

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**50-670/S-015**

**50-693/S003**

**50-730/S005**

**MEDICAL REVIEW**

**Medical Officer Review of NDA 50-730, SE1-005:  
Azithromycin (Zithromax™)**

Date Submitted: January 13, 2000  
Date Received: January 13, 2000  
Date Assigned: January 20, 2000  
Date Final Draft: November 17, 2000  
Date Completed: December 5, 2000

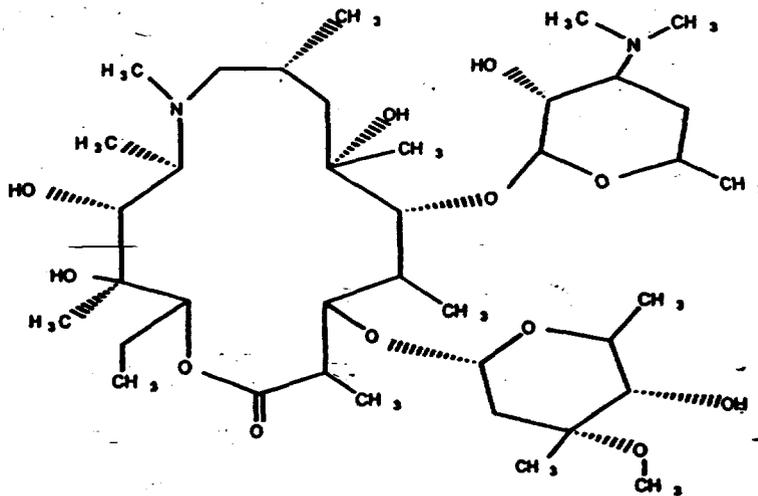
Applicant: Pfizer INC  
Drug: Proprietary name - Zithromax®  
Generic name - azithromycin  
Chemical name-

(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)  
-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl- $\alpha$ -L-  
ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,  
8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethyl-  
amino)- $\beta$ -D-xylo-hexopyranosyl]oxy]-1-oxa-6-  
azacyclopentadecan-15-one

Molecular formula - C<sub>38</sub>H<sub>72</sub>N<sub>2</sub>O<sub>12</sub>

Molecular weight - 749.0

Molecular structure -



Drug Class: Macrolide antibiotic  
Formulation: 600 Tablet, 250 mg Capsule  
Route of administration: Oral

Related NDAs: 50-670, 50-693

Related IND:

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## 1. Executive summary

### **Historical Perspective:**

Disseminated *Mycobacterium avium* complex (MAC) infection in HIV infected patients has been one of the most frequently diagnosed opportunistic infections in patients with "advanced" AIDS. In the early days of the AIDS epidemic it was diagnosed based upon a cluster of non-specific clinical symptoms, including weight loss, night sweats, anemia, splenomegaly, and liver function abnormalities. It was later recognized that this syndrome was frequently associated with the finding of MAC in the blood cultures from these patients.

In the late 1980's the most frequently recommended regimen for the treatment of disseminated MAC was four- or five-drug regimens with included rifampin or rifabutin [redacted] ethambutol, clofazimine, ciprofloxacin [redacted]. This regimen was poorly tolerated and did not appear to result in much clinical improvement.

Clinical trials initiated in the early 1990's demonstrated the degree to which MAC could be eliminated from the blood of disseminated MAC infected patients. Although these studies were small in size, it became obvious that the macrolides had the ability to rid the blood of MAC as well as, or better than some of the older multi-drug regimens. In 1993, clarithromycin was approved for the treatment of disseminated MAC. In the registrational database, monotherapy was studied. It was noted that bacteremia was cleared in a dose response relationship (no placebo group was used), symptomatic response was loosely associated with sterilization of blood cultures, and the durability of response was limited with monotherapy and was associated with the emergence of clarithromycin resistance.

Two factors have contributed to the decrease in the number of cases of HIV-associated disseminated MAC infection, the availability of prophylactic therapy for MAC infection, and of more effective anti-retroviral therapy. This is most strikingly related to the protease inhibitor combinations. The ultimate outcome measure for the clinical resolution of disseminated MAC at the time of the clarithromycin approval was felt to be survival. It is difficult to compare this outcome measure from studies done in the early 1990s to those performed after the protease inhibitors became widely available. The protease inhibitors had a profound effect on the prolongation of life in patients infected with HIV.

### **Current Application:**

The current application requests an indication for the treatment of disseminated MAC in HIV-infected individuals. In support of this indication the applicant has submitted one, controlled, pivotal trial (Study 189) and 2 open label non-comparative studies. The controlled, pivotal study was initiated on 26 Aug 94 and the last patient enrolled on 16 Sep 98. The study was initiated before the approval and wide availability of the protease inhibitors, and was closed prior to accrual of the intended number of study subjects, because fewer patients were being diagnosed with disseminated MAC.

Azithromycin (Zithromax ® 600 mg tabs x 2, weekly) was approved for the prevention of disseminated *Mycobacterium avium* complex (MAC) infections in patients with AIDS on June 12, 1996.

**Results:**

The following is a summary, by the applicant, of the efficacy data in study 189 from the final draft label.

“ One randomized, double blind clinical trial (Study 189) was performed in patients with disseminated MAC. In this trial, 246 HIV infected patients with disseminated MAC received either azithromycin 250 mg qd (N=65), azithromycin 600 mg qd (N=91) or clarithromycin 500 mg bid (N=90), each administered with ethambutol 15 mg/kg qd, for 24 weeks. Patients were cultured and clinically assessed every 3 weeks through week 12 and monthly thereafter through week 24. After week 24, patients were switched to any open label therapy at the discretion of the investigator and followed every 3 months through the last follow up visit of the trial. Patients were followed from the baseline visit for a period of up to 3.7 years (median: 9 months). MAC isolates recovered during study treatment or post-treatment were obtained whenever possible.

The primary endpoint was sterilization by week 24. Sterilization was based on data from the central laboratory, and was defined as two consecutive observed negative blood cultures for MAC, independent of missing culture data between the two negative observations. Analyses were performed on all randomized patients who had a positive baseline culture for MAC.

The azithromycin 250 mg arm was discontinued after an interim analysis at 12 weeks showed a significantly lower clearance of bacteremia compared to clarithromycin 500 mg bid.

Efficacy results for the azithromycin 600 mg qd and clarithromycin 500 mg bid treatment regimens are described in the following table:

Response to therapy of patients taking ethambutol and either azithromycin 600 mg qd or clarithromycin 500 mg bid			
	Azithromycin 600 mg qd	Clarithromycin 500 mg bid	**95.1% CI on difference
Patients with positive culture at baseline	68	57	
Week 24			
Two consecutive negative blood cultures*	31/68 (46%)	32/57 (56%)	[-28, 7]
Mortality	16/68 (24%)	15/57 (26%)	[-18, 13]
* Primary endpoint			
** [95% confidence interval] on difference in rates (azithromycin-clarithromycin)			

The primary endpoint, rate of sterilization of blood cultures (two consecutive negative cultures) at 24 weeks, was lower in the azithromycin 600 mg qd group than in the clarithromycin 500 mg bid group.

### Sterilization by Baseline Colony Count

Within both treatment groups, the sterilization rates at week 24 decreased as the range of MAC cfu/mL increased.

