

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-085**

**CORRESPONDENCE**



Jensen - 570

## Record of Teleconference

**Date of Teleconference:** July 20, 1999

**IND:** [redacted]

**Drug:** Avelox™ (moxifloxacin hydrochloride)

**Sponsor:** Bayer

**Indication(s):** Anti-infective

**Subject:** Protocol 100214 entitled, "Prospective, Randomized, Non-Blinded, Multi-Center Comparison of the Safety and Efficacy of Oral Moxifloxacin 400mg QD For 5 Days Versus Oral Azithromycin 250mg QD For 5 Days For the Treatment Of Acute Exacerbation Of Chronic Bronchitis (AECB) Or Oral Moxifloxacin 400mg QD For 10 Days Versus Oral Amoxicillin/Clavulanate 875mg BID For 10 Days For The Treatment Of Acute Maxillary Sinusitis Infection".

**FDA Attendees:** Robert Hopkins, M.D., M.P.H. & T. M., Medical Team Leader  
Leonard Sacks, M.D., Medical reviewer  
Valerie Jensen, R.Ph., Project Manager

**Bayer Attendees:** E. Paul MacCarthy, MD, Vice President, Medical Affairs  
Felix Moneaguedo, MD, Vice President, Anti-Infectives  
Deborah Church, MD, Director, Anti-Infectives  
Al Heyd, PhD, Deputy Director, Anti-Infectives  
Andrew S. Verderame,  
Associate Director, Regulatory Affairs

**Type of Meeting:** FDA-requested teleconference

**Objective(s):** The purpose of the teleconference was to discuss issues relating to Protocol 100214.

**Background:** Bayer submitted a new protocol, Protocol 100214, to [redacted] on June 17<sup>th</sup>, 1999. [redacted] is for Avelox™ (moxifloxacin hydrochloride) BAY 12-8039, a synthetic broad spectrum C-8-methoxy-fluoroquinolone antibiotic. The objective of Protocol 100214 is to compare the safety and efficacy of oral moxifloxacin 400mg QD for 5 days versus oral azithromycin 250mg QD (500mg the first day) for 5 days for the treatment of documented AECB and the safety and efficacy of oral moxifloxacin 400mg QD for 10 days versus oral amoxicillin/clavulanate 875mg BID for 10 days for the treatment of documented acute maxillary sinusitis. The FDA requested a teleconference with Bayer to discuss issues relating to this protocol.



Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175

September 3, 1999

Mark Goldberger, MD, MPH, Director  
Division of Special Pathogens and Immunologic Drug Products  
Office of Drug Evaluation IV (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

**RE: NDA 21-085 AVELOX™ (moxifloxacin hydrochloride) Tablets  
Response to FDA Request for Information  
Clinical Pharmacology and Biopharmaceutics**

Dear Dr. Goldberger,

Reference is made to an email message from Joette Meyer, PharmD, Clinical Pharmacology and Biopharmaceutics Reviewer, regarding the AVELOX New Drug Application. Dr. Meyer requested individual QTc readings obtained in the studies listed below.

0143 Multiple Dose PK study of 400 mg QD x 10 days

0149 Single dose safety study of 400 mg and 600 mg IV

0154(D97-021) Single and multiple dose safety study of 400 mg IV

0163 Single dose safety study of 400 mg IV and PO and 800 mg PO

Find enclosed the individual QTc values for these studies as requested by Dr. Meyer.

Please do not hesitate to contact me at (203) 812-5172 if there are any questions or if further information is needed.

Sincerely,



Andrew S. Verderame  
Associate Director, Regulatory Affairs

Desk Copies : Valerie Jensen, RPh, Project Manager (with enclosure)  
Joette Meyer, PharmD,



## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**DATE:** 14 September 1999

**TO:** Andrew S. Verderame  
Associate Director, Regulatory Affairs

**ADDRESS:** Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
(203) 812-5172  
(203) 812-5029 (fax)

**FROM:** Valerie Jensen RPh., Project Manager  
Division of Special Pathogen and Immunologic Drug Products

**THROUGH:** Liji Shen, PhD., Statistical Reviewer  
Division of Biometrics III

**SUBJECT:** Request for dataset analysis

We would like to request a dataset analysis to help the review team with the safety review of Avelox. Specifically we would like to see if there are any patients (on either moxifloxacin or comparator) from the moxifloxacin datasets who start normal (before treatment) on all three liver function tests (bilirubin, AST, and ALT) and increase above normal at any point in the study (1) on bilirubin and AST, (2) on bilirubin and ALT, and (3) on all three. We would request that these patients be reported by ID number, treatment (moxifloxacin or comparator), and study.

Note: By "above normal", we are referring to greater than ULN and not 1.5 x ULN or 3 x ULN. We appreciate your help with this. Please contact Valerie Jensen RPh., Project Manager with any questions relating to this request. If possible, we would like to look at this analysis by the end of September and appreciate any help you can provide us with.

