CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21085, 21277
Priority or Standard	Priority
Submit Date(s)	September 11, 2015
Received Date(s)	September 11, 2015
PDUFA Goal Date	March 11, 2016
Division / Office	DAIP/OAP
Reviewer Name(s)	Amol Purandare, MD Yuliya Yasinskaya, MD
Review Completion Date	February 12, 2016
Established Name	Moxifloxacin HCl
(Proposed) Trade Name	Avelox
Therapeutic Class	Fluoroquinolone antibacterial
Applicant	Bayer Pharmaceuticals
Formulation(s)	Injection, oral tablet
Dosing Regimen	400mg daily
Indication(s)	Complicated intra-abdominal infections
Intended Population(s)	(b) (4)

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 5

1.1 Recommendation on Regulatory Action 5
1.2 Risk Benefit Assessment 5
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies 5
1.4 Recommendations for Postmarket Requirements and Commitments 6

2 INTRODUCTION AND REGULATORY BACKGROUND 6

2.1 Product Information 6
2.2 Tables of Currently Available Treatments for Proposed Indications 7
2.3 Availability of Proposed Active Ingredient in the United States 9
2.4 Important Safety Issues With Consideration to Related Drugs 9
2.5 Summary of Presubmission Regulatory Activity Related to Submission 9

3 ETHICS AND GOOD CLINICAL PRACTICES 10

3.1 Submission Quality and Integrity 10
3.2 Compliance with Good Clinical Practices 10
3.3 Financial Disclosures 10

4 SIGNIFICANT (b) (4) SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 10

4.1 Chemistry Manufacturing and Controls 10
4.2 Clinical Microbiology 10
4.3 Preclinical Pharmacology/Toxicology 11
4.4 Clinical Pharmacology 11

5 SOURCES OF CLINICAL DATA 13

5.1 Tables of Studies/Clinical Trials 13
5.2 Review Strategy 22

(b) (4)

6.1 Indication 22
6.1.1 Methods 22
6.1.2 Demographics 22
6.1.3 Subject Disposition 26

(b) (4) 27
.....27
.....28
.....28
.....29
.....29
.....30
.....32

7 REVIEW OF SAFETY 32

7.1 Methods 32
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 33
7.1.2 Categorization of Adverse Events 33
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 35
7.2 Adequacy of Safety Assessments 35
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 35
7.2.2 Explorations for Dose Response 36
7.2.3 Special Animal and/or In Vitro Testing 36
7.2.4 Routine Clinical Testing 36
7.2.5 Metabolic, Clearance, and Interaction Workup 36
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class 37
7.3 Major Safety Results 37
7.3.1 Deaths 37
7.3.2 Nonfatal Serious Adverse Events 37
7.3.3 Dropouts and/or Discontinuations 38
7.3.5 Submission Specific Primary Safety Concerns 39
7.4 Supportive Safety Results 42
7.4.1 Common Adverse Events 42
7.4.2 Laboratory Findings 44
7.4.3 Vital Signs 47
7.4.4 Electrocardiograms (ECGs) 47
7.4.5 Special Safety Studies/Clinical Trials 48
7.4.6 Immunogenicity 48
7.5 Safety Summary and Conclusion 48

9 APPENDICES 50

9.1 Clinical Investigator Financial Disclosure Review 50
9.2 Labeling Recommendations 51
9.3 Advisory Committee Meeting 51

Table of Tables

Table 1: Currently Treatment for cIAI in the US 7
(b) (4) 11
..... 12
Table 4: Clinical Studies/Trials for cIAI in Pediatric Patients 13
Table 5: Demographic Characteristics, Safety Analysis Set 23
Table 6 Symptoms at Study Entry 23
Table 7 Baseline Disease Characteristics Pediatric Patients 24
Table 8 Baseline Disease Characteristics in Adults 24
Table 9 Surgery Prior to Treatment 25
Table 10 Causative Organisms at baseline, mITT (≥10 organisms) 25
Table 11 Study Subject Disposition 26
Table 12 Analysis Populations 27
(b) (4) 27
..... 28
..... 29
..... 29
..... 30
s
..... 30
..... 31
..... 31
..... 33
Table 22 Adverse Event Characterization Summary 34
Table 23 Occurrence of Adverse Events Across Age Groups 34
Table 24 Summary of Study Medication Exposure 35
Table 25 Study Drug Completion 36
Table 26 Serious Adverse Events 37
Table 27 Adverse Events Resulting in Study Drug Discontinuations 38
Table 28 Cardiac Adverse Events 39
Table 29 Musculoskeletal Adverse Events 40
Table 30 Hepatic Adverse Events 41
Table 33 Common Adverse Events 42
Table 32 Hematology Parameter Changes from Baseline (Lowest Value Post Baseline) 45
Table 33 Liver Function Changes from Baseline (Maximum Value Post Baseline) 45
Table 34 Change in Vital Signs from Baseline to TOC Visit 47

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant has submitted a response to a final amended Pediatric Written Request (PWR) from May 2, 2012 to provide information on the use of moxifloxacin in pediatric patients with complicated intra-abdominal infections (cIAI). Moxifloxacin is currently approved in adults for treatment of complicated intra-abdominal infections at a dose of 400 mg once a day.

(b) (4)

1.2 Risk Benefit Assessment

(b) (4)

Moxifloxacin's safety profile in pediatric patients is similar to what has been seen in the adult clinical trials and in postmarketing reports. The most frequently reported drug-related adverse events in pediatric patients receiving moxifloxacin were ECG QT prolonged (9.3%), vomiting (6.6%), diarrhea (3.7%) and arthralgia (3%). Although no clinically significant cardiac adverse reactions were noted in the pediatric cIAI trial, moxifloxacin's potential to prolong QT interval was no different in pediatric patients (mean change of QTcF 7 - 15 ms) as compared to adults (mean change of QTcF 7 - 10 ms) at the exposures observed at 400 mg adult dose. Incidence of musculoskeletal events on moxifloxacin arm (4.3%) was comparable to that of the comparator (3.3%) with 95% CI (-2.7, 4.7).

(b) (4)

.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

none

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

Moxifloxacin hydrochloride is a synthetic broad spectrum antimicrobial agent available as tablets for oral administration and as an aqueous solution for intravenous administration.

Moxifloxacin tablets and intravenous aqueous solution are currently indicated for the treatment of adults at least 18 years of age with infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

- Acute bacterial sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis.*
- Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Staphylococcus aureus, or Moraxella catarrhalis.*
- Community acquired pneumonia caused by *Streptococcus pneumoniae (including multi- drug resistant strains), Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae, or Chlamydia pneumoniae.*
- Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus or Streptococcus pyogenes.*
- Complicated skin and skin structure infections caused by *methicilllin susceptible Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae or Enterobacter cloacae.*
- Complicated Intra-Abdominal Infections including polymicrobial infections such as abscess caused by susceptible isolates of *Escherichia coli, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, Enterococcus faecalis, Proteus mirabilis, Clostridium perfringens, Bacteroides thetaiotaomicron, or Peptostreptococcus* species

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Currently Treatment for cIAI in the US

Drug	Indication	Pediatrics
metronidazole	Complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis*, *B. thetaiotaomicron*, and *Peptostreptococcus* species.	Yes- >0
clindamycin	Intra-abdominal infections including peritonitis and intra-abdominal abscess caused by susceptible anaerobic organisms.	Yes- >0
amikacin	Serious intra-abdominal infections (including peritonitis) due to susceptible strains of Gram-negative bacteria, including *Pseudomonas* species, *Escherichia coli*, species of indole-positive and indole-negative *Proteus*, *Providencia* species, *Klebsiella-Enterobacter-Serratia* species, and *Acinetobacter* (Mima-Herellea) species.	Yes >0
tobramycin	Intra-abdominal infections, including peritonitis, caused by *E. coli*, *Klebsiella* spp, and *Enterobacter* spp	Yes- >0
ampicillin/sulbactam	Intra-abdominal infections caused by beta-lactamase producing strains of *Escherichia coli, Klebsiella* spp. (including *K. pneumoniae), Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.	Yes ≥1 year
piperacillin/tazobactam	Appendicitis (complicated by rupture or abscess) and peritonitis caused by piperacillin-resistant, (beta)-lactamase producing strains of *Escherichia coli* or the following members of the *Bacteroides fragilis* group: *B. fragilis, B. ovatus, B. thetaiotaomicron,* or *B. vulgatus*.	Yes >8 months
cefoxitin	Intra-abdominal infections, including peritonitis and intra-abdominal abscess, caused by *Escherichia coli, Klebsiella* species, *Bacteroides* species including *Bacteroides fragilis*, and *Clostridium* species	Yes >3 months
cefotaxime	Intra-abdominal infections including peritonitis caused by *Streptococcus* species, *Escherichia coli, Klebsiella* species, *Bacteroides* species, and anaerobic cocci (including *Peptostreptococcus* species and *Peptococcus* species) *Proteus mirabilis*, and *Clostridium* species.	Yes- >0
ceftriaxone	Intra-abdominal infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Bacteroides fragilis*, *Clostridium* species (Note: most strains of *Clostridium difficile* are resistant) or *Peptostreptococcus* species.	Yes >28 days
ceftazidime	Intra-abdominal infections, including peritonitis caused by *Escherichia coli, Klebsiella* spp., and *Staphylococcus aureus* (methicillin-susceptible strains) and polymicrobial infections caused by aerobic and anaerobic organisms and *Bacteroides* spp. (many strains of *Bacteroides fragilis* are resistant).	Yes >0
ceftazidime/avibactam	complicated intra-abdominal infections (cIAI) caused by the following susceptible microorganisms*: Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii, Enterobacter cloacae, Klebsiella oxytoca, and Pseudomonas aeruginosa*	no
ceftolozane/tazobactam	(in combination with metronidazole) complicated intra-abdominal infections (cIAI) caused by the following Gram-negative and Gram-positive microorganisms*: Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius.*	no
cefepime	Complicated intra-abdominal infections (used in combination with	no

Drug	Indication	Pediatrics
	metronidazole) caused by *Escherichia coli*, viridans group streptococci, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterobacter* species, or *Bacteroides fragilis*.	
ceftizoxime	Intra-Abdominal Infections caused by *Escherichia coli; Staphylococcus epidermidis; Streptococcus* spp. (excluding enterococci); *Enterobacter* spp.; *Klebsiella* spp.; *Bacteroides* spp. including *B. fragilis*; and anaerobic cocci, including *Peptococcus* spp. and *Peptostreptococcus* spp.	Yes >6 months
cefotetan	Intra-abdominal Infections caused by *E. coli, Klebsiella* species (including *K. pneumoniae*), *Streptococcus* species (excluding enterococci), *Bacteroides* species (excluding *B. distasonis, B. ovatus, B. thetaiotaomicron*) and *Clostridium* species*.	no
aztreonam	Intra-abdominal Infections, including peritonitis caused by *Escherichia coli, Klebsiella species* including *K. pneumoniae, Enterobacter* species including *E. cloacae, Pseudomonas aeruginosa, Citrobacter* species including *C. freundii*, and *Serratia* species including *S. marcescens*	Yes ≥9 months
imipenem/cilastin	Intra-abdominal infections. *Enterococcus faecalis, Staphylococcus aureus* (penicillinase-producing strains), *Staphylococcus epidermidis, Citrobacter* species, *Enterobacter* species, *Escherichia coli, Klebsiella* species, *Morganella morganii, Proteus* species, *Pseudomonas aeruginosa, Bifidobacterium* species, *Clostridium* species, *Eubacterium* species, *Peptococcus* species, *Peptostreptococcus* species, *Propionibacterium* species, *Bacteroides* species including *B. fragilis, Fusobacterium* species	Yes >0
meropenem	Complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, B. thetaiotaomicron,* and *Peptostreptococcus* species.	Yes->2 months
ertapenem	Complicated intra-abdominal infections due to *Escherichia coli, Clostridium clostridioforme, Eubacterium lentum, Peptostreptococcus* species, *Bacteroides fragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron*, or *Bacteroides uniformis*	Yes->2 months
tigacycline	Complicated intra-abdominal infections caused by *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus anginosus* grp. (includes *S.anginosus, S.intermedius*, and *S. constellatus*). *Bacteroides fragilis, Bacteroides thetaiotamicron, Bacteroides uniformis, Bacteroides vulgatus, Clostridium perfringens,* and *Peptostreptococcus micros*.	If no alternative ≥8 years
ciprofloxacin	Complicated Intra-abdominal infections (used in conjunction with metronidazole) caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.*	no
moxifloxacin	Complicated Intra-Abdominal Infections including polymicrobial infections such as abscess caused by *Escherichia coli, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, Enterococcus faecalis, Proteus mirabilis, Clostridium perfringens, Bacteroides thetaiotaomicron, or Peptostreptococcus species*	no

2.3 Availability of Proposed Active Ingredient in the United States

Moxifloxacin is currently available in the US marketed as a brand name Avelox and generic equivalents in both injection and tablet dose forms.