	Azithromycin 600 mg (N=68)	Clarithromycin 500 mg bid (N=57)
Groups Stratified by MAC Colony Counts at Baseline	No. (%) Subjects in Stratified Group Sterile at Week 24	No. (%) Subjects in Stratified Group Sterile at Week 24
≤ 10 cfu/mL	10/15 (66.7%)	12/17 (70.6%)
11-100 cfu/mL	13/28 (46.4%)	13/19 (68.4%)
101-1,000 cfu/mL	7/19 (36.8%)	5/13 (38.5%)
1,001-10,000 cfu/mL	1/5 (20.0%)	1/5 (20%)
>10,000 cfu/mL	0/1 (0.0%)	1/3 (33.3%)

### Susceptibility Pattern of MAC Isolates:

Susceptibility testing was performed on MAC isolates recovered at baseline, at the time of breakthrough on therapy or during post-therapy follow-up. The [redacted] broth method was employed to determine azithromycin and clarithromycin MIC values. Azithromycin MIC values ranged from [redacted] µg/ml and clarithromycin MICs ranged from [redacted]. The individual MAC susceptibility results demonstrated that azithromycin MIC values could be 4 to 32 fold higher than clarithromycin MIC values.

During study treatment and post-treatment follow up for up to 3.7 years (median: 9 months) in study 189, a total of 6/68 (9%) and 6/57 (11%) of the patients randomized to azithromycin 600 mg daily and clarithromycin 500 mg bid, respectively, developed MAC blood culture isolates that had a sharp increase in MIC values. All twelve MAC isolates had azithromycin MIC's ≥256 µg/ml and clarithromycin MIC's >32 µg/ml. These high MIC values suggest development of drug resistance. However, at this time, specific breakpoints for separating susceptible and resistant MAC isolates have not been established for either macrolide." (End quote)

### Strengths and Limitations of the Evidence for Efficacy:

#### Strengths:

- One of the largest comparative, double-blind, randomized studies performed in disseminated MAC
- Demonstration of microbiologic activity within the pivotal study
- Microbiologic and pre-clinical animal models which demonstrate activity
- High Concentrations of drug in the macrophages, the cell within which MAC resides in the human host
- Demonstration of efficacy for the prevention of disseminated MAC in HIV infected patients

**Limitations:**

- Failure to demonstrate efficacy equivalent to that of the approved, standard of therapy
- Difficulty in comparing the data to historical controls due to change in underlying HIV disease over time, specifically, survival rates and baseline clinical status (eg colony counts of MAC)
- Inability to perform additional studies in disseminated MAC do to the paucity of patients with this disease
- Difficulty comparing to previous studies due to the various ways in which microbiologic outcomes were defined and measured.

**Medical Officer Comments Regarding Efficacy Evaluation:**

The efficacy of treatment of disseminated MAC with the combination of azithromycin and ethambutol is based upon the evidence from in vitro, animal models, and clinical studies. The pivotal clinical trial utilized an active comparator, clarithromycin and ethambutol. The statistical outcome demonstrated a confidence interval that included zero, where the lower limits of the 95.1% CI (azithromycin to clarithromycin) was -28%. Sensitivity analyses were performed by the applicant which demonstrated similar confidence interval ranges. The actual rates for the primary efficacy endpoint, sterilization of blood cultures, were 46% and 56% for azithromycin and clarithromycin, respectively. An analysis was performed by this reviewer which was similar to that upon which the clarithromycin NDA data were evaluated (see review). The results showed that while clarithromycin was able to clear the blood of MAC somewhat more rapidly after the initiation of therapy, the overall outcomes appeared to be similar. In addition, individual plots of actual patient microbiology data were reviewed. The overall pattern was one that demonstrated microbiologic activity. Patients' colony counts improved on either therapy.

Based upon all of the data available to this reviewer, it would appear that azithromycin and ethambutol are not quite as active as clarithromycin ethambutol regimen for the treatment of disseminated MAC. However, the combination of azithromycin and ethambutol is likely to be equal to or better than the other older regimens. Also, we know that left untreated, disseminated MAC does add significant morbidity and contributes to mortality in end-stage AIDS patients. Blood cultures in these patients do not usually become negative and stay negative once the disease establishes a foothold. Therefore, it is not difficult to say that azithromycin plus ethambutol for the treatment of disseminated MAC is better than placebo based upon extrapolation from natural history information.

There is still much "art" in the description of the ultimate clinical outcome for disseminated MAC studies. This is due to the fact that, while there is an association between clinical improvement and absence of MAC in blood cultures, it is an imperfect one which is not described well enough to apply to statistical modeling.

**Safety:**

Regarding safety, the results of clinical studies in more than 1600 subjects, who received azithromycin for MAC and opportunistic infections, demonstrate that safety profile of

azithromycin at the high doses used in the treatment of opportunistic infections, including MAC, is acceptable, given the serious or life-threatening nature of MAC infection. The most common toxicities reported were related to the gastrointestinal tract. Episodes of reversible hearing impairment were noted in a small number of individuals at all ages.

**Benefit/Risk Assessment:**

The efficacy of treatment of disseminated MAC with the combination of azithromycin and ethambutol is based upon the evidence from *in vitro* experiments, animal models, and clinical studies. Survival was similar when compared to combination therapy with clarithromycin and ethambutol. Outcome correlated with baseline MAC colony counts, and survival correlated with use of protease inhibitor therapy (only 1/3 of patients on each group had received protease inhibitors and a time during the study). This was the background upon which these regimens were tested. Azithromycin is a once a day therapy compared to a twice daily dose of clarithromycin. This may provide a modest benefit to compliance in patients who may already be on a complicated anti-retroviral regimen.

No real advantage was seen regarding pharmacokinetic interactions when comparing azithromycin to clarithromycin, even though clarithromycin is a much more potent inhibitor of cytochrome P450 isoenzymes. Neither drug would be expected to jeopardize the efficacy of the patients anti-retroviral therapy. If there were an interaction it would elevate the protease inhibitor level mildly. On the other hand, the levels of the macrolides may increase substantially and their dosage may have to be modified.

Risk of giving an inferior therapy, given the cross resistance that exists between clarithromycin and azithromycin, would be that the potential development of resistance while on azithromycin, if it was chosen to be used first, would leave the patient with less effective treatment options. This was not the case seen in these data. Resistance to either agent was seen at a low level, and most patients that failed to have a microbiologic response did so with organisms that were sensitive to both drugs. There are no additional safety concerns raised by this application when compared to the already approved labeling.

**Recommendation:**

This medical officer would recommend approval of azithromycin 600 mg daily in combination with ethambutol for the treatment of disseminated MAC in HIV infected patients. It is important to stress in the labeling, especially in the clinical studies section, that the efficacy of this regimen, as measured by the sterilization of the blood, is slower and less frequent than that of the clarithromycin regimen. This will enable the clinician to judge which patients may benefit from the use of this drug and provide information on dosing for treatment of disseminated MAC.

## 2. Review Team

Medical Reviewer: Joyce Korvick, M.D., M.P.H.  
Project Manager: Diana Willard  
Biometrics: Nancy Silliman, Ph.D.  
Microbiologist: Linda Gosey  
Toxicologist: Owen McMaster, Ph. D.  
Chemistry: Gene Holbert, Ph.D.  
Biopharmaceutics: Phil Colangelo, Ph.D., Pharm.D.  
Medical Team Leader: Marc Cavallé-Coll, M.D. Ph.D.

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### 3. Introduction

Azithromycin (Zithromax ® 600 mg tabs x 2 weekly) was approved for the prevention of disseminated *Mycobacterium avium* complex (MAC) infections in patients with AIDS on June 12, 1996. Previously, azithromycin capsules were approved on November 1, 1991 for the treatment of mild/moderate acute bacterial exacerbation of chronic bronchitis in COPD, pneumonia, pharyngitis /tonsillitis (second-line), uncomplicated skin infections and non-gonococcal urethritis and cervicitis. Azithromycin oral suspension was approved on September 28, 1994. These latter two applications are under the review of the Division of Anti-Infective Drug Products (HFD-590). There are three approved Zithromax product labels, only one of which includes the MAC prophylaxis indication.

