CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-277

STATISTICAL REVIEW(S)

Statistical Review

NDA#:	21-277
Name of Drug:	Moxifloxacin hydrochloride (Avelox) I.V. Solution
Applicant:	Bayer Corporation
Indication:	Intended to have all the indications as the tablet formulation, i.e., the treatment of mild or moderate community-acquired pneumonia (CAP), acute exacerbation of chronic bronchitis, skin infection, and acute sinusitis. In addition, the I.V. formulation will cover severe CAP and penicillin-resistant streptococcus pneumoniae (PRSP).
Documents Reviewed:	Summary and statistical sections from electronic submission received on November 2, 2000
Medical Reviewer:	Andrea Meyerhoff, MD
Statistical Reviewer:	Qian Li, Sc.D.
Dates of Review:	November 2000 - October 2001

I. Introduction:

In this NDA, the sponsor pursues marketing approval for the use of moxifloxacin I.V. solution 400 mg QD infused over at least 60 minutes. The active ingredient in moxifloxacin I.V. is moxifloxacin hydrochloride, which is the same drug substance used in moxifloxacin tablets 400 mg QD approved in 1999 for the treatment of mild and/or moderate CAP, acute sinusitis, acute exacerbation of chronic bronchitis, and skin infection (approved in 2001). In this moxifloxacin I.V. application, the sponsor proposes to use combination therapy of I.V. and tablets and requests approval of all the moxifloxacin tablet indications. In addition, the sponsor also requests approvals of severe CAP and penicillin-resistant streptococcus pneumoniea.

Two large multi-center, multi-national trials (Studies 100039 and 200036) were conducted to assess the safety and efficacy of moxifloxacin I.V./oral sequential therapy for patients with CAP. These were the only two phase III studies conducted for the efficacy evaluation of I.V. formulation in this submission.

This statistical review focuses on the efficacy evaluation of CAP presented in the two phase III studies. For the proposed new indication of severe CAP for moxifloxacin I.V., the subgroup with severe CAP will be evaluated as well. Since there were very few cases of PRSP available in both phase III studies, the efficacy assessment for PRSP indication will not be covered in this statistical review. The results of the two phase III studies on CAP as well as PK bio-equivalence studies will be used to assess other efficacy indications that are available for moxifloxacin tablets.

II. Study Design and Statistical Methodology:

The two multi-center, multi-national studies for efficacy evaluation were conducted in patients with documented mild/moderate or severe CAP and over 1,100 patients were enrolled. Study 100039 was a randomized, double blind study conducted in North America for the comparison of safety and efficacy of moxifloxacin sequential I.V. to PO 400/400 mg QD for 7-14 days versus sequential alatrofloxacin I.V. 200 mg QD followed by trovafloxacin PO 200 mg QD for 7-14 days. During the study (after 165 patients enrolled), alatrofloxacin/trovafloxacin was dropped as the active control due to safety concerns. With agreement between the sponsor and the agency, levofloxacin 500/500 mg I.V. to PO was replaced as the active control for the rest of the trial. Also the sample size was increased in order to obtain sufficient number of valid patients. Study 200036 was an open label, randomized, multi-center, active-controlled study conducted in Europe, Israel and South Africa. The objective of the study was to compare the safety and efficacy of moxifloxacin sequential I.V. to PO 400/400 mg versus amoxicillin/clavulanate sequential I.V./PO 1200/625 mg TID with or without clarithromycin 500 mg I.V./PO BID for 7-14 days in the treatment of patients with CAP.

Reviewer's comments: For the efficacy analysis of Study 100039, the comparison between the combined control groups and moxifloxacin was specified as the primary analysis. However, the safety concerns of alatrofloxacin/trovafloxacin may have affected their efficacy in treating CAP patients, which could potentially lead to a bias in favor of moxifloxacin. If the two control treatments did not have the same efficacy effect, combining the two control groups would yield an average effect, which would depend on the proportion of patients allocated in each control. This average treatment effect can be difficult to interpret. For this reason, analyses for each control phase and using only levofloxacin as the control will be looked at closely.