2.4 Important Safety Issues With Consideration to Related Drugs

Moxifloxacin as other members of fluoroquinolone class of antibacterials is associated with number of serious and life-threatening adverse reactions described in the boxed warning and warnings and precautions section of the approved product labeling:

- Tendinopathy and tendon rupture
- Exacerbation of myasthenia gravis
- Hypersensitivity Reactions
- Other Serious and Sometimes Fatal Reactions
- Hepatotoxicity
- Central Nervous System Effects
- Peripheral Neuropathy
- Prolongation of the QT Interval
- Arthropathic Effects in Animals
- Blood Glucose Disturbances
- Photosensitivity/Phototoxicity

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Because the armamentarium of antibacterial drugs approved for the treatment of complicated intra-abdominal infections (cIAI) in pediatric patients is limited (e.g., beta-lactams), studies of moxifloxacin hydrochloride in pediatric patients might have provided a public health benefit by offering an additional treatment option in a different class of antibacterial drugs. Moxifloxacin is approved for the treatment of cIAI in adults; 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 needed pediatric information on moxifloxacin for use in cIAI and in response to the Sponsor's Proposed Pediatric Study Request (PPSR) from August 14, 2009 (submission S-266) to the NDA 21-277, the Food and Drug Administration (FDA) issued a formal Written Request (PWR), pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, on December 7, 2009. The PPSR submitted to FDA is similar to the pediatric investigation plan (PIP) for moxifloxacin submitted to the European Medicines Agency (EMEA). The PWR was amended on May 2, 2012.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

eCRFs were employed on the study and the sites and data flow were audited by Bayer and respective IRBs.
OSI inspections were requested to assess the integrity of the pharmacokinetic data collected. The results of the inspections are pending at the time of the completion of this review.

3.2 Compliance with Good Clinical Practices

The studies submitted were stated to be compliant with Good Clinical Practices.

3.3 Financial Disclosures

The applicant submitted financial disclosure form 3454 and debarment certification for all investigators involved in the studies conducted. The form states that the applicant had not entered into any financial arrangement with the listed clinical investigators in which compensation to the investigator could be affected by the outcome of the study. See Appendix 9.1.

4 Significant (b) (4) Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No new CMC information was submitted in this supplement.

4.2 Clinical Microbiology

(b) (4)

(b) (4)

4.3 Preclinical Pharmacology/Toxicology

No new pharmacology-toxicology information was submitted for review.

4.4 Clinical Pharmacology

(b) (4)

(b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Clinical Studies/Trials for cIAI in Pediatric Patients

	PWR May 28, 2010	(b) (4)
Type of studies:	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 3 months following moxifloxacin or non-quinolone antimicrobial control drug exposure in pediatric patients. The study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities.	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, 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 The study enrolled proportional to the study population ethnic and racial minorities and described the racial composition of the study in the demographics section of the study report
Indication(s) to be studied/Objectives	Study 1: Primary: To characterize the pharmacokinetics, safety and tolerability of moxifloxacin following single dose IV administration in infected male and female pediatric patients ages 3 months to <14 years weighing <45 kg, and to identify the appropriate dosing regimen(s) to be evaluated in subsequent clinical trials evaluating safety and efficacy of moxifloxacin in pediatric patients with complicated intra-abdominal infections. The results of this study must be analyzed by the sponsor, and the analysis findings reviewed by	Study 1: The primary objective of this study was to describe the pharmacokinetics of moxifloxacin in children of different ages, in order to determine a dose that would provide a similar exposure as seen in adults treated with the approved therapeutic dose of 400 mg. The secondary objectives of this study were to assess the safety and tolerability of single dose intravenous moxifloxacin in children, particularly with regard to cardiovascular and musculoskeletal safety. Study 2: *Inclusion criteria:*

	the FDA prior to initiating enrollment of patients <14 years weighing <45 kg in Study 2 to ensure appropriate moxifloxacin dose selection for this age and weight cohort. Secondary: To characterize the pharmacokinetics of moxifloxacin metabolites, sulfamoxifloxacin (M1) and moxifloxacin glucuronide (M2), in these pediatric patients. Study 2: Primary: To evaluate the safety and tolerability of IV and oral moxifloxacin in pediatric patients 3 months to <17 years with cIAI. The overall incidence of musculoskeletal events occurring in pediatric patients 3 months after exposure to moxifloxacin or non-quinolone antimicrobial therapy will also be assessed. Secondary: To investigate the pharmacokinetics and the absolute bioavailability of the pediatric formulation(s) of moxifloxacin in a subset of pediatric patients enrolled in this trial and to evaluate efficacy of moxifloxacin in pediatric patients with cIAI.	1. Hospitalized males or females 3 months to < 18 years of age. 2. Parental or legal guardian written informed consent and assent from subjects as applicable. 3. Negative pregnancy test in a female subject of child-bearing potential, practicing protocol methods of contraception through 1 month after TOC 4. Surgically confirmed cIAI with ≥1 of the following: • Gross peritoneal inflammation with purulent exudate within the abdominal cavity, **and/or** • Intra-abdominal abscess, **and/or** • Macroscopic intestinal perforation with diffuse peritonitis **OR** Suspected cIAI with radiological evidence (US, abdominal plain films, CT, MRI) of gastrointestinal perforation or localized collections of potentially infected material **AND** ≥1 of the following: • Symptoms referable to the abdominal cavity (eg, anorexia, nausea, vomiting or pain) • Tenderness (with or without rebound), involuntary guarding, absent or diminished bowel sounds, or abdominal wall rigidity • Fever (body T > 38.0°C oral; > 38.5°C rectal or tympanic membrane) • Leukocytosis (WBC≥ 12,000 cells/mm3) **AND** A surgical procedure (laparotomy or laparoscopy) or percutaneous drainage scheduled *Exclusion criteria:* 1. An indwelling peritoneal catheter 2. Spontaneous bacterial peritonitis 3. cIAI secondary to pancreatitis 4. Liver or splenic abscess 5. Upper gastrointestinal tract (stomach or duodenum) perforation < 24 hours duration before surgery 6. Nonperforated appendicitis 7. Need for antibiotic irrigations of the abdominal cavity or surgical wound 8. "open abdomen" or marsupialization, or multiple planned re-laparotomies 9. Female genital tract infections 10. Severe, life-threatening disease with a life expectancy < 48 hours and or rapidly fatal underlying disease (death within 2 months) 11. Known severe immunosuppression (ANC < 1000/mm3, CD4 + < 200/mm3, AIDS-defining event and/or concomitant antiretroviral therapy, immunosuppressive therapy≥ 2

		weeks or any other congenital or acquired immune defect) 12. Significant renal impairment with Cr > 1.5xULN 13. Documented QT prolongation 14. Concomitant treatment with QT prolonging drugs 15. Clinically relevant bradycardia 16. Clinically relevant heart failure and/or reduced left ventricular ejection fraction 17. History of symptomatic arrhythmias 18. Uncorrected electrolytes, particularly hypokalemia 19. Clinical manifestation of intestinal malabsorption 20. Severe acute hepatic impairment (transaminases > 3x ULN) or chronic hepatic impairment (Child-Pugh C) 21. History of tendon disease/disorder related to quinolone treatment 22. CNS disorders predisposing to seizures 23. Quinolone use within the previous 12 months 24. Hypersensitivity to a study drug/related compounds 25. Pathogenic organisms resistant to a study drug 26. Systemic antibacterial treatment within the previous 7 days (≤24 hours of empiric pre- and perioperative antibiotic treatment other than study drug is allowed) 27. Concomitant systemic antibacterial agents 28. Abnormal musculoskeletal findings at baseline 30. Participation in any clinical study within 30 days 31. Body weight less than the 5th percentile 32. Sepsis or suspected sepsis (septic shock) <u>Primary objective:</u> • To evaluate the safety of treatment with moxifloxacin (compared to the safety of IV ertapenem followed by PO amoxicillin/clavulanate) <u>Secondary objectives:</u> • To evaluate musculoskeletal adverse events (arthropathy, tendinopathy, gait abnormality, etc) • To evaluate electrocardiogram (ECG) profiles obtained on Day 1 and Day 3 pre-treatment and post- treatment (serum peak level) • To evaluate the clinical and bacteriological response at the Test-of-Cure (TOC) visit • To evaluate the clinical response at the TOC visit among subjects with a bacteriologically confirmed complicated intra-abdominal infection (cIAI) • To evaluate the clinical and bacteriological response to treatment at a “during therapy” visit (Day 3-5)

		• To evaluate the clinical and bacteriological response to treatment at the End-of-Treatment (EOT) visit • A separate evaluation of pharmacokinetics (PK) and absolute bioavailability will be performed for at least 18 subjects per age group enrolled
Age group in which studies will be performed:	Study 1: The following age subgroups will be enrolled in a staggered fashion, starting with the oldest subgroup of pediatric patients. Younger children will be enrolled only after favorable evaluation of the safety, tolerability and PK data from the preceding older age groups. Pre-adolescents from 6 to < 14 years weighing < 45kg Pediatric patients from 2 to <6 years Infants from 3 months to < 2 year Study 2: The following age cohorts will be studied: 3 months to <2 years; 2 years to < 6 years; 6 years to <12 years; 12 years to <18 years.	Study 1: • 6 to 14 years of age • 2 to less than 6 years of age • 3 months to less than 2 years of age Study 2 • 12 to less than 18 years of age • 6 to less than 12 years of age • 2 to less than 6 years of age • 3 months to less than 2 years of age
Number of patients to be studied:	Study1: A minimum of 12 evaluable patients per defined age subgroup and a minimum of 6 evaluable patients aged 3 months to 1 year will be studied. Justification on number of samples per patient for each group should be provided. A combination of rich and sparse sampling strategy may be used to adequately characterize pharmacokinetics of moxifloxacin following single IV administration. Study 2: Approximately 300 moxifloxacin-treated patients and 150 non-quinolone antimicrobial-treated patients will be enrolled and complete 3 months of follow-up. With this number of moxifloxacin-treated patients, if no specific adverse event is seen, an event rate of that specific adverse event can be assumed with 95% confidence to be < 1%. Attempt should be made to enroll pediatric patients with cIAI of all causes. At least 30 moxifloxacin and 15 non-quinolone treated patients (10%) should have a cIAI other than appendicitis-related cIAI. For the pharmacokinetic portion of the study, justification on the number of samples per patient during IV and oral moxifloxacin administration will be provided. A combination of rich and sparse sampling strategy may be used to adequately	Study1: A total of 31 subjects were assigned to treatment and received a dose of moxifloxacin according to their assigned dose level. Cohorts 1 and 2 each included 12 subjects, while cohort 3 included 7 subjects. All 31 subjects remained on study through at least the 3 month follow-up visit, and therefore all 31 subjects were valid for PK and safety analysis. Study 2: • 451 pediatric subjects (ages 3 months to less than 18 years) with cIAI matching the criteria for eligibility received either moxifloxacin (n = 301) or comparator (n = 150) and were evaluable for safety. • A separate evaluation of pharmacokinetics (PK) and absolute bioavailability was performed for at least 18 subjects per age group enrolled under this protocol. An age-adapted sparse sampling strategy was applied to minimize the frequency and volume of blood drawings for PK analysis.

