U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA#:	21277, 21085
Supplement #:	SDN103, SDN108
Drug Name:	AVELOX® (moxifloxacin hydrochloride)
Indication(s):	Treatment of complicated intra-abdominal infections
Applicant:	Bayer Healthcare
Date(s):	September 11, 2015 (Stamp Date)
	October 26, 2015 (Assigned to Statistical Reviewer)
	March 11, 2016 (PDUFA Date)
Review Priority:	6 months
Biometrics Division:	Division of Biometrics IV
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Keywords: moxifloxacin resistance, bacteriological/clinical response, pediatric study

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1 EXECUTIVE SUMMARY

This is a statistical review of a Prior Approval Labeling Supplement by Bayer Healthcare Inc. for Avelox® Tablets (NDA21277) and Avelox® IV (NDA21085). Avelox® (moxifloxacin hydrochloride) is a fluoroquinolone antibacterial that is indicated for treatment of adults, at least 18 years old, with infections caused by susceptible isolates of the designated microorganisms in the following conditions: acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, community acquired pneumonia, uncomplicated skin and skin structure infections, complicated skin and skin structure infections, complicated intra-abdominal infections and plague[1]. The submission contains the results of two studies, one pharmacokinetics study and one controlled clinical trial, which were conducted in response to a formal Pediatric Written Request[2] that was made to the Applicant in response their proposed Pediatric Study Request to fulfill the Pediatric Research Equity Act (PREA) for complicated intra-abdominal infections (cIAI). In the submission, the Applicant proposes revisions to the Use in Specific Populations: Pediatric Use section of the US Prescribing Information (PI), based on the results of these studies. (b) (4)

(b) (4)

The trial under review, BAY11643, is a prospective, randomized, double-blind, active-controlled clinical trial to investigate the safety, tolerability, pharmacokinetics, and efficacy of IV to oral moxifloxacin in pediatric patients 3 months to less than 18 years with cIAI. In this trial, pediatric patients were randomized (2:1) to receive sequential intravenous/oral Avelox® or comparator (intravenous ertapenem followed by oral amoxicillin/clavulanate) for 5 to 14 days. Clinical response is assessed at the test-of-cure (TOC) visit (28 to 42 days after end of treatment) and is evaluated in two protocol-defined populations in this review: the valid for safety population and the modified intent to treat (mITT) population. Following recommendations in the aforementioned guidance, the mITT population, defined in the protocol as all randomized patients who received at least one dose of study medication and had at least one pre-treatment causative organism of cIAI, is considered the primary efficacy analysis population in this review.

The trial, BAY11643, enrolled a total of 451 patients who were treated with at least one dose of study medication, 301 patients were randomized to Avelox®, and 150 patients were randomized to comparator. The mITT population comprises a total of 381 patients (248 patients randomized to Avelox® and 133 patients randomized comparator). (b) (4)

[1] Refer to US Prescribing Information; initial approval 1999.
[2] Refer to Written Request by Dr. Edward Cox, Director of the Office of Antimicrobial Products, dated December 9, 2009.
[3] Refer to clinical pharmacology review by Dr. Tracey Wei for review of pharmacokinetics study contained in the submission.

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(b) (4)

(b) (4)

(b) (4)

The results from safety analyses suggest increased risks of cardiac events in Avelox® relative to comparator. These events occurred within the first few days of treatment and were primarily driven by QT prolongation events.

(b) (4)

There were no new safety findings discovered in this review for the pediatric patients in trial BAY11643 that warrant updates to the label. Safety concerns regarding the use of Avelox® and QT prolongation has also previously been identified in adult patients and is currently included in the Warnings and Precautions section of the USPI. The recommendations for the information that may be included in the Use in Special Populations: Pediatric Use section of the USPI are provided in Section 5.4.

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2 INTRODUCTION

2.1 Overview and Regulatory Background

This is a statistical review of a Prior Approval (PA) Labeling Supplement that was submitted by Bayer Pharmaceuticals Healthcare Inc., hereafter referred to as the Applicant, on September 11, 2015 for Avelox® tablets (NDA 21277) and Avelox IV (NDA 21085). Avelox® (moxifloxacin hydrochloride) is a fluoroquinolone antibacterial that is indicated for treatment of adults, at least 18 years old, with infections caused by susceptible isolates of the designated microorganisms in the following conditions: acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, community acquired pneumonia, uncomplicated skin and skin structure infections, complicated skin and skin structure infections, complicated intra-abdominal infections, and plague[4]. The currently approved dose of Avelox® is 400 mg (orally or as intravenous infusion) once daily; the duration of therapy depends on the type of infection being treated.

On December 7, 2009, FDA made a formal Pediatric Written Request[5] in response to a proposed Pediatric Study Request that was submitted by the Applicant in order to fulfill the Pediatric Research Equity Act (PREA) for complicated intra-abdominal infections (cIAI). The Written Request noted that "the course of the disease and the response to treatment in pediatric patients is considered comparable to adults, allowing extrapolation of efficacy from adults to children once adequate characterization of the pharmacokinetics, dosing, and safety data of moxifloxacin in pediatric subjects are available". To obtain this pediatric information, the following two studies were requested:

Study 1: An open label study to investigate the pharmacokinetics, safety, and tolerability of moxifloxacin following single dose intravenous (IV) administration in pediatric patients diagnosed with an infectious disease requiring IV antibacterial drug therapy.

