCP			Deaths		
	Atovaquone 750 mg/d	**Atovaquone 1500 mg/d**	**Aerosolized Pentamidine**	**Atovaquone 750 mg/d**	**Atovaquone 1500 mg/d**	**Aerosolized Pentamidine**
Aerosolized Pentamidine at Entry						
Events/N	26/94	24/89	15/93	22/94	12/89	22/93
%	28%	27%	16%	23%	13%	24%
Rate per 100 person-years	27.8	23.3	14.7	20.2	9.9	19.8
Relative risk	1.68	1.77	–	1.03	0.53	–
97.5% CI	(0.81, 3.50)	(0.83, 3.76)		(0.52, 2.04)	(0.23, 1.21)	
p-value	0.11	0.09		0.92	0.08	
Neither Aerosolized Pentamidine nor Atovaquone at Entry						
Events/N	21/90	15/85	16/89	20/90	15/85	13/89
%	23%	18%	18%	22%	18%	15%
Rate per 100 person-years	25.0	19.9	21.9	21.2	18.3	15.8
Relative risk	1.20	0.81	–	1.26	1.16	–
97.5% CI	(0.57, 2.51)	(0.36, 1.83)		(0.55, 2.87)	(0.49, 2.74)	
p-value	0.59	0.56		0.53	0.70	

Subgroup Analysis by Age, Race and Gender

There were too few subjects >65 years of age in either study for a meaningful analysis in elderly patients.

In study 115-211, PCP during or within 30 days of stopping originally assigned treatment occurred more commonly in white patients (129/679=19%) than in black patients (30/231=13%). Among white patients, the rate of PCP was significantly lower for patients treated with atovaquone than for those treated with dapsone. Among black patients there was no significant difference between treatment groups (Table 22). There were no significant differences between the treatment groups for mortality in either white or black patients.

Table 22. Endpoint Comparison by Race (Study 115-211, As-treated)

	PCP		Deaths	
	Atovaquone 1500 mg/d	**Dapsone 100 mg/d**	**Atovaquone 1500 mg/d**	**Dapsone 100 mg/d**
White				
Events/N % Rate per 100 person-years	53/352 15% 16	76/327 23% 25	147/352 42% 25	126/327 39% 23
Relative risk 95% CI p-value	0.61 (0.43, 0.86) 0.005	–	1.03 (0.81, 1.31) 0.79	–
Black				
Events/N % Rate per 100 person-years	16/110 15% 18	14/121 12% 12	56/110 51% 34	52/121 43% 26
Relative risk 95% CI p-value	1.50 (0.73, 3.07) 0.27	–	1.33 (0.91, 1.94) 0.14	–

Similar analyses were not performed for study 115-213 because of the small number of black patients.

In study 115-211, PCP during or within 30 days of stopping originally assigned treatment occurred with similar frequency in male patients (160/926=17%) and female patients (21/131=16%). Among male patients, the rate of PCP was significantly lower for patients treated with atovaquone than for those treated with dapsone. Among female patients there was no significant difference between treatment groups (Table 23). There were no significant differences between the treatment groups for mortality in either male or female patients.

Table 23. Endpoint Comparison by Gender (Study 115-211, As-treated)

	PCP	
	Atovaquone 1500 mg/d	**Dapsone 100 mg/d**
Male		
Events/N % Rate per 100 person-years	71/476 15% 17	89/450 20% 22
Relative risk 95% CI p-value	0.72 (0.53, 0.99) 0.04	–
Female		
Events/N % Rate per 100 person-years	9/60 15% 16	12/71 17% 17
Relative risk 95% CI p-value	0.93 (0.39, 2.22) 0.87	–

Similar analyses were not performed for study 115-213 because of the small number of female patients.

Toxoplasmosis

There were 170 patients in Study 115-211 who had a positive *Toxoplasma* serology at baseline. A total of eight patients (four treated with atovaquone and four treated with dapsone plus pyrimethamine and folinic acid) developed toxoplasmosis during or within 30 days of stopping initially assigned therapy (Table 24).

