

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

JUL 7 2000

STATISTICAL REVIEW AND EVALUATION

NDA#(s): 50-730, SE1-005 and SE1-006

Name of Drug: ZITHROMAX® tablets (azithromycin)

Applicant: Pfizer Inc.

Indication(s): Treatment of infections due to *Mycobacterium avium* Complex (MAC)

Documents Reviewed: Volumes 1-3 and 12-55, dated Jan. 13, 2000 and electronic submission

Review Type: Clinical data

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I. INTRODUCTION

The sponsor submitted one pivotal, Phase III, controlled clinical trial in support of the use of oral azithromycin 600 mg once daily in combination with ethambutol for the treatment of *Mycobacterium avium* complex (MAC)-infection. This is trial 066-189, hereafter referred to as study 189. This trial also included an open-label, noncomparative, maintenance phase, referred to as trial 066-189B, which was conducted in patients who initially responded to treatment. This phase assessed long-term safety. Patients in trial 066-189B were given oral azithromycin 250 mg plus ethambutol once daily. Study 189 will be the focus of this review.

Other "supportive" studies submitted by the sponsor for treatment of MAC infection are not reviewed here as they used different dosing regimens. In addition, the two trials submitted by the sponsor in support of the use of azithromycin in pulmonary MAC infection will not be reviewed here as they are both single-center, uncontrolled clinical trials. The lack of a control group in these two trials precludes this reviewer from making any statements about efficacy of azithromycin in pulmonary MAC infection.

Study 189 was designed to assess the safety and efficacy of azithromycin for the treatment of disseminated MAC in patients with AIDS. The study began with three treatment arms: azithromycin 250 mg once daily plus ethambutol, azithromycin 600 mg once daily plus ethambutol, and clarithromycin 500 mg twice daily plus ethambutol, each

administered orally for 24 weeks. The low dose azithromycin arm was dropped during an interim analysis due to the fact that it had a significantly lower 12 week sterilization rate compared to the clarithromycin arm. There was no significant difference between the two azithromycin arms at the interim analysis. The final study analysis compared high dose azithromycin (600 mg) plus ethambutol to clarithromycin plus ethambutol. For the primary efficacy endpoint, sterilization rates at week 24, azithromycin 600 mg plus ethambutol failed to show that it was similar to the clarithromycin plus ethambutol regimen. In the intent-to-treat analysis, the lower bound of the confidence interval around the difference in rates suggested that high dose azithromycin could be as much as 30% less effective than clarithromycin. In the per-protocol analysis, the lower bound of the confidence interval around the difference in rates suggested that high dose azithromycin could be as much as 46% less effective than clarithromycin. High dose azithromycin was not found to be significantly worse than clarithromycin, however. Analyses of the secondary endpoints generally confirmed the conclusion from the primary analysis, i.e., that high dose azithromycin plus ethambutol is not similar to clarithromycin plus ethambutol.

Study 189B followed patients for long-term safety and efficacy, using a non-comparative, open-label format. Patients in study 189B were given a "maintenance" dose of oral azithromycin 250 mg plus ethambutol once daily. Relapse rates tended to be higher in patients who were originally randomized to the high dose azithromycin arm, compared to rates in patients originally randomized to clarithromycin. Differences were not significant, however.

Section II describes study 189 in more detail. Section III summarizes the highlights of study 189B. Section IV provides conclusions.

II. STUDY 189

Reviewer's Comment: Much of the following is taken directly from the sponsor's electronic submission. Reviewer comments will be highlighted in italics, and analyses performed by this reviewer will be marked as such.

Study Objectives

The purpose of study 189 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 *Mycobacterium avium* complex (MAC) infection and to determine whether a regimen containing azithromycin was at least as safe and effective as clarithromycin plus ethambutol.

STUDY DESIGN

This was a multicenter, double-blind, double-dummy, randomized study comparing azithromycin 600 mg/day plus ethambutol, azithromycin 250 mg/day plus ethambutol, and clarithromycin 500 mg twice daily plus ethambutol administered orally for 24 weeks to subjects with AIDS for treatment of disseminated MAC. Subjects were to have culture evidence of MAC infection at baseline [subjects at European sites were permitted to enroll subjects with MAC diagnosed on the basis of clinical signs/symptoms and/or a positive culture]. For both US and European sites, the diagnosis was to be confirmed by a positive quantitative culture at baseline for the subject to remain in the study. Subjects were to be reevaluated bacteriologically and clinically for signs/symptoms every three weeks for the first 12 weeks, and monthly thereafter through week 24.

It should be noted that an interim analysis of blinded data was performed in July 1996 and as a result the azithromycin 250 mg treatment arm was terminated due to a relative lack of efficacy compared to the other treatment arms.

Reviewer's Note: The azithromycin 250 arm was found to be significantly less effective than clarithromycin in terms of week 12 sterilization rates in the observed case analysis (there was no difference in the ITT LOCF analysis). There was no difference between the azithromycin 250 and azithromycin 600 arms in terms of week 12 sterilization rates in either analysis. Finally, there were no significant treatment differences in death rates (between any of the treatment groups).