The current application requests an indication for the treatment of disseminated MAC in HIV-infected individuals. In support of this indication the applicant has submitted one controlled, pivotal trial (Study 189) and 2 open label non-comparative studies (supportive). In addition, the applicant has performed 4 drug interaction studies with indinavir, nelfinavir, fluconazole, and bactrim DS. There were no interactions with these drugs except in the case of nelfinavir (see below). In addition, reference is made to the sustiva Label wherein a description of no interaction between azithromycin and sustiva appears. Finally, Single and multiple dose PK studies in asymptomatic HIV+ Patients with 600 mg QD x 22 days (also 250mg QD x 22 Days) were undertaken.

### 4. Background

#### Disseminated MAC in HIV Infected Patients

Clarithromycin is the only approved antibiotic for the treatment of disseminated MAC in HIV infected individuals (approval 12/3/93). On October 12, 1995 it was approved for use as prophylactic treatment of MAC in HIV positive individuals. In the mid to-late 1990's the protease inhibitor type of antiretroviral drugs were approved and became widely used. This dramatically changed the face of HIV /AIDS in the United States. The rates of MAC infection decreased dramatically. This was the same time period during which the azithromycin treatment trial was underway. It took 4 years to accrue the patients in this study. As the rate of enrollment dropped dramatically, the study was stopped early when it was noted that it might take more than a year to enroll the last 20-30 patients.

The diagnosis of disseminated MAC is usually made when a patient's CD4 cell count is under 100 cells/mm<sup>3</sup>, and is associated with a symptom complex including night sweats, weight loss, anemia, splenomegaly, and positive blood culture for MAC. In the early days of HIV treatments, patients with disseminated MAC used to be diagnosed in the very late stages with very high colony counts of organisms in the blood. As the disease became more readily diagnosable, it became routine for physicians to order blood cultures. In recent studies of MAC, it appears that the disease may not be as advanced compared to the earlier studies, and that colony counts were lower on entry than in previous studies. The significance of this finding is relevant in the analysis of the data from the current study. The FDA has evaluated MAC therapies based upon the drug's ability to clear the blood culture (sterilization) and not a change in log<sub>10</sub>CFU. In the early

days of AIDS, many patients did not even have a colony count performed on the culture upon entry to therapy. Thus, making it difficult to provide a good historical, placebo-control group. Finally, it is known that antibiotics alone will not cure the patient of this organism. Studies have shown that even though the blood is cleared of the organism, the bone marrow or spleen can still harbor live organisms. There is a loose association between clearance of MAC organisms from the blood culture and clinical symptom response. In fact, the original approval of clarithromycin was based upon the sterilization

[REDACTED] The current approach recommended by the CDC for the treatment and prophylaxis of MAC includes the use of both protease inhibitors (effective anti-retroviral therapies) and MAC treatments. It is recommended that if a patient has had an immunologic response to the protease inhibitors then long term treatment with the MAC drugs can be stopped if the patients have received up to 6 months of therapy. This approach has been accepted among clinicians. Data is being collected in academic centers regarding this approach.

In the U.S. "During 1992-1997, both the frequency at which MAC occurred first and the incidence of MAC decreased, but the percentage of persons who had MAC diagnosed during the course of AIDS remained stable. MAC prophylaxis and antiretroviral therapy probably have contributed to the decline in the incidence of MAC, but occurrence at low CD4+ T-lymphocyte counts (despite prescription of prophylaxis) and poor compliance with therapy may result in eventual development of MAC in some persons"(CDC, 1999).

#### **4.1. Relevant Human Experience**

As mentioned above, azithromycin has been approved for the prevention of MAC in HIV-infected patients. The original NDA presented chronic use data of a weekly dose of Azithromycin of 1200mg. Safety data did not demonstrate any unexpected side-effects from the previously approved tablet or suspension (10-14 day therapies). Concern for the potential of reversible hearing loss at the higher doses was studied. Several cases were reported, however, only in small number. As with the other macrolides, it is well documented that high doses can cause short term hearing loss.

##### **4.1.1. Important information from related INDs and NDAs**

A Sustiva drug interaction study was reported in the Sustiva NDA and label (Please See Biopharmaceutics Review for further details).

##### **4.1.2. Foreign Experience**

Azithromycin 600 mg tablets were approved for use in MAC prophylaxis in the following countries: Australia, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Hong Kong, Ireland, Italy, Malaysia, Netherlands, Portugal, Spain, Sweden, Switzerland. Approvals have not been withdrawn for safety of lack of efficacy in any country.

#### **4.2. Materials reviewed**

NDA supplement provided a paper copy of the ISS/ISE and study reports, as well as an electronic submission which contained patient summaries, case reports and data tables.

The JMP program was utilized by the FDA to review patient data, SAS transport data supplied by the applicant, during the safety and efficacy review.

#### 4.3. Pharmacokinetics/Pharmacodynamics

A potentially important advantage that azithromycin presents in the therapy of MAC is that it is not as potent an inhibitor of cytochrome P450 isoenzymes. Many HIV (human immunodeficiency virus) infected patients are on multiple antiretroviral therapies that are metabolized by the CYP P450 pathway. Thus, the applicant has performed 4 drug interaction studies with indinavir, nelfinavir, fluconazole, and bactrim DS. There were no interactions with these drugs, except for the effect of nelfinavir on azithromycin levels (see below). In addition, reference is made to the sustiva label, where no interaction between azithromycin and sustiva was identified. Finally, single and multiple dose PK studies in asymptomatic HIV+ patients with 600 mg QD x 22 Days (also 250mg QD x 22 Days) were undertaken. It does not appear that the Azithromycin accumulates with repeated dosing.

The interaction between [ ] and azithromycin is best summarized in the wording of the final draft of the package insert:

"Coadministration of a single oral dose of 1200 mg azithromycin (2 x 600 mg ZITHROMAX® tablets) with steady-state nelfinavir (750 mg tid) to healthy adult subjects produced a decrease of approximately 15% in mean AUC<sub>0-∞</sub> of nelfinavir and its M8 metabolite. Mean C<sub>max</sub> of nelfinavir and its M8 metabolite were not significantly affected. No dosage adjustment of nelfinavir is required when nelfinavir is coadministered with azithromycin."

"Coadministration of nelfinavir (750 mg tid) at steady state with a single oral dose of 1200 mg azithromycin increased the mean AUC<sub>0-∞</sub> of azithromycin by approximately a factor of 2-times (range of up to 4 times) of that when azithromycin was given alone. The mean C<sub>max</sub> of azithromycin was also increased by approximately a factor of 2-times (range of up to 5 times) of that when azithromycin was given alone. Dose adjustment of azithromycin is not recommended. However, when administered in conjunction with nelfinavir, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted."

For a more detailed review, please refer to the Pharmacokinetics/Pharmacodynamics review by Dr. Colangelo.

#### 4.4 Microbiology

##### Summary of Preclinical Microbiology Data (by Linda Gosey):

"Azithromycin, an erythromycin derivative, inhibits cell-free protein synthesis by binding to the conserved domain V of the 23S rRNA. Because the mechanism of action is the same for the macrolides cross resistance between these agents is observed. Thus, MAC organisms developing resistance to clarithromycin would also be resistant to azithromycin and vice versa. It is estimated that the frequency of macrolide-resistant MAC mutants is between 10<sup>-8</sup> to 10<sup>-10</sup>.

As with other macrolides, azithromycin MICs can vary depending on the conditions of the susceptibility test. Macrolide MICs are pH sensitive. The higher the pH (i.e. 7.4 versus 6.6) the lower the MIC values.

*In vitro* azithromycin does not appear to be very active with MICs ranging from [ ] for MAC isolates. However, azithromycin accumulates intracellularly where MAC organisms reside. Using the macrophage model, investigators have demonstrated that azithromycin in combination with rifabutin, rifapentine, tumor necrosis factor or granulocyte-macrophage colony-stimulating factor (GM-CSF) produced greater intracellular killing of MAC than any of the agents alone.