There were 49 patients in Study 115-213 who had a positive *Toxoplasma* serology at baseline. A total of six patients (three treated with low-dose atovaquone, three treated with aerosolized pentamidine and none treated with high-dose atovaquone) developed toxoplasmosis during or within 30 days of stopping initially assigned therapy (Table 25).

Table 24. Toxoplasmosis Endpoints (As-treated)

	Study 115-211		Study 115-213		
	Atovaquone 1500 mg/d (n=527)	Dapsone 100 mg/d (n=510)	Atovaquone 750 mg/d (n=188)	Atovaquone 1500 mg/d (n=172)	Aerosolized Pentamidine (n=169)
Toxoplasmosis events	4	4	3	0	3
%	0.8%	0.8%	1.6%		1.8%
Rate per 100 person-years	0.82	0.82	2.0		1.9
Relative risk	0.96	–	0.99	nc[a]	–
CI	(0.24, 3.85)		(0.16, 6.16)	nc	
p-value	0.96		0.99	0.11	

[a] nc = not calculable

Medical Officer's Note: The number of cases of toxoplasmosis is too small to draw definitive conclusions about relative efficacy of these therapies.

PCP Endpoints and Gastrointestinal Adverse Events

During a previous study of atovaquone for treatment of PCP, a correlation was found between the presence of diarrhea at baseline and a poor response to therapy and higher mortality. While this correlation was not evident in a second treatment study, concern remains about the possible correlation of gastrointestinal symptomatology with absorption, and therefore effectiveness, of atovaquone. The Applicant therefore compared the incidence of PCP in patients who reported at least one episode of nausea, vomiting, or diarrhea during the study with the incidence in patients who reported no such adverse events. Data are summarized below in Table 25.

Table 25. Effect of Gastrointestinal Symptoms on Incidence of PCP

	Atovaquone 750 mg/day N (%)	Atovaquone 1500 mg/day N (%)	Aerosolized Pentamidine N (%)
Absence of GI Symptoms[a]			
PCP events	18 (26)	10 (13)	11 (15)
Rate per 100 person-years	51.9	21.5	22.7
p-value	0.12	0.90	
Presence of GI Symptoms[b]			
PCP	26 (22)	21 (22)	18 (19)
Rate per 100 person-years	22.7	22.9	16.8
p-value	0.34	0.50	

Includes only events that occurred during or within 30 days of discontinuation of assigned medication.
[a]Numbers per group = 69, 78 and 74 respectively.
[b]Numbers per group = 119, 94 and 95 respectively.

Patients in the High-Dose and AP groups who experienced nausea, vomiting, or diarrhea during the study had a higher incidence of PCP while patients in the Low-Dose group had a lower incidence when compared to patients who did not experience nausea, vomiting, or diarrhea in the corresponding treatment group. In neither case were there significant differences between AP and either atovaquone group. The Applicant speculates that both the higher incidence of PCP in the AP group, where gastrointestinal absorption is not relevant, and the lower incidence of PCP in the Low-Dose patients with gastrointestinal symptoms, argue that the difference seen in the High-Dose group is unlikely to be related to gastrointestinal symptomatology.

Medical Officer's Note: There is, however, a trend in high dose Atovaquone group for higher incidence of PCP with gastro-intestinal illness.

ACTG 227- Phase I, multiple dose, dose-escalation, safety, tolerability, and pharmacokinetic study

ACTG 227 was a Phase I, multiple dose, dose-escalation, safety, tolerability, and pharmacokinetic study of MEPRON (atovaquone) Suspension in HIV-infected infants and children. Adult PCP patients with a $C_{avg,ss}$ greater than 15 μg/mL have a 95% or better chance of being successfully treated. The objective of the present study was to identify the dose of MEPRON Suspension that was capable of producing $C_{avg,ss}$ >15μg/mL in infants and children.

Subjects were stratified by age (1 to 3 months, 3 to 24 months, and 2 to 12 years) and MEPRON Suspension was administered at a dose of 10, 30, or 45 mg/kg body weight once daily for 12 days. Because atovaquone absorption is enhanced by food, subjects were to take their doses with food or formula. Concentrations of atovaquone in plasma were obtained before dosing on days 1, 3, 5, 7, 9, and 12 and at regular intervals up to 288 hours after the last dose. Steady-state pharmacokinetic parameters were estimated from

plasma concentrations obtained on the last day of dosing using non-compartmental methods.