The sample size was originally planned to be 300 with 100 subjects in each of three treatment arms. Assuming the given study size of 100 subjects per group yielded approximately 75 evaluable subjects per group, and assuming that clarithromycin has a 75% true rate of positive bacteriological response (sterilization or partial mycobacteremia), then, for any azithromycin dose that has the same true rate, the probability that the lower endpoint of the 2-sided 95% confidence interval on the difference in response rates (azithromycin-clarithromycin) will be above -20% (the protocol specified delta for equivalence) was calculated to be 0.81.

Reviewer's Note: The delta of 20% was specified for the endpoint "positive bacteriologic response", defined as either sterilization or a 1 log reduction in colony count (cfu/ml) since the beginning of therapy. At the time that the sponsor specified 20% as the delta, FDA reviewers cautioned the sponsor that 20% was a rather large difference and asked them to consider a smaller delta. In addition, FDA reviewers stated that if the lower bound of the confidence interval for the difference in rates (azithromycin minus clarithromycin) actually approached 20%, this would be a cause for concern and that the division would be especially interested in the analysis of durability of treatment response (i.e., relapse rates).

The primary endpoint was changed to "sterilization at week 24" before data analysis began. This was agreed to by both the sponsor and FDA. As the expected response rate for this endpoint is necessarily lower than that for "positive bacteriologic response", which is a combination of either sterilization or a 1 log reduction in colony counts, it would seem that use of a 20% delta for equivalence for this endpoint is even more concerning. Note that in this study the observed sterilization rate for clarithromycin at week 24 was only 56%.

The actual sample size deviated from the protocol and there were 65 subjects in the azithromycin 250 mg arm, 91 subjects in the azithromycin 600 mg arm, and 90 subjects in the clarithromycin arm. Only subjects with a baseline positive culture were eligible for the efficacy analysis. In the azithromycin 250 mg arm there were 47 (72.3 %) subjects eligible, in the azithromycin 600 mg arm there were 68 (74.7 %) subjects eligible, and, in the clarithromycin arm, there were 57 (63.3 %) subjects eligible. These numbers do not account for other sources of dropouts. Since the actual sample size was smaller than planned (and the azithromycin 250 mg arm had fewer subjects since this arm was terminated as a result of the interim analysis) and the percentage of subjects eligible for efficacy analyses was also smaller than planned (especially in light of the evaluability criteria), the bounds of the two-sided 95.1% confidence intervals (adjusted for the interim

analysis) for the difference in response rates (azithromycin - clarithromycin) are broader than originally anticipated.

Reviewer's Note: In addition, the observed response rate of the primary efficacy variable (sterilization at week 24) for the azithromycin 600 mg arm was about 10% lower than that for clarithromycin. This contributes greatly to the failure of the azithromycin 600 arm to demonstrate equivalence to clarithromycin. In fact, while the observed 95.1% confidence interval for the difference in sterilization rates failed to demonstrate equivalence using a 20% delta, had the azithromycin 600 arm been able to obtain the same sterilization rate as clarithromycin, the 95.1% confidence interval for this hypothetical scenario would have shown equivalence using a 20% delta. More specifically, the trial showed a 46% response rate for azithromycin 600 and a 56% response rate for clarithromycin, with a 95.1% confidence interval for the difference in sterilization rates (azithromycin 600 minus clarithromycin) of (-29.7, 8.6). If azithromycin 600 had also been able to obtain a 56% response rate, then the 95.1% confidence interval for the difference in rates would have been (-19.4, 18.9). These intervals are constructed using the normal approximation to the binomial distribution incorporating the continuity correction.

EFFICACY ANALYSIS

Primary Endpoint

The primary endpoint was:

Sterilization at Week 24 - Defined as two consecutive negative 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 method for the missing data.

Secondary Endpoints

The secondary bacteriologic endpoints included sterilization (using both central and local laboratory data), time to sterilization, time to first positive culture after sterilization (relapse), positive bacteriologic response [sterilization and/or reduction from baseline of \geq 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). Secondary clinical endpoints included 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.

SUBJECT SUBSETS AND 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 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)

STATISTICAL METHODOLOGY

General

Per protocol, the comparison between the azithromycin 600mg group and the clarithromycin group would be examined first. If the confidence interval for the true difference in response rates met the requirements of equivalence, then the confidence interval for the difference between azithromycin 250 mg (therapeutic) and clarithromycin would be examined. No adjustments for multiple comparisons were made since this procedure kept the rate of false inference of equivalence for either of the azithromycin doses with clarithromycin to no more than 5% per efficacy variable.

The primary model tested for equivalent treatment effects unadjusted for center. This model was used for dichotomous, ordinal and continuous endpoints. Additional analyses are described in the sensitivity analysis section below.

One subject received a concomitant antibiotic potentially effective against MAC for treatment failure and this subject was considered both a clinical and bacteriologic failure from the time of receiving the concomitant antibiotic.

