

In the intent-to-treat analysis at week 24, more azithromycin 600 mg subjects than clarithromycin subjects had experienced fever (41.2% vs. 29.2%) or night sweats (47.1% vs. 33.3%) since the previous visit. However, an uneven distribution of signs/symptoms at baseline may be affecting these results. Mean weights at week 24 in both treatment groups increased (0.36 kg in the azithromycin 600 mg group vs. 2.94 kg in the clarithromycin group; 95.1% CI -5.809, 0.638;  $p=0.112$ ). From the quality of life questionnaire, the mean Perceived Health Index scores (higher scores on a scale of 100 are positive) at week 24 were 38.42 in the azithromycin group and 39.33 in the clarithromycin group.

#### **Azithromycin 250 mg (Double-Blind Therapeutic Phase)**

The azithromycin 250 mg arm was terminated as the result of a blinded interim analysis showing a relative lack of efficacy compared to azithromycin 600 mg and clarithromycin.

Azithromycin 250 mg as double-blind, active therapy showed both bacteriologic and clinical efficacy against MAC. However, in the comparison to the azithromycin 600 mg dose, in the week 24 intent-to-treat analysis, the differences between these two dose groups was statistically significantly different in favor of the 600 mg dose for sterilization, time to sterilization, MAC colony count, and change from baseline in MAC colony count ( $p \leq 0.032$ ). Although the rates of a positive bacteriologic response were nominally lower in the azithromycin 250 mg group (63.8%) compared to the 600 mg group (76.5%), overall they were comparable (95.1% CI -29.8, 4.5;  $p=0.141$ ). The time to the first positive culture after sterilization (relapse) and to a positive bacteriologic response were comparable between groups. In the interim analysis, the comparison of the number of deaths occurring during the study or post-study were higher in the intent-to-treat azithromycin 250 mg group (62.5%) than the azithromycin 600 mg group (52.6%); but the difference was not statistically significant (95% CI -12.0, 31.7; 99.9% CI -26.8, 46.5). Additionally, a similar trend was seen in the final intent-to-treat analysis of death rates for the subset of subjects in the interim analysis, with death rates through last follow-up of 87.5% for azithromycin 250 mg compared to 78.9% for azithromycin 600 mg (95.1% CI -8.0, 25.1;  $p=0.311$ ). In the final analysis, in which subjects originally assigned to azithromycin 250 mg were followed through the close of the trial, the overall incidence of death and time to death analysis showed a statistically significant difference between groups ( $p \leq 0.011$ ), with a hazard ratio of 1.84 in favor of the 600 mg dose. — Additionally, deaths occurred earlier in the azithromycin 250 mg group compared to the azithromycin 600 mg group, with the first quartile estimated at 127 days and 201 days, respectively. Week 24 clinical cure rates in the sponsor's assessment of clinical response were similar (approximately 26%) between the two dose groups. However, although noting that the denominator in the 250 mg group was small ( $N=11$ ), the investigator's assessment of clinical response showed more subjects improved in the azithromycin 250 mg group (90.9%) than the 600 mg group (71.0%). The number of days with fever was similar between the azithromycin 250 mg and 600 mg groups (risk ratio 0.964). However, the number of days with night sweats was greater in the azithromycin 600 mg group than the 250 mg group, with a risk ratio of 0.619 ( $p < 0.001$ ). At week 24, mean changes in Perceived Health Index scores (higher scores on a scale of 100 are positive) from baseline were -15.30 in the azithromycin 250 mg group and -2.87 in the azithromycin 600 mg group ( $p=0.0484$ ).

**Medical Officer Comment:**

The planned statistical interim analysis (see statistical review) was to compare the primary endpoint for the azithromycin groups to clarithromycin. There was no provision (adjustment of p-values) for the comparison between the two doses of azithromycin. The conclusion was that there was a statistically significant difference between clarithromycin and azithromycin 250 mg, and a numerical superiority of the azithromycin 600 mg dose. FDA conclusion from this analysis is that treatment of MAC with azithromycin 250 mg and ethambutol is inadequate and is not recommended.

**Azithromycin 250 mg (Open-Label Maintenance Phase)**

In the intent-to-treat analysis of the open-label phase of the study at month 12, the observed rate of sterilization was  (11 of 12) of subjects and the observed rate of subjects cured in the sponsor's assessment of clinical response 50.0%. The observed rate of death at month 12 was 48.3% and through last follow-up was 58.6%.

**5.1.4 Safety (Study 189)**

The overall assessment of safety was very similar for the subjects receiving azithromycin 600 mg and those receiving clarithromycin 500 mg bid. However, the actual duration of therapy was 25% greater for azithromycin 600 mg with a median of 86 days versus the median of 69.0 days for clarithromycin 500 mg.

Treatment-emergent, all causality side effects were reported by 63.1% of subjects receiving azithromycin 600 mg and 65.9% of the individuals assigned to clarithromycin. Severe side effects were noted in 20.2% of the azithromycin 600 mg recipients and 23.5% of the subjects receiving clarithromycin 500 mg. Discontinuations due to side effects occurred in 9.5% and 5.9% of subjects receiving azithromycin 600 mg and clarithromycin, respectively. Clinically significant laboratory abnormalities were reported in 80% of the subjects assigned to azithromycin 600 mg and 68% of clarithromycin recipients.

**Body Systems in Which at Least 5% of Subjects Within Either Treatment Group Experienced**

**An All Causality, Treatment-Emergent Side Effect**

Number (%) of Subjects	Azithromycin 600 mg	Clarithromycin 500 mg
Subjects Evaluable for Side Effects	84	85
Body As A Whole	31 (36.9%)	28 (32.9%)
Digestive	39 (46.4%)	29 (34.1%)
Hemic and Lymphatic	7 (8.3%)	6 (7.1%)
Metabolic and Nutritional	7 (8.3%)	5 (5.9%)
Nervous	13 (15.5%)	14 (16.5%)
Respiratory	7 (8.3%)	7 (8.2%)
Skin and Appendages	10 (11.9%)	17 (20.0%)
Special Senses	14 (16.7%)	9 (10.6%)
Urogenital	5 (6.0%)	3 (3.5%)

Source Data: Table 6.2.1  
 (Reference: Vol 14, p. 108)

The distribution of side effects among body systems was very similar between the two treatment groups. Among those subjects receiving azithromycin 600 mg, 39/84 (46.4%)

reported side effects associated with the digestive system as compared to 29/85 (34.1%) of subjects receiving clarithromycin. The digestive system side effects among 600 mg recipients included 16/84 (19.0%) complaints of vomiting compared to 7/85 (8.2%) for subjects receiving clarithromycin. However, complaints of nausea were very similar for the two groups, 14/84 (16.7%) for subjects receiving azithromycin and 13/85 (15.3%) for subjects assigned to clarithromycin. In addition, within the 16/84 (19.0%) of individuals that received azithromycin 600 mg and reported complaints of vomiting, five of them (07G0965, 53E0007, 79E0263, 54E0028 and 59E0077) had reported vomiting as a symptom present at baseline. Within the 7/85 (8.2%) of subjects that received clarithromycin 500 mg and reported complaints of vomiting, there were no subjects reporting vomiting as a symptom present at baseline.

The most common complaints attributed to the special senses body system (all causality) were abnormal vision and deafness. Six (7.1%) subjects assigned to azithromycin 600 mg and two (2.4%) subjects receiving clarithromycin 500 mg reported abnormal vision. Four (4.8%) of the subjects receiving azithromycin 600 mg and five (5.9%) who were assigned to clarithromycin complained of deafness. Another three subjects (3.6%) receiving azithromycin 600 mg reported ear disorder.

The following table displays the distribution and frequency of the treatment-related side effects.

**Incidence of Treatment-Related, Treatment-Emergent Side Effects  
 In Which at Least 5% of Subjects Within Any One Treatment Group Experienced The Side Effect**

Body System	Side Effect	Azithromycin 600 mg (N = 84)		Clarithromycin 500 mg (N = 85)	
		# Subjects	Percent	# Subjects	Percent
Body As A Whole	Abdominal Pain	12	14.3%	13	15.3%
Digestive	Diarrhea	10	11.9%	8	9.4%
Digestive	Flatulence	4	4.8%	10	11.8%
Digestive	Nausea	12	14.3%	10	11.8%
Digestive	Vomiting	11	13.1%	6	7.1%
Skin & Appendages	Rash	2	2.4%	5	5.9%

Source Data: Table 6.3.2

(Reference: vol. 14, p 110)

For treatment-related side effects of the gastrointestinal system, vomiting was reported by 13.1% of subjects on azithromycin 600 mg but only 7.1% of clarithromycin 500 mg recipients. However, the incidence of nausea was very similar in both groups, i.e., 14.3% of subjects assigned to azithromycin 600 mg and 11.8% of subjects receiving clarithromycin 500 mg.