MEPRON Suspension was well tolerated by all study subjects.

The results from this study demonstrate that $C_{avg,ss}$ greater than 15 μg/mL can be achieved with a dose of 30 mg/kg in infants 1 to 3 months of age and in children 2 to 12 years of age. This dose was not adequate to achieve these levels in children 3 to 24 months of age. In this group, a dose of 45 mg/kg was necessary.

A target concentration of atovaquone has not yet been established for PCP prophylaxis, but the recommended total daily dose of atovaquone suspension in adults will be the same for prophylaxis (1500 mg once daily) and treatment (750 mg twice daily).

Medical Officer's Comment: *Dosing recommendations are not appropriate, based on the pharmacokinetic data collected in pediatric patients. The doses recommended by the applicant did not result in atovaquone $C_{avg,ss}$ values between 15-25 mcg/mL. No safety and efficacy data has been submitted to date in children. Please refer to the pharmacokinetic review for further details regarding ACTG 227.*

Summary and Conclusions Regarding Efficacy

The most effective agent for prevention of PCP is TMP/SMX; however, it is associated with a high rate of adverse events, often necessitating the use of alternative agents. Several agents have been used in this setting including aerosolized pentamidine, dapsone, dapsone/pyrimethamine and primaquine/clindamycin. Desensitization to TMP/SMX and gradual escalation of the dose, lower doses or less frequent dosing with TMP/SMX have also been used. Atovaquone is an effective agent for the treatment of mild to moderate PCP. However, prior to the studies reported here, there had been no study to evaluate the efficacy and safety of atovaquone for PCP prophylaxis.

Study 115-211 was the first large clinical study to compare two systemic agents in a population at risk for PCP and with a history of T/S intolerance. This study was also the first to evaluate the efficacy and safety of atovaquone for the prevention of PCP and to assess the efficacy of dapsone among a significant number of patients receiving secondary prophylaxis.

Study 115-211 demonstrated that patients assigned prophylaxis with either atovaquone or dapsone had similar rates of confirmed or probable PCP and survival. There were trends favoring atovaquone when the analysis was restricted to confirmed PCP episodes(Table 17), for an on-treatment analysis of confirmed or probable PCP(Table 16), and for the subgroup of patients who were not receiving either study drug at baseline.(Table 22,23)

Medical Officer's Note: *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 statistically significant, and 2) PCP event rates decreased greatly after study drug discontinuation. Possible reasons for the latter observation include better antiretroviral treatment, use of macrolides for Mycobacterium avium complex 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 subgroup analyses 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.

Study 115-213 was designed to enroll 816 patients during 15 months. However, the accrual period had not been complete at 30 months and the study drop-out rate was higher than anticipated (50% vs 30%). The study was stopped by Glaxo because, in their opinion, the original study objective would never be realized. As an alternative to full enrollment and completion of follow-up, the study was powered to detect a 50% reduction in PCP following the occurrence of 110 PCP endpoints, and 117 PCP endpoints were observed. The difference in efficacy between the most and least effective therapies (aerosolized pentamidine and low-dose atovaquone, respectively) was small in magnitude and not statistically significant (p=0.14). However relative risk ranged from .63 to 2.06 in the As-treated analysis for confirmed or presumed/probable PCP.

The overall percentages of the various efficacy endpoints from studies 115-211 and 115-213 are summarized in Table 26. Taken as a whole, these data provide evidence of the effectiveness of atovaquone suspension for prevention of PCP.

Table 26. Overall Comparisons of Efficacy Endpoints

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[a]	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[b]	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

a Values are percentages of patients enrolled in each group.

b NA = not analyzed

Dose Justification for Adolescents and Adults

Study 115-213 evaluated two doses of atovaquone (750 mg once daily and 1500 mg once daily) for prophylaxis of PCP. There were no significant differences for any efficacy endpoint between patients treated with either dose of atovaquone compared to

aerosolized pentamidine. However, there was a generally consistent trend for efficacy endpoints to occur more frequently in patients treated with 750 mg atovaquone daily than in patients treated with 1500 mg atovaquone daily (Table 26).