For Study 100039, no penalty was imposed on the efficacy assessment due to the sample size increase during the trial. The sample size was increased based on a blinded assessment that the proportion of evaluable patients was lower than expected. Therefore, such increase did not inflate the type I error.

For Study 200036, the open label study design makes it very difficult to control bias and therefore, to assess treatment difference. Some of the potential biases can be patient selection bias that can occur during treatment assignment as well as during the conduct of the trial and bias that can occur during the conduct of the trial in evaluating safety and efficacy information. It is not always possible to assess these biases statistically. To maintain the validity of the comparison between the treatments, double blinded trials are highly recommended if it is feasible. For this particular study, because of the open label study design, the use of a different control regimen and a different study population than those used in Study 100039 makes the results of this study even more difficult to assess. Note that this study's protocol was not submitted as part of the IND and, therefore, did not receive any comments regarding study design or analysis by the Agency.

1. Efficacy evaluation:

The overall clinical response, which was based on a combination assessment of several clinical parameters, was used to evaluate efficacy. The evaluations were conducted at the pre-therapy visit, on the day of switch from I.V. to oral therapy, during therapy (day 3-5), at the end of therapy on Days 0 to +2 (only for Study 100039), at the test of cure time point (defined as +10 to +14 days post therapy for Study 100039 and +5 to +7 days post therapy for Study 200036), and a late follow-up. At the test of cure (TOC) and follow-up visits, the clinical responses were graded as cure, failure, and indeterminate, while at the other visits, the clinical responses were graded as clinical improvement, clinical failure, and indeterminate.

Bacteriological response based on the results of the appropriate cultures was also used to evaluate efficacy response to study medications. Bacteriological response was evaluated at pre-therapy, on the day of switch from I.V. to oral therapy, during therapy (day 3-5), at the end of therapy, and at the test of cure post-treatment time. The bacteriological response was graded as eradication, presumed eradication, persistence, presumed persistence, and indeterminate.

Primary efficacy endpoints:

The primary efficacy parameter for Study 100039 was the overall clinical response at the TOC visit. The original TOC window was +10 to +14 days post-therapy but this was expanded to +7 to +30 days post-therapy because many of the TOC assessments were performed outside the original window. Subjects were considered as failures in the overall clinical response if they were determined to be failures at any time.

The TOC window for the primary efficacy endpoint defined in Study 200036 was +5 to +7 days post therapy in order to satisfy European regulatory requirement.

Reviewer's comment: In this review, the response rate at +21 to +28 days post therapy visit was used as the primary endpoint for study 200036 in order to remove possible early relapse post therapy (after TOC visit), as well as to be more consistent with Study 100039.

Secondary efficacy variables:

The following were the secondary efficacy variables.

- Bacteriological response at the TOC visit;
- Clinical and bacteriological response at the day of switch from I.V. to oral therapy, during study drug therapy (day 3 to 5), at the end of therapy (day 0 to +2);
- Radiological response at the TOC visit.

2. Analysis populations:

There were three analysis populations: valid for safety, valid for efficacy and microbiologically valid.

The valid for safety population includes all patients who received at least one dose of the study drug. This is also referred to as the intent-to-treat (ITT) population.

Valid for efficacy, also referred to as the per protocol or efficacy evaluable, population was defined on page 2-604 of the study protocol for Study 100039 and page 2-3802 of the study protocol for Study 200036. This population was pre-specified by the sponsor to be the population used in primary efficacy analysis.

Microbiologically valid population, the sub-population with microbiologically-documented CAP, includes efficacy evaluable patients with an infection-causing organism(s) isolated from a pre-therapy sputum culture, blood culture, or pleural fluid culture. For Study 200036, an appropriate post-baseline assessment was also required.

Reviewer's comments: Although the valid for efficacy (per protocol) population was specified as the primary efficacy analysis by the sponsor, it is important that the results observed in the ITT (valid for safety) and microbiologically valid population are consistent with the results from the per protocol population. Therefore, the analyses based on ITT, per protocol, and microbiological evaluable subgroup will be evaluated collectively.

