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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
 Caroline J. Jjingo, MD, MPH
 NDA 208,610 and NDA 208,611
 BAXDELA™ (delafloxacin meglumine)

Application Type	New Drug Application (NDA)
Application Number(s)	NDA 208,610 and NDA 208,611
Priority or Standard	Priority
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Division/Office	Division of Anti-Infective Products
Reviewer Name(s)	Caroline J. Jjingo, MD, MPH
Review Completion Date	June 13, 2017
Established Name	Delafloxacin
(Proposed) Trade Name	BAXDELA™
Applicant	Melinta Therapeutics, Inc.,
Formulations	Powder for Intravenous Injection 300-mg 450-mg oral tablet
Dosing Regimen	Intravenous: 300-mg IV every 12 hours; Oral: 450-mg tablet by mouth every 12 hours
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI)

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Glossary

Ab	antibody
ABSSSI	acute bacterial skin and skin structure infections
AC	advisory committee
ADME	absorption, distribution, metabolism, and excretion (elimination)
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the curve
BA	bioavailability
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CE	Clinical Evaluable
CFR	Code of Federal Regulations
CG	cockcroft-gault
CI	confidence interval
CKD	chronic kidney disease
CMC	chemistry, manufacturing, and controls
CMQ	customized MedDRA query
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
cSSSI	complicated skin and skin structure infections
CT	computed tomography
DAIDS	Division of AIDS
DBP	diastolic blood pressure
DMC	data monitoring committee
ECG	electrocardiogram
ECR	early clinical response
eCRF	electronic case report form
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate

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EMA	European Medicines Agency
EOT	End of Treatment
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FQ	fluoroquinolones
FU	follow-up
GCP	good clinical practice
GERD	gastroesophageal reflux
GI	gastrointestinal
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HLT	high level term
HR	heart rate
HTN	hypertension
ICF	informed consent form
ICH	International Conference on Harmonization
IDSA	Infectious Diseases Society of America
IND	Investigational New Drug
iPSP	initial pediatric study plan
IR	informational request
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LFT	liver function test
LFU	late follow-up
LL	lower limit
MDRD	Modification of Diet in Renal Disease
ME	microbiologically evaluable
MED	minimal erythema dose
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimal inhibitory concentration
MITT	microbiological intent-to-treat
mITT	modified intent to treat
MRSA	methicillin resistant <i>Staphylococcus aureus</i>
MSSA	methicillin sensitive <i>Staphylococcus aureus</i>
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PE	pulmonary embolism

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PeRC	pediatric review committee
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PSP	pediatric study plan
PSUR	Periodic Safety Update report
PT	preferred term
QIDP	qualified infectious disease product
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
Scr	serum creatinine
SIRS	systemic inflammatory response syndrome
SMQ	standardized MedDRA query
SOC	standard of care
SOC	system organ classification
SSTI	skin and soft tissue infections
Tbili	total bilirubin
TDM	therapeutic drug monitoring
TEAE	treatment emergent adverse event
TQT	thorough QT
TOC	test of cure
UL	upper limit
ULN	upper limit of normal
US	United States
uSSSI	uncomplicated skin and skin structure infections
UVA	ultraviolet A
UVB	ultraviolet B
ULN	upper limit of normal
VRE	vancomycin resistant enterococci
VTE	venous thromboembolism
wnl	within normal limits
XRPD	x-ray powder diffraction

1 Executive Summary

1.1 Product Introduction

Delafloxacin *N*-methylglucamine salt (BAXDELA™; RX-3341; ABT-492; A-319492^{(b)₍₄₎}; and WQ-3034), which from hereon will be referred to as delafloxacin, is an investigational new molecular entity (NME) antibacterial agent belonging to the fluoroquinolone (FQ) drug class. Delafloxacin, an anionic FQ, is purported to have broad spectrum activity against Gram-positive and Gram-negative pathogens. The Applicant, Melinta Therapeutics, Inc., developed delafloxacin in two formulations: a 450-mg oral tablet formulation and as a 300-mg intravenous (IV) formulation for treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). While this application pertains solely to the ABSSSI indication, a trial in CABP is actively ongoing. As a member of the FQ drug class, delafloxacin, like other FQ antibacterial agents, inhibits bacterial DNA gyrase (topoisomerase II) and topoisomerase IV which are both responsible for DNA replication, transcription, repair and recombination.

Melinta Therapeutics, Inc. is seeking the Agency's approval of delafloxacin for treatment of ABSSSI for adults aged 18 and older. The Applicant submitted a new drug application (NDA) for delafloxacin 450-mg oral tablets (NDA 208,610) and for delafloxacin 300-mg IV formulation (NDA 208,611). NDA 208,610 presents the compiled results of nonclinical toxicology, clinical pharmacology, clinical microbiology, and clinical safety and efficacy studies for both the oral and IV formulations of delafloxacin, whereas, NDA 208,611 discusses product quality issues pertaining to delafloxacin IV injection and cross-references NDA 208,610 for the oral tablet formulation. The review will refer to both NDAs as to a single NDA submission throughout the review.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The data from the Applicant's pivotal Phase 3 trials, RX-3341-302 (IV only) and RX-3341-303 (IV with mandatory oral switch), in conjunction with the data from the Applicant's two Phase 2 studies in support of delafloxacin's safety and the 23 Phase 1 PK studies were reviewed, analyzed and discussed in this clinical review of delafloxacin. These studies form the basis of the conclusions for this NDA.

In RX-3341-302, the first of two Phase 3 pivotal trials, evaluating the safety and efficacy of twice daily IV delafloxacin 300-mg over a 5 to 14 day treatment course, delafloxacin was found to be non-inferior (NI), at the 10 % NI margin, to the comparator vancomycin (\pm aztreonam), with 78.2% of subjects in the delafloxacin arm achieving an objective clinical response at 48 to 72 hours in the ITT population (FDA primary endpoint) versus 80.9% in the comparator arm, 95% CI -2.6 (-8.8, -3.6). Likewise in RX-3341-303, the second Phase 3 trial, patients were administered delafloxacin via intravenous infusion for 6 doses followed by a mandatory switch to oral delafloxacin, delafloxacin was found to be non-inferior at the 10% NI margin to vancomycin (\pm aztreonam) with a clinical response rate of 83.7% in the delafloxacin arm versus 80.6% in the comparator arm at the FDA primary endpoint, 95 CI 3.1 (-2.0, 8.3).

Based on the totality of the data presented in the two pivotal Phase 3 trials comprising this NDA application, this reviewer has determined that, as required under 21 CFR 314.126(a)(b), there is substantial evidence of effectiveness to support the approval of delafloxacin.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Delafloxacin N-methylglucamine salt (BAXDELA™; RX-3341; ABT-492; A-319492^{(b) (4)} and WQ-3034), which from hereon will be referred to as delafloxacin, is an investigational new molecular entity (NME) antibacterial agent belonging to the fluoroquinolone (FQ) class. Delafloxacin, an anionic FQ, is purported to have broad spectrum activity against Gram-positive and Gram-negative pathogens.

Acute bacterial skin and soft tissue infections (ABSSSIs) are ubiquitous and are major causes of inpatient hospitalizations and ambulatory care visits in the United States and worldwide. The infections result from breaches in the cutaneous surface which in turn predisposes the host to microbial invasion of the epidermis, dermis and/or subcutaneous tissues. For the purposes of this application and in accordance with the FDA ABSSSI guidance for industry the following infections are discussed in this review: cellulitis/erysipelas, wound infections, major cutaneous abscess, and burn infections.

Gram positive microorganisms account for the majority of ABSSSIs. *Staphylococcus aureus*, both methicillin sensitive and methicillin resistant strains, and beta hemolytic *Streptococcus* species, particularly *Streptococcus pyogenes* (Group A streptococcus or GAS), are the species most frequently implicated in ABSSSIs. Gram negative pathogens, such as *Escherichia coli* and *Pseudomonas aeruginosa* are less common causes of ABSSSIs. (Dryden, *MS J Antimicrob Chemother* 2010; Jeng, *A Medicine* 2010; Stevens, *DL IDSA practice guidelines CID* 2014). While the majority of patients with ABSSSI infections are treated as outpatients, a certain percentage of patients require inpatient hospitalizations

No major safety issues unique to delafloxacin were identified in this review. The most frequent adverse drug reactions were nausea, diarrhea, vomiting.

Approval of delafloxacin for the treatment of adult patients with ABSSSI infections is fully supported by the available evidence of efficacy and safety.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> Acute bacterial skin and skin structure infections (ABSSSIs) are common and are major causes of inpatient hospitalizations and ambulatory care visits in the United States and worldwide. Gram positive microorganisms account for the majority of ABSSSIs. 	<ul style="list-style-type: none"> ABSSSIs are common and are increasingly responsible for many adult inpatient and emergency department visits in the United States, particularly with the emergence of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Staphylococcus aureus, both methicillin sensitive and methicillin resistant strains, and beta hemolytic Streptococcus species, particularly Streptococcus pyogenes (Group A streptococcus or GAS), are the species most frequently implicated in ABSSSIs.</p> <ul style="list-style-type: none"> Some authors have estimated that admissions for primary ABSSSI infections accounted for 1.8% of all adult hospital admissions in the US from 2005 through 2011 (Kaye KS et al. PLOS One Nov 2015). With the emergence of methicillin resistant Staphylococcus aureus (MRSA), emergency department visits for ABSSSI have also increased. 	<p>MRSA skin infections.</p>
<p><u>Current Treatment Options</u></p>	<ul style="list-style-type: none"> There are several classes of antibacterial drugs, and many FDA approved antibacterial agents, which are currently approved for the treatment of ABSSSIs, including several currently marketed fluoroquinolones (FQ). Recommended duration of treatment for most ABSSSIs may be anywhere from 5 to 7 days; however, in immunocompromised persons treatment recommendations can be extended to as many as 14 days. MRSA resistance to FQ antibiotics is common. 	<ul style="list-style-type: none"> While several classes of antibacterial drugs are available for the treatment of ABSSSI, as compared to other quinolones delafloxacin provides more reliable activity against MRSA which could be valuable when concomitant infection with gram-negative pathogens and MRSA is suspected or proven. There are several therapeutic antimicrobial options presently marketed for persons infected with ABSSSIs; this includes several FQs. Several sub-populations of patients including the immunocompromised, diabetics, and obese individuals may encounter more treatment challenges when infected with ABSSSIs.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> The clinical efficacy of delafloxacin was established based on two pivotal Phase 3 clinical trials, Trial 302 (an IV only trial) and Trial 303 (an IV-to-oral switch trial), which cumulatively evaluated 1510 subjects: 754 subjects in the pooled delafloxacin treatment arm and 756 subjects in the pooled vancomycin (\pm aztreonam) comparator arm. The trial populations were distinguished from each other in the following ways: <ul style="list-style-type: none"> The primary FDA efficacy endpoint for both Phase 3 trials was achieving a clinical response-- defined as a $\geq 20\%$ reduction in the ABSSSI lesion erythema area, as determined by digital planimetry measurements of the leading edge-- 48 to 72 hours after initiation of treatment when compared to the baseline lesion erythema area size. To achieve non-inferiority with its comparator at the 10% non-inferiority margin, delafloxacin need to be greater than -10% at the lower limit of the 2-sided 95% CI in the ITT population. Based on pivotal Phase 3 trials, 5 to 14 days of treatment with delafloxacin resulted in favorable clinical response rates in 81.3% of delafloxacin treated ABSSSI subjects. However, insufficient numbers of subjects with moderate (CKD Stage 3), severe (CKD Stage 4) renal impairment and kidney failure (CKD Stage 5) made it difficult to draw conclusions on delafloxacin's clinical efficacy in these subpopulations. There were also fewer numbers of subjects aged ≥ 65 years old and ≥ 75 years in the pivotal Phase 3 cohort. At the 48 to 72 hour primary FDA efficacy end point, the clinical efficacy of delafloxacin was comparable to that of its comparator for both pivotal Phase 3 trials: In Trial 302, a total of 259 of 331 (78.3%) and 266 of 329 (80.9%) subjects in the delafloxacin and vancomycin comparator arms, 	<ul style="list-style-type: none"> The Applicant's two pivotal Phase 3 trials provide substantial evidence of delafloxacin's effectiveness for the treatment of ABSSSIs in adults aged ≥ 18 years of age. The recommended dosage adjustment for patients with severe renal impairment (CKD Stage 4; eGFR 15-29 mL/min/1.73m²) who are administered delafloxacin's IV formulation is 200-mg every 12 hours, as opposed to 300-mg every 12 hours for patients with normal, mild (CKD Stage 2; eGFR 30-59 mL/min/1.73m²), and moderate (CKD Stage 3; eGFR 30-59 mL/min/1.73m²). Neither the oral nor IV formulations of delafloxacin is recommended for the treatment of persons with kidney failure (with or without hemodialysis (CKD Stage 5; eGFR <15 mL/min/1.73m²).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>respectively, achieved a clinical response at the 48 to 72 hour time point (Difference: -2.6; 95% CI -8.8%, 3.6%). Therefore, with the lower limit of the 95% CI being -8.8%, delafloxacin was established as non-inferior to vancomycin at the -10% inferiority margin. In Trial 303, 354 out of 423 (83.7%) subjects and 344 out of 427 (80.6%) subjects in the delafloxacin and vancomycin (± aztreonam) comparator arms, respectively, achieved a clinical response at the 48 to 72 hour primary FDA time point (difference: -3.1; 95% CI -2.0, 8.3). The lower limit of the 95% non-inferiority margin (delafloxacin – vancomycin) was greater than -10% (-2.0%), indicating that delafloxacin was non-inferior to vancomycin (± aztreonam).</p> <ul style="list-style-type: none"> • The clinical efficacy of delafloxacin was established as non-inferior to its comparator vancomycin (± aztreonam), in secondary FDA efficacy endpoint (and the primary EMA efficacy endpoint) of investigator-assessed response of signs and symptoms of infection at the follow-up (FU) visit. • Clinical efficacy response rates were comparable between delafloxacin and its comparator vancomycin (± aztreonam) across key demographic sub-populations, namely by age, race, and gender. Although not powered for multiple comparisons, subgroup analyses demonstrated that clinical efficacy response rates were comparable between delafloxacin and vancomycin (± aztreonam) in diabetics and non-diabetics, and in persons with BMIs <30 kg/m² and those with BMIs ≥ 30 kg/m². • Overall, there were no significant differences observed in the clinical efficacy of delafloxacin among key demographic sub-populations. 	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Risk</u></p>	<ul style="list-style-type: none"> Delafloxacin’s safety database was primarily comprised of the 1,492 subjects included in the two pivotal Phase 3 trials, Trial 302 and Trial 303 and two Phase 2 trials, Trial 201 and Trial 202, each with 150 and 256 subjects, respectively. No major safety issues, including FQ-associated safety issues, were encountered in the Phase 2 and 3 safety populations. Most observed adverse reactions were gastrointestinal related. The most commonly reported adverse drug reactions in the combined Phase 3 trials were nausea, diarrhea, vomiting, transaminase elevations, and headaches. Infusion site reactions were also commonly observed. A 300-mg every 12 hours intravenous (IV) formulation of delafloxacin and a 450-mg every 12 hours oral tablet formulation of delafloxacin were approved for the treatment of ABSSSIs in persons with normal (CKD Stage 1), mild (CKD Stage 2) and moderate (CKD Stage 3) renal impairments. However, due to the presence of (b)(4) SBEβCD, which may accumulate in patients with poor renal function, and based on population PK studies, dosage adjustments of 200-mg every 12 hours are recommended for persons with (b)(4) renal impairment administered the IV formulation of delafloxacin; whereas, no dosing adjustments are recommended for moderate renally impaired persons administered the oral formulation of delafloxacin. 	<ul style="list-style-type: none"> Delafloxacin’s overall pre-market safety profile is acceptable. Most adverse drug reactions are GI related (i.e., nausea, diarrhea, and vomiting); however, headaches and infusion site reactions (i.e., infusion site pain, infusion site phlebitis, infusion site erythema, infusion site swelling, infusion site thrombosis) were frequently encountered.
<p><u>Risk Management</u></p>	<ul style="list-style-type: none"> Neither the oral nor the IV formulations of delafloxacin are recommended for persons with kidney failure (CKD Stage 5). The Applicant has recommended using the estimated glomerular filtration rate (eGFR) as calculated by the modified diet in renal 	<ul style="list-style-type: none"> Section 5 of the delafloxacin label will include FQ specific safety warnings. The delafloxacin label recommends that

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>disease (MDRD) equation for the determination of renal impairment.</p> <ul style="list-style-type: none"> Although no significant safety signals were detected in this review of pre-market safety events, the delafloxacin prescribing information will include a boxed warning with FQ-class associated serious adverse reactions such as tendinitis and tendon rupture, peripheral neuropathy and central nervous system effects. 	<p>serum creatinine (Scr) levels and eGFR be closely monitored during ABSSSI treatment, particularly among individuals with severe renal impairment.</p>

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2 Therapeutic Context

2.1 Analysis of Condition

Definition, Epidemiology and Microbiology

Bacterial skin and soft tissue infections are common and are major causes of inpatient hospitalizations and ambulatory care visits in the United States and worldwide. Bacterial skin infections result from breaches in the cutaneous surface which in turn predispose the host to microbial invasion of the epidermis, dermis and/or subcutaneous tissues. These infections represent a spectrum of disease presentations. The following infections are discussed in this review: cellulitis/erysipelas, wound infections, major cutaneous abscess, and burn infections.

According to the Infectious Diseases Society of America (IDSA) erysipelas may be defined as “an infection limited to the upper dermis including superficial lymphatics” and is distinguished from cellulitis by clearly delineated borders. In contrast, cellulitis involves the deeper dermis and subcutaneous fat. However, both of these infections are responsible for “rapidly spreading areas of erythema, swelling, tenderness, and warmth” and “may be accompanied by lymphangitis (inflammation of the lymphatic channels that result from infection at a distal site) and inflammation of regional lymph nodes (lymphadenopathy).” In many European countries, erysipelas and cellulitis are considered synonymous with each other. Host factors such as obesity, previous episodes of trauma (including surgery) or cellulitis, venous insufficiency or lymphedema and conditions, such as immunocompromise secondary to extremes of age, neutropenia or HIV/AIDS, may contribute to the development (or worsening) of erysipelas/skin cellulitis in the setting of a compromise to barrier integrity (Stevens, DL *et al.* *CID* 2014).

Cutaneous abscesses are defined as collections of pus within the dermis and deeper skin tissues and are commonly described as red, painful, tender and fluctuant nodules. Traditionally, the recommended treatment for abscesses is incision and drainage (I&D) of purulent material. Systemic antibacterial drugs are usually recommended in the presence of systemic inflammatory response syndrome (SIRS), as manifested by a temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or a white blood cell count of $>12,000$ or <400 cells/ μL , where systemic antibiotics, in combination with (I&D) (Stevens, DL IDSA Practice Guidelines *CID* 2014). Wound infections can be either traumatic or surgical in origin.

Deep infections involving the fascial and/or muscle compartments, such as necrotizing fasciitis can result in major tissue destruction and an increased mortality risk; however, for the purposes of this application, the ABSSSI indication excludes necrotizing infections and ulcerations, including diabetic foot infections. Such infections require more complex regimens and are not recommended for inclusion in ABSSSI trials as per the 2013 FDA ABSSSI Guidance. (Guidance for Industry October 2013 <https://www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf>).

This review will focus on ABSSSI infections as defined in the FDA 2013 ABSSSI Guidance. The guidance defines ABSSSI as bacterial infection of the skin with a lesion size area of at least 75 cm² and lists cellulitis/erysipelas, wound infection, and major cutaneous abscess as the infection types that can be enrolled in ABSSSI clinical trials. This review will also discuss burn infections because these infections were included in the clinical trials submitted in the NDA.

Gram positive microorganisms account for the majority of ABSSSIs. *Staphylococcus aureus*, both methicillin sensitive and methicillin resistant strains, and beta hemolytic *Streptococcus* species, particularly *Streptococcus pyogenes* (Group A streptococcus or GAS), are the species most frequently implicated in ABSSSIs; whereas, other *Streptococci* such as *Streptococcus agalactiae* (Group B streptococcus), *Streptococcus dysgalactiae*, and *Enterococci* are less common microbiologic agents implicated in ABSSSIs. Gram negative pathogens, such as *Escherichia coli* and *Pseudomonas aeruginosa*, and anaerobes are less common causes of ABSSSIs, but are frequently associated with surgical site infections or soft tissue infections in the anal and perineal regions. Polymicrobial infections, those involving both Gram positive and Gram negative pathogens, are typically associated with areas of compromise to vascular perfusion (Dryden, MS *J Antimicrob Chemother* 2010; Jeng, *A Medicine* 2010; Stevens, DL IDSA practice guidelines *CID* 2014).

Within the US, patients have increasingly sought treatment for ABSSSIs in ambulatory settings, with some data indicating that, between 1997 and 2005, a 50% increase in patient visits to physicians' offices, hospital outpatient departments, and emergency departments was observed. While the majority of patients with bacterial skin infections are treated as outpatients, a certain percentage of patients require inpatient hospitalizations. Between 2000 and 2004, studies found that hospital admissions for bacterial skin infections increased by 29%. This stands in contrast with hospital admissions for pneumonia which saw no increases in hospital admissions during this same time period. Of the over 275 million patients hospitalized with bacterial skin infections, the most common co-morbid conditions associated with these infections included diabetes, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), moderate to severe renal disease, peripheral vascular disease, obesity and diabetes with complications (Kaye, KS PLOS ONE, 2015).

Hospitalizations for *Staphylococcus aureus* skin infections increased by 123% from 2001 and 2009. Simultaneously, there was a rise in the incidence of *S. aureus* skin infections, during this period, with the incidence doubling from 57 infections per 100,000 persons in 2001 to 117 infections per 100,000 persons in 2009 and with total annual costs associated with *S. aureus* skin infections hospitalizations amounting to \$4.5 billion in 2009 (Kaye, KS PLOS ONE, 2015). This rise was driven primarily by the emergence of methicillin-resistant *S. aureus* (MRSA).

MRSA isolates began to emerge in the early 1960s, but were largely confined to the hospital setting. However, by the mid-1990s, MRSA infections were increasingly being reported in community settings among individuals with no previous exposure to healthcare environments. Throughout the US and globally, MRSA is now among the most commonly identified causes of skin and soft-tissue infections. Moran *et al.*, in a study of emergency departments in 11 major US cities, discovered that MRSA was isolated from 61% of abscesses, 53% of purulent wounds

and 47% of cellulitis with purulent exudate. Community-acquired MRSA (CA-MRSA) strains may be distinguished from healthcare-associated strains by the presence of Panton-Valentine leucocidin, an exotoxin associated with skin necrosis, necrotizing pneumonias and abscess formations; by gene complexes encoding small DNA cassettes which confer methicillin resistance via the *mecA* gene; and by distinct pattern of pulsed-field electrophoretic as demonstrated by genotype USA300. Risk factors for community acquired MRSA infections include a history of colonization or recent infection with a CA-MRSA, household contacts of persons infected with MRSA isolates, incarcerated individuals, intravenous (IV) drug users, soldiers, athletes (largely those in contact sports), and among certain racial groups (i.e. African-Americans, Native Americans and Pacific Islanders) (Daum, RS *NEJM* 2007; Moran, GJ *et al. NEJM* 2006).

Diagnosis

The yield of needle or tissue aspirates when culturing pathogens implicated in skin infections is typically poor in the diagnosis of cellulitis/erysipelas. Results typically range anywhere from $\leq 5\%$ to 40%. Likewise, in most cases the diagnostic yield of blood cultures is similarly low, approximately $\leq 5\%$. While obtaining cultures via punch biopsies, yields only slightly improved results, organisms are typically cultured in only 20% to 30% of all cases. For these reasons, blood, tissue aspirates and skin biopsies are not routinely collected in the diagnosis of cellulitis/erysipelas infections and the IDSA states that in immunocompetent individuals such diagnostic tools are unnecessary. However, in instances when the host is immunocompromised either due to a malignancy, neutropenia, signs of severe systemic infection, or severe cell-mediated immunodeficiency, recommendations indicate that blood cultures should be collected and a skin biopsy or tissue aspirate should be considered. Treatment should not be delayed while attempting to collect cultures. As stated above, abscesses typically undergo I&Ds.

Therapies and treatment Duration

Oral therapy is recommended for patients in whom there is no evidence to suggest the presence of systemic inflammatory response syndrome (SIRS), alterations in mental status or hemodynamic instability. Adjunctive treatments such as dressing changes or elevation of the affected limb may also help to accelerate response to treatment. Inpatient hospitalization with the receipt of IV antibacterial therapy is recommended in severe infections or in immunocompromised hosts. A selected listing of currently available therapeutic options in the treatment of skin and skin structure infections is found in **Table 1** below.

The recommended treatment duration in uncomplicated infections is typically 5 days, particularly if the patient responds well to initial therapy. For more complicated cases or in immunocompromised hosts the recommended duration of therapy may be up to 10 to 14 days, at the discretion of the physician.

FDA and ABSSSI

In November 2008, FDA convened an Advisory Committee (AC) to discuss establishing appropriate primary endpoints for trials evaluating complicated skin and skin structure infections (cSSSIs), as they were referred to at that time; the appropriate time to assess the primary endpoint for the cSSSI indication; non-inferiority (NI) margins; and elements of trial designs.

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Citing historical data from the 1930s, it was decided that evaluation of the treatment effect of antibacterial therapy on the *cessation of the spread of a lesion* (and not the resolution), would serve as the basis for adopting an early time point of 48 to 72 hours when determining clinical response (or non-response) to therapy. The AC members found the 48-72 hour endpoint, along with a 10% non-inferiority margin, as acceptable. These elements, in addition to a discussion on the types of infections subsumed under cSSSI were debated and formed the basis of FDA ABSSSI 2010 and 2013 Guidance for Industry. The clinical efficacy of delafloxacin, is evaluated in accordance with the 2013 guidance recommendations, and will be discussed in **Section 7 Integrated Review of Effectiveness** of this clinical review.

FQ Safety Profile

Delafloxacin is a FQ antibacterial drug. In 2015, the FDA convened an AC on the benefits and risks of systemic FQs currently marketed at the time, namely ciprofloxacin, levofloxacin, and moxifloxacin, and the use of these drugs for several disease indications. During this AC, a discussion of the safety profile of these FQs and adverse events of special interest (AESIs), including tendinopathies, peripheral neuropathy, central nervous system (CNS) effects, QT prolongation were described at length, and culminated with the Agency issuing a drug safety communication on FQ. Section 8.7 of this review will further elaborate on any associations between these AESIs and delafloxacin.

2.2 Analysis of Current Treatment Options

Below, **Table 1** provides a selected list of currently available FDA approved therapies for skin infection, including therapies for the treatment of MRSA.

Table 1: Selected List of Currently Available FDA-approved Therapies for Skin Infections

Agent Name/ Drug Class	Approval Date	Mechanism of action	Approved Skin Indication	Normal dosage	Route	Adjustment for renal impairment
Vancomycin (tricyclic glycopeptide)	1958	Inhibition of bacterial cell-wall synthesis	Treatment of complicated SSSI (cSSSI) susceptible isolates: <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , <i>Streptococcus bovis</i> , <i>Viridans streptococci group</i> , and <i>Enterococcus faecalis</i>	15-mg/kg every 12 hours	IV	Yes
Cefazolin (cephalosporin)	October 1973	Inhibition of bacterial cell-wall synthesis	Treatment of skin and skin structure infections due to <i>S. aureus</i> (penicillin-sensitive and penicillin-resistant), group P beta-hemolytic streptococci, and other strains of streptococci.	500 mg to 1 gm every 6 to 8 hours	IV	Yes
Aztreonam (monobactam)	1986	Inhibition of bacterial cell-wall synthesis	Treatment of skin and skin-structure infections, including those associated with postoperative wounds, ulcers and burns caused by: <i>Escherichia coli</i> ; <i>Proteus mirabilis</i> ; <i>Serratia marcescens</i> ; <i>Enterobacter</i> species; <i>Pseudomonas aeruginosa</i> ; <i>Klebsiella pneumoniae</i> ; and <i>Citrobacter</i> species	1 gm or 2 gm every 8 or 12 hours	IV	Yes

Ciprofloxacin (fluroquinolone)	1987	Inhibition of bacterial DNA gyrase and topoisomerase IV	Treatment of SSSI (SSSI) susceptible isolates: <i>Staphylococcus aureus</i> (MSSA), <i>S. epidermidis</i> (MSSE), <i>Strep. pyogenes</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter cloacae</i> , <i>Proteus mirabilis</i> , <i>Proteus vulgaris</i> , <i>Pseudomonas aeruginosa</i>	500-750 mg every 12 hours	po	Yes
Clindamycin (lincomycin)	1989	Inhibits protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome.	Treatment of skin and skin structure infections caused by: <i>Streptococcus pyogenes</i> , <i>Staphylococcus aureus</i> (including methicillin-susceptible (b)(4)), and anaerobes.	IV: 600-mg IV every 8 hours PO: 300-450 mg IV every 6 hours	IV or po	No
Meropenem (carbapenem)	1996	Inhibition of bacterial cell-wall synthesis	Treatment of complicated skin and skin structure infections (cSSSI) due to: <i>Staphylococcus aureus</i> (methicillin-susceptible isolates only), <i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , viridian group streptococci, <i>Enterococcus faecalis</i> (vancomycin-susceptible isolate only), <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , <i>Proteus mirabilis</i> , <i>Bacteroides fragilis</i>	500 mg every 8 hours (for skin and skin structure infections)	IV	Yes
Levofloxacin	December	Inhibition of		Treatment of uSSSI:	IV or	Yes

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(fluoroquinolone)	1996	bacterial DNA gyrase and topoisomerase IV	Treatment of uSSSI susceptible isolates: <i>S. aureus</i> or <i>Strep. pyogenes</i> ; Treatment of cSSSI susceptible Gram positive and Gram negative isolates: <i>S. aureus</i> (MSSA only), <i>Strep. pyogenes</i> , <i>E. faecalis</i> , and <i>Proteus mirabilis</i>	500-mg every 24 hours; Treatment of cSSSI: 750-mg every 24 hours	po	
Linezolid (oxazolidinone)	April 2000	Ribosomal protein synthesis inhibition (50S ribosomal subunit)	Treatment of uSSSI caused by susceptible isolates: <i>Staphylococcus aureus</i> (MSSA only) or <i>Streptococcus pyogenes</i> . Treatment of cSSSI (including diabetic foot infections) caused by susceptible isolates: <i>S. aureus</i> (MSSA/MRSA), <i>Strep. pyogenes</i> , or <i>Strep. agalactiae</i>	600-mg every 12 hours	IV or po	No
Moxifloxacin (fluoroquinolone)	November 2001	Inhibition of bacterial DNA gyrase and topoisomerase IV	Treatment of uSSSI susceptible isolates: <i>S. aureus</i> or <i>Strep. pyogenes</i> ; Treatment of cSSSI susceptible Gram positive <i>S. aureus</i> (MSSA only), <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , or <i>Enterobacter cloacae</i>	400-mg every 24 hours	IV or po	No

Ertapenem sodium	November 2001	Inhibition of bacterial cell-wall synthesis	Treatment of cSSSI (including diabetic foot infections) caused by susceptible Gram positive and Gram negative isolates: <i>S. aureus</i> (MSSA (b)(4), <i>Strep. pyogenes</i> , <i>Strep. agalactiae</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>Proteus mirabilis</i> , <i>Bacteroides fragilis</i> , <i>Peptostreptococcus</i> species, <i>Porphyromonas asaccharolytica</i> or <i>Prevotella bivia</i>)	1 gram every 24 hours	IV or IM	Yes
Daptomycin (cyclic lipopeptide)	2003	Membrane depolarization resulting in inhibition of DNA, RNA and protein synthesis	Treatment of cSSSI susceptible Gram positive isolates: <i>S. aureus</i> (including MRSA), <i>Strep. pyogenes</i> , <i>Strep. agalactiae</i> , <i>Strep. dysgalactiae</i> , <i>E. faecalis</i> (vanco susc. isolates only)	4-mg/kg every 24 hours	IV	Yes
Tigecycline (glycylcycline)	June 2005	Ribosomal protein synthesis inhibition (30S ribosomal subunit)	Treatment of cSSSI caused by susceptible isolates: <i>E. coli</i> , <i>S. aureus</i> (MSSA/ MRSA), <i>Strep. anginosus</i> group, <i>Strep. pyogenes</i> , <i>Strep. agalactiae</i> , <i>E. faecalis</i> (vanco susc.), (b)(4)	50-mg/kg every 12 hours (100-mg initial dose)	IV	No
Telavancin (lipoglycopeptide)	September 2009	Inhibition of cell-wall synthesis; Binds bacterial membrane and disrupts membrane barrier function	Treatment of cSSSI caused by Gram positive: <i>S. aureus</i> (MSSA/ MRSA), <i>Strep. pyogenes</i> , <i>Strep. agalactiae</i> , <i>Strep. anginosus</i> group, <i>E. faecalis</i> (vanco susc isolates only)	10-mg/kg every 24-hours	IV	Yes
Ceftaroline	October	Inhibition of	Treatment of ABSSSI caused by susceptible Gram	600-mg	IV	Yes

fosamil (cephalosporin)	2010	bacterial cell-wall synthesis	positive and Gram negative isolates: <i>S. aureus</i> (MSSA/MRSA), <i>Strep. pyogenes</i> , <i>Strep. agalactiae</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>K. oxytoca</i>	every 12 hours		
Dalbavancin (semisynthetic lipoglycopeptide)	May 2014	Cell-wall synthesis inhibition	Treatment of ABSSSI caused by susceptible Gram positive isolates: <i>S. aureus</i> (MSSA/MRSA), <i>Strep. pyogenes</i> , <i>Strep. agalactiae</i> , <i>Strep. anginosus</i> group, (b)(4)	Single dose: 1500-mg (≥ 30 min/mL or HD); Two dose: 1000 mg x 1 wk, then 500-mg (≥ 30 min/mL or HD);	IV	Yes
Tedizolid phosphate (oxazolidinone)	June 2014	Ribosomal protein synthesis inhibition (50S ribosomal subunit)	Treatment of ABSSSI caused by susceptible Gram positive isolates: <i>S. aureus</i> (MSSA/MRSA), <i>Strep. pyogenes</i> , <i>Strep. agalactiae</i> , <i>Strep. anginosus</i> group, <i>E. faecalis</i> (b)(4)	200-mg every 24-hours	IV or po	No
Oritavancin (semi-synthetic lipoglycopeptide)	August 2014	Inhibition of bacterial cell-wall synthesis; Disruption of bacterial membrane integrity	Treatment of ABSSSI caused by susceptible Gram positive isolates: <i>S. aureus</i> (MSSA/MRSA), <i>Strep. pyogenes</i> , <i>Strep. agalactiae</i> , <i>Strep. dysgalactiae</i> , <i>Strep. anginosus</i> group, <i>E. faecalis</i> (vancomycin susceptible isolates only)	A single 1200-mg dose infused over 3 hours	IV	No
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; cSSSI, complicated skin and skin structure infections; MRSA, methicillin resistant staphylococcus aureus; MSSA, methicillin susceptible staphylococcus aureus; MSSE, methicillin susceptible staphylococcus epidermidis; susc, susceptible; uSSSI, uncomplicated skin and skin structure infections; vanco, vancomycin						

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Source: Adapted from Stryjewski, M and Chambers, HF *CID* 2008 and Melinta Therapeutics, Inc. Agreed Pediatric Study Plan

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3 Regulatory Background

3.1 U. S. Regulatory Actions and Marketing History

Delafloxacin is a new molecular entity (NME). NDA 208,610 and NDA 208,611 (for product quality) were submitted by the Applicant, Melinta Therapeutics, Inc. in support of their delafloxacin application for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Delafloxacin is not presently marketed within the U.S. This is the first marketing application submitted for this product. Please note that for all pre-NDA interactions, the Applicant is referred to as the “Sponsor.”