Study 2: A prospective, randomized, active-controlled clinical trial to investigate the safety, tolerability, pharmacokinetics, and efficacy of IV and oral moxifloxacin in pediatric patients 3 months to < 17 years with cIAI. This study will also evaluate long-term musculoskeletal adverse events occurring during the first year following moxifloxacin or non-quinolone antimicrobial control drug exposure in pediatric patients.

In this PA Labeling Supplement, the Applicant submits the results of the two studies conducted in response to the aforementioned Pediatric Written Request. The subject of the PA Labeling Supplement is to implement changes to the U.S. Prescribing Information (USPI). The Applicant has proposed revisions to the Use in Specific Populations: Pediatric Use section of the USPI, based upon the results of these studies. It is important to note that the Applicant is not requesting that Avelox® receive an indication for cIAI in pediatrics. (b) (4)

[redacted]

[4] Refer to US Prescribing Information; initial approval 1999.
[5] Refer to Written Request by Dr. Edward Cox, Director of the Office of Antimicrobial Products, dated December 9, 2009.

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(b) (4)

This statistical review focuses on an assessment of the results of Study 2, titled "A randomized, double-blind, multicenter trial to evaluate the safety and efficacy of sequential (intravenous, oral) moxifloxacin versus comparator in pediatric subjects with complicated intra-abdominal infection", also referred to as BAY11643. This review provides recommendations to the Division of Anti-Infective Products (DAIP) for the USPI based on the findings from this trial. (b) (4)

2.2 Data Sources

The supplement was submitted electronically and includes a full study report as well as analysis datasets that are relevant for the analyses of trial BAY11643 that are presented in this review. Datasets and corresponding definition files, submitted in response to data requests[6,7] can be found at the following locations:

\\CDSESUB1\evsprod\NDA021277\0106\m5\datasets\11643\analysis\legacy\datasets
\\CDSESUB1\evsprod\NDA021277\0115\m5\datasets\11643\analysis\legacy\datasets

The following datasets were used in this statistical review:

- adae.xpt contains the adverse events data
- adsl.xpt contains the demographic data
- adclinev.xpt contains the efficacy data for clinical responses
- baevinf.xpt contains the bacteriological response data
- endpoint.xpt contains the disposition data
- iadiag.xpt contains the baseline intra-abdominal diagnosis details
- iainf.xpt contains the intra-abdominal primary diagnosis leading to inclusion in the trial
- mitt.xpt contains the data for assessing resistance to moxifloxacin
- orgid.xpt contains the data for identifying baseline organisms
- patinfo.xpt contains duration of treatment exposure data

The quality and integrity of the data included in the submission will be discussed in Section 3.1.

[6] Refer to Acknowledgment of PA Approval Supplement letter, dated September 25, 2015.
[7] Refer to Information Request dated November 25, 2015.

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There were two notable issues identified related to data and analysis quality.

Firstly, the datasets were not submitted using standard data formats, such as, CDISC. Although standardized data were not required for this submission, the lack of a standardized format posed challenges for the reviewer in identifying the datasets and variables necessary for the statistical analyses. For example, the dataset named "endpoint.xpt", which is suggestive of clinical endpoints information, contained instead the data necessary to summarize subject withdrawals and treatment discontinuations.

Secondly, missing data were inappropriately handled in the analyses presented in study report

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3.2.1 Study Design and Efficacy Endpoints

3.2.1.1 Study Design

The trial, BAY11643, that is under review in this document, was a multinational, multicenter, prospective, 2:1 (moxifloxacin to comparator), double-blind, comparative trial in pediatric patients with complicated intra-abdominal infections (cIAI). To be eligible for the trial, patients had to be male or female children, aged 3 months to less than 18 years, with a clinical diagnosis of cIAI requiring hospitalization and initial IV therapy. Eligible patients were to obtain parental or legal guardian written informed consent and provide assent as applicable by local laws.

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The primary diagnosis for each patient was cIAI, defined as an intra-abdominal infection that extends beyond a hollow viscus into a normally sterile area of the abdomen, and treatment with a surgical or other interventional procedure to control the source of the infection. Findings at surgery must confirm the presence of a cIAI, that is, patients must have had one of the following infections requiring anti-infective therapy and an operative procedure, prior to enrollment:

- Appendicitis with perforation and purulent peritonitis
- Appendicitis with intra-abdominal abscess
- Single or multiple intra-abdominal abscesses secondary to previous surgery
- Bacterial peritonitis secondary to bowel perforation after bowel obstruction
- Bacterial peritonitis secondary to bowel perforation or bacterial enterocolitis.

Patients with suspected cIAI, which must be supported by radiological evidence of gastrointestinal perforation or localized collections of potentially infected material as well as clinical signs and symptoms, could have also been enrolled in the trial. The protocol provides additional details regarding diagnoses of cIAI and suspected cIAI for inclusion in the trial. In addition, there are 34 exclusion criteria described in the protocol.