An interim analysis was performed when 50% of the patients had completed week 12 of the study. The sterilization rates and corresponding confidence intervals for each pairwise comparison of treatment groups at Week 12 were presented to the clinical team. An azithromycin treatment group was to be dropped if it is shown to be clinically less efficacious compared with one or both of the other treatment groups based on the 99.9% confidence intervals in sterilization rates. Specifically, an azithromycin treatment group will be dropped if the upper limit of the 99.9% confidence interval for the difference in sterilization rates (Azithromycin - comparison group) is less than zero. A treatment group will also be dropped if it is shown to be "poorly tolerated" relative to one or both of the other treatment groups based on the 95% confidence intervals for the difference in death rates. Specifically, an azithromycin treatment group will be dropped if the lower limit of the 95% confidence interval for the difference in death rates (Azithromycin - comparison group) is greater than zero.

Reviewer's Note: In the original protocol, the sponsor only mentions a comparison of each azithromycin group to clarithromycin during the interim analysis. Azithromycin 250 was to be compared to clarithromycin first to determine whether to drop the azithromycin 250 arm. After that decision had been made, azithromycin 600 was to be compared to clarithromycin to determine whether to continue the study or stop for lack of efficacy.

The level of significance for the final analysis is 0.049 as a result of the 0.001 adjustment for the interim analysis. Therefore, 95.1% confidence intervals were used for all inferences.

As a result of the interim analysis the azithromycin 250 mg arm was dropped. Therefore, the procedure described above was not used. Thus, the primary comparison was azithromycin 600 mg versus clarithromycin 500 mg. Comparisons of azithromycin 250 mg and clarithromycin were not emphasized. Comparisons of the terminated azithromycin 250 mg arm were made with the azithromycin 600 mg arm.

Reviewer's Note: As the sponsor was unable to demonstrate equivalence between high dose azithromycin and clarithromycin, they compared high dose azithromycin to low dose azithromycin in an attempt to establish efficacy for the high dose azithromycin regimen. This comparison was not planned in the protocol. It is not appropriate to compare the terminated azithromycin 250 mg arm with the azithromycin 600 mg arm for several reasons. The first is that this comparison was not planned as part of the multiple comparisons procedure. In effect, the sponsor has "used up" all of their alpha with their plan to first examine azithromycin 600 mg vs. clarithromycin and then only to examine azithromycin 250 mg vs. clarithromycin if the first comparison demonstrated equivalence. The second reason it is not appropriate to compare these two arms is that the azithromycin 250 mg arm was dropped during the interim analysis. There is no hybrid method in the published literature that would allow the combination of the interim azithromycin 250 data with the final azithromycin 600 data. Putting the multiple comparisons issue aside for the moment, we would know neither the appropriate alpha level to use (it would seem that the alpha of .001 from the interim analysis would be too conservative, while the alpha of .049 from the final analysis would be too liberal), nor the appropriate variance to use for the difference between treatment arms.

Missing Data

In general, the intent-to-treat analyses used a last observation carried forward (LOCF) algorithm for missing data for sterilization, positive bacteriologic response, colony count and sponsor defined clinical response. For the other clinical endpoints including signs and symptoms, weight, and investigator defined clinical response, only observed cases were used for the intent-to-treat analysis. For sterilization and positive bacteriologic response, the last observation was carried forward except for specific instances as specified in the algorithm. For colony count, the last observation was carried forward including baseline, if necessary. For sponsor defined clinical response, if one of the three symptoms used in the definition were missing, then that symptom was carried forward. However, baseline symptoms were not carried forward since the possibility existed of carrying forward a good response for that symptom.

Reviewer's Note: It is not clear whether LOCF is a realistic method for estimating missing data in this clinical trial. However, the sponsor performed a large number of sensitivity analyses to assess the impact of imputing missing data on conclusions (including multiple imputation, which this reviewer prefers to LOCF). These analyses will be summarized later in the review.

Sensitivity Analyses

Sensitivity analyses were performed for the following variables: binary sterilization at week 24, time to sterilization, time to death, and time to first positive culture after sterilization (durability of blood sterilization). These analyses fell into three categories: endpoint definition, missing data, and covariate analysis and applied only to the azithromycin 600 mg versus clarithromycin comparison.

Endpoint definition sensitivity analyses involved the definition of sterilization for binary sterilization at week 24 and time to first positive culture after sterilization (durability of blood sterilization). In the protocol, analysis plan, and tables, sterilization is defined as two consecutive negative cultures. For a sensitivity analysis, sterilization was defined as one negative culture and the analyses were performed. For another sensitivity analysis,

sterilization was defined as two consecutive negative cultures with all MAC colony counts recorded as "1" assumed to be zero. When the local laboratory culture (colony count not recorded) was positive, the colony count was assumed to be greater than 1 cfu/ml.

In the protocol, analysis plan, and tables, relapse was defined as any nonzero colony count. A sensitivity analysis was performed for time to first positive culture after sterilization (durability of blood sterilization) where relapse was defined to be two consecutive nonzero MAC colony counts. When local laboratory qualitative cultures (colony count not recorded) were used, two consecutive relapses from the telephone follow-ups were required. A second definition was also used for time to first positive culture after sterilization (durability of blood sterilization) where MAC colony counts recorded as "1" were assumed to be zero. When the local laboratory culture (colony count not recorded) was positive, the colony count was assumed to be greater than 1 cfu/ml.