3.2 Summary of Presubmission/Submission Regulatory Activity

Section 3.2 summarizes the regulatory highlights of the delafloxacin development program conducted under IND 62,772 (oral tablet formulation) and IND 76,096 (intravenous formulation).

Initial Application Submission (oral formulation), 21, June 2001. The original Sponsor, Abbott Laboratories (Pharmaceutical Products Division), submitted an Investigational New Drug (IND) application, under 62,772 (oral tablet formulation), for ABT-492.

Initial Application Submission (IV formulation), 20 March 2007. The Sponsor Rib-X Pharmaceuticals, Inc., submitted an IND application for the drug RX-3341 (Intravenous formulation), under IND 76,096.

End of Phase 2 meeting, 14 April 2010.

The Sponsor and the Agency discussed the delafloxacin Phase 3 development plan including the study design and study endpoints for the Sponsor’s two planned Phase 3 trials. Following a December 2009 Advisory Committee, the Agency notified the Sponsor (Rib-X Pharmaceuticals, Inc) that based on historical data, the Agency’s new primary efficacy endpoint for **clinical success** for ABSSSI trials would be assessed at **48 to 72 hours**, an earlier time point than was previously recommended. The Agency believed that this change would permit the demonstration of “a greater treatment effect between antibacterial agents and placebo compared to a later time point, based upon literature data.”

The Sponsor informed the Agency of the following **key** elements of their pivotal Phase 3 trials, including their decision to: (a) conduct 2 trials, one evaluating delafloxacin’s IV formulation and the other an IV to oral switch trial; (b) have a(n) NI margin of 10% with respect to the primary endpoint; (c) limit the number of subjects with major abscesses to $\leq 20\%$ of all infections; and (d) conduct an absolute bioavailability (BA) study of the oral formulation of delafloxacin relative to the IV formulation prior to initiation of the Phase 3 trial RX-3341-303.. The Agency recommended that the Sponsor have the results of their thorough QT (TQT) study prior to submitting their NDA application.

Qualified Infectious Disease Product (QIDP) Designation, 8 September 2012.

On 17 July 2012, the Sponsor requested a QIDP designation for delafloxacin for the acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia

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(CABP) treatment indications. The Agency granted delafloxacin a QIDP designation, for both indications, on 08 September 2012.

Fast Track Designation, 17 October 2012.

The Sponsor requested a Fast Track designation for both the oral tablet and IV formulations of delafloxacin for both the ABSSSI and CABP treatment indications.

Special Protocol Agreement (SPA), 8 February 2013. The Sponsor submitted an SPA dated 21 December 2012. The Agency agreed to the following **key** elements of the Sponsor's proposed Phase 3 trials: (a) the primary efficacy endpoint will be a $\geq 20\%$ decrease in lesion erythema size compared to baseline in the ITT population at 48 to 72 hours after initiation of treatment as determined by digital measurements of the leading edge; (b) hierarchical testing for superiority of secondary efficacy endpoints; (c) identified specific signs/symptoms of systemic infection that patients must manifest in order to be eligible for inclusion into Phase 3 trials; and (d) highlighted changes to the statistical analysis plan (SAP). The Agency issued an SPA agreement on 7 February 2013.

Special Protocol Agreement (SPA), 19 August 2013. The Sponsor submitted an SPA dated 12 August 2013. On 19 August 2013, the Agency issued a Special Protocol Agreement in which they agreed to the following **key** points: (a) the 450-mg delafloxacin oral tablet is appropriate to proceed with an IV-to-oral switch Phase 3 trial, as had previously been proposed; (b) a proposal to test for superiority for the secondary endpoint of investigator's assessment of cure at the follow-up visit was acceptable and would be a review issue; (c) dose adjustments in patients with severe renal impairment appeared to be supported by preliminary data, with the Agency "recommend[ing] that the Sponsor should consider the inclusion of patients with severe renal impairment in the Phase 3 trials to help evaluate the performance of the dose adjustment."

(b) (4)

Type A CMC meeting request, 6 February 2015.

The Sponsor and the Agency discussed (b) (4) registration stability lots of the lyophilized IV formulation. The Agency informed the Sponsor that this issue would "be examined in detail during facility inspections." However, at this meeting, the Agency believed that the (b) (4) appeared appropriate; however, the Agency indicated that "additional assessment of manufacturing process[es] be pursued so as to identify, correct and implement measures (b) (4)

SPA-No Agreement, 22 May 2015. The Sponsor submitted an SPA dated 23 April 2015 to which the Agency issued an SPA NO AGREEMENT on 22 May 2015 for the following reasons: (b) (4)

The Agency recommended that the Sponsor either exclude patients with severe renal impairment from proposed Protocol RX-3341-303 *or* decrease the dose of IV delafloxacin in these patients. In addition, the Agency recommended that patients with a BMI ≥ 30 kg/m² be limited to *no more than* 50% of all enrollees for generalizability purposes.

CMC Pre-NDA Meeting, 5 April 2015. The Sponsor and the Agency discussed (b) (4)

(b) (4) In response to these issues, the Agency requested that the Sponsor provide in-use stability testing for (b) (4) vials, and that the Sponsor conduct a shipping study. In addition, the Agency requested that all completed batch records be made available to FDA facility inspectors at the time of the facility site inspection.

Pre-NDA Meeting, February 2016. The Sponsor submitted a request for a Pre-NDA Type B meeting “to discuss the proposed content and format of their upcoming NDA” for both the oral and IV formulations of delafloxacin.

Agreed Initial Pediatric Study Plan (iPSP) Agreement, 17 March 2016. The Agency granted the Sponsor’s request for a full pediatric waiver for delafloxacin in pediatric patients aged 0 to < 18 years old for the ABSSSI treatment indication. A full waiver was approved pursuant to Section 505B(a)(4)(A) of the Food, Drug and Cosmetic Act for the following reasons: (a) the product would be deemed ineffective or unsafe in pediatric patients aged 0 to <18 and (b) delafloxacin “fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients.”

Submission of NDA 208,610 and NDA 208,611, 18 October 2016.

120 Day Safety Update, February 2017.

Overall, clinical protocols and the development plan were reviewed by the Agency/Division throughout the delafloxacin development program, with feedback provided regarding issues of dose selection, treatment duration, treatment regimen, and trial population.

3.3 Foreign Regulatory Actions and Marketing History

At the time of this review, delafloxacin has not been marketed in any country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

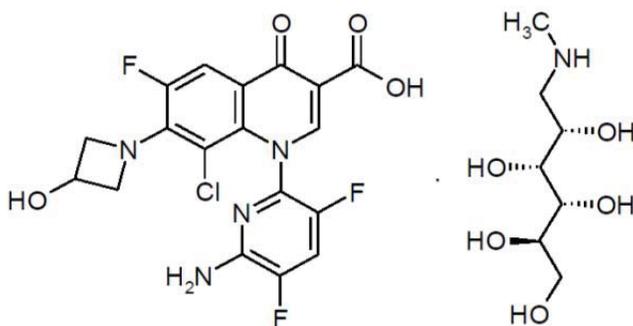
Subjects for both pivotal Phase 3 trials were recruited from various sites in the US and abroad. Using the OSI site selection tool, the clinical and statistical reviewers in conjunction with the OSI team, Drs. Bei Yu and Janice Pohlman, selected a total of four clinical sites, two from each of the Phase 3 trials, from which to conduct inspections. All four selected inspection sites were located within the US. The sites were as follows: Sites 840-002 and 840-014 from Protocol 3341-302 and sites 840-302 and 840-327 from Protocol 303. These four sites were selected for *at least* one of the following reasons: having a high number of enrollees, high efficacy rates, high numbers of SAEs, and/or having no prior inspections. No site inspections were conducted at abroad sites.

Medical Reviewer's Comments: *At the time of this review, preliminary results from Site 840-002 revealed several discrepancies between information contained in source documents and the eCRF for 34 of 154 subjects. These discrepancies were considered minor and were not deemed significant enough to preclude the drug's approval. No major issues were identified at the other three inspection sites. Office of Regulatory Affairs (ORA) investigators discovered that a total of 8 subjects from sites 840-002 and 840-302 enrolled in each of these sites; however, these subjects were enrolled at different times in the two separate Phase 3 trials. Site inspectors determined that these findings were not significant due to the different eligibility criteria for each protocol. A planned inspection of the Applicant was underway at the time of this review.*

4.2 Product Quality

Delafloxacin-*N*-methylglucamine salt is a novel investigational fluoroquinolone antibiotic characterized by broad spectrum antibacterial activity indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Its proprietary name is Baxdela™ and its non-proprietary name is delafloxacin meglumine. Its structure and pertinent chemical information are presented below. **Table 2** below lists delafloxacin's nomenclature.

Figure 1 **Delafloxacin Structure**



Molecular Formula: C₂₅H₂₉ClF₃N₅O₉

Molecular Weight: 635.97 g/mol (N-methylglucamine salt)

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 BAXDELA™ (delafloxacin meglumine)

Molecular Weight: 440.76 g/mol (free acid)

Table 2: Nomenclature of Drug Substance/Drug Product

Recommended International Nonproprietary Name (INN)	Delafloxacin meglumine
Compendial name	Delafloxacin meglumine
Proprietary name	Baxdela™
Chemical name(s)	D-Glucitol, 1-deoxy-1-(methylamino)-, 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-1,4-dihydro-7-(3-hydroxy-1-azetidiny)-4-oxo-3-quinolinecarboxylate (salt)
Company or laboratory codes	RX-3341, ABT-492, A-319492 ^{(b) (4)} and WQ-3034
Other non-proprietary name(s)	
National name	Delafloxacin meglumine
United States Adopted Name (USAN)	Delafloxacin meglumine
Chemical Abstracts Service (CAS) number	352458-37-8

Source: Adapted from Module 2.6.1 Nonclinical Written Summary

Delafloxacin is manufactured as two formulations: a sterile 300-mg lyophilized formulation containing Captisol® (^{(b) (4)} sulfobutylether ^{(b) (4)} β cyclodextrin ^{(b) (4)} for IV administration and as a 450-mg oral tablet formulation. Delafloxacin is intended to be marketed as a 300-mg IV infusion administered over 60 minutes every 12 hours or as a 450-mg oral tablet administered every 12 hours. The Applicant recommends that each formulation be administered, at physicians' discretion, for a total treatment course of 5-14 days, (Module 2.6.1 Nonclinical Written Summary).

A single tablet contains 649^{(b) (4)} mg of delafloxacin meglumine which is the equivalent of 450-mg of delafloxacin free acid. The chemical composition of a single oral tablet of delafloxacin includes the following excipients: delafloxacin meglumine salt (drug substance); microcrystalline cellulose ^{(b) (4)} crospovidone ^{(b) (4)} sodium bicarbonate; sodium phosphate monobasic; ^{(b) (4)} and magnesium stearate ^{(b) (4)}. The tablet will appear as a “modified capsule shape in beige to mottled beige color and debossed with RX3341 on one side.”

Each vial of delafloxacin IV (for injection) contains 300-mg of a light yellow to tan cake lyophilized product contained in a ^{(b) (4)} clear ^{(b) (4)} glass vial. Before administration, this powder should be reconstituted with either sterile 5% dextrose solution or 0.9% saline for a final volume of 12^{(b) (4)} mL. The drug product appears as “a yellow- to ^{(b) (4)}-amber-colored solution containing 25 mg/mL of delafloxacin (as free acid); ^{(b) (4)} sulfobutyl ether ^{(b) (4)} 200-mg/mL, meglumine ^{(b) (4)}-mg/mL, EDTA disodium ^{(b) (4)} mg/mL ^{(b) (4)}. The final drug product is filled into ^{(b) (4)} glass vials, ^{(b) (4)}, sealed ^{(b) (4)}, and packaged into carton boxes containing 10 vials per carton (Application Section 2.3.P.1 Description and Composition of the Drug Product).

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(b) (4) is responsible for the manufacturing, testing and release of delafloxacin meglumine drug substance on behalf of Melinta Therapeutics, Inc. (b) (4) manufactures and performs release and stability testing for delafloxacin for injection.

Please refer to the CMC Reviews authored by Dr. Yushi Feng, Dr. Danuta Gromek-Woods, and Dr. Balajee Shanmugam for further details on the manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity and quality of delafloxacin drug substance and drug product.

Medical Reviewer's Comments: During the review process the Drug Product Quality team raised several concerns about the potential (b) (4) of the lyophilized powder. Stability studies of vials (b) (4) were performed. (b) (4)

4.3 Clinical Microbiology

The Applicant's originally proposed delafloxacin label stated the following:

“Delafloxacin is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, (b) (4), *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group, (b) (4) *Streptococcus pyogenes*, and *Enterococcus faecalis*, and by the following Gram-negative organisms: *Escherichia coli*, *Enterobacter cloacae*, (b) (4) *Klebsiella pneumoniae*, (b) (4) and *Pseudomonas aeruginosa*.”

As with all other FQs, delafloxacin acts via the inhibition of DNA synthesis by targeting bacterial DNA gyrase and topoisomerase IV. FQ-mediated resistance is induced by mutations in the enzymes DNA gyrase and topoisomerase IV or through the expression of efflux pumps which interfere with the FQ drugs' ability to reach its target. The Applicant reports, that at concentrations 4X the MIC or greater, they found a “very low frequency ($\leq 10^{-9}$)” of delafloxacin-resistant mutants generated during spontaneous mutation frequency studies. Laboratory derived delafloxacin mutants containing the quinolone resistance-determining regions (QRDR) displayed higher MICs, particularly following the acquisition of the *gyrA* and *parC/grlA* mutations. The predominant mutations in laboratory derived and clinical *S. aureus* isolates were Ser84-Leu in *gyrA*/Ser80-Tyr or Ser80-Phe in *grlA*.

After conducting several *in vivo* efficacy murine infection model studies including systemic lethal infection, soft tissue infections, experimental abscess infections (rat granuloma infection), pneumonia, and pyelonephritis, the Applicant concluded that delafloxacin has good activity against both Gram-positive and Gram-negative pathogens (i.e. *S. aureus* including MRSA, *Strep. pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*). Delafloxacin's efficacy was established, irrespective of the route of administration (i.e. oral, IV or subcutaneous), in non-clinical therapeutic studies.

Delafloxacin agar dilution MIC values were tested for all species, and demonstrated that, aside from *Strep. pneumoniae*, this form of testing had a good correlation with broth microdilution MIC values. Due to the overall reliability between disk diffusion zone sizes and broth microdilution MIC values, delafloxacin's susceptibility can be reliably determined by disk diffusion testing using a 5 µg disk for target pathogens. The Applicant proposed pathogen specific breakpoints based on surveillance data, PD studies in the neutropenic mouse thigh infection model, susceptibility of baseline isolates and the outcomes of clinical trials. The Applicant proposed broth microdilution and disk diffusion susceptibility breakpoints for the following ABSSSI associated pathogens:

Gram Positive Pathogens

- MIC (b) (4) µg/mL is the recommended susceptibility breakpoint for the following pathogens: *Staphylococcus aureus* (both MSSA and MRSA isolates), *S. haemolyticus*, (b) (4), (b) (4), and *E. faecalis* (b) (4)
- MIC (b) (4) µg/mL is the recommended susceptibility breakpoint for the following pathogens: *Strep. pyogenes*, *Strep. agalactiae*, (b) (4), *Strep. anginosus* Group, (b) (4)

Gram Negative Pathogens

- MIC (b) (4) µg/mL is the recommended susceptibility breakpoint for the following pathogens: *E. coli*, *K. pneumoniae*, (b) (4), *E. cloacae*, (b) (4) and *P. aeruginosa*.

Medical Reviewer's Comments: For further details on the Applicant's clinical microbiology development program, including a discussion on probability target analysis (PTA) and susceptibility breakpoints, the reader is directed to the Clinical Microbiology and Clinical Pharmacology Reviews authored by Drs. Jalal Sheikh and Kunyi Wu, respectively.

4.4 Nonclinical Pharmacology/Toxicology

Section 4.4 provides a high level summary of relevant outcomes of the pharmacology/toxicology review. The information contained in this section largely reflects the content contained in Module 2.4 the Nonclinical Overview and Module 2.6.6 Toxicology Written Summary. Please refer to the Pharmacology/Toxicology review authored by Dr. Amy Nostrandt (pharmacology-toxicology reviewer) for further details.

4.4.1 Single –Dose Toxicity Studies (Oral and IV)

Single dose toxicity Good Laboratory Practice (GLP)-compliant studies, evaluating both oral and IV administration of delafloxacin, were conducted in mice, rats, and dogs.

- **Oral Toxicity Studies: Mice and Rats**
 - CD-1 mice (3/sex/group) and Sprague-Dawley rats (3/sex/group) were administered single doses of delafloxacin 0, 208-, 416-, 832-, 1,664-, and 3,328-mg/kg in 0.2% hydroxypropyl methylcellulose (HPMC) and vehicle administered controls were observed for 2-weeks post-dose, with body weights measured weekly. All mice (dead and surviving) were subsequently euthanized and necropsied.

- **In mice**, mortality was observed at $\geq 1,664$ mg/kg in females and at 3,328 mg/kg in males. The following post-dose findings were observed in delafloxacin treated mice: “decreased activity, dyspnea, squinting, and ataxia at ≥ 416 -mg/kg, tremors at ≥ 832 -mg/kg, and prostration and rough coats at 3,328-mg/kg.” Morphologic changes related to delafloxacin therapy were not observed.
- **In rats**, mortality occurred at $\geq 1,664$ mg/kg and the following post-dose observations were noted: “decreased activity and salivation at ≥ 416 -mg/kg, soft stools at ≥ 832 -mg/kg, and dyspnea, ataxia, lacrimation, rales, prostration, tremors, and dehydration at ≥ 1664 -mg/kg”. No gross findings were observed upon necropsy.
- **Oral Toxicity Studies: Dogs**
 - **Two exploratory studies evaluating single-dose oral toxicity in dogs** were conducted. One study was conducted in beagle dogs (1/sex/dose) in an escalating dose design beginning at 10-mg/kg and increasing by a factor of 2 up to 320-mg/kg. A minimum of 72 hours separated each dose escalation. No deaths were observed. At doses ≥ 40 -mg/kg and 80-mg/kg, respectively, **post-dose emesis and diarrhea** were observed.
 - In the **second oral toxicity study**, one male and one female beagle dogs each were administered delafloxacin twice daily at 160-mg/kg (320 mg/kg/day) followed 72 hours afterwards with an initial dose of 320-mg/kg (640 mg/kg/day). Daily emesis was noted in the male and, in the female. Loose stools and emesis were observed after the second dose of 160-mg/kg and after the second dose of 320-mg/kg, respectively.

***Medical Reviewer’s Comments:** Dose escalating oral toxicity studies in dogs demonstrated GI-related findings, such as vomiting and diarrhea, that were subsequently observed in human clinical trials. Rats administered oral concentrations of delafloxacin (≥ 416 -mg/kg) were observed to have soft stools as well as signs of neurotoxicity.*

- **IV Toxicity Studies: Rats**
 - **Single doses of delafloxacin 180-mg/kg** (from two separate lots) were administered as a 60-minute IV infusions in the lateral tail vein of Sprague-Dawley rats (10/sex/group). Control rats received vehicle. Rats were observed for 2 weeks post-dose and afterwards were necropsied either on Day 3 (5/sex/group) or at the post-dose observation period. No delafloxacin-treated females died but mortality was observed in males. Delafloxacin treated rats displayed languid behavior. No gross pathologic changes were observed, with the exception of the tail/injection site.
- **IV Toxicity Studies: Dogs** Two exploratory IV delafloxacin toxicity studies were conducted in beagle dogs, with IV infusions administered over 60 minutes
 - In the first of these studies, dogs were administered a dose of 20-mg/kg followed by 60-mg/kg 3 days afterwards. Dogs were observed postdose. No deaths occurred. At both doses, post-dose continuous body tremors and emesis were observed.
 - The second exploratory IV infusion study was a single dose escalating study divided into two phases: (a) phase 1 beagle dogs (1/sex/group) were **administered single escalating doses** of delafloxacin, separated by a minimum of 48-hours, up to 300-mg/kg and (b) **a 4-day repeat-dose phase in naïve dogs** (1 male and 1 female) administered 150-mg/kg for 4 consecutive days followed by a dose of 225-mg/kg on day five.
 - **Single Escalating Dose Phase:** Lethality occurred in both dogs receiving 300-mg/kg in single escalating dose phase. The dogs receiving 300-mg/kg displayed

“severe, prolonged toxicity (labored breathing, severe ataxia, ptosis, contracted nictitating membranes).” Emesis was observed at ≥ 75 -mg/kg.

- **Repeat-dose Phase:** Emesis, increased salivation and pale ears occurred at 225-mg/kg. After receiving the 225-mg/kg dose the male dog died. “The female was euthanized moribund.” Other notable observations included decreased activity, ataxia, ptosis, diarrhea, deep respiration, cold to touch, swollen limb. ALT, AST, alkaline phosphatase (ALP), and gamma glutamyltransferase (GGT) were noted in both sexes dosed as 150-mg/kg for 4 days.

***Medical Reviewer’s Comments:** As in oral toxicity studies, dogs administered 60 minute IV infusions of delafloxacin experienced episodes of emesis (vomiting). In canine repeat dose studies, liver enzyme elevations (ALT, AST, ALP and GGT) were observed.*

4.4.2 Pivotal Repeat –Dose Toxicity Studies (Oral and IV)

Pivotal oral and IV 4 and 13 week trials were conducted in rats and dogs with each followed by postdose reversal periods lasting 2 and 4 weeks, respectively. Whereas rats were able to tolerate delafloxacin administered twice daily, increased emesis prevented dogs from receiving twice daily delafloxacin dosing.

- **Oral Gavage Toxicity Studies in Rats**

- Cecal dilatation (occurring at ≥ 200 -mg/kg/day), with no associated histopathologic changes, was the most commonly observed finding in rats receiving oral delafloxacin by gavage.
- Sprague-Dawley rats (10/sex/group tox, 5/sex/group TK) at doses of 0, 100, 300, and 800-mg/kg BID for 3-months, with an additional 5/sex/group rats in the control and 1600-mg/kg/day group, were followed for 4-weeks post dose reversal period. No dose related deaths occurred. At 1600-mg/kg/day, the highest evaluated delafloxacin dose in the 3-month rat pivotal trial, male rats were noted to have decreased body weights (by approximately 14%) relative to their control counterparts and both sexes were noted to have “abnormal stools” at this dose.
- The no-adverse-effect level (NOAEL) for male rats administered oral delafloxacin for 3 consecutive months was 600-mg/kg/day. The NOAEL in females was determined to be 1600-mg/kg/day, the highest dose, in spite of delafloxacin treated females experiencing a <10% decline in mean body weight relative to controls.
- The NOAEL for the 4-week toxicity study in rats was 1200-mg/kg/day, the highest dose level. No deaths occurred in this study.

- **Oral Toxicity Studies in Dogs**

- In the 4-week dog oral (gelatin capsule) toxicity study where delafloxacin treated beagle dogs (3/sex/group) were dosed at 0, 80, 160, and 320-mg/kg/day and an additional group of controls and delafloxacin dogs treated at the highest dose were retained for a 2-week recovery period, there were no delafloxacin related deaths. Emesis and diarrhea occurred at all dose levels, and no elevations in transaminases or ALP were observed in dosing up to the highest dose tested, 320-mg/kg/day.
- Gelatin capsules dosed up to 320-mg/kg/day were orally administered to dogs for up to 3 months, with the primary delafloxacin related adverse effects being “emesis, salivation, and abnormal stool/diarrhea.” The incidence and severity of these findings were dose dependent. No deaths occurred. Three male dogs and a single female dog receiving 320-

mg/kg/day were found to have reversible elevations in serum ALT and ALP and/or GGT at various times during the 3-month study. However, no concomitant histopathologic changes were noted on electron microscopy in the livers of the 2 males with the highest liver enzyme elevations.

- The NOAELs for dogs in the 4-week study and the 3-month study were 320-mg/kg/day and 160-mg/kg/day, respectively.

***Medical Reviewer's Comments:** In the pivotal 4-week and 3-month oral toxicity studies in dogs, once again emesis (vomiting) and abnormal stools/diarrhea, were the most prominently observed side effects. Several dogs were noted to have reversible elevations in serum ALT and ALP and/or GGT at various times during the 3-month study.*

- **IV Toxicity Studies in Rats**

- In the **pivotal IV rat toxicity studies**, rats were enrolled in either: (a) a once daily 60-minute delafloxacin infusion (2-week study) at 0, 10, 60, and 180-mg/kg/day with additional controls and delafloxacin treated rats in the 180-mg/kg/day dose level evaluated during a 1-week reversal period or (b) a 90-minute infusion (4-week study) where rats were dosed at 0, 10, 75, and 150-mg/kg/day and additional control rats and rats in the 150-mg/kg/day group were observed during a 2-week reversal group. In each study, study drug was administered via an indwelling femoral catheter.
- In the **2-week study**, **several deaths** occurred after the initial dose of 180-mg/kg dose. These observed deaths prompted the lowered of the dose level to 120-mg/kg/day beginning on Study Day 2. Post-dose observations of delafloxacin treated rats from Day 3 onward included descriptions of the following: languid appearance, prostration, rapid respiration and tremors in females at 10-mg/kg and in males and females receiving 180/120 mg/kg/day. Males in the 180/120-mg/kg dose group had **decreased body weights** and both sexes in this group exhibited **decreased food consumption**. Injection site inflammation was noted in both delafloxacin treated and control rats.
- In the **4-week toxicity study**, mortality was observed at all doses levels (including in controls) with most deaths occurring at the highest dose level (150-mg/kg/day). Some rats were removed from the study due to loss of catheter patency. Males in the 150-mg/kg/day dose level had statistically significant **decreases in mean body weight and food consumption**. **Injection site lesions** (i.e. thrombosis, necrosis, fibrosis, focal and multifocal hemorrhage) were observed in pathology of both drug treated and control rats.
- NOAEL for the 2-week study was 60-mg/kg/day. In the 4-week study, the NOAEL in male and female rats were 75-mg/kg/day and 150-mg/kg/day, respectively.

- **IV Toxicity Studies in Dogs**

- Beagle dogs were administered 60-minute IV infusions of 0 (placebo), 10, 25, or 75-mg/kg/day of study treatment daily during the 2-week and 4-week toxicity studies. Additional controls and rats in the 75-mg/kg/day group were observed during a 1-week post-dose reversal period in the 2-week study and during a 2-week reversal period in the 4-week study.
- **In the 2-week toxicity study**, there were no delafloxacin related deaths. Dose dependent post-dose findings were observed at ≥ 25 -mg/kg/dose and included “emesis, salivation, soft and/or mucoid feces and diarrhea.” The incidence and severity of post-dose clinical

findings increased with dose level. Findings consistent with **injection site irritation** were observed **in both controls and delafloxacin** treated animals.

- Clinical findings in the **4-week toxicity trial** were similar to those found in the 2-week trial (**emesis, salivation, abnormal feces**) and additionally included decreased activity, and vocalization all at the 75-mg/kg/day dose. Dog in the 25-mg/kg/day group were noted to have abnormal feces.
 - On Day 29, **statistically significant increases in ALT and ALP** were noted in **males** at the 75-mg/kg/day dose group (driven largely by one dog). Non-significant ALT elevations were noted in females at 75-mg/kg/day. However, increased liver enzymes did not correlate with hepatic histopathologic changes.
- **The NOAEL** in the 2-week study and the 4-week study were 75-mg/kg/day and 25-mg/kg/day, respectively.

***Medical Reviewer's Comments:** Dogs in two- and four-week IV toxicity canine studies exhibited GI-related findings of emesis (vomiting) and abnormal stools/diarrhea. This was consistent with previous non-clinical canine studies and human clinical trials. Several dogs demonstrated significant elevations in serum ALT and ALP. Injection site reactions (i.e. irritations) and injection site lesions were observed among both controls and delafloxacin in rat and dog studies. Near equal numbers of injection/infusion site reactions were also observed in human clinical trials.*

4.4.3 Genotoxicity

- Delafloxacin was not demonstrated to be mutagenic by the bacterial reverse mutation assay (Ames test).
- Delafloxacin was not found to be clastogenic (inducing breakage or damage of chromosomes), at doses up to 2000-mg/kg/day (1000-mg/kg BID) in the *in vivo* mouse bone marrow micronucleus assay.

***Medical Reviewer's Comments:** In non-clinical studies, delafloxacin was demonstrated to be neither mutagenic nor clastogenic.*

4.4.4 Carcinogenicity Studies

- Given its limited recommended duration of therapy (5-14 days), no carcinogenicity studies with delafloxacin were conducted.

***Medical Reviewer's Comments:** Due to its limited duration of therapy, delafloxacin is unlikely to be carcinogenic. Therefore, carcinogenicity studies were not conducted. site reactions were also observed in human clinical trials.*

4.4.5 Reproductive Toxicity

Many embryo/fetal and peri-/postnatal development studies were conducted in rats and rabbits to better understand any effects delafloxacin may have on reproductive indices.

- **Fertility and Embryonic Development**
 - Delafloxacin was not observed to impact - male or female fertility or early embryonic development in males administered 60-minute IV infusions of delafloxacin for 4 weeks

or females administered delafloxacin for 2 weeks prior to mating. (via an indwelling catheter).

- In up to the highest tested dose (120-mg/kg/day), delafloxacin reportedly had “no effect on male and female reproductive performance (mating, fertility, and conception), estrus, cyclicity, pre-coital interval, spermatogenic endpoints and the numbers of implantation sites, resorption sites, or viable embryos.”
- The NOAEL for reproductive was 120-mg/kg/day.