According to the Pediatric Written Request, 450 pediatric patients were to be enrolled and randomized to receive moxifloxacin (300 patients) or comparator (150 patients). Note that because the trial was not designed as a confirmatory efficacy trial, the number of patients randomized was not based on an estimate of treatment effect of moxifloxacin over comparator or noninferiority margin; refer to Section 3.2.3 for specifics regarding trial enrollment. Prior to randomization, patients were stratified according to the following four age groups:

- Group 1: Adolescents, 12 to less than 18 years
- Group 2: School children, 6 to less than 12 years
- Group 3: Preschool children, 2 to less than 6 years
- Group 4: Infants and toddlers, 3 months to less than 2 years

Within each age group, patients were randomized to receive moxifloxacin or comparator. Randomized patients were to be treated with assigned therapy for a minimum of 5 days to a maximum of 14 days. After the first 3 days of treatment with IV therapy, patients may have switched to oral therapy at the investigator's discretion. Patients randomized to moxifloxacin started with IV moxifloxacin and could be switched to oral moxifloxacin while patients randomized to comparator received ertapenem IV and if switched to oral, they received amoxicillin/clavulanate[8]. Patients weighing less than 20 kg as well as patients in age group 4 (i.e.

[8] Per the protocol, oral amoxicillin/clavulanate is only used to enable stepdown from IV ertapenem to oral antibiotic because oral ertapenem is not available.

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3 months to less than 2 years) were not to be administered any oral treatments; these patients were to continue assigned IV therapy for the duration of the trial. To maintain the study blind, each patient was to receive, in addition to the assigned study medication, a placebo matched as closely as possible in its visual physical characteristics to the study medication.

Patients were enrolled in a step-wise program that will begin with adolescents and then add younger patients as dosing data becomes available from the Phase 1 trial, Bayer Healthcare AG study 11826[9]. BAY11643 was expected[10] to be complete in 66 months, which was the estimated time taken for the last patient to have the last visit across centers in all participating countries. Patients underwent regular visits during the course of the trial (pre-treatment, treatment Day 1, during therapy, at switch to IV from oral therapy, end of treatment and test of cure); refer to Figure 1 for the schedule of procedures and assessments that were planned during the trial.

Patients were to be withdrawn from the trial for the following reasons:

- At their own request or at the request of their legally acceptable representative
- At any time during the trial and without giving reasons, a patient may decline to participate further
- If in the investigator's opinion, continuation of the trial would be harmful to the patient's well-being
- At any specific request of the Applicant

Patients were to be discontinued from study medication for various reasons, but remain enrolled in the trial for safety follow-up. The reasons for premature withdrawal from the study or discontinuation from study medication were to be documented on the electronic case report form. Patients who discontinued treatment prematurely, failed treatment, or had a relapse could have received alternate therapy at the discretion of their treating physician. In such instances, all AEs, SAEs, and deaths were to be recorded through the 30 days following premature discontinuation of study medication or the date when clinical failure became evident and alternate therapy was started. All patients exposed to study medication were to regularly undergo musculoskeletal assessments during the course of the trial. Patients with unresolved musculoskeletal AEs 1 year after the EOT visit were to be followed-up yearly for up to 5 years or until resolution, whichever occurred earlier.

An external data monitoring committee (DMC) was established to provide safety oversight for the trial as well as to make recommendations for stopping the trial in the case of a negative risk to benefit assessment.

[9] Study 1 was requested in the Pediatric Written Request dated December 7, 2009; refer to review by clinical pharmacology.
[10] According to the study report, the actual study dates were January 21, 2010 (first patient in) through January 21, 2015 (last patient last visit date).

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Figure 1 Schedule of Procedures and Assessments for Trial BAY11643

	Pre-treatment[a]	Treatment Day 1[b]	(only) One "during therapy" visit to be performed	Switch from IV to PO therapy[c,q]	EOT[d]	TOC (28-42 days post-EOT)	Follow-up	
							3-month (90 days post-EOT)	1-year (365 days post-EOT)
Study Day[e]		**1**	**3-5**		**5-14**	**33-56**	**95-104**	**370-379**
Diary card[p]				Dispense	Collect			
Informed consent form	X							
Inclusion/exclusion criteria	X							
Demographic details and medical history	X							
Vital signs	X	X	X	X	X	X		
Physical examination (including abdomen)	X	X	X	X	X	X		
Evaluation of surgical wound		X	X	X	X	X		
Hematology and blood chemistry (local lab)	X[o]	X	X	X	X	X[n]		
Coagulation parameters (PT, PTT, INR) (local lab) *(as of Amd 1, Amd 2, and Amd 3)*	X[o]				X			
Urine or serum pregnancy test[f] (local lab) *(as of Amd 3)*	X[o]				X			
Urinalysis (local lab) *(as of Amd 3)*	X[o]	X	X	X	X	X[n]		
Pre-surgical radiological procedure	X							
Surgical procedure[g]	X							
Blood culture and susceptibility testing[h] (local lab)	X							
Peritoneal culture and susceptibility testing[i] (local lab)	X							

	Pre-treatment[a]	Treatment Day 1[b]	(only) One "during therapy" visit to be performed	Switch from IV to PO therapy[c,q]	EOT[d]	TOC (28-42 days post-EOT)	Follow-up	
							3-month (90 days post-EOT)	1-year (365 days post-EOT)
Study Day[e]		**1**	**3-5**		**5-14**	**33-56**	**95-104**	**370-379**
Adverse events[j]	<----------X---------->							
Musculoskeletal assessment	X		X		X	X	X	X
Concomitant therapy and medications[k]	<----------X---------->							
Electrocardiogram[l]		X	X (Day 3)					
Blood sampling for PK[m]			X (Day 3 and 5)					
Study drug administration	<----------X---------->							
Clinical response			X	X	X	X		