	characterize pharmacokinetics of moxifloxacin. Justification on number of pediatric patients per defined age subgroup should also be provided. Modeling and simulation may be used for the above justifications	
Study endpoints	Study 1: The following pharmacokinetic parameters will be determined for IV moxifloxacin and its M1 and M2 metabolites: Cmax, Tmax and AUCτ. Concentration-time profiles will be plotted for each moxifloxacin dose evaluated. Comparison between pediatric and adult reference pharmacokinetic parameters will be performed. The effect of age and bodyweight on moxifloxacin pharmacokinetics will be evaluated using population pharmacokinetic approach. Study1 and 2: Safety endpoints to be evaluated must include musculoskeletal, cardiac, hypersensitivity, dermatologic, and central and peripheral nervous system adverse events, and study clinical laboratory and ECG assessments. Structured musculoskeletal assessments, i.e., evaluations of the joints (especially all weight-bearing joints) and gait will be conducted at the initiation of therapy (or up to 72 hours after therapy initiation), at the test of cure visit and at approximately three months following exposure. The assessments at therapy initiation and test of cure will be performed by rheumatologists, trained physical therapists experienced in musculoskeletal examinations, or clinicians who are trained to perform developmentally appropriate and thorough examination of the musculoskeletal system. The subsequent evaluations will be performed by a trained interviewer, and if any signs or symptoms suggestive of arthropathy develop, assessment by a clinician experienced in evaluating the musculoskeletal system will be obtained. Patients who develop joint effusions will have joint fluid evaluations if deemed clinically necessary by the treating physician and/or rheumatologist. Patients that develop arthropathy, defined as joint disease diagnosed by a clinician experienced in evaluating the musculoskeletal system, should be evaluated with the goal of establishing the cause and extent of the	Study1: The following parameters were derived from the plasma and urine concentration data of moxifloxacin and its M-1 and M-2 metabolites: AUC and Cmax (primary); AUC(tn-∞), t1/2, Cl, VSS, AUCnorm, Cmax,norm, tmax and Aeur (secondary). A non-compartmental analysis will be performed to analyze both, observed study data and physiologically-based PK simulations. Study 2: The *Safety* parameters were assessed by monitoring AEs, treatment-related AEs, premature terminations due to AEs, SAEs, deaths, and treatment related changes in the study-specific clinical laboratory tests, vital signs, and physical examination findings. Special emphasis was placed on AEs associated with the musculoskeletal and cardiac systems. Structured musculoskeletal assessments and gait were conducted pre therapy, days 3-5 of therapy, end of therapy, at the test of cure visit and at approximately three and twelve months following exposure. Musculoskeletal clinical assessment included a questionnaire and detailed examination of extremities joints. Abnormalities in clinical assessment resulted in initiation of relevant diagnostic procedures. All patients that report musculoskeletal adverse events were evaluated yearly for 5 years, if resolution did not occur before. All AEs were recorded through the 7 days following premature termination of study drug. All adverse events present at that point were followed until resolved or stabilized. All SAEs (including "Hy's Law" cases) and deaths were recorded through the 30 days following discontinuation of study drug. *Pharmacokinetics:* The absolute bioavailability of the oral moxifloxacin, and the steady state pharmacokinetic parameters were determined using population pharmacokinetic methods. Quantitative analysis of moxifloxacin and metabolites M-1 and M-2was performed using a fully validated liquid chromatography (LC) - mass spectrometry/mass spectrometry (MS/MS) assay. A full term population PK evaluation including determination of absolute bioavailability was also performed. Population PK methods were used to provide parameter estimates describing the PK behavior of moxifloxacin and to identify possible covariates related to age.

	disease. Concomitant medications administered will be reported. All patients that report musculoskeletal adverse events will be asked to undergo evaluation until resolution or yearly for 5 years, if resolution does not occur before. All patients that report cardiac, hypersensitivity and serious adverse reactions will be monitored until symptom resolution or stabilization. Study2: Pharmacokinetic Endpoints: The absolute bioavailability of the oral pediatric formulation(s) of moxifloxacin, and the following steady state pharmacokinetic parameters for IV and oral moxifloxacin will be determined using population pharmacokinetic methods: Cmax, Tmax and AUCτ. Other pharmacokinetic parameters (e.g., F, V/F and CL/F) of moxifloxacin will also be determined to the extent possible. Concentration-time profiles will be plotted for each dose and pediatric formulation evaluated. The effect of age and bodyweight on moxifloxacin absolute bioavailability, pharmacokinetics and PK/PD parameters (e.g., AUC/MIC) must be evaluated using population pharmacokinetic approach. Efficacy Endpoints: Efficacy data including clinical and bacteriological responses on treatment days 3 to 5, at the end of therapy, and at the test of cure visit will be summarized.	*Efficacy Assessment of Clinical Response* **Prior to the EOT**, clinical responses were graded as improvement, failure, or indeterminate: • Improvement: reduction in the severity and/or the number of signs and symptoms of infection. • Failure: a failure to respond or insufficient lessening of the signs and symptoms of infection requiring a modification or addition of antibacterial therapy; subjects who required a second surgical intervention for the treatment of persistent infection, unless the original surgery was deemed inadequate (in this case, the clinical response - indeterminate); the development of a wound infection requiring alternative or additional antibiotic therapy. For a subject to be considered a failure, 3 full days of therapy must have been administered. • Indeterminate is defined as those subjects in whom a clinical assessment is not possible to determine (eg, early withdrawal) **At the EOT** clinical responses were graded as resolution, failure, or indeterminate: • Resolution: a disappearance of signs and symptoms related to the infection or sufficient improvement of clinical signs and symptoms related to the infection and the subject does not require any further antibiotic therapy or surgical intervention. • Failure and indeterminate outcome are defined as above for prior to the EOT assessment **At the TOC (28-42 days after EOT)** clinical responses were be graded as clinical cure, failure, or indeterminate: • Clinical cure: a resolution or sufficient improvement of clinical signs a systemic antibiotic treatment. • Failure: a reappearance of the signs and symptoms of the original infection, or wound infection requiring further systemic antimicrobial therapy. • Indeterminate is defined as above for prior to the EOT assessment *Bacteriological response (assessed by the central lab)* **Prior to the EOT, at the time of early termination of study drug, and at the EOT,** bacteriological responses were graded as eradication, presumed eradication, persistence, presumed persistence, superinfection, or indeterminate: • Eradication: 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: 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. • Persistence: the presence of the original causative organism(s) on culture obtained from any site within the intra-abdominal cavity or from blood. • Presumed persistence: clinical failure and appropriate culture material is not available for

		evaluation. • Superinfection: is isolation of (a) new infectious cIAI organism(s) (ie, an organism not previously isolated at baseline), during therapy (ie, including the EOT sample, and any samples collected after baseline and before the EOT) associated with clinical signs and symptoms and requiring systemic antibacterial. • Indeterminate is applicable when the bacteriological response to the study drug is not valid for any reason (e.g. negative culture when material was available and the subject is not judged a clinical failure). **At the TOC**, bacteriological responses will be graded as eradication, presumed eradication, persistence, presumed persistence, superinfection, indeterminate (as above), or re-infection: • Re-infection: isolation of (a) new infectious cIAI organism(s) after therapy (ie, including the TOC sample, and any sample collected after the EOT and before the TOC) associated with clinical signs and symptoms and requiring systemic antibacterial.
Drug information • *dosage form* • *route of administration* • *regimen*	• *dosage form*: IV injection, tablets and liquid • *route of administration*: Intravenous and oral • *regimen*: The IV and oral dosage regimens of moxifloxacin will be determined from the PK findings of Study 1. IV moxifloxacin will be followed by comparable doses of the oral moxifloxacin formulation	• *dosage form*: IV injection, tablets (liquid formulation has not been developed) • *route of administration*: Intravenous and oral • *regimen*: Study1: 6-14 years 5mg/kg and 6 mg/kg 2-<6 years 7 mg/kg and 8 mg/kg 3 months -<2 years 9 mg/kg and 10 mg/kg Study 2: IV and oral dosage regimens of moxifloxacin were determined from the PBPK modeling PK findings of Study 1. IV moxifloxacin was followed by comparable doses of the oral moxifloxacin formulation in Study 2: Intravenous moxifloxacin (IV): • For subjects 12 to less than 18 years of age and weighing at least 45 kg, the dose of moxifloxacin was 400 mg, once daily (OD). • For subjects 12 to less than 18 years of age and weighing less than 45 kg, the dose of moxifloxacin was 4 mg/kg twice daily, every 12 hours (q12h), not exceeding 400 mg/day. • For subjects 6 to less than 12 years of age the dose of moxifloxacin was 4 mg/kg, q12h, not exceeding 400 mg/day. • For subjects 2 to less than 6 years of age the dose of moxifloxacin was 5 mg/kg, q12h, not exceeding 400 mg/day.

		• For subjects 3 months to less than 2 years of age the dose of moxifloxacin was 6mg/kg q12h IV, not exceeding 400 mg/day. Oral (PO): • For those subjects who could be switched from IV to PO therapy, 400 mg or 50 mg moxifloxacin tablets were provided. • For subjects 12 to less than 18 years of age and weighing at least 45 kg the dose of moxifloxacin was 400 mg OD provided as a 400 mg moxifloxacin tablet. • For subjects 12 to less than 18 years of age and weighing less than 45 kg, the dose of moxifloxacin was 4 mg/kg q12h. The daily oral dose of moxifloxacin was administered as multiples of 50 mg tablets. • For subjects 6 to less than 12 years of age, the dose of moxifloxacin was 4 mg/kg, q12h, not exceeding 400 mg/day. The daily oral dose of moxifloxacin was administered as multiples of 50 mg tablets. Subjects weighing less than 20 kg or who were unable to swallow tablets could not be switched to oral treatment. • For subjects 2 to less than 6 years of age, the dose of moxifloxacin was 5 mg/kg, q12h, not exceeding 400 mg/day. The daily oral dose of moxifloxacin was administered as multiples of 50 mg tablets. Subjects weighing less than 20 kg or who were unable to swallow tablets could not be switched to oral treatment. • For children 3 months to less than 2 years of age there was no oral dose of moxifloxacin. Subjects remained on IV moxifloxacin
Drug-Specific Safety Concerns:	Musculoskeletal adverse events, specifically arthropathy, arthritis, tendinopathy and tendon rupture, and cardiac events, specifically arrhythmia and prolonged QT are the major safety concerns. Hypersensitivity, dermatologic, and central and peripheral nervous system adverse events should also be monitored.	Musculoskeletal adverse events: arthropathy, arthritis, tendinopathy and tendon rupture, and cardiac events: arrhythmia and prolonged QT are the major safety focus of study. Adverse events were monitored throughout the study.
Statistical information, including power of study(ies) and statistical assessments:	Study1: For pharmacokinetic analyses, see the section *Number of Patients to be Studied.* Study 2: The study will enroll approximately 300 moxifloxacin-treated patients and approximately 150 non-quinolone antimicrobial-treated patients who complete follow-up through 3 months. This sample size is based on providing 95% confidence that the serious adverse event rate is no greater than 1 in 100 (1%) in patients if no serious adverse event is observed among 300 moxifloxacin-exposed patients.	*Study1:* A total of 31 subjects were assigned to treatment and received a dose of moxifloxacin according to their assigned dose level. Cohorts 1 and 2 each included 12 subjects, while cohort 3 included 7 subjects. All 31 subjects remained on study through at least the 3 month follow-up visit, and therefore all 31 subjects were valid for PK and safety analysis. <u>Study 2:</u> • 451 pediatric subjects (ages 3 months to less than 18 years) with cIAI matching the criteria for eligibility received either moxifloxacin (n = 301) or comparator (n = 150).