- **Embryo-Fetal Development**

- In their **pivotal embryo-fetal rat study**, the Applicant reportedly found “reversible dose-related fetal ossification delays of the caudal vertebrae, metatarsals, and phalanges” but “no teratogenic effects were observed [in] up to the highest dose tested, 1600-mg/kg/day” when pregnant rats were administered oral delafloxacin during the period of major organogenesis.
 - The Applicant reported maternal toxicity as decreases in maternal body weights and food consumption.
- Among **orally-delafloxacin dosed pregnant New Zealand White rabbits**, a species very sensitive to antibiotics, embryo-fetal developmental toxicity was not reportedly observed following the administration of oral delafloxacin doses shown to induce maternal toxicity. The Applicant stated, “No delafloxacin-related effects occurred in the numbers of implantation sites, resorption sites, or viable fetuses.”
 - Delafloxacin, reportedly, had no effect on body weight or on external, visceral, and skeletal development of the rabbit fetuses at doses of up to 1.6-mg/kg/day, the highest dose tested in the pivotal study.”

- **Prenatal and Postnatal Development and Maternal Function**

- **Decreases in F0 maternal body weights and food consumption** were reported as evidenced by the unkempt appearance of delafloxacin treated rats when compared to their control counterparts. Such findings correlated with increased numbers of early pup deaths during lactation and decreases in pup body weight.
- F1 offspring showed no changes in learning and memory, sensory function, locomotor activity, developmental landmarks, or reproductive performance even when receiving up to the highest tested dose of 120-mg/kg/day.
- The Applicant reports a NOAEL of 60-mg/kg/day for maternal (F0) systemic toxicity and related F1 neonatal/developmental toxicity. The reported NOAEL for F1 reproductive toxicity and F2 neonatal toxicity was 120-mg/kg/day.”

Medical Reviewer’s Comments: In animal studies, delafloxacin did not appear to impact either male or female fertility or embryo fetal development. Please consult the Pharmacology-Toxicology review for further details.

- **Juvenile Studies**

- Juvenile dogs orally administered delafloxacin up to the maximal tolerated dose of 320-mg/kg/day for 2-weeks, were not observed to display adverse effects, including arthropathy, in a dedicated juvenile study.
- The NOAEL in juvenile animals was 320-mg/kg/day.

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Medical Reviewer's Comments: *Earlier FQ were known to induce arthropathies in juvenile beagles. No such findings were observed in the delafloxacin dedicated canine juvenile study. However, there was a reported instance of a non-clinical*

4.5 Clinical Pharmacology

Section 4.5 highlights key features of delafloxacin pharmacokinetics (PK) and pharmacodynamics (PD). Please refer to the Clinical Pharmacology reviews authored by Drs. Kunyi Wu and Luning Zhuang for further details.

4.5.1. Mechanism of Action

Like other members of the fluoroquinolone class, delafloxacin inhibits DNA synthesis by targeting bacterial DNA gyrase and topoisomerase IV.

4.5.2 Pharmacodynamics

- **Exposure-Efficacy Response**
The murine-neutropenic thigh model for *S. aureus* and *E. coli* demonstrated a “high degree of target attainment observed with skin and wound isolates” at the to-be-marketed doses of delafloxacin. Similar to other FQs, the *free* AUC₂₄/MIC ratio is the PK/PD parameter was the best correlate of delafloxacin efficacy.
- **Exposure-Safety Response-QT Prolongation**
Non-clinical studies showed that delafloxacin had no activity on the hERG assay, the dog Purkinje study, or *in vivo* dog cardiovascular studies. A thorough QT (TQT) study (RX-3431-118) showed that delafloxacin is unlikely to cause QTc interval prolongation. Please refer to the Clinical Pharmacology review as well as Section 8.7 “Specific Safety Studies/Clinical Trials” of this review for further details on the TQT study (RX-3431-118).
- **Exposure-Safety Response-Phototoxicity**
According to the Applicant, both nonclinical and clinical studies demonstrated that delafloxacin has minimal potential to induce photosensitivity reactions. The results of M01-284, the dedicated phototoxicity study, are described in greater detail in Section 8.7 “Specific Safety Studies/Clinical Trials.”

4.5.3 Pharmacokinetics

The information contained in this section largely reflects the content of Module 2.7.2 Summary of Clinical Pharmacology.

- **Absorption**
 - According to the Applicant, delafloxacin is rapidly absorbed from the gastrointestinal (GI) tract, particularly following administration of the to-be-marketed 450-mg oral tablet formulation, which has a mean absolute bioavailability of 58.8%.
 - Delafloxacin’s overall clinical efficacy correlates with the *free* AUC/MIC ratio. Both of delafloxacin’s IV and oral to-be-marketed formulations are considered to be bioequivalent in relation to AUC. However, the C_{max} following oral administration is noted to be approximately 50% of the IV formulation’s C_{max}.
 - Delafloxacin can be administered with or without food.

- **Plasma Protein Binding**
 - In human plasma, delafloxacin binds to approximately 84% of protein, with albumin appearing to account for the majority of *in vitro* plasma protein binding.
 - A renal impairment study (RX-3341-110) demonstrated that plasma protein binding ranged from 84%, 80%, and 75% in healthy subjects, severely renally impaired subjects, and subjects with ESRD, respectively.
- **Distribution**
 - Following both IV and oral administration, delafloxacin was well distributed throughout the body with a **steady state volume of distribution (V_{ss})** of ~ 30 to 48 L (Module 2.7.2 Summary of Clinical Pharmacology).
- **Metabolism**
 - Unchanged delafloxacin is the primary metabolite circulating in plasma in humans, with over 80% of delafloxacin eliminated as unchanged drug following either IV or oral administration.
 - Metabolism is responsible for <20% of delafloxacin elimination.
 - **Direct glucuronidation** of delafloxacin is the major metabolic pathway in humans, as similarly reflected in non-clinical studies of rat and dogs.
 - Human radiolabeled ADME studies identified ester (M3 and M5) and ether 9M6A) glucuronides as the major metabolites of delafloxacin.
 - Metabolism of delafloxacin to glucuronides is primarily mediated by uridine diphosphate glucuronosyltransferase (UGT) UGT1A1, UGT1A3, and UGT2B15.
 - Cytochrome P450 metabolism is minimal in all three of the above-mentioned species.
- **Elimination**
 - Delafloxacin is **primarily eliminated by renal excretion**. However, elimination by biliary clearance and transintestinal elimination is also presumed.
- **Excretion**
 - An open-label radiolabeled ADME study in healthy human male volunteers, following a single 300-mg IV dose of ¹⁴C-labeled delafloxacin, demonstrated that 65% of radioactivity was **excreted unchanged in the urine** and 28% was **excreted unchanged in the feces**. Based on the findings of this study, the Applicant concluded that approximately half of the administered radioactivity was recovered from urine and feces within 24-hours of the infusion start (Module 2.7.2 Summary of Clinical Pharmacology).
 - Following a 200-mg oral dose of ¹⁴C-delafloxacin, the mean dose of unchanged drug recovered in the urine was 50% and likewise, the mean dose of unchanged delafloxacin eliminated in feces was 48%.
- **Intrinsic Factors**
Age, gender, sex, race, obesity, hepatic impairment
 - Clinical pharmacology studies or population PK analyses failed to demonstrate any clinically significant effects of delafloxacin on subject age, gender, sex, race, body weight (obesity), disease (ABSSSI), or hepatic impairment.
 - *Hepatic Impairment:* In ML-3341-112, the Applicant's dedicated hepatic impairment study, the Applicant determined that total delafloxacin exposure (AUC) in subjects with mild, moderate, and severe hepatic impairment increased by 1.1-fold, 1.1-to 1.2-fold, and

1.1- to 1.4-fold, respectively. Either no change (mild impairment) or just slight reductions (10% for moderate impairment and 8% for severe impairment) were observed in the C_{max} of hepatically impaired subjects. Based on these findings, the Applicant determined that no dose adjustments were required for subjects with mild, moderate or severe hepatic impairment (as defined by Child-Pugh categorization).

Medical Reviewer's Comments: For further commentary on ADME studies and the impact of a patient's intrinsic factors, the reader is referred to the Clinical Pharmacology review.

Renal Impairment

Protocol RX-3341-110 was the Applicant's dedicated renal impairment study. Please refer to Section 8.7 Specific Safety Studies of this review and the Clinical Pharmacology review for further details. Otherwise, based on pre-specified eligibility criteria limited numbers of subject with severe and ESRD were enrolled in either of the Applicant's pivotal Phase 3 trials.

Delafloxacin

- According to the Applicant, following administration of a single 300-mg IV infusion of delafloxacin, delafloxacin's total exposure (AUC) was observed to increase with worsening renal impairment.
- They further reported that, compared to subjects with normal renal function, the "delafloxacin AUC to the last observable concentration at time t (AUC_t) values" were 2.1-, 3.5-, and 4.1-fold higher, respectively, for severely renally impaired subjects and subjects with kidney failure who were either receiving or not receiving HD.
- After a single IV infusion, "mean C_{max} values for the severe renal impairment group and the ESRD group with or without HD were 2.1-, 5.9-, and 6.4-fold higher, respectively," when compared with their counterparts with normal renal function.
- Following administration of 400-mg oral delafloxacin, observed AUC_t values in the moderate and severe renal impaired groups were approximately 1.5-fold higher than the normal renal function group.
- Following administration of a single 300-mg IV infusion of delafloxacin and of a single oral (450-mg) dose, renal clearance of delafloxacin was decreased among subjects in the mild, moderate, and severe impairment groups when compared with those subjects in the normal renal function group.
- The Applicant additionally observed that "the clearance of delafloxacin in dialysate was 4.21 L/h with 19.2% of IV (300-mg) delafloxacin removed during a 4-hour period of HD."

Sulfobutylether Beta-Cyclodextrin (SBE β CD)

- SBE β CD (Captisol®) (b) (4) whose plasma clearance is reduced with worsened renal function. A 300-mg IV infusion of delafloxacin is delivered with 2,400-mg of Captisol®.
- Mean SBE β CD AUC_t was observed to be 5-fold higher in the severe renal impairment group relative to in the normal renal group, whereas, following delafloxacin IV administration, the AUC_t for the ESRD group (with and without HD) increased 30-fold higher.
- SBE β CD is cleared from dialysate with 56.1% of the dose being removed in dialysate over a 4-hour HD session with a mean CI of 4.74 L/hr.

Medical Reviewer's Comments: Although renal function in both of the Applicant's pivotal Phase 3 trials was calculated using the Cockcroft-Gault (CG) equation (creatinine clearance, CrCl), the estimated glomerular filtration rate (eGFR) was used to determine renal function in their dedicated renal

impairment study. The Modification of Diet in Renal Disease (MDRD) equation, from which the eGFR is derived, is recommended for the calculation of subjects' renal function in the Applicant's proposed label.

In their original proposed label, the Applicant suggested similar delafloxacin dosing for patients with mild (eGFR 60-89 mL/min/1.73m²) to moderate (eGFR 30-59 mL/min/1.73m²) renal impairment, as that for persons with normal renal function: 300-mg IV every 12 hours or 450-mg oral tablet every 12 hours. However, for patients with severe renal impairment (eGFR 15-29 mL/min/1.73m²), the Applicant originally proposed dosing delafloxacin at 200-mg IV every 12-hours (b) (4). Recommended dosing for kidney failure (including persons with ESRD) (eGFR <15 mL/min/1.73m² with or without HD) (b) (4).

The Clinical Pharmacology reviewers, Drs. Kunyi Wu and Ada Luning, conducted simulations, based on population PK models, across all renal functions using the Applicant's proposed IV dosing of delafloxacin 300-mg IV twice daily. They predicted that patients with mild to moderate renal impairment would have 1.1-fold and 1.3-fold higher AUCs when compared with persons with normal renal function (renal function ≥90). In contrast, persons with moderate, severe and ESRD (without HD) were predicated to have AUCs 1.3-, 1.6-, and 2.1-fold higher than their non-impaired counterparts. Similarly, when conducting simulations with the Applicant's proposed oral dosage, across all renal functions, persons with moderate, severe, and ESRD (without HD) were anticipated to have elevated AUCs similar to those observed with the IV formulation. For further details, this reviewer refers you to the Clinical Pharmacology review.

Albeit, there were limited numbers of subjects in the Applicants pivotal Phase 3 trials, despite having higher overall exposure (AUCs) to delafloxacin, subjects with moderate renal impairment did not appear to have any increased safety findings upon receipt of IV delafloxacin. There were too few subjects with severe or ESRD who were administered IV delafloxacin to make a definitive conclusion on the safety of this drug in this sub-group of patients. For this reason this reviewer believes a PMC may be required to study any findings in this sub-population. Please see Section 8.7 of this review for further commentary. It is noted that no studies were conducted in which subjects with renal impairment were treated solely with the oral tablet formulation of delafloxacin. Based on the above-described PK information and the paucity of information to substantiate the safety of delafloxacin in persons with severe renal impairment or ESRD, the Clinical Pharmacology team has proposed that both IV and oral delafloxacin not be recommended in patientss with kidney failure (eGFR <15 mL/min/1.73m²) regardless of whether they are on HD or not. For persons with severe renal impairment, they recommend delafloxacin 200-mg IV every 12 hours or 450-mg by mouth every 12 hours in addition to closely monitoring serum creatinine levels and eGFR while being administered delafloxacin. For more details, please refer to the Clinical Pharmacology review.

- **Extrinsic Factors**

- *Drug-Drug Interactions (DDI)*

- *In vitro* studies conducted by the Applicant purportedly demonstrated that, at clinically relevant concentrations, delafloxacin was not shown to inhibit ligand binding of receptors for gamma-aminobutyric acid (GABA), benzodiazepine (BZD), *N*-methyl D-aspartate (NMDA), adenosine, or acetylcholine. For example, BZD and GABA_A receptors were inhibited 47%-to 59% at 100 μM after IV dosing in humans; whereas, the mean C_{max} plasma concentration of delafloxacin was 9.29 μg/mL and, after accounting for 84% protein binding of the drug, 1.49 μg/mL. These concentrations are well below 100 μM (44.1 μg/mL), the required concentration to inhibit BZD and GABA receptors.
- Delafloxacin was not shown to inhibit CYP450 isozymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4/5 activities at 300-500 μM, concentrations well-above the delafloxacin C_{max} of 300-

mg every 12 hours and 450-mg by mouth every 12 hours. Based on this, the Applicant anticipates no clinically significant drug-drug interactions (DDI) resulting from the inhibition or activation of CYP isozymes with co-administration of delafloxacin with drugs metabolized by CYP isozymes.

- *In vitro* studies indicated that delafloxacin is a substrate of BCRP and a potential substrate of P-gp. However, the Applicant anticipates that the likelihood of clinically significant interactions between delafloxacin and inhibitors of breast cancer related protein (BCRP), or P-gp are minimal and would most likely lead to modest increases in the delafloxacin C_{max}.
- An *in vivo* DDI study showed that after multiple doses of delafloxacin 450-mg every 12 hours and a single oral dose of midazolam (5-mg) had no effect on midazolam PK, indicating that delafloxacin is not a CYP3A inducer.
- In addition, the Applicant conducted studies which demonstrated that delafloxacin is not an inhibitor of human P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 and BSEP-mediated transport.

4.6 Devices and Companion Diagnostic Issues

Not applicable

5 Sources of Clinical Data and Review Strategy

5.1 Table of Clinical Studies

Table 3 contains a summary of the two pivotal Phase 3 trials and the two key Phase 2 trials, all four of which support delafloxacin's safety profile.

Table 1: Summary of the Two Pivotal Phase 3 Trials and the Two Key Phase 2 Trials

Trial	Phase	Trial Design	Regimen/ Schedule/Route	Treatment Duration/ Follow-Up	Study Endpoints	Number of Patients Enrolled	Study Population	Number of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
Protocol 302: (IV ONLY)	3	Randomize d, double-blind, multicenter, active-comparator trial	Delafloxacin: Delafloxacin 300-mg IV every 12 hours Comparator: Vancomycin 15-mg/kg IV every 12 hours ± aztreonam 2 gm every 12 hours	<ul style="list-style-type: none"> • Treatment: 5-14 days, at investigator discretion • Follow-up (FU): Day 14 ± 1 day, after treatment initiation • Late Follow-Up (LFU): Days 21- 28, after treatment initiation • Follow-Up Call: 30 days after final study drug dose 	Primary: ≥20% reduction in lesion erythema at 48 to 72 hours, ITT analysis population	<p>N= 660 patients</p> <p>n = 331 patients in delafloxacin arm</p> <p>n = 329 patients in vancomycin ± aztreonam arm</p>	<p>ITT analysis set: 660</p> <p>Safety analysis set: 650</p>	34 clinical centers North America: 15 sites Europe: 19 sites
Protocol 303: (IV to ORAL switch)	3	Randomize d, double-blind, multicenter, active-comparator trial	Delafloxacin: Delafloxacin 300-mg IV every 12 hours Comparator: Vancomycin 15-mg/kg IV every 12 hours ± aztreonam 2 gm every 12 hours	<ul style="list-style-type: none"> • Treatment: 5-14 days, at investigator discretion • Follow-up (FU): Day 14 ± 1 day, after treatment initiation • Late Follow-Up (LFU): Days 21- 28, after treatment initiation • Follow-Up Call: 30 days (+ 3 days) after final study drug dose 	Primary: ≥ 20% reduction in lesion erythema at 48 to 72 hours, ITT analysis population	<p>N= 850 patients</p> <p>n = 423 patients in delafloxacin arm</p> <p>n = 427 patients in vancomycin + aztreonam arm</p>	<p>ITT analysis set: 850</p> <p>Safety analysis set: 842</p>	76 clinical centers North America: 21 sites Europe and Central Asia: 32 sites Latin America: 14 Sites Asia: 9 sites
Studies to Support Safety (in addition to Phase 3 Trials)								
Protocol 201: (IV ONLY)	2	Randomize d, double-blind, multicenter, active-	Delafloxacin: Delafloxacin 300-mg IV every 12 hours	<ul style="list-style-type: none"> • Treatment: 5-14 days, at investigator discretion End of Treatment (EOT): at least 12 	Primary: Investigator assessment of signs and symptoms of	<p>N=150 patients</p> <p>Delafloxacin 300-mg IV: n=49</p> <p>Delafloxacin 450-mg</p>	<p>ITT analysis set: 150</p> <p>Safety</p>	14 U.S. clinical centers

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5.2 Review Strategy

Dr. Caroline J. Jjingo was the primary clinical reviewer evaluating the clinical efficacy and safety of the delafloxacin new drug application (NDA) for the treatment of ABSSSIs.

The clinical review of efficacy was based upon the review and analysis of the Applicant's two pivotal Phase 3 trials, RX-3341-302 and RX-3341-303. The clinical reviewer collaborated extensively with the clinical pharmacology reviewers, Drs. Kunyi Wu and Luning Zhuang; the microbiology reviewer, Dr. Jalal Sheikh; and the biostatistical reviewer, Dr. Janelle Charles during the review process. Additional interactions occurred between the clinical reviewer and the pharmacology/toxicology reviewer, Dr. Amy Nostrandt, and the CMC reviewer, Dr. Danuta Gromek-Wood. A summary of the principle highlights of each review discipline is provided in Section 4 of this review. However, for a more detailed description of each discipline's assessments, please refer to the reviews completed by the appropriate review team.

The efficacy review will be a focused discussion of the following: (a) the primary clinical efficacy endpoint for the two pivotal Phase 3 trials (objective response of 20% reduction of erythema at 48 to 72 hours); (b) secondary endpoints, namely clinical cure, success and failure at the FU and the LFU visits; (c) the clinical outcome by subjects infected with key target Gram positive and Gram-negative pathogens; and (d) cure rates in key sub-groups. For a description of additional statistical analyses, the clinical reviewer refers the reader to the statistical review authored by Dr. Janelle Charles.

The clinical safety review is based largely on review of the four aforementioned clinical studies, in addition to review of any salient safety findings contained in the Applicant's earlier Phase 1 trials. Pooled safety data from the pivotal Phase 3 trials, RX-3341-302 and RX-3341-303 formed the basis of the integrated safety population. Due to differences in the comparator arms and primary efficacy endpoints, the two Phase 2 clinical trials were analyzed separately from each other and from the pivotal Phase 3 trials. Treatment emergent adverse reactions and any notable adverse reactions found in earlier Phase 1 and 2 trials and the pivotal Phase 3 trials formed the basis of delafloxacin's safety profile. Dr. Jjingo primarily utilized the reviewer's software JReview and MAED to conduct the safety analyses presented in this review. When necessary, analyses conducted by the Applicant are identified in this review.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1 Trial 302 Study Design

Overview and Objective

RX-3341-302 was a Phase 3 randomized, double-blind, multicenter, active-comparator trial evaluating the safety and efficacy of delafloxacin. The primary FDA objective was the assessment of an objective clinical response following 5-14 days of intravenous (IV) delafloxacin compared with IV vancomycin (\pm IV aztreonam) in the treatment of adult patients aged 18 and older with ABSSSI.

Trial Design

Basic Study Design

RX-3341-302 was a randomized, double-blind, multicenter, Phase 3 pivotal non-inferiority trial evaluating the clinical efficacy and safety of IV delafloxacin compared with vancomycin ± aztreonam in adult patients with ABSSSIs. The switch to oral therapy was not permitted in either treatment arm.

Study enrollment commenced on 25 April 2013 and was completed on 6 June 2014. Enrollees were recruited from 34 clinical centers located in seven different countries: Croatia, Hungary, Israel, Latvia, Spain, Ukraine, and the United States. Subjects were subsequently grouped according to geographical regions: (a) North America and (b) Europe, with Israel categorized within the European geographical region.

Eligible, consenting patients were randomly assigned, in a 1:1 ratio to receive either delafloxacin 300-mg IV every 12 hours + placebo **or** vancomycin 15-mg/kg IV every 12 hours (based on actual body weight) ± aztreonam 2 gm every 12 hours. Placebo and aztreonam were discontinued if baseline cultures were demonstrated to be negative for gram-negative organisms. Subjects were stratified according to one of the following four primary ABSSI infection types:

- **Cellulitis/erysipelas:** A diffuse skin infection characterized by spreading areas of redness
- **Wound infection:** An infection characterized by purulent draining from a traumatic or surgical wound
- **Major cutaneous abscess:** An infection characterized by a collection of pus within the dermis or deeper
- **Burn infections:** An infection characterized by purulent drainage and redness and accounting for <10% of burn victim's body surface area.

Moreover, the study was designed such that:

- **No more than 25%** of enrollees were to have **major cutaneous abscesses**
- **No more than 35%** of enrollees were to have **wound infections**
- There were **no limitations on the enrollment of patients with** the remaining infection types (**cellulitis/erysipelas or burn infection**)
- **No more than 25%** of all enrollees were to have **received treatment for ABSSI** in the **preceding 14 days**

RX-3341-302 was divided into 3 study periods:

- **Screening** (Days -1 to 1)
- **Treatment period** (Days 1 to 14), including end of treatment (EOT)
- **Follow-up period**, including a:
 - *Follow-Up visit* (Day 14 ± 1 day)
 - *Late Follow-Up (LFU) visit* (Days 21 to 28)
 - *Follow-Up Call* (30 days after final study drug dose), intending to capture 28-day mortality, AEs, and post-treatment medications

Key Inclusion/Exclusion Criteria

Eligible prospective enrollees were males and non-pregnant, non-lactating females aged 18 years of age and older who met such **key inclusion criteria** as having a primary infection from one of the four above-mentioned designated ABSSSI infection types, all of which were characterized by “a minimum surface area of 75 cm²” with surrounding erythema. In addition, subjects were to demonstrate *at least 2* of the following signs of systemic infection:

- Lymph node enlargement due to the present infection
- Documented fever $\geq 38^{\circ}\text{C}/100.4^{\circ}\text{F}$ taken orally (or the equivalent value for the temperature recording method used)
- Lymphangitis
- Elevated white blood cells (WBCs) of $\geq 10\,000$ cells/ μL in the 48 hours prior to first dose of study drug
- Elevated C-reactive protein ($>10 \times$ upper limit of normal [ULN]) in the 48 hours prior to first dose of study drug
- Purulent or seropurulent drainage or discharge

Key exclusion criteria included the exclusion of individuals with:

- Any chronic or underlying skin condition at the site of infection that might complicate the assessment of response (eg, atopic dermatitis or eczema). Any other skin condition that, in the opinion of the investigator, would interfere with objective measurement of the ABSSSI under treatment.
- Infection associated with a prosthetic joint or the removal of a prosthetic joint, or infection involving other prosthetic materials or foreign bodies (eg, catheter tunnels) unless that other prosthetic material was removed within 24 hours after starting study drug.
- Infection associated with any of the following:
 - Human or animal bite (insect bites were not considered animal bites)
 - Osteomyelitis
 - Decubitus ulcer
 - Diabetic foot ulcer
 - Septic arthritis
 - Mediastinitis
 - Sternal wound
 - Necrotizing fasciitis, anaerobic cellulitis, or synergistic necrotizing cellulitis
 - Myositis
 - Tendinitis
 - Endocarditis
 - Toxic shock syndrome
 - Sustained shock (blood pressure <90 mm Hg for >2 hours despite adequate fluid resuscitation, with evidence of hypoperfusion or use of sympathomimetic agents to maintain blood pressure)
 - Gangrene or gas gangrene
 - Burns covering $\geq 10\%$ of body surface area

- Severely impaired arterial blood supply to an extremity with an ABSSSI (a patient with a palpable distal pulse or an audible distal pulse by Doppler could have been enrolled)
- Current evidence of deep vein thrombosis or superficial thrombophlebitis
- Any infection types with poor circulatory status in the opinion of the investigator
- Minor abscesses, unless present with 1 of the 4 acceptable types of ABSSSIs.
- Any infection expected to require other systemic antibacterial agents in addition to study drug.
- Receipt of systemic antibiotic therapy within 14 days *unless* any of the following was documented:
 - The patient received *at least* 48 hours of antibiotic therapy for ABSSSI AND the clinic notes or photographs documented the clinical progression of ABSSSI (ie, not by patient history alone).
 - The patient recently (within 7 days) completed a treatment course with an antibacterial drug for an infection other than ABSSSI and the drug did not have activity against bacterial pathogens that cause ABSSSI.
 - The patient received only 1 dose of either a single, potentially effective, short-acting (half-life ≤ 12 hours) antimicrobial drug or a short-acting antimicrobial drug regimen for treatment of the ABSSSI under study before enrollment. (Note: 1 dose of a regimen was defined as the standard therapy for ABSSSI at the study site.)
 - Patients who received 1 dose of either a single, potentially effective, short-acting antimicrobial drug or regimen for treatment of the ABSSSI under study in the 14 days before study entry were limited to no more than 25% of total randomly assigned patients.
- Known history of Child-Pugh Class B or C liver disease.
- Alanine aminotransferase (ALT) $>3 \times$ ULN.
- Patients with end-stage renal disease on hemodialysis or peritoneal dialysis or creatinine clearance (CrCl) of ≤ 30 mL/minute using the Cockcroft-Gault (CG) formula
- Body weight >140 kg (308-lbs)

Medical Reviewer Comments:

*RX-3341-302 was initially designed to reflect the recommendations of the 2010 FDA ABSSSI Guidance for Industry which represented a departure from the earlier 1998 guidance's categorization of skin and skin structure infections as either complicated or uncomplicated SSSIs. The 2010 guidance inaugurated the use of the term ABSSSI which encompassed the aforementioned types of skin infections all of which were characterized by a minimal surface area of 75 cm² with surrounding redness, edema and/or induration. Many of the clinical trial design issues discussed in the 2008 AC were incorporated into the 2010 guidance, including the early clinical response endpoint of "cessation of the spread of the redness, edema, and/or induration of the lesion or reduction in the size (length, width, and area) of redness, edema, and/or induration at 48 to 72 hours after enrollment **and** resolution (absence) of fever," an NI margin of 10%. The 48 to 72 hour time point was selected based on historical evidence demonstrating that antimicrobial therapy versus historical control (i.e. UV light) resulted in significant resolution in the spread of the skin lesion and in fever within 48 hours (Food and*

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Drug Administration Guidance for Industry Acute Bacterial Skin and Skin Structure Infections; August 2010).

*In 2013, FDA issued a revised ABSSSI Guidance for Industry in which the primary FDA efficacy endpoint was now “based on the percent **reduction** in the lesion size at 48 to 72 hours compared to baseline, measured in patients who did not receive rescue therapy and are alive.” The 2013 revised primary endpoint no longer considered cessation of spread or resolution of fever as necessary elements in the definition of a clinical cure. RX-3341-302 study design, primary endpoint, NI and key eligibility criteria are in accordance with the 2013 ABSSSI Guidance for Industry.*

Dose Selection:

The Applicant explained that the delafloxacin dose of 300-mg IV administered every 12 hours was selected based on previous MRSA MIC₉₀ data; Phase 1 PK data; PK and pharmacodynamic (PD) data from murine neutropenic thigh infection models; clinical PK/PD modeling; and the Phase 2 trial, RX-3341-202, whereby subjects receiving 300-mg IV mg every 12 hours were observed to have exposures which exceeded those necessary for efficacy in an MRSA neutropenic murine-thigh infection.

Medical Reviewer’s Comments:

Please refer to the Clinical Pharmacology Review, authored by Drs. Kunyi Wu and Ada Luning for further details on how PK/PD data was used to determine delafloxacin dosing.

Study Treatments

Assignment to Treatment/Blinding

An independent statistician created randomization codes which were entered into an interactive web response system (IWRS) and were subsequently obtained from an unblinded pharmacist/study designee responsible for administering the randomly assigned treatment. Those subjects randomized to the comparator arm were initially administered vancomycin in combination with IV aztreonam 2-gm IV every 12 hours. However, if baseline cultures failed to identify a gram-negative organism, IV aztreonam was discontinued. Those subjects assigned to the delafloxacin arm were administered a blinded placebo infusion alongside IV delafloxacin so as to maintain blinding. This placebo infusion was discontinued if a subject’s baseline cultures (blood or skin) did not identify a gram-negative organism.

Enrolled subjects were to receive, at investigator discretion, 10 to 28 doses (or 5 to 14 days) of study drug.

For subjects in the vancomycin arm, vancomycin therapeutic dose monitoring (TDM) was conducted, at all study sites, on Days 2 (+1 day) and 6 (± 1 day). Dose adjustments were conducted by an unblinded pharmacist (or study designee) who was privy to vancomycin TDM results on Days 3 and 7 (± 1 day) to maintain trough concentrations between 15-20 µg/mL.

Medical Reviewer’s Comments:

The study design ensured adequate blinding of treatment arms.

Procedures and schedule

A schedule of activities conducted under RX-3341-302 is found in **Table 4**.

Table 4: Trial RX-3341-302 Schedule of Events

Assessment or Procedure	Screening	Treatment Period						End of Treatment	Follow-up	Late Follow-up	Follow-up Call	
		-1 to 1	1	2	3	4	5					6-14
Study Day												
Informed consent	X											
Verify entry criteria	X											
Demographic data/Medical history	X											
Prior medications	X											
Local laboratory tests for eligibility	X											
Pregnancy test (local laboratory)	X							X	X			
Hematology, serum chemistry, urinalysis (central laboratory)	X			X			X	X	X	X		
Vital signs	X	X				X		X	X	X		
12-lead electrocardiogram	X											
Body temperature	X	X	X	X	X			X	X	X		
Complete physical examination with height and weight	X											
Targeted physical examination						X			X	X		
Clinical infection site signs and symptoms	X	X	X	X	X	X	X	X	X	X		
Digital photography and manual measurements for demarcation of ABSSSI	X	X	X	X	X			X	X	X		
Document surgical procedures	X	X	X	X	X	X	X		X	X		

Assessment or Procedure	Screening	Treatment Period						End of Treatment	Follow-up	Late Follow-up	Follow-up Call
		1	2	3	4	5	6-14				
Study Day	-1 to 1	1	2	3	4	5	6-14	5-14	14 ± 1	21-28	30 days (+3 days) after last dose
ABSSSI specimen for microbiologic culture and local Gram stain	X										
Blood culture	X										
Randomization by IWRS	X										
Notify IWRS of continued treatment status						X					
Contact IWRS to report treatment completion status on last day of treatment								X			
Study drug administration every 12 ± 2 hours		X	X	X	X	X	X				
Investigator assessment of clinical response								X	X	X	
Concomitant medications		X	X	X	X	X	X	X			
Pain assessment	X	X	X	X	X	X	X	X	X	X	
Assess AEs	X	X	X	X	X	X	X	X	X	X	X
PK sampling				X							
Glucose monitoring				X							
Vancomycin therapeutic drug monitoring			X				X				
Adjust vancomycin dose level or duration of treatment, as necessary				X			X				
Posttreatment medications									X	X	X

Assessment or Procedure	Screening	Treatment Period						End of Treatment	Follow-up	Late Follow-up	Follow-up Call
		1	2	3	4	5	6-14				
Study Day	-1 to 1	1	2	3	4	5	6-14	5-14	14 ± 1	21-28	30 days (+3 days) after last dose
<p>Abbreviations: ABSSSI: acute bacterial skin and skin structure infections; IWRS: interactive web response system; PK: pharmacokinetic.</p> <p>Source: Table 9-2, Trial RX-3341-302 Clinical Study Report</p>											

Notable procedures included:

- Screening occurred within 24 hours of the first dose. The first dose could have been administered on the same day as Screening.
- The following laboratory tests were collected to determine patient eligibility and were performed by a local laboratory: pregnancy test, serum chemistry (including CrCl), hematology (inclusive of white blood cell count with differential, prothrombin time, and international normalized ratio), and a standard serum C-reactive protein test, to assess for systemic inflammation.
- Investigator’s assessment of clinical response was performed at 48 to 72 hours (± 2 hours), the End-of-Treatment Visit, the Follow-Up Visit, and the Late Follow-up Visit.
- Blood samples for PK and intensive glucose analyses were obtained from patients at select sites (~50% of subjects) on Day 3 (± 1 day) of treatment within 30 minutes before the first study drug administration and at 1.5 and 3 hours after the first study drug administration.
- Microbiologic cultures of the primary infection site could be obtained in the following ways: for cellulitis/erysipelas punch biopsy or aspirate of erythematous area; biopsy, needle aspiration, or surgical specimen of purulent material from a burn or wound infection; aspirate of purulent material from a cutaneous abscess; swab of drainage collected from deep cavity of a post-incision and drainage wound, abscess, or burn infection.