Ten subjects (11.9%) who received azithromycin 600 mg and four subjects (4.7%) who received clarithromycin had treatment-related side effects related to the special senses body system. Four subjects (42E0118, 5500971, 74E1013 and 80E0268) treated with azithromycin 600 mg reported abnormal vision. Terms used by the investigator to describe these vision abnormalities were "visual floaters", "blurred vision", "different color perception", and "bilateral amblyopia and scotomas". All were mild in severity except the bilateral amblyopia which was moderate. One subject (74E1013) reported abnormal color perception which was not found on color vision testing. Another subject

(42E0118) with a complaint of visual floater and later found to have defective red-green color vision did not have a recurrence while on treatment. The last subject (5500971) had blurred vision which resolved on therapy.

In addition to the vision abnormalities attributed to the special senses body system, four subjects (4.8%) assigned to azithromycin 600 mg (64E0024, 42B0180, 42B0373 and 80E0268) and two subjects (2.4%) assigned to clarithromycin 500 mg (42B0220 and 57B0234) reported deafness. Three of these four subjects assigned to azithromycin 600 mg (64E0024, 42B0373 and 80E0268) and one of the subjects assigned to clarithromycin 500 mg (42B0220) had audiometric examinations. Subject 64E0024 was noted to have mild, left-sided, sensorineural loss with no right-sided deficit. Subject 42B0373 had no loss on either side. No results were provided for subject 80E0268. The one subject (42B0220) assigned to clarithromycin 500 mg had no loss on either side.

Azithromycin-250 mg treatment group:

Treatment-emergent, all causality side effects were reported by 65.1% of the subjects assigned to the azithromycin 250 mg treatment phase. Severe side effects were noted in 22.2% of these individuals and discontinuations due to side effects occurred in 4.8%. At least one intercurrent illness was noted in 79.4% of the subjects and the overall incidence of clinically significant laboratory abnormalities was 73% for these individuals. There were no significant findings related to ophthalmologic and audiometric exams.

Azithromycin 250 mg continuation therapy group:

Treatment-emergent, all causality side effects occurred in 17/34 of the subjects enrolled in the azithromycin maintenance regimen. Severe side effects were noted in 8/34 of these subjects. At least one intercurrent illness occurred in 32/34 of subjects and clinically significant laboratory abnormalities were noted in 19/29 subjects. There were no significant findings apparent during ophthalmologic exam.

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**Laboratory Test Abnormalities:**

The applicant provided an analysis of laboratory data for patients with normal baseline values and for all patients regardless of baseline abnormalities. These are displayed in the following two tables.

**All Patients:**

Incidence of Selected (either group $\geq$ 15%) Clinically Significant Laboratory Test Abnormalities				
Parameter	Criteria*	Azithromycin 600 mg	Clarithromycin 500 mg	
Hemoglobin	<0.8 X baseline	18/75 (24%)	16/72 (22%)	
Hematocrit	<0.8 X baseline	18/75 (24%)	14/72 (19%)	
RBC count	<0.75X baseline	16/75 (21%)	15/72 (21%)	
WBC count	<2.5 X10 <sup>3</sup> /mm <sup>3</sup>	31/75 (41%)	18/73 (25%)	
Neutrophils (abs)	<0.5 X LLN	16/75 (21%)	9/73 (12%)	
Lymphocytes (abs)	<0.5 X LLN	22/75 (29%)	9/73 (12%)	
Albumin	<0.8 X LLN	13/79 (16%)	9/76 (12%)	
SGOT (AST)	>3.0 X ULN	15/79 (19%)	8/76 (11%)	
Alkaline Phosphatase	>3.0 X ULN	16/80 (20%)	15/77 (19%)	
BUN	>1.3 X ULN	12/81 (15%)	8/78 (10%)	

\*Secondary criteria were applied when baseline was abnormal (Appendix I, Tables 4.1, 4.2)  
 Source Data: Table 7.1

**Incidence of Clinically Significant Laboratory Abnormalities in Subjects with Initial Normal Baseline**

Parameter	Criteria*	Azithromycin 600 mg	Clarithromycin 500 mg
Overall Incidence		16/80 (20%)	9/75 (12%)
Hemoglobin	<8 G/DL	4/8 (50%)	2/6 (33%)
Platelets	<50 X 10 <sup>3</sup> /MM <sup>3</sup>	2/59 (3%)	0/56 (0%)
WBC count	<1.0 X 10 <sup>3</sup> /MM <sup>3</sup>	1/25 (4%)	1/22 (5%)
Neutrophils (abs)	<0.5 X LLN	10/52 (19%)	6/36 (16%)
SGOT (AST)	>5.0 X ULN	1/35 (3%)	0/37 (0%)
SGPT (ALT)	>5.0 X ULN	2/56 (4%)	0/56 (0%)
Alkaline Phosphatase	>5.0 X ULN	3/36 (8%)	0/41 (0%)

\* = Criteria utilized in the past to characterize this subject population with many laboratory abnormalities

LLN = lower limit of normal; ULN = upper limit of normal

Source Data: Table 7.3

**Medical Officer Comment:**

*There were similar differences in laboratory outliers between the clarithromycin and azithromycin treatment groups. There was a slightly higher number of patients reported to have elevated liver function tests compared to baseline. A further analysis of the effect of azithromycin on liver function is discussed in the review of the integrated summary of safety (See below).*

**Medical Officer Summary of Safety:**

*In general, there were no new, unexpected adverse events seen in these studies. There is a general impression that there was slightly more nausea and vomiting in the azithromycin 600 mg daily group than in the clarithromycin 500 mg bid group. The clinician should be aware that rare cases of reversible hearing impairment can occur with this treatment.*

*Please refer to section 6 for further review of integrated summary of safety.*

## 5.2 FDA Efficacy Analyses (Study 189)

This section will deal with the various FDA analyses performed to evaluate the efficacy of azithromycin for the treatment of MAC. The emphasis will be on the azithromycin 600 mg dose. In general, the FDA statistical reviewer was able to validate the various analyses the applicant performed (for complete review see Dr. Silliman's review). The efficacy seen with azithromycin 600 mg compared to clarithromycin 500 mg bid was less rapid and fewer patients reached the endpoint of sterilization of blood cultures by 24 weeks. The degree of certainty regarding this analysis was questioned due to the wide confidence intervals. In addition to this evidence, the applicant provided a literature review of the efficacy of other treatments for MAC. Most of these were older studies, with small numbers of patients. A straightforward statistical evaluation of these studies could not be done. However, the general impression based upon these studies, in vitro data and animal models is that azithromycin is active against MAC.

The Medical Officer and the Microbiology Reviewer performed additional exploratory analyses (see details below). Because of the nature of the endpoint (sterilization of blood cultures, [REDACTED] missing culture results at various timepoints, and the fact that other studies analyzed this data in a different manner, it was felt that an analysis similar to the one performed for the original approval of clarithromycin for this indication would be warranted. The medical officer also plotted individual patient's colony counts over time. Finally, the microbiology reviewer performed a microbiologically evaluable analysis. In general, these analysis were consistent with the demonstration of activity of azithromycin for the treatment of MAC.

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**Medical Officer Analysis of Culture Data from Clinical Study 189:**

Within the Intent-to-Treat patient set a categorical, longitudinal analysis was performed similar to that in the original clarithromycin treatment NDA. The display of data enables the reader to discover what effect missing data and discontinuations have on the overall efficacy outcome. It appears that the addition of ethambutol has resulted in a relatively small number of relapses during therapy, which had not been the case in the original clarithromycin (monotherapy) studies. In general, it can be seen that approximately 1/3 of patients discontinued or died during the 24 week study. Clarithromycin was able to sterilize blood cultures more rapidly than azithromycin, as was expected. Statistical testing was not applied to these rates, however, it appears that the two treatments have a similar efficacy by 24 weeks in this analysis.