	Statistical analyses will be descriptive. Safety data, including adverse events, laboratory tests, ECG data, and concomitant medications will be summarized using appropriate summary statistics. Efficacy response data will be summarized using appropriate summary statistics. Summaries by age group will also be presented. Adverse event rates will be calculated for all events. Ninety-five percent confidence intervals should be calculated for the rates of all musculoskeletal adverse events and serious adverse events occurring through test of cure visit following moxifloxacin or non-quinolone control drug exposure. Ninety-five percent confidence intervals should be calculated for the rates of all musculoskeletal adverse events occurring after the test of cure visit through the one year follow-up visit. Rates and confidence intervals will be generated separately for moxifloxacin-treated and non-quinolone antimicrobial-treated pediatric patients and differences in rates and 95% confidence intervals on the differences between treatment arms will also be calculated. Lifetime tables should be provided to present cumulative incidence rates for events occurring at these time points in the moxifloxacin and non-quinolone comparator groups, for all patients as well as stratified by pubescence stage (where prepubescence is defined as girls < 9 years, boys <11 years, pubescence is defined as girls 9-14 years, boys 11-15 years, and postpubescence is defined as girls >14 years and boys >15 years). Descriptive summaries of the ECG data will be provided by treatment group. Descriptive statistics for laboratory data (n, mean, standard deviation, minimum and maximum) will be provided by visit and treatment group. Descriptive summaries of demographic, efficacy, and safety data will be provided for each of the age groups included in the study	• Statistical analyses were descriptive. Safety data, including adverse events, laboratory tests, ECG data, and concomitant medications were summarized. Efficacy response data were summarized using appropriate summary statistics. Summaries by age group were also presented.

5.2 Review Strategy

The focus of (b) (4) safety reviews was on study 11643, a prospective randomized, double-blind, multicenter trial to evaluate the safety and efficacy of sequential (intravenous, oral) moxifloxacin versus comparator (IV ertapenem followed by amoxicillin/clavulanate) in pediatric subjects with complicated intra-abdominal infection.

(b) (4)

6.1 Indication

Complicated intraabdominal infections (cIAI) usually require surgical management, extend beyond the organ or organs into the peritoneal space and are usually associated with abscess formation or peritonitis. Majority of these infections are polymicrobial and caused by bacteria normally found within the gastrointestinal tract. cIAI of the stomach, duodenum, biliary system and proximal small bowel are usually associated with Gram positive and Gram negative aerobic and facultative anaerobic organisms. Anaerobes are commonly found in cases of gastrointestinal obstruction. Distal small bowel infections are usually due to Gram negative aerobic and facultative anaerobic organisms along with anaerobes. Large bowel infections are usually found to be caused by facultative and obligate anaerobes along with Gram positive and Gram negative organisms.

6.1.1 Methods

A single randomized double blind active control clinical trial in pediatric patients 3 months to <18 years of age with cIAI comparing moxifloxacin to ertapenem/amoxicillin/clavulanate was evaluated (Table 4). Clinical and bacteriological response at EOT and TOC were assessed. The primary analysis population was the safety population (all subjects who received at least one dose of the study drug). Effect preservation in the modified intention to treat analysis population (all subjects who had organisms isolated at baseline) was also examined.

6.1.2 Demographics

478 subjects were enrolled from 38 study sites in 15 countries: Bulgaria (5), Canada (3), Chile (1), Czech Republic (2), Germany (3), Greece (1), Hungary (2), Lithuania (2), Latvia (3), Mexico (3), Peru (3), Romania (2), Russia (2), Ukraine (4) and USA (2). 458 of 478 were randomized and 451 have received at least 1 dose of the study drug and were valid for safety. Table 5 below depicts demographic characteristics of patients treated with study drugs.

Table 5: Demographic Characteristics, Safety Analysis Set

		Moxifloxacin N = 301	Comparator N = 150	Total N = 451
Sex:	Male	179 (59.5%)	98 (65.3%)	277 (61.4%)
	Female	122 (40.5%)	52 (34.7%)	174 (38.6%)
Race:	White	289 (96.0%)	142 (94.7%)	431 (95.6%)
	Black	1 (0.3%)	1 (0.7%)	2 (0.4%)
	Hispanic	8 (2.7%)	6 (4.0%)	14 (3.1%)
	Asian	1 (0.3%)	0	1 (0.2%)
Age (years):	12 - <18	186 (61.8%)	92 (61.3%)	278 (61.6%)
	6 - <12	100 (33.2%)	51 (34.0%)	151 (33.5%)
	2 - <6	14 (4.7%)	7 (4.7%)	21 (4.7%)
	3 mo - <2 years	1 (0.3%)	0	1 (0.2%)
Age (years)	Mean (SD)	12.0 (3.7)	12.0 (3.5)	12.0 (3.6)
	Min, max	0.25 , 17.0	3.0 , 17.0	0.25 , 17.0
	Median	13.0	13.0	13.0
Weight (kg)	Mean (SD)	46.6 (17.8)	46.4 (15.8)	46.5 (17.1)
	Min, max	6.5 , 110.0	14.0 , 84.0	6.5 , 110.0
	Median	58.0	57.0	58.0
Height (cm)	Mean (SD)	153.2 (20.5)	154.6 (20.0)	153.6 (20.4)
	Min, max	70.0 , 190.0	97.0 , 190.0	70.0 , 190.0
	Median	156.0	160.0	157.0
BMI (kg/m^2)	Mean (SD)	19.1 (4.7)	18.8 (4.6)	19.0 (4.7)
	Min, max	8.4 , 39.7	9.1 , 28.6	8.4 , 39.7
	Median	25.4	25.0	25.3
ECG findings				
	Missing	3 (1.0%)	2 (1.3%)	5 (1.1%)
	Normal or normal variant	200 (66.4%)	103 (68.7%)	303 (67.2%)
	Abnormal	98 (32.6%)	45 (30.0%)	143 (31.7%)

Adapted from p.75 of 11643 study report (correction: median weight is 48kg for moxifloxacin arm and 47 kg for ertapenem)

MO comment: *The study groups were well balanced according to demographic characteristics. It is notable that overall there were few children in the youngest age groups of 3 months to 6 years (22/451) with a single child less than 1 year of age on moxifloxacin arm. Also notable is that the study population was primarily Caucasian with only 17/451 being non-white subjects.*

The presence and severity of clinical signs and symptoms at pre-treatment were typical for patients with a cIAI. No differences were apparent between the treatment arms as seen the Table 6 below.

Table 6 Symptoms at Study Entry

Sign/symptom of cIAI	*Moxifloxacin N=301 (%)*	*Ertapenem N=150 (%)*
Abdominal pain	252 (83.7)	124 (82.6)
Vomiting	123 40.9)	51 (34.0)

Sign/symptom of cIAI	*Moxifloxacin N=301 (%)*	*Ertapenem N=150 (%)*
Abdominal distension	209 (69.4)	106 (70.7)
Absent or decreased bowel sounds	186 (62.8)	93 (62.0)
Rebound tenderness	185 (61.5)	93 (62.0)
Abdominal tenderness, no rebound	43 (14.3)	18 (12.0)
Abdominal wall rigidity	213 (70.8)	102 (68)
Absent passage of gas	101 (33.6)	47 (33.3)
Absent or abnormal stool	176 (58.5)	84 (56.0)
Liquid intolerance	88 29.2)	39 (26.0)
Solids intolerance	104 34.6)	46 (30.7)

There were 7 (2.3%) subjects on moxifloxacin arm and 5 (3.3%) subjects on ertapenem arm who were enrolled with suspected cIAI. Subsequent surgery confirmed the cIAI diagnosis.
In the adult cIAI moxifloxacin trials it was found that moxifloxacin performed worse in the walled-off infections. The incidence of abscesses and peritonitis in pediatric and adult patients is presented in the tables below.

Table 7 Baseline Disease Characteristics Pediatric Patients

	Moxifloxacin N = 301 (%)	*Ertapenem N = 150 (%)*
Abscess single	50 (16.6)	23 (15.3)
Abscess multiple	2 (0.7)	0
Peritonitis local (1 quadrant)	148 (49.2)	74 (49.3)
Peritonitis diffuse	101 (33.6)	53 (35.3)

Table 8 Baseline Disease Characteristics in Adults

Diagnosis Type[a]	**Study 100272**				**Study 10209**			
	Moxifloxacin		Comparator		Moxifloxacin		Comparator	
	N[b]**= 183**		**N= 196**		**N**[b]**= 246**		**N= 265**	
	n[c]	(%)	n	(%)	n[c]	(%)	n	(%)
Single Intra-abdominal Abscess	28	(13.7)	36	(17.4)	26	(10.6)	28	(10.6)
Multiple Intra-abdominal Abscess	7	(3.4)	6	(2.9)	6	(2.4)	5	(1.9)
Bacterial Peritonitis	6	(2.9)	3	(1.4)	53	(21.5)	74	(27.9)
Appendicitis with Evidence of Perforation	88	(43.1)	91	(44.0)	74	(30.1)	80	(30.2)
Appendicitis with Evidence of Abscess	23	(11.3)	22	(10.6)	61	(24.8)	66	(24.9)
Acute Perforations of Stomach and Duodenum	7	(3.4)	7	(3.4)	0	(0.0)	0	(0.0)
Traumatic Bowel Perforation	4	(2.0)	4	(1.9)	12	(5.0)	15	(5.7)
Perforation Unrelated to Trauma of Small or Large Bowel	24	(11.8)	18	(8.7)	23	(9.4)	26	(9.8)
Intra-Abdominal Infection Related to Previous Surgery	8	(3.9)	9	(4.3)	9	(3.7)	8	(3.0)
Other Diagnoses[d]	12	(6.6)	15	(7.7)	5	(2.0)	2	(0.8)

* Excerpted from MO review by Vicky Moncada, MD

MO comment: *The overall incidence of intra-abdominal abscesses in adult patients in cIAI trials was higher than that of pediatric patients, ~30% vs 17%, respectively.*

Enrollment criteria specified that cIAI in pediatric patients should be confirmed during surgery or if suspected clinically by biomarkers and radiological findings. Majority of pediatric patients (98%) in the trial underwent diagnostic/interventional surgical prior to study treatment initiation.

Table 9 Surgery Prior to Treatment

Type of surgical intervention	***Moxifloxacin N=301 (%)***	***Ertapenem N=150***
Number of subjects (%) with at least one surgical intervention	295 (98.0%)	145 (96.7%)
Appendectomy	284 (94.4%)	142 (94.7%)
Incision and drainage	1 (0.3%)	0
Abscess drainage	29 (9.6%)	11 (7.3%)
Plastic surgery	1 (0.3%)	0
Drainage	20 (6.6%)	8 (5.3%)
Hemicolectomy	2 (0.7%)	0
Suture gastrointestinal (ulcer)	1 (0.3%)	0
Excision of diverticula	0	1 (0.7%)
Bowel repair	0	1 (0.7%)
Ostomy	1 (0.3%)	1 (0.7%)
Gastrorrhaphy	1 (0.3%)	0
Adhesiolyses	2 (0.7%)	0
Bowel obstruction reduction	2 (0.7%)	0
Resection of partial small intestine	1 (0.3%)	0
Resection of omentum	25 (8.3%)	12 (8.0%)
Removal of suppurated cyst	1 (0.3%)	0

MO comment: *As seen from the procedures performed, cIAI in pediatric patients were primarily localized to the appendix. Less than 30% of patients required additional procedures to contain the source of infection. The study arms were comparable in types of surgery performed.*

Overall as compared to adults with cIAI, pediatric patients were more likely to have microbiologically confirmed infection 84.5% versus 69% of patients. 141 subjects on moxifloxacin arm and 73 subjects on ertapenem arm had >1 organisms isolated at baseline.

Table 10 Causative Organisms at baseline, mITT (≥10 organisms)

Organism	***Avelox N= 248 (%)***	***Ertapenem N = 133 (%)***
Polymicrobic infection	**141 (56.9)**	**73 (54.9)**
Monomicrobic infection	**107 (43.1)**	**60 (45.1)**
Escherichia coli	200 (80.6)	121 (91.0)
Pseudomonas aeruginosa	54 (21.8)	19 (14.3)

Organism	*Avelox N= 248 (%)*	*Ertapenem N = 133 (%)*
Streptococcus constellatus	38 (15.3)	19 (14.3)
Bacteroides fragilis	37 (14.9)	24 (18.0)
Bacteroides thetaiotaomicron	24 (9.7)	14 (10.5)
Peptostreptococcus micros	14 (5.6)	8 (6.0)
Klebsiella oxytoca	11 (4.4)	6 (4.5)
Klebsiella pneumoniae	11 (4.4)	5 (3.8)
Bacteroides ovatus	11 (4.4)	2 (1.5)
Bacteroides uniformis	10 (4.0)	2 (1.5)

MO comment: *Overall bacteriological profile of cIAI, including presence of polymicrobic infection was similar between the study arms. Slightly more P. aeruginosa isolates were identified on moxifloxacin arm, while E.coli was more prevalent in ertapenem subjects.*

6.1.3 Subject Disposition

Subject disposition is displayed in the Table 11 below.