Adjunctive Therapies/ Concomitant Medications

Trial RX-3341 302 permitted the use of adjunctive therapies, including: daily dressing changes to infected site provided that dressings contained neither topical solutions nor antibacterial properties; the use of local anesthetics, packing, irrigation with normal saline; and elevation of affected body part. The application of silver coated/impregnated dressings to the affected area was also permitted during the study. While unplanned incision and drainage, major debridement procedures, and other major surgical procedures on the ABSSSI area were **not** permitted, minor bedside debridement procedures and/or vacuum-assisted wound closure were permitted.

Subjects were permitted to receive short-acting antipyretics (i.e., nonsteroidal anti-inflammatory drugs, acetaminophen/paracetamol). Unless otherwise indicated, concomitant antimicrobial

treatments were prohibited. Any medications used 14 day prior to Screening, including dietary supplements and non-prescription drugs, were documented in each subject’s eCRF. Any antibacterial treatments administered within 30 days prior to first dose of study drug were also documented.

Compliance

Compliance with study medication was ascertained through review of drug administration records and, for those subjects receiving oral tablets, by mouth check to ensure each subject swallowed the study drug.

Subject completion, discontinuation, or withdrawal

Key study drug discontinuation criteria were:

- Subject received a concomitant medication that could potentially interfere with the study objective/assessments and/or patient safety.
- Subject developed a blood glucose value of <40 mg/dL at any time during the study.
- Subject experienced an intolerable AE
- Subject experienced LFT elevations of >5x ULN or a total bilirubin of > 3 x ULN.
- Failure to comply with inclusion/exclusion criteria

Subjects who failed study treatment during the study period, and thereby required an alternative antimicrobial agent, were permitted to complete End-of-Treatment (EOT) assessments and procedures. However, they were not expected to return for any further study visits.

Subjects who prematurely withdrew from the study prior to study completion were encouraged to return for follow-up safety evaluations.

Study Endpoints

The applicant devised 2 separate primary efficacy endpoints to satisfy the FDA and EMA, respectively, the U.S. and European regulatory approval agencies.

- **Primary FDA efficacy endpoint: Objective response assessed at 48 to 72 hours** (± 2 hours) after initiation of treatment, whereby a subject could either be classified as either: (a) having a clinical response, and hence be deemed a responder, or (b) as having a clinical failure, and be deemed a non-responder. **Table 5** below provides the applicant’s definition of a clinical response/responder and a clinical failure/non-responder.

Table 5: FDA Primary Efficacy Endpoints

Objective Response at 48 to 72 hours in the ITT analysis set	
Clinical Response	Clinical Failure
(a) A ≥20% reduction of the ABSSSI lesion spread of erythema area as determined by digital planimetry of the	(a) A <20% reduction of the ABSSSI lesion spread of erythema area as determined by digital planimetry of the leading edge at the assessment made at 48 to 72 hours (± 2

leading edge	hours) after initiation of study drug.
(b) The subject experienced none of the reasons given for clinical failure.	(b) Administration of rescue antibacterial drug therapy or administration of non-study antibacterial drug therapy for treatment of the ABSSSI before the primary efficacy endpoint assessment at 48 to 72 hours (± 2 hours)
	(c) Need for unplanned surgical intervention except for limited bedside debridement and standard wound care before the primary efficacy endpoint assessment at 48 to 72 hours (± 2 hours)
	(d) Death by 74 hours after initiation of study drug

Source: RX-3341-302 Clinical Study Report Section 9.7.1.8.1.1 Objective Response (Including Primary Efficacy Endpoint for FDA Submission)

Any subject for whom digital planimetry was unavailable at **48 to 72 hours (± 2 hours)** was classified as “missing” and subsequently deemed a clinical failure/non-responder in the ITT primary analysis. Subjects were analyzed according to the treatment group to which they were randomly assigned.

Medical Reviewer’s Comments:

The Applicant’s timing of the primary efficacy endpoint, 48 to 72 hours, is consistent with the 2013 FDA ABSSSI guidance. Digital planimetry was used in the determination of the objective response assessment. Digitally obtained images of each lesion’s total area of erythema and induration were analyzed independently by [REDACTED] ^{(b) (4)} a third party company which provides digital photography for clinical trials. It is noted, however, that digital measurements were based on contour lines of the lesion’s surface area of erythema/induration, as traced by the site investigator. Such a measure may not obtain total objectivity depending on external variables that may affect the quality of the digital photography. Manual measurements, “using the longest perpendicular width of erythema and induration,” were also obtained by the site investigator.

- **Microbiologic Assessment.** Microbiologic response was assessed using both the microbiologically evaluable (ME) and the MITT analysis sets according to baseline and post-baseline culture results through FU and LFU visits, susceptibility testing, and investigator assessed clinical response. Microbiologic response was evaluated at both the patient and the pathogen levels at the FU and LFU visits. Responses were classified as follows in **Table 6**:

Table 6: Investigator-Assessed Response of Signs and Symptoms of Infection

Microbiological Efficacy Response		Definition
Cure	Documented Eradicated	The baseline pathogen was absent in cultures of the original site of infection at the visit. Investigator-assessed response was not considered a determining factor for this microbiologic response definition.
	Presumed Eradicated	There was no material available for culture and the patient had an investigator-assessed response of success.
Failure	Documented Persisted	The baseline pathogen was present in cultures of the original site of infection at the visit. Investigator-assessed response was not considered a determining factor for this microbiologic response definition.
	Presumed Persisted	There was no material available for culture and the patient had an investigator-assessed response of failure (where failure included investigator assessment of failure + indeterminate or the assessment was missing). In the clinically evaluable (CE) and ME analysis sets, indeterminate and missing were excluded.
Emergent Infections	Superinfection	A new pathogen known to cause ABSSSI was cultured from the original site of infection in the presence of signs and/or symptoms of infection during treatment.
	New Infection	A new pathogen known to cause ABSSSI was cultured from the original site of infection in the presence of signs and/or symptoms of infection after treatment.

Source: RX-3341-302 Clinical Study Report Section 9.7.1.8.1.4 Microbiological Efficacy Response Definitions

Medical Reviewer’s Comments:

For discussion of the Microbiologic Efficacy Response the reader is referred to the Clinical Microbiology review authored by Clinical Microbiologist, Dr. Jalal Sheikh.

Secondary Endpoints

If the applicant achieved non-inferiority at the primary efficacy endpoint, secondary efficacy endpoints were assessed for superiority using a hierarchical testing strategy. Ordered hierarchically, **key** FDA secondary endpoints are listed below:

- **Secondary Endpoint # 1:** Investigator-assessed response of signs and symptoms of infection at the FU visit (Day 14 ± 1) (EMA primary endpoint)
- **Secondary Endpoint # 2:** Investigator-assessed response of signs and symptoms of infection in patients with baseline BMI ≥30 kg/m² at the FU visit
- **Secondary Endpoint # 3:** Investigator-assessed response of signs and symptoms of infection at the LFU visit (Day 21 to 28)
- **Secondary Endpoint # 6:** Investigator-assessed response of success (defined as a response of cure or improved) of signs and symptoms of infection at the FU visit (Day 14 ± 1) where no further antibiotic was required

“Investigator-assessment of signs and symptoms of infection” was classified as cure, improved, success, failure or indeterminate, all of which are further defined in **Table 7** below.

Table 7: Investigator-Assessed Response of Signs and Symptoms of Infection

Investigator-assessed response	Definition
Cure	The complete resolution of all baseline signs and symptoms of ABSSSI at EOT, FU, and LFU visits; however, if erythema was the only sign of infection remaining at EOT or FU visit, and the erythema was absent at LFU visit, then the case was classified as a cure at EOT (derived), FU (derived), and LFU visits.
Improved	Some symptoms remained, but the patient was improved to an extent that no additional antibiotic treatment was necessary. Conservatively, improved responses were considered failures in the primary analysis, except in analyses where success denoted cure or improved.
Success	A response of cure or improved where the investigator felt that no further antibiotics were needed.
Failure	Response was classified as failure for any of the following reasons: (a) administration of non-study antibacterial drug therapy was required because of lack of efficacy after at least 4 doses of study drug or for a treatment-related AE; (b) study antibacterial drug therapy was required for longer than 28 doses;

	<p>(c) and/or unplanned surgical intervention was needed after study entry except for limited bedside debridement and standard wound care.</p> <p>Note: If a patient was considered a failure at FU visit, then the patient was also considered a failure at LFU (derived). A missing response was classified as failure in the ITT and MITT analysis sets and excluded from the CE and ME analysis sets.</p>
<p>Indeterminate</p>	<p>A response could not be assigned because an assessment was not completed at the FU or LFU or because the patient received potentially effective non-study antibacterial drug therapy for treatment of a condition other than ABSSSI unless that patient was a failure.</p> <p>Indeterminate responses were considered failures in the ITT and MITT analyses and were excluded from the CE and ME analysis sets.</p>

Source: RX-3341-302 Clinical Study Report Section 9.7.1.8.1.3 Investigator-Assessed Response of Signs and Symptoms of Infection

Statistical Analysis Plan:

RX-3341-302 was designed to demonstrate delafloxacin’s non-inferiority against its comparator vancomycin (± aztreonam) at the FDA primary efficacy endpoint of “objective response of ≥ 20% reduction in baseline lesion size erythema at 48 to 72 hours (± 2 hours) after treatment initiation using digital planimetry.” The primary efficacy analysis was performed using the ITT analysis set. The NI margin was set at 10%, based on the assumption that subjects in the vancomycin (± aztreonam) arm would have a 78% response rate. The applicant determined that a sample size of 660 subjects (330 subjects per group) was required to provide greater than 90% power in establishing delafloxacin’s non-inferiority relative to vancomycin (± aztreonam). If the NI margin was met at the primary efficacy endpoint, then superiority of all secondary hypotheses, using a hierarchical testing strategy, was conducted. Delafloxacin was deemed superior to vancomycin + aztreonam if “the upper limit (UL) CI was less than 0.”

Medical Reviewer’s Comments:

The proposed non-inferiority margins were consistent with the FDA 2013 ABSSSI Guidance for Industry. For further commentary on the justification of NI margins the reader is referred to the statistical review authored by Biostatistical Reviewer, Dr. Janelle Charles.

Analysis Sets

Six distinct analysis sets were utilized when analyzing primary and secondary efficacy endpoints. They were the:

- **Intent-to-Treat (ITT) Analysis Set:** All patients randomly assigned to study treatment. Patients were analyzed according to the treatment to which they were assigned at randomization.
- **Safety Analysis Set:** All enrolled patients who received *at least 1* dose of study drug. Patients were analyzed according to the treatment they received most frequently.

- **Modified Intent-to-Treat (ModITT) Analysis Set:** All patients in the ITT analysis set, excluding those who received both treatments and those patients who did not receive any study drug.
- **Microbiological Intent-to-Treat (MITT) Analysis Set:** All patients in the ITT analysis set who had baseline cultures identifying a bacterial pathogen known to cause ABSSSI. Patients were analyzed according to the treatment to which they were assigned at randomization.
- **Clinically Evaluable (CE) Analysis Sets:** There were 7 CE analysis sets each based on the type of assessment (investigator-assessed or objective) and timing of the assessment (48 to 72 hours, EOT, FU, LFU, or PTE visits). Patients in the CE analysis sets were analyzed according to their randomized assignment.
- **Microbiologically Evaluable Analysis Sets (ME):** The ME analysis set consisted of all patients in the MITT analysis set who also met criteria for the CE analysis set according to type of assessment (investigator-assessed or objective) and timing of the assessment (48 to 72 hours, EOT, FU, LFU, WFU, or PTE visits). Patients in the CE analysis sets were analyzed according to their randomized assignment.

Efficacy analyses of the objective and investigator-assessed clinical response endpoints were analyzed according to the ITT, MITT, CE and ME analysis sets; whereas, microbiologic analyses were conducted using the MITT and ME analysis sets.

The Applicant conducted sensitivity analyses of the primary efficacy endpoint so as to evaluate the robustness of the primary efficacy results. In addition, secondary analyses were performed to establish any additional potential relationships between the primary endpoint and other endpoints. Subgroup analyses were conducted using the ITT and other analysis sets to determine if any imbalances between treatment groups existed at the subgroup.

Medical Reviewer's Comments:

For further details on the SAP, please refer to Dr. Janelle Charles' statistical review.

Protocol Amendments:

The Applicant submitted two protocol amendments updating Trial RX-3411-302. Protocol Amendment highlights are summarized below:

Amendment 1 (dated: 04 December 2013): Protocol Amendment 1 included the following key protocol changes:

- The enrollment of patients with wound infections would be limited to no more than 35% of overall patients.
- No more than 25% of total randomly assigned patients receiving 1 dose of either a single, potentially effective, short-acting antimicrobial drug or regimen for the treatment of ABSSSI in the 14 days prior to study entry. This was changed from previous statement

that such individuals would be limited to 25% of total randomly assigned patients at **each site**.

- Removal of interim analysis

Amendment 2 (dated: 11 June 2014): Protocol Amendment 2 occurred after the final patient had enrolled, but prior to Data Lock. Changes made with to the original protocol following this amendment neither impacted subject treatments or study procedures. The most salient changes were as follows:

- The inclusion of three additional FDA secondary efficacy endpoints:
 - Investigator-assessed response of signs and symptoms of infection in patients with a baseline BMI ≥ 30 kg/m² at the FU visit.
 - Reduction in area of erythema (digital planimetry) of $\geq 80\%$ at FU visit (Day 14 \pm 1).
 - Investigator-assessed response of success (defined as a response of cure or improved) of signs and symptoms of infection at the FU visit (Day 14 \pm 1) where no further antibiotic was required.
- Clarified that the “reduction of erythema of $\geq 30\%$ at 48 to 72 hours,” using digital measurements, was considered an objective response.
- Updated the microbiologic response evaluation to include the MITT analysis set. The definition of the microbiological response “presumed eradicated” was changed from the patient having a “clinical response of cure” to having a “clinical response of success.”

Data Quality Assurance:

Clinical monitors, both blinded and unblinded, periodically visited study staff, study facilities (blinded) and pharmacy facilities (unblinded). These individuals were tasked with observing and maintaining knowledge of the study, reviewing study records and source documentation, and discussing study conduct with the staff, sub-investigators, and the principal investigator. The unblinded monitor ensured that both hospital and outpatient pharmacy staff maintained appropriate study drug accountability and dose-preparation records, that study drug was stored appropriately, and that study drug randomization assignments remained **blinded** to all staff. Study investigators and/or sub-investigators were subject to audits, IRB/IEC review and regulatory inspections. Audits were conducted at a total of 9 investigational sites.

The Applicant reported that the last subject visit occurred on 6 June 2014 and the last patient telephone FU call occurred on 24 June 2014. The last eCRF was entered on 27 June 2014 and hence, the database was “softlocked” for cleaning on 8 June 2014. The Applicant conducted a blinded protocol deviation review. Once data review was completed, the database was officially locked on 30 August 2014.

Medical Reviewer’s Comments:

Data quality assurance measures for Trial 302 appear acceptable.

6.1.2 Study Results

A complete discussion of key results for Trial 302 is found in **Section 7 Integrated Review of Effectiveness**.

6.2. Trial RX-3341-303

6.2.1 Study Design

Overview and Objective

RX-3341-303 was a Phase 3 randomized, double-blind, multicenter, active-comparator trial evaluating the safety and efficacy of 5-14 days of intravenous (IV) **and** oral delafloxacin compared with the comparator drug(s) IV vancomycin (\pm IV aztreonam) in the treatment of adult patients aged 18 and older with ABSSSIs. Trial RX-3341-303, implemented a mandatory IV-to-oral switch for all subjects in the delafloxacin arm. The patients in the vancomycin arm were switched to oral placebo. The primary FDA study objective was the assessment of clinical efficacy in both treatment arms at 48 to 72 hours after the initiation of study treatment.

Trial Design

Basic Study Design

RX-3341-303 was a randomized, double-blind, multicenter, active-comparator Phase 3 pivotal trial evaluating delafloxacin against the comparator(s) vancomycin (\pm aztreonam) in adult patients with ABSSSIs. RX-3341-303's study design is distinguished from RX-3341-302 in the following ways:

- *Implementation of a mandatory IV-to-oral switch:* Subjects with normal, mild and moderate renal impairment ($\text{CrCl} \geq 30$ mL/min) initially received delafloxacin 300-mg IV every 12 hours for a total of 6 doses. For all remaining doses, subjects were administered delafloxacin 450-mg orally every 12 hours.
- *Inclusion of subjects with severe renal impairment (CrCl of 15 to 29 mL/min):* All subjects with severe renal impairment (CrCl of 15 to 29 mL/min), who were randomized to the delafloxacin arm, received delafloxacin 200-mg IV for **all** doses. No subjects with severe renal impairments received delafloxacin oral tablets. Individuals with a CrCl of ≤ 30 mL/min (severe renal impairments and kidney failure, CKD Stages 4 and 5, respectively) were **not** evaluated in Protocol RX-3341-302.
- *Enrichment for individuals with body mass index (BMIs) of ≥ 30 kg/m².* However, subjects weighing ≥ 200 -kg (440-lbs) were excluded from the study.

Medical Reviewer's Comments:

Obesity is a risk factor for ABSSSI. Post-hoc analyses from the Applicant's Phase 2 Trial RX-3341-202, a randomized, double-blind Phase 2 trial comparing IV delafloxacin against the comparators IV linezolid and IV vancomycin for the treatment of ABSSSI, demonstrated that in obese subjects ($\text{BMI} \geq 30$) clinical success rates were 78.8%, 58.8% and 48.8% in the delafloxacin, linezolid, and vancomycin arms, respectively. This difference was statistically significantly higher in the delafloxacin group compared with the vancomycin group ($P=0.009$), but was not statistically significantly different in the delafloxacin group compared with the

linezolid group ($P=0.080$). In non-obese subjects, there were no statistically significant differences in the success rates between the delafloxacin and linezolid groups (64.6% and 69.8%, respectively) or between the delafloxacin and vancomycin groups (64.6% and 57.9%, respectively). Based on these findings, the sponsor proposed to enrich Trial 303 for subjects with BMIs ≥ 30 . In an agreed Special Protocol Assessment, both FDA and the Applicant agreed that “patients with a BMI ≥ 30 should be limited to no more than 50% of the enrolled population to allow for the trial results to be generalizable.”

The trial commenced on 2 May 2014, with the screening of its first patient, and was completed on 29 January 2016, the date of the final patient’s final visit. Enrollees were recruited from 76 clinical centers located in 15 countries. Clinical sites were further divided into four geographical regions: Asia (9 sites), Eastern Europe (32); Latin America (14), and North America (21).

Key Inclusion/Exclusion Criteria:

The **key** inclusion criteria for Trial RX-3341-303 were unchanged from those in Trial RX-3341-302. Please refer to **Section 6.1 Sub-section “Key Inclusion/Exclusion Criteria”** for further details.

Key exclusion criteria for Trial RX-3341-303 were unchanged from those in Trial RX-3341-302 with the following notable exceptions:

- Patients with end-stage renal disease on hemodialysis or peritoneal dialysis or CrCl of < 15 mL/min (Stage 5) using the Cockcroft-Gault formula.
- Body weight > 200 kg (440-lbs).

Medical Reviewer’s Comments:

Eligibility criteria were consistent with the FDA 2013 ABSSSI Guidance for industry.

Study treatments/Blinding:

An anticipated 850 eligible, consenting patients were randomly assigned, in a 1:1 ratio, to receive a total of 5 to 14 days of either: (a) delafloxacin IV every 12 hours + placebo infusion for six doses (3 days) followed by delafloxacin 450-mg (1 tablet) orally every 12 hours **or** (b) Vancomycin dosing was 15-mg/kg based on actual body weight (or according to local standard of care) and renal function. Aztreonam dosing was 2-gm IV twice daily for subjects with a CrCl ≥ 30 mL/min or 1-gm IV every 12 hours for subjects with a CrCl between 15 to 29 mL/min. As in Trial RX-3341-302, if baseline cultures failed to grow gram-negative bacteria, in either treatment arm, either IV aztreonam or the placebo infusion (in the delafloxacin arm) was discontinued.

All subjects assigned to delafloxacin **only** received IV study drug for the first 6 doses. Subjects with CrCl ≥ 30 mL/min (mild; CKD Stage 3 and higher) received delafloxacin 300-mg IV every 12 hours; whereas, subjects with a CrCl between 15 to 29 mL/min (moderate; CKD Stage 4) were dosed at 200-mg IV every 12 hours throughout the study’s duration. These subjects never received oral study drug. The Applicant indicated that baseline renal function was calculated according to the Cockcroft-gault equation. IV placebo infusions were used to maintain blinding

with the IV vancomycin (± aztreonam) arm for all subjects in the delafloxacin arm, regardless of CrCl.

After 6 doses, all subjects in the delafloxacin arm with a CrCl ≥30 mL/min (Stage 3 and higher) were required to switch from delafloxacin 300-mg IV every 12 hours to 450-mg orally every 12 hours for the remainder of treatment. To preserve the blind after receiving an initial 6 doses of study drug, all subjects in the comparator arm with a CrCl ≥30 mL/min also received an oral placebo tablet every 12 hours. Subjects in the comparator vancomycin (±aztreonam) arm with a CrCl between 15 to 29 mL/min did not receive oral placebo tablets.

As in Trial 302, vancomycin TDM was recommended following at least 3 doses of study, on Day 2 (+ 1 day) and on Day 6 (± 1 day), to maintain vancomycin troughs between 15 to 20 µg/mL. Dose adjustments, based on TDM, were recommended by an unblinded pharmacist or study designee.

Medical Reviewer’s Comments:

Randomization procedures, study blinding and study comparator were all acceptable.

Procedures and schedule

A schedule of activities conducted under Trial RX-3341-303 is found in **Table 8** below:

Table 8: Trial RX-3341-303 Schedule of Events

Assessment or Procedure	Screening	Treatment Period						End of Treatment	Follow-up	Late Follow-up	Follow-up Call
		1	2	3	4	5	6-14				
Study Day	-1 to 1	1	2	3	4	5	6-14	5-14	14 ± 1	21-28	30 days (+3 days) after last dose
Informed consent	X										
Verify entry criteria	X										
Demographic data/Medical history	X										
Prior medications	X										
Local laboratory tests for eligibility	X										
Pregnancy test (local laboratory)	X							X			
Hematology, serum chemistry, urinalysis (central laboratory)	X			X		X	X	X	X	X	

Assessment or Procedure	Screening	Treatment Period						End of Treatment	Follow-up	Late Follow-up	Follow-up Call
		1	2	3	4	5	6-14				
Study Day	-1 to 1	1	2	3	4	5	6-14	5-14	14 ± 1	21-28	30 days (+3 days) after last dose
Vital signs	X	X				X		X	X	X	
12-lead electrocardiogram	X										
Body temperature	X	X	X	X	X			X	X	X	
Complete physical examination with height and weight	X										
Targeted physical examination						X		X	X	X	
Clinical infection site signs and symptoms	X	X	X	X	X	X	X	X	X	X	
Digital photography and manual measurements for demarcation of ABSSSI	X	X	X	X	X	X		X	X	X	
Document surgical procedure	X	X	X	X	X	X	X		X	X	
ABSSSI specimen for microbiologic culture and local Gram stain	X										
Blood culture	X										
Randomization by IWRS	X										
Notify IWRS of continued treatment status						X					
Contact IWRS to report treatment completion status on last day of treatment								X			
Study drug administration every 12 ± 2 hours		X	X	X	X	X	X				

Assessment or Procedure	Screening	Treatment Period						End of Treatment	Follow-up	Late Follow-up	Follow-up Call
		1	2	3	4	5	6-14				
Study Day	-1 to 1	1	2	3	4	5	6-14	5-14	14 ± 1	21-28	30 days (+3 days) after last dose
Investigator assessment of clinical response								X	X	X	
Concomitant medications		X	X	X	X	X	X	X			
Pain assessment	X	X	X	X	X	X	X	X	X	X	
Assess AEs	X	X	X	X	X	X	X	X	X	X	X
PK sampling				X							
Recommended vancomycin therapeutic drug monitoring			X				X				
Recommended adjustment of vancomycin dose level or duration of treatment, as necessary				X			X				
Posttreatment medications									X	X	X

Source: Table 7, Trial RX-3341-303 Clinical Study Report

Adjunctive Therapies/ Concomitant Medications

Trial RX-3341-303 permitted the same adjunctive therapies and concomitant medications as those permitted in Trial RX-3341-302.

Study Endpoints

Trial RX-3341-303 evaluated the same 6 analysis populations as Trial RX-3341-302, with the one exception being that the CE analysis set in Trial 303 included 6 analysis sets, instead of the 7 CE analysis sets included in Trial 302. To be included in the CE analysis set, subjects must have received at least 8 doses of study drug. After receipt of 4 doses of study drug, subjects could be deemed by the study investigator to be a treatment failure.

If delafloxacin was determined, in the ITT population, to be non-inferior to the comparator, then secondary endpoints would be assessed for superiority in a hierarchical fashion in the following order, by **key** secondary endpoints:

Clinical Review
Caroline J. Jjingo, MD, MPH
NDA 208,610 and NDA 208,611
BAXDELA™ (delafloxacin meglumine)

Secondary Endpoint # 1: Investigator-assessed response to signs and symptoms of infection in patients with a baseline BMI ≥ 30 kg/m² at the Late Follow-up (LFU) Visit

Secondary Endpoint # 2: Investigator-assessed response to signs and symptoms of infection in patients with a baseline BMI ≥ 30 kg/m² at the Follow-up (FU) Visit

Secondary Endpoint # 3: Investigator-assessed response of signs and symptoms of infection at the LFU Visit

Secondary Endpoint # 4: Investigator-assessed response of signs and symptoms of infection at the FU Visit

Secondary analyses were performed using non-stratified Miettinen and Nurminen methodology for binary endpoints. Mixed models repeated measures analysis was used to analyze the reduction in pain endpoint. All secondary statistical tests and 95% CI were 2-sided and were calculated with a test-wise type 1 error rate of $\alpha=0.05$.

To assess the robustness of the primary and secondary efficacy endpoints, as in Trial 302, the Applicant conducted sensitivity, subgroup and exploratory analyses in the ITT and various other analysis populations.

Statistical Analysis Plan

Delafloxacin would be declared non-inferior to vancomycin and aztreonam if the lower limit (LL) of the 2-sided 95% confidence interval (CI) for the primary efficacy analysis endpoint, in the ITT analysis population, was greater than -0.10.

Medical Reviewer's Comments:

Trial RX-3341-303 shared many of the same FDA and EMA primary and secondary efficacy endpoints as Trial 302; however, it differed from its predecessor with its emphasis on subjects with a baseline BMI ≥ 30 kg/m². In this reviewer's opinion, the clinical significance of investigator assessment of clinical response at the FU visit (Day 14 \pm 1 day) for the entire study cohort carries greater significance than the LFU visit (Days 21 to 28), as this could be considered the equivalent of a test of cure visit. Nevertheless, this reviewer understands that a sustained response is both desirable and of clinical importance to physicians and patients alike. For further details on the SAP, please refer to Dr. Janelle Charles' statistical review.

Obesity is an independent risk factor for ABSSSIs. It is well-appreciated that as the numbers of overweight and obese individuals increase worldwide, it is important to ensure that antimicrobials are as equally efficacious in overweight and obese individuals as they are in the non-obese population. However, it is this reviewer's opinion that signs of a clinical response for the entire cohort is of greater clinical importance than having individuals with BMIs of ≥ 30 kg/m² account for the first secondary endpoint. Therefore, the reviewer questions the Applicant's hierarchical ordering of secondary endpoints.

Protocol Amendments

Four protocol amendments were published during Trial 303.

Amendment 1; 3 March, 2014: A country-specific amendment for all Korean study sites permitted dose adjustments for patients, in the vancomycin arm, with renal impairment. This amendment further indicated that patients with severe renal impairments (CKD stage 4; CrCl of 15 to 29 mL/min) who were receiving combination therapy with vancomycin and aztreonam who also had severe renal impairment were permitted to receive aztreonam 1 gram of every 12 hours.

Amendment 2; dated 3 March 2014 (approved 09 May 2014): A global amendment included the updates made at Korean sites in addition to the following salient revisions:

- Specified that vancomycin dosing at 15-mg/kg based on actual body weight was no longer a requirement but instead a recommendation. No longer required vancomycin TDM to maintain vancomycin troughs between 15µg/mL to 20 µg/mL. Instead maintaining vancomycin troughs between 15µg/mL to 20 µg/mL became a recommendation and no longer a requirement.
- Eliminated glucose monitoring
- Clarified that concomitant medications were to be recorded from initial receipt of study drug and not from when the patient signed the informed consent.
- Specified that CrCl should be calculated with every chemistry panel and that the international normalized ratio should be calculated at Screening.
- Permitted missing dates for AEs and concomitant medications to be imputed.

Amendment 3; dated 9 May 2014 (approved 6 April 2015):

The following **key** protocol revisions were included in Amendment 3:

- Indicated that for patients in the delafloxacin arm dosing would **not** be modified for creatinine clearance.
- Indicated that patients with a BMI ≥ 30 kg/m² should comprise *at least* 40% of the enrolled population.
- Specified that *no more than* 30% of enrolled patients were permitted to have wound infections.
- Explained secondary efficacy endpoints were to be tested using a fixed-sequence testing procedure, and the difference (vancomycin-delafloxacin) and confidence intervals for all secondary endpoints were to be reported.
- Secondary efficacy endpoints were updated.

Amendment 4; dated 3 June 2015 (approved 3 June 2015):

The following **key** protocol revisions were incorporated in Amendment 4:

- In the delafloxacin arm, any dosing modifications were to be based on Screening CrCl levels.
- Subjects with a BMI ≥ 30 kg/m² would comprise *no more than* 50% of the enrolled population.

- Treatment differences between the primary and secondary efficacy endpoints were updated from “vancomycin-delafloxacin” to “delafloxacin-vancomycin.”

6.2.2 Trial 303 Study Results

A complete discussion of key results for Trial 303 is found in **Section 7 Integrated Review of Effectiveness**.

6.3 Phase 3 Trials Protocol Violations, Subject Disposition, Adjunctive Therapies

Section 6.3 will provide a general overview of key outcome features in each of the pivotal Phase 3 trials. The reader is referred to **Section 7 Integrated Review of Effectiveness** for a detailed discussion of the following outcomes/analyses: the primary FDA efficacy endpoint at 48 to 72 hours, the key secondary clinical outcomes at the follow-up and late follow-up visits, subject treatment outcomes by key target pathogens, subject demographics, and efficacy outcomes by key sub-groups.

Compliance with Good Clinical Practices

The Applicant attests that all clinical trials were conducted in compliance with the principles of the International Conference on Harmonisation (ICH) (E6) Good Clinical Practice and the Declaration of Helsinki, thereby ensuring subject protections. The Institutional Review Boards (IRB) of each clinical study site approved all original protocols, all subsequent protocol amendments, and the informed consent form (ICF). Each prospective enrollee (or their legally authorized representative) was required to sign a written copy of the ICF after they expressed an understanding of the study protocol

6.3.1 Protocol Deviations/ Violations

The Applicant defined a protocol deviation as “an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the principal investigator or sub-investigator.” A significant deviation was defined as one which “occurs when there is nonadherence to the protocol that results in significant, additional risk to the patient when the patient when the patient, principal investigator, or subinvestigator has failed to adhere to significant protocol requirements.” The Applicant provided a listing of all subjects who incurred protocol deviations for Trials 302 and 303. Section 6.2.1 provides a brief description of protocol deviations/violations which occurred in each of the Applicant’s pivotal Phase 3 trials.