3. Statistical Analyses:

The primary efficacy analysis was to construct a two-sided 95% confidence interval (CI) for the difference in response rates between the two treatment groups using Mantel-Haenzel test statistic which can be adjusted for stratification factors. For Study 100039, CAP severity, and phase of study (trovafloxacin or levofloxacin) were specified in protocol amendment to be the stratification factors. The sponsor added another factor, order of I.V. infusion (active first or placebo first), as the stratification factor in the study report. For Study 200036, the protocol specified that the stratification factors would depend on post-hoc exploratory analyses. Non-inferiority would be determined if the lower bound of the two-sided 95% CI on the difference of response rates between the moxifloxacin group and the controls was greater than -15% for Study 100039, and -10% for Study 200036 to satisfy the European regulatory agency.

Reviewer's comment: In current review practice, the post-hoc defined stratification factors were not acceptable for a primary analysis. Post-hoc defined stratification factors

can be explored in sensitivity analyses to support the primary finding. The primary analysis for both studies will adjust for factors that are part of the study design, using only the stratification factors pre-specified in the analysis if different analysis results from the sponsor's were obtained.

III. Study Results for Study 100039

1. Patient accounting and baseline variables:

Sixty-three study centers in the United States and Canada enrolled 516 subjects between December 28, 1998 to July 14, 2000. Two hundred fifty-three patients received moxifloxacin and 263 received the control, trovafloxacin or levofloxacin. Five hundred seven patients were in the ITT analysis, while 362 patients were in the valid for efficacy analysis. Only about 30% of the randomized population were microbiologically valid (80 in moxifloxacin and 78 in control). Patient accounting information is summarized in Table 1.

Table 1: Patient Accounting Information for Study 100039.

	Moxifloxacin	Control
All Patients	253	263
Valid for Safety	249 (98%)	258 (98%)
Valid for Efficacy	182 (72%)	180(68%)
Microbiologically Valid	80 (32%)	78 (30%)
Discontinuation	64 (25%)	69 (26%)
Adverse event	23 (9%)	24 (9%)
Patient non-compliance	4 (2%)	4 (2%)
Consent withdrawn	8 (3%)	11 (4%)
Insufficient therapeutic effect	11 (4%)	6 (2%)
Lost to follow-up	6 (2%)	9 (3%)
Death	2 (<1%)	3 (1%)
Protocol violation	5 (2%)	6 (2%)
Study terminated by sponsor	1 (<1%)	2 (<1%)
Investigator request	4 (2%)	4 (2%)

The sponsor reported two types of errors occurring during the trial conduct. The first was that twenty-five patients did not receive the treatment that was assigned by randomization. Twelve patients who were randomized to trovafloxacin were identified as having received moxifloxacin, 10 randomized to moxifloxacin received trovafloxacin, and 1 randomized to moxifloxacin received levofloxacin. Two patients received both moxifloxacin and control treatments. The analyses provided by the sponsor were based on the actual treatment that the patients received. The second type of error was that some patients with severe CAP were randomized in the mild/moderate stratum due to diagnostic errors.

For the valid for safety patients, demographic information was reasonably balanced between treatment groups except for the variables such as age and duration of infection. However, these imbalances were not considered to be clinically meaningful. There were also some imbalances in medical history and baseline signs and symptoms.

For the valid for efficacy patients, demographic information was reasonably balanced between treatment groups except for some imbalances in CAP severity and smoking history. There were more severe patients in moxifloxacin group (34%) than in the control group (27%). Slightly more patients in the moxifloxacin group had a history of smoking (81% in moxifloxacin vs. 75% in the control). There were also some imbalances in medical history and baseline signs and symptoms. The impact of some of the imbalances on efficacy assessment will be discussed in the reviewer's comments.

Only about 30% of the randomized population constituted the microbiologically valid patient population. The demographic information showed imbalances in age, weight, disease stratum, as well as smoking status. More imbalances occurred in previous anti-microbial uses and clinical signs and symptoms at study entry in this sub-population compared to the randomized population. However, in the medical reviewer's opinion these imbalances would not have a large impact on the efficacy assessment.