Table 11 Study Subject Disposition

Patient Status	Moxifloxacin N=301(%)	Ertapenem N=150 (%)
Completed study	**287 (95.4)**	**149 (99.3)**
Withdrawn from study	**14 (4.7)**	**1 (0.7)**
Consent withdrawn	5 (1.7)	0 (0)
Insufficient therapeutic effect	1 (0.3)	0 (0)
Lost to follow-up	7 (2.3)	1 (0.7)
Protocol violation	1 (0.3)	0 (0)
Completed treatment	**275 (91.4)**	**146 (97.3)**
Discontinued treatment	**26 (8.6)**	**4 (2.7)**
Adverse event	15 (5.0)	2 (0.7)
Study terminated by sponsor	0 (0)	1 (0.3)
Protocol driven decision point	1 (0.3)	0 (0)
Consent withdrawn	4 (1.3)	0 (0)
Technical problems	2 (0.7)	0 (0)
Insufficient therapeutic effect	2 (0.7)	1 (0.3)
Protocol violation	2 (0.7)	0 (0)

a Subjects are counted in at most one category. Subjects discontinuing treatment may remain on study in follow-up.
b Subjects are counted in at most one category.
*One subject may have had more than one reason for premature termination
Adapted from the study report p.71

MO comment: *More subjects on the moxifloxacin arm discontinued the study treatment and the study relative to subjects on comparator arm. The primary reason for discontinuation was adverse reaction and loss to follow up.*

Seven subjects randomized to the study did not receive study treatment due to either not conforming to inclusion/exclusion criteria or due to consent withdrawal. Seventy subjects were

excluded from the mITT analysis population due to the missing clinical microbiology data at baseline.

Table 12 Analysis Populations

	Moxifloxacin N = 305 (%)	***Ertapenem N = 153 (%)***
Safety analysis Set	301 (98.7)	150 (98.0)
mITT analysis Set	248 (81.3)	133 (86.9)

MO comment: *Greater proportion of patients on the moxifloxacin arm did not have microbiological confirmation of their cIAI as compared to those on the ertapenem arm.*

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

7 Review of Safety

Sources of safety data
Although the pediatric development program for moxifloxacin included 2 studies: single dose pharmacokinetics and a randomized double blind active control multicenter PK and safety clinical trial in complicated intra-abdominal infections, due to the size and multiple dosing regimen, the latter was the focus of the safety analyses for moxifloxacin in pediatric population.

Study design focused on safety as a primary objective. Any subject who received at least 1 dose of moxifloxacin or comparator (ertapenem with a switch to oral amoxicillin-clavulanate) was included in analysis. Safety was gauged through monitoring adverse events (AEs), drug related AEs, premature discontinuation due to AEs, serious AEs (SAEs), deaths, and treatment related changes in vital signs, physical examination, ECG findings, and laboratory values. Specific focus was placed on musculoskeletal and cardiac safety.

7.1 Methods

The safety data were collected across 38 clinical locations in 15 countries in the Americas and Europe. Overall, the safety database included 451 treated pediatric patients who received at least one dose of study medication. Incidence of adverse events, changes in vital sign, laboratory, and ECG parameters were compared between the study groups with a particular focus on musculoskeletal and ECG changes.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study 11643 enrolled pediatric patients 3 months to <18 years of age with complicated intraabdominal infections (cIAI) in the age-descending order: 12-<18, 6-<12, 2-<6 years, and 3 months -<2 years, as the PK/safety results became available from similar cohorts in the single dose PK study. The data collected in the Phase 1 single intravenous dose PK and safety study were used in modeling moxifloxacin dosing regimen for pediatric patients in the cIAI trial to achieve moxifloxacin exposures similar to that of adults at 400mg daily dose.
The table below depicts the number of children in specific age cohorts and their respective study drug regimens.

Table 21 Dosing regimens by Age per Treatment Group, cIAI trial 11643

Treatment group	*12 to <18 years*	*6 to <12 years*	*2 to <6 years*	*3 months to <2 years*
400 mg Moxifloxacin OD IV/ PO	169 (60.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4 mg/kg Moxifloxacin BID IV/ PO	17 (6.1%)	98 (64.9%)	0 (0.0%)	0 (0.0%)
4 mg/kg Moxifloxacin BID IV	0 (0.0%)	2 (1.3%)	0 (0.0%)	0 (0.0%)
5 mg/kg Moxifloxacin BID IV/ PO	0 (0.0%)	0 (0.0%)	2 (9.5%)	0 (0.0%)
5 mg/kg Moxifloxacin BID IV	0 (0.0%)	0 (0.0%)	12 (57.1%)	0 (0.0%)
6 mg/kg Moxifloxacin BID IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
1 g Ertapenem OD IV/ 22.5 mg/kg Amoxicillin + 3.2 mg/kg Clavulanate BID PO	83 (29.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
15 mg/kg Ertapenem BID/ 22.5 mg/kg Amoxicillin + 3.2 mg/kg Clavulanate BID PO	9 (3.2%)	50 (33.1%)	2 (9.5%)	0 (0.0%)
15 mg/kg Ertapenem BID IV	0 (0.0%)	1 (0.7%)	5 (23.8%)	0 (0.0%)
Total subjects(filtered)	278 (100.0%)	151 (100.0%)	21 (100.0%)	1 (100.0%)

7.1.2 Categorization of Adverse Events

The adverse events (AE) in this study were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. The AEs were categorized by preferred term and system organ class. Safety data in subjects valid for safety were analyzed for the incidence of AEs, drug-related AEs, SAEs, drug-related SAEs, deaths, and treatment related discontinuations. Study placed particular emphasis on cardiac and musculoskeletal AEs.

Table 22 Adverse Event Characterization Summary

Subjects with AEs	*Moxifloxacin N= 301 (%)*	*Ertapenem/Amoxicillin Clavulanate N = 150 (%)*	*Total N = 451 (%)*
Any AE	175 (58.1%)	82 (54.7%)	257 (57.0%)
Any Study Drug related	43 (14.3%)	10 (6.7%)	53 (11.8%)
Any related to procedures required by protocol	14 (4.7%)	3 (2.0%)	17 (3.8%)
Maximum Intensity for any AE			
Missing	1 (0.3%)	1(0.7%)	2 (0.4%)
Mild	100 (33.2%)	51(34.0%)	151 (33.5%)
Moderate	62 (20.6%)	27(18.0%)	89 (19.7%)
Severe	12 (4.0%)	3 (2.0%)	15 (3.3%)
Maximum Intensity for drug related AE			
Mild	32 (10.6%)	6 (4.0%)	38 (8.4%)
Moderate	9 (3.0%)	4 (2.7%)	13 (2.9%)
Severe	2 (0.7%)	0	2 (0.4%)
AE with outcome death	0	0	0
Any SAE	20 (6.6%)	6 (4.0%)	26 (5.8%)
Drug-related	0	0	0
Related to procedures in protocol	0	0	0
Discontinuation of study drug due to AE	16 (5.3%)	2 (1.3%)	18 (4.0%)
Discontinuation of study drug due to SAE	1 (0.3%)	0	1 (0.2%)

MO Comment: *Adverse events listed as related to procedures required by protocol included primarily complications during IV infusion: pain, infiltration, and phlebitis. Some investigators listed QT_c prolongation and elevated GGT as protocol related adverse events and drug related adverse events, given that they were noted solely due to protocol-specific evaluations. Continued intraabdominal infection post surgery, postoperative pain and inflammation of healing surgical site were also listed as protocol-related. There is one patient with a protocol related AE of insomnia, without further explanation.*

Table 23 Occurrence of Adverse Events Across Age Groups

Age Group	***Moxifloxacin N = 301 (%)***		***Ertapenem N= 150 (%0***	
	No	**Yes**	**No**	**Yes**
2 - <6 years	9 (3.0%)	5 (1.7%)	2 (1.3%)	5 (3.3%)
3 months - <2 years	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
6 - <12 years	42 (14.0%)	58 (19.3%)	22 (14.7%)	29 (19.3%)
12 - <18 years	75 (24.9%)	111 (36.9%)	44 (29.3%)	48 (32.0%)
Subjects	126 (41.9%)	175 (58.1%)	68 (45.3%)	82 (54.7%)

MO Comment: *There is a similar incidence of adverse events with moxifloxacin and comparator when stratified across age groups.*

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable; data from a large multi-dose safety trial in pediatric patients with cIAI, protocol 11643, were analyzed for safety.

7.2 Adequacy of Safety Assessments

Study was divided into two arms: moxifloxacin and ertapenem/amoxicillin clavulanate. Dosing was based on weight, guided by the pharmacokinetic parameters determined from the adult data. Adverse events were reported throughout the treatment phase, up to 42 days post treatment for all safety assessments. Adverse events were labeled as drug-related, serious, or those resulted in premature termination per investigator's assessment. Laboratory safety monitoring included routine hematology, chemistry, and urinalysis. ECG monitoring as well as musculoskeletal examination were included in the protocol given the known safety profile of moxifloxacin. Reports of musculoskeletal changes, in particular tendinopathy and arthralgia, were followed until reported resolved, for minimum of one year and up to 5 years if not resolved by 1 year visit. Cardiac events, in particular QT and QRS changes, were routinely monitored and allowed investigator to adjust or stop medication if felt warranted.

MO comment: *Overall safety assessments performed seem adequate given the safety profile of moxifloxacin.*

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Per study protocol, the treatment duration was specified to last 5-14 days. Table below summarizes the actual length of study treatment per arm.

Table 24 Summary of Study Medication Exposure

Duration of treatment (days)	***Moxifloxacin N = 301***	***Ertapenem/Amoxicillin Clavulanate N = 150***	***Total N = 451***
Mean (SD)	8.7 (3.0)	8.7 (2.5)	8.7 (2.9)
Median	8.0	9.0	8.0
Min-Max	1 to 24	1 to 14	1 to 24

Modified from applicant's study report table 10-1

MO Comment: *Majority of subjects received study drug within the specified duration of 5-14 days.*

Greater than 90% of subjects completed study treatments. Twenty six subjects (8.5%) on moxifloxacin arm and 4 subjects (2.6%) on ertapenem arm prematurely discontinued study drug. Study drug discontinuations on moxifloxacin arm were primarily due to adverse events (5.3%).

Table 25 Study Drug Completion

Study Medication completed	***Moxifloxacin N = 301 (%)***	***Ertapenem/Amoxicillin Clavulanate N = 150 (%)***
Not Completed	26 (8.5%)	4 (2.6%)
Complete	275 (90.2%)	146 (95.4%)

Modified from applicant's study report table 14.1/5

MO Comment: *Moxifloxacin has nearly 3 times greater incidence of subjects not completing study drug. This driven by AE-related discontinuations, in particular, by asymptomatic QT prolongation noted on routine protocol ECGs.*

7.2.2 Explorations for Dose Response

The study did not evaluate dose-response. Doses selected for this study were the result of exposure data analysis generated in the single dose PK study in pediatric patients designed to target moxifloxacin exposures at the approved 400mg daily doses in adults (30-60 mg*h/L of AUC_{0-24} and 2-6 mg/L of C_{max}).

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Routine clinical testing while on study treatment included evaluation of the parameters potentially affected by moxifloxacin, such as: complete blood count and comprehensive metabolic panel including liver function tests. Electrocardiogram was also part of routine testing while on study treatment.

7.2.5 Metabolic, Clearance, and Interaction Workup

PBPK and population PK modeling and simulation were performed to guide IV single dose PK study in pediatrics. Modeled data from adult exposure indicated targets of 30-60 mg*h/L for AUC0-24 and 2-6 mg/L for C_{max} for pediatric patients. Projections in the single dose PK study showed AUC below lower target thresholds. The C_{max} in some cases exceeded upper target threshold.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Class specific adverse reactions, particularly musculoskeletal and cardiac were collected and analyzed in this study.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in this clinical study and the overall pediatric development program.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events were defined in protocol as those resulted in death, were life-threatening, required hospitalization or prolonged current hospitalization, resulted in persistent/significant disability, congenital anomaly, or were deemed medically important by the investigator. There were no treatment-related serious adverse events. Twenty subjects (6.6%) in the moxifloxacin treatment group and six subjects (4.0%) in comparator treatment group reported experiencing serious adverse events.