Trial 302

Seventeen subjects in the delafloxacin arm sustained a total of 19 protocol violations in Trial 302; whereas 14 subjects sustained a total of 15 protocol violations in Trial 302’s vancomycin arm. The breakdown is as follows:

- **Dosing or Randomization Errors:** There were eight protocol deviations classified as “dosing or randomization errors” which occurred in 3 subjects in the delafloxacin arm (Subjects: 840-003-0021; 840-003-0022; and 840-003-0029). Four such violations occurred among four subjects in the vancomycin arm, two of these violations were

pharmacy errors which resulted in incorrect vancomycin dosing. These three subjects in the delafloxacin arm were from a single investigational site (Site 840-003). Instead of being administered delafloxacin 300-mg IV twice daily, subjects 840-003-0022 and 840-003-0029 each received 600-mg of IV delafloxacin for several doses/days.

- **Procedural Errors:** A total of 11 procedural errors occurred in 11 subjects in the delafloxacin arm. In the vancomycin arm, a total of 10 procedural violations occurred among nine subjects.
- **Violations of inclusion/exclusion criteria:** There was a single subject in the vancomycin arm in whom a violation of eligibility criteria occurred. However, there were no reported eligibility violations in the delafloxacin arm.

Trial 303

Sixteen subjects in the delafloxacin arm sustained a total of 18 protocol violations in Trial 303; whereas, 21 subjects in the vancomycin arm sustained a total of 22 protocol violations. The breakdown is as follows:

- **Dosing or Randomization Errors:** There were 13 dosing or randomization protocol violations that occurred in 12 subjects in the delafloxacin arm and seven such violations occurred among seven subjects in the vancomycin arm. Subjects 840-365-3522, 840-365-3544, 840-365-3551, all of whom had baseline severe renal impairments (CKD Stage 4; CrCl of 15-29) were incorrectly dosed in spite of their known renal impairments. Instead of the proposed delafloxacin 200-mg IV every 12 hours, these subjects were erroneously administered delafloxacin 300-mg IV with the mandatory switch to delafloxacin 450-mg oral tablets. Records additionally noted that Subject 840-365-3522 was non-compliant with study medication.

Subjects 410-336-3075, 840-308-3123, 840-321-3227 and 840-490-3882 received either one or more double doses of delafloxacin 300-mg IV or were simultaneously administered delafloxacin oral and IV formulations instead of the mandatory IV to oral switch.

- **Procedural Errors:** A single procedural error (i.e. subject non-compliant with study medication) occurred in one subject in the delafloxacin arm; whereas two such violations occurred among two subjects in the vancomycin arm.
- **Violations of inclusion/exclusion criteria:** Four violations of eligibility criteria occurred in four subjects in the delafloxacin arm; whereas, there were eight such violations which occurred in eight subjects in the vancomycin arm.
- **Informed Consent:** There were three informed consent violations in the vancomycin arm among three subjects. There were no such violations in the delafloxacin arm.
- **Administration of concomitant medications:** There were two protocol violations in which two subjects in the vancomycin arm were concomitantly administered antibacterial agents while actively in receipt of study drug. This occurrence resulted in one subject

being withdrawn from Trial 303. There were no such violations reported in the delafloxacin arm.

6.3.2 Subject Disposition

Table 9 below summarizes overall subject dispositions for each pivotal Phase 3 trial.

Table 9: Subject Disposition in Delafloxacin Phase 3 Trials

Study Completion Status	Trial 302		Trial 303		Pooled Phase 3 Trials	
	Delafloxacin n N= 331	Vancomycin ± Aztreonam N=329	Delafloxacin n N=423	Vancomycin ± Aztreonam N=427	Delafloxacin N= 754	Vancomycin ± Aztreonam N=756
Completed Study	276 (83.4%)	271 (82.4%)	366 (86.5%)	368 (86.2%)	642 (85.1%)	639 (84.5%)
Failed to Complete Study	55 (16.6%)	58 (17.6%)	57 (13.5%)	59 (13.8%)	112 (14.9%)	117 (15.5%)
	331 (100.0%)	329 (100.0%)	423 (100.0%)	427 (100.00%)	754 (100.0%)	756 (100.0%)
Primary Reason for Study Withdrawal	Delafloxacin n N= 331	Vancomycin ± Aztreonam N=329	Delafloxacin n N=423	Vancomycin ± Aztreonam N=427	Delafloxacin N= 754	Vancomycin ± Aztreonam N=756
Death	1 (0.3%)	2 (0.6%)	0 (0.0%)	2 (0.5%)	1 (0.1%)	4 (0.5%)
Adverse Event	3 (0.9%)	9 (2.7%)	8 (1.9%)	12 (2.8%)	11 (1.5%)	21 (2.8%)
Lack of Efficacy	3 (0.9%)	1 (0.3%)	3 (0.7%)	6 (1.4%)	6 (0.8%)	7 (0.9%)
Physician Decision	2 (0.6%)	0 (0.0%)	4 (0.9%)	2 (0.5%)	6 (0.8%)	2 (0.3%)
Non-Compliance with Study Drug	2 (0.6%)	2 (0.6%)	1 (0.2%)	2 (0.5%)	4 (0.5%)	3 (0.4%)
Protocol Deviation	0 (0.0%)	0 (0.0%)	5 (1.0%)	2 (0.5%)	5 (0.5%)	2 (0.3%)
Lost to Follow-up	25 (7.3%)	29 (8.8%)	26 (5.9%)	24 (5.6%)	49 (6.6%)	53 (7.1%)
Withdrawal of Subject	15 (4.5%)	9 (2.7%)	8 (1.9%)	9 (2.1%)	23 (3.1%)	18 (2.4%)
Missing	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)

Source: ISE Population. ADSL data set. There are minor discrepancies between the Applicant and reviewer's calculations which are highlighted in red.

Medical Reviewer's Comments:

Overall, the percentages of subjects completing and discontinuing the study in both treatment arms were nearly similar in each of the pivotal Phase 3 trials, as illustrated above. The primary reason cited for discontinuation of the study was lost to follow-up, with 7.1% (53/751) vs 6.6% (49/741) subjects in the comparator arm and the delafloxacin arms, respectively being lost to follow-up. This was followed by subject withdrawals (comparator arm 2.4% [18/751] vs delafloxacin arm 3.1% [23/741]) and adverse events (comparator arm 2.8% [21/751] vs delafloxacin arm 1.5% [11/741]). Upon closer inspection of the 11 subjects in the delafloxacin arm who were prematurely discontinued from the study due to AEs, 5 of 11 (45.5%) of these subjects TEAEs were coded to the PT terms hypersensitivity, allergic dermatitis, or urticaria. Several subjects experienced more than one TEAE. **Section 8 Review of Safety** of this review provides a detailed discussion of all subject deaths and TEAEs resulting in study discontinuation.

There was a minor discrepancy, by one subject, between the reviewer’s analysis of subjects discontinuing delafloxacin due to lack of efficacy and the Applicant’s analysis. This reviewer noted that all six subjects in the pooled delafloxacin arm who were discontinued from the study treatment due to a lack of efficacy either had cellulitis 4 of 6 (66.7%) or a major cutaneous abscess 2 of 6 (33.3%). Three of the four subjects in the delafloxacin arm who were discontinued from the study due to protocol violations did so because they were never administered delafloxacin.

6.3.3 Adjunctive Therapies

Both Phase 3 trials documented the types, locations, and timing of surgical procedures (debridements, I&Ds, and lavage of wounds). During the course of this review, the reviewer noted that, in both treatment arms, considerable numbers of subjects classified as having cellulitis or wound infections received I&Ds prior to receipt of study drug, as **Table 11** below illustrates. The reviewer further observed that when looking at subjects receiving I&Ds < 72 hours and/or ≥ 72 hours after the first dose of study drug that many subjects had I&Ds performed who did not receive I&Ds <72 or ≥ 72 hours after first dose of treatment and who had missing information to indicate when I&Ds were performed. The reviewer was able to correlate when I&Ds with missing times were performed relative to the start of either delafloxacin or vancomycin (± Aztreonam) treatment. In most all instances, the dates that these I&Ds were performed were usually on the day prior to the first dose of study drug or on the first day of treatment. Furthermore, when looking at the “findings of surgical procedure” variable under the ADCE data sets, this reviewer was also able to ascertain that for most all subjects with cellulitis and wound infection who received pre-treatment I&Ds, the surgical finding was described as “presence of purulent secretions.”

			Pre-treatment Incision and Drainage Performed , (# of subjects)	
	BAXDELA N=754	Vancomycin N=756	BAXDELA N=754	Vancomycin N=756
Type of Infection	N	N	n/N (%)	n/N (%)
Cellulitis	330	334	34/330 (10.3%)	32/334 (9.6%)

Major Abscess	190	189	130/190 (68.4%)	133/133 (70.3)
Wound Infection	227	228	94/227 (41.0%)	103/228 (45.2%)
<i>Source: ISE population. ADCE data set. Table created by clinical reviewer using Jreview. Only 7 and 5 subjects were burn subjects in the delafloxacin and vancomycin (± aztreonam) arms, respectively. These 12 subjects were not included in this exploratory analysis.</i>				

Irrespective of treatment arm, the combined numbers of subjects with cellulitis and wound infections who received pre-treatment I&Ds nearly matched the numbers of subjects with major cutaneous abscesses who received I&Ds prior to treatment. Typically, I&Ds are performed prior to antibacterial treatment, as a means of source control, in persons with abscesses. I&Ds are not typically performed on patients with cellulitis or wound infections prior to initiation of antibacterial treatment. Further investigation of the medical histories of subjects with cellulitis or wound infections who received pre-treatment I&Ds also revealed that, in most cases, these individuals had a history of drug addiction, and in many instances IV drug use, although information on IV drug abuse was not consistently captured by the Applicant.

Medical Reviewer Comments:

This reviewer considered that many “traumatic” wound infections resulted from the puncturing of the skin with syringes in IV drug users. This reviewer questions whether this classification of “wound infection,” as such, was consistent with the accepted definition of a wound infection. Persons with IV drug histories, in particular, are more likely to develop abscesses. It is this reviewer’s understanding, based on the information described above, that many subjects classified as having a “cellulitis” or “wound infection” actually may have had an abscess instead of a true cellulitis or wound infections. Table 11 below provides the clinical outcomes at 48-72 hours of subjects with pre-treatment I&Ds by study treatment and type of infection.

Table 11: Surgical Procedures Performed in Delafloxacin Phase 3 Trials				
	Delafloxacin N=754		Vancomycin (± Aztreonam) N=756	
Type of Infection	Incision and Drainage, Pre-treatment			
	Clinical Failure	Clinical Cure	Clinical Failure	Clinical Cure
	48-72 HOURS VISIT		48-72 HOURS VISIT	
CELLULITIS/ ERYSIPELAS	7 (0.9%)	27 (3.6%)	3 (0.4%)	29 (3.8%)
MAJOR CUTANEOUS ABSCESS	15 (2.0)	115 (15.3%)	14 (1.9%)	119 (15.7%)
WOUND INFECTION	12 (1.6%)	81 (10.7%)	12 (1.6%)	91 (12.0%)
Subjects(filtered)	34 (4.5%)	223 (29.6%)	29 (3.8%)	239 (31.6%)
Denominator	754 (100.0%)	754 (100.0%)	756 (100.0%)	756 (100.0%)

Source: ISE population. ADCE data set. Table created by clinical reviewer using Jreview.

6.4 Phase 2 Trials Rx-3341-202 and RX-3341-201

The Applicant conducted two Phase 2 ABSSSI trials, RX-3341-201 and RX-3341-202. For the purposes of this NDA, these 2 trials will be discussed in support of delafloxacin safety for the ABSSSI indication. Therefore, the review will not engage in a discussion of the clinical efficacy of these trials. Rather Section 6.4 will be devoted to providing a broad overview of the Phase 2 study objectives, trial designs and endpoints. Safety assessments/analysis will be provided in **Section 8 Review of Safety** of this review.

6.4.1 Trial RX-3341-202: Study Design

Overview and Objective

RX-3341-202 was a randomized, double-blind, multicenter, active-comparator Phase 2 trial evaluating the safety and efficacy of IV delafloxacin compared with IV linezolid and IV vancomycin in the treatment of adult patients with ABSSSI. Trial 202 had two primary objectives:

- To assess the clinical efficacy of delafloxacin, linezolid, and vancomycin, using the investigator’s assessment of clinical response.
- To assess the utility, variability, and measurement techniques of several objective measures of clinical efficacy for use in future clinical studies in subjects with ABSSSI.

Trial Design

Basic Study Design

RX-3341-202 was a randomized, double-blind, multicenter Phase 2 trial evaluating the efficacy and safety of 5 to 14 days of IV delafloxacin, compared with IV linezolid and IV vancomycin in patients aged ≥ 18 years old with ABSSSIs. Enrolled patients could either be treated in the inpatient or outpatient setting and were randomized in a 1:1:1 ratio to receive either IV delafloxacin 300-mg every 12 hours, IV linezolid 600-mg every 12 hours, or IV vancomycin 15-mg/kg every 12 hours. Subjects were stratified according to infection type (cellulitis/erysipelas; wound infection; major cutaneous abscess; and burn infection). Aztreonam was added to the treatment regimen, *at investigator discretion*, if microbiologic cultures yielded gram-negative bacteria. No more than 30% of enrollees were permitted to have major cutaneous abscess. All other infection types were equally stratified between treatment arms and by receipt of prior antibiotics. Subjects receiving prior antibiotic therapy were to account for no more than $\leq 30\%$ of all enrollees.

Trial 202 commenced with the screening of its first subject on 1 February 2011 and was completed on 14 November 2011 upon final contact with the last subject. Subject visits were scheduled at Screening, daily on Days 1 through 14 (or upon completion of treatment), at the Follow-up visit (Day 14 \pm 1 day), and at the Late Follow-up visit (Days 21-28). Investigator-assessed clinical response was determined at the Follow-up and Late Follow-up visits based on his/her subjective evaluation of signs and symptoms of infection.

Key Inclusion/Exclusion Criteria

Eligible prospective enrollees were males and non-pregnant, non-lactating females aged 18 years and older who met such **key inclusion criteria** as having a primary infection from one of the four aforementioned ABSSSI infection types, all of which were characterized by “a minimum surface area of 75 cm²” with surrounding erythema. Eligible candidates demonstrated *at least 1* of the following signs of systemic infection:

- Fever $\geq 38^{\circ}\text{C}$
- Lymphangitis
- Elevated white blood cells (WBCs) $\geq 15,000$ cells/ μL
- Elevated CRP (> 5.0 mg/L)

Key exclusion criteria for RX-3341-202 were similar to those of the pivotal Phase 3 studies with the following notable exceptions:

- Receipt of **> 24 hours** of systemic antibiotic therapy in the 14 days before enrollment, unless one of the following was documented:
 - The clinic notes or photographs objectively documented the clinical progression of ABSSSI (i.e., not by subject history alone).
 - The subject received a single dose of a short-acting antibacterial drug 3 or more days before clinical study enrollment for surgical prophylaxis.
 - The subject had recently completed a treatment course with an antibacterial drug for an infection other than ABSSSI, and the drug did not have antibacterial activity against bacterial pathogens that cause ABSSSI.

- Receipt of more than 1 dose of a potentially effective antibacterial agent for treatment of the ABSSSI under study before enrollment. Subjects who received a single dose of a potentially effective antibiotic therapy for treatment of the ABSSSI under study within 24 hours of study entry were stratified for enrollment purposes and were limited to *no more than 30%* of total enrolled subjects.
- History of severe renal impairment (CKD Stage 4) defined as creatinine clearance of < 30 mL/minute. The Cockcroft-Gault equation was used to determine renal function.
- Subjects > 140 kg (308-lbs) in body weight.

Randomization/Blinding

An independent statistician who was unaffiliated with the study’s conduct, generated subject randomization codes, which were then retrieved via interactive web response system (IWRS) by the study site pharmacist.

Investigators, sub-investigators, subjects, and study personnel remained blinded to each subject’s assigned treatment arm. Assignments remained unblinded until study completion. To ensure that the study drug’s identity remained undisclosed and that study drug administration was appropriately monitored, the study pharmacist and select staff members were not blinded.

Medical Reviewer’s Comments:

This reviewer finds the study design, selected comparators, eligibility criteria, randomization schema, and masking of treatments in Trial 202 acceptable.

Procedures and schedule

A schedule of activities conducted under RX-3341-202 is found in below:

Assessment or Procedure	Screening	Treatment Period						Follow-up	Late Follow-up	Follow-up Call
	-1 to 1	1	2	3	4	5	6-14	14 ± 1	21-28	30 days (+3 days) after last dose
Informed consent	X									
Verify entry criteria	X									
Medical/Surgical history	X									
Prior medications	X									
Pregnancy test (local laboratory)	X							X		
Hematology, serum chemistry, urinalysis (central laboratory)	X					X	X	X	X	
Blood glucose test		X	X	X	X	X	X			

Table 12: Schedule of Events in Trial RX-3341-202

Assessment or Procedure	Screening	Treatment Period						Follow-up	Late Follow-up	Follow-up Call
	-1 to 1	1	2	3	4	5	6-14	14 ± 1	21-28	30 days (+3 days) after last dose
IL-6 and CRP measurements	X	X	X	X	X	X	X	X	X	
Vital signs	X	X				X		X	X	
12-lead electrocardiogram	X	X						X		
Body temperature	X	X	X	X	X	X		X	X	
Complete physical examination with height and weight	X									
Targeted physical examination						X		X		
Clinical infection site signs and symptoms	X	X	X	X	X	X	X	X	X	
Digital photography and manual measurements for demarcation of ABSSSI	X	X	X	X	X	X		X	X	
Document any surgical procedures performed on infection site	X	X	X	X	X	X	X	X	X	
ABSSSI specimen for microbiologic culture and local Gram stain	X							X	X	
Blood culture	X	X	X	X	X	X	X	X	X	
Randomization by IWRS	X									
Contact IWRS to report treatment completion status on last day of treatment							X			
Study drug administration every 12 ± 2 hours		X	X	X	X	X	X			
Investigator assessment of clinical response								X	X	
Concomitant medications		X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Pharmaockinetic sampling				X						
Vancomycin therapeutic drug monitoring			X				X			

Table 12: Schedule of Events in Trial RX-3341-202

Assessment or Procedure	Screening	Treatment Period						Follow-up	Late Follow-up	Follow-up Call
	-1 to 1	1	2	3	4	5	6-14	14 ± 1	21-28	30 days (+3 days) after last dose
Study Day										
Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CRP, C-reactive protein; ECG, electrocardiogram; IL-6, interleukin-6; IWRS: interactive web response system.										
<i>Source: Adapted from Table 4; Trial RX-3341-202 Clinical Study Report</i>										

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was investigator assessment of the clinical response rate at the Follow-up visit (Day 14 ± 1 day), in the ITT analysis population. Clinical response was to be classified as any of the following:

- **Cure:** Complete resolution of all baseline signs and symptoms of ABSSSI at the FU and LFU visits.
- **Improved:** Despite the persistence of several symptoms, the subject's primary infection has improved such that no additional antibiotic treatment was required. Improved responses were considered failures in the primary analysis.
- **Failure:** The subject required additional antibiotics for any one of several reasons: lack of efficacy after at least 2 days (4 doses) of study drug; treatment related AEs; requiring more than 14 days of antibiotic therapy; and the need for an unplanned surgical intervention for >48 hours following study entry.
- **Indeterminate:** Investigator unable to assign a clinical response for infection due to incomplete information at the FU or LFU visits.

A medical monitor independently assessed each subject's clinical response to confirm the robustness of the investigator's clinical response assessment.

Safety Analyses

Adverse events were classified according to MedDRA dictionary version 13.1. SOC and PT terms were summarized by: (a) all TEAEs by SOC and PT; (b) TEAEs by severity and relationship to study drug; (c) AEs resulting in discontinuation of study drug; and (d) SAEs according to SOC and PT. The sponsor also determined the extent of exposure to study drug according to the duration of treatment in days and the number of infusions

Statistical Analysis Plan

Analysis Population

There were six analysis populations in Trial 202, including the (a) safety population (all enrolled subjects receiving at least 1 dose of study drug); (b) ITT population (all randomized subjects); (c) MITT population (all subjects in the ITT population with a baseline bacterial pathogen known to cause ABSSSI); (d) Clinically Evaluable Population (all subjects in the ITT population

with no major protocol deviations, who received at least 80% of total doses, did not receive any concomitant antibacterial therapy with activity against the causative pathogen, had all follow-up visits within the appropriate timeframe); (e) Microbiologically Evaluable population (all subjects in the MITT population meeting criteria for the CE population); and (g) a pharmacokinetic analysis set population (PKAS).

Interim Analysis

A single blinded interim analysis was performed once 75% of all subjects had completed the study. The interim analysis was conducted for business and administrative reasons. The results were reviewed by an independent unblinded team. The purpose of the interim analysis was to recommend an early termination to the study if any safety concerns were identified. No changes to the study protocol were to be made based on findings from the interim analysis.

Sample Size

The sponsor determined that a sample size of 240 subjects was sufficient to achieve the study objectives. Sample size was based on the sponsor's clinical and practical considerations, and not on any formal sample size calculations. Two hundred fifty six subjects were finally enrolled into the study after multiple stratifications resulted in an imbalance in the size of the three treatment groups.

Protocol Amendments

Trial 202 was originally submitted on 4 November 2010. Three protocol amendments were subsequently issued: Amendment 1 (approved 11 February 2011); Amendment 2 was never submitted but changes were incorporated into Amendment 3 which was approved on 08 August 2011.

Amendment 1 (11 February 2011) incorporated the following **key** changes:

- Amended instructions to vancomycin dosing
- Lymphangitis and lymphadenopathy were added to the infection-site assessment.
- The interim analysis was changed from 2 planned analyses to 1 interim analysis.

Amendment 2 (dated 2 June 2011) incorporated the following **key** changes:

- Exclusion criterion 1 was modified to exclude subjects with a "significant" hypersensitivity or allergic reaction to quinolones, linezolid, vancomycin, or vancomycin derivatives.
- Exclusion criterion 4 was modified to indicate that subjects with severely impaired blood supply to an extremity could have been enrolled if they had a palpable pulse or an audible distal pulse by Doppler.
- A 12-lead ECG was added to the FU visit (Day 14±1 day)

Amendment 3 (dated 8 August 2011) incorporated the following **key** changes:

- Exclusion criterion 21, changed subject maximal weight requirement from > 133 kg to > 140 kg.

- Exclusion criterion was added stating subjects who needed a dose of vancomycin for ≥ 2 hours of total infusion time per dose were ineligible for study enrollment.

6.4.2 Trial RX-3341-201 Study Design

Primary Objectives

RX-3341-201 was a randomized, double-blind, multicenter, active-comparator Phase 2 trial evaluating the safety and efficacy of 5 to 14 days of IV delafloxacin compared with tigecycline. The primary objectives of Trial 201 were as follows:

- To assess the clinical efficacy of two dosing regimens of delafloxacin, compared to that of tigecycline, in patients with complicated skin and skin structure infections (cSSSI)
- To assess the safety and tolerability profiles of two dosing regimens of delafloxacin, compared to that of tigecycline, in patients with cSSSI

Secondary Objectives

Key secondary objectives were as follows:

- To assess the clinical efficacy of two dosing regimens of delafloxacin, compared to that of tigecycline, in patients with cSSSI caused by MRSA
- To assess the microbiologic efficacy of two dosing regimens of delafloxacin, compared to that of tigecycline, in all patients
- To assess the microbiologic efficacy of two dosing regimens of delafloxacin, compared to that of tigecycline, in all patients with infections caused by MRSA

Basic Study Design

RX-3341-201 was a randomized, double-blind, multicenter Phase 2 trial evaluating the efficacy and safety of 300-mg IV delafloxacin every 12 hours, 450-mg IV delafloxacin every 12 hours, and tigecycline 100-mg IV initially followed by 50-mg IV every 12 hours. One hundred fifty eligible patients, with cSSSI ages 18 years and older were randomly assigned in a 1:1:1 ratio to receive one of the three abovementioned treatments. Each randomized subject received anywhere from 5-14 days of treatment, based on the investigator's discretion.

The end of treatment (EOT) assessment occurred at least 12 hours after and within 72 hours of the final dose of study drug; whereas, the test of cure (TOC) visit was evaluated 14 to 21 days after the final dose of study drug. Patients categorized as Cures at the TOC visit were contacted, via phone, for a late follow-up contact on study days 28 to 35 after the final day of therapy.

Otherwise the specifics of this study were similar to the above-described trials.

Key Inclusion/Exclusion Criteria

Eligible prospective enrollees were males and non-pregnant, non-lactating females aged 18 years and older who met the following **key inclusion criteria**:

- Patients were required to have a diagnosis of cSSSI, i.e., an infection involving subcutaneous tissues or requiring surgical intervention. Patients could have had 1 or more of the following 3 infection types:
 - a. A **wound infection** that had developed within 30 days of surgery, trauma (including partial thickness burns over <10% of the body surface), or an animal or insect bite injury. Patients were required to have either:
 - Purulent drainage from the wound, or
 - Three or more of the following symptoms:
 - Rectal temperature >38°C, tympanic temperature >38.5°C or oral temperature >37.5°C
 - Swelling
 - Erythema of ≥10 mm
 - Pain
 - Tenderness
 - b. An **abscess**, without an open wound, that had developed in the 7 days before enrollment, with purulent drainage or a purulent aspirate. Patients were required to have both:
 - Evidence of a loculated fluid collection that required intervention within 48 hours of enrollment, and
 - Erythema and/or induration of ≥20 mm in diameter, or tenderness.
(Note: Patients with abscesses in the perirectal area were allowed to enroll).
 - c. **Cellulitis** that had developed in the 7 days before enrollment, with advancing edema, erythema, or induration; in addition, patients must have had at least one of the following:
 - Documented fever, or reported fever, in the 3 days before enrollment
 - A white blood cell count of 10,000 cells/μL, or ≥10% band forms
 - Lymphangitis and adenopathy

Exclusion criteria were similar to those in the previously described protocols, with the most notable exclusion as follows:

- History of severe renal impairment (defined as creatinine clearance of <30 mL/minute using the Cockcroft-Gault formula).

Study Treatments

As stated above, subjects were randomly assigned to one-hour infusions of either IV delafloxacin, 300-mg every 12-hours daily; IV delafloxacin, 450-mg, every 12 hours for 5 to 14 days, or IV tigecycline, initial dose 100-mg with all subsequent doses administered at 50-mg every 12 hours for 5 to 14 days. Tigecycline is FDA approved for the treatment of cSSSI and intra-abdominal infections. An unblinded pharmacist prepared all study treatments.

Randomization/Blinding

Clinical Review
Caroline J. Jjingo, MD, MPH
NDA 208,610 and NDA 208,611
BAXDELA™ (delafloxacin meglumine)

All subject's random treatment assignments were obtained via an interactive voice response system. Subjects were stratified according to cSSSI category. Investigators, sub-investigators, laboratory and study personnel remained blinded to each subject's randomization and treatment assignments. Whereas, the clinical research organization (CRO) staff, study pharmacists, and the independent statistician who generated the randomization codes were unblinded to treatment assignments.

Concomitant Therapy

Concomitant antimicrobial therapies were prohibited in this study. Any subjects who required alternate antimicrobial products were deemed clinical failures.

Compliance

Compliance was assessed via review of drug administration and dispensing records

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Schedule of Events

Table 13 below summarizes Trial 201’s schedule of events.

Table 13: Schedule of Events in Trial RX-3341-201								
Assessment or Procedure	Screening	Treatment Period, Day				End of Treatment (EOT) Visit	Test of Cure (TOC) Vist	Late Follow-up (LFU) Visit
		1-3	4	5	6-14			
Study Day								
Informed consent	X							
Medical/Surgical history	X							
Prior medications	X							
Pregnancy test	X					X		
Hematology & serum chemistry	X			X		X	X	
Vital signs	X	X		X		X	X	
Complete physical examination	X							
Targeted physical examination				X		X	X	
Electrocardiogram	X	X				X		
Infection site assessment	X	X	X	X	X	X	X	
Photography and measurement	X			X		X	X	
Document surgical procedures	X	X	X	X	X	X	X	
cSSSI specimen for microbiologic culture	X					X	X	
Blood culture	X					X	X	
Randomization by IWRS	X							
Call IWRS to report treatment completion status				X	X			
Drug administration every 12 (± 1 hour)		X	X	X	X			
Concomitant medications		X	X	X	X	X	X	X
Assess adverse events		X	X	X	X	X	X	X
Pharmaockinetic sampling			X					
Abbreviations: cSSSI: complicated skin and skin structure infections; IWRS: interactive web response system Source: Adapted from Trial RX-3341-201 Clinical Study Report, Table 3 Schedule of Events								

Study Endpoints

Clinical efficacy was assessed via signs and symptoms of infection, measurement of the extent of infection and culture and susceptibility testing of bacterial isolates. Signs and symptoms of cSSSI were reviewed at each visit.

Primary Efficacy Endpoint

The primary efficacy endpoint was the investigator's assessment of clinical response, via assessment of signs and symptoms of infection, in the CE population at the TOC visit. Clinical response was classified as either: cure, failure, or indeterminate.

Secondary Efficacy Endpoints:

Secondary efficacy endpoints were:

- Clinical response rate in patients with infections caused by MRSA
- Microbiological response rate in all patients
- Microbiological response in patients with infections caused by MRSA

Analysis Population

Seven study populations were analyzed in this study. They were as follows:

- **All-randomized population**, which included all patients who were enrolled in the study and randomized to 1 of 3 study arms
- **ITT population**, included all randomly assigned patients who received at least 1 dose of study drug.
- **Modified ITT (mITT) population**, included all ITT patients with a clinical diagnosis of a protocol defined cSSSI
- **Clinically evaluable (CE) population**, as defined in earlier described trials
- **Microbiologically evaluable (ME) population**, all subjects in the CE population with a study drug susceptible pathogen at baseline.
- **Safety population**, all randomly assigned patients who received at least 1 dose of study drug.
- **PK population**, all randomly assigned patients who received a dose of delafloxacin and who had any measureable plasma concentrations of study drug.

Subjects in the all-randomized, ITT, mITT, CE and ME populations were analyzed according to the treatment to which they were randomized, and not according to the treatment that they actually received. Whereas, subjects in the safety and PK populations were analyzed according to actual treatment received as opposed to randomly assigned treatment.

Safety Assessments and Safety Analysis

Safety assessments consisted of the evaluation of the incidence of AEs, laboratory assessments, vital signs, and physical exam findings. The incidence of AEs was a secondary study endpoint. All AEs were assessed for severity grade, relationship to study drug, and if it resulted in an SAE and/or study drug discontinuation.

Protocol Amendments

The original version of Trial 201 (Version 1.0) was issued on 18 April 2008 and the final version, Version 2, was issued on 3 June 2008. There was 1 protocol amendment dated 10 July 2008.

Protocol Amendment 1 (dated 10 July 2008):

The following **key** change was outlined in Protocol amendment 1:

- Diabetic foot ulcer was removed from the inclusion criteria and randomization procedures and was added as an exclusion criterion.

7 Integrated Review of Effectiveness

7.1 Assessment of Efficacy Across Trials

The primary FDA efficacy endpoint for both Phase 3 pivotal trials was a clinical response defined as $\geq 20\%$ reduction in the ABSSSI lesion erythema area compared with baseline at 48 to 72 hours after initiation of treatment, as determined by digital measurements of the leading edge.

Clinical failure (a clinical non-responder) for both Phase 3 trials was defined as the occurrence of any of the following:

- A $<20\%$ reduction in ABSSSI lesion erythema, as determined by digital planimetry at 48 to 72 hours post-study drug initiation;
- The need to administer a rescue antibacterial therapy prior to the 48 to 72 hour primary efficacy endpoint assessment;
- Need for an unplanned surgical intervention prior to the 48 to 72 hour primary efficacy endpoint assessment; and
- Death by 74 hours post-initiation of study drug.

As so defined, the Applicant's primary FDA efficacy endpoint is consistent with the FDA's 2013 ABSSSI Guidance for Industry's recommended definitions of clinical responders (cures) and clinical non-responders (failures) for the ABSSSI indication.

Efficacy Analysis Methodology

In accordance with FDA's ABSSSI Guidance and 21 CFR 314, the Applicant conducted two adequate and well-controlled trials to provide evidentiary support of delafloxacin's overall efficacy compared with the comparator (vancomycin \pm aztreonam). The efficacy data for each of the Phase 3 trials were reviewed separately to ensure that the evidence in support of efficacy was reproducible. Furthermore, despite similarities in study comparators, treatment duration, primary efficacy endpoint, in this reviewer's view, because Trial 302 included the administration of delafloxacin IV alone and Trial 303 included IV to oral switch, the difference additionally justified that efficacy outcomes for each of the Phase 3 trials be reviewed separately.

To achieve greater objectivity in the assessment of the primary FDA endpoint, digital planimetry (as determined by digital measurements of the leading edge) was used. Digital photographs of

lesion size reduction were not made available with this application, however, as discussed at the pre-NDA meeting, photographs would be made available to the review team upon request. Furthermore, investigator obtained manual measurements alone (but not digital measurements) were made available in subject eCRFs. This made it rather difficult for the reviewer to independently confirm lesion size reductions by review of subject eCRFs.