Abbreviations: PO = oral, IV = Intravenous, EOT = End-of-Treatment, TOC = Test-of-Cure, PK = pharmacokinetics

a Baseline evaluations may be performed before surgery in instances of enrollment for a suspected cIAI or after surgery if the diagnosis of a cIAI has been surgically confirmed. Pre-treatment and Day 1 can occur on the same day.
b All procedures only need to be done if pre-treatment and start of therapy do not occur on the same day.
c Subjects switched from IV to PO therapy on Days 4 or 5 and without a prior "during therapy" visit should receive a "during therapy" visit instead of the "switch from IV to PO" visit. Switch back from PO to IV is only allowed if the subject does not tolerate PO administration. *(as of Amd 3)*
d If EOT coincides with a 'during therapy" visit on Day 5, only the EOT visit is required. For subjects participating in PK sampling, the second profile should be taken at EOT. A 24 h time window between last dose and EOT visit is allowed even if the last dose was given on study day 14 *(as of Amd 3)* with the exception of vital signs. Vital signs have to be recorded 2 times; once within 10 min prior to the start of study drug administration and once within a 20 minutes time window starting 10 minutes before the end of study drug administration and ending 10 minutes after the end of study drug administration. If the subject has been switched to oral treatment, the second measurement should be done approximately 2 hours after the end of drug administration. *(as of Amd 4)*
e For subjects who prematurely terminate the study, a premature termination visit needs to be documented in the eCRF (see Section 7.1.2.8).
f Pregnancy test for females of child-bearing potential only. Urine test is preferred.
g Within 24 hours before starting drug therapy or up to 24 hours post-enrollment.
h Blood cultures will be drawn only if clinically indicated and there is suspicion of bacteremia. Blood cultures will only be repeated if initially positive or if clinically indicated.
i If a repeat laparotomy, laparoscopy, or percutaneous drainage is performed, specimens must be taken for aerobic and anaerobic culture.
j All AEs, SAEs, including "Hy's Law" cases, and deaths must be reported up to the TOC visit. *(as of Amd 2)* All AEs and SAEs present at this point must be followed until resolved or stabilized. All musculoskeletal AEs will be checked and documented if occurring up to 1 year post-EOT visit. *(as of Amd 1)* Subjects with unresolved musculoskeletal AEs 1 year after the EOT visit will be followed-up yearly for up to 5 years or until resolution, whichever occurs first. *(as of Amd 1)*
k Concomitant medications will be recorded through the TOC visit or until the resolution of any AEs that required treatment with a concomitant medication. Concomitant medication given for musculoskeletal AEs need to be documented up to 1 year after EOT. Antibacterial treatment to be recorded on pre-treatment visit. All medication given up to 48 hours before first study drug intake should be documented as well. *(as of Amd 3)*
l Pre- and post-treatment (on Day 1 before and after the first drug administration for subjects on a q12h dosing regimen) (within ± 5 min of the end of infusion) electrocardiograms will be evaluated. *(as of Amd 3)*
m PK sampling will be performed in a subgroup of subjects (see Section 7.4).
n Only if clinically indicated.
o Pre-treatment local lab values can be used if they have been taken up to 24 h prior to enrollment. *(as of Amd 3)*
P A diary card should only be handed out to the subject or the subject's parents in case the subject is discharged from hospital. *(as of Amd 3)*
q Subjects weighing less than 20 kg can not be switched to oral administration and have to stay on IV treatment for the entire treatment duration. (as of Amd 3)

Source: Extracted from the protocol, Table 2 (pages 43-45)

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3.2.1.2 Efficacy Objectives and Endpoints

This section summarizes the efficacy objectives and endpoints that are of interest in this statistical review. Note that because the trial was primarily designed for assessing safety, the following efficacy objectives were listed as secondary objectives in the trial protocol:

- To evaluate the clinical response to treatment at End of Treatment (EOT) visit at Day 5 to 14
- To evaluate the clinical response at Test of Cure (TOC) visit, i.e. 28 to 42 days after EOT
- To evaluate the bacteriological response at EOT and TOC visit among subjects with bacteriologically confirmed cIAI

The definitions of clinical and bacteriological response varied based on the time point (EOT or TOC) that the patient was evaluated.

At the EOT, clinical responses were to be reported as resolution, failure, or indeterminate. A resolution was defined as a disappearance of signs and symptoms related to the infection or sufficient improvement of clinical signs and symptoms related to the infection and the patient does not require any further antibiotic therapy or surgical intervention. At the TOC, clinical responses were to be reported as clinical cures, failure, or indeterminate. A clinical cure was defined as resolution or sufficient improvement of clinical signs and symptoms related to the infection and the patient does not require any antibiotic therapy or surgical intervention and without the occurrence of wound infections requiring a systemic antibiotic treatment. Failure, at EOT and TOC, was defined as worsening (or insufficient lessening) and reappearance, respectively, of signs and symptoms of original infection. Indeterminate meant that a clinical assessment was not possible (e.g. due to early withdrawal from the trial due to AEs).