	WEEK 3 % (n)	WEEK 6 % (n)	WEEK 12 % (n)	WEEK 16 % (n)	WEEK 24 % (n)
<b>Azithromycin 600 mg/d</b>					
Negative culture	22.4 (15)	41.8 (28)	41.8 (28)	40.3 (27)	34.3 (23)
Decreased	28.4 (19)	17.9 (12)	14.9 (10)	7.5 (5)	6.0 (4)
Persistent	40.3 (27)	14.9 (10)	1.5 (1)	0.0 (0)	0.0 (0)
Relapse	0.0 (0)	1.5 (1)	4.5 (3)	11.9 (8)	10.4 (7)
Not determined	1.5 (1)	6.0 (4)	7.5 (5)	9.0 (6)	0.0 (0)
Discontinued	4.5 (3)	11.9 (8)	19.4 (13)	16.4 (11)	25.4 (17)
Death	3.0 (2)	6.0 (4)	10.4 (7)	14.9 (10)	23.9 (16)
<b>TOTAL</b>	<b>100.0 (67)</b>	<b>100.0 (67)</b>	<b>100.0 (67)</b>	<b>100.0 (67)</b>	<b>100.0 (100)</b>
<b>Clarithromycin 500 mg/bid</b>					
Negative culture	32.7 (18)	41.8 (23)	49.1 (27)	41.8 (23)	30.9 (17)
Decreased	25.5 (14)	14.5 (8)	5.5 (3)	3.6 (2)	1.8 (1)
Persistent	20.0 (11)	9.1 (5)	3.6 (2)	0.0 (0)	3.6 (2)
Relapse	0.0 (0)	1.8 (1)	5.5 (3)	7.3 (4)	12.7 (7)
Not determined	9.1 (5)	12.7 (7)	7.3 (4)	10.9 (6)	0.0 (0)
Discontinued	10.9 (6)	14.5 (8)	16.4 (9)	16.4 (9)	25.5 (14)
Death	1.8 (1)	5.5 (3)	12.7 (7)	20.0 (11)	25.5 (14)
<b>TOTAL</b>	<b>100.0 (55)</b>				

**Definitions:**

**Negative:** CFU = 0

**Decreased:**  $\geq 1$  log decrease from baseline AND NO prior negative response

**Persistent:** CFU with  $< 1$  log decrease or any increase from baseline AND no prior negative response

**Relapse:** ANY positive CFU FOLLOWING A NEGATIVE BACTERIOLOGIC RESPONSE

**Not determined:** no culture result recored within visit window

**Discontinue:** discontinuation with no further bacteriologic reports

**Death.**

**Assessment of Microbiology Data from Clinical Study 189 and 89B: Treatment of Disseminated MAC (by Linda Gosey, quoted from her NDA review)**

**Incidence of Microbiologically proven MAC events:**

A total of 68 and 57 subjects were enrolled in the azithromycin and clarithromycin arms of study 189, respectively. As per the protocol design subjects were to receive therapy for a total of 24 weeks. After completing 24 weeks of therapy subjects were enrolled in study 189B and followed for relapse. After looking at the data it was noted that a number of the subjects enrolled in the study did not have routine blood drawn for mycobacterial culture at weeks, 3, 6, 9, 12, 16, 20 and 24. This is unfortunate, as these data were needed to address the primary and secondary microbiologic objectives.

In an effort to address the microbiologic objectives (i.e. microbiologic outcome after 24 weeks of treatment, durability of sterility of blood and the incidence of relapse) this reviewer chose to focus on subjects that had blood cultures routinely evaluated for MAC up to weeks 20 or 24. However, to include as many subjects as possible in this analysis 4 additional patients were added. Three additional patients were added to the clarithromycin arm, one who completed 12 weeks and 2 who completed 16 weeks of therapy. One patient that completed 17 weeks of therapy was added to the azithromycin arm. As a consequence, there were 40/68 (59%) azithromycin and 32/57 (56%) clarithromycin patients that were considered microbiologically evaluable.

For study 189 microbiologic efficacy was defined as follows:

Microbiologic cure: patients whose blood was MAC free at the end of therapy

Microbiologic failure: patients who continued to have MAC in their blood at week 20 or 24

Relapse: subjects who were MAC free at the end of therapy but had a positive blood culture for MAC during the post therapy follow-up period

A number of observations were made regarding this FDA microbiologically evaluable subset of subjects. The first evaluation measured the number of microbiologic cures, failures and relapses broken down by the baseline mycobacterial burden (See tables below).

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**Clarithromycin Therapeutic Response Rates  
 Separated by Baseline Mycobacterial Burden**

BASELINE MAC CFU/mL	CURE	RELAPSE	FAILURE	TOTAL
1-10	8	4	0	12
11-25	1	2	0	3
26-50	2	0	0	2
51-100	3	0	2	5
101-200	1	0	0	1
201-500	2	1	1	4
501-1000	0	0	0	0
>1001	2	2	1	5
<b>TOTAL</b>	<b>19</b>	<b>9</b>	<b>4</b>	<b>32</b>

\*- One patient developed a drug resistant strain on day 141 of therapy and only had one additional culture on day 197, which was negative for MAC.

**Azithromycin 600 mg Therapeutic Response Rates  
 Based on Baseline MAC Burden**

BASELINE MAC CFU/ml	CURE	RELAPSE	FAILURE	TOTAL
1-10	4	4	1	9
11-25	6	4	2	12
26-50	2	0	0	2
51-100	0	0	1	1
101-200	3	3	0	6
201-500	3	1	2	6
501-1000	0	0	0	0
>1001	1	1	2	4
<b>TOTAL</b>	<b>19</b>	<b>13</b>	<b>8</b>	<b>40</b>

It is well known that MAC burden in the blood is a surrogate marker for severity of disease. Thus the hypothesis would be that the higher the MAC burden at baseline the more likely these patients will either fail or relapse. MAC burden at baseline was looked at in log10 increments. In the azithromycin and clarithromycin arms the total number of subjects that failed were 8/40 (20%) and 4/32 (12.5%), respectively. For azithromycin

patients with baseline MAC cultures of <10, <100, <1000 and >1000 CFU/mL there was a failure rate of 11%, 33%, 8% and 50%, respectively. In the clarithromycin arm the failure rate was 0%, 29%, 20% and 20% for patients with baseline MAC burdens of <10, <100, <1000 and >1000 CFU/mL, respectively. While these numbers are small there is a slight trend suggesting that patients with a high CFU count at baseline who received azithromycin versus clarithromycin therapy were more likely to fail.

**Assessment of Relapse:**

At the end of 24 weeks of therapy (in a few cases the end of therapy was at week 20) 32/40 (80%) subjects in the azithromycin arm and 28/32 (87.5%) subjects in the clarithromycin arm had cleared MAC from their blood. Patients receiving complete therapy were chosen for this assessment to determine if the proposed therapeutic dosing would be adequate not only to sterilize the blood but reduce the incidence of relapse. Of the 32 azithromycin patients that cleared MAC from the blood 13 (41%) relapsed. Only 9/28 (32%) of the clarithromycin subjects that were MAC free at week 24 relapsed.

Patients were further evaluated to determine the length of time patients remained MAC free, as well as the time relapse occurred. For these evaluations a time point of 6 months post therapy (180 days post therapy) was chosen.

**Rate of Relapse in Microbiologically Evaluable Patients who had Sterile Blood Cultures after Receiving 20 or 24 weeks of Azithromycin or Clarithromycin Therapy**

NUMBER OF PATIENTS	AZITHROMYCIN	CLARITHROMYCIN
PATIENTS WITH < 180 DAYS FOLLOW-UP DATA	15	8
STERILE BLOOD CULTURES or ASYMPTOMATIC	7	5*
RELAPSE MAC POSITIVE BLOOD CULTURES	8	3
PATIENTS WITH > 180 DAYS FOLLOW-UP DATA	10	16
STERILE BLOOD CULTURES or ASYMPTOMATIC	5	10
RELAPSE MAC POSITIVE BLOOD CULTURES	5	6
NO FOLLOW-UP DATA	7	4

\*- One patient developed a drug resistant strain on day 141 of therapy and only had one additional culture on day 197, which was negative for MAC.

The above data table shows that 25/32 (78%) and 24/28 (86%) of the patients who obtained sterile blood cultures at the end of therapy and received azithromycin and clarithromycin therapy, respectively, had follow-up data. In the azithromycin arm 10/25 (40%) subjects were followed for greater than 180 days post therapy. In the clarithromycin arm 16/24 (67%) of the patients completing therapy were followed for greater than 6 months post therapy.

When relapse rates were assessed it was observed that 13/25 (52%) and 9/28 (32%) of the subjects in the azithromycin and clarithromycin arms, respectively, relapsed. In the azithromycin arm approximately one-half of the subjects followed for < 180 days, as well as > 180 days post therapy relapsed. In the clarithromycin arm, 3/8 and 6/16 (38% each) of the subjects followed for less than 180 days and greater than 180 days relapsed. While the number of subjects followed post therapy are small, the data do suggest that patients who received clarithromycin therapy are less likely to relapse than are those who received azithromycin therapy. The data also suggest that the time to relapse is longer for those subjects who received clarithromycin versus azithromycin.