Efficacy analyses performed by the clinical reviewer were compared against those performed by the Applicant and are presented in this section (and/or the appendix). While this review will focus on the primary efficacy endpoint—early clinical response (ECR) at the 48 to 72 hour time point-- for both the ITT and the microbiological Intent-to-Treat (MITT) analysis populations, for a more detailed review of all statistical analyses the reader is referred to statistician’s Dr. Janelle Charles’ Biometrics review and clinical microbiologist’s, Dr. Jalal Sheikh’s review, for discussion of the primary microbiologic endpoint.

Efficacy Analysis Populations

The primary efficacy analysis was conducted using the ITT population which was defined as all subjects randomized to treatment. A total of 1,510 subjects were analyzed in the combined ITT population of the Applicant’s two pivotal Phase 3 trials. **Table 14** provides a tabular summary of all subjects comprising the 10 analysis sets in each of the two Phase 3 trials and in the pooled analysis. Please refer to **Section 6 Review of Relevant Individual Trials** for a review of the definitions for each analysis population.

Analysis Sets	Trial RX-3341-302		Trial RX-3341-303		Pooled Phase 3 Trials	
	Delafloxacin	Vancomycin (± Aztreonam)	Delafloxacin	Vancomycin (± Aztreonam)	Delafloxacin	Vancomycin (±Aztreonam)
Intent-to-Treat (ITT)	331 (100%)	329 (100%)	423 (100%)	427 (100%)	754 (100%)	756 (100%)
Microbiological Intent-to-Treat (MITT)	243 (73.4%)	247 (75.1%)	275 (65.0%)	277 (64.9%)	518 (68.7%)	524 (69.3%)
Clinically Evaluable (CE) Objective Endpoint at 48-72 Hours	294 (88.8%)	297 (90.3%)	395 (93.4%)	387 (90.6%)	689 (91.4%)	684 (90.5%)
CE Investigator Assessed Endpoint at End of Treatment (EOT)	292 (88.2%)	300 (91.2%)	391 (92.4%)	380 (89.0%)	683 (90.6%)	680 (89.9%)
CE Investigator Assessed Endpoint at Follow-Up	240 (72.5%)	244 (74.2%)	353 (83.5%)	329 (77.0%)	593 (78.6%)	573 (75.8%)

(FU)))))
CE Investigator Assessed Endpoint at Late Follow-Up (LFU)	245 (74.0%)	244 (74.2%)	337 (79.7%)	323 (75.6%)	582 (77.2%)	567 (75.0%)
Medically Evaluable (ME) Objective Endpoint at 48-72 Hours	220 (66.5%)	225 (68.4%)	264 (62.4%)	250 (58.5%)	484 (64.2%)	475 (62.8%)
ME Investigator Assessed Endpoint at End of Treatment (EOT)	217 (65.6%)	229 (69.6%)	258 (61.0%)	245 (57.4%)	475 (63.0%)	474 (62.7%)
ME Investigator Assessed Endpoint at Follow-Up (FU)	179 (54.1%)	184 (55.9%)	231 (54.6%)	212 (49.6%)	410 (54.4%)	396 (52.4%)
ME Investigator Assessed Endpoint at Late Follow-Up (LFU)	183 (55.3%)	186 (56.5%)	227 (53.7%)	210 (49.2%)	410 (54.4%)	396 (52.4%)

Sources: ISE Population. ADSL Dataset with additional reference to Table 10 in Module 2.7.3 Summary of Clinical Efficacy

Medical Reviewer’s Comments: As illustrated in Table 14 above, the overall percentages of subjects in each of the 10 analysis sets were similar across treatment arms for both Phase 3 trials.

FDA Primary Objective Response at 48 to 72 Hours —ITT and MITT Analysis Sets

Table 15 below provides a tabular summary of all clinical responders (cures) versus all clinical non-responders (failures) across treatment arms for each Phase 3 trial and for the pooled Phase 3 analysis. For the primary FDA endpoint, non-inferiority was estimated using the two-sided 95% confidence interval (CI) based on the difference in response rates (delafloxacin – vancomycin) for the two treatment arms at the 48 to 72 hours (± 2 hours) time point. For delafloxacin to be considered non-inferior to its comparator, vancomycin (± aztreonam), delafloxacin would need to be **greater** than -10% at the lower limit of the 2-sided 95% CI in the ITT population.

In Trial 302, the 300-mg delafloxacin IV only versus comparator trial, a total of 259 of 331 (78.3%) and 266 of 329 (80.9%) subjects in the delafloxacin and vancomycin comparator arms, respectively, achieved a clinical response at the 48 to 72 hour time point (Difference: -2.6; 95% CI -8.8%, 3.6%). Therefore, with the lower limit of the 95% CI being -8.8%, delafloxacin was established as non-inferior to vancomycin at the -10% inferiority margin.

In Trial 303, the delafloxacin IV-to-oral switch versus comparator study, 354 out of 423 (83.7%) subjects and 344 out of 427 (80.6%) subjects in the delafloxacin and vancomycin (± aztreonam) comparator arms, respectively, achieved a clinical response at the 48 to 72 hour primary FDA time point (Difference: -3.1; 95% CI -2.0, 8.3). The lower limit of the 95% non-inferiority margin (delafloxacin – vancomycin) was greater than -10% (-2.0%), indicating that delafloxacin was non-inferior to vancomycin (± aztreonam).

Table 15: FDA Primary Endpoint: Clinical Response at 48 to 72 Hours (±2 Hours), (ITT and MITT Analysis Sets)

Clinical Response at 48-72 hours	Trial 302 Delafloxacin	Trial 302 Vancomycin	Trial 303 Delafloxacin	Trial 303 Vancomycin	Pooled Phase 3 Delafloxacin	Pooled Phase 3 Vancomycin
ITT population	N=331	N=329	N=423	N=427	N=754	N=756
Clinical Responder	259 (78.3%)	266 (80.9%)	354 (83.7%)	344 (80.6%)	613 (81.3%)	610 (80.7%)
<i>Clinical Non-Responder</i>	<i>72 (21.8%)</i>	<i>63 (19.2%)</i>	<i>69 (16.3%)</i>	<i>83 (19.4%)</i>	<i>141 (18.7%)</i>	<i>146 (19.3%)</i>
Difference (95% CI)	-2.6 (-8.8, 3.6)		3.1 (-2.0, 8.3)		0.8 (-3.2, 4.7)	
MITT population	N=243	N=247	N=275	N=277	N=518	N=524
Clinical Responder	197 (81.1%)	207 (83.8%)	241 (87.6%)	228 (82.3%)	438 (84.6%)	435 (83.0%)
<i>Clinical Non-Responder</i>	<i>46 (18.9%)</i>	<i>40 (16.2%)</i>	<i>34 (12.4%)</i>	<i>49 (17.7%)</i>	<i>80 (15.4%)</i>	<i>89 (17.0%)</i>
Difference (95% CI)	-2.7 (-9.5, 4.0)		5.3 (-0.7, 11.4)		1.8 (-2.7, 6.3)	
<i>Source: ISE Population. ADSL and ADEFF Data Sets and confirmed against Table 18 in Applicant's Summary of Clinical Efficacy. Non-inferiority margin: 10%</i>						

As illustrated above, in the IV-to-oral switch study, delafloxacin response rates were slightly more favorable than delafloxacin response rates in Trial 302, the IV only study.

Medical Reviewer's Comments: As stated previously, the FDA and EMA each have separate primary efficacy endpoints, with the FDA primary endpoint being "a >20% reduction in ABSSSI lesion spread of erythema area as measured by digital planimetry" at 48 to 72 hours in the ITT population. The difference in clinical response rates in the pooled ITT analysis favored the delafloxacin arm.

As **Table 15** illustrates, clinical response and non-response rates were fairly similar across treatment arms in the ITT and MITT analysis populations.

Table 16 summarizes the reasons for failure to attain a clinical response to treatment.

Table 16: FDA Primary Endpoint: Clinical Non-Responders at 48 to 72 Hours (\pm 2 hours), by Reasons for Non-Response, ITT Population				
Clinical Response at 48-72 hours	Trial 302 Delafloxaci n	Trial 302 Vancomyci n (\pm Aztreonam)	Trial 303 Delafloxaci n	Trial 303 Vancomyci n (\pm Aztreonam)
ITT population	N=331	N=329	N=423	N=427
<i>Clinical Responder</i>	259 (78.3%)	266 (80.9%)	354 (83.7%)	344 (80.6%)
Clinical Non-Responder	72 (21.8%)	63 (19.2%)	69 (16.3%)	83 (19.4%)
Reasons for Non-Response, n/N (%)				
<i><20% reduction of erythema area</i>	46 (13.9%)	40 (12.2%)	49	61
<i>Missing baseline or 48-72 hours assessment of erythema area</i>	26 (7.9%)	22 (6.7%)	20 (4.7%)	21 (4.9%)
<i>Administration of rescue or non-study antibacterial therapy up to the 48-72 hours assessment</i>	1 (0.3%)	1 (0.3%)	0	2 (0.5%)
<i>Need for unplanned surgical intervention up to the 48-72 hours assessment</i>	0	0	0	1 (0.2%)
Source: ADEFF dataset and Table 14.2.1.1. *A patient may have more than one reason for nonresponse and is counted once for each reason.				

In the ITT population, there were a total of 135 clinical non-responders across both treatment arms of Trial 302 at the 48 to 72 hour time point. Slightly more subjects in the delafloxacin arm, 72 (21.8%) demonstrated a clinical non-response at the 48 to 72 hour time point than subjects in the comparator arm where 63 (19.1%) subjects were clinical non-responders at this time point. No subjects met criteria for a clinical non-response due to death at 74 hours after treatment initiation or for an unplanned surgical procedure. Rather, the most frequent reason for clinical non-response among subjects in either treatment arm was failure to achieve a \geq 20% reduction in the area of lesion erythema (or conversely having a $<$ 20% reduction in the area of lesion erythema). Most subjects experiencing a non-response due to a $<$ 20% reduction, in either treatment arm, had cellulitis/erysipelas (delafloxacin 30/331 [91%] vs. vancomycin 27/329 [8.2%]); followed by wound infection (delafloxacin 9/331 [2.7%] vs. vancomycin 4/329 [1.2%]); major cutaneous abscess (delafloxacin 7/331 [2.1%] vs. vancomycin 9/329 [2.7%]) and burns

(delafloxacin 0/331 [0.0%] vs. vancomycin 0/329 [0.0%]). A single subject in each treatment arm was administered a non-study rescue antibacterial therapy (0.3% for each).

Of the total 152 subjects in Trial 303 who were clinical non-responders at the 48 to 72 hour time point, slightly more of these subjects, 83 (19.4%), were from the vancomycin arm than from the delafloxacin arm where 69 subjects (11.6%) were non-responders. Irrespective of treatment arm, the most commonly cited reason for clinical non-response at the FDA primary endpoint (48 to 72 hours) was achieving a <20% reduction in area of erythema. This occurred in 49 (11.6%) and 61 (14.3%) subjects in the delafloxacin and vancomycin arms, respectively. No subjects in the vancomycin arm and only 2 subjects in the delafloxacin arm, were deemed clinical non-responders due to the administration of a rescue or non-study antibacterial. There were no deaths in either arm at the 74 hour time point. Likewise similar numbers of subjects, 20 (4.7%) and 21 subjects (4.9%) in the delafloxacin and vancomycin arm, respectively, were clinical non-responders at the 48 to 72 hour time point because they had missing data pertaining to the area of erythema at either the baseline or 48 to 72 hour time points.

In Trial 303, most subjects with a non-response due to a <20% reduction, in either treatment arm, had cellulitis/erysipelas (delafloxacin 36/423 [8.5%] vs. vancomycin 46/427 [10.7%]); followed by wound infection (delafloxacin 9/423 [2.1%] vs. vancomycin 8/427 [1.9%]); major cutaneous abscess (delafloxacin 2/423 [0.5%] vs. vancomycin 5/427 [1.2%]) and burns (delafloxacin 2/423 [0.5%] vs. vancomycin 2/427[0.5%]). A single subject in each treatment arm was administered a non-study rescue antibacterial therapy (0.1% for each).

Early Clinical Response (48-72 Hours) by Infection Type

As illustrated in **Table 17** below, when evaluating clinical response rates at the ECR time point by infection type, rates of response appeared to be fairly balanced across both treatment arms and between trials. The highest response rates at the ECR time point occurred among those subjects with major cutaneous abscesses followed by subjects with wound infection in both the delafloxacin and vancomycin comparator arms. Response rates for cellulitis/erysipelas were consistent across treatment arms and trials. There were few subjects in the burn group, making it difficult to make any definitive statements on the clinical impact of treatment among subjects with this infection type.

Table 17: Clinical Response at 48-72 Hours by Infection Type, (ITT Population)				
	Trial RX-3341-302		Trial RX-3341-303	
	Delafloxacin Every 12h N=331	Vancomycin (± Aztreonam) N=329	Delafloxacin Every 12h N=423	Vancomycin (± Aztreonam) N=427
Infection Type				
Cellulitis/Erysipelas				
n	128	128	202	206

Table 17: Clinical Response at 48-72 Hours by Infection Type, (ITT Population)				
	Trial RX-3341-302		Trial RX-3341-303	
	Delafloxacin	Vancomycin	Delafloxacin	Vancomycin
Clinical Responder, n/N (%)	89 (69.5%)	95 (74.2%)	155 (76.7%)	151 (73.3%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>39 (30.5%)</i>	<i>33 (25.8%)</i>	<i>47 (23.3%)</i>	<i>55 (26.7%)</i>
<i>Difference in Clinical Response (95% CI)</i>	-4.7 (-15.7, 6.4)		3.4 (-5.0, 11.8)	
Major Cutaneous Abscess				
n	84	83	106	106
Clinical Responder, n/N (%)	68 (81.0%)	69 (83.1%)	98 (92.5%)	96 (90.6%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>16 (19.0%)</i>	<i>14 (16.9%)</i>	<i>8 (7.5%)</i>	<i>10 (9.4%)</i>
<i>Difference in Clinical Response (95% CI)</i>	-2.1 (-13.8, 9.5)		1.9 (-6.0, 10.0)	
Wound Infection				
n	116.0	116.0	111	112
Clinical Responder, n/N (%)	99 (85.3%)	100 (86.2%)	99 (89.2%)	96 (85.7%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>17 (14.7%)</i>	<i>16 (13.8%)</i>	<i>12 (10.8%)</i>	<i>16 (14.3%)</i>
<i>Difference in Clinical Response (95% CI)</i>	-0.9 (-10.1, 8.4)		3.5 (-5.5, 12.1)	
Burn Infection				
n	3	2	4	3
Clinical Responder, n/N (%)	3 (100.0%)	2 (100.0%)	2 (50.0%)	1 (33.3%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>2 (50.0%)</i>	<i>2 (66.7%)</i>
<i>Difference in Clinical Response (95% CI)</i>	0 (-, -)		16.7 (-59.3, 81.6)	
Source: ISE Population. ADEFF dataset.				
*In certain instances, percentages will not equal 100% due to rounding of numbers.				
N.B. 95% CI were obtained from Statistical Reviewer's Dr. Janelle Charles' statistical analysis.				

Early Clinical Response (48-72 Hours) by Geographic region and Infection Type

Subjects from both of the Applicant's Phase 3 trials were recruited from several geographic regions. Trial 302 recruited subjects from the U.S., five European countries and Israel; whereas, subjects in Trial 303 were recruited from a larger geographic distribution, including the U.S, Europe (7 countries, all from Eastern Europe), Latin America (5 countries), and Asia (2 countries). A table summarizing the percentage of subjects in ITT population by geographic region and country can be found in the Appendix.

Medical Reviewer's Comments:

In each trial, cellulitis/erysipelas accounted for the majority of ABSSSI infections across most regions and countries with the exception of the United States where wound infections accounted for the majority of infections. Cellulitis/erysipelas was the only infection type represented by subjects from Asian countries. Due to smaller subject numbers, from Asian and Latin American sites, clinical response rates were combined for these sites. No burn subjects were represented from these two geographic regions.

Table 18 describes ECR at the 48-72 hour time point by geographic region and type of infection.

Table 18: Objective Clinical Response at 48-72 Hours by Geographic Region and Infection Type, (ITT Population)				
	Trial RX-3341-302		Trial RX-3341-303	
	Delafloxacin N=331	Vancomycin (± Aztreonam) N=329	Delafloxacin N=423	Vancomycin (± Aztreonam) N=427
Geographic Region and Infection Type				
UNITED STATES, N	268	274	202	196
Cellulitis/Erysipelas				
n	75	81	54	54
Clinical Responder, n/N (%)	51 (68%)	61 (75.3%)	44 (81.5%)	42 (77.8%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>24 (32%)</i>	<i>20 (24.7%)</i>	<i>10 (18.5%)</i>	<i>12 (22.2%)</i>
Major Cutaneous Abscess				
n	76	76	69	65
Clinical Responder, n/N (%)	62 (81.6%)	63 (82.9%)	62 (89.9%)	60 (92.3%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>14 (18.4%)</i>	<i>13 (17.1%)</i>	<i>7 (10.1%)</i>	<i>5 (7.7%)</i>
Wound Infection				
n	114	115	79	77
Clinical Responder, n/N (%)	97 (85.1%)	100 (87.0%)	74 (93.7%)	68 (88.3%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>17 (14.9%)</i>	<i>15 (13.05)</i>	<i>5 (6.3%)</i>	<i>9 (11.7%)</i>

Table 18: Objective Clinical Response at 48-72 Hours by Geographic Region and Infection Type, (ITT Population)				
	Trial RX-3341-302		Trial RX-3341-303	
	Delafloxacin N=331	Vancomycin (± Aztreonam) N=329	Delafloxacin N=423	Vancomycin (± Aztreonam) N=427
Geographic Region and Infection Type				
<i>(%)</i>				
Burn Infection				
n	3	2	0	0
Clinical Responder, n/N (%)	3 (100.0%)	2 (100.0%)	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
<i>Clinical Non-Responder, n/N (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
EUROPE, N	63	55	165	173
Cellulitis/Erysipelas				
n	53	47	100	98
Clinical Responder, n/N (%)	38 (71.7%)	34 (72.3%)	77 (77.0%)	72 (73.5%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>15 (28.3%)</i>	<i>13 (26.7%)</i>	<i>23 (23.0%)</i>	<i>26 (26.5%)</i>
Major Cutaneous Abscess				
n	8	7	30	39
Clinical Responder, n/N (%)	6 (75.0%)	6 (85.7%)	29 (96.7%)	34 (87.2%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>2 (25.0%)</i>	<i>1 (14.3%)</i>	<i>1 (3.3%)</i>	<i>5 (12.8%)</i>
Wound Infection				
n	2	1	31	33
Clinical Responder, n/N (%)	2 (100.0%)	0 (0.0%)	24 (77.4%)	27 (81.8%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>0 (0.0%)</i>	<i>1 (100.0%)</i>	<i>7 (22.6%)</i>	<i>6 (18.2%)</i>
Burn Infection				
n	0	0	4	3
Clinical Responder, n/N (%)	0 (0.0%)	0 (0.0%)	2 (50.0%)	1 (33.3%)
<i>Clinical Non-Responder, n/N (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>2 (50.0%)</i>	<i>2 (66.7%)</i>
ASIA AND LATIN AMERICA				
Cellulitis/Erysipelas				
n	0	0	48	54
Clinical Responder, n/N (%)	N/A	N/A	34 (70.8%)	37 (68.5%)

Table 18: Objective Clinical Response at 48-72 Hours by Geographic Region and Infection Type, (ITT Population)				
	Trial RX-3341-302		Trial RX-3341-303	
	Delafloxacin N=331	Vancomycin (± Aztreonam) N=329	Delafloxacin N=423	Vancomycin (± Aztreonam) N=427
Geographic Region and Infection Type				
<i>Clinical Non-Responder, n/N (%)</i>	N/A	N/A	14 (29.2%)	17 (31.5%)
Major Cutaneous Abscess				
n	0	0	7	2
Clinical Responder, n/N (%)	N/A	N/A	7 (100.0%)	2 (100.0%)
<i>Clinical Non-Responder, n/N (%)</i>	N/A	N/A	0 (0.0%)	0 (0.0%)
Wound Infection				
n	0	0	1	2
Clinical Responder, n/N (%)	N/A	N/A	1 (100.0%)	1 (50.0%)
<i>Clinical Non-Responder, n/N (%)</i>	N/A	N/A	0 (0.0%)	1 (50.0%)
Burn Infection				
n	0	0	0	0
Clinical Responder, n/N (%)	N/A	N/A	N/A	N/A
<i>Clinical Non-Responder, n/N (%)</i>	N/A	N/A	N/A	N/A

Source: ISE population. ADSL and ADEFF data sets.

Across both treatment arms and within each trial, response rates by infection type and geographic regions were fairly balanced, with the most favorable response rates observed among those subjects with major cutaneous abscesses (82%-92%) and wound infections (85%-93%) in the North American/U.S. region. In Europe, response rates to major cutaneous abscesses and wound infections ranged from 75%-96% and 77%-100%, respectively. However, there were fewer numbers of European subjects represented in these two infection types when compared to the U.S. In the U.S., response rates by infection type were fairly balanced across treatment arms in both trials, with the exception of clinical response rates of subjects with wound infections in Trial 303 where the delafloxacin arm outperformed the vancomycin arm by several percentage points (93.7% vs 88.3%). However, the reverse was true for U.S. subjects with major cutaneous abscess in Trial 303 where responses in the vancomycin arm outperformed those in the delafloxacin arm 92.3% vs 89.9%, respectively.

Cellulitis/erysipelas response rates were fairly balanced across treatment arms and trials among European subjects. However, in the U.S. cohort, vancomycin subjects outperformed delafloxacin subjects 75.3% vs 68.0%, respectively, in Trial 302. The reverse was true for Trial 303 with delafloxacin performing better than comparator, 81.5% to 77.8%, respectively. The numbers of burn subjects in the U.S. and Europe were too few to be able to make any substantive comments on response rates. However, it was noted that clinical response rates among U.S. subjects were comparable in both treatment arms in Trial 302. No U.S. burn subjects were enrolled in Trial 303. The European region had no burn subjects in Trial 302; however, in Trial 303 slightly better clinical response rates were observed among European burn subjects in the delafloxacin arm than in the vancomycin arm (50.0% vs 33.3%), respectively, despite limited numbers of recruited subjects (4 subjects in the delafloxacin vs 3 subjects in the vancomycin arm).

Few subjects of any infection type were enrolled from Asian and Latin American sites. The highest numbers of enrolled subjects from these regions were those with cellulitis. Notably, only a single subject with cellulitis was recruited from the Asian geographic region. Response rates across treatment arms, in this infection type, were slightly more favorable in delafloxacin treated subjects than in vancomycin treated subjects (70.8% vs 68.5%). For the remaining infection types, although there were few subjects, response rates were fairly balanced for these two geographic regions.

Medical Reviewer’s Comments: Overall, efficacy findings by region and infection type support the claims that delafloxacin is non-inferior to vancomycin in both pivotal Phase 3 trials.

Microbiological Intent-to-Treat (MITT) Population

Table 19 provides a summary of subjects, by treatment arm, in the MITT population for Trials 302 and 303.

Table 19: MITT Population in Phase 3 Trials			
Planned Treatment	Trial 303 N=552	Trial 302 N=490	Pooled Phase 3 MITT Population N=1042
Delafloxacin	275 (49.8%)	243 (49.6%)	518 (49.7%)
Vancomycin + Aztreonam	277 (50.2%)	247 (50.4%)	524 (50.3%)
<i>Source: ISE population. ADMB data set.</i>			

Medical Reviewer’s Comment:

The proportion of subjects across treatment arms in the MITT population of each of the pivotal Phase 3 trials, was comparable.

Baseline Key Target Pathogens (Pooled Phase 3 MITT Population)

The Applicant is seeking a treatment indication for ABSSSI infections caused by susceptible isolates for the following Gram-positive organisms:

- *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] and methicillin-susceptible [MSSA] isolates),
- *Staphylococcus haemolyticus*
- (b) (4)
- *Streptococcus agalactiae*
- *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*)
- (b) (4)
- (b) (4)
- *Streptococcus pyogenes*
- *Enterococcus faecalis*

The Gram-negative pathogens for which the Applicant is seeking a labeling indication include:

- *Escherichia coli*
- *Enterobacter cloacae*
- (b) (4)
- *Klebsiella pneumoniae*
- (b) (4)
- *Pseudomonas aeruginosa*

Medical Reviewer's Comments:

This reviewer evaluated the pathogens for which the Applicant was seeking a labeling indication against the following: (a) the numbers of each of these pathogens represented in their pooled Phase 3 trials, with the threshold for acceptability being a minimum of 10 clinical isolates; (b) labels for other FQs and the most recently approved antimicrobials for ABSSSIs **and** (c) the relationship between the selected pathogen and the ABSSSI indication.

(b) (4)

(b) (4) Additionally, in the view of this reviewer, *Klebsiella oxytoca*, which is part of the human intestinal microbiota, is a less commonly encountered than *K. pneumoniae*, and in addition is less frequently implicated in ABSSSIs. In the literature, *Klebsiella oxytoca* is most frequently cited in association with antibiotic-associated hemorrhagic colitis and respiratory tract infections and only rarely associated with neonatal septicemia, urinary tract infections, and complicated skin and skin structure infections. Only 6 (1.2%) clinical isolates of *K. oxytoca* were identified in the pooled Phase 3 delafloxacin arm and 11 (1.1%) in the entire Phase 3 program. *Proteus mirabilis* was

identified in only 8 subjects (1.5%) in the pooled delafloxacin arm and (b) (4) was included in the secondary list.

Table 20 below provides a listing of baseline key target Gram-positive and Gram pathogens cultured from ABSSSI sites in the pooled MITT population of 1,042 subjects.

Table 20: Baseline ABSSSI Pathogens (MITT Population)			
Baseline Key Target Pathogens by ABSSSI Source	Delafloxacin	Vancomycin (± Aztreonam)	Pooled Phase 3 MITT Population
# of Subjects with Baseline Gram-Positive aerobes	419 (80.9%)	415 (79.2%)	834 (80.0%)
<i>Staphylococcus aureus</i>	319 (61.6%)	323 (61.6%)	642 (61.6%)
MRSA	144 (27.8%)	141 (26.9%)	285 (27.4%)
MSSA	177 (34.2%)	183 (34.9%)	360 (34.5%)
Streptococcus anginosus Group	65 (12.5%)	66 (12.6%)	131 (12.6%)
<i>Streptococcus intermedius</i>	28 (5.4%)	30 (5.7%)	58 (5.6%)
<i>Streptococcus anginosus</i>	23 (4.4%)	23 (4.4%)	46 (4.4%)
<i>Streptococcus constellatus</i>	14 (2.7%)	13 (2.5%)	27 (2.6%)
<i>Streptococcus pyogenes</i>	23 (4.4%)	17 (3.2%)	40 (3.8%)
<i>Staphylococcus haemolyticus</i>	15 (2.9%)	8 (1.5%)	23 (2.2%)
<i>Streptococcus agalactiae</i>	14 (2.7%)	12 (2.3%)	26 (2.5%)
<i>Enterococcus faecalis</i>	11 (2.1%)	16 (3.1%)	27 (2.6%)
<i>Staphylococcus lugdunensis</i>	11 (2.1%)	9 (1.7%)	20 (1.9%)
<i>Streptococcus dysgalactiae</i>	6 (1.2%)	10 (1.9%)	16 (1.5%)
# of Subjects with Eligible Baseline Gram-negative aerobes	58 (11.2%)	63 (12.0%)	121 (11.6%)
<i>Klebsiella pneumoniae</i>	21 (4.1%)	23 (4.4%)	44 (4.2%)
<i>Enterobacter cloacae</i>	14 (2.7%)	11 (2.1%)	25 (2.4%)
<i>Escherichia coli</i>	14 (2.7%)	20 (3.8%)	34 (3.2%)
<i>Pseudomonas aeruginosa</i>	10 (1.9%)	11 (2.1%)	21 (2.0%)
<i>Proteus mirabilis</i>	8 (1.5%)	8 (1.5%)	16 (1.5%)
Total # of Subjects (MITT Denominator)	518 (100.0%)	524 (100.0%)	1042 (100.0%)
<i>Source: ISE Population. ADSL and ADMB data sets. *Please note that several subjects were infected with >1 baseline pathogen. Therefore, accounting for the reason why column totals may differ from the actual numbers of subjects. †For several pathogens there were minor differences between the clinical reviewer's and the Applicant's analysis calculations.</i>			

A total of seventeen subjects in each treatment arms grew a key target pathogen from a blood culture source.

Table 21: Baseline Key Target Pathogens from Blood Culture Isolates

(MITT Population)			
Baseline Key Target Pathogens	Delafloxacin N= 518	Vancomycin (± Aztreonam) N= 524	Pooled Phase 3 MITT Population
Gram Positive Key Target Pathogens, n	10	11	21
<i>Staphylococcus aureus</i>	6 (1.2%)	8 (1.5%)	14 (1.3%)
<i>Streptococcus dysgalactiae</i>	3 (0.6%)	2 (0.4%)	5 (0.5%)
<i>Streptococcus intermedius</i>	1 (0.2%)	0 (0.0%)	1 (0.1%)
<i>Streptococcus pyogenes</i>	0 (0.0%)	1 (0.2%)	1 (0.1%)
Gram Negative Key Target Pathogens, n	2	1	3
<i>Klebsiella pneumoniae</i>	1 (0.2%)	0 (0.0%)	1 (0.1%)
<i>Pseudomonas aeruginosa</i>	1 (0.2%)	1 (0.2%)	2 (0.2%)
Total # of Subjects by Treatment Arm Columns	11 (2.1%)	12 (2.3%)	23 (2.2%)
Total # of Subjects (MITT Denominator)	518 (100.0%)	524 (100.0%)	1042 (100.0%)
<i>Source: ADSL and ADMB data sets.</i>			
<i>*Please note that several subjects were infected with >1 baseline pathogen. Therefore, accounting for why column totals may differ from the # of subjects.</i>			
<i>†For some pathogens there are minor differences between the reviewer's and the Applicant's subject numbers.</i>			

Approximately 2% of subjects in both treatment arms had baseline eligible pathogens cultured from a blood culture source. As with ABSSSI cultured sites, the predominant pathogen found in blood cultures, in either treatment arm, was *Staphylococcus aureus* followed by *Streptococcus dysgalactiae*. Two subjects in the delafloxacin arm and three subjects in the vancomycin comparator arm grew MRSA positive blood cultures. Subject 303/840-386-3626 a 51 year old female heroin abuser grew both MRSA and MSSA in her blood cultures. Most subjects who had *S. aureus* bacteremia (MRSA or MSSA) were from the US and had a history of either IV drug abuse or diabetes. Two subjects in the delafloxacin arm (Subjects 302-784-063-0696 and 302/840-017-0403) were dually infected with MSSA and *Streptococcus dysgalactiae* and *Streptococcus intermedius*, respectively.

Medical Reviewer's Comments:

Across treatment arms, and with few exceptions, the numbers of subjects with baseline eligible Gram-positive and Gram-negative pathogens were fairly balanced. Unsurprisingly, there were considerably more subjects with Gram positive ABSSSI infections, than subjects with Gram negative infections, given the ABSSSI treatment indication. Gram positive pathogens are most frequently implicated in skin infections.

Staphylococcus aureus was the most frequently cultured organism from ABSSSI or blood culture sites in either treatment arm. Among delafloxacin subjects, MRSA accounted for 45% (144/319)

of all subjects whose ABSSSI infection sites grew *S. aureus*, whereas MSSA accounted for the majority (55.5%; 177/319) of all *S. aureus* clinical isolates in this arm. There were slightly more subjects in the delafloxacin arm than in the comparator arm from whom *Streptococcus pyogenes* and *Staphylococcus haemolyticus*--the two next most frequently cultured pathogens--were cultured. The reverse was true of *Escherichia coli* and *Enterococcus faecalis*. Interestingly, the sponsor did not seek a claim for *E. faecium*. A total of 6 subjects, 3 subjects in each treatment arm, grew this pathogen. Both *Streptococcus dysgalactiae* and *Proteus mirabilis* were cultured from fewer than ten subjects in the delafloxacin arm, (b) (4).

MITT Population by Monomicrobial and Polymicrobial Infections

The Applicant characterized infections according to organism Gram stain status (i.e., Gram negative, Gram positive, Gram mixed) and by whether the ABSSSI infection was a monomicrobial or polymicrobial infection. **Table 22** displays infections by monomicrobial and polymicrobial infection status and Gram stain status.