At EOT, bacteriological responses were to be reported as eradication, presumed eradication, persistence, presumed persistence, superinfection, or indeterminate. At TOC, bacteriological responses were reported as eradication, presumed eradication, persistence, presumed persistence, re-infection, superinfection, or indeterminate. Eradication, at either time point, was defined as the absence of the original causative organism(s) from a culture obtained from any site within the intra-abdominal cavity or from blood where previously positive. Presumed eradication was defined as the absence of appropriate culture material for evaluation because the subject has clinically responded (with a response as a resolution or cure) and invasive procedures are not warranted.

Refer to Section 7.3.2 of the protocol for more detailed definitions of these efficacy outcomes.

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3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Trial BAY11643 enrolled 478 patients at 38 global sites. Most patients (approximately 35%) were enrolled in sites in Ukraine and only 6 patients were enrolled in sites in the United States; see Table 2. Twenty subjects were considered screen failures and the remaining 458 patients were randomized to the Avelox® arm (305 patients) which consisted of sequential IV Avelox followed by PO Avelox or to the comparator arm (153 patients) which consisted of ertapenem IV followed by oral amoxicillin/clavulanate. Of the randomized patients, 7 patients did not receive their assigned medication; therefore, the valid for safety population comprised 451 patients (301 Avelox® and 150 comparator). The valid for safety population includes 12 patients (7 Avelox and 5 comparator) who had suspected, rather than confirmed cIAI, at study enrollment. According to the study report, 70 patients (53 Avelox® and 17 comparator) were found to have "essential data missing or invalid", e.g. culture results not available at baseline, and were therefore excluded from the mITT population. Thus, a total of 381 patients (248 Avelox® and 133 comparator) are contained in the mITT population.

Table 2 Number of Enrolled Patients by Country

Country	No. of Centers	Date of first consent	Date of last visit	Number of subjects enrolled[a]	Treatment group	Randomized[b]	Valid for safety	Valid for mITT
		21JUL2010	21JAN2015	478	Total	458	451	381
					Moxifloxacin	305	301	248
					Comparator	153	150	133
Bulgaria	5	24MAR2011	22DEC2014	69	Total	67	65	63
					Moxifloxacin	45	44	43
					Comparator	22	21	20
Canada	3	08FEB2012	07NOV2014	16	Total	15	15	14
					Moxifloxacin	9	9	9
					Comparator	6	6	5
Chile	1	02AUG2011	22AUG2012	2	Total	2	2	1
					Moxifloxacin	1	1	1
					Comparator	1	1	0
Czech Republic	2	30OCT2011	24JUN2014	9	Total	9	9	5
					Moxifloxacin	5	5	3
					Comparator	4	4	2
Germany	3	04NOV2010	04DEC2013	8	Total	8	6	5
					Moxifloxacin	5	4	3
					Comparator	3	2	2
Greece	1	03FEB2012	24OCT2013	5	Total	5	5	1
					Moxifloxacin	4	4	0
					Comparator	1	1	1
Hungary	2	11JAN2011	03DEC2014	25	Total	25	24	24
					Moxifloxacin	18	17	17
					Comparator	7	7	7
Lithuania	2	12AUG2010	06NOV2014	25	Total	24	24	21
					Moxifloxacin	18	18	16
					Comparator	6	6	5
Latvia	3	21JUL2010	21JAN2015	88	Total	88	88	86
					Moxifloxacin	60	60	59
					Comparator	28	28	27
Mexico	3	18APR2011	31JAN2014	27	Total	18	17	14
					Moxifloxacin	12	12	9
					Comparator	6	5	5
Peru	3	26AUG2011	01SEP2012	3	Total	3	3	1
					Moxifloxacin	3	3	1
Romania	2	24SEP2010	05NOV2014	26	Total	20	19	13
					Moxifloxacin	11	10	7
					Comparator	9	9	6
Russia	2	02JUL2012	02DEC2014	10	Total	9	9	9
					Moxifloxacin	7	7	7
					Comparator	2	2	2
Ukraine	4	08APR2011	24DEC2014	159	Total	159	159	118
					Moxifloxacin	103	103	69
					Comparator	56	56	49
United States	2	03NOV2010	01APR2014	6	Total	6	6	6
					Moxifloxacin	4	4	4
					Comparator	2	2	2

Abbreviations: mITT=modified intent-to-treat population
a. Number of subjects enrolled is the number of subjects who signed informed consent
b. 7 subjects were randomized but never received treatment
Source: Extracted from the study report: Table 8-1 (page 68)

The majority of patients (>95%) in both treatment arms completed the trial; see Table 3. The most commonly reported reason for withdrawal from the trial was "lost to follow-up", which had

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a higher proportion in the Avelox arm than comparator. This table also shows that the percentage patients who completed treatment exceeded 90% in both treatment arms. The overall treatment discontinuation rates were notably higher in Avelox® patients compared to comparator patients (e.g. 8.9% versus 1.5% for mITT population). Most notably, there was a higher percentage of patients with treatment discontinuations due to adverse event in Avelox® patients than comparator (e.g. 5.3% versus 0.8% for mITT population).