**Assessment of Susceptibility Data:**

(For complete description of susceptibility methodology, please refer to Microbiology Review.)

In clinical trial 189 susceptibility testing was conducted against the MAC isolates recovered at baseline, at the time of relapse (post therapy) or failure. Azithromycin MIC values ranged from [redacted] 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.

The ability to determine which MAC isolates were resistant to azithromycin or clarithromycin is impossible as the breakpoint for separating susceptible and resistant MAC isolates has not been established for either macrolide. However, it is of interest to note that all twelve MAC isolates that had clarithromycin MICs >32 µg/ml also had azithromycin >128 µg/ml, suggesting total cross resistance between the two drugs.

The ability to interpret MAC isolates with azithromycin MICs of [redacted] is less clear as there were only a few isolates that fell into this drug susceptibility range. At this point in time it is unknown if MAC isolates with azithromycin MIC values in this range indicate resistance to azithromycin or reduced activity against MAC. As a consequence, clinicians should be cautious when interpreting azithromycin MIC values as an indicator for drug activity against MAC infections.

The reviewing microbiologist also assessed the relationship between azithromycin and clarithromycin MIC values to determine if MAC isolates with high azithromycin MICs also had high clarithromycin MICs. For the purpose of this review a sharp increase in MICs over time was used as a guide to suggest emergence of drug resistance. The FDA microbiology reviewer grouped the MAC isolates from the evaluable patients under the

following MICs values; azithromycin at <16, >16-<32, >32-<128, >128µg/mL and clarithromycin at <1, >1-<4, >4-<32, >32µg/mL.

The following tables show the number of MAC isolates from the evaluable subset of patients falling under the various drug categories. Because the number of patients that were microbiologically evaluable is small, the in vitro susceptibility data can, at best, only enlighten us as to the rate with which MAC organisms develop resistance to azithromycin as well as the frequency of cross resistance between azithromycin and clarithromycin.

**SUSCEPTIBILITY PATTERNS OF MAC ISOLATES  
AT VARIOUS TIME POINTS-AZITHROMYCIN 600 MG ARM**

MAC ISOLATE	AZITHROMYCIN (µg/mL) MIC					CLARITHROMYCIN (µg/mL) MIC				
	<16	≥16-<32	≥32-<128	≥128	ND	≤1	≥1-<4	≥4-<32	≥32	ND
BASELINE	27	10	3			23	16	1		
RELAPSE	2	1*	1	4**3	6	1	3*		4*	6
FAILURE	4	2	0	2		4	2	0	2	

\*: One patient had a mixed culture with MAC isolates having high and low MICs

**SUSCEPTIBILITY PATTERNS OF MAC ISOLATES  
AT VARIOUS TIME POINTS-CLARITHROMYCIN ARM**

MAC ISOLATE	AZITHROMYCIN (µg/mL) MIC					CLARITHROMYCIN (µg/mL) MIC				
	<16	≥16-<32	≥32-<128	≥128	ND	≤1	≥1-<4	≥4-<32	≥32	ND
BASELINE	23	6	3			15	16	1		
RELAPSE		1		4	4		1		4	4
FAILURE	1	2		1			3		1	

Susceptibility test results obtained from the reference laboratory were used to assess potential drug resistance. There was a total of 6 MAC isolates in the azithromycin arm that had high MICs for both azithromycin and clarithromycin, >128 µg/mL and >32 µg/mL, respectively. In the clarithromycin arm there were five MAC isolates with high macrolide MIC values. It should be noted that the sponsor identified an additional patient-

with high macrolide MICs, however, the susceptibility testing was conducted at the local laboratory and the MIC data were not available for an independent review. These results suggest that the rate of drug resistance development is low in both treatment arms. A total of 4/6 (66%) and 4/5 (80%) of the MAC isolates with high macrolide MICs in the azithromycin and clarithromycin arms, respectively, occurred in patients who relapsed. The remaining MAC isolates occurred in patients who failed therapy. These data show that MAC isolates that develop high azithromycin MICs also develop high clarithromycin MICs indicating cross resistance.

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## **6 Safety Evaluation (Integrated Summary of Safety)**

The integrated summary of safety provided by the applicant included 716 subjects in the Phase II/III clinical studies of azithromycin in the treatment of MAC, 630 of whom received azithromycin and 86 of whom received a comparative drug. Safety data are also presented for 923 subjects who received azithromycin for non-MAC infections, for 15 subjects in miscellaneous and terminated studies, and for 90 subjects treated in Phase I clinical trials, including 75 subjects who received azithromycin. Safety data for studies not conducted by the sponsor were presented separately (these represent the pulmonary MAC studies).

The primary aim of the applicant in presenting this data was to describe the safety in patients treated for disseminated MAC as well as pulmonary MAC. In addition, subset analyses were performed to describe the experience in the geriatric and pediatric data sets. No studies were performed exclusively for these subsets of patients. Given the long term daily exposure of azithromycin that the treatment of disseminated MAC or pulmonary MAC would necessitate, it is important to review this safety database to ensure a profile similar to that which has been already described in the current label. One major concern was the effect of long-term dosing and its potential for inducing reversible hearing loss, which is reported among antibiotics in the macrolide class. To this end the applicant performed audiograms within these studies.

The major results of the safety analyses are reported by the applicant and followed by medical officer comments.

### **6.2 Extent of drug exposure**

The majority of individuals who participated in the MAC treatment studies were male (86.5%) and between 18 and 44 years of age (74.0%). This is not unexpected, given that three of the protocols limited enrollment to subjects with AIDS, who (at the time and place these studies were conducted) were predominantly young men. Most subjects in the MAC treatment studies were White (71.3%), but Black and Hispanic subjects were also represented (17.3% and 8.0% of subjects, respectively). In the MAC treatment studies, the mean age of the pediatric subjects was 7.7 years (range: 1.2 to 17.6 years).

Overall, the mean duration of treatment exposure to azithromycin was longer for both the pediatric subjects (241.9 days) and the geriatric subjects (206.8 days) than for the adult, non-geriatric subjects (107.1 days). The mean overall exposure (all patients in the database regardless of treatment assignment) was greater for the geriatric subjects (113326.7 mg) than for the adult, non-geriatric subjects (71693.9 mg). The overall exposure for the pediatric subjects was less than for either of the other two groups, but valid comparisons are not possible because no adjustment is made for the lower body weight of the pediatric subjects.

When considering only the studies for disseminated MAC and those treated with azithromycin the duration of exposure was longer in general. The duration of treatment was shorter for the adult, non-geriatric subjects (119.8 days) than for either the pediatric subjects (385.0 days) or the geriatric subjects (237.0 days). The mean overall exposure

was less for the adult, non-geriatric subject (64494.6 mg) than for the geriatric subjects (128716.0 mg) and was also less than the mean extent of exposure for the pediatric subjects (77178.0 mg), even without any adjustment for the low body weight of the pediatric patients. This may result from the exclusion of the pediatric and geriatric subjects from some fixed-duration protocols.

The duration of clarithromycin treatment in the MAC studies included only the clarithromycin treatment arm from study 189 (planned duration 3 months); therefore the duration of treatment was close to 3 months (88 days). In contrast, subjects received azithromycin in compassionate use or extension studies of indefinite length. Therefore, the majority of azithromycin-treated subjects received more than 90 days of azithromycin treatment.

**Medical Officer Comment:**

*It is important to evaluate this data base due to the higher exposure and longer duration of therapy with azithromycin administered here than that given for the Non-HIV indications (usual recommended dose 250 mg for approximately 5-10 days). In addition, the comparison with clarithromycin in the 189 study will be important to place adverse events into perspective, given the extensive co-morbidities associated with patients with "advanced" HIV disease.*

**6.3 Adverse events**

**6.3.1 All causalities and treatment related (overall)**

In the pivotal and primary supportive MAC studies, subjects who received 1200 mg of azithromycin (78.7% [all causality] and 68.1% [treatment-related]) had higher overall incidences of side effects (all causality and treatment-related) than subjects who received the 600 mg-dose (61.5% and 63.1% [all causality] and 53.8% and 50.0% [treatment-related]) or the 250 mg dose (65.1% [all causality] and 55.6% [treatment-related]). The body systems most commonly affected at all azithromycin doses were the digestive system and the body as a whole. The incidences of digestive system and special senses side effects were higher for subjects receiving the 1200 mg dose of azithromycin than for subjects receiving the 250 mg dose or the 600 mg dose. Gastrointestinal disturbances (nausea, vomiting, diarrhea and abdominal pain [body as a whole]) were the predominant side effects (all causality and treatment-related) reported in the pivotal and primary supportive MAC studies. Treatment-related hearing impairment was also reported (from a low of 0% to a high of 10.6% in the pivotal and primary supportive studies).