Missing data sensitivity analyses for binary sterilization at week 24 were performed to determine the effect of the missing data and the last observation carried forward algorithm. A summary of observations that had been carried forward was provided. An additional analysis was done where if a subject had missing data at week 24 because of death, then that subject was considered to be a failure for sterilization at week 24. A second missing data sensitivity analysis was done using post-study central laboratory cultures that were drawn between week 26 and week 32, inclusive. These cultures were used as the subsequent assessment as described in the sterilization algorithm for the week 24 assessment, therefore only the week 24 timepoint was affected by this analysis.

For sterilization at week 24 for the intent-to-treat subset, a multiple imputation analysis was performed as an alternative to the last observation carried forward for missing observations. The colony counts that were collected over time were imputed using the [REDACTED] for missing data analysis 1.0. [REDACTED] for multiple imputation as described by Lavori, Dawson, and Shera (Lavori PW, Dawson R, Shera D. A multiple imputation strategy for clinical trials with truncation of patient data. *Statistics in Medicine* 1995,14:1913-25.) Then sterilization at week 24 was derived from the imputed data. The results from the five imputed data sets were combined to form a confidence interval for the difference in the proportion of subjects sterile.

The following list of covariates collected at baseline were examined for the impact on binary sterilization at week 24, time to sterilization, and time to death: colony count (log base 10), CD4 count (cells/mm³), hemoglobin, alkaline phosphatase, composite score from patient questionnaire (PHI), age, number of previous opportunistic infectious diseases (divided as < 2 diseases to ≥2 diseases), time since CD4 count has been <100 (cells/mm³), MAC prophylaxis use, gender, race (categorized as White and non-White), concomitant protease inhibitor usage (at baseline or at any time during study), location of center (U.S. subjects versus ex-U.S. subjects), timing of enrollment of centers (centers enrolled after the interim analysis versus those enrolled before), daily vs. nondaily fever, and daily vs. nondaily night sweats. Each covariate was examined for the following: unbalanced allocation of the covariates to the treatment groups, significant effects of the covariate which might reduce the width of the confidence interval for the difference in response rates for the treatment groups, and interaction effects where there might be a different effect of the covariate in the treatment groups. If any of these three

criteria were met, then inferences with the model were presented. Other covariates which did not meet these criteria but were of interest were presented without inferences.

RESULTS

Study Subjects

Subject evaluation groups are listed in Table 1. The disposition of the subjects was as follows:

Table 1. Subject Evaluation Groups

Number of Subjects	Azithromycin 250 mg	Azithromycin 600 mg	Clarithromycin 500 mg
Randomized	65	91	90
Treated	65	88	86
Completed Treatment	12	33	29
Discontinued Treatment	53	55	57
Completed Study	13	35	29
Discontinued Study	52	53	57
Completed Treatment and Study	12	33	29
Side Effect Assessment	63	84	85
Laboratory Data Assessment	60	81	78

Seven subjects were randomized but not treated. The primary reasons for not receiving treatment were not meeting selection criteria and subject default.

Reviewer's Note: Note that a higher percentage of azithromycin 250-mg patients discontinued study. This is consistent with the lower efficacy observed in that arm which led to its being dropped during the interim analysis.

Analysis Groups

Table 2 summarizes the number of patients available for each analysis group at the end of the study. The only reason patients were excluded from the ITT analysis was "no baseline pathogen" (23 azithromycin 600 and 33 clarithromycin patients). The main reason patients were excluded from the evaluable analysis, other than no baseline pathogen, was "insufficient data" (28 azithromycin 600 and 26 clarithromycin patients).

Table 2. Analysis Groups

	Azithromycin 600 mg	Clarithromycin
Patients Randomized	91	90
ITT	68 (75%)	57 (63%)
Evaluable (Week 24)	28 (31%)	22 (24%)

Reviewer's Note: Note that approximately a third of patients in each treatment arm are missing data at week 24. This weakens conclusions for both the ITT analysis (where this data is imputed) and the evaluable analysis (where such patients are excluded).

Baseline Characteristics

Baseline characteristics were generally comparable between treatment arms in all populations evaluated (all patients treated, ITT patients, and evaluable patients). Prior use of MAC prophylaxis was similar between treatment groups (approximately 25%), as was the use of protease inhibitors (approximately 33%) before and during therapy.

Reviewer's Note: The sponsor argues that the data in the ITT subgroup suggests a trend in which azithromycin 600 patients were clinically more compromised at baseline than clarithromycin subjects. This reviewer does not agree with that contention, since baseline MAC colony counts were actually lower in the azithromycin 600 group (median log base 10 colony counts were 1.4 cfu/ml in the azithromycin 600 group and 1.8 cfu/ml in the clarithromycin group), which would suggest a trend in the opposite direction (i.e., that clarithromycin patients actually had higher levels of disease at baseline).

Efficacy (Azithromycin 600 mg vs. Clarithromycin)

Table 3 summarizes response rates for various bacteriologic and clinical endpoints in the ITT group at week 24. Recall that sterilization is the primary endpoint of the study. There did not appear to be any large differences in week 24 sterilization rates for different gender, race, or age groups. However, the numbers of patients examined in most of these subgroups were small.