**/S/**

Valerie Jensen RPh., Regulatory Project Manager



Pharmaceutical  
Division

REGULATORY AFFAIRS  
400 MORGAN LANE  
WEST HAVEN, CT 06516

PHONE (203) 812-5172  
FAX (203) 812-5029

FACSIMILE MESSAGE

Date: September 16, 1999 # Pages : 6 Total

To: Valerie Jensen, Project Manager

From: Andy Verderame

Subject: **AVELOX (moxifloxacin hydrochloride) Tablets**  
**NDA 21-085**  
**CONFIDENTIAL**

Dear Ms. Jensen,

Reference is made to your facsimile message dated September 14, 1999 sent through Dr. Liji Shen, Statistical Reviewer, concerning AVELOX and liver function test data set analyses. Dr. Shen requested information on AVELOX and comparator treatments for three liver function tests (bilirubin, AST, and ALT).

Bayer is pleased to provide the results of these analyses of our safety database. Please forward a copy of this message to Dr. Shen.

NOTE : For this analysis Bayer identified patients with baseline and post-baseline values for bilirubin, SGOT and SGPT. In addition, these patients had to have normal bilirubin, SGOT and SGPT at baseline. Controlled and uncontrolled studies were considered separately.

**Controlled studies:** 200mg Moxifloxacin: N=364, 400mg Moxifloxacin: N=3,131,  
Comparators: N=2,819  
**Uncontrolled studies:** 400mg Moxifloxacin: N=537

The analysis is based on the 4-month safety update pool. Lab values >ULN were considered abnormal.

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To summarize the results:

Patients with abnormal post-baseline bilirubin and post-baseline SGOT and post-baseline SGPT - Comparative Studies 200mg Moxifloxacin: N=0, 400mg Moxifloxacin: N=5 (0.16%), Comparators: N=5 (0.18%)

Patients with abnormal post-baseline bilirubin and post-baseline SGOT and normal post-baseline SGPT - Comparative Studies 200mg Moxifloxacin: N=1 (0.27%), 400mg Moxifloxacin: N=6 (0.19%), Comparators: N=7 (0.25%)

Patients with abnormal post-baseline bilirubin and post-baseline SGPT and normal post-baseline SGOT - Comparative Studies 200mg Moxifloxacin: N=0, 400mg Moxifloxacin: N=7 (0.22%), Comparators: N=3 (0.11%)

Patients with abnormal post-baseline bilirubin and post-baseline SGOT and post-baseline SGPT - Uncontrolled Studies (400mg Moxifloxacin: N=1 (0.19%)

There were no patients from uncontrolled studies with 'abnormal post-baseline bilirubin and SGOT only' or 'abnormal post-baseline bilirubin and SGPT only'.

Please find attached the listings which identify the study numbers and patient numbers described above.

If there are any questions or if I can provide any further information, please contact me at (203) 812-5172.

Sincerely,



Andrew S. Verderame  
Associate Director, Regulatory Affairs

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Pharmaceutical  
Division

Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175

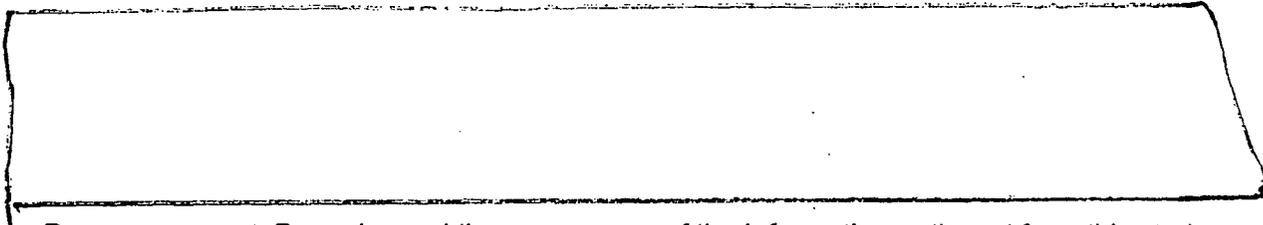
October 22, 1999

Mark Goldberger, MD, MPH, Director  
Division of Special Pathogens and Immunologic Drug Products  
Office of Drug Evaluation IV (HFD-590)  
Center for Drug Evaluation and Research  
Food and Drug Administration  
9201 Corporate Blvd.  
Rockville, MD 20850

**RE: NDA 21-085 AVELOX™ (moxifloxacin hydrochloride) Tablets  
Response to FDA Request for Information**

Dear Dr. Goldberger,

Reference is made to a telephone discussion held between yourself and Carl Calcagni, Vice President, Regulatory Affairs, of Bayer Corporation on October 13, 1999. A portion of this discussion concerned some additional preclinical information, which the Division had asked Bayer to provide in an August 25, 1999 facsimile message, concerning other quinolones and their effect on QTc.



Per your request, Bayer is providing a summary of the information gathered from this study. The final report will be submitted to the moxifloxacin IND  when completed.

Please do not hesitate to contact me at (203) 812-5172 if there are any questions or if further information is needed.