Table 26 Serious Adverse Events

MEDDRA SYSTEM ORGAN CLASS TERM	MEDDRA PREFERRED TERM	Moxifloxacin N = 301 (%)	Ertapenem/Amoxicillin Clavulanate N = 150 (%)
Infections and infestations	Abdominal abscess	3 (1.0%)	0 (0.0%)
	Abdominal infection	1 (0.3%)	0 (0.0%)
	Abdominal wall abscess	1 (0.3%)	0 (0.0%)
	Cellulitis	0 (0.0%)	1 (1.2%)
	Peritoneal abscess	1 (0.3%)	0 (0.0%)
	Wound infection	1 (0.3%)	0 (0.0%)
Injury, poisoning and procedural complications	Abdominal wound dehiscence	1 (0.3%)	0 (0.0%)
	Facial bones fracture	0 (0.0%)	1 (1.2%)
	Forearm fracture	1 (0.3%)	0 (0.0%)
Blood and lymphatic system disorders	Anaemia	1 (0.3%)	0 (0.0%)
Gastrointestinal disorders	Constipation	1 (0.3%)	0 (0.0%)
	Crohn's disease	1 (0.3%)	0 (0.0%)
	Enterocutaneous fistula	1 (0.3%)	0 (0.0%)
	Faecalith	1 (0.3%)	0 (0.0%)
	Functional gastrointestinal disorder	2 (0.7%)	0 (0.0%)
	Ileal perforation	1 (0.3%)	0 (0.0%)
	Intestinal obstruction	2 (0.7%)	0 (0.0%)
	Mechanical ileus	3 (1.0%)	2 (1.3%)
Musculoskeletal and	Fasciitis	1 (0.3%)	0 (0.0%)

MEDDRA SYSTEM ORGAN CLASS TERM	MEDDRA PREFERRED TERM	Moxifloxacin N = 301 (%)	Ertapenem/Amoxicillin Clavulanate N = 150 (%)
connective tissue disorders			
Nervous system disorders	Generalized tonic-clonic seizure	0 (0.0%)	1 (0.7%)
Metabolism and nutrition disorders	Hyponatremia	1 (0.3%)	0 (0.0%)
Nervous system disorders	Idiopathic generalized epilepsy	0 (0.0%)	1 (0.7%)
Congenital, familial and genetic disorders	Phimosis	0 (0.0%)	1 (0.7%)
General disorders and administration site conditions	Surgical failure	1 (0.3%)	0 (0.0%)
Total Subjects(filtered)		20 (6.6%)	6 (4.0%)

MO comment: *The reported serious adverse events were noted by investigator and sponsor to be unrelated to study drug. Overall there was a greater incidence of serious adverse events in the moxifloxacin arm (6.6%) as compared to the ertapenem/amoxicillin clavulanate (4.0%) arm. Of the SAEs, one was designated as a surgical failure. It is difficult to assess whether the abdominal infections listed were secondary to surgical or antibacterial treatment failure. As discussed in next section 7.3.3, in four of these patients moxifloxacin was discontinued and alternative therapy was followed by SAE resolution.*

7.3.3 Dropouts and/or Discontinuations

Thirty of 451 subjects (6.6%) discontinued the study. Of these 30 subjects, 26 discontinued moxifloxacin treatment and 4 discontinued ertapenem. Primary reasons for drug discontinuation were adverse events and consent withdrawal. Of the discontinuations, eighteen were due to AEs, twelve of those were listed as drug related: eleven subjects from the moxifloxacin group and one from the comparator group. One discontinuation due to abdominal infection was labeled as a serious adverse event in the moxifloxacin group.

Table 27 Adverse Events Resulting in Study Drug Discontinuations

MEDDRA SYSTEM ORGAN CLASS TERM	MEDDRA PREFERRED TERM	Moxifloxacin N = 301 (%)	Ertapenem/Amoxicillin Clavulanate N = 150 (%)
Cardiac disorders	Tachycardia	1 (0.3%)	0 (0.0%)
Infections and infestations	Abdominal infection	4 (1.3%)	0 (0.0%)
Investigations	Electrocardiogram QT prolonged	10 (3.3%)	2 (1.3%)
	Hepatic enzyme increased	1 (0.3%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1 (0.3%)	0 (0.0%)
Surgical and medical procedures	Abscess drainage	1 (0.3%)	0 (0.0%)
Subjects(filtered)		16 (5.3%)	2 (1.3%)

MO comment: *There was greater incidence of adverse events resulting in study drug discontinuation on the moxifloxicin arm (5.3%) as compared to the ertapenem/amoxicillin clavulanate (1.3%) arm. QT prolongation was the most common cause of dropouts, but all of these events were rated mild. The QT prolongation AEs prompting subjects' dropouts were expected given the focus of this safety study. All patients recovered on follow up. There were four patients on the moxifloxacin arm who were discontinued due to abdominal infection. Three of these subjects were listed as having retention of purulent material/ ongoing infection, while one patient was listed as having surgical site inflammation and poor wound healing. It is difficult to ascertain whether these were treatment or surgical failures. One patient in the moxifloxacin arm who dropped out due to abdominal infection secondary to retained purulent exudate had the event labeled as a serious.*

7.3.5 Submission Specific Primary Safety Concerns

Cardiac safety

There was a broad range of cardiac-related adverse events reported on the study. A similar proportion of patients on both treatment arms experienced adverse events captured in the Cardiac disorders system organ class (SOC): 1.6% of patients on the moxifloxacin arm and 1.4% of patients on the comparator arm. However, when the standardized MedDRA query (SMQ) for cardiac disorders was applied to the search, there was a greater proportion of patients who experienced cardiac adverse events on the moxifloxacin arm (12.6%) vs comparator (4.0%). These findings were driven by the ECG changes (Investigations SOC), QT_c changes in particular (see discussion in Section 7.4.4). Additionally, other cardiac-associated adverse events were more common on the moxifloxacin arm: chest pain, dyspnea, and blood pressure changes. The majority of these events were rated as mild by investigator. Cardiac adverse events that resulted in study drug discontinuation were tachycardia, dyspnea, and QT_c prolongation. None of these events were labeled as serious.

Table 28 Cardiac Adverse Events

MEDDRA SYSTEM ORGAN CLASS TERM	MEDDRA PREFERRED TERM	Moxifloxacin N = 301 (%)	Ertapenem/Amoxicillin Clavulanate N = 150 (%)
Cardiac disorders	Arrhythmia supraventricular	1 (0.3%)	0 (0.0%)
	Atrioventricular block first degree	1 (0.3%)	0 (0.0%)
	Metabolic cardiomyopathy	1 (0.3%)	0 (0.0%)
	Sinus tachycardia	0 (0.0%)	1 (0.7%)
	Supraventricular extrasystoles	0 (0.0%)	1 (0.7%)
	Tachycardia	2 (0.7%)	0 (0.0%)
General disorders and administration site conditions	Chest pain	1 (0.3%)	0 (0.0%)
Investigations	Blood pressure decreased	1 (0.3%)	0 (0.0%)
	Electrocardiogram QT	28 (9.3%)	4 (2.7%)

MEDDRA SYSTEM ORGAN CLASS TERM	MEDDRA PREFERRED TERM	Moxifloxacin N = 301 (%)	Ertapenem/Amoxicillin Clavulanate N = 150 (%)
	prolonged Electrocardiogram T wave abnormal	1 (0.3%)	0 (0.0%)
	Electrocardiogram T wave inversion	1 (0.3%)	0 (0.0%)
	QRS axis abnormal	1 (0.3%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	2 (0.7%)	0 (0.0%)
Vascular disorders	Hypertension	1 (0.3%)	0 (0.0%)
Subjects filtered		38 (12.6%)	6 (4.0%)

MO comment*: There was an 8.6% difference in the proportion of patients who experienced cardiac-related adverse events on moxifloxacin arm as compared to ertapenem arm. Per calculations of Dr. Janelle Charles, statistical reviewer, this difference was statistically significant with 95% CI of [3.7, 13.5].*

Musculoskeletal Safety

Musculoskeletal safety was a key focus of this pediatric cIAI study. Animal studies on fluoroquinolone-induced arthropathy document changes in cartilage, collagen loss, and damage of chondrocytes. Fluoroquinolone adult human safety data also indicated a risk of tendon rupture or tendinitis.

Table 29 Musculoskeletal Adverse Events

MEDDRA SYSTEM ORGAN CLASS TERM	MEDDRA PREFERRED TERM	Severity	Moxifloxacin N = 301 (%)	Ertapenem/Amoxicillin Clavulanate N = 150 (%)
Injury, poisoning and procedural complications	Forearm fracture	Mild	1 (0.3%)	0 (0.0%)
	Joint injury		0 (0.0%)	1 (0.7%)
	Ligament sprain		1 (0.3%)	1 (0.7%)
	Muscle strain		0 (0.0%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	Arthralgia		9 (3.0%)	2 (1.5%)
	Joint swelling		0 (0.0%)	2 (1.5%)
	Musculoskeletal pain		2 (0.7%)	0 (0.0%)
		Moderate	1 (0.3%)	0 (0.0%)
	Myalgia	Mild	1 (0.3%)	0 (0.0%)
Total Subjects(filtered)			13 (4.3%)	5 (3.3%)

There was a no difference in the proportion of patients with musculoskeletal AEs in the moxifloxacin group relative to the ertapenem/amoxicillin clavulanate group (difference of 1% with 95% CI [-2.7, 4.7] per calculations by the statistical reviewer, Dr. Janelle Charles).

Majority of AEs were categorized as mild and moderate. Only one serious AE of a forearm fracture was reported, with patient narrative describing its onset after a car accident. Other musculoskeletal events occurred in the post treatment period, primarily 24 to 361 days from therapy initiation. One patient was listed as having knee pain 715 days after treatment while playing basketball; pain resolved the following day.

MO comment: *There is a one patient difference in comparator arm in the reviewer analysis of musculoskeletal adverse events compared to the study report; a patient with joint swelling was not labeled as a musculoskeletal event in the dataset variable AE_Type.*

As with other fluoroquinolone drugs and consistent with adult data, arthralgia was the most common musculoskeletal AE reported in pediatric patients treated with moxifloxacin. Symptoms were documented as resolved at the follow up visits. Thus, moxifloxacin did not have any significant near term effect (up to 5 years follow up) on musculoskeletal system in pediatric patients at the doses studied.

Hepatic Safety

One percent of subjects in the moxifloxacin group experienced adverse events in the Hepatobiliary disorders SOC compared to none of on the ertapenem arm. However, when liver function test abnormalities recorded as adverse events were counted, there were 2.7% and 2% of subjects who experienced liver-related adverse events on the moxifloxacin and ertapenem arms, respectively.

Table 30 Hepatic Adverse Events

MEDDRA SYSTEM ORGAN CLASS TERM	**MEDDRA PREFERRED TERM**	***Moxifloxacin N = 301 (%)***	***Ertapenem/Amoxicillin Clavulanate N = 150 (%)***
Hepatobiliary disorders	Hyperbilirubinaemia	2 (0.7%)	0 (0.0%)
	Jaundice	1 (0.3%)	0 (0.0%)
Investigations	Alanine aminotransferase increased	3 (1.0%)	2 (1.3%)
	Aspartate aminotransferase increased	2 (0.7%)	3 (2.0%)
	Gamma-glutamyltransferase increased	2 (0.7%)	2 (1.3%)
	Hepatic enzyme increased	1 (0.3%)	0 (0.0%)
Subjects filtered		8 (2.7%)	3 (2.0%)

MO comment: *There was no significant difference between the study arms in the overall incidence of hepatic adverse events. Please refer to pertinent laboratory investigation section below.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The majority of subjects, 257/451 (57.0%), in the clinical study experienced at least one adverse event. The percentage of subjects who experienced an adverse event was similar between the two randomized groups, with 175/301 (58%) subjects in the moxifloxacin group and 82/150 (54.7%) subjects in the comparator group. However, the incidence of drug-related AEs in the moxifloxacin subjects [43/301 (14.3%)] was higher as compared to ertapenem group [10/150 (6.7%)]. This difference is related to the greater number of subjects with QTc prolongation in the moxifloxacin group versus comparator.