Medical Officer's Note: This trend was most striking for PCP during or shortly after treatment and for mortality, which are the two most clinically relevant endpoints. PCP occurred during or within 30 days of discontinuing initially assigned study drug in 18% of patients in the high-dose atovaquone group and 23% of patients in the low-dose atovaquone group. The overall mortality rate was 15% in patients randomized to the high-dose atovaquone group and 22% in patients randomized to the low-dose atovaquone group.

Safety Summary -General Safety Conclusions

Atovaquone has been marketed since 1992 for the treatment of PCP. The tablet formulation was approved initially, at a dose of 750 mg three times daily for 21 days. The suspension formulation, which has oral bioavailability approximately twice that of the tablet formulation, was approved in 1995 at dose of 750 mg twice daily for 21 days. Both the tablet and suspension formulations have been generally safe and well tolerated at these doses. Data from studies 115-211 and 115-213 provide important additional information on the long-term safety of prolonged administration of atovaquone suspension at a dose of 1500 mg once daily. Results of safety analyses are described in detail in the sponsor's Integrated Summary of Safety and are summarized below.

Extent of Exposure

The median duration of exposure to atovaquone was 7.1 months in study 115-211 and 6.0-6.2 months in study 115-213. In the two studies combined, there were 708 patients treated with 1500 mg atovaquone daily, of whom 378 were treated for >6 months and 238 were treated for >1 year (Table 27).

Table 27. Study Drug Exposure

	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)**
Median duration of therapy (months)	7.2	7.3	6.2	6.0	7.8
Time on therapy (N, %)					
<=3 months	170 (32%)	175 (34%)	53 (28%)	49 (28%)	50 (27%)
3 to <= 6 months	77 (14%)	58 (11%)	39 (21%)	38 (22%)	27 (15%)
6 to <= 9 months	48 (9%)	54 (10%)	24 (13%)	24 (14%)	26 (14%)
9 to <= 12 months	45 (8%)	37 (7%)	14 (7%)	20 (11%)	14 (8%)
>12 months	196 (36%)	197 (38%)	58 (31%)	44 (25%)	69 (37%)

(Note that for study 115-211, the duration of exposure in the analysis of safety is different from the duration of exposure in the analysis of efficacy. For the safety analysis in study 115-211, duration of exposure was calculated from the date of randomization to

the date of permanent discontinuation of originally assigned treatment, ignoring temporary interruptions of study drug for treatment of acute episodes of PCP or other reasons. For the efficacy analysis in study 115-211, and for both the safety and efficacy analyses in study 115-213, duration of exposure was calculated from the date of randomization to the date of a study endpoint (PCP or death) or date of permanent discontinuation of originally assigned treatment.)

Summary of Adverse Events

All Adverse Events

Reviewers' Note: In study 115-211, only treatment-limiting adverse events that were at least possibly attributable to study drug were reported. In contrast, all adverse events were reported in study 115-213. Thus information about the overall adverse event profile is based on results of study 115-213.

In study 115-213, subjects were questioned about possible adverse events at clinical assessments that took place during screening, at weeks 4 and 12, and every 12 weeks thereafter until the study was completed. All adverse events that occurred while the subjects received study medication or within 12 weeks of discontinuing study medication were recorded on the case report forms with the investigator's assessment of intensity, seriousness and attributability to study medication. Beginning 12 weeks after permanent discontinuation of study drug, only adverse events considered serious were collected.

Medical Officer's Note: Signs and symptoms associated with HIV disease(ex. AIDS defining illnesses etc.) and its complications were not considered adverse events for the purposes of the study.

All available adverse event data for all randomized patients that had a date of onset during treatment or within 30 days after permanent discontinuation of originally assigned study drug are included in the following analyses.