2. Results on primary efficacy variables:

Results of clinical response at TOC visit (7-30 days post therapy) for the valid for efficacy, valid for safety, and microbiologically valid populations are summarized in Table 2. As can be seen from the table, the response rates in the moxifloxacin treatment group were consistently lower than the response rates in the control group in all three analysis populations. However, the lower bounds of the 95% CIs of the treatment differences were within the pre-specified non-inferiority margin of 15% for the valid for efficacy and valid for safety populations.

The response rates from the severe CAP stratum at TOC visit are also summarized in Table 2. For the severe stratum, the response rates between the two treatment groups were numerically close in the valid for safety and valid for efficacy populations. In the microbiologically valid population the response rate in the moxifloxacin treatment group for the severe stratum was numerically lower than that in the control.

Reviewer's comments: The 95% Mantel-Haenszel CIs calculated by the sponsor were stratified by CAP severity, order of infusion and control phase. The 95% CIs stratifying only CAP severity are close to the sponsor's analysis (95% CI for valid for efficacy is [-9.0%, 4.2%]). Note, the 95% Mantel-Haenszel CIs calculated by the reviewer in Table 2-1 are adjusted only for the strata of CAP severity for the overall response rates. The normal approximations are the analyses without any stratification.

3. Secondary analysis:

The bacteriological response rates for microbiologically valid patients at TOC visit were 78.7% (59/75) for the moxifloxacin treatment group and 88.4% (61/69) for the control in respiratory site. The response rates in blood site were 92.3% (12/13) for the moxifloxacin treatment group and 100% (15/15) for the control.

Table 2: Clinical response at TOC for Study 100039.

Valid for Efficacy	All strata	Moxifloxacin	157/182 (86%)
		Control	161/180 (89%)
		95% CI (Mantel-Haenszel)	(-8.9%, 4.2%)
		95% CI (Normal approx.)	(-10.5%, 4.1%)
	Severe stratum	Moxifloxacin	48/61 (78.7%)
		Control	39/49 (79.6%)
		95% CI (Normal approx.)	(-16.2%, 14.4%)*
Valid for Safety	All strata	Moxifloxacin	168/249 (67%)
		Control	173/258 (67%)
		95% CI (Mantel-Haenszel)	(-7.5%, 8.7%)
		95% CI (Normal approx.)	(-8.1%, 9.0%)
	Severe stratum	Moxifloxacin	48/83 (57.8%)*
		Control	41/75 (54.7%)*
		95% CI (Normal approx.)	(-12.3%,18.7%)*
Microbiologically valid patients	All strata	Moxifloxacin	66/80 (83%)
		Control	70/78 (90%)
		95% CI (Mantel-Haenszel)	(-17.2%, 4.1%)*
		95% CI (Normal approx.)	(-18.0%, 3.5%)*
	Severe stratum	Moxifloxacin	24/31 (77.4%)*
		Control	20/24 (83.3%)*
		95% CI (Normal approx.)	(-26.9%, 15.0%)*

* Calculated by the reviewer.

4. Subgroup analyses:

Results of some subgroup analyses for those subgroups which had statistically significant subgroup effects are summarized in Table 3. As can be seen from the table, females responded better than males. Patients with mild/moderate CAP responded better than severe patients. Patients with no history of smoking responded better than those who had smoking history. Success rates declined with decreasing general health status and increasing APACHE II score.

Breslow-Day test for common odds ratios stratified by CAP severity, order of infusion, and control phase yielded a p-value of 0.062, which suggested inconsistent response rates among the strata (treatment by strata interactions). The interactions are summarized in Table 4. The treatment by order of infusion interaction was due to the low response rate for active infusion first in moxifloxacin treatment. There were strong treatment by control

phases interactions within each severity stratum. The interaction in mild/moderate CAP stratum was due to the lower response rate of Trovafloxacin phase in moxifloxacin treatment group. The interaction in the severe stratum was due to the reversed response rates between the two treatment groups in the two control phases.

Table 3: Subgroup analyses for Study 100039.