Table 22: Baseline ABSSSI Monomicrobial and Polymicrobial Pathogens		
Eligible Baseline Pathogens	Delafloxacin (N=514)	Vancomycin (± Aztreonam) (N=519)
Monomicrobial ABSSSI Infections		
Monomicrobial Gram Positive Pathogens	337 (65.6%)	352 (67.8%)
Monomicrobial Gram Negative Pathogens	16 (3.1%)	28 (5.4%)
Polymicrobial ABSSSI Infections		
Polymicrobial Gram Positive Pathogens	82 (16.0%)	68 (13.1%)
Polymicrobial Gram Negative Pathogens	7 (1.4%)	2 (0.4%)
Polymicrobial Mixed Gram Positive and Gram Negative Pathogens	72 (14.0%)	69 (13.3 %)
<i>Source: ADMB data set. Reviewer generated table. Only subjects flagged as having polymicrobial and monomicrobial infections are included in this table, accounting for the difference in the subject denominator in this population of subjects compared with those in the MITT population.</i>		

Gram Positive Monomicrobial and Polymicrobial ABSSSI Infections

Among subjects randomized to the delafloxacin arm, Gram-positive, monomicrobial ABSSSI infections accounted for over half, or 65.6% (337/514), of all ABSSSI site infections. Similarly, subjects with Gram-positive monomicrobial ABSSSI organisms comprised 67.8% (352/519) of all subjects in the vancomycin (± aztreonam) comparator arm. Unsurprisingly, in both treatment arms, *S. aureus* was the most commonly cultured pathogen from these Gram-positive monomicrobial ABSSSI infections. Irrespective of treatment arm, over 25% of subjects in the MITT population who had MRSA infections were recruited from US sites: 136 (26.3%) and 137 (26.2%) in the delafloxacin and vancomycin arms, respectively.

Among subjects administered delafloxacin, *S. aureus* infections were followed by subjects infected with *Streptococcus anginosus* group (29/514 [5.6%]) and *Streptococcus pyogenes* (11/514 [2.1%]) as the second and third most frequently cultured monomicrobial Gram positive ABSSSI infections. Both treatment arms had near equal numbers of subjects cultured with monomicrobial Gram positive infections as assessed by infection type, with wound infections being the most frequently encountered infection type (delafloxacin 113/514 [22.0%] vs vancomycin 114/519 [22.0%]); followed by major cutaneous abscess (delafloxacin 91/514 [17.7%] vs vancomycin 100/519 [19.3%]); cellulitis/erysipelas (delafloxacin 82/514 [16.0%] vs 89/519 [17.1%]); and lastly burn infections (delafloxacin 4/514 [0.8%] vs vancomycin 1 [0.2%]). Most monomicrobial Gram-positive ABSSSI infections were from the U.S. and Europe.

In the Appendix, a table summarizing Gram positive pathogens by key target pathogens (those for which the Applicant is seeking a treatment indication) and according to monomicrobial versus polymicrobial status can be found.

Clinical Response in Gram Positive Infections at FDA Primary Endpoint at 48 to 72 Hours and Follow-up Visit (Day 14 ± 1 day)

Table 23 below provides the efficacy outcomes for all subjects with key target Gram positive pathogens at the 48 to 72 hour and FU visits.

Table 23: Objective Clinical Response at Follow-Up Visit (Day 14 ± 1 day) for Key Gram-Positive Pathogens in Polymicrobial Gram-Mixed Infections			
Gram Positive Pathogen	Analysis Value	Delafloxacin	Vancomycin (± Aztreonam)
<i>Staphylococcus aureus</i> , N=	Cure	16 (2.1%)	16 (2.1%)
	Improved	13 (1.7%)	19 (2.5%)
	Indeterminate	1 (0.1%)	0 (0.0%)
	Failure	0 (0.0%)	2 (0.3%)
	Missing	2 (0.3%)	3 (0.4%)
<i>Streptococcus anginosus</i> Group			
<i>Streptococcus anginosus</i> , N=	Cure	4 (0.5%)	3 (0.4%)
	Improved	5 (0.7%)	3 (0.4%)
	Indeterminate	1 (0.1%)	0 (0.0%)
	Missing	1 (0.1%)	3 (0.4%)
<i>Streptococcus intermedius</i> , N=	Cure	4 (0.5%)	1 (0.1%)
	Improved	1 (0.1%)	1 (0.1%)
	Failure	0 (0.0%)	1 (0.1%)
	Missing	1 (0.1%)	1 (0.1%)
<i>Streptococcus</i>	Cure	0 (0.0%)	3 (0.4%)

<i>constellatus</i> , N=	Improved	3 (0.4%)	3 (0.4%)
	Missing	1 (0.1%)	0 (0.0%)
<i>Streptococcus pyogenes</i> , N=	Cure	1 (0.1%)	0 (0.0%)
	Improved	1 (0.1%)	1 (0.1%)
<i>Staphylococcus haemolyticus</i> , N=	Cure	2 (0.3%)	1 (0.1%)
	Improved	2 (0.3%)	0 (0.0%)
	Missing	1 (0.1%)	0 (0.0%)
<i>Streptococcus agalactiae</i> , N=	Cure	3 (0.4%)	2 (0.3%)
	Improved	1 (0.1%)	1 (0.1%)
	Failure	1 (0.1%)	0 (0.0%)
<i>Enterococcus faecalis</i> , N=	Cure	3 (0.4%)	5 (0.7%)
	Improved	1 (0.1%)	1 (0.1%)
	Failure	0 (0.0%)	1 (0.1%)
<i>Staphylococcus lugdunensis</i> , N=	Cure	1 (0.1%)	0 (0.0%)
<i>Streptococcus dysgalactiae</i> , N=	Cure	2 (0.3%)	3 (0.4%)
	Improved	2 (0.3%)	0 (0.0%)
Source: ISE population. ADMB and ADEFF data sets.			

Monomicrobial Gram Negative ABSSSI Infections

Subjects from whom monomicrobial Gram-negative infections were cultured from ABSSSI sites accounted for 3.1% (16/514) and 5.4% (28/519) of all subjects in the delafloxacin and vancomycin (± aztreonam) comparator treatment arms, respectively. However, when pathogens for which the Applicant was seeking a labeling claim were considered, the numbers of subjects were further reduced to 10 subjects (1.9%) in the delafloxacin arm and 19 subjects (3.6%) in the vancomycin (± aztreonam) arm. Most Gram-negative monomicrobial ABSSSI infections, cultured in either treatment arm were categorized as wound infections (delafloxacin: 6 subjects [6/514; 1.2%] vs. vancomycin 11 subjects [11/519; 2.1%]); followed by major cutaneous abscess (delafloxacin: 2 subjects [0.4%] vs vancomycin 5 subjects [1.0%]); and cellulitis/erysipelas infections (delafloxacin: 2 subjects [0.4%] vs 3 subjects [0.6%]). There were no subjects with burn infections in this category of ABSSSI infection.

Over half of all subjects with Gram-negative, monomicrobial ABSSSI infections were from the U.S (delafloxacin: 7 subjects [7/16; 43.8%] vs. vancomycin: 9 subjects [9/28; 32.1%]). Most of these subjects either had chronic illnesses (i.e. diabetes mellitus, hypertension, ischemic heart disease, atrial fibrillation) or were IV drug users with a history of hepatitis C infection (HCV).

The reader is referred to **Table 24** below for full frequency counts and percentages of subjects with monomicrobial and polymicrobial ABSSSI infections (Gram mixed) who were infected with key Gram-negative target pathogens.

Table 24: Key Target Gram Negative Pathogens by Polymicrobial vs Monomicrobial Infection, MITT Population (ABSSSI Source)		
	Delafloxacin N=514	Vancomycin (± Aztreonam) N=519
Key Target Gram Negative Pathogens		
<i>Escherichia coli, N</i>	14	20
Monomicrobial Gram Negative Infections	2 (14.3%)	7 (35.0%)
Polymicrobial Gram Negative Infections	1 (7.1%)	1 (5.0%)
Polymicrobial Gram Mixed Infections	11 (78.6%)	12 (60.0%)
<i>Klebsiella pneumoniae, N</i>	21	23
Monomicrobial Gram Negative Infections	4 (19.1%)	8 (34.8%)
Polymicrobial Gram Negative Infections	2 (9.5%)	1 (4.4%)
Polymicrobial Gram Mixed Infections	15 (71.4%)	14 (60.9%)
<i>Proteus mirabilis, N</i>	8	8
Monomicrobial Gram Negative Infections	2 (25.0%)	0 (0.0%)
Polymicrobial Gram Negative Infections	2 (25.0%)	0 (0.0%)
Polymicrobial Gram Mixed Infections	4 (50.0%)	8 (100.0%)
<i>Pseudomonas aeruginosa, N</i>	10	11
Monomicrobial Gram Negative Infections	0 (0.0%)	4 (36.4%)
Polymicrobial Gram Negative Infections	1 (10.0%)	0 (0.0%)
Polymicrobial Gram Mixed Infections	9 (90.0%)	7 (63.6%)
<i>Enterobacter cloacae, N</i>	14	11
Monomicrobial Gram Negative Infections	2 (14.3%)	0 (0.0%)
Polymicrobial Gram Negative Infections	3 (21.4%)	0 (0.0%)
Polymicrobial Gram Mixed Infections	9 (64.3%)	11 (100.0%)

Source: ISE population. ADMB data set. Table generated by the clinical reviewer using JReview.

Gram Negative Infections at FDA Primary Endpoint at 48 to 72 Hours and Follow-up Visits (Day ± 1 day)

Table 25 below provides the efficacy outcomes for all subjects with key target Gram negative pathogens at the 48 to 72 hour. A table of efficacy outcomes for all subjects with key Gram negative pathogens at the FU visit can be found in the Appendix. *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter cloacae* were the three most frequently cultured pathogens from ABSSSI sites and most of these pathogens were cultured from individuals with polymicrobial gram mixed infections as displayed in the table below.

Table 25: Gram Negative Infections at FDA Primary Endpoint at 48 to 72 Hours (MITT Population)			
Key Target Gram Negative (ABSSSI Source)	Subject Objective Clinical Response at 48-72 hours	Delafloxacin N= 514	Vancomycin (±Aztreonam) N=519
<i>Escherichia coli</i>	N	14	20
Monomicrobial Gram Negative Infections	<i>n</i>	2	7
	Clinical Responder	2 (100.0%)	6 (85.7%)
	Clinical Non Responder	0 (0.0%)	1 (14.3%)
Polymicrobial Gram Negative Infections	<i>n</i>	1	1
	Clinical Responder	1 (100.0%)	1 (100.0%)
	Clinical Non Responder	0 (0.0%)	0 (0.0%)
Polymicrobial Gram Mixed Infections	<i>n</i>	11	12
	Clinical Responder	9 (81.8%)	9 (75.0%)
	Clinical Non Responder	2 (18.2%)	3 (25.0%)
<i>Klebsiella pneumoniae</i>	N	21	23
Monomicrobial Gram Negative Infections	<i>n</i>	4	8
	Clinical Responder	4 (100.0%)	8 (100.0%)
	Clinical Non Responder	0 (0.0%)	0 (0.0%)
Polymicrobial Gram Negative Infections	<i>n</i>	2	1
	Clinical Responder	1 (50.0%)	1 (50.0%)
	Clinical Non Responder	1 (50.0%)	0 (0.0%)
Polymicrobial Gram Mixed Infections	<i>n</i>	15	14
	Clinical Responder	13 (86.7%)	13 (92.9%)
	Clinical Non Responder	2 (13.3%)	1 (7.1%)
<i>Proteus mirabilis</i>	N	8	8
Monomicrobial Gram Negative Infections	<i>n</i>	2	0
	Clinical Responder	1 (50.0%)	0 (0.0%)
	Clinical Non Responder	1 (50.0%)	0 (0.0%)
Polymicrobial Gram Negative Infections	<i>n</i>	2	0
	Clinical Responder	1 (50.0%)	0 (0.0%)
	Clinical Non Responder	1 (50.0%)	0 (0.0%)
Polymicrobial Gram Mixed Infections	<i>n</i>	4	8
	Clinical Responder	4 (100.0%)	5 (62.5%)
	Clinical Non Responder	0 (0.0%)	3 (37.5%)
<i>Pseudomonas aeruginosa</i>	N	10	11
Monomicrobial Gram Negative Infections	<i>n</i>	0	4
	Clinical Responder	0 (0.0%)	4 (100.0%)
	Clinical Non Responder	0 (0.0%)	0 (0.0%)
Polymicrobial Gram Negative Infections	<i>n</i>	1	0
	Clinical Responder	1 (100.0%)	0 (0.0%)
	Clinical Non Responder	0 (0.0%)	0 (0.0%)
Polymicrobial Gram Mixed Infections	<i>n</i>	9	7

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 BAXDELA™ (delafloxacin meglumine)

	Clinical Responder	7 (77.8%)	6 (85.7%)
	Clinical Non Responder	2 (22.2%)	1 (14.3%)
<i>Enterobacter cloacae</i>	N	14	11
	n	2	0
Monomicrobial Gram Negative Infections	Clinical Responder	1 (50.0%)	0 (0.0%)
	Clinical Non Responder	1 (50.0%)	0 (0.0%)
	n	3	0
Polymicrobial Gram Negative Infections	Clinical Responder	2 (66.7%)	0 (0.0%)
	Clinical Non Responder	1 (33.3%)	0 (0.0%)
	n	9	11
Polymicrobial Gram Mixed Infections	Clinical Responder	7 (77.8%)	8 (72.7%)
	Clinical Non Responder	2 (22.2%)	3 (27.3%)
Subjects(filtered)		58 (11.3%)	63(12.1%)
DENOMINATOR		514 (100.0%)	519 (100.0%)
<i>Sources: ISE Population. ADMB and ADEFF data sets.</i>			

Table 26: Gram Negative Infections at FDA Primary Endpoint at Follow-Up Visit (Day 14 ± 1 day) (MITT Population)			
Key Target Gram Negative Pathogens (ABSSI Source)	Subject Clinical Response	Delafloxacin	Vancomycin (± Aztreonam)
<i>Escherichia coli</i>	N	14	20
	n	2	7
	Cure	2 (100.0%)	6 (85.7%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	0 (0.0%)	1 (14.3%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
Monomicrobial Gram Negative Infections	n	1	1
	Cure	1 (100.0%)	1 (100.0%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	0 (0.0%)	0 (0.0%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
	n	11	12
Polymicrobial Gram Negative Infections	Cure	6 (54.6%)	5 (41.7%)
	Failure	2 (18.2%)	1 (8.3%)
	Improved	3 (27.3%)	5 (41.7%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
	N	21	23
	<i>Klebsiella pneumoniae</i>	n	4
Cure		1 (25.0%)	5 (62.5%)
Failure		0 (0.0%)	0 (0.0%)
Improved		2 (50.0%)	3 (37.5%)
Indeterminate		0 (0.0%)	0 (0.0%)
Missing		0 (0.0%)	1 (8.3%)
N		21	23
Monomicrobial Gram Negative Infections	n	4	8
	Cure	1 (25.0%)	5 (62.5%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	2 (50.0%)	3 (37.5%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	1 (8.3%)
	N	21	23

Polymicrobial Gram Negative Infections	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	1 (25.0%)	0 (0.0%)
	n	2	1
	Cure	1 (50.0%)	1 (100.0%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	1 (50.0%)	0 (0.0%)
Polymicrobial Gram Mixed Infections	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
	n	15	14
	Cure	9 (60.0%)	6 (42.9%)
	Failure	0 (0.0%)	1 (7.1%)
	Improved	5 (33.3%)	6 (42.9%)
<i>Proteus mirabilis</i>	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	1 (6.7%)	1 (7.1%)
	N	8	8
	n	2	0
	Cure	1 (50.0%)	0 (0.0%)
	Failure	0 (0.0%)	0 (0.0%)
Monomicrobial Gram Negative Infections	Improved	1 (50.0%)	0 (0.0%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
	n	2	0
	Cure	2 (100.0%)	0 (0.0%)
	Failure	0 (0.0%)	0 (0.0%)
Polymicrobial Gram Negative Infections	Improved	0 (0.0%)	0 (0.0%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
	n	4	8
	Cure	2 (50.0%)	7 (87.5%)
	Failure	0 (0.0%)	0 (0.0%)
Polymicrobial Gram Mixed Infections	Improved	2 (50.0%)	1 (12.5%)
	Indeterminate	0 (0.0%)	0 (0.0%)

	Missing	0 (0.0%)	0 (0.0%)
	N	10	11
<i>Pseudomonas aeruginosa</i>	n	0	4
	Cure	0 (0.0%)	3 (75.0%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	0 (0.0%)	1 (25.0%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
	n	1	0
	Cure	1 (100.0%)	0 (0.0%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	0 (0.0%)	0 (0.0%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
	n	9	7
	Cure	5 (55.6%)	4 (57.1%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	4 (44.4%)	3 (42.9%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
	N	14	11
<i>Enterobacter cloacae</i>	n	2	0
	Cure	1 (50.0%)	0 (0.0%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	1 (50.0%)	0 (0.0%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
	n	3	0
	Cure	1 (33.3%)	0 (0.0%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	2 (66.7%)	0 (0.0%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	N	14	11
<i>Enterobacter cloacae</i>	n	2	0
	Cure	1 (50.0%)	0 (0.0%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	1 (50.0%)	0 (0.0%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	0 (0.0%)	0 (0.0%)
	n	3	0
	Cure	1 (33.3%)	0 (0.0%)
	Failure	0 (0.0%)	0 (0.0%)
	Improved	2 (66.7%)	0 (0.0%)
	Indeterminate	0 (0.0%)	0 (0.0%)

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	Missing	0 (0.0%)	0 (0.0%)
	n	9	11
Polymicrobial Gram Mixed Infections	Cure	3 (33.3%)	8 (72.7%)
	Failure	0 (0.0%)	1 (9.1%)
	Improved	5 (55.6%)	2 (18.2%)
	Indeterminate	0 (0.0%)	0 (0.0%)
	Missing	1 (11.1%)	0 (0.0%)
Subjects(filtered)	58 (11.3%)	63(12.1%)	
DENOMINATOR	514 (100.00%)	519 (100.0%)	

Source: ADMB and ADEFF data sets. Please note that several subjects are infected with more than one pathogen, therefore, sub-totals do not equal the number of subjects filtered. Table generated by clinical reviewer using JReview.

The issue of gram mixed polymicrobial gained distinction when it was observed that of the subjects with Gram negative infections, few had Gram negative monomicrobial infections, but rather most Gram negative pathogens were cultured alongside Gram positive pathogens. Given the limited numbers of baseline Gram negative pathogens coupled with the fact that the majority of Gram negative pathogens were cultured alongside other pathogens, the review team discussed whether there were sufficient numbers of Gram negative infections to determine which pathogen was contributing to overall clinical symptomatology and therefore merit a labeling claim.

In the combined Phase 3 trials, a total of 73 subjects (73/514; 14.2%) in the delafloxacin arm and 69 subjects (69/519; 13.3%) in the comparator arm had mixed gram negative and gram positive infections. When looking solely at all gram mixed polymicrobial infections in the delafloxacin arm, it was observed that most were cultured from wound infections 34 (34 of 73 subjects; 46.6%), followed by 22 subjects (22/73; 30.1%) with major cutaneous abscess and 17 subjects (17/73; 23.3%) with cellulitis. The most common sites of ABSSSI infection were as follows: the legs (28 of 73 subjects); the “other” body sites category (20 of 73 subjects), and the arms (14 of 73 subject). An overwhelming number of these gram mixed polymicrobial infections were found among US subjects (48/73; 65.8%), with Estonia, which had 7 such subjects (7/73; 9.6%), as a distant second. Higher U.S. rates of polymicrobial infections were observed to be driven by large numbers of U.S. IV drug abusers. A total of 9 subjects with polymicrobial gram mixed infections were diabetic in both Phase 3 trials: 6 of these 9 subjects were in the delafloxacin arm (1 from Trial 302 and 5 from Trial 303) and 3 of 9 were randomized to the vancomycin arm (1 subject from Trail 302 and 2 subjects from Trial 303).

Table 27: Overall Efficacy Analysis of Polymicrobial Gram Mixed Infections at 48 to 72 Hours and Follow-Up Visit, MITT Population			
Analysis Visit	Analysis Value	Delafloxacin	Vancomycin (± Aztreonam)
48 to 72 Hours			
Y	Clinical Responder	59 (11.4%)	59 (11.3%)
	Clinical Non-Responder	13 (2.5%)	10 (1.9%)
	Total # Subjects (filtered)	72 (13.9%)	69 (13.2%)
	Denominator	518 (100.0%)	524 (100.0%)
Follow-Up Visit			
Y	Cure	32 (6.2%)	32 (6.1%)
	Failure	1 (0.2%)	4 (0.8%)
	Improved	25 (4.8%)	25 (4.8%)
	Indeterminate	2 (0.2%)	0 (0.0%)
	Missing	13 (2.5%)	8 (1.5%)
	Total # Subjects (filtered)	73 (14.1%)	69 (13.2%)
	Denominator	518 (100.0%)	524 (100.0%)
<i>Source: ISE Population. ADEFF and ADMB data sets. * The reviewer notes that there was a slight discrepancy in the numbers of subjects with polymicrobial infections in the delafloxacin arm at the 48 to 72 hour time point and the FU visit, 72 subjects vs 73 subjects, respectively.</i>			

Medical Reviewer's Comments: As observed in the table above, clinical cure and clinical failure rates among individuals infected with polymicrobial gram mixed infections were fairly balanced across both treatment arms at the 48 to 72 hour time point and at the FU visit. At the FU visit, it is noted that when compared with their counterparts in the comparator arm, there was a slight imbalance in the numbers of subjects in the delafloxacin arm whose data were missing/unavailable at the FU visit when compared with the vancomycin (± aztreonam) arm. In conclusion, it appears as though having a polymicrobial mixed infection did not negatively impact efficacy outcomes. Furthermore, in clinical practice, frequently culture data on whether an infection is polymicrobial or not is unavailable.

FQ Non Susceptible Pathogens

Near equal numbers of subjects, in both treatment arms, grew FQ non-susceptible clinical isolates as displayed in **Table 28** below:

Table 28: Fluoroquinolone (FQ) Non-Susceptible Pathogens (MITT Population)		
	Delafloxacin N=518	Vancomycin (± Aztreonam) N=524
FQ Non-Susceptible Pathogens	117 (22.6%)	135 (25.8%)
Gram Positive Pathogens		
<i>Staphylococcus aureus</i>	107 (20.7%)	120 (22.9%)
MSSA	18 (3.5%)	27 (5.2%)
MRSA	93 (18.0%)	97(18.5%)
<i>Staphylococcus haemolyticus</i>	4 (0.7%)	5 (1.0%)
Gram Negative Pathogens		
<i>Pseudomonas aeruginosa</i>	2 (0.4%)	4 (0.8%)
<i>Enterococcus faecalis</i>	1 (0.2%)	2 (0.4%)
<i>Proteus mirabilis</i>	1 (0.2%)	2 (0.4%)
<i>Klebsiella pneumoniae</i>	1 (0.2%)	0 (0.0%)
<i>Escherichia coli</i>	1(0.2%)	1 (0.2%)
<i>Enterobacter cloacae</i>	1 (0.2%)	1 (0.2%)
<i>Source: ISE Population. ADSL and ADMB data sets. *Please note that several subjects were infected with >1 baseline pathogen; therefore, accounting for why column totals may differ from the number of subjects. †For some pathogens there are minor differences between the reviewer's and the Applicant's subject numbers.</i>		

Medical Reviewer's Comments:

Most all of the FQ-non-susceptible *S. aureus*, in both arms, were from the United States. Nearly equal numbers of Gram-negative FQ-non-susceptible organisms were from Europe and the United States. Aside from the two subjects with *Pseudomonas aeruginosa* in the delafloxacin arm, the other Gram-negative FQ-non-susceptible organisms were from Europe and the United States.

Gram Negative and Gram Positive (non-Staphylococcus species) FQ non-susceptible subjects
 Since delafloxacin is a FQ, the reviewer was interested in knowing the numbers of subjects infected with FQ non-susceptible pathogens and the impact on FQ resistance on delafloxacin clinical cure rates. There were 3 species of Gram-negative organisms represented among the FQ non-susceptible Gram negative infected subjects. Although their numbers were limited, 2 of 2 (100%) of *Pseudomonas aeruginosa* infected subjects in the delafloxacin arm and 1 of 4 (25%) of subjects in the vancomycin ± aztreonam arm were clinical failures. The only *E.coli* FQ-non-susceptible subject in the delafloxacin arm was a clinical failure. However, each of the delafloxacin subjects infected with *Enterococcus faecalis*, *Proteus mirabilis*, and *Klebsiella pneumoniae* were objective clinical responders at the 48-72 hour primary endpoint. Six of the 10 Gram-negative, FQ-non-susceptible subjects in the vancomycin (± aztreonam) comparator arm were clinical responders at the 48-72 hour time point.

At the Early Clinical Response Visit (Objective Response at 48 to 72 hours) 9 of the 93 (9.7%) FQ non-susceptible MRSA positive delafloxacin treated subjects were objective clinical failures; whereas 90.3% (84/93) of the MRSA positive delafloxacin subjects were clinical responders at this time point. Comparatively, 16.5% (16/97) and 83.5% (81/97) subjects in the vancomycin comparator arm were clinical non-responders and clinical responders, respectively. However, in both instances the numbers of subjects per treatment arm were too limited to make any definitive conclusions on efficacy rates among subjects infected with FQ non-susceptible pathogens.

Parameter	Subject Objective Clinical Response	Delafloxacin N=518	Vancomycin (± Aztreonam) N=524
Total # Gram Organisms		124 (23.9%)	138 (26.3%)
Key Target Pathogens			
<i>Staphylococcus aureus</i>		N=107	N=120
	Clinical Responder	96 (77.4%)	100 (72.5%)
	Clinical Non-Responder	11 (8.1%)	20 (14.5%)
<i>Staphylococcus haemolyticus</i>		N=4	N=5
	Clinical Responder	3 (2.4%)	4 (2.9%)
	Clinical Non-Responder	1 (0.8%)	1 (0.7%)
<i>Enterococcus faecalis</i>	Clinical Responder	1 (0.8%)	2 (1.5%)
<i>Escherichia coli</i>		N=1	N=1
	Clinical Responder	0 (0.0%)	1 (0.7%)
	Clinical Non-	1 (0.8%)	0 (0.0%)

Table 29: Clinical Response at 48-72 Hours for Key Target Pathogens with FQ Non-Susceptibility			
Parameter	Subject Objective Clinical Response	Delafloxacin N=518	Vancomycin (± Aztreonam) N=524
	Responder		
<i>Proteus mirabilis</i>		N=1	N=2
	Clinical Responder	1 (0.8%)	1 (0.7%)
	Clinical Non Responder	0 (0.0%)	1 (0.7%)
<i>Pseudomonas aeruginosa</i>		N=2	N=4
	Clinical Responder	0 (0.0%)	3 (2.2%)
	Clinical Non-Responder	2 (1.6%)	1 (0.7%)
<i>Enterobacter cloacae</i>	Clinical Responder	0 (0.0%)	1 (0.7%)
<i>Enterococcus faecalis</i>	Clinical Responder	1 (0.8%)	2 (1.5%)
<i>Klebsiella pneumoniae</i>	Clinical Responder	1 (0.8%)	0 (0.0%)
<i>Source: ISE Population. ADSL and ADMB data sets.</i>			

Four of the 18 (22.2%) MSSA positive, FQ non-susceptible subjects in the delafloxacin arm and 4 of 27 (14.8%) such subjects in the vancomycin comparator arm were clinical non responders. Slightly more MSSA, FQ non-susceptible subjects in the vancomycin comparator arm were clinical responders at this time point when compared to their delafloxacin counterparts (vanco: 85.2%; [23/27]; vs. delafloxacin: 14/18 [77.8%]).

Table 30: Investigator-Assessed Response at Follow-Up Visit for Key Target Pathogens with FQ Non-Susceptibility			
Parameter	Subject Objective Clinical Response	Delafloxacin N=518	Vancomycin (± Aztreonam) N=524
Gram-Positive Pathogens			
<i>Staphylococcus aureus</i>	Cure	48 (38.71%)	52 (37.68%)
	Improved	44 (35.48%)	48 (34.78%)
	Failure	1 (0.81%)	1 (0.72%)
	Indeterminate	3 (2.42%)	0 (0.0%)
	Missing	11 (8.87%)	19 (13.77%)
<i>Staphylococcus haemolyticus</i>	Cure	3 (2.42%)	3 (2.17%)
	Improved	1 (0.81%)	1 (0.72%)
	Indeterminate	0 (0.00%)	1 (0.72%)

	e		
Gram-Negative Pathogens			
<i>Proteus mirabilis</i>	Cure	1 (0.81%)	1 (0.72%)
	Improved	0 (0.0%)	1 (0.72%)
<i>Pseudomonas aeruginosa</i>	Cure	0 (0.0%)	2 (1.45%)
	Improved	2 (1.61%)	2 (1.45%)
<i>Enterobacter cloacae</i>	Improved	0 (0.0%)	1 (0.72%)
<i>Enterococcus faecalis</i>	Cure	1 (0.81%)	2 (1.45%)
<i>Escherichia coli</i>	Cure	1 (0.81%)	1 (0.72%)
<i>Klebsiella pneumoniae</i>	Improved	1 (0.81%)	0 (0.0%)
<i>Source: ISE Population. ADSL and ADMB data sets.</i>			

Subjects with Extended Spectrum Beta-lactamase (ESBL) Pathogens

Resistance to antimicrobial drugs remains a growing public health concern. Therefore, this reviewer evaluated how many subjects in the pivotal Phase 3 trials were infected with ESBL positive pathogens. ESBL data was available for several subjects as seen in **Table 31** below:

Table 31: Baseline ABSSSI Pathogens by ESBL Status (MITT Population)		
	Delafloxacin (N=47)	Vancomycin (± Aztreonam) (N=51)
ESBL Status		
N	47	51
Non-ESBL Pathogen	41(87.3%)	50 (98.0%)
ESBL Pathogen	6 (12.8%)	1 (2.0%)
<i>Source: ISE population. ADSL and ADMB data sets.</i>		

A total of seven subjects were infected with ESBL pathogens: six in the delafloxacin arm and one in the vancomycin comparator arm. **Table 32** summarizes the demographics and microbiologic characteristics of these subjects.

Table 32: Subjects with ESBL Infections

Unique Subject Identifier	Age	Sex	Country	Type of Infection	Parameter	Delafloxacin N=6	Vancomycin (±Aztreonam) N=1
MEL303/100-435-3846	76	F	Bulgaria	Wound Infection	<i>Escherichia coli</i>	1	0 (0.0%)
MEL303/268-446-3858	40	F	Georgia	Wound Infection	<i>Escherichia coli</i>	1	0 (0.0%)
MEL303/498-470-3841	54	M	Moldova	Wound Infection	<i>Escherichia coli</i>	0 (0.0%)	1
RIBX302/428-041-0463	45	F	Latvia	Major Cutaneous Abscess	<i>Escherichia coli</i>	1	0 (0.0%)
RIBX302/784-060-0538	58	M	Ukraine	Major Cutaneous Abscess	<i>Klebsiella oxytoca</i>	1	0 (0.0%)
MEL303/498-470-3844	55	F	Moldova	Cellulitis/Erysipelas	<i>Proteus mirabilis</i>	1	0 (0.0%)
MEL303/642-479-3480	59	F	Romania	Cellulitis/Erysipelas	<i>Klebsiella pneumoniae</i>	1	0 (0.0%)
# of Subjects						6	1

Source: ISE population. ADSL and ADMB data sets.

Medical Reviewer’s Comments:

All six ESBL subjects were from Eastern Europe, ranged from ages 40 to 76, and in most cases had a history of chronic illness (i.e. diabetes mellitus, HTN, ischemia heart disease). All ESBL infected subjects, regardless of treatment arm, achieved a clinical success at the follow-up visit and one the 6 subjects in the delafloxacin arm outcome data was indeterminate/missing at the LFU visit.

7.1.2 Secondary and Other Endpoints

Both pivotal Phase 3 trials specified that should delafloxacin prove non-inferior to its comparator arm, vancomycin (± aztreonam), secondary efficacy endpoints would be tested sequentially for superiority.