Table 31 Common Adverse Events

MEDDRA SYSTEM ORGAN CLASS TERM	MEDDRA PREFERRED TERM	Moxifloxacin N = 301 (%)	Ertapenem/Amoxicillin Clavulanate N = 150 (%)
Blood and lymphatic system disorders	Anaemia	4 (1.3%)	0 (0.0%)
	Coagulopathy	0 (0.0%)	1 (0.7%)
	Eosinophilia	1 (0.3%)	1 (0.7%)
	Leukocytosis	3 (1.0%)	0 (0.0%)
Cardiac disorders	Sinus tachycardia	0 (0.0%)	1 (0.7%)
	Supraventricular extrasystoles	0 (0.0%)	1 (0.7%)
	Tachycardia	2 (0.7%)	0 (0.0%)
Congenital, familial and genetic disorders	Phimosis	0 (0.0%)	1 (0.7%)
Gastrointestinal disorders	Abdominal distension	1 (0.3%)	1 (0.7%)
	Abdominal pain	8 (2.7%)	3 (2.0%)
	Constipation	3 (1.0%)	1 (0.7%)
	Diarrhoea	11 (3.7%)	1 (0.7%)
	Epigastric discomfort	0 (0.0%)	1 (0.7%)
	Functional gastrointestinal disorder	3 (1.0%)	0 (0.0%)
	Gastritis	2 (0.7%)	0 (0.0%)
	Gastrooesophageal reflux disease	2 (0.7%)	0 (0.0%)
	Intestinal obstruction	2 (0.7%)	0 (0.0%)
	Localized intraabdominal fluid collection	2 (0.7%)	0 (0.0%)
	Mechanical ileus	3 (1.0%)	2 (1.3%)
	Nausea	1 (0.3%)	2 (1.3%)
	Vomiting	20 (6.6%)	12 (8.0%)
General disorders and administration site conditions	Administration site pain	0 (0.0%)	1 (0.7%)
	Infusion site phlebitis	4 (1.3%)	0 (0.0%)
	Pyrexia	6 (2.0%)	4 (2.7%)
	Vessel puncture site pain	2 (0.7%)	0 (0.0%)
Hepatobiliary disorders	Hyperbilirubinaemia	2 (0.7%)	0 (0.0%)
Immune system disorders	Drug hypersensitivity	3 (0.9%)	0 (0.0%)

MEDDRA SYSTEM ORGAN CLASS TERM	MEDDRA PREFERRED TERM	Moxifloxacin N = 301 (%)	Ertapenem/Amoxicillin Clavulanate N = 150 (%)
Infections and infestations	Abdominal abscess	5 (1.7%)	0 (0.0%)
	Abdominal infection	4 (1.3%)	1 (0.7%)
	Cellulitis	0 (0.0%)	1 (0.7%)
	Gastroenteritis	0 (0.0%)	1 (0.7%)
	Helminthic infection	0 (0.0%)	1 (0.7%)
	Pelvic abscess	0 (0.0%)	1 (0.7%)
	Postoperative wound infection	3 (1.0%)	1 (0.7%)
	Wound infection	14 (4.7%)	6 (4.0%)
Injury, poisoning and procedural complications	Contusion	0 (0.0%)	1 (0.7%)
	Facial bones fracture	0 (0.0%)	1 (0.7%)
	Incision site inflammation	2 (0.7%)	3 (2.0%)
	Incision site pain	26 (8.6%)	14 (9.3%)
	Inflammation of wound	0 (0.0%)	1 (0.7%)
	Joint injury	0 (0.0%)	1 (0.7%)
	Ligament sprain	1 (0.3%)	1 (0.7%)
	Muscle strain	0 (0.0%)	1 (0.7%)
	Post procedural discharge	3 (1.0%)	0 (0.0%)
	Postoperative wound complication	3 (1.0%)	2 (1.3%)
	Procedural pain	16 (5.3%)	10 (6.7%)
	Procedural vomiting	0 (0.0%)	4 (2.7%)
	Seroma	0 (0.0%)	1 (0.7%)
	Suture rupture	2 (0.7%)	0 (0.0%)
	Wound complication	4 (1.3%)	2 (1.3%)
	Wound dehiscence	0 (0.0%)	1 (0.7%)
Investigations	Alanine aminotransferase increased	3 (1.0%)	2 (1.3%)
	Amylase increased	0 (0.0%)	1 (0.7%)
	Aspartate aminotransferase increased	2 (0.7%)	3 (2.0%)
	Blood creatine phosphokinase increased	4 (1.3%)	2 (1.3%)
	Blood lactate dehydrogenase increased	0 (0.0%)	1 (0.7%)
	Body temperature increased	1 (0.3%)	1 (0.7%)
	C-reactive protein increased	3 (1.0%)	0 (0.0%)
	Electrocardiogram QT prolonged	28 (9.3%)	4 (2.7%)
	Gamma-glutamyltransferase increased	2 (0.7%)	2 (1.3%)
	Lipase decreased	1 (0.3%)	1 (0.7%)
	Lipase increased	1 (0.3%)	2 (1.3%)
	Platelet count increased	0 (0.0%)	1 (0.7%)
Metabolism and nutrition disorders	Hyperlipasaemia	1 (0.3%)	2 (1.3%)
	Hypokalaemia	2 (0.7%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Arthralgia	9 (3.0%)	2 (1.3%)
	Joint swelling	0 (0.0%)	2 (1.3%)
	Musculoskeletal pain	3 (1.0%)	0 (0.0%)

MEDDRA SYSTEM ORGAN CLASS TERM	MEDDRA PREFERRED TERM	Moxifloxacin N = 301 (%)	Ertapenem/Amoxicillin Clavulanate N = 150 (%)
Nervous system disorders	Dizziness	0 (0.0%)	1 (0.7%)
	Generalized tonic-clonic seizure	0 (0.0%)	1 (0.7%)
	Headache	6 (2.0%)	2 (1.3%)
	Idiopathic generalised epilepsy	0 (0.0%)	1 (0.7%)
Renal and urinary disorders	Haematuria	0 (0.0%)	1 (0.7%)
	Haemorrhage urinary tract	0 (0.0%)	1 (0.7%)
Reproductive system and breast disorders	Haemorrhagic ovarian cyst	0 (0.0%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	Cough	3 (1.0%)	1 (0.7%)
	Dyspnoea	2 (0.7%)	0 (0.0%)
	Epistaxis	0 (0.0%)	1 (0.7%)
	Rhinorrhoea	2 (0.7%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Dermatitis allergic	0 (0.0%)	1 (0.7%)
Surgical and medical procedures	Abdominal cavity drainage	0 (0.0%)	2 (1.3%)
Vascular disorders	Phlebitis	8 (2.7%)	0 (0.0%)

(Cross table data comparing organ class, adverse event, against treatment groups)

MO comment: *There is a wide range of adverse events experienced by the subjects in the study. However, the majority of these AEs are in less than 1% of the study population for the study drug or comparator.*
There were similar proportions of adverse events in both moxifloxacin and comparator groups. The spectrum of adverse events listed is similar to those occurring in adults per current moxifloxacin package insert. The increased proportion of pediatric patients with QT prolongation reported as an adverse event in this study (9.3%) relative to adult clinical program (0.1-1%) is due to reporting bias: ECGs in the pediatric study were collected in all patients on Days 1 and 3 post dose per protocol while in adult studies the reports of QT prolongation were spontaneous.
There are a greater number of abdominal abscesses and infections listed as AEs in the moxifloxacin arm. Treatment outcomes for these patients were listed as clinical failure by investigator.
There were 3 subjects with adverse event of hypersensitivity; these were not related to study drug or comparator, but rather were associated with remedial drugs used after study drug discontinuation for another adverse event.

7.4.2 Laboratory Findings

All subjects on the study underwent hematology, blood chemistry, and urinalysis checks before, during, and after therapy. Data collected were analyzed for treatment-emergent abnormalities and change from pre-therapy baseline.

Table 32 Hematology Parameter Changes from Baseline (Lowest Value Post Baseline)

TEST	*Min Value Post Baseline*	*Moxifloxacin* Baseline value			*Ertapenem* Baseline value		
		Low	Normal	High	Low	Normal	High
WBC	**High**	0 (0%)	1 (1.2%)	15 (7.1%)	0 (0%)	0 (0%)	4 (3.7%)
	Normal	1 (100.0%)	66 (77.6%)	189 (89.1%)	2 (100.0%)	31 (75.6%)	98 (91.6%)
	Low	0 (0%)	18 (21.2%)	8 (3.1%)	0 (0%)	10 (24.4%)	5 (4.6%)
	Total Subjects	1 (0.3%)	85 (28.2%)	212 (70.4%)	2 (1.3%)	41 (27.3%)	107 (71.3%)
	Decrease from baseline	26/297 (8.8%)			15/148 (10.1%)		
Hemoglobin	**High**	0 (0%)	3 (1.5%)	1 (5.0%)	0 (0%)	2 (2.3%)	0 (0%)
	Normal	21 (25.9%)	148 (75.1%)	15 (75.0%)	17 (32.7%)	61 (70.1%)	8 (72.7%)
	Low	60 (74.1%)	46 (23.3%)	4 (20.0%)	35 (67.3%)	24 (27.6%)	3 (27.3%)
	Total Subjects	81 (26.9%)	197 (65.4%)	20 (6.6%)	52 (34.7%)	87 (58.0%)	11 (7.3%)
	Decrease from baseline	50/217 (23%)			27/98 (27.5%)		
Hematocrit	**High**	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	1 (1.2%)	0 (0%)
	Normal	22 (25.3%)	152 (80.4%)	20 (100.0%)	14 (31.1%)	72 (83.7%)	17 (89.5%)
	Low	65 (74.7%)	36 (19.0%)	0 (0%)	31 (68.9%)	13 (15.1%)	2 (10.5%)
	Total Subjects	87 (28.9%)	189 (62.8%)	20 (6.6%)	45 (30.0%)	86 (57.3%)	19 (12.7%)
	Decrease from baseline	36/209 (17.2%)			15/105 (14.2%)		
Platelets	**High**	0 (0%)	6 (2.3%)	4 (25.0%)	0 (0%)	1 (0.7%)	0 (0%)
	Normal	12 (63.2%)	245 (95.7%)	12 (75.0%)	7 (70.0%)	127 (96.9%)	5 (100.0%)
	Low	7 (36.8%)	5 (19.5%)	0 (0%)	3 30.0%)	3 (2.0%)	0 (0%)
	Total Subjects	19 (6.3%)	256 (85.0%)	16 (5.3%)	10 (6.7%)	131 (2.3%)	5 (3.3%)
	Decrease from baseline	5/272 (1.8%)			3/136 (2.2%)		

(Shift tables were obtained comparing baseline flag value, with min change flag of values. Given multiple data points, values then compared against report browsed of ADLB data sorting values by flag, day, and change.)