Medical Officer's Note: As expected in a long-term study in patients with advanced HIV disease, most patients reported at least one adverse event. Adverse events were reported more frequently among the two atovaquone groups (96% and 98%) than in the aerosolized pentamidine group (89%). Frequent adverse events, reported by >15% of patients in any treatment arm, included diarrhea, rash, asthenia, increased cough, fever, headache, nausea, abdominal pain, infection, dyspnea, rhinitis, vomiting, sweating, dizziness and anorexia (Table 28). Less frequent adverse events, reported by 10-14% of patients in any treatment arm, included pruritus, pain, insomnia, sinusitis, flu syndrome, chest pain, depression, pharyngitis, myalgia, anemia, peripheral neuritis, pneumonia, bronchitis, acne and bronchospasm.

Table 28. Frequent Adverse Events in Study 115-213

Event	Atovaquone 750 mg/day (n = 188)	Atovaquone 1500 mg/day (n = 175)	Aerosolized Pentamidine (n = 186)
Diarrhea	42[a]	42	35
Rash	46[b]	39	28
Asthenia	31	22	31
Cough increased	25	25	31
Fever	31[b]	25	18
Headache	31	28	22
Nausea	32	26	23
Abdominal pain	21	20	20
Infection	18	22	19
Dyspnea	21	15	16
Rhinitis	18	24	17
Vomiting	22	15	11
Sweating	16	15	13
Arthralgia	13	9	9
Pruritus	12	10	8
Dizziness	15	9	8
Anorexia	15	9	8
Pain	9	13	11
Insomnia	13	10	13
Sinusitis	11	13	11
Flu syndrome	10	14	10
Chest pain	12	9	12
Depression	12	10	8
Pharyngitis	9	9	12
Myalgia	12	10	5
Anemia	13[b]	7	4
Peripheral neuritis	8	6	11
Pneumonia	7	7	10
Bronchitis	6	7	10
Acne	6	5	11
Bronchospasm	2[b]	4[b]	11
At Least One Event	96	98	89

a Values are percentages of patients enrolled in each group.

b $p<0.025$ for comparison with aerosolized pentamidine.

Medical Officer's Note: Details regarding extent, type, and temporal sequence of rashes has not been provided neither in the data files nor the CRF.

The rates of frequent adverse events in the two atovaquone arms were generally comparable to the rates in the aerosolized pentamidine arm, with the exception of rash which was reported by significantly more low-dose atovaquone recipients (46%) than aerosolized pentamidine recipients (28%) ($p<0.025$). Additional differences that were statistically significant compared to the aerosolized pentamidine arm were fever, vomiting and anemia, which occurred significantly more often in the low-dose

atovaquone recipients but not in the high-dose atovaquone recipients. Given the lack of an appropriate dose-response effect, it is unlikely that these statistically significant differences are clinically meaningful.

Bronchospasm is a well-known side effect of aerosolized pentamidine. The incidence of bronchospasm was 11% in the aerosolized pentamidine arm compared to 2% and 4% in the low-dose and high-dose atovaquone arms ($p<0.001$ and $p=0.016$, respectively).

Frequent Adverse Events by Age

Patients> 65 years old comprised only 0.4% of the total study population. Thus, a separate analysis to evaluate elderly patients was not performed. However an age-related analysis dividing the population into two groups, above and below the median age of 37 years, was performed for common adverse events. The adverse event profile was similar in these two age groups.

Frequent Adverse Events by Gender

Females comprised only 10.3 % of the total population, and thus the power to detect differences based on gender is limited. There were no statistically significant differences among the treatment groups for any adverse event among female subjects. Headache was the most frequently reported adverse event and occurred more frequently in females (44%) than in males (25%). Arthralgia was also reported more frequent by females (27%) than males (9%). Otherwise the adverse event profile was similar for patients of either gender.

Frequent Adverse Events by Race

Information on racial categories was not recorded in a consistent manner in the two studies. Whites totaled 69.4% of the total population. All other racial categories were combined as a non-white group for analysis of potential racial differences in safety. In general, the adverse event rates were lower in the non-white population. The only statistically significant differences among the treatment arms in the non-white population was in the category 'sweating' where there were no reports in the aerosolized pentamidine group and 16% and 14% in the low-dose and high-dose atovaquone groups ($p=0.03$ and $p=0.026$, respectively).