		Moxifloxacin	Control	p-value*
Gender	Male	82/100 (82.0%)	75/85 (88.2%)	0.004
	Female	75/82 (91.5%)	80/84 (95.2%)	(0.04)
Severity	Mild/mod. CAP	109/121 (90.1%)	122/131 (93.1%)	0.001
	Severe CAP	48/61 (78.7%)	39/49 (79.6%)	
History of smoking	No	33/35 (94.3%)	44/45 (97.8%)	0.016
	Yes	124/147 (84.4%)	117/135 (86.7%)	(0.022)
General health status	Excellent	24/24 (100.0%)	18/19 (94.7%)	0.0004
	Good	74/83 (89.2%)	79/86 (91.9%)	(0.005)
	Fair	51/62 (82.3%)	58/68 (85.3%)	
	Poor	7/12 (58.3%)	5/6 (83.3%)	
Apache II score	≤10	81/90 (90.0%)	87/97 (89.7%)	0.01
	>10, ≤15	55/61 (90.2%)	50/53 (94.3%)	
	>15	21/31 (67.7%)	24/30 (80.0%)	

*The p-values in the parentheses were based on logistic regression analyzed by the reviewer.

Table 4: Treatment by factor interactions in Study 100039.

Factors	Subgroup	Moxifloxacin	Control
Order of infusion	Active first	76/92 (82.6%)	86/95 (90.5%)
	Placebo first	81/90 (90.0%)	75/85 (88.2%)
Mild/moderate CAP	Trovafloxacin phase	34/42 (81%)	37/39 (95%)
	Levofloxacin phase	75/79 (95%)	85/92 (92%)
Severe CAP	Trovafloxacin phase	14/15 (93%)	9/14 (64%)
	Levofloxacin phase	34/46 (74%)	30/35 (86%)

5. Reviewer's comments on Study 100039:

1) Combining the control phases:

Combining the moxifloxacin treatment group over the two control phases should not be an issue since there was no intrinsic difference in this treatment arm over the two phases. However, the differences in the response rates between the two controls leave much doubt about the validity of combining the two control groups. It was not clear that the difference was due to the different effects on CAP of the two treatments or differences in

patients enrolling into the two phases. If it was the former case, as it was discussed earlier, such combination by averaging the two different treatment effects could cause difficulties in interpreting the study results.

To assess the level of impact that the trovafloxacin phase had on the primary analysis, sensitivity analyses using levofloxacin only as the control were conducted.

The first analysis combined the moxifloxacin patients from the two phases and compared them to the levofloxacin control. The results of this sensitivity analysis in valid for the efficacy population are listed in Table 5. Again it showed that the overall response rate was slightly lower in the moxifloxacin group compared to the levofloxacin group. However, the two-sided 95% CI was still within the non-inferiority margin of 15%. For the severe stratum, the point estimates showed the response rate in moxifloxacin was about 8% lower than that in the levofloxacin treatment group. However, caution should be exercised in interpreting this analysis due to small sample size in the levofloxacin group and the possible loss of balances between the two treatments from the original randomization.

Table 5: Sensitivity analysis using the control in levofloxacin-phase only for Study 100039.

Stratum	*Moxifloxacin*	*Levofloxacin*	*95% CI*
All strata	*157/182 (86%)*	*115/128 (89.8%)*	*(-10.8%, 27%)**
Mild/moderate	*109/121 (90%)*	*85/92 (92%)*	*(-9.9%, 5.3%)***
Severe	*48/61 (78.7%)*	*30/36 (86%)*	*(-20.6%, 11.3%)***

** The two-sided 95% CI is stratified by CAP severity.*

*** The two-sided 95% CIs are based on normal approximation.*

The other sensitivity analysis is to compare the two treatment groups using the levofloxacin phase only. The results are listed in Table 6. As can be seen from this table, the lower bound of the two-sided 95% CI for the difference of the overall response rates between the two treatment groups was still within the non-inferiority margin of 15%. However, the response rate in the moxifloxacin treatment group in the severe CAP stratum was about 12% lower than the response rate in the control.

Table 6: Sensitivity analysis using levofloxacin-phase only for Study 100039.