Table 3. Bacteriologic and Clinical Endpoints; ITT Analysis of Week 24

	Azithromycin 600 mg		Clarithromycin			
Bacteriologic Endpoints****						
	N	Obs Rate (%)	N	Obs Rate (%)	95.1% CI*	P-value*
Sterilization	68	45.6	57	56.1	-28.1, 7.0	0.240
Pos Bact Res	68	76.5	57	73.7	-12.5, 18.1	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	--	--
Clinical Endpoints						
	N	Obs Rate (%)	N	Obs Rate (%)	95.1% CI*	P-value*
Death Rate	68	23.5	57	26.3	-18.1, 12.5	0.719
Sponsor Assessment						
Complete Resolution (Cure)	62	25.8	47	36.2	-28.0, 7.2	0.243
Investigator Assessment						
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.

Reviewer's Note: As the pre-specified delta chosen by the sponsor for demonstrating equivalence was 20%, azithromycin 600 plus ethambutol cannot be considered equivalent to clarithromycin plus ethambutol in the treatment of MAC infections as measured by sterilization rates at week 24. The observed sterilization rate for azithromycin 600 plus ethambutol was 10% lower than that of clarithromycin plus ethambutol, and the lower bound of the 95.1% confidence interval around the difference in rates suggests that azithromycin 600 plus ethambutol could be as much as 28% less effective than clarithromycin plus ethambutol. If one uses the continuity correction when constructing the confidence interval, the inference is that azithromycin 600 plus ethambutol could be 30% less effective than clarithromycin plus ethambutol. This is rather concerning given the fact that clarithromycin plus ethambutol only achieved a 56% sterilization rate. For example, if ethambutol alone could be assumed to achieve somewhere in the range of a 26% sterilization rate, then azithromycin 600 would appear to contribute no efficacy to the combination regimen of azithromycin 600 and ethambutol. This reviewer was unable to find a historical control rate for ethambutol given alone in the literature.

Recall that the sponsor has tried to argue that the small sample size of the study is mostly to blame for the lack of equivalence demonstrated. Suppose for a moment that azithromycin 600 plus ethambutol had, in fact, been able to achieve the same observed sterilization rate as clarithromycin plus ethambutol (i.e., 56%). If this had happened, then the lower bound of the two-sided 95.1% confidence interval around the difference in rates (constructed using the continuity correction) would have been -19% and the study would, in fact, have demonstrated equivalence of the two treatment regimens. At any rate, a small sample size is a possible explanation for a failed study, but is not grounds for establishing efficacy.

Finally, note that the rates for positive bacteriologic response and clinical improvement are similar between treatment groups, while the rates for sterilization and complete clinical cure are substantially lower in the azithromycin 600 group. This suggests that while azithromycin 600 may be similar to clarithromycin in terms of achieving partial response, it is not able to achieve a similar complete response rate.

Table 4 summarizes sterilization rates at week 24 for azithromycin 600 and clarithromycin patients who were considered evaluable.

Table 4. Sterilization at Week 24; Evaluable Analysis

	Azithromycin 600 n/N (%)	Clarithromycin n/N (%)	95.1% CI (azithromycin – clarithromycin)
Sterilization	18/28 (64%)	18/22 (82%)	(-41.6, 6.5)

Reviewer's Note: The difference in observed sterilization rates is even larger in the evaluable patients than it is in the ITT patients. Azithromycin 600 plus ethambutol achieved 18% lower sterilization rates than clarithromycin plus ethambutol. The lower bound of the 95.1% confidence interval around the difference in rates suggests that azithromycin 600 plus ethambutol could be as much as 42% less effective than clarithromycin plus ethambutol. If the continuity correction is used in calculating the confidence interval, this potential difference widens to 46%.

Table 5 provides a sensitivity analysis of week 24 sterilization rates using alternative endpoint definitions. Sterilization is alternatively defined as two consecutive negative cultures with a colony count of zero (the primary definition for the submission), one negative culture with a colony count of zero, and two consecutive negative cultures based on the assumption that a colony count of 1 cfu/ml was equal to zero. The latter definition serves mostly to quantify the impact of a low burden of organisms on relative bacteriologic efficacy. In an additional analysis, nonsterile subjects included those subjects who had a colony count of greater than zero or who had missing count data due to death (i.e., missing data due to death assumed to be a failure). The latter analysis was done to eliminate potentially unfair attribution of sterility at week 24 due to the last observation carried forward algorithm. Lastly, as described previously, a sensitivity analysis was done using post-study central laboratory cultures obtained between weeks 26 through 32 to determine week 24 sterilization rates. This additional window was used in conjunction with data from the prior visit when week 24 culture data were missing. It was also used to fulfill the definition of sterile (two consecutive negative cultures) when a negative week 24 culture was preceded by a positive culture from the previous visit but followed by a negative post-study culture.