In the paper "Rationale for the use of Azithromycin as *Mycobacterium avium* Chemoprophylaxis". 1997. Am. J. Med.;102(5C):37-49, Dunne et. al. summarized the data from the published literature on the pharmacokinetics, *in vitro* activity and intracellular activity of azithromycin. In general, while azithromycin MICs were 2-32 fold higher than clarithromycin, both demonstrated equivalent activity in the beige mouse infection model of disseminated MAC.

When azithromycin or clarithromycin mono-therapy was administered to MAC infected beige mice, comparable activity was demonstrated between the two treatments. However, it was noted that a higher incidence of drug resistance development occurred in the clarithromycin arm versus the azithromycin arm. When cross resistance was evaluated it was determined that complete cross resistance occurred due to a single point mutation at position 2058 or 2059 of the 23 rRNA. The lower incidence of drug resistance development in the azithromycin arm may be due to the high intracellular concentrations obtained with azithromycin versus clarithromycin.

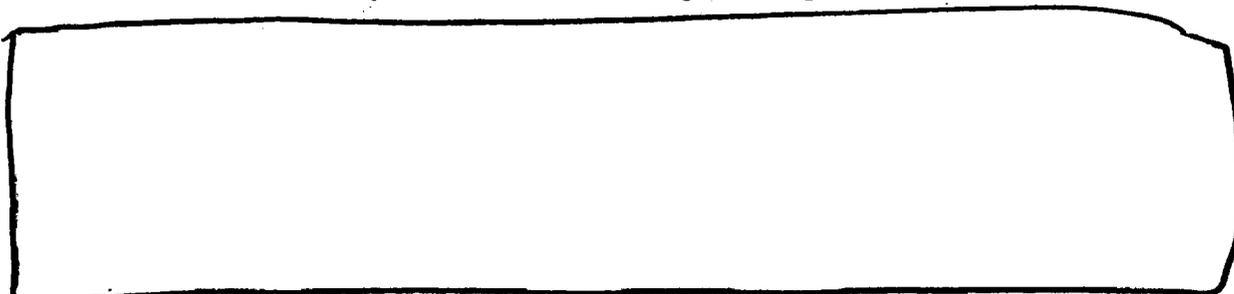
Intermittent dosing with azithromycin is achievable due to the drug's long half-life and the high intracellular concentrations. In one human pharmacokinetic study mean leukocyte concentrations following a single 1200 mg oral dose were >32 g/mL for 3 days and >16 g/mL for 5 days. "

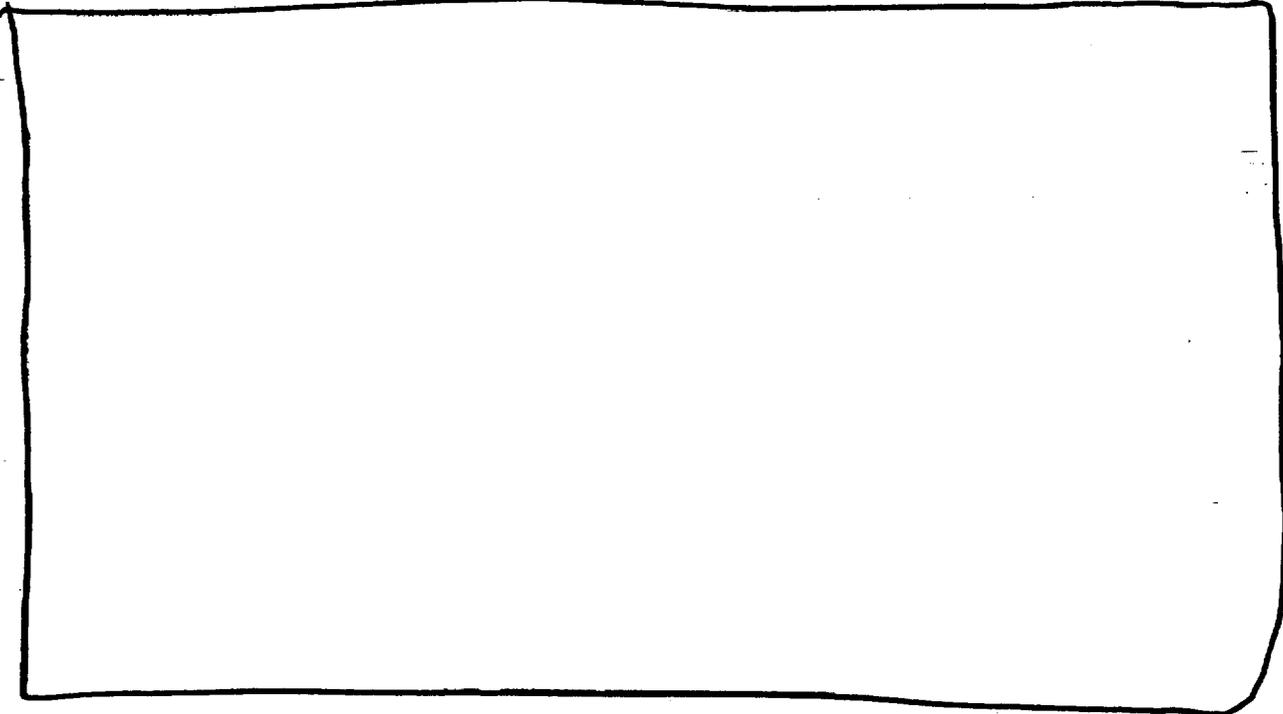
#### 4.5 Pharmacotoxicology

No changes submitted to the label with this application. No issues currently pending.

#### 4.6 Chemistry

The applicant submitted a claim for categorical exclusion from the environmental assessment. The chemistry reviewer found this request acceptable.





*Medical Officer Comment:*  
*This is acceptable to the FDA.*

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## 5 Efficacy Evaluation MAC treatment in HIV positive patients

The pivotal study for this indication is protocol 006-189/189B "A randomized, double blind, comparative study of azithromycin vs clarithromycin in combination with ethambutol for the treatment of disseminated *Mycobacterium avium* complex (MAC) infection in AIDS patients"

Primary supportive studies include:

- Study 148 (a randomized, double-blind, non-comparative study of two different doses of azithromycin [600 mg/day and 1200 mg/day]).
- Study 131 (an open-label pilot study of azithromycin in subjects with AIDS and MAC bacteremia)

The pivotal study is reviewed below

### 5.1 Protocol 066-189/189B

**Dates for Conduct of Study:** 066-189: 26 Aug 94 - 16 Sep 98  
066-189B: 23 Mar 95 - 10 Mar 99

**Study Objectives:** The purpose of study 189/189B was to evaluate the efficacy and safety of azithromycin administered at two different dose levels (600 mg or 250 mg single daily dose) in combination with ethambutol for treatment of disseminated *Mycobacterium avium* complex (MAC) infection and to determine whether a regimen containing azithromycin was at least as safe and effective as clarithromycin plus ethambutol. The primary purpose of the maintenance phase (189B) of study 189/189B was to continue to provide treatment and assess long-term safety in subjects who initially responded to treatment. A secondary objective was to assess the efficacy of azithromycin in combination therapy (with ethambutol) to maintain the initial bacteriologic and clinical improvement.

Therapy for mycobacterial disease has in general required combination regimens not only to enhance efficacy but also to decrease the incidence of resistance. Treatment for disseminated *Mycobacterium avium* complex (MAC) infection has usually involved four to five drug combinations with a substantial failure and intolerance rate. Clarithromycin has been approved for the treatment of MAC in subjects with AIDS. Treatment with 500 mg administered orally twice daily was associated with a reduction in MAC cfu/ml in the majority of patients. However, while early reduction of mycobacteria was documented, resistance was found to develop if patients remained on monotherapy suggesting that combination therapy may be advantageous.