Sincerely,



Andrew S. Verderame  
Associate Director, Regulatory Affairs

Desk Copy : Valerie Jensen, RPh, Project Manager



**MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE**

**DATE:** 17 September 1999

**TO:** Andrew S. Verderame  
Associate Director, Regulatory Affairs

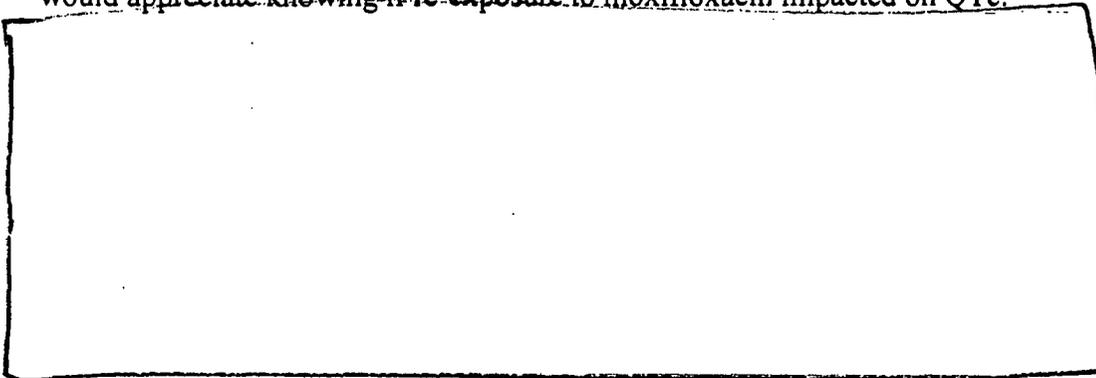
**ADDRESS:** Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
(203) 812-5172  
(203) 812-5029 (fax)

**FROM:** Valerie Jensen RPh., Project Manager  
Division of Special Pathogen and Immunologic Drug Products

**THROUGH:** Robert Hopkins, M.D., M.P.H., T.M, Medical Team Leader  
Joette Meyer, Pharm D., Clin. Pharm. & Biopharm. Reviewer

**SUBJECT:** FDA response to Bayer's electronic message sent September 17<sup>th</sup> regarding specific patients identified by patient number with outlying QT prolongation after exposure to moxifloxacin and request for follow-up information.

The following patients have been identified as "outliers". These are the patients where we would appreciate knowing if re-exposure to moxifloxacin impacted on QTc.



Thank-you for addressing this request for further information. Please contact Valerie Jensen, Project Manager with any questions.



## MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

**DATE:** 27 September 1999

**TO:** Andy Verderame  
Associate Director, Regulatory Affairs

**ADDRESS:** Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
(203) 812-5172  
(203) 812-5029 (fax)

**FROM:** Valerie Jensen RPh., Project Manager  
Division of Special Pathogen and Immunologic Drug Products.

**SUBJECT:** Response to electronic message received from Bayer September 22, 1999 regarding facsimile sent by DSPIDP September 17, 1999 containing specific patients identified as outliers and request for follow-up.

The list of patients sent September 17, 1999, for whom we wanted case narratives is the same list as the one previously mentioned except that a repeated entry was deleted.

Regarding that list, we were able to find narratives in volume 353 on the following cases from study 140: 10544, 10368, 10669, 10074, 10046.

We could not find narratives on patient 10255 in study 140, and on the following patients in study 161: 28001, 31002, and 37016.

We request that Bayer provide these case narratives or if they are in the NDA, please let us know their location in the NDA. The information needed would be similar to that already provided on the patients in volume 353.

With regard to our suggestion that repeat testing be performed on these subjects, we felt that if repeat challenge did not demonstrate reproducible significant QTc prolongation, this would reduce the level of concern with these findings.

Thank-you for your attention to this request. Please contact Valerie Jensen RPh., Project Manager, with any questions related to this correspondence.



**MEMORANDUM**

**DATE:** 29 October 1999

**TO:** Andrew Verderame  
Associate Director, Regulatory Affairs

**ADDRESS:** Bayer Corporation  
400 Morgan Lane  
West Haven, CT 06516-4175  
(202) 812-5029

**FROM:** Valerie Jensen RPh., Project Manager  
Division of Special Pathogen and Immunologic Drug Products

**SUBJECT:** Request for information regarding Creatinine Clearance data and also patients with Child Pugh Class of B or C.

1. Are there any patients with a creatinine clearance of  $>30$  but  $\leq 60$  mL/min or  $< 30$  mL/min enrolled in any of the clinical trials? If yes, how does the efficacy profile (i.e. microbiologic and/or clinical success rates for each indication) for these patients compare to that of patients with a creatinine clearance of  $> 60$  mL/min?
2. Are there any patients with a Child Pugh Class of B or C enrolled in any of the clinical trials? If yes, how does the safety profile for these patients compare to that of normals?

**APPEARS THIS WAY  
ON ORIGINAL**