Table 5. Sensitivity Analysis of Week 24 Sterilization Based on Alternative Endpoint Definitions

Definition**	Azithromycin 600 mg		Clarithromycin		Obs Diff (%)	95.1% CI*	P-value*
	N	Obs Rate (%)	N	Obs Rate (%)			
Intent-to-Treat Analysis:							
Two negative cultures	68	45.6	57	56.1	-10.6	-28.1, 7.0	0.240
One negative culture	68	58.8	57	61.4	-2.6	-19.9, 14.7	0.769
MAC cfu/ml of ≤1	68	52.9	57	59.6	-6.7	-24.2, 10.8	0.452
Death=missing=failure	68	41.2	57	47.4	-6.2	-23.7, 11.3	0.487
Post-study data	68	48.5	57	56.1	-7.6	-25.2, 10.0	0.396
Evaluable Subgroup Analysis:							
Two negative cultures	28	64.3	22	81.8	-17.5	-41.6, 6.5	0.171
One negative culture	28	78.6	22	81.8	-3.2	-25.5, 19.0	0.776
MAC cfu/ml of ≤1	28	71.4	22	81.8	-10.4	-33.7, 12.9	0.393
Death=missing=failure	33	54.5	29	62.1	-7.5	-32.1, 17.1	0.549
Post-study data	30	73.3	27	85.2	-11.9	-32.7, 9.0	0.273

Source Data: Table 5.1.1 and Appendix III, Tables 2.1-2.2.2

Obs Rate = Observed Rate; Obs Diff = Observed Difference; CI = Confidence Interval

* Statistical tests: 95.1% confidence interval on the difference (azithromycin 600 mg-clarithromycin) in observed rates and P-value are based on normal approximation; ** All definitions define "sterile" except for death=missing=failure which signifies that missing data due to death equals "bacteriologic failure" and post-study data which signified use of post-study data from weeks 26-32 to determine week 24 sterilization rates (see Section 4, Data

Reviewer's Note: *The sensitivity analysis confirms the results of the original analysis; azithromycin 600 plus ethambutol is not able to achieve similar sterilization rates when compared to clarithromycin plus ethambutol.*

It is not clear from the information submitted by the sponsor whether these sensitivity analyses were planned before or after the data was examined.

Table 6 summarizes the results of an ITT sensitivity analysis of sterilization that was performed using multiple imputation to account for missing data relating to MAC colony counts as an alternative to the last observation carried forward rule used for the primary analysis. Two different models were used: in the first model, treatment was considered a "covariate" for predicting the probability of a subject discontinuing the study for any

reason (dropout), but the imputation was done on all data combined (i.e., azithromycin 600 mg-plus clarithromycin), and in the second model, the imputations were performed separately for each treatment group.

In the imputation analysis using treatment as a covariate, the probability of dropout was modeled from a stepwise selection from treatment group, age, gender, race, protease inhibitor use at any time, baseline night sweats, and number of previous opportunistic infections. These covariates and others were also used for the analysis by treatment groups separately, and different subsets of covariates were selected for each treatment group. For both models, missing colony counts were imputed within a quintile of similar subjects based on the propensity to drop out. Each subject in each of five imputed data sets was classified as either sterile or not sterile at week 24 based on the observed or imputed colony counts. In this analysis, a subject was considered sterile if the colony count was <1 cfu/ml for both weeks 20 and 24; thus colony counts were not rounded to integers.

As can be seen in Table 6, results using multiple imputation were similar to those seen using last observation carried forward.

Table 6. Sterilization at Week 24 Based on Multiple Imputation for Missing Data (ITT Analysis)

Model Used	Az 600 mg		Clarithromycin		Mean Obs Diff	95.1% CI
	N	Mean Obs Rate	N	Mean Obs Rate		
Treatment as Covariate	68	53.5%	57	56.8%	-3.3%	-30.1, 23.5
By Treatment	68	55.9%	57	72.6%	-16.7%	-36.1, 2.6

Source Data: Appendix III, Attachment IV; Appendix III, Attachment IV; Tables 6.1 and 6.2; N=Number of subjects evaluated; Obs Rate=Observed Rate; CI=Confidence Interval; * Sterile equals <1 cfu/ml for both weeks 20 and 24

Colony count at baseline was determined to be the best predictor of sterility at week 24 among the various baseline covariates assessed, with a lower colony count associated with a greater probability of becoming sterile. Protease inhibitor use and prior MAC prophylaxis therapy each were found to have no significant effect on sterility at week 24.

Time to sterilization was also examined. 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. This difference was not significant.

The overall time to relapse (first positive culture after sterilization) or the "durability of sterilization" was not significantly different between groups. However, in general the durability of sterilization appeared to be longer with clarithromycin than azithromycin 600 mg. The hazard ratio (risk of event for azithromycin 600 relative to clarithromycin) on the time to relapse using data from the central laboratory was 2.02 with a 95% confidence interval of (0.50, 8.13), suggesting that patients receiving azithromycin 600 are about twice as likely to experience a relapse compared to clarithromycin. Note that the confidence interval suggests that patients receiving azithromycin 600 could be as much as 8 times more likely to experience a relapse. The corresponding hazard ratio and 95% confidence interval using both central and local laboratory data were 1.71 and (0.73, 3.99), respectively.

Table 7 summarizes death rates at week 12, week 24, and last follow-up for both treatment groups. Death rates were generally comparable. However, confidence intervals were relatively wide due to the small number of patients in the study.