Stratum	*Moxifloxacin*	*Levofloxacin*	*95% CI*
All strata	*109/125 (87.2%)*	*115/127 (90.6%)*	*(-9.4%, 5.4%)**
Mild/moderate	*75/79 (95%)*	*85/92 (92%)*	*(-4.7%,9.8%)***
Severe	*34/46 (74%)*	*30/35 (86%)*	*(-29.0%, 5.4%)***

** The two-sided 95% CI is stratified by CAP severity.*

*** The two-sided 95% CIs are based on normal approximation.*

2) Baseline imbalances:

There were some imbalances in demographic information and baseline disease characteristics in this study in the valid for efficacy population which were unfavorable to the moxifloxacin treatment group. These imbalances included the CAP severity stratum, smoking history, and number of patients diagnosed to have shock in the severe stratum.

There were more severe CAP cases in moxifloxacin group (34%) than in the control group (27%). As mentioned in this review, there was a statistically significant stratum effect, with the response rates in the severe stratum about 12% lower than the mild/moderate stratum. Since the majority of the analyses were stratified by CAP severity, the imbalance would not affect the two-sided 95% CIs for the difference of the overall response rates.

There were more patients in the moxifloxacin group who had a history of smoking (81%) than in the control group (75%). Patients with a history of smoking had response rates about 10% lower than patients with no smoking history. Because of this, an analysis that does not adjust for smoking history could be unfavorable to the moxifloxacin group. However, this imbalance was not serious enough to have a large impact on the efficacy analysis, which can be seen from the analysis stratifying history of smoking and CAP severity performed by the reviewer. The two-sided 95% CI on valid for efficacy population stratifying both smoking history and CAP severity is [-8.7%, 5.0%], with a small shifting in favor of the moxifloxacin treatment.

There were 16 moxifloxacin patients and 8 control patients diagnosed as having severe CAP due to shock. The response rates among patients with shock were 81.3% (13/16) for the moxifloxacin group and 87.5% (7/8) for the control. As it can be seen, the unfavorable impact on the overall response rate of the moxifloxacin treatment was not only caused by the imbalance between the two treatment groups, but also due to the low response rate in patients with shock in the moxifloxacin treatment group. Since the number of patients with shock was small, the impact is not expected to be large.

3) Randomization errors:

As it was stated earlier, 23 patients did not take the medication that they were randomized to receive. In this reviewer's opinion since the study was blinded, it was acceptable to analyze the data based on the actual treatment the patients received instead of actual randomization, as long as the balance generated by the randomization was not destroyed. To understand the response pattern of these patients, Table 7 lists the response pattern in the three analysis populations.

Table 7: Cure rates and population distribution for those patients who did not receive the randomized treatments for Study 100039.

Population	*Randomized to control, receive moxifloxacin Response/switched patients*	*Randomized to moxifloxacin, received control Response/switched patients*
Valid for Safety	*6/12*	*4/11*
Valid for efficacy	*6/7*	*4/7*
Microbiological valid	*0*	*2/4*

A sensitivity analysis was conducted to use the randomized treatment assignment instead of the actual treatment received and was based on the valid for efficacy population. The number of patients in each treatment group remains the same as there was equal number of patients in valid for efficacy population switched to the opposite treatment group. The response rates for moxifloxacin and control were 84.6% and 90.1% respectively. The 95% CI was [-11.7%, 1.5%] stratified by CAP severity, with a small shift in favor of the control.

IV. Study Results for Study 200036:

1. Patient accounting and baseline variables:

Sixty-five study centers in 10 countries enrolled 628 subjects between February 12, 1999 to May 28, 2000. Three hundred six patients were randomized to receive moxifloxacin and 322 were randomized to active comparator treatment group (amoxicillin/clavulanate with or without clarithromycin). Five hundred seven patients were in the ITT population, while 362 patients were in the valid for efficacy population. About 20% of the randomized patients were identified to be microbiologically valid. Patient accounting information is summarized in Table 8.

Table 8: Patient accounting information for Study 200036.

	Moxifloxacin	Control
All Patients	306	322
ITT	301 (98%)	321 (100%)
Valid per protocol	258 (84%)	280 (87%)
Microbiologically Valid	64 (21%)	71 (22%)
Discontinuation	44 (14%)	63 (20%)
Adverse event	9 (3%)	9 (3%)
Consent withdrawn	7 (2%)	9 (3%)
Insufficient therapeutic effect	5 (2%)	16 (5%)
Lost to follow-up	17(6%)	15 (5%)
Death	6 (2%)	14 (4%)

Demographic information for the ITT population, per protocol population and microbiological valid patients was properly balanced between treatment groups except that there were more previous smokers in the control group in the microbiological valid

patient population. The imbalances that occurred in medical history and baseline signs and symptoms were not considered to have an impact on the efficacy assessment.