Serious Adverse Events

A serious adverse event (SAE) was defined as an adverse event, regardless of attributability to study medication, that was life-threatening, fatal, permanently or significantly disabling, required or extended hospitalization, caused congenital anomaly or malignancy, or otherwise constituted a significant hazard to the subject. Overdose was always considered serious. In study 115-213, all serious adverse events were reported, with the exception of signs and symptoms associated with HIV disease and its complications. In study 115-211, only adverse events that resulted in permanent discontinuation of treatment were reported, and serious adverse events were not reported systematically.

In study 115-213, the incidence of adverse events considered by the investigator to be serious was similar in the three treatment groups. Serious adverse events during therapy or within 30 days of discontinuation were reported in 114 patients (43 in the low-dose atovaquone group, 36 in the high-dose atovaquone group and 35 in the aerosolized pentamidine group). Pneumonia was the most frequently reported serious adverse event in each group; none were considered related to study drug. Of the two most frequently reported adverse events (rash and diarrhea), only six were considered serious: two patients with rash (one in each of the atovaquone groups) and four patients with diarrhea (three in the low-dose atovaquone group and one in the aerosolized pentamidine group). Serious adverse events reported by more than 2% of patients are summarized in Table 29.

Table 29. Serious Adverse Events in Study 115-213

Treatment	Number of Patients with Any SAE	Frequently Reported SAEs (%)	SAEs Considered Related to Treatment
Low-dose atovaquone (n=188)	43	pneumonia (3) cellulitis (3) abdominal pain (3) fever (2) infection (2) diarrhea (2) vomiting (2) anemia (2)	3 Patients •rash, vomiting & fever •diarrhea, colitis & CMV •pancreatitis
High-dose atovaquone (n=175)	36	pneumonia (5) convulsions (2) cough (2)	3 Patients •elevated liver enzymes •abdominal distention •rash
Aerosolized pentamidine (n=186)	35	pneumonia (4) fever (2) sepsis (2) anemia (2)	None

Medical Officer's Note: No serious adverse events in the aerosolized pentamidine group were considered to be related to study medication. Drug association of the adverse events were only described in relation to SAEs and not as a separate category. Three patients in each atovaquone group experienced serious adverse events that were considered related to study medication. These are described by the sponsor as follows:

Serious Adverse Events Related to Study Drug:

- Pt 02303: Within 3 weeks of starting prophylaxis with atovaquone (750 mg daily) the patient exhibited a diffuse rash, vomiting, pruritus, darkening of urine, chills, sweats, fever, and elevated liver function tests. He discontinued atovaquone and his condition improved. He had no history of liver disease and had negative serologies for hepatitis A, B, and C.
- Pt 03303: The patient began treatment with atovaquone (750 mg daily) on 1 November 1994. In January of 1996 (~430 days on therapy) the patient experienced the first episode of severe pancreatitis. Following subsequent episodes of pancreatitis, atovaquone was permanently discontinued in July of 1996.

Medical Officer's Note: No further details are provided.

- Pt 11203: Approximately 2 weeks after beginning atovaquone prophylaxis (750 mg daily) the patient experienced onset of diarrhea. Stool culture was negative for bacterial pathogens, but positive for fungi. Fluconazole was ineffective. Proctoscopic exam demonstrated pseudomembranous colitis and stool sample was positive for *C. difficile* toxin. Metronidazole and loperamide were ineffective, but vancomycin and cholestryramine provided improvement. Diarrhea again worsened and atovaquone was discontinued. An IND Safety Report was filed for this adverse event. Three weeks later the patient continued to experience moderate diarrhea, weight loss, and physical and mental deterioration. Biopsy revealed non-specific colitis. The patient died 1 week later due to renal failure and hyperkalemia secondary to CMV colitis. It was the investigator's opinion these later events are unlikely to be related to the use of study medication.
- Pt 02205: Approximately 2 months after starting atovaquone therapy (1500 mg daily) the patient was admitted with fulminant hepatitis, increasing liver enzymes, increasing prothrombin time and elevated bilirubin. Atovaquone, which was felt to be a possible cause, was discontinued. Hepatitis A serology was reactive but IgM was negative. Hepatitis B antibody was positive and hepatitis B antigen was negative. Hepatitis C and D were non-reactive. *C. difficile* was isolated from stool and the patient was successfully treated with metronidazole. The patient died 7 months later of wasting syndrome
- Pt 07201: Approximately 3.5 months after starting atovaquone prophylaxis (1500 mg daily) the patient experienced abdominal distention and obstipated bowel. Megestrol and lamivudine were discontinued with no improvement in distention. The patient discontinued atovaquone and his condition improved. The investigator felt the events could have been caused by one or more of the patient's medications, including atovaquone.
- Pt 32303: Approximately 9 months after starting atovaquone prophylaxis (1500 mg daily), the patient was hospitalized with a diffuse, erythematous rash. Atovaquone was discontinued and the patient was treated with diphenhydramine, hydroxyzine, amytriptyline, acyclovir and oxacillin, with gradual improvement. It was unclear in the investigator's judgment whether the rash was caused by atovaquone or herpes infection.