Treatment-Emergent Side Effects (All Causality) by Body System - Pivotal and Primary Supportive MAC Studies						
	Number (%) of Subjects					
	Azithromycin				Clarithromycin	
	250 mg	500 mg	600 mg	1200 mg	500 mg bid	189
Study Number	189	131	148	189	148	189
Evaluable	63	28	39	64	47	65
With at least one Side Effect	41 (65.1)	20 (71.4)	24 (61.5)	53 (83.1)	37 (78.7)	56 (86.9)
Body System						
Body as a whole	11 (17.5)	6 (21.4)	9 (23.1)	31 (38.9)	18 (38.3)	28 (32.9)
Cardiovascular	1 (1.6)	0	1 (2.6)	0	1 (2.1)	2 (2.4)
Digestive	27 (42.9)	19 (67.9)	15 (38.5)	39 (48.4)	30 (63.8)	29 (34.1)
Hemic and Lymphatic	3 (4.8)	0	0	7 (8.3)	1 (2.1)	6 (7.1)
Metabolic and Nutritional	5 (7.9)	0	2 (5.1)	7 (8.3)	1 (2.1)	5 (5.9)
Musculoskeletal	2 (3.2)	0	0	3 (3.6)	0	1 (1.2)
Nervous	11 (17.5)	3 (10.7)	3 (7.7)	13 (15.5)	6 (12.6)	14 (16.5)
Respiratory	2 (3.2)	0	2 (5.1)	7 (8.3)	1 (2.1)	7 (8.2)
Skin and Appendages	9 (12.7)	0	2 (5.1)	10 (11.9)	4 (8.5)	17 (20.0)
Special Senses	4 (6.3)	0	5 (12.6)	14 (16.7)	10 (21.3)	9 (10.6)
Urogenital	3 (4.8)	0	2 (5.1)	5 (6.0)	0	3 (3.5)

Ref: 131-Table 6.2.1, 148-Table 6.2.1 and 189-Table 6.2.1

Treatment-Emergent Side Effects (Treatment-Related) by Body System - Pivotal and Primary Supportive MAC Studies						
	Number (%) of Subjects					
	Azithromycin				Clarithromycin	
	250 mg	500 mg	600 mg	1200 mg	500 mg bid	189
Study Number	189	131	148	189	148	189
Evaluable	63	28	39	64	47	65
With at least one Side Effect	35 (55.6)	19 (67.9)	21 (53.8)	42 (50.0)	32 (68.1)	41 (48.2)
Body System						
Body as a whole	8 (12.7)	5 (17.9)	8 (20.5)	21 (25.0)	13 (27.7)	19 (22.4)
Cardiovascular	1 (1.6)	0	1 (2.6)	0	1 (2.1)	0
Digestive	24 (38.1)	17 (60.7)	13 (33.3)	31 (38.9)	28 (59.5)	25 (29.4)
Hemic and Lymphatic	1 (1.6)	0	0	1 (1.2)	1 (2.1)	1 (1.2)
Metabolic and Nutritional	2 (3.2)	0	0	4 (4.8)	0	2 (2.4)
Musculoskeletal	0	0	0	1 (1.2)	0	0
Nervous	7 (11.1)	2 (7.1)	0	3 (3.6)	4 (8.5)	8 (9.4)
Respiratory	0	0	1 (2.6)	0	1 (2.1)	0
Skin and Appendages	8 (9.5)	0	2 (5.1)	4 (4.8)	1 (2.1)	9 (10.6)
Special Senses	3 (4.8)	0	4 (10.3)	10 (11.9)	6 (12.6)	4 (4.7)
Urogenital	1 (1.6)	0	2 (5.1)	2 (2.4)	0	1 (1.2)

Ref: 131-Table 6.2.2, 148-Table 6.2.2 and 189-Table 6.2.2

**Medical Officer Comment:**

*In general, it appears that the side effect profile of azithromycin is similar to that of clarithromycin, especially when comparing the results from study 189. However, there does appear to be a dose relationship for azithromycin regarding some of the adverse events. This will be explored below within specific categories of events, e.g. hearing impairment, gastrointestinal toxicity.*

*The side effect data from the other studies included in this submission (MAC and non-MAC) support the conclusions derived from the pivotal and primary supportive MAC studies discussed above.*

**6.3.2 All causality and treatment related (600 mg Azithromycin)**

Clarithromycin was provided as a comparative agent in Study 189. The overall incidence of side effects (all causality) was similar for subjects receiving 600 mg of azithromycin

(63.1%) and subjects receiving 500 mg bid clarithromycin (65.9%) in Study 189. The body systems most frequently involved were the digestive system, the body as a whole, the skin and appendages and the nervous system. The azithromycin treatment group had higher incidences of digestive system and special senses side effects, while the clarithromycin treatment group had higher incidences of side effects attributed to the skin and appendages. The distribution of the side effects affecting the remaining body systems was comparable for subjects receiving azithromycin (600 mg) and clarithromycin in Study 189. Gastrointestinal disturbances (such as nausea, vomiting, diarrhea and abdominal pain [body as a whole]) were the most commonly reported side effects for azithromycin- and clarithromycin-treated subjects. The incidence of severe side effects was similar for the azithromycin (20.2%) and clarithromycin (23.5%) treatment groups. The all causality incidence of deafness was similar for azithromycin (4.8%) and clarithromycin-treated subjects (5.9%).

In Study 189, the incidences of treatment-related side effects were similar for the azithromycin (50.0%) and clarithromycin (48.2%) treatment groups. The azithromycin treatment group had higher incidences of digestive system side effects (treatment-related), while the clarithromycin treatment group had higher incidences of side effects (treatment-related) attributed to the skin and appendages and the nervous system. Gastrointestinal disturbances (such as nausea, vomiting, diarrhea and abdominal pain [body as a whole]) were the most commonly reported treatment-related side effects for azithromycin- and clarithromycin-treated subjects.

Treatment-Emergent Side Effects (≥5% in any Group [All Causality])						
Study Number	Number (%) of Subjects					
	Azithromycin 600mg				Clarithromycin 500 mg bid	
	148		189		189	
	All Caus	Tri-Rel	All Caus	Tri-Rel	All Caus	Tri-Rel
Evaluable	39	39	84	84	85	85
With at least one side effect Event (Preferred Term)	24 (61.5)	21(53.6)	53 (63.1)	42 (50.0)	50 (58.9)	41 (48.2)
Abdominal Pain	6 (15.4)	6(15.4)	15 (17.9)	12 (14.3)	16 (18.8)	13 (15.3)
Asthenia	0	0	6 (7.1)	1 (1.2)	2 (2.4)	1 (1.2)
Back Pain	0	0	0	0	5 (5.9)	0
Fever	2 (5.1)	1(2.6)	2 (2.4)	2 (2.4)	1 (1.2)	0
Headache	1 (2.6)	1(2.6)	7 (8.3)	4 (4.8)	5 (5.9)	2 (2.4)
Constipation	2 (5.1)	1(2.6)	2 (2.4)	0	7 (8.2)	3 (3.6)
Diarrhea	4 (10.3)	3(7.7)	15 (17.9)	10 (11.9)	11 (12.9)	8 (9.6)
Flatulence	1 (2.6)	1(2.6)	6 (7.1)	4 (4.8)	11 (12.9)	10 (11.9)
Nausea	10 (25.6)	8(20.1)	14 (16.7)	12 (14.3)	13 (15.3)	10 (11.9)
Vomiting	4 (10.3)	1(2.6)	16 (19.0)	11 (13.1)	7 (8.2)	6 (7.1)
Agonia	0	0	6 (7.1)	1 (1.2)	2 (2.4)	1 (1.2)
Hypokalemia	2 (5.1)	0	1 (1.2)	1 (1.2)	0	0
Isomnia	0	0	5 (6.0)	1 (1.2)	1 (1.2)	1 (1.2)
Cough increased	2 (5.1)	1(2.6)	2 (2.4)	0	1 (1.2)	0
Dysnea	0	0	2 (2.4)	0	5 (5.9)	0
Alopecia	0	0	1 (1.2)	1 (1.2)	5 (5.9)	1 (1.2)
Maculopapular Rash	0	0	2 (2.4)	0	5 (5.9)	2 (2.4)
Rash	2 (5.1)	2(5.1)	3 (3.6)	2 (2.4)	9 (10.6)	5 (5.9)
Abnormal Vision	1 (2.6)	0	6 (7.1)	4 (4.8)	2 (2.4)	0
Deafness	4 (10.3)	4(10.3)	4 (4.8)	4 (4.8)	5 (5.9)	2 (2.4)