Azithromycin is potentially a useful drug in combination therapy for MAC infection given its in vivo activity, high tissue concentrations, and relative lack of toxicity and paucity of drug interactions. Consequently, it was decided to evaluate its effectiveness

and safety at two different doses when used in combination with ethambutol and to compare azithromycin to the previously approved clarithromycin when the two are used under similar conditions.

### 5.1.1 Study design

The treatment phase (189) of this study was a multicenter, double-blind, randomized study comparing azithromycin (250 mg and 600 mg) plus ethambutol and clarithromycin plus ethambutol administered orally for 24 weeks to subjects with AIDS for treatment of disseminated MAC. Subjects were to be reevaluated bacteriologically and clinically for signs/symptoms every 3 weeks for 12 weeks and monthly thereafter through week 24. Global assessments of clinical response were to be made at weeks 12 and 24. At the investigator's discretion, subjects with a complete response to treatment by week 24 could enter the open-label, noncomparative phase (189B), receiving oral azithromycin 250 mg plus ethambutol once daily. Follow-up assessments were to be made every 3 months.

#### *Medical Officer Comment:*

*Given the state-of-the art of treatment of MAC, it was not possible to conduct a placebo-controlled study. Previous studies with other macrolides have suggested that the essential components in the regimen for MAC therapy include a macrolide and ethambutol. Studies where rifabutin has been added to the combination of clarithromycin and ethambutol have not demonstrated an additional advantage over two drug therapy. Thus, the FDA agreed with the sponsor that the clarithromycin and ethambutol combination was an adequate control arm for this study.*

#### 5.1.1.1 Eligibility Criteria

##### **Inclusion Criteria:**

1. At least 13 years of age.
2. Male or females. Women of childbearing potential must have had a negative urine or serum gonadotropin pregnancy test prior to entry into the study and must have been using adequate contraception both during and for 3 months after the end of treatment.
3. Outpatient or inpatient.
4. Subjects with disseminated Mycobacterium avium-complex infection as defined by a positive blood culture for MAC drawn within two months prior to study entry. Note (inclusion criteria for European sites only): Subjects with disseminated MAC defined as either (a) one week of fever and night sweats with weight loss of 2.25 kg within the last month and/or (b) positive blood culture for MAC drawn within the two months prior to study entry.
5. No therapy for MAC infection in the interim from time last positive blood culture drawn to study entry. Subjects who had been on single agent prophylaxis during this time remained eligible.
6. Subject expected to live at least 2 months.
7. AST and ALT <5X the upper range of normal.

Bilirubin <3.0 mg/dl.  
Stable creatinine <3.0 mg/dl.  
Neutrophils >500 cells/mm.

8. Subjects must have been HIV seropositive confirmed on the basis of ELISA and/or Western blot and/or polymerase chain reaction.
9. The investigator was to be responsible for obtaining informed written consent from each subject prior to his/her inclusion in the study. In states in which the legal age of consent for medical procedures was 21, subjects below the age of 21 were to have, in addition to the above consent, written permission and Informed Consent from a parent or guardian.

**Exclusion Criteria:**

1. Pregnant or lactating women.
2. Known hypersensitivity to macrolide antibiotics (erythromycin, azithromycin, or clarithromycin), or ethambutol.
3. Concomitant therapy with another investigational drug started in the week prior to study entry.
4. Subjects with an inability to take oral medications, or with conditions likely to interfere with drug absorption (e.g., gastrectomy, malabsorption syndromes).
5. Prior treatment for disseminated MAC.

**Criteria for Maintenance Treatment (189B):**

1. Clinical - partial or complete resolution of presenting signs and symptoms attributable to MAC infection.
2. Negative blood cultures for MAC on the prior two cultures done one month apart.
3. Safety - no significant adverse effects of therapy.

**5.1.1.2 Study drugs and randomization methods**

Subjects entering the 189 treatment phase were to be randomized in sequence to one of the three treatment groups (azithromycin 600 mg, azithromycin 250 mg, clarithromycin) according to a computer-generated randomization schedule. For randomization numbers 0001-0804, the actual randomization was in a 1:1:1 ratio in blocks of 6. Between 25-30 sites were to be used.

**Medical Officer Comment:**

*During the study the applicant had to adjust the randomization methods due to a number of problems, slow enrollment and outdated of materials, under enrollment, and the early termination of the azithromycin 250-mg treatment group. Effort was made to maintain the blinding and balance between groups by the applicant.*

**Dosage Form:** Azithromycin 600 mg tablet, azithromycin 250 mg tablet, clarithromycin 500 mg tablet, ethambutol 400 mg tablet and both azithromycin and clarithromycin placebo tablets were provided under various lot/FID numbers. Azithromycin lot numbers were as follows: 600 mg tablets: N4270, N4373, ED-B-275-794, ED-B-295-894, ED-B-274-794, ED-O-114-493; 250 mg tablets: N4272, ED-G-120-494, ED-G-121-494, ED-B-387-292.

**Dosing :** Azithromycin 600 mg or 250 mg (plus dummy placebo in treatment phase)  
single daily dose  
Clarithromycin 500 mg bid (plus dummy placebo)  
Ethambutol 15 mg/kg once daily (800 mg or 1200 mg)  
(study medications were taken without regard to meals)

**Duration:** 24 weeks (treatment phase); indefinite (maintenance phase)

### **5.1.1.3 Evaluability Rules**

#### **Intent-to-Treat (ITT) Analysis**

The intent-to-treat subgroup included data from all randomized subjects regardless of whether they took treatment. Eligible subjects were determined by the following criteria:

**Subject Level Exclusion Criterion:**

- **No Baseline Pathogen** - Subject's baseline blood culture must have been positive for MAC. The baseline blood culture was defined as the culture drawn at the baseline visit (beginning of therapy). If there was no baseline culture or the subject was positive for another pathogen other than Mycobacterium avium, then that subject was excluded.

**Time Specific Exclusion Criteria:** NONE

**Endpoint Specific Exclusion Criteria:** NONE

#### **Evaluable Subgroup Analysis**

The evaluable subgroup included data from eligible subjects while on treatment. This subgroup was used in an on-drug analysis. Eligible subjects were determined by the following criteria:

**Subject Level Exclusion Criteria:**

- **No Baseline Pathogen** - Subject's baseline blood culture must have been positive for MAC. The baseline blood culture was defined as the culture drawn at the baseline visit (beginning of therapy). If there was no baseline culture or the subject was positive for another pathogen, then that subject was excluded.
- **Baseline Pathogen Resistant to Study Drug** - The baseline positive culture cannot be resistant to the macrolide. Resistance was defined as MIC > 256 micrograms/ml for azithromycin or > 16 micrograms/ml for clarithromycin. If there was no MIC value for the baseline culture, then the subject was assumed to be not resistant at baseline.
- **HIV Negative** - Subject must not have been HIV negative at baseline. If the results of all three HIV tests were missing, the subject was assumed to be HIV positive.

**Time Specific Exclusion Criteria:**

- **Concomitant Antibiotic for Intercurrent Illness** - Subject cannot have taken a concomitant antibiotic potentially effective against MAC, given prior to visit of

analysis and lasting longer than 2 weeks, unless for MAC treatment failure. All data after taking the concomitant antibiotic for 2 weeks was ignored.

- **Insufficient Therapy** - Subject must have been on therapy at least 50% of the days since beginning of therapy. If a subject is on therapy less than 50% of the days since beginning of therapy, all data after that point was ignored. However, this rule did not apply until day 30 after the beginning of therapy, i.e., starting on day 31. On therapy was defined as taking azithromycin or clarithromycin; ethambutol was not taken into consideration. This criterion deviated from the protocol which specified on therapy to be 80% of days.