Reviewer's comment: As stated in the table above, more patients died in the control group compared to the moxifloxacin group (14 in the control group and 6 in the moxifloxacin group). The difference in the death rates between the two treatment groups was tested using Fisher's exact test. The two-sided p-value approaches statistical significance (p=0.112). If there was indeed a difference between the two treatment groups, it would not be clear if the difference was due to the treatments or bias, possibly introduced in patient selection process, as the open label design is not immune from patient selection bias.

It was mentioned in the study report that a total of 326 patients had cultures or serology performed at baseline, which is about 50% of the total patients enrolled into the study. This was inconsistent with the requirement specified in the study protocol. The protocol requires that "all patients will undergo microbiological examination of blood and sputum obtained within 24 hours before start of study drug treatment". This is considered to be a major protocol violation, which affects the assessment of the patient population selected in this study. Especially since this is an open label study, such violation may introduce possible selection bias to the subgroup of patients that had cultures and serology performed, which leads to the question of the validity of the microbiologically valid patient population.

2. Results on primary efficacy variables:

Results of the clinical response at TOC visit (5-7 days post-therapy) and at visit 21-28 days post-therapy using per protocol populations, the ITT population, and microbiological valid population at visit 21-28 days post-therapy are summarized in Table 9. As can be seen from the table, the response rate in the moxifloxacin treatment group was consistently statistically significantly higher than that in the control group (marginally significant for the microbiologically valid population). Such treatment differences were also observed in the severed CAP stratum, though not statistically significantly different for the valid for safety or microbiologically valid.

Reviewer's comments: The sponsor did not state which factors were used to adjust the 95% CIs as stated in the protocol. However, confidence intervals based on the normal approximation which are unadjusted are similar to the sponsor's analyses. Also, analyses stratifying only by CAP severity yielded similar results.

3. Secondary analyses:

Bacteriological response rates were 54/64 (84.4%) and 50/71 (70.4%) for moxifloxacin and control, respectively, in microbiologically valid population at the visit 21-28 days post therapy. The 95% CI for the difference of the rates between the two treatment groups was [0.00, 27.91%].

4. Subgroup analyses:

The sponsor only reported subgroup analyses by regions (Western Europe and non-western Europe), no region effect was observed.

Table 9: Clinical response for Study 200036.

Per protocol at TOC visit	All strata	Moxifloxacin	241/258 (93.4%)
		Control	239/280 (85.4%)
		95%CI	(2.91 %, 13.19%)
	Severe stratum	Moxifloxacin	119/129 (92.2%)
		Control	116/137 (84.7%)
		95%CI(Normal approx.)	(0.0%, 15.2%)*
Per protocol at visit 21-28 days post therapy	All strata	Moxifloxacin	216/258 (83.7%)
		Control	208/280 (74.3%)
		95%CI	(2.60%, 16.27%)
	Severe stratum	Moxifloxacin	105/129 (81.4%)
		Control	97/137 (70.8%)
		95%CI(Normal approx.)	(0.4%, 20.7%)*
Valid for Safety ITT at visit 21-28 days post therapy	All strata	Moxifloxacin	220/301 (73.1%)
		Control	209/321 (65.1%)
		95%CI	(1.63%, 15.96%)
	Severe stratum	Moxifloxacin	108/158 (68.4%)
		Control	98/163 (60.1%)
		95%CI(Normal approx.)	(-2.2%, 18,7%)*
Microbiologically Valid at follow-up	All strata	Moxifloxacin	56/64 (87.5%)
		Control	53/71 (74.6%)
		95%CI	(-0.21%, 25.91%)
	Severe stratum	Moxifloxacin	32/37 (86.5%)
		Control	31/40 (77.5%)
		95%CI(Normal approx.)	(-8.0%, 26.0%)*

* Calculated by the reviewer.