Ref: 148-Tables 6.3.1 and 6.3.2 and 189-Tables 6.3.1 and 6.3.2  
 All Caus = All Causality; Tri-Rel = Treatment-Related

**Medical Officer Comment:**

*It is of interest to note that there may be a relationship between hearing impairment and increasing doses of azithromycin. This will be explored in a later section discussing this side effect specifically. Abnormal vision was monitored because of the use of ethambutol in study 189. While it was reported more frequently in the azithromycin group, the numbers are small. Most of the effect appeared to be related to impairment of red-green color vision which is a known side effect of ethambutol.*

**6.3.3 Serious adverse events**

Of the 1685 subjects who received azithromycin and the 218 subjects who received a comparative agent or placebo in the development program (including the 42 subjects in ACTG Study 156), a total of 1647 serious adverse event cases were entered into the SAE database as of the November 22, 1999 cutoff date, including 1545 cases for subjects receiving azithromycin, 96 cases for subjects receiving comparative drugs and 6 cases for subjects receiving placebo. Fifty (50) cases reported by azithromycin-treated subjects and 2 cases reported by comparative agent-treated subjects were considered treatment-related by the investigators.

Seven hundred and seventeen (717) serious adverse event cases were reported for 630 azithromycin-treated MAC subjects and 96 cases were reported for 86 comparative agent-treated MAC subjects. Twenty-seven (27) cases reported by azithromycin-treated MAC subjects and 2 cases reported by comparative agent-treated MAC subjects were considered treatment-related by the investigators.

Seven hundred and seventeen (717) serious adverse event cases were reported for 630 azithromycin-treated MAC subjects and 96 cases were reported for 86 comparative agent-treated MAC subjects. The most commonly affected body systems (all causality) for azithromycin-treated MAC subjects were resistance mechanisms (341 cases), respiratory (130 cases) and gastrointestinal (90 cases). The most common events for azithromycin-treated MAC subjects were AIDS (239 events), bacterial infection (84 events), fever (51 events), pneumonia (42 events), procedures (41 events), sepsis (41 events) and retinitis (40 events). Resistance mechanisms (39 cases) and respiratory (18 cases) were the most frequently involved body systems for subjects receiving comparative agents. The most common event reported by comparative agent-treated MAC subjects was AIDS (26 events).

Twenty-seven (27) cases reported by azithromycin-treated MAC subjects and 2 cases reported by comparative agent-treated MAC subjects were considered treatment-related by the investigators. The body systems most frequently involved for azithromycin-treated MAC subjects were the gastrointestinal system (13 cases), body as a whole (6 cases), hearing/vestibular (7 cases) and resistance mechanisms (6 cases). The most commonly reported treatment-related events were fever (6 events), vomiting (6 events) and decreased hearing (6 events).

**Medical Officer Comment:**

*Narratives of serious adverse events were reviewed. From that review, it is clear that the types and distribution of serious adverse events reported reflects more the nature of the*

*severity of the underlying disease, AIDS, status of the patients enrolled in these studies. When treatment related events are reviewed, the expected profile of events is seen. Note that hearing disturbances will be discussed below. As noted in the pivotal comparative study (189); treatment-emergent events were similar between the two groups and were mostly related to the gastrointestinal system.*

### **6.3.3.1 Deaths**

#### **Overall Rates Entire Data Base:**

As of November 22, 1999, 871 (51.7%) of the 1685 subjects who received azithromycin during the clinical program died. Additionally, 44 (33.3%) of the 132 comparative-agent treated subjects and 2 (2.3%) of the 86 placebo-treated subjects died. This difference in the overall number of deaths for azithromycin-treated subjects and comparative agent and placebo-treated subjects is expected since the majority of the studies in this submission were open-label, non-comparative studies of no fixed duration. Only two of the 871 deaths reported for azithromycin-treated subjects (cardiomyopathy and cerebral toxoplasmosis plus AIDS) were considered possibly related to study drug by the investigators. The sponsor attributed the death due to cerebral toxoplasmosis and AIDS to the subject's pre-existing AIDS and the death due to cardiomyopathy to complications of the underlying disease.

#### **Rates for Patients Treated for MAC:**

Included in the total number of deaths (871) are the deaths of 367 (58.3%, 367/630) azithromycin-treated subjects and 44 (51.2%, 44/86) comparative agent-treated subjects with MAC.

#### **Rates in Study 189:**

In study 189 there were similar rates of death for azithromycin and clarithromycin (at 24 weeks: 23.5% (16/68) for azithromycin 600 mg vs 26.3% (15/57) for clarithromycin).

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

*Case reports and narratives provided by the applicant were reviewed regarding death (n=31). The review again confirmed the advanced nature of the comorbid disease, AIDS, which underlies the disease being treated, MAC. It does not appear that azithromycin 600 mg directly contributed to the death of the patients being studied.*

## **6.4 Discontinuation from study**

### **6.4.1 Discontinuation due to adverse events**

In Study 189, the overall incidences of discontinuation from the study for subjects receiving azithromycin (600 mg) and those receiving clarithromycin (500 mg bid) were similar (60.3% vs 66.4%). However, the incidence of discontinuation due to side effects (all causality) was nominally higher for subjects receiving azithromycin (9/88, 10.2%) than for subjects receiving clarithromycin (4/86, 4.7%). The incidence of discontinuation due to treatment-related side effects was 8.0% (7/88) for subjects receiving azithromycin (600 mg) and 4.7% (4/86) for subjects receiving clarithromycin. Gastrointestinal disturbances were the most common side effects leading to discontinuation for both

azithromycin and clarithromycin-treated subjects. There were no reports of discontinuation from Study 189 due to hearing abnormalities.

Throughout the clinical program the most common side effects leading to discontinuation of the study were gastrointestinal in nature (i.e., diarrhea, vomiting, abdominal pain [body as a whole], nausea etc.). Discontinuation due to hearing abnormalities (including tinnitus) were also reported.

**Medical Officer Comment:**

*FDA review is in agreement with the above. Again the most common adverse events were related to the gastrointestinal system.*

**6.4.2 Discontinuation due to laboratory abnormalities**

In most of the studies of azithromycin in the treatment of MAC and non-MAC opportunistic infections, the majority of subjects had laboratory abnormalities. Hematological abnormalities were especially frequent. There were also a small number of subjects who discontinued treatment because of liver function test elevations. However, it is not possible to associate any specific abnormalities with azithromycin treatment because many of these subjects had serious underlying or intercurrent illnesses and received a wide variety of concomitant medications. Furthermore, there were no apparent consistent changes from baseline.

The overall incidence of discontinuation due to laboratory test abnormalities was low (1.1% for subjects receiving 600 mg in Study 189) with increased liver function tests being the most frequently reported abnormality leading to discontinuation from the study.

**Medical Officer Comment:**

*Discontinuation due to laboratory abnormalities did not uncover any unexpected events. Liver function abnormalities will be discussed below. Patients entering these studies frequently have increased liver function tests at baseline. The liver function abnormalities are considered below.*

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6.5 Laboratory Abnormalities:

Laboratory Abnormalities - MAC Studies						
Study Number	Number (%) of Subjects					
	Azithromycin					Clarithromycin
	250 mg	500 mg	600 mg	1000 mg	148	500 mg bid
Total Number of Subjects	85	29	41	88	47	86
Lab Parameter (criteria*)	Number Abnormal/ Number Evaluable (%)					
Any Laboratory Abnormality	44/80 (73)	20/28 (71)	25/38 (66)	65/81 (80)	32/45 (71)	53/78 (68)
Hemoglobin (<0.5x baseline)	14/54 (26)	7/28 (27)	14/38 (38)	18/75 (24)	9/44 (20)	18/72 (22)
Hematocrit (<0.8x baseline)	11/83 (21)	3/28 (12)	13/38 (38)	19/75 (24)	9/44 (20)	14/72 (19)
RBC count (<0.75x baseline)	8/54 (15)	3/28 (12)	NA	18/75 (24)	NA	15/72 (21)
Platelets (<75 10 <sup>9</sup> /mm <sup>3</sup> )	3/54 (6)	2/28 (8)	3/38 (8)	4/75 (6)	1/44 (2)	7/71 (10)
Platelets (>700 10 <sup>9</sup> /mm <sup>3</sup> )	0/54 (0)	1/28 (4)	0/38 (0)	1/75 (1)	0/44 (0)	1/71 (1)
WBC count (<2.5 10 <sup>9</sup> /mm <sup>3</sup> )	12/54 (22)	5/28 (19)	10/38 (28)	31/75 (41)	10/44 (23)	18/73 (25)
WBC Count (>17.5 10 <sup>9</sup> /mm <sup>3</sup> )	3/54 (6)	0/28 (0)	0/38 (0)	4/75 (6)	0/44 (0)	1/73 (1)
Neutrophils (<0.5x LLN)	8/53 (17)	1/28 (4)	3/31 (10)	18/75 (21)	5/38 (13)	8/73 (12)
Neutrophils (>1.5x ULN)	4/53 (8)	0/28 (0)	0/31 (0)	7/75 (9)	0/38 (0)	3/73 (4)
Eosinophils (>1.5x ULN)	3/53 (6)	0/25 (0)	1/31 (3)	2/75 (3)	0/37 (0)	0/73 (0)
Lymphocytes (<0.5x LLN)	8/53 (17)	14/28 (54)	12/31 (39)	22/75 (28)	9/38 (24)	8/73 (12)
Lymphocytes (>1.5x ULN)	0/53 (0)	0/28 (0)	0/31 (0)	1/75 (1)	0/38 (0)	0/73 (0)
Total bilirubin (>1.5x ULN)	3/58 (5)	1/28 (4)	0/38 (0)	3/79 (4)	0/45 (0)	1/78 (1)
Total Protein (<0.8x LLN)	1/8 (11)	0/28 (0)	1/38 (3)	0/18 (0)	0/45 (0)	1/15 (7)
Total Protein (>1.2x ULN)	0/8 (0)	0/28 (0)	0/38 (0)	0/18 (0)	1/45 (2)	1/15 (7)
Albumin (<0.8x LLN)	12/58 (21)	4/28 (15)	4/38 (11)	13/79 (16)	3/45 (7)	8/78 (12)
Albumin (>1.2x ULN)	0/58 (0)	0/28 (0)	0/38 (0)	0/79 (0)	0/45 (0)	0/78 (0)
SGOT (>3.0x ULN)	8/58 (14)	0/28 (0)	4/38 (11)	15/79 (19)	5/45 (11)	8/78 (11)
SGPT (>3.0x ULN)	4/58 (7)	0/28 (0)	2/38 (6)	10/80 (13)	6/45 (13)	4/77 (5)
AP (>3.0x ULN)	8/58 (14)	1/28 (4)	8/38 (21)	18/80 (22)	3/45 (7)	15/77 (19)
BUN (>1.3x ULN)	7/58 (12)	2/28 (8)	2/38 (6)	12/81 (15)	2/45 (4)	8/78 (10)
Creatinine (>1.3x ULN)	3/58 (6)	1/28 (4)	2/38 (6)	3/81 (4)	2/45 (4)	8/78 (10)
Sodium (<0.85x LLN)	0/58 (0)	1/28 (4)	0/38 (0)	2/81 (2)	0/45 (0)	1/77 (1)
Sodium (>1.05x ULN)	1/58 (2)	0/28 (0)	0/38 (0)	0/81 (0)	0/45 (0)	1/77 (1)
Potassium (<0.9x LLN)	3/58 (6)	0/28 (0)	5/38 (14)	4/81 (5)	0/45 (0)	3/77 (4)
Potassium (>1.1x ULN)	1/58 (2)	0/28 (0)	0/38 (0)	0/81 (0)	1/45 (2)	2/77 (3)

\* Criteria - Primary abnormality criteria (applied to on-treatment laboratory data for subjects with normal baseline).  
 Secondary criteria were used for subjects with abnormal baseline value.  
 NA = Not Applicable  
 Ref: 131-Tables 1.1 and 7.1, 148-Tables 1.1 and 7.1, 189-Tables 1.1 and 7.1

The most common laboratory abnormalities were decreased hematocrit, hemoglobin, WBC and lymphocyte counts.

**Azithromycin 600 mg Dose:**

In the 600 group for Study 148, the overall rate of laboratory test abnormalities was 25 of 36 subjects (69.4%). The most frequently reported laboratory abnormalities were decreased hemoglobin (14 of 36 subjects, or 38.9%), decreased hematocrit (13 of 36 subjects, or 36.1%) and decreased lymphocytes (12 of 31 subjects, or 38.7%).

Any effect of azithromycin treatment on clinical laboratory tests would be difficult to detect in the pivotal and primary supportive studies, given the high rate of laboratory abnormalities in the study population. Thus, the results of Study 189, which included a clarithromycin comparator arm, are particularly important in elucidating the laboratory safety profile for azithromycin at the dose recommended for treatment of MAC infection.

The majority of subjects in both of the treatment groups had at least one laboratory abnormality; i.e., azithromycin 600 mg: 65 of 81 subjects (80.2%) and clarithromycin 500mg bid, 53 of 78 subjects (67.9%). The most common abnormalities involved hematologic and liver function tests. Generally, the incidence of these abnormalities was similar between the two dosing groups with the exception of decreases in WBC count, neutrophils and lymphocytes. These occurred with slightly greater frequency in those subjects receiving azithromycin.

**Azithromycin at Other Doses:**

Azithromycin was provided at a dose of 500 mg for 10, 20 or 30 days in Study 131. In the 500 mg treatment phase of Study 131, the most common laboratory test abnormalities predominantly involved hematologic tests, particularly decreases in hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, and absolute lymphocytes. The incidence of decreased serum albumin was 4 of 26 subjects, or 15.4%.

The overall incidence of clinically significant laboratory test abnormalities in the 1200 mg group in Study 148 was 71.1% (32 of 45) of subjects (148-Table 7.1). The most common abnormalities were decreased lymphocytes (9 of 38 subjects, or 23.7%), decreased WBC count (10 of 44 subjects, or 22.7%), decreased hematocrit and hemoglobin (9 of 44 subjects, or 20.4%). The laboratory abnormalities seen in the azithromycin 250 mg treatment arm of Study 189 were similar to those in the study's other treatment regimens. The overall rate of clinically significant abnormalities were 73.3% (44 of 60 subjects), and the most common types of abnormalities involved hematologic and liver function tests.

**Medical Officer Comment:**

*Since this drug is being given chronically and at high doses, it is important to understand the significance of laboratory abnormalities. Attribution of abnormal test results is very difficult given the underlying disease (AIDS) and the multidrug regimens these patients are receiving.*

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In order to elucidate the drug effect on the liver, a review of patients in study # 189 was conducted. This allows the comparison of azithromycin to that of the approved therapy clarithromycin in this extremely ill patient population. Patients who had SGOT levels 3 times the upper limit of normal were selected for review. From this group further assessment as to morbidity or adverse outcome was reviewed. The table which follows illustrates the maximum SGOT abnormality measured, and associated maximum Total Bilirubin levels.