**Endpoint Specific Exclusion Criteria:** NONE (other than missing data)

The ITT and evaluable subgroup analyses should lead to similar conclusions. However, for this study we focused on the ITT subgroup analysis since in most cases, the evaluable subgroup contains so few subjects that the confidence intervals used for statistical inference were wider than expected.

**Medical Officer Comment:**

*The general approach taken by the FDA for the approval of an agent for MAC therapy has been to use the clearance of MAC from the blood culture at a certain time point. In the clarithromycin studies it was assessed at week 12 of therapy. Based upon pre-clinical studies, it was felt that the rate at which azithromycin could clear the blood would be slightly longer and thus the 24-week endpoint (sterilization of blood culture) was chosen as the primary endpoint. However, given the fact that this is a [redacted] symptom resolution and survival were considered important co-primary factors in the evaluation of this therapy, as well as time to relapse. The applicant performed these analyses and several sensitivity analyses that were all similar to the primary outcome analysis that is described below.*

**5.1.1.4 Sample size and Statistical plan**

The level of significance was 0.049 due to a 0.001 adjustment from the interim analysis. Bacteriologic and clinical endpoints were compared between treatment groups by 95.1% confidence intervals (CI) on the differences (azithromycin 600 mg-clarithromycin) in observed rates (sterilization, positive bacteriologic response, clinical response, death) and in mean values (MAC cfu/ml, change from baseline in MAC cfu/ml and in weight), and a p-value determined based on normal approximation or normal distribution using a t-test (colony count endpoints, weight change only). Time to event analyses were performed for sterilization, first positive culture after sterilization (relapse), positive bacteriologic response, and death using Cox Regression with a 95.1% CI on the hazard ratio. Descriptive statistics are presented for the incidence of fever and night sweats since the previous visit controlling for daily fever and night sweats, respectively, at baseline. The primary timepoint was week 24.

**Medical Officer Comment:**

*It should be noted that the azithromycin 250 mg arm was terminated early due to a blinded interim analysis performed in July 1996 which suggested a lack of relative*

efficacy compared to the clarithromycin treatment arm. The statistical implications for the final analysis are discussed later in this review. For additional discussion of interim analysis see statistical review.

### 5.1.2 Study Results

#### 5.1.2.1 Enrollment and description of patients

Study 189 Enrollment by Treatment Group

Number of Subjects:	Treatment			Maintenance
	Az 600 mg	Az 250 mg	Clarithro	Az 250 mg
Randomized/Enrolled (189B)	91	65	90	35
Entered Study (treated)	88	65	86	34
Completed Study	35	13	29	0
Discontinued Study	53	52	57	34
Discontinued Treatment	55	53	57	34
Evaluated for Efficacy:				
Intent-to-Treat	68	47	57	29
Evaluable Wk. 24 Sterilization*	28	9	22	NA
Assessed for Safety:				
Side Effects	84	63	85	34
Laboratory Tests	81	60	78	29

Az=azithromycin, Clarithro=clarithromycin, NA=not applicable

\* Sterilization=two consecutive cultures negative for MAC

(Reference: Vol14, p9)

#### Medical Officer Comment:

It should be noted that the numbers of patients that complete the study and are evaluable for the microbiologic endpoint are small in each group. Thus, in several of the analyses the applicant performed data was imputed, censored or carried forward to 24 weeks.

The FDA reviewed both the primary analysis and the observed microbiologic analysis. Additional FDA analyses were performed (see section 5.2).

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**5.1.2.2 Patient demographics and baseline factors**

Male/female HIV-infected inpatients/outpatients  $\geq 13$  years old, with culture (and clinical in Europe) evidence of MAC infection. The actual mean age of subjects in both the azithromycin 600 mg and clarithromycin groups in the therapeutic phase was approximately 38 years.

**Demographics in All Treated Patients**

	<b>Azithromycin 600 mg (Daily) N = 88</b>	<b>Clarithromycin 500 mg (BID) N = 86</b>
<b>Gender:</b>		
Male	74	73
Female	14	13
<b>Age:</b>		
(mean age years)	38.3	36.7
(range years)	23-58	24-58
<b>Race:</b>		
Black	25	28
Caucasian	49	44
Hispanic	11	10
Other	3	4
<b>Mean Weight (kg)</b>		
Male	63.1	62.5
Female	53.5	54.8

(Reference: Table 2.1.2; Appendix IIIA, Table 2.3).

**Azithromycin 600 mg vs. Clarithromycin (Therapeutic Phase)**

The demographic characteristics of the 174 treated subjects who received azithromycin 600 mg (88 subjects) or clarithromycin (86 subjects) are presented in the table above; subjects treated with azithromycin 250 mg are discussed separately below.

Baseline demographic characteristics were similar between the azithromycin 600 mg and clarithromycin groups. In each treatment group, approximately 85% of subjects were male, the mean age was approximately 38 years, the mean body weight was approximately 63 kg in males and 54 kg in females, and approximately half the subjects were White, approximately 30% Black, and approximately 12% Hispanic. Similarly, the demographic characteristics relating to age, gender, race, and weight for the subset of 68 azithromycin 600 mg subjects and 57 clarithromycin subjects included in the intent-to-treat analysis were similar to each other and to those of all treated subjects discussed above.

Lastly, the demographic characteristics relating to age, gender, race, and weight for the subset of subjects included in the evaluable subgroup analysis of sterilization at week 24 were similar between the 28 azithromycin 600 mg subjects and 22 clarithromycin subjects. They were also generally similar to those of all treated subjects in these groups except for a slightly greater proportion of Whites (approximately 64% in each group) and a somewhat greater mean weight for female subjects (60.5 kg for azithromycin 600 mg, 64.1 kg for clarithromycin) in the evaluable subgroup analysis.

**Azithromycin 250 mg (Therapeutic Phase)**

Among 65 subjects treated with azithromycin 250 mg in the double-blind phase (189) of this study, Males accounted for 90.8% of subjects, the mean age was 35.8 years, the mean body weight was 63.7 kg in males and 46.3 kg in females, and 56.9% of subjects were White and 27.7% Black. The demographic characteristics relating to age, gender, race and weight for the subsets of subjects included in the intent-to-treat analysis and evaluable subgroup analyses of week 24 sterilization were generally similar to those of all treated subjects, except that in the evaluable subgroup at week 24 only 66.7% (6 of 9) subjects were male.

**Azithromycin 250 mg (Maintenance Phase)**

Among the 34 subjects treated with azithromycin 250 mg in the open-label maintenance therapy phase (189B) of this study. Males accounted for 88.2% of subjects, the mean age was 37.2 years, the mean body weight was 69.2 kg in males and 54.6 kg in females, and 67.6% of subjects were White and 20.6% were Black.

***Medical Officer Comment:***

*It is noted that the population enrolled was predominantly male and white. This represented the demographics of HIV/AIDS at the time of this study.*

***FDA Analysis of Baseline Criteria in the ITT Population***

<b>Baseline Characteristic</b>	<b>Azithromycin 600 mg/day</b>		<b>Clarithromycin 500 mg BID</b>	
	<b>Mean</b>	<b>Median</b>	<b>Mean</b>	<b>Median</b>
<b>Colony count # (log<sub>10</sub>)</b>	1059 (3.03)	25 (1.39)	3818 (3.58)	59 (1.77)
<b>CD4 (cells/mm<sup>3</sup>)</b>	20.3	10.0	21.0	10.0
<b>Hemoglobin (g/dL)</b>	9.7	9.7	9.1	9.0
<b>Alkaline Phosphatase (IU/L)</b>	243	128	225	139
<b># symptoms at baseline</b>	2.8	4.0	2.0	2.0
<b>Weight (kg)</b>	60.6	58.5	60.5	60.9
<b>Duration of Therapy (weeks)</b>	16	22	16.1	20.7

*(Reference: Electronic Submission via JMP program)*

*From the above table it is noted that the baseline colony count was somewhat lower for the azithromycin group. Hemoglobin, alkaline phosphatase, weight and CD4 counts were similar at baseline. The number of symptoms was slightly higher for the azithromycin group. It is difficult from this data to definitely state whether either group was "sicker" at baseline. Because baseline colony count is a predictor of sterilization of the blood culture, the azithromycin group may have had a slight advantage over the clarithromycin group. About 1/3 of the patients in either group received protease inhibitors during the study.*

### 5.1.3 Applicant Analyses

The following are the major analysis undertaken by the applicant to describe the efficacy of azithromycin compared to clarithromycin for the treatment of MAC in study 186.