Table 3 Patient Status in the mITT and Valid for Safety Populations

Patient Status	mITT Population		Valid for Safety Population	
	Avelox N=248 n (%)	**Comparator N=133 n (%)**	**Avelox N=301 n (%)**	**Comparator N=150 n (%)**
Completed Study	237 (95.6)	132 (99.3)	287 (95.4)	149 (99.3)
Withdrawal from Study	11 (4.4)	1 (0.8)	14 (4.7)	1 (0.7)
Primary reason for withdrawal				
Consent withdrawn	3 (1.2)	0 (0)	5 (1.7)	0 (0)
Insufficient therapeutic effect	1 (0.4)	0 (0)	1 (0.3)	0 (0)
Lost to follow-up	6 (2.4)	1 (0.8)	7 (2.3)	1 (0.7)
Protocol violation	1 (0.4)	0 (0)	1 (0.3)	0 (0)
Completed Treatment	226 (91.1)	131 (98.5)	275 (91.4)	146 (97.3)
Treatment Discontinuation	22 (8.9)	2 (1.5)	26 (8.6)	4 (2.7)
Primary reason for discontinuation				
Adverse event	13 (5.3)	1 (0.8)	15 (5.0)	2 (1.3)
Study terminated by sponsor	0 (0)	0 (0)	0 (0)	1 (0.7)
Protocol driven decision point	1 (0.4)	0 (0)	1 (0.3)	0 (0)
Consent withdrawn	2 (0.8)	0 (0)	4 (1.3)	0 (0)
Technical problems	2 (0.8)	0 (0)	2 (0.7)	0 (0)
Insufficient therapeutic effect	2 (0.8)	1 (0.8)	2 (0.7)	1 (0.7)
Protocol violation	2 (0.8)	0 (0)	2 (0.7)	0 (0)

Source: Created by the statistical reviewer using dataset "endpoint.xpt"

The distributions of treatment duration were similar for the Avelox® and comparator arms for the mITT and the valid for safety populations. The mean duration of treatment was approximately 8.7 days for both treatment arms. The majority of patients were treated for 6 to 14 days.

The distributions of demographic characteristics were similar across the Avelox® and comparator treatment arms in the mITT and valid for safety populations; refer to Table 4. Most subjects were between 6 and 18 years old (95%), white (96%), and male (61%). The average BMI was approximately 19 kg/m^2 and most subjects (63%) had BMI less than 20 kg/m^2.

The distributions of baseline characteristics by primary diagnosis of intra-abdominal infection were similar for the treatment arms; see Table 5. The most common diagnosis was peritonitis localized.

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Table 4 Demographic Characteristics in mITT and Valid for Safety Populations

Demographic Characteristic	mITT Population		Valid for Safety Population	
	Avelox N=248	Comparator N=133	Avelox N=301	Comparator N=150
Age Group, n (%)				
12 to less than 18 years	158 (63.7)	80 (60.2)	186 (61.8)	92 (61.3)
6 to less than 12 years	82 (33.1)	46 (34.6)	100 (33.2)	51 (34.0)
2 to less than 6 years	7 (2.8)	7 (5.3)	14 (4.7)	7 (4.7)
3 months to less than 2 years*	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Age, in years				
Mean (SD)	12.3 (3.6)	11.9 (3.6)	12.0 (3.7)	12.0 (3.5)
Range	0.3 – 17.0	3.0 – 17.0	0.3 – 17.0	3.0 – 17.0
Sex, n (%)				
Male	147 (59.3)	90 (67.7)	179 (58.5)	98 (65.3)
Female	101 (40.7)	43 (32.3)	122 (40.5)	52 (34.7)
Race, n (%)				
White	239 (96.4)	126 (94.7)	289 (96.0)	142 (94.7)
Non-white	9 (3.6)	7 (5.3)	12 (4.0)	8 (5.3)
Geographic Location, n (%)				
Europe	224 (90.3)	121 (91.0)	272 (90.4)	136 (90.7)
North America	22 (8.9)	12 (9.0)	25 (8.3)	13 (8.7)
Latin America	2 (0.8)	0 (0.0)	4 (1.3)	1 (0.7)
BMI Group, n (%)				
Less than 20*	154 (62.1)	87 (65.4)	185 (61.5)	98 (65.3)
20 or greater	94 (37.9)	46 (34.6)	116 (39.5)	52 (34.7)
BMI, in kg/m^2				
Mean (SD)	19.1 (4.2)	18.8 (3.6)	19.1 (4.3)	18.8 (3.5)
Range	8.4 – 39.7	9.1 – 28.6	8.4 – 39.7	9.1 – 28.6

Non-white contains Black, Hispanic, or Asian
*Per protocol, these subjects were to be treated with IV therapy only throughout the course of the trial.
Source: Created by the statistical reviewer using dataset "adsl.xpt"

Table 5 Primary Diagnosis at Baseline in mITT and Valid for Safety Populations

	mITT Population		Valid for Safety Population	
	Avelox N=248 n (%)	Comparator N=133 n (%)	Avelox N=301 n (%)	Comparator N=150 n (%)
Primary Diagnosis				
Single intra-abdominal abscess	39 (15.7)	21 (15.8)	50 (16.6)	23 (15.3)
Multiple intra-abdominal abscess	2 (0.8)	0 (0.0)	2 (0.7)	0 (0.0)
Peritonitis localized	123 (49.6)	62 (46.6)	148 (49.2)	74 (49.3)
Peritonitis diffuse	84 (33.9)	50 (37.6)	101 (33.6)	53 (35.3)

Source: Created by the statistical reviewer using dataset "iadiag.xpt" and "adsl.xpt"

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Table 6 shows the most prevalent causative organisms, occurring in at least 5% of patients, as reported in the data submitted by the Applicant for the mITT population. The most frequently reported causative organism was *Escherichia coli* which occurred in 200 (81%) Avelox® patients and 121 (91%) comparator patients.