<b>SGOT VALUES &gt; 3.0 x ULN in Study 189</b>				
<b>Azithromycin 600 mg</b>	<b>SGOT max (uln 36)</b>	<b>T. Billi (uln 1.2)</b>	<b>Baseline SGOT ABN?</b>	<b>Death (Time post RX)</b>
189 07G0965	229 (Decreasing)	1.8 then back to nl	Y (45)	N
189 16G0350	516 (NF)	nl	Y (56)	Y (4 mos)
189 31A0601*	173 (NF)	1.4	Y (120)	Y (9 days)
189 42B0063	104 (NF)	1.1	Y (126)	Y (3 mos)
189 42B0089	139 (NF)	nl	Y (69)	Y (6 mos)
189 54E0026	173 (Resolved)	nl	Y (49)	Y (7 mos)
189 54E0028	126 (Resolved)	nl	Y (66)	Y (12 mos)
189 54E0079	226 (Cont'd)	nl	Y (174)	Y (5 mos)
189 5500339	446 (NF)	2.6	UNKN	Y (6 mos)
189 57B0067*	283 (NF)	1.6	Y (55)	Y (3 days)
189 57B0314*	153 (Resolved)	nl	Y (80)	Y (1 day)
189 64E0024	133 (NF)	nl	Y (54)	Y (2.5 mos)
189 65E0131	118 (NF)	nl	N (27)	Y (2 mos)
189 76A0050	133 (Resolved)	nl	Y (258)	Y (2 mos)
189 78E0632	196 (Resolved)	nl	Y (74)	Y (3 mos)
189 7990214	119 (NF)	--	Y (56)	N
189 7990307	132 (NF)	1.2	Y (50)	Y (4 mos)
189 80E0200	115 (Resolved)	1.02	N (31)	Y (4 mos)
189 82E0146	119 (NF)	nl	Y (54)	Y (4 mos)
<b>Clarithromycin</b>	<b>SGOT max (uln 36)</b>	<b>T. Billi (uln 1.2)</b>	<b>Baseline SGOT ABN?</b>	<b>Death</b>
189 19A0031	108 (NF)	nl	N (28)	Y (4 mos)
189 32A0013	107 (Resolved)	1.3	Y (66)	N
189 42B0178	121 (Resolved)	1.7	Y (73)	N
189 42B0217	106 (Resolved)	1.0	Y (79)	N
189 54E0025	119 (Resolved)	nl	Y (43)	N
189 54E0080	195 (Decreasing)	nl	Y (67)	Y (24 mos)
189 54E0225	325 (Decreasing)	nl	Y (53)	Y (7 mos)
189 57B0315	188 (Resolved)	nl	Y (81)	N
189 59E0076	262 (Decreasing)	1.8	Y (88)	N
189 7990614	158 (NF)	nl	Y (40)	N
189 79E0441*	106 (Resolved)	1.3	N (24)	Y (1 mo)
189 80E0272	169 (Resolved)	1.3	Y (44)	Y (14 mos)

\*Note: patients who died in less than 35 days post treatment were reported in narratives by the applicant. These deaths were due to AIDs progression, PCP pneumonia, AIDS wasting, and pneumonia. There were no reports of death due to liver disease.

NF= not followed

It should be noted that all of the patients had accompanying total bilirubin levels that were normal or slightly elevated during study. Most of these patients had abnormal SGOT values at baseline. Finally, patient status regarding death was reviewed. While

*more patients on the azithromycin arm in this analysis died, none were reported to have died due to liver failure. All death reports attributed deaths to progression of HIV/AIDS.*

#### **6.6 Assessment of drug relationship for selected adverse events**

The overall incidence of treatment-related hearing abnormalities coding to deafness, in the combined opportunistic infection database, was 4.6% (68/1475) for azithromycin-treated subjects and 2.4% (2/85) for clarithromycin-treated subjects. Deafness is a COSTART term. These subjects had a reduction in their hearing threshold, but did not have a complete loss of hearing. For azithromycin-treated subjects, the majority of these abnormalities were mild or moderate in severity (86%, 78/91 events) and were known to have resolved or were not reported at subsequent visits. The mean day of onset was day 96 with a mean total exposure at onset of 59,297 mg. Subjects reporting severe deafness had higher mean total exposure at onset (118,904 mg) than subjects reporting mild or moderate deafness (49,430 mg). Audiological testing was performed in the treatment phase of Study 189 with any suspicion of hearing loss. Comparison of the audiometric assessments revealed no apparent differences between the azithromycin 600 mg group and the clarithromycin group.

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

*Review of these data demonstrate that reversible hearing impairment does occur within the treatment groups in < 5% of patients. Clarithromycin had a slightly lower rate. It appears that this is an effect that did lead to discontinuation in a small number of patients. Most events were graded mild or moderate. The applicant was asked to place this information in the label.*

#### **7 Special populations: Gender, age and ethnic group**

The applicant performed analyses by all subsets, gender, age and ethnic group. As the majority of the patient population was white and male, the analysis of the gender and ethnic groups was not helpful due to the small number of patients in these groups. No conclusions could be drawn. Below are analyses by age group for the pediatric and geriatric populations.

#### **7.2 Geriatric population**

Thirty (30) geriatric subjects (i.e., 65 years of age or older) received azithromycin in clinical studies of the treatment of MAC and non-MAC opportunistic infections. Eleven (11) of the subjects (36.7%) had side effects (10 treatment-related, 1 non-treatment-related) given as the reason for discontinuation. The most frequently reported treatment-related side effects by body system were for the digestive system and special senses (7 subjects, 23.3%); an observation also made in studies of azithromycin (not conducted by the sponsor) that included elderly subjects with pulmonary MAC. There were a total of 14 deaths; 8 were during or within 35 days of treatment. In addition to the deaths, there were 5 other subjects with SAEs; 1 of these was considered related to study drug(s) (i.e., vertigo, emesis and nystagmus).

*Medical Officer Comment: In general these events are similar to those seen in the overall patient group. There was a somewhat higher rate of adverse events related to the*

*gastrointestinal system and special senses. Given the fact that no additional studies will be performed for this infection, it is important to include some information in the labeling regarding this patient experience.*

### **7.3 Pediatric population**

Seventy-two (72) pediatric subjects (i.e., less than 18 years of age) received azithromycin in clinical studies of the treatment of MAC and non-MAC opportunistic infections. Two subjects (2.8%) discontinued due to side effects. Two more subjects had side effects or SAEs that were noted as leading to discontinuation, although their discontinuations were attributed to reasons other than adverse events. Treatment-related side effects by body system were most frequent for the digestive system (10 subjects, 13.9%), and the most frequently reported adverse event was abdominal pain (6 subjects, or 8.3%). Forty-eight (48) of the 72 pediatric subjects had SAEs; 31 of these subjects died and 22 of these deaths were within 35 days of treatment. There were 2 additional deaths in subjects less than 18 years of age who (as a result of demographic and treatment information missing from the case report form database) were not included among the 72 treated pediatric subjects. Four of the SAEs among the 72 treated pediatric subjects were considered related to study drug(s) (i.e., manic behavior (1), hearing loss (2), and tinnitus, fever, oral thrush, herpes simplex and hearing loss (1)).

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

*This information is important to convey in the label because the dose is higher and prolonged compared to the usual dose and duration used to treat upper respiratory tract infections. As stated above, no additional studies will be performed for this indication due to the very limited number of cases that occur presently. It is felt that the disease, disseminated MAC, has the same pathogenesis in pediatric patients as in adults. Pharmacokinetic studies were performed and submitted in this NDA. Please see clinical biopharmacokinetics report for further information. The applicant was instructed to include information on adverse events regarding hearing. In addition, a description of the duration and dosage given to these patients with opportunistic infections should be included in the label. Consideration for a pediatric indication for the treatment of disseminated MAC will be further considered in the future based upon additional information which will be supplied by the applicant.*

### **8 FDA summary of efficacy and safety**

It is the opinion of this reviewer that the regimen of azithromycin 600 mg daily plus ethambutol has been demonstrated to be effective in the treatment of disseminated MAC infection in HIV infected patients. In comparison with the combination of clarithromycin and ethambutol, the rate at which blood cultures are sterilized is somewhat slower, and the overall rates of microbiologic response is somewhat less. This difference is acceptable given the information presented by the applicant regarding other studies and clinical reports of the natural history and outcomes of various poorly tolerated therapies. While no statistical comparison can be made due to the nature of the historical database and the lack of comparability of the data, it is apparent that this serious infection was treated by this regimen as discussed within the body of this review.

Regarding safety, the results of clinical studies in more than 1600 subjects who received azithromycin 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. Cases of reversible hearing impairment were noted in a small number of cases at all ages.

### 9 Regulatory recommendations

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.

### 10 Label review

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 disseminated MAC.

### References:

CDC: Surveillance for AIDS-Defining Opportunistic Illnesses, 1992-1997. Jeffrey L. Jones, M.D., M.P.H.(1) Debra L. Hanson, M.S.(1) Mark S. Dworkin, M.D., M.P.H.T.M. (1) David L. Alderton, Ph.D.(1) Patricia L. Fleming, Ph.D.(1) Jon E. Kaplan, M.D.(1),(2) John Ward, M.D.(1) 1 Division of HIV/AIDS Prevention-Surveillance and Epidemiology, National Center for HIV, STD, and TB Prevention 2 Division of AIDS, STD, and TB Laboratory Research, National Center for Infectious Diseases. MMWR April 16, 1999 / 48(SS-2);1-22

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Original NDA 21-061  
HFD-590/Div. Dir/Goldberger  
HFD-590/Dep. Div. Dir/Albrecht

HFD-590/TI/Cavaillé-Coll  
HFD-590/MO/Korvick  
HFD-590/Chem/Holbert  
HFD-520/Micro/Gosey  
HFD-880/BioPharm/Colangelo  
HFD-520/Pharmtox/McMaster  
HFD-725/Biometrics/Silliman  
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