Intent-to-treat (last observation carried forward) and evaluable subgroup analyses were performed. Bacteriologic endpoints were sterilization [zero colony count in blood; primary], time to sterilization, time to first positive culture after sterilization (relapse), positive bacteriologic response [sterilization and/or reduction from baseline of <sup>3</sup>ten-fold (1 log) reduction in MAC colony forming units/ml of blood, cfu/ml], time to a positive bacteriologic response, and change from baseline in MAC colony count (log base 10). Clinical endpoints were death, time to death, sponsor (based on fever, night sweats, weight loss) and investigator (based on any sign/symptom) assessments of overall clinical response, investigator assessment of individual signs/symptoms (including but not limited to fever, night sweats, weight loss), and Perceived Health Index (derived from the quality of life questionnaire). Safety was assessed by incidences of side effects, laboratory test abnormalities, intercurrent illnesses, median changes from baseline in selected laboratory tests, serious adverse events including deaths and specific ophthalmologic and audiometric exams.

#### 5.1.3.1 Primary analysis

**Sterilization** - Defined as two consecutive negative blood cultures from the central laboratory. The first negative culture was considered to be the date of sterilization and only one of the two negative cultures was required to be in the analysis window. If a positive culture was also in the window, then the nearest observation, negative or positive, to that week was used in determining sterilization. If the assessment in the window was missing, then for the evaluable observed cases analysis, the subject was not evaluable unless both the previous and subsequent assessments were negative, in which case the subject was sterile, or both the previous and subsequent assessments were positive, in which case the subject was not sterile. The ITT analysis used the last observation carried forward for the missing data. The detailed algorithm for defining sterilization is contained near the end of the data analysis methods section. In the protocol week 12 was specified as primary. All weeks are reported in the tables although emphasis was placed on week 24 as described in the Statistical Analysis Plan submitted to the Food and Drug Administration (FDA) in 1996. A distinction was not made in the protocol that the evaluable analysis was an observed case analysis.

#### 5.1.3.2 Secondary analyses

##### 5.1.3.2.1 Bacteriologic (MAC Blood Cultures)

The bacteriologic endpoints were computed based on only the culture data from the central laboratory and also were computed based on culture data from the central and local laboratories.

- **Sterilization** - Central and Local Laboratory Data - Local lab data was used when there was missing data from the central laboratory.
- **Time to Sterilization** was the number of days since the beginning of therapy to the first of the two consecutive negative cultures.

- **Time to First Positive Culture after Sterilization** (Durability of Blood Sterilization) – Defined for subjects achieving sterilization only was the number of days from the date of the first of the two negative cultures to the next positive culture.
- **Positive Bacteriologic Response** - Defined as sterilization and/or a = ten-fold (1 log) reduction in colony count (cfu/ml) since the baseline visit (beginning of therapy).
- **Time to Positive Bacteriologic Response** was the number of days from beginning of therapy until the date of the first of two consecutive negative cultures or the date of a = ten-fold (1 log) reduction in colony count (cfu/ml) since the beginning of therapy.

MAC Colony Count (cfu/ml, log base 10). Colony counts of  $\log(0.099) = -1.044$  since log base 10 of zero is undefined.

- **Change in Log Colony Count** (cfu/ml, log base 10) Since the Baseline Visit (beginning of therapy).
- **Resistance** - Defined as MIC > 256 micrograms/ml for azithromycin or > 16 mcg/ml for clarithromycin.
- **MIC Results** - summarized for each treatment group and visit.

#### 5.1.3.2.2 Clinical

**Sponsor Defined Clinical Response** - Four point scale as follows:

(3) **Complete Resolution of Signs & Symptoms** - Defined as absence of fever (daily temperature > 100.5°F) and night sweats since last visit, and weight loss of less than 5% of total body weight since baseline. The last visit must have occurred at least 7 days prior to the current visit. If this did not happen then the first visit that was at least 7 days prior to the current visit was used.

(2) **Partial Resolution of Signs & Symptoms** (2 of 3 symptoms) - Absence of two of the three symptoms needed to define complete resolution without the worsening of the other condition (weight loss of  $\geq 5\%$  of total body weight (TBW) since baseline was an automatic failure).

**Partial Resolution of Signs & Symptoms** (1 of 3 symptoms) - Absence of one of the three symptoms needed to define complete resolution without worsening of the other conditions (weight loss of 35% of TBW since baseline was an automatic failure).

(0) **Failure** - No improvement or worsening of fever, night sweats and weight loss.

#### ***Medical Officer Comment:***

*In addition to the sponsor defined clinical response there was an investigator's overall clinical response assessment. It ranged from Markedly Improved to Markedly Deteriorated. These different clinical evaluations did not share a 1:1 correspondence for outcome. For example, there were several cases where the patient had a negative blood culture, all symptoms resolved and the clinical investigator rated the outcome as markedly deteriorated. This example illustrates the difficulty in clinical assessment in advanced AIDS patients who have many other co-morbid conditions. Attribution to MAC is difficult in these circumstances.*

**5.2.1 Results Azithromycin 600 mg versus Clarithromycin**

In this study the majority of subjects were male with AIDS, reflective of the normal disease population for MAC at the time of the study. The discussion of efficacy results in the therapeutic phase is based on the intent-to-treat analysis, either at the primary timepoint of week 24 or a time to event analysis.

**Bacteriologic and Clinical Endpoints – Azithromycin 600 mg vs. Clarithromycin - Observed Rates - Intent-to-Treat Analysis - Week 24**

	Azithromycin 600 mg		Clarithromycin			
<b>Bacteriologic Endpoints****</b>						
	N	Obs Rate (%)	N	Obs Rate (%)	95.1% CI*	P-value*
Sterilization --	68	45.6	57	58.1	-28.1, 7.0	0.240
Pos Bact Res	68	78.5	57	73.7	-12.5, 16.1	0.719
	N	Median	N	Median	NA	NA
Colony Count (log base 10, cfu/ml)	68	-1.00***	57	-1.00***	-	-
Change Count (log base 10, cfu/ml)**	68	-1.91	57	-1.73	-	-
<b>Clinical Endpoints</b>						
	N	Obs Rate (%)	N	Obs Rate (%)	95.1% CI*	P-value*
Death Rate	68	23.5	57	28.3	-18.1, 12.5	0.719
<b>Sponsor Assessment†</b>						
Complete Resolution (Cure)	62	25.8	47	38.2	-28.0, 7.2	0.243
<b>Investigator Assessment</b>						
Improved**	31	71.0	23	73.9	-27.1, 21.2	0.811
	N	Mean	N	Mean	NA	NA
Perceived Health Index Score+++	67	38.42	55	39.33	-	-

Obs Rate = Observed Rate (%) is based on the number of subjects with events (sterilization, positive bacteriologic response, death) or proportions of subjects (sponsor and investigator assessments); CI = confidence interval, Pos Bact Res=positive bacteriologic response; NA=Not Applicable. \*Statistical tests: 95.1% confidence interval on the difference (azithromycin 600 mg-clarithromycin) in observed rates and p-value are based on normal approximation (sterilization, positive bacteriologic response, clinical response, death); \*\* Change from baseline in MAC colony count (log base 10); \*\*\* log (0 cfu/ml)=-1.00=no growth;\*\*\*\* Bacteriologic endpoints based on quantitative blood culture data from a central laboratory; † Based on resolution of fever, night sweats, weight loss; ++ Improved=Assessed with marked, moderate, or mild improvement; +++ Score (scale of 0-100 in which higher scores indicate a more favorable response) at week 24.