Table 6 Most Prevalent (≥5%) Causative Organism at Baseline in the mITT Population

Organism*	**Avelox , N=248 n (%)**	**Comparator, N=133 n (%)**
Escherichia coli**	200 (80.6)	121 (91.0)
Pseudomonas aeruginosa	54 (21.8)	20 (15.0)
Streptococcus constellatus**	38 (15.3)	19 (14.2)
Bacteroides fragilis**	37 (14.9)	24 (18.0)
Bacteroides thetaiotamicron**	26 (10.5)	14 (10.5)
Peptostreptococcus micros**	15 (6.0)	8 (6.0)

*Table contains only those organisms as reported in the Applicant's dataset which were determined by central lab. Patients may have had multiple organisms that were classified as causative of cIAI.
**These organisms are included in the US Prescribing Information for cIAI indication in adults.
Source: Created by the statistical reviewer using datasets: "orgid.xpt" and "iadiag.xpt"

3.2.4 Results and Conclusions

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3.3 Evaluation of Safety

This section presents the safety evaluation performed by the statistical reviewer. Refer to review by Dr. Amol Purandare and Dr. Yuliya Yasinskaya for clinical review of safety.

Recall that the primary objective of BAY11643 was to assess the safety of treatment with Avelox® in response to a Pediatric Written Request. According to the protocol, special emphasis was to be placed on adverse events related to the musculoskeletal and cardiac systems; as such, detailed evaluations of these outcomes are presented in this review. The adverse events used for the analysis of musculoskeletal or cardiac events were provided by Dr. Yuliya Yasinskaya.

3.3.1 Safety Objectives and Analyses

The safety objectives in this review are:

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1. To summarize adverse events (AEs) and serious adverse events (SAEs) for the Avelox® and comparator arms

2. To compare the incidence of musculoskeletal AEs in the Avelox® and comparator arms

3. To compare the incidence of cardiac AEs in the Avelox® and comparator arms

The safety analysis population, also referred to as the valid for safety population, consists of all randomized patients who had at least one dose of study medication.

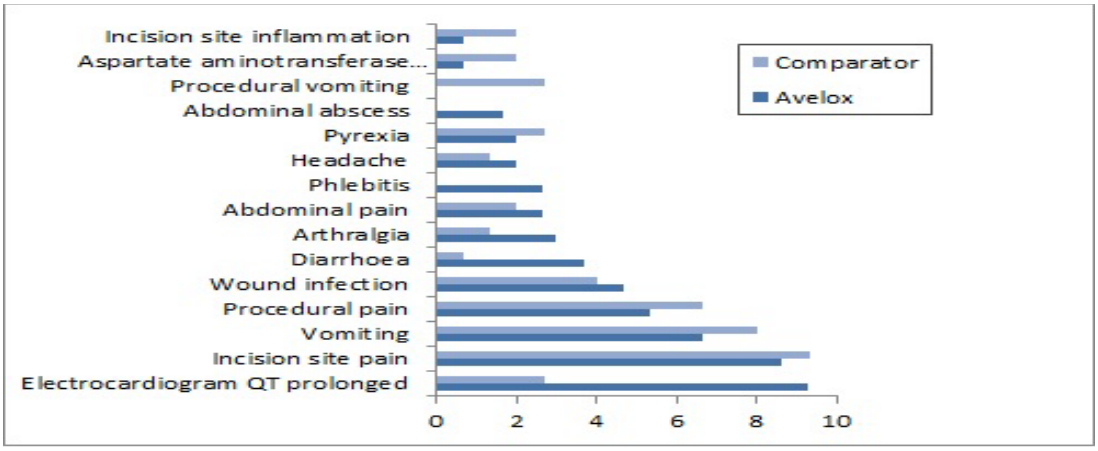
Descriptive summaries of the percentages of AEs and SAEs, using MedDRA preferred terms version 17.1, are provided for each treatment arm. For analyses of musculoskeletal AEs and cardiac AEs, the risk difference (Avelox® – comparator) and 95% CIs based on normal approximations to the binomial or exact methods, where the event rate is low. A risk difference of zero suggests that the incidence of the event is similar in the Avelox® and comparator arms; a positive risk difference suggests that the incidence of the event is higher in the Avelox® arm and a negative risk difference suggests that the incidence of the event is lower in the Avelox® arm.

In the case of significant risk differences (i.e. lower bound of 95% CI exceeds zero), Kaplan-Meier plots are presented to investigate the timing of the respective event. These plots are produced using Stata Version 11.1.

3.3.2 Results of Safety Analyses

The percentage of patients who reported any adverse event during the trial was 175/301 (58.1%) in Avelox® and 82/150 (54.7%) in comparator. The most commonly reported AEs, that is, AEs occurring in at least 2% of patients in either treatment arm, were electrocardiogram QT prolonged, 28/301 or 9.3% Avelox® patients and 4/150 or 2.7% comparator patients, and incision site pain, 26/301 or 8.3% Avelox® patients and 14/150 or 9.3% comparator patients; see Figure 2.