MO Comments: *Shift tables were constructed to evaluate for treatment emergent anemia and thrombocytopenia seen in adult data. The percent of low values and shifts were similar in both moxifloxacin and comparator arms. There are no prominent shifts to lower values. Looking at the subject data individually, there were no laboratory parameters which had a sustained change greater than 2x the lower limit of normal. None of the flagged hematology parameters caused study drug discontinuation.*

Table 33 Liver Function Changes from Baseline (Maximum Value Post Baseline)

TEST	*Max Value Post Baseline*	*Moxifloxacin* Baseline value			*Ertapenem/Amoxicillin Clavulanate* Baseline value		
		Low	Normal	High	Low	Normal	High
Alkaline Phosphatase	**Low**	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Normal	2 (66.7%)	86 (93.5%)	0 (0%)	0 (0%)	23 (92.0%)	1 (14.3%)
	High	0 (0%)	6 (6.5%)	17 (100.0%)	0 (0%)	2 (8.0%)	6 (82.7%)
	Total Subjects	3 (2.3%)	92 (70.7%)	17 (13.1%)	0 (0%)	25 (75.7%)	7 (21.2%)

TEST	*Max Value Post Baseline*	*Moxifloxacin* Baseline value			*Ertapenem/Amoxicillin Clavulanate* Baseline value		
		Low	**Normal**	**High**	**Low**	**Normal**	**High**
	Increase from baseline	6/95 (6.3%)			2/25 (8%)		
Total Bilirubin	**Normal**	3 (100.0%)	94 (97.9%)	21 (16.2%)	0 (0%)	30 (100.0%)	1 (33.3%)
	High	0 (0%)	2 (2.1%)	6 22.2%)	0 (0%)	0 (0%)	2 (66.7%)
	Total Subjects	3 (2.3%)	96 (73.8%)	27 (20.7%)	0 (0%)	30 (90.9%)	3 (9.1%)
	Increase from baseline	2/99 (2%)			0/30 (0%)		
GGT	**Low**	6 (54.5%)	0 (0%)	0 (0%)	1 (33.3%)	0 (0%)	0 (0%)
	Normal	4 (36.4%)	82 (83.7%)	2 (50.0%)	2 (66.6%)	25 (89.3%)	0 (0%)
	High	1 (9.1%)	16 (16.3%)	2 (50.0%)	0 (0%)	3 (10.7%)	0 (0%)
	Total Subjects	11 (8.4%)	98 (75.4%)	4 (3.1%)	3 (9.1%)	28 (84.8%)	0 (0%)
	Increase from baseline	17/109 (15.6%)			3/31 (9.7%)		
AST	**Normal**	0 (0%)	106 (90.6%)	1 (25.0%)	0 (0%)	28 (93.3%)	1 (50.0%)
	High	0 (0%)	11 (9.4%)	3 (75.0%)	0 (0%)	2 (6.7%)	1 (50.0%)
	Total Subjects	0 (0%)	117 (90.0%)	4 (3.1%)	0 (0%)	30 (90.9%)	2 (6.0%)
	Increase from baseline	11/117 (9.4%)			2/30 (6.7%)		
ALT	**Low**	1(20.0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Normal	4 (80.0%)	104 (89.7%)	1 (100.0%)	0 (0%)	28 (93.3%)	1 (50.0%)
	High	0 (0%)	11 (9.5%)	0 (0%)	0 (0%)	2 (6.7%)	1 (50.0%)
	Total Subjects	5 (3.8%)	116 (89.2%)	1 (0.7%)	0 (0%)	30 (90.9%)	2 (6.0%)
	Increase from baseline	11/121 (9.1%)			2/30 (6.7%)		

(Shift tables obtained comparing baseline flag value, with max change flag of values. Given multiple data points, values then compared against report browsed of ADLB data sorting values by flag, day, and change.)

MO comment: *Both alkaline phosphatase and bilirubin did not undergo significant changes from baseline; all were < 2x ULN and normalized or remained similar to baseline at the end of treatment. As seen in the shift table above, 17 subjects in the moxifloxacin arm developed an elevated post baseline GGT. Upon review of the data for individual subjects, 7 of them developed an elevated post baseline GGT > 2x ULN with 2 of the subjects having values near 5x ULN, and 3 over 10x ULN. This does contrast with the 3 subjects on the comparator arm who developed an elevated GGT over 2x ULN, all of whom had values 5x ULN or less. Thirteen subjects developed elevated AST, 11 on moxifloxacin and 2 on the comparator arm, with only one of them >2x ULN at the 2nd visit during IV therapy. There were 11 subjects on moxifloxacin arm who developed an elevated ALT versus 2 subjects on the comparator arm. In one moxifloxacin-treated subject ALT was >2x ULN, while in the second one ALT exceeded 3x ULN at the end of treatment. Liver function test elevations of >2x ULN have not resulted in study drug*

discontinuation. A single patient, who was otherwise healthy with diffuse peritonitis secondary to ruptured appendicitis on the moxifloxacin arm was characterized as having hepatic enzyme elevation as cause for withdrawal, had a GGT value increase by 15x baseline (6.2xULN) at 2nd IV therapy visit. The value returned to baseline at TOC follow up. There were no patients on either study arm who showed a rise in more than one hepatic marker simultaneously.
There were no patients on moxifloxacin or comparator arm who presented with persistent or significant changes in renal function.

7.4.3 Vital Signs

Table 34 Change in Vital Signs from Baseline to TOC Visit

	Moxifloxacin		*Ertapenem/Amoxicillin Clavulanate*	
	N	**Mean ± SD**	**N**	**Mean ± SD**
Systolic blood pressure (mmHg)	277	-1.7 ± 10.4	142	-1.3 ± 10.2
Diastolic blood pressure (mmHg)	277	-0.6 ± 9.7	142	0.8 ± 10.4
Heart rate (BPM)	277	-17.4 ± 16.0	142	-15.3 ± 13.9
Temperature (°C)	277	-1.1 ± 0.7	142	-1.0 ± 0.7
Respiratory Rate (breaths per minute)	277	-3.3 ± 4.0	142	-2.7 ± 4.4

Modified from the applicant's study report table 10-17

MO comment: *Study data indicate no remarkable changes in the vital signs assessed. No safety concerns in relation to moxifloxacin or comparator. There were no drug-related abnormalities in vital signs. Clinically relevant changes in heart rate, respiration rate and temperature values noted from baseline to EOT and TOC were consistent with recovery from cIAI.*

7.4.4 Electrocardiograms (ECGs)

Data from animal and adult studies support moxifloxacin-related QTc prolongation. Pre and post infusion ECG measurements were performed on day 1 and day 3 of treatment to assess QT_c prolongation. Overall, the pediatric cIAI study data confirmed prolonged QTc potential in children treated with moxifloxacin at doses resulting in the exposures similar to that of adults. This fits the established paradigm of moxifloxacin-induced prolongation of ventricular repolarization. Moxifloxacin prolongs QT_cF with a mean value of approximately 7 to 15 ms at the therapeutic exposure in pediatric subjects which similar to QTc interval changes demonstrated in adults (7-10 ms). There were no observed absolute QTcF values >480 ms or >500 ms. An increase in QTcF >30 ms from baseline occurred in 54 (17.9%) of moxifloxacin-treated subjects and in 5 (3.4%) of comparator-treated subjects. An increase in QTcF >60 ms from baseline (on day 3 post-dose) was documented in 4 (1.3%) moxifloxacin-treated and 1 (0.7%) comparator-treated subjects. There were 10 (3.3%) subjects on the moxifloxacin arm,

and 2 (1.3%) on the comparator arm in whom study drugs were discontinued due to QT_c prolongation. While moxifloxacin induced prolongations of QT interval in pediatric patients, those were mild and did not result in an increase in the number of cardiac events. No morbidity or mortality associated with QTc prolongation was documented in the pediatric cIAI trial.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Safety Summary and Conclusion

Overall, moxifloxacin dosed up to 400 mg a day has been shown to have a similar safety profile in the pediatric population as in adults. In comparing overall clinical trial safety between moxifloxacin and ertapenem followed by oral amoxicillin/clavulanate, the incidence of adverse events was similar. Moxifloxacin-treated patients were noted to have more drug-related adverse events, particularly QT prolongation. Study design and safety findings are similar to data in adult trials. There were no deaths reported in this cIAI trial.

The majority of AEs were ranked as either mild or moderate with resolution or recovery back to baseline at EOT or TOC. The severe AEs were more likely to have occurred in the moxifloxacin group (4.0%) as compared to ertapenem group (2.0%). Severe AEs included prolonged QT, abdominal pain, diarrhea, fecalith, anemia, headache, fasciitis, bronchospasm, abdominal wound dehiscence, and procedural pain. There were 26 subjects with serious adverse events: 20 subjects were in the group treated with moxifloxacin and 6 subjects in the group treated with comparator. The SAEs were not related to study drug, but rather to the conditions under treatment.

There was similar proportion of study subjects reporting at least one AE between moxifloxacin and comparator groups (58.1% vs 54.7%, respectively). The moxifloxacin group reported more drug related AEs than the comparator (14.3% vs 6.7%).The most common adverse events noted to occur in moxifloxacin group vs comparator included prolonged QTc (7.0% vs 1.3%), diarrhea (2.0% vs 0%), and infusion site phlebitis (1.3% vs 0%).

In the clinical trial of the 451 subjects, 30 (6.6%) prematurely discontinued study treatment. Of those who discontinued, 26 subjects (8.6%) were treated with moxifloxacin and 4 (2.7%) with ertapenem. Consent withdrawal and AEs were primary causes of discontinuation. Of subjects who discontinued due to the drug-related AEs, 16 (5.3%) were in the moxifloxacin treatment group, and 2 (1.3%) were in the comparator treatment group. Prolonged QT was the most common AE which prompted moxifloxacin discontinuation. Additional AEs leading to study drug withdrawal were abdominal infection, dyspnea, tachycardia, and increased hepatic enzymes, which were infrequent in either study group.

Prolongation of QTc interval is a well-known effect of moxifloxacin. Pediatric cIAI study findings were consistent with the adult data. Moxifloxacin prolongs QT_cF with a mean change of approximately 7 to 15 ms in pediatric subjects at the therapeutic (adult) exposure. No substantial age effect on moxifloxacin-inducted QT prolongation was observed. There were no cases of morbidity or mortality related to QTc interval prolongation in the study.

Besides QT prolongation, there were no other significant adverse reactions to moxifloxacin as described in the current product label was evident in this pediatric clinical trial. There were no cases of moxifloxacin-associated hypersensitivity, phototoxicity, CNS toxicity, peripheral neuropathy, *Clostridium difficile*-associated disease, or myasthenia gravis exacerbation in the study.

Musculoskeletal safety of moxifloxacin was the key focus in the cIAI pediatric study given increased risk of tendinitis and tendon rupture in adult patients, as well as arthropathic changes seen in animal models treated with fluoroquinolones, including moxifloxacin. In the study under review, pediatric patients in both moxifloxacin and comparator groups had similar frequency of musculoskeletal adverse events: 13/301 (4.3%) in the moxifloxacin group and 5/150 (3.3%), respectively. Musculoskeletal AEs were followed for one year and were documented as resolved. None of the musculoskeletal events in the moxifloxacin or comparator group resulted in treatment discontinuation. Events were described primarily as arthralgia or myalgia. One fracture was reported; however, it was associated with accident-related trauma. All events were self-resolving, and occurred primarily after study treatment. No musculoskeletal events were deemed to be related to the study drug by investigators. No drug-related effects on growth or developing musculoskeletal system were identified.

Moxifloxacin-associated changes in laboratory parameters were seen in some adult patients. In the pediatric study population there were no clinically significant changes in serum sodium, blood glucose, and kidney function. More subjects on moxifloxacin arm experienced treatment emergent elevations of hepatic markers (GGT, bilirubin, AST and ALT). LFT abnormalities were mild, and have occurred in isolation. One patient was withdrawn from study due to GGT increase of >15x baseline. This was characterized as mild per investigator assessment, and not as an SAE. There were no clinically significant cases of anemia, thrombocytopenia, or pancytopenia in the pediatric study.

No adverse events appeared to be age-related. Older and younger children were similarly affected, based on the incidence and type of AEs. (b) (4)

9 Appendices

9.1 Clinical Investigator Financial Disclosure Review

Application Number: 21085, 21277

Submission Date(s): September 11, 2015

Applicant: Bayer Pharmaceuticals

Product: Avelox (moxifloxacin HCl)

Reviewer: Yuliya Yasinskaya, MD

Date of Review: March 1, 2016

Covered Clinical Study: A prospective 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, Protocol # 11643

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 43 primary investigators who enrolled subjects		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

minimize potential bias provided:		from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] There were no interests/arrangements between the sponsor and its investigators that affected the study outcome; none of the clinical investigators on the study were sponsor employees.

9.2 Labeling Recommendations

Labeling changes are pending at the time of the completion of this review. The review team determined to include (b) (4) findings from pediatric cIAI trial in the Pediatric Use 8.4 Subsection of the PI.

9.3 Advisory Committee Meeting

Not conducted

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMOL PURANDARE
03/17/2016

YULIYA I YASINSKAYA
03/17/2016

THOMAS D SMITH
03/17/2016
I concur with this review.