Adverse Events Requiring Discontinuation (Treatment-Limiting)

Treatment-limiting adverse events were defined as any adverse event that resulted in permanent discontinuation of study medication. For study 115-211, only treatment-limiting events that were at least possibly related to study medication were reported. For study 115-213, all treatment-limiting events were reported.

In study 115-211, adverse events necessitating discontinuation of originally assigned treatment occurred in 24% of patients assigned to treatment with atovaquone and 26% of patients assigned to treatment with dapsone. Although the overall frequency of treatment-limiting adverse events was similar, the nature of the treatment-limiting events differed between the two treatment arms. Patients treated with atovaquone were more likely to have a gastrointestinal event (nausea, vomiting, diarrhea), while patients

treated with dapsone were more likely to have a hypersensitivity reaction (rash, fever, allergic reaction) or anemia (Table 30).

Table 30. Adverse Events Necessitating Discontinuation of Originally Assigned Therapy (Percent of Patients)- Study 115-211

Event	Atovaquone	Dapsone
Any Event	24	26
Rash	6	9
Nausea	4[a]	1
Vomiting	2[a]	1
Diarrhea	3[a]	<1
Fever	1	3[a]
Allergic Reaction	1	3[a]
Anemia	0	2[a]

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

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

The rates of treatment-limiting adverse events for patients assigned to treatment with dapsone were highly dependent on whether or not patients were taking dapsone at enrollment into the study. Among patients who were taking dapsone at enrollment, the rate of any treatment-limiting event was higher for patients assigned to treatment with atovaquone (28%) than for patients assigned to continued treatment with dapsone (10%). In contrast, among patients who were taking neither dapsone nor atovaquone at enrollment, the rate of any treatment-limiting event was higher for patients assigned to treatment with dapsone (43%) than for patients assigned to treatment with atovaquone (20%) (Table 31).

Table 31. Summary of Treatment Limiting Adverse Events by Dapsone Use at Baseline (Percent of Patients)- 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 occurring in ≥2% of patients in either therapy group

In study 115-213, treatment-limiting adverse events developed in 16%, 25% and 7% of patients treated with low-dose atovaquone, high-dose atovaquone or aerosolized

pentamidine, respectively (Table 32). The differences in incidence of any treatment-limiting adverse events between the atovaquone groups and the aerosolized pentamidine group were statistically significant (p=0.004 for low-dose atovaquone vs aerosolized pentamidine; p=0.0001 for high-dose atovaquone vs aerosolized pentamidine).

Reviewers' Note: The most common treatment-limiting adverse events for patients treated with atovaquone were rash, diarrhea, nausea and vomiting. The most common treatment-limiting adverse event for patients treated with aerosolized pentamidine was bronchospasm.

Table 32. Frequent Treatment Limiting Adverse Events in Study 115-213

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

a Values are percentages of patients enrolled in each group.

b $p<0.05$ compared to aerosolized pentamidine, Fisher's Exact Test.

Summary of IND Safety Reports Submitted to FDA

As of 1 August 1997, a total of 27 15-Day IND Safety Reports pertaining to studies 115-211 or 115-213 had been submitted to the FDA. A summary of these reports by event category is presented in Table 33.