Figure 2 Most Commonly (≥ 2%) Reported Adverse Event in Valid for Safety Population



The horizontal axis represents the percentage of patients with reported AE.
Source: Created by the statistical reviewer using "adae.xpt" dataset

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The percentage of patients with SAEs was higher in the Avelox® arm (20/301 or 6.6%) compared to comparator (6/150 or 4%); no notable differences observed for particular events. There were no deaths reported in the trial.

The incidence of musculoskeletal events was 4.3% in Avelox® patients compared to 3.3% in comparator patients resulting in a risk difference of 1.0% and 95% CI (-2.7%, 4.7%); shown in Table 9. The timing of these events for both treatment groups occurred up to a year after randomization, well beyond the end of the treatment period.

The incidence of cardiac events was 12.6% in Avelox® patients compared to 4.0% in comparator patients resulting in a risk difference of 8.6% with 95% CI (3.7%, 13.5%). As shown in this table, the imbalance in cardiac events is primarily driven by QT events.

Table 9 Analysis of Musculoskeletal and Cardiac Events in the Valid for Safety Population

Safety Outcome	**Avelox, N=301 n (%)**	**Comparator, N=150 n (%)**	**Risk Difference* (95% CI)**
Musculoskeletal Events[1]	13 (4.3)	5 (3.3)	1.0 (-2.7, 4.7)
Arthralgia	9 (3.0)	2 (1.3)	
Ligament sprain	1 (0.3)	1 (0.7)	
Other musculoskeletal events	3 (1.0)	2 (1.3)	
Cardiac Events[2]	38 (12.6)	6 (4.0)	8.6 (3.7, 13.5)
QT prolonged	28 (9.3)	4 (2.7)	
Tachycardia	2 (0.7)	0 (0)	
Other cardiac events	6 (2.3)	2 (1.3)	

[1]Based on MedDRA SOC of Musculoskeletal and connective tissue disorders (excluding fasciitis) or preferred terms: forearm fracture, joint injury, ligament sprain, muscle strain.
[2] Based on MedDRA preferred terms: electrocardiogram QT prolonged, chest pain, electrocardiogram T wave abnormal, electrocardiogram T wave inversion, QRS axis abnormal, blood pressure decreased, hypertension, dyspnea or system organ class of cardiac disorders.
*A risk difference of zero suggests that no difference in the incidence of the event between Avelox and comparator arms; a positive risk difference suggests that the incidence of the event is higher in the Avelox arm, and a negative risk difference suggest that the incidence of the event is lower in the Avelox arm.
Source: Created by the statistical reviewer using datasets “adae.xpt” and “adsl.xpt”

Figure 3 shows the first 15 days after randomization, during which time all of the cardiac events occurred; refer to clinical review by Dr. Amol Purandare and Dr. Yuliya Yasinskaya for further investigation of safety.

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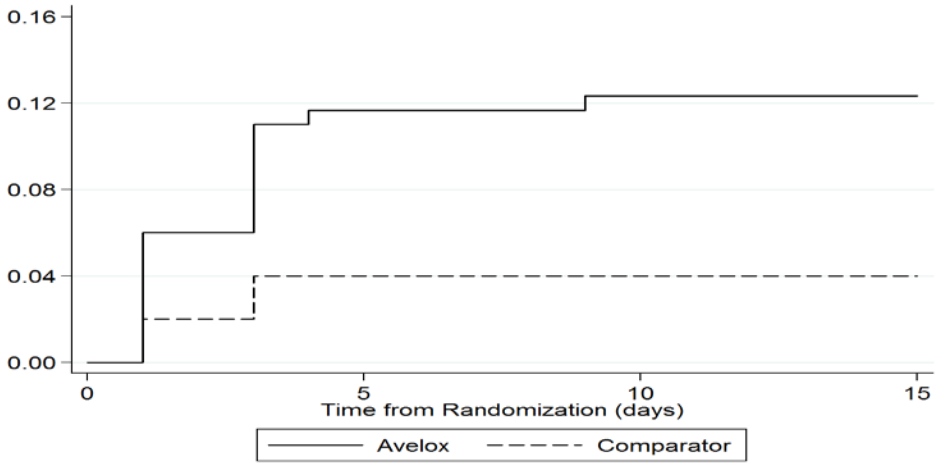
Figure 3 Kaplan-Meier Failure Plot of Cardiac Events



Source: Created by the statistical reviewer using dataset "adae.xpt"

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

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[redacted]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were a few important issues discovered during the review of the Applicant's submission.

Firstly, missing data were inappropriately handled in the analyses presented in study report [redacted]

[redacted]

5.2 Collective Evidence

[redacted] There were no new safety findings discovered in this review.

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5.3 Conclusions and Recommendations

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5.4 Labeling Recommendations

This section summarizes labeling recommendations for Section 8.4: Pediatric Use of the Avelox® USPI. (b) (4)

Note that label negotiations are ongoing at the time of this statistical review.

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/s/

JANELLE K CHARLES
02/11/2016

KAREN M HIGGINS
02/11/2016
I concur.