Table 7. Death Rates

Timepoint	Azithromycin 600 mg		Clarithromycin		95.1% CI*	P-value*
	N	Obs Rate (%)	N	Obs Rate (%)		
Intent-to-Treat Analysis						
Week 12	68	10.3	57	12.3	-13.2, 9.2	0.726
Week 24	68	23.5	57	26.3	-18.1, 12.5	0.719
Last Follow-up	68	69.1	57	63.2	-10.8, 22.7	0.482
Evaluable Subgroup Analysis						
Week 12	47	10.6	42	9.5	-11.5, 13.7	0.862
Week 24	44	11.4	39	17.9	-21.9, 8.7	0.395
Last Follow-up	44	68.2	39	64.1	-16.4, 24.6	0.695

Source Data: Table 5.5.1; Obs Rate = Observed Rate based on number of subjects with events; CI=Confidence Interval; * Statistical tests: 95.1% confidence interval on the difference (azithromycin 600 mg-clarithromycin) in observed rates and p-value are based on normal approximation

The overall time to death was comparable between treatment groups, supported by a hazard ratio (risk of event for azithromycin 600 relative to clarithromycin) of 1.08 and corresponding 95% confidence interval of (0.70, 1.67). 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.

Safety (Azithromycin 600 mg vs. Clarithromycin)

Table 8 summarizes treatment-emergent, all causality side effects by treatment group. There appeared to be no substantial differences between the two treatment groups with respect to either incidence of side effects, severity of side effects, or frequency of discontinuation due to side effects.

Table 8. Summary of Treatment-Emergent, All Causality Side Effects

Number (%) of Subjects	Azithromycin 600 mg	Clarithromycin 500 mg
Subjects Evaluable for Side Effects	84	85
Subject-Days of Drug Exposure	8836	8051
Subjects with Side Effects	53 (63.1%)	56 (65.9%)
Side Effects	204	187
Subjects With Severe Side Effects	17 (20.2%)	20 (23.5%)
Subjects Discontinued Due to Side Effects	8 (9.5%)	5 (5.9%)

Table 9 provides a listing of body systems in which at least 5% of subjects in either treatment group experienced a side effect. For the most part, the distribution of side effects among body systems was similar between the two treatment groups. Somewhat more subjects receiving azithromycin 600 mg reported side effects associated with the digestive system (39 of 84, or 46.4%) than did subjects receiving clarithromycin (29 of 85, or 34.1%). The digestive system side effects among azithromycin 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. Side effects attributed to the skin/appendages including alopecia and rash occurred with slightly greater frequency in subjects receiving clarithromycin. Alopecia and rash were reported by 1/84 (1.2%) and 3/84 (3.6%), respectively, of subjects receiving azithromycin 600 mg while 5/85 (5.9%) and 9/85 (10.6%), respectively, of subjects receiving clarithromycin had similar complaints.

Table 9. 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%)

III. STUDY 189B

Study Objectives

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.

Study Design

At the investigator's discretion, subjects with a complete response to treatment by week 24 of study-189 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.

Results

A total of 29 subjects enrolled into the maintenance phase were included in the intent-to-treat analysis. Six additional subjects were excluded from the ITT analysis (2 failed to meet inclusion criteria for the maintenance phase, 3 were positive for MAC at the study 189B baseline, and 1 had been excluded from the study 189 ITT analysis due to no baseline pathogen).

The rate of relapse was 58.3% in subjects randomized to double-blind therapy with azithromycin 600 mg and 27.3% in subjects randomized to clarithromycin. The time to relapse for the first quartile was estimated at 85 days in subjects from the azithromycin 600 mg group and 356 days in subjects from the clarithromycin group. The median time

to relapse was 435 days for subjects in the azithromycin 600 mg group and could not be estimated for subjects in the clarithromycin group. Both the analysis based on quantitative blood cultures and on quantitative and qualitative cultures suggest that the rate of relapse was greater and the time to relapse was earlier in subjects randomized to double-blind therapy with azithromycin 600 mg compared to clarithromycin.

IV. CONCLUSIONS (Which May be Conveyed to the Applicant)

The applicant submitted one controlled clinical study (study 189) conducted in support of the use of azithromycin 600 mg once daily in combination with ethambutol for the treatment of MAC infection and two single-center, uncontrolled clinical studies in support of the use of azithromycin for the treatment of pulmonary MAC infection.

Treatment of MAC Infection

Study 189 began with three treatment arms: azithromycin 250 mg once daily plus ethambutol, azithromycin 600 mg once daily plus ethambutol, and clarithromycin 500 mg twice daily plus ethambutol administered orally for 24 weeks to subjects with AIDS for treatment of disseminated MAC. The low dose azithromycin arm was dropped during an interim analysis due to the fact that it had significantly lower 12 week sterilization rates compared to the clarithromycin arm. There was no difference between the two azithromycin arms at the interim analysis.

The final study analysis compares high dose azithromycin (600 mg) plus ethambutol to clarithromycin plus ethambutol. In terms of the primary efficacy endpoint, sterilization rates at week 24, azithromycin 600 mg plus ethambutol failed to show that it was similar to the clarithromycin plus ethambutol regimen. In the intent-to-treat analysis, the lower bound of the confidence interval around the difference in rates suggested that high dose azithromycin could be as much as 30% less effective than clarithromycin (observed rates were 46% for azithromycin 600 mg plus ethambutol and 56% for clarithromycin plus ethambutol). In the per-protocol analysis, the lower bound of the confidence interval around the difference in rates suggested that high dose azithromycin could be as much as 46% less effective than clarithromycin (observed rates were 64% for azithromycin 600 mg plus ethambutol and 82% for clarithromycin plus ethambutol). High dose azithromycin was not found to be significantly worse than clarithromycin. Analyses of the secondary endpoints generally confirmed the conclusion from the primary analysis, i.e., that high dose azithromycin plus ethambutol may not be considered similar to clarithromycin plus ethambutol.