(Reference: Vol. 14, p. 10)

Median baseline MAC colony counts (log 10) were 1.41 cfu/ml in the azithromycin 600 mg group and 1.77 cfu/ml in the clarithromycin group. The two treatment groups were similar in the objective measurement of change from baseline to week 24 in MAC colony count (log 10), with median changes of -1.91 cfu/ml in the azithromycin 600 mg group compared to -1.73 cfu/ml in the clarithromycin group. In both treatment groups the median colony counts (log 10) at week 24 were zero. The MIC90 of azithromycin was 32 mg/ml, and the MIC90 of clarithromycin was 2 mg/ml. Colony count at baseline was determined to be the best predictor of sterility among the covariates assessed, with a lower colony count associated with a greater probability of becoming sterile.

**Medical Officer Comment:**

*As noted in the demographic section, the patients treated with azithromycin had slightly lower baseline colony counts compared to the clarithromycin treated patients.*

Overall, the observed rates of sterilization (two consecutive negative blood cultures with a colony count of zero) at week 24 were comparable between groups, although somewhat lower in the azithromycin 600 mg group (45.6%) compared to the clarithromycin group

(56.1%) (95.1% CI -28.1, 7.0; p=0.240). When employing this protocol-specified definition of sterilization as the primary endpoint, the observed difference in sterilization rates between groups was -10.6% in favor of clarithromycin. Alternative definitions of sterilization reduced this difference. Additionally, the overall time to sterilization was comparable (hazard ratio 0.74; 95.1% CI 0.459, 1.181). Sterilization appeared to occur somewhat sooner with clarithromycin, with the median time to sterilization estimated at 64 days in the azithromycin 600 mg group and 48 days in the clarithromycin group.

Similarly, in an analysis based on all documented quantitative and qualitative culture data from sterile sites (central and local laboratory data), the overall time to relapse (first positive culture after sterilization) was comparable between groups (hazard ratio 1.71; 95.1% CI 0.734, 3.987). In general, the durability of sterilization appeared to be longer with clarithromycin than azithromycin 600 mg. No subjects receiving azithromycin 600 mg compared to 2 subjects receiving clarithromycin with susceptible pathogens at baseline developed a resistant pathogen postbaseline. In the small subgroup of subjects ( $\leq 16$ /group) who continued on their double-blind therapy after the study, the hazard ratio (0.86; 95.1% CI 0.268, 2.761) on the time to relapse was brought closer to 1 compared to the main analysis, supporting the similarity of these compounds for long-term therapy of disseminated MAC.

**Time to Event Endpoints – Azithromycin 600 mg vs. Clarithromycin - Observed Rates -Intent-to-Treat Analysis**

Time to Event Endpoint	Treatment	N	Observed Rate (%)**	First Quartile*	Median*	Time to Event Analysis		
						Cox Regression		
						Hazard Ratio***	95.1% CI on Hazard Ratio	P-Value
<b>Bacteriologic Endpoints***:</b>								
Sterilization	Az 600 mg	68	36 (52.9%)	40	64	0.74	0.459, 1.181	0.203
	Cl	57	34 (59.6%)	27	48			
Pos Bact Res	Az 600 mg	68	55 (80.9%)	22	25	1.03	0.690, 1.548	0.874
	Cl	57	42 (73.7%)	22	23			
Relapse	Az 600 mg	36	6 (16.7%)	-	-	2.02	0.502, 8.134	0.320
	Cl	34	3 (8.8%)	-	-			
Relapse****	Az 600 mg	36	14 (38.9%)	154	562	1.71	0.734, 3.987	0.212
	Cl	34	9 (26.5%)	294	-			
<b>Clinical Endpoints:</b>								
Death+	Az 600 mg	68	47 (69.1%)	201	370	1.08	0.698, 1.671	0.729
	Cl	57	36 (63.2%)	163	336			

Relapse=First Positive Culture after sterilization, Pos Bact Res=Positive Bacteriologic Response, Az=Azithromycin, Cl=Clarithromycin; \* Number of days until 25% (first quartile) or 50% (median) of the events occurred as estimated by the Kaplan-Meier curve; \*\* Observed rate is based on number of subjects with events; \*\*\* Hazard ratio refers to the risk of having the event for azithromycin 600 mg relative to clarithromycin; \*\*\*\* Bacteriologic endpoints based on quantitative blood culture data from a central laboratory unless otherwise specified; \*\*\*\*\* Second analysis of relapse based on documented quantitative and qualitative culture data from sterile sites from central and local laboratories; + Based on deaths through last follow-up  
 (Reference: Vol.14, p.11)

The observed rates of a positive bacteriologic response (sterilization and/or a  $\geq 1$  log reduction from baseline of MAC cfu/ml of blood) were equivalent between the azithromycin 600 mg group (76.5%) and the clarithromycin group (73.7%) (95.1% CI -

12.5, 18.1). The hazard ratio for the time to a positive bacteriologic response was 1.03 and one group did not appear to experience a positive response sooner than the other. The observed rates of death were comparable between groups. When subjects were followed beyond the study period, the observed rates were 69.1% for azithromycin 600 mg and 63.2% for clarithromycin (95.1% CI -10.8, 22.7;  $p=0.482$ ). The overall time to death was comparable between the two treatment groups (hazard ratio 1.08, 95.1% CI 0.698, 1.671;  $p=0.729$ ). The estimated time to death for the first quartile was 201 days in the azithromycin 600 mg group and 163 days in the clarithromycin group. Extending beyond the 24-week active treatment phase, the median time to death was estimated at 370 days in the azithromycin 600 mg group and 336 days in the clarithromycin group. Protease inhibitor use at any time during the study was found to be the most important of the covariates assessed in influencing time to death, with those subjects using protease inhibitors tending to live longer.

***Medical Officer Comment:***

*Small numbers of patients were followed post 24 weeks due to death and dropouts. The patients who were followed had varying lengths of follow-up, in a few cases up to 3 years.*

Overall, the data suggest that azithromycin 600 mg subjects may have been somewhat more compromised clinically at baseline than clarithromycin subjects relative to the frequency of signs/symptoms of MAC and other indicators of health status, and this may have influenced the clinical course of the subjects. In addition, comparison of symptom resolution on the azithromycin 600 mg vs. 250 mg arm supports the possibility that underlying disease beyond that caused by MAC may have contributed to the lower rates of clinical improvement in the 600 mg treatment arm.

***Medical Officer Comment:***

*This is a confusing argument by the applicant. There was only a very weak inference that the azithromycin patients may have been "sicker" at baseline based upon number of clinical symptoms. In addition, if colony count at baseline was a predictor of sterilization of blood cultures, azithromycin had a slight advantage there. In general, this reviewer concludes that no meaningful clinical difference existed between the groups at baseline.*

In the week 24 sponsor's assessment of clinical response (based on fever, night sweats, weight loss), the proportions of subjects cured (resolution of all 3 signs/symptoms) was 25.8% in the azithromycin group and 36.2% in the clarithromycin group (95.1% CI -28.0, 7.2). In the corresponding investigator's assessment of clinical response (based on all signs/symptoms data), the proportions of subjects showing some degree of improvement was similar at approximately 70% in both groups.

***Medical Officer Comment:***

*These measures can only be taken in the most general way, because they have not been validated as specific clinical measures of the microbiological outcomes. As discussed above, the correlation between the sponsor's assessment and the investigator's assessment is disparate in several cases.*