Treatment of Pulmonary MAC Infection

The lack of a control group in each of the studies submitted precludes this reviewer from making any judgements about efficacy of azithromycin in the treatment of pulmonary MAC infection.

RECOMMENDED REGULATORY ACTION:

The data provided by the applicant in this submission fail to demonstrate efficacy for a regimen of oral azithromycin (250 or 600 mg) once daily in combination with ethambutol for 24 weeks in the treatment of either MAC infection or pulmonary MAC infection.

/S/

7/7/00

Nancy Silliman, Ph.D.
Statistical Reviewer, DB III

/S/

7/7/00

Concur: Karen Higgins, Sc.D.
Acting Team Leader, DB III

cc:

Orig. NDA #50-730/SE1-005

Orig. NDA #50-730/SE1-006

HFD-590

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HFD-725/Dr. Huque

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HFD-725/Dr. Silliman

HFD-725/chron.

This review contains 17 pages.

STATISTICAL REVIEW AND EVALUATION (ADDENDUM)

NDA#(s): 50-730, SE1-005 and SE1-006 **OCT 23 2000**

Name of Drug: ZITHROMAX[®] tablets (azithromycin)

Applicant: Pfizer Inc.

Indication(s): Treatment of infections due to *Mycobacterium avium* Complex (MAC)

Documents Reviewed: Clinical Information Amendment, dated 8/23/00

Review Type: Clinical data

Statistical Reviewer: Nancy Silliman, Ph.D.

Medical Officer: Joyce Korvick, MD, HFD-590

Project Manager: Diana Willard, HFD-590

In their original submission, the sponsor submitted data from one pivotal, Phase III, controlled clinical trial (study 066-189) to support the use of oral azithromycin 600 mg once daily in combination with ethambutol for the treatment of *Mycobacterium avium* complex (MAC) infection. This study compared azithromycin 600 mg once daily plus ethambutol with clarithromycin 500 mg twice daily plus ethambutol, but failed to demonstrate similar efficacy rates between treatments (observed sterilization rates were lower with the azithromycin treatment regimen). In response to a FDA request for more information regarding expected sterilization rates for ethambutol administered alone and placebo sterilization rates, the sponsor submitted a clinical information amendment. This amendment is reviewed here.

The sponsor submitted an extensive review of published studies for MAC treatment. Unfortunately, there are no trials that compare azithromycin to placebo, or azithromycin plus ethambutol to ethambutol alone, which would allow us to demonstrate efficacy of azithromycin directly. The submission includes two trials that included placebo arms (but no azithromycin-containing regimen; Dautzenberg 1991 and Jacobson 1993), one trial which included an untreated arm (but no azithromycin-containing regimen; Agins 1989), one trial which included an ethambutol alone arm (but no azithromycin-containing regimen; Kemper 1994), and one trial which compared the effect of adding ethambutol to a clarithromycin-based regimen (Dube 1997). Several other trials of additional treatment regimens are also included.

Most of the trials are small, and it is difficult to make cross-study comparisons due to the differing study designs (study populations included, endpoints examined, etc.). Unfortunately, none of the published studies appears to have examined sterilization rates, which are of primary interest in study 066-189. Of the two studies which included placebo arms, one showed an increase in mean and median MAC colony counts over time (Dautzenberg), while the other showed a decrease in mean and median MAC

colony counts over time (Jacobson). The Agins study included an untreated arm with only 3 patients, and was plagued by missing data. The Kemper study showed a decrease in mean MAC colony counts for ethambutol alone that was smaller in magnitude than that observed for the azithromycin-containing regimens, but it is hard to know what to make of this difference. The Dube study suggests that ethambutol actually adds quite a bit to a regimen of clarithromycin and clofazimine. Table 2 in the Dube paper examines the proportion of patients with a negative culture over time during the study, and finds a significant difference between clarithromycin/clofazimine and clarithromycin/clofazimine/ethambutol at weeks 16 (40% vs. 82%), 20 (24% vs. 61%), and 28 (15% vs. 63%). (Note that these are not sterilization rates, they are simply the proportions of patients with a negative culture at each time point.)

In summary, the sponsor has diligently reviewed all available published data, but there does not appear to be any data that could be used to support a claim of efficacy for azithromycin in the treatment of MAC. The Dautzenberg study suggests that patients receiving placebo worsen over time, while the Jacobson study suggests the opposite. The Kemper study suggests that ethambutol given alone is not a very effective regimen, but the Dube study suggests that when ethambutol is added to a clarithromycin-containing regimen, it actually improves response rates substantially. Thus, we are still left to wonder whether the sterilization rates for azithromycin plus ethambutol in study 066-189 are significantly better than would be found in patients receiving ethambutol alone.

ISI

10/18/00

Nancy Silliman, Ph.D.
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10/23/00

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