The Applicant’s key secondary endpoints for **Trial 302** were as follows:

- Investigator-assessed response of signs and symptoms of infection in patients at the Follow-up Visit (EMA primary endpoint)
- Investigator-assessed response of signs and symptoms of infection in patients with a baseline \geq BMI 30 kg/m² at the Follow-up Visit
- Investigator-assessed response of signs and symptoms of infection in patients at the Late Follow-up Visit

The Applicant's key secondary endpoints for **Trial 303**, which was enriched for individuals with BMI's \geq 30 kg/m² were as follows:

- Investigator-assessed response of signs and symptoms of infection in patients with a baseline BMI \geq 30 kg/m² at the Late Follow-up Visit
- Investigator-assessed response of signs and symptoms of infection in patients with a baseline BMI \geq 30 kg/m² at the Follow-up Visit
- Investigator-assessed response of signs and symptoms of infection in patients at the Late Follow-up Visit
- Investigator-assessed response of signs and symptoms of infection in patients at the Follow-up Visit

The secondary endpoints that will be addressed in this review are those most pertinent to the delafloxacin label. Therefore, this review will focus on the secondary analysis endpoints that are of the greatest clinical relevance, namely:

- Investigator-assessed response of signs and symptoms of infection at the Follow-up Visit (EMA primary endpoint)

In a more abbreviated discussion, this review will also address other secondary endpoints and other general endpoints of interest, namely:

- Investigator-assessed response of signs and symptoms of infection in patients at the Late Follow-up Visit
- Investigator-assessed response of signs and symptoms of infection in patients at the Follow-Up Visit with baseline key target pathogens (as discussed in the Microbiological Intent to Treat sub-section 7.1.1 of this review)

Key Secondary Endpoints

Investigator-assessed response of signs and symptoms of infection at the Follow-up Visit (Day 14 \pm 1 day) (EMA primary endpoint)

In Trial 302, near similar clinical response rates were observed between treatment arms at the Follow-up visit among the ITT population in Trial 302, with delafloxacin being slightly more numerically favorable than the vancomycin (\pm aztreonam) comparator arm (52.0% vs 50.5%). However, when evaluating the CE population, at the FU visit, clinical response rates were essentially equal. The reverse was true for both the ITT and CE populations at the FU visit in Trial 303. In both instances, clinical response rates were more favorable in the comparator arm

than in the delafloxacin arm, at 59.7% vs 57.7%, respectively in the ITT population and 68.1% vs 62.3%, respectively, in the CE population. For the MITT population, sensitivity analyses for Trials 302 and 303 marginally favored the vancomycin arm; whereas clinical cures rates for delafloxacin exceeded those of vancomycin arm in Trial 302 alone within the MITT population. The same outcome was not observed for Trial 303. **Table 33** summarizes efficacy outcomes in the ITT, CE, and MITT populations at the FU visit.

(b) (4)

(b) (4). Again, sensitivity analyses equated clinical success as the equivalent of “cure + improved,” with clinical improvement assessed as patients demonstrating “complete or near resolution of signs and symptoms” of ABSSSI with no need for further antibacterial treatment. By analyzing the data this way delafloxacin’s overall clinical impact appears considerably better than in the ITT analysis.

Table 33: Investigator-Assessed Response at the Follow-Up Visit by Infection Type, (ITT Population)				
	Trial-302		Trial-303	
Investigator-Assessed Response at the Follow-Up Visit	Delafloxacin N=331	Vancomycin (± Aztreonam) N=329	Delafloxacin N=423	Vancomycin (± Aztreonam) N=427
Infection Type				
Cellulitis/Erysipelas				
N	128	128	202	206
Cure, n/N (%)	86 (67.2%)	78 (60.9%)	121 (59.9%)	130 (63.1%)
Failure Category, n/N (%)	42 (32.8%)	50 (39.1%)	81 (40.1%)	76 (36.9%)
<i>Failure</i>	4 (3.1%)	6 (4.7%)	11 (5.5%)	15 (7.3%)
<i>Improved</i>	21 (16.4%)	30 (23.4%)	50 (24.8%)	43 (20.9%)
<i>Indeterminate</i>	1 (0.8%)	3 (2.3%)	2 (1.0%)	4 (1.9%)
<i>Missing</i>	16 (12.5%)	11 (8.6%)	18 (8.9%)	14 (6.8%)
Sensitivity Analysis				
N	128	128	202	206
Success: Cure + Improve, n/N (%)	107 (83.6%)	108 (84.4%)	171 (84.7%)	173 (84.0%)
Failure Category, n/N (%)	21 (16.4%)	20 (15.6%)	31 (15.3%)	33 (16.0%)
<i>Failure, n/N(%)</i>	4 (3.1%)	6 (4.7%)	11 (5.5%)	15 (7.3%)
<i>Indeterminate, n/N (%)</i>	1 (0.8%)	3 (2.3%)	2 (1.0%)	4 (1.9%)
<i>Missing, n/N (%)</i>	16 (12.5%)	11 (8.6%)	18 (8.9%)	14 (6.8%)
Major Cutaneous Abscess				
N	84	83	106	106

Table 33: Investigator-Assessed Response at the Follow-Up Visit by Infection Type, (ITT Population)				
	Trial-302		Trial-303	
Investigator-Assessed	Delafloxacin	Vancomycin	Delafloxacin	Vancomycin
Cure, n/N (%)	44 (52.4%)	40 (48.2%)	68 (64.2%)	61 (57.6%)
Failure Category, n/N (%)	40 (47.6%)	43 (51.8%)	38 (35.8%)	45 (42.5%)
<i>Failure, n/N (%)</i>	<i>2 (2.4%)</i>	<i>0 (0.0%)</i>	<i>3 (2.8%)</i>	<i>1 (0.9%)</i>
<i>Improved, n/N (%)</i>	<i>26 (31.0%)</i>	<i>30 (36.1%)</i>	<i>27 (25.5%)</i>	<i>34 (32.1%)</i>
<i>Indeterminate, n/N (%)</i>	<i>3 (3.6%)</i>	<i>2 (2.4%)</i>	<i>0 (0.0%)</i>	<i>1 (0.9%)</i>
<i>Missing, n/N (%)</i>	<i>9 (10.7%)</i>	<i>11 (13.3%)</i>	<i>8 (7.6%)</i>	<i>9 (8.5%)</i>
Sensitivity Analysis				
N	84	83	106	106
Success: Cure + Improve, n/N (%)	70 (83.3%)	70 (84.3%)	95 (89.6%)	95 (89.6%)
Failure Category, n/N (%)	14 (16.7%)	13 (15.7%)	11 (10.4%)	11 (10.4%)
<i>Failure, n/N (%)</i>	<i>2 (2.4%)</i>	<i>0 (0.0%)</i>	<i>3 (2.8%)</i>	<i>1 (0.9%)</i>
<i>Indeterminate, n/N (%)</i>	<i>3 (3.6%)</i>	<i>2 (2.4%)</i>	<i>0 (0.0%)</i>	<i>1 (0.9%)</i>
<i>Missing, n/N (%)</i>	<i>9 (10.7%)</i>	<i>11 (13.3%)</i>	<i>8 (7.6%)</i>	<i>9 (8.5%)</i>
Wound Infection				
N	116	116	111	112
Cure, n/N (%)	39 (33.6%)	48 (41.4%)	52 (46.9%)	61 (54.5%)
Failure Category, n/N (%)	77 (66.4%)	68 (58.6%)	59 (53.1%)	51 (45.5%)
<i>Failure, n/N (%)</i>	<i>3 (2.6%)</i>	<i>1 (0.9%)</i>	<i>3 (2.7%)</i>	<i>5 (4.5%)</i>
<i>Improved, n/N (%)</i>	<i>51 (44.0%)</i>	<i>46 (39.7%)</i>	<i>47 (42.3%)</i>	<i>30 (26.8%)</i>
<i>Indeterminate, n/N (%)</i>	<i>6 (5.2%)</i>	<i>2 (1.7%)</i>	<i>1 (0.9%)</i>	<i>3 (2.7%)</i>
<i>Missing, n/N (%)</i>	<i>17 (14.7%)</i>	<i>19 (16.4%)</i>	<i>8 (7.2%)</i>	<i>13 (11.6%)</i>
Sensitivity Analysis				
N	116	116	111	112
Success: Cure + Improve, n/N (%)	90 (77.6%)	94 (81.0%)	99 (89.2%)	91 (81.3%)
Failure Category, n/N (%)	26 (22.4%)	22 (19.0%)	12 (10.8%)	21 (18.8%)
<i>Failure, n/N (%)</i>	<i>3 (2.6%)</i>	<i>1 (0.9%)</i>	<i>3 (2.7%)</i>	<i>5 (4.5%)</i>
<i>Indeterminate, n/N (%)</i>	<i>6 (5.2%)</i>	<i>2 (1.7%)</i>	<i>1 (0.9%)</i>	<i>3 (2.7%)</i>
<i>Missing, n/N (%)</i>	<i>17 (14.7%)</i>	<i>19 (16.4%)</i>	<i>8 (7.2%)</i>	<i>13 (11.6%)</i>
Burn Infection				
N	3	2	4	3
Cure, n/N (%)	3 (100.0%)	0 (0.0%)	3 (75.0%)	3 (100.0%)
Failure Category, n/N (%)	0 (0.0%)	2 (100.0%)	1 (25.0%)	0 (0.0%)
<i>Failure, n/N (%)</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
<i>Improved, n/N (%)</i>	<i>0</i>	<i>2 (100.0%)</i>	<i>1 (25.0%)</i>	<i>0</i>

Table 33: Investigator-Assessed Response at the Follow-Up Visit by Infection Type, (ITT Population)				
	Trial-302		Trial-303	
Investigator-Assessed	Delafloxacin	Vancomycin	Delafloxacin	Vancomycin
<i>Indeterminate, n/N (%)</i>	0	0	0	0
<i>Missing, n/N (%)</i>	0	0	0	0
Sensitivity Analysis				
<i>N</i>	3	2	4	3
Success: Cure + Improve, n/N (%)	3 (100.0%)	2 (100.0%)	4 (100.0%)	3 (100.0%)
Failure Category, n/N (%)	0	0	0	0
<i>Failure, n/N(%)</i>	0	0	0	0
<i>Indeterminate, n/N (%)</i>	0	0	0	0
<i>Missing, n/N (%)</i>	0	0	0	0
<i>Source: ADCR dataset. *In certain instances, percentages will not equal 100% due to rounding of numbers.</i>				

Table 34 below, summarizes the primary reasons for clinical failure or an indeterminate result at the FU visit. In most instances, clinical failure was due to treatment with a non-study drug resulting from lack of efficacy of either delafloxacin or vancomycin (± aztreonam) comparator.

Table 34: EMA Primary Endpoint (Key FDA Secondary Endpoint): Reason for Clinical Failure or Indeterminate at Follow-Up Visit (ITT Population)				
Reason for Failure or Indeterminate	Trial 302		Trial 303	
	Delafloxacin	Vancomycin (± Aztreonam)	Delafloxacin	Vancomycin (± Aztreonam)
	Trial302 (N=331)	Trial302 (N=329)	Trial 303 (N=423)	Trial 303 (N=427)
Administration of nonstudy antibacterial drug therapy due to lack of efficacy after at least 4 doses of study treatment, n/N (%)	6 (1.8%)	2 (0.6%)	8 (1.9%)	4 (0.9%)
Failure carried from EOT/FU, n/N (%)	0 (0.0%)	0 (0.0%)	4 (1.0%)	10 (2.3%)
Received potentially effective nonstudy antibacterial drug therapy for condition other than ABSSEI, n/N (%)	3 (0.9%)	3 (0.9%)	1 (0.2%)	6 (1.4%)
Need for unplanned surgical intervention after study entry ^a , n/N (%)	1 (0.3%)	2 (0.6%)	3 (0.7%)	5 (1.2%)
Administration of nonstudy antibacterial drug therapy for a treatment related Adverse Event, n/N (%)	0 (0.0%)	1 (0.3%)	2 (0.5%)	2 (0.5%)
Antibacterial drug therapy required after 28 doses of study treatment, n/N (%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

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Number of Subjects	11 (3.3%)	8 (2.4%)	18 (4.3%)	27 (6.3%)
<i>Source: ISE Population. ADEFF data sets. ^aExcept for limited bedside debridement and standard wound care.</i>				

Efficacy Analysis at Late Follow-up Visit (Days 21-28)

Table 35 below provides efficacy results for Trials 302 and 303 at the Late Follow-up Visit.

Table 35: Efficacy Analysis at Late Follow-up Visit (Days 21-28)				
Clinical Response at LFU Visit	Trial 302		Trial 303	
	Delafloxacin	Vancomycin ± Aztreonam	Delafloxacin	Vancomycin ± Aztreonam
Intent-to-Treat (ITT) population				
N	331	329	423	427
Cure, n (%)	233 (70.4%)	219 (66.6%)	287 (67.8%)	303 (71.0%)
Failure, n (%)	98 (29.6%)	110 (33.4%)	136 (32.2%)	124 (29.0%)
<i>Failure, n (%)</i>	9 (2.7%)	6 (1.8%)	21 (5.0%)	24 (5.6%)
<i>Improved, n (%)</i>	32 (9.7%)	48 (14.6%)	66 (15.6%)	48 (11.2%)
<i>Indeterminate, n (%)</i>	14 (4.2%)	12 (3.6%)	7 (1.7%)	11 (2.6%)
<i>Missing, n (%)</i>	43 (13.0%)	44 (13.4%)	42 (9.9%)	41 (9.6%)
Difference (95% CI)	3.8 (-3.3, 10.9)		-3.2 (-9.3, 3.1)	
Sensitivity Analysis				
N	331	329	423	427
Success: Cure + Improved, n (%)	265 (80.1%)	267 (81.2%)	353 (83.5%)	351 (82.2%)
Failure Category, n/N (%)	66 (19.9%)	62 (18.8%)	70 (16.5%)	76 (17.8%)
<i>Failure, n/N (%)</i>	9 (2.7%)	6 (1.8%)	21 (5.0%)	24 (5.6%)
<i>Indeterminate, n/N (%)</i>	14 (4.2%)	12 (3.6%)	7 (1.7%)	11 (2.6%)
<i>Missing, n/N (%)</i>	43 (13.0%)	44 (13.4%)	42 (9.9%)	41 (9.6%)
Difference (95% CI)	-1.1 (-7.2, 5.0)		1.3 (-3.8, 6.3)	
Clinically Evaluable (CE) population				
N	245	244	337	323
Cure, n (%)	208 (84.9%)	201 (82.4%)	259 (76.9%)	267 (82.7%)
Failure, n (%)	37 (15.1%)	43 (17.6%)	78 (23.1%)	56 (17.3%)
<i>Failure, n (%)</i>	8 (3.3%)	3 (1.2%)	15 (4.5%)	13 (4.0%)
<i>Improved, n (%)</i>	29 (11.8%)	40 (16.4%)	63 (18.7%)	43 (13.3%)

Table 35: Efficacy Analysis at Late Follow-up Visit (Days 21-28)				
Clinical Response at LFU Visit	Trial 302		Trial 303	
	Delafloxacin	Vancomycin ± Aztreonam	Delafloxacin	Vancomycin ± Aztreonam
Difference (95% CI)	2.5 (-4.1, 9.2)		-5.8 (-11.9, 0.3)	
Sensitivity Analysis				
N	245	244	337	323
Success: Cure + Improved, n (%)	237 (96.7%)	241 (98.8%)	322 (95.5%)	310 (96.0%)
Failure Category, n/N (%)	8 (3.3%)	3 (1.2%)	15 (4.5%)	13 (4.0%)
Failure, n/N (%)	8 (3.3%)	3 (1.2%)	15 (4.5%)	13 (4.0%)
Difference (95% CI)	-2.1 (-5.2, 0.7)		-0.6 (-3.7, 2.8)	
Microbiologically Intent-to-Treat (MITT) Population				
N	243	247	275	277
Cure, n (%)	174 (71.6%)	161 (65.2%)	194 (70.5%)	194 (70.0%)
Failure, n (%)	69 (28.4%)	86 (34.8%)	81 (29.5%)	83 (30.0%)
Failure, n (%)	5 (2.1%)	3 (1.2%)	9 (3.3%)	15 (5.4%)
Improved, n (%)	25 (10.3%)	42 (17.0%)	45 (16.4%)	31 (11.2%)
Indeterminate, n (%)	12 (4.9%)	9 (3.6%)	3 (1.1%)	9 (3.3%)
Missing, n (%)	27 (11.1%)	32 (13.0%)	24 (8.7%)	28 (10.1%)
Difference (95% CI)	6.4 (-1.8, 14.6)		0.5 (-7.1, 8.1)	
Sensitivity Analysis				
N	243	247	275	277
Success: Cure + Improved, n (%)	199 (81.9%)	203 (82.2%)	239 (86.9%)	225 (81.2%)
Failure Category, n/N (%)	44 (18.1%)	44 (17.8%)	36 (13.1%)	52 (18.8%)
Failure, n/N (%)	5 (2.1%)	3 (1.2%)	9 (3.3%)	15 (5.4%)
Indeterminate, n/N (%)	12 (4.9%)	9 (3.6%)	3 (1.1%)	9 (3.3%)
Missing, n/N (%)	27 (11.1%)	32 (13.0%)	24 (8.7%)	28 (10.1%)
Difference (95% CI)	-0.3 (-7.2, 6.5)		5.7 (-0.4, 11.8)	
Source: ISE Population. ADEFF data set.				

Medical Reviewer's Comments:

As Table 35 illustrates, clinical efficacy at the LFU visit across both treatment arms of each Phase 3 trial was nearly equivalent in the ITT population, with delafloxacin results looking slightly better than the comparator in Trial 302 and the reverse being true for Trial 303. When sensitivity analyses were conducted, where subject success (defined as cure + improved) was

now evaluated, clinical efficacy rates were in most instances similar for both delafloxacin and its comparator; however, the percentage of subjects demonstrating clinical efficacy also increased--across treatment arm and analysis populations—as the incidence subjects formerly considered failures in the investigator assessed “improved” category were now considered with those assessed as cures. The review team considered the analysis of cure versus failure in the ITT population provided as more realistic characterization of the clinical effectiveness of both delafloxacin and its comparator; whereas, the success category “inflates” each drugs appearance of effectiveness.

Clinical Efficacy at the Follow-Up Visit for Key Demographic Subgroups

Table 36 below provides a summary of efficacy outcome of various sub-populations at the FU Visit.

Table 36: Investigator-Assessed Clinical Response at Follow-up Visit for Key Sub-groups, (ITT Population)				
	Trial 302		Trial 303	
	Delafloxacin	Vancomycin (± Aztreonam)	Delafloxacin	Vancomycin (± Aztreonam)
AGE CATEGORIES, n/N (%)				
18-64				
N	305	309	338	346
Cure, n (%)	154 (50.5%)	157 (50.8%)	191 (56.5%)	198 (57.2%)
Failure, n (%)	151 (49.5%)	152 (49.2%)	147 (43.5%)	148 (42.8%)
<i>Failure, n (%)</i>	<i>8 (2.6%)</i>	<i>6 (1.9%)</i>	<i>11 (4.0%)</i>	<i>15 (4.3%)</i>
<i>Improved, n (%)</i>	<i>94 (30.8%)</i>	<i>100 (32.4%)</i>	<i>103 (29.6%)</i>	<i>90 (26.0%)</i>
<i>Indeterminate, n (%)</i>	<i>10 (3.3%)</i>	<i>5 (1.6%)</i>	<i>3 (0.7%)</i>	<i>8 (2.3%)</i>
<i>Missing, n (%)</i>	<i>39 (12.8%)</i>	<i>41 (13.3%)</i>	<i>30 (8.0%)</i>	<i>35 (10.1%)</i>
Sensitivity Analysis				
N	305	309	338	346
Success: Cure + Improved, n (%)	248 (81.3%)	257 (83.2%)	294 (87.2%)	288 (83.2%)
Failure Category, n/N (%)	57 (18.7%)	52 (16.8%)	44 (13.0%)	58 (16.8%)
<i>Failure, n/N (%)</i>	<i>8 (2.6%)</i>	<i>6 (1.9%)</i>	<i>11 (4.0%)</i>	<i>15 (4.3%)</i>
<i>Indeterminate, n (%)</i>	<i>10 (3.3%)</i>	<i>5 (1.6%)</i>	<i>3 (0.7%)</i>	<i>8 (2.3%)</i>
<i>Missing, n (%)</i>	<i>39 (12.8%)</i>	<i>41 (13.3%)</i>	<i>30 (8.0%)</i>	<i>35 (10.1%)</i>
N	17	10	42	48

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Cure, n (%)	12 (70.6%)	5 (50.0%)	20 (47.6%)	35 (72.9%)
Failure, n (%)	5 (29.4%)	5 (50.0%)	22 (52.4%)	13 (27.1%)
<i>Failure, n (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>3 (7.1%)</i>	<i>3 (6.3%)</i>
<i>Improved, n (%)</i>	<i>4 (23.5%)</i>	<i>3 (30.0%)</i>	<i>15 (35.7%)</i>	<i>9 (18.7%)</i>
<i>Indeterminate, n (%)</i>	<i>0 (0.0%)</i>	<i>2 (20.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
<i>Missing, n (%)</i>	<i>1 (5.9%)</i>	<i>0 (0.0%)</i>	<i>4 (9.5%)</i>	<i>1 (2.1%)</i>
Sensitivity Analysis				
N	17	10	42	48
Success: Cure + Improved, n (%)	16 (94.1%)	8 (80.0%)	35 (83.3%)	44 (91.7%)
Failure Category, n/N (%)	1 (5.9%)	2 (20.0%)	7 (16.7%)	4 (8.3%)
<i>Failure, n/N (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>3 (7.1%)</i>	<i>3 (6.3%)</i>
<i>Indeterminate, n (%)</i>	<i>0 (0.0%)</i>	<i>2 (20.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
<i>Missing, n (%)</i>	<i>1 (5.9%)</i>	<i>0 (0.0%)</i>	<i>4 (9.5%)</i>	<i>1 (2.1%)</i>
≥75				
N	9	10	43	33
Cure, n (%)	6 (66.7%)	4 (40.0%)	33 (76.7%)	22 (66.7%)
Failure, n (%)	3 (33.3%)	6 (60.0%)	10 (23.3%)	11 (33.3%)
<i>Failure, n (%)</i>	<i>1 (11.1%)</i>	<i>1 (10.0%)</i>	<i>3 (7.0%)</i>	<i>3 (9.1%)</i>
<i>Improved, n (%)</i>	<i>0 (0.0%)</i>	<i>5 (50.0%)</i>	<i>7 (16.3%)</i>	<i>8 (24.2%)</i>
<i>Indeterminate, n (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
<i>Missing, n (%)</i>	<i>2 (22.2%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
Sensitivity Analysis				
N	9	10	43	33
Success: Cure + Improved, n (%)	6 (66.7%)	9 (90.0%)	40 (93.0%)	30 (90.9%)
Failure Category, n/N (%)	3 (33.3%)	1 (10.0%)	3 (7.0%)	3 (9.1%)
<i>Failure, n/N (%)</i>	<i>1 (11.1%)</i>	<i>1 (10.0%)</i>	<i>3 (7.0%)</i>	<i>3 (9.1%)</i>
<i>Indeterminate, n (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
<i>Missing, n (%)</i>	<i>2 (22.2%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
SEX, n/N (%)				
Male				
N	206	209	262	276
Cure, n (%)	99 (48.1%)	109 (52.2%)	143 (54.6%)	162 (58.7%)
Failure, n (%)	107 (51.9%)	100 (47.8%)	119 (45.4%)	114 (41.3%)
<i>Failure, n (%)</i>	<i>7 (3.4%)</i>	<i>5 (2.4%)</i>	<i>9 (3.4%)</i>	<i>16 (5.8%)</i>
<i>Improved, n (%)</i>	<i>65 (31.6%)</i>	<i>75 (35.9%)</i>	<i>86 (32.8%)</i>	<i>70 (25.4%)</i>
<i>Indeterminate, n (%)</i>	<i>5 (2.4%)</i>	<i>4 (1.9%)</i>	<i>2 (0.8%)</i>	<i>6 (2.2%)</i>
<i>Missing, n (%)</i>	<i>30 (14.6%)</i>	<i>16 (7.7%)</i>	<i>22 (8.4%)</i>	<i>22 (8.0%)</i>
Sensitivity Analysis				
N	206	209	262	276

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Success: Cure + Improved, n (%)	164 (79.6%)	184 (88.0%)	229 (87.4%)	232 (84.1%)
Failure Category, n/N (%)	42 (20.4%)	25 (12.0%)	33 (12.6%)	44 (15.9%)
<i>Failure, n/N (%)</i>	7 (3.4%)	5 (2.4%)	9 (3.4%)	16 (5.8%)
<i>Indeterminate, n (%)</i>	5 (2.4%)	4 (1.9%)	2 (0.8%)	6 (2.2%)
<i>Missing, n (%)</i>	30 (14.6%)	16 (7.7%)	22 (8.4%)	22 (8.0%)
Female				
N	125	120	161	151
Cure, n (%)	73 (58.4%)	57 (47.5%)	101 (62.7%)	93 (61.6%)
Failure, n (%)	52 (41.6%)	63 (52.5%)	60 (37.3%)	58 (38.4%)
<i>Failure, n (%)</i>	2 (1.6%)	2 (1.7%)	8 (5.0%)	5 (3.3%)
<i>Improved, n (%)</i>	33 (26.4%)	33 (27.5%)	39 (24.2%)	37 (24.5%)
<i>Indeterminate, n (%)</i>	5 (4.0%)	3 (2.5%)	1 (0.6%)	2 (1.3%)
<i>Missing, n (%)</i>	12 (9.6%)	25 (20.8%)	12 (7.5%)	14 (9.3%)
Sensitivity Analysis				
N	125	120	161	151
Success: Cure + Improved, n (%)	106 (84.8%)	90 (75.0%)	140 (87.0%)	130 (86.1%)
Failure Category, n/N (%)	19 (15.2%)	30 (25.0%)	21 (13.0%)	21 (13.9%)
<i>Failure, n/N (%)</i>	2 (1.6%)	2 (1.7%)	8 (5.0%)	5 (3.3%)
<i>Indeterminate, n (%)</i>	5 (4.0%)	3 (2.5%)	1 (0.6%)	2 (1.3%)
<i>Missing, n (%)</i>	12 (9.6%)	25 (20.8%)	12 (7.5%)	14 (9.3%)
RACE, n/N (%)				
White*				
N	297	304	348	355
Cure, n (%)	157 (52.9%)	153 (50.3%)	201 (57.8%)	206 (58.0%)
Failure, n (%)	139 (46.8%)	150 (49.3%)	147 (42.2%)	149 (42.0%)
<i>Failure, n (%)</i>	6 (2.0%)	6 (2.0%)	10 (2.9%)	15 (4.2%)
<i>Improved, n (%)</i>	89 (30.0%)	101 (33.2%)	108 (31.0%)	92 (25.9%)
<i>Indeterminate, n (%)</i>	8 (2.7%)	5 (1.6%)	3 (0.9%)	8 (2.3%)
<i>Missing, n (%)</i>	36 (12.1%)	39 (12.8%)	26 (7.5%)	34 (9.6%)
Sensitivity Analysis				
N	297	304	348	355
Success: Cure + Improved, n (%)	246 (82.8%)	254 (83.6%)	309 (88.8%)	298 (83.9%)
Failure Category, n/N (%)	50 (16.8%)	50 (16.5%)	39 (11.2%)	57 (16.1%)
<i>Failure, n/N (%)</i>	6 (2.0%)	6 (2.0%)	10 (2.9%)	15 (4.2%)
<i>Indeterminate, n (%)</i>	8 (2.7%)	5 (1.6%)	3 (0.9%)	8 (2.3%)
<i>Missing, n (%)</i>	36 (12.1%)	39 (12.8%)	26 (7.5%)	34 (9.6%)

Black or African American				
N	27	19	13	18
Cure, n (%)	11 (40.7%)	11 (57.9%)	5 (38.5%)	12 (66.7%)
Failure, n (%)	16 (59.3%)	8 (42.1%)	8 (61.5%)	6 (33.3%)
<i>Failure, n (%)</i>	<i>3 (11.1%)</i>	<i>1 (5.3%)</i>	<i>2 (15.4%)</i>	<i>0 (0.0%)</i>
<i>Improved, n (%)</i>	<i>8 (29.6%)</i>	<i>3 (15.8%)</i>	<i>3 (23.0%)</i>	<i>6 (33.3%)</i>
<i>Indeterminate, n (%)</i>	<i>1 (3.7%)</i>	<i>2 (10.5%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
<i>Missing, n (%)</i>	<i>4 (14.8%)</i>	<i>2 (10.5%)</i>	<i>3 (23.0%)</i>	<i>0 (0.0%)</i>
Sensitivity Analysis				
N	27	19	13	18
Success: Cure + Improved, n (%)	17	14 (73.7%)	8 (61.5%)	18 (100.0%)
Failure Category, n/N (%)	8	5 (26.3%)	5(38.5%)	0 (0.0%)
<i>Failure, n/N (%)</i>	<i>3 (11.1%)</i>	<i>1 (5.3%)</i>	<i>2 (15.4%)</i>	<i>0 (0.0%)</i>
<i>Indeterminate, n (%)</i>	<i>1 (3.7%)</i>	<i>2 (10.5%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
<i>Missing, n (%)</i>	<i>4 (14.8%)</i>	<i>2 (10.5%)</i>	<i>3 (23.0%)</i>	<i>0 (0.0%)</i>
≥75				
N	9	10	43	33
Cure, n (%)	6 (66.7%)	4 (40.0%)	33 (76.7%)	22 (66.7%)
Failure, n (%)	3 (33.3%)	6 (60.0%)	10 (23.3%)	11 (33.3%)
<i>Failure, n (%)</i>	<i>1 (11.1%)</i>	<i>1 (10.0%)</i>	<i>3 (7.0%)</i>	<i>3 (9.1%)</i>
<i>Improved, n (%)</i>	<i>0 (0.0%)</i>	<i>5 (50.0%)</i>	<i>7 (16.3%)</i>	<i>8 (24.2%)</i>
<i>Indeterminate, n (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
<i>Missing, n (%)</i>	<i>2 (22.2%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
Sensitivity Analysis				
N	9	10	43	33
Success: Cure + Improved, n (%)	6 (66.7%)	9 (90.0%)	40 (93.0%)	30 (90.9%)
Failure Category, n/N (%)	3 (33.3%)	1 (10.0%)	3 (7.0%)	3 (9.1%)
<i>Failure, n/N (%)</i>	<i>1 (11.1%)</i>	<i>1 (10.0%)</i>	<i>3 (7.0%)</i>	<i>3 (9.1%)</i>
<i>Indeterminate, n (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
<i>Missing, n (%)</i>	<i>2 (22.2%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>
Source: ISE Population. ADSL and ADEFF data sets.				

7.1.3 Subpopulations

Table 37 summarizes the demographics for key sub-populations as well as several key clinical features found in the ITT populations for both Phase 3 trials.

Table 37: Subject Demographics and Baseline Characteristics (ITT Population)

	Trial 302		Trial 303		Pooled Phase 3 Trials	
	Delafloxacin N=331	Vancomycin (± Aztreonam) N=329	Delafloxacin N=423	Vancomycin (± Aztreonam) N=427	Delafloxacin N=754	Vancomycin (± Aztreonam) N=756
Age (Years)						
n	331	329	423	427	754	756
Mean (SD)	46.3 (13.9)	45.3 (14.4)	51.2 (16.0)	50.2 (16.0)	49.0 (15.3)	48.1 (15.5)
Median	47.0	46.0	51.0	50.0	49.0	48
Min, Max	18, 94	19, 90	18, 89	19, 93	18, 94	19, 93
Age Categories (Years), n (%)						
18-44	136 (41.1%)	146 (44.4%)	148 (35.0%)	162 (37.9%)	284 (37.7%)	308 (40.7%)
45-64	169 (51.1%)	163 (49.5%)	190 (44.9%)	184 (43.1%)	359 (47.6%)	347 (45.9%)
65-74	17 (5.1%)	10 (3.0%)	42 (9.9%)	48 (11.2%)	59 (7.8%)	58 (7.7%)
≥ 75	9 (2.7%)	10 (3.0%)	43 (10.3%)	33 (7.7%)	52 (6.9%)	43 (5.7%)
Sex, n (%)						
Male	206 (62.2%)	209 (63.5%)	262 (61.9%)	276 (64.6%)	468 (62.1%)	485 (64.2%)
Female	125 (37.8%)	120 (36.5%)	161 (38.1%)	151 (35.4%)	286 (37.9%)	271 (35.8%)
Race, n (%)						
White	297 (89.7%)	304 (92.4%)	348 (82.3%)	355 (83.1%)	645 (85.5%)	659 (87.2%)
Black or African American	27 (8.2%)	19 (5.8%)	13 (3.1%)	18 (4.2%)	40 (5.3%)	37 (4.9%)
Native American or Alaska Native	5 (1.5%)	2 (0.6%)	12 (2.8%)	7 (1.6%)	17 (2.3%)	9 (1.2%)
Asian	1 (0.3%)	1 (0.3%)	11 (2.6%)	15 (3.5%)	12 (1.6%)	16 (2.1%)
Native Hawaiian or other Pacific Islander	1 (0.3%)	2 (0.6%)	2 (0.5%)	2 (0.5%)	3 (0.4%)	4 (0.5%)
Other	0 (0.0%)	1 (0.3%)	37	30	37	31

Table 37: Subject Demographics and Baseline Characteristics (ITT Population)						
	Trial 302		Trial 303		Pooled Phase 3 Trials	
	Delaflox	Vancom	Delaflox	Vancom	Delaflox	Vancom
			(8.7%)	(7.0%)	(4.9%)	(4.1%)
Ethnicity, n (%)						
Hispanic or Latino	101 (30.5%)	103 (31.3%)	132 (31.2%)	99 (23.4%)	233 (30.9%)	202 (26.7%)
Non Hispanic or Non Latino	230 (69.5%)	226 (68.7%)	291 (68.8%)	328 (76.8%)	521 (69.1%)	554 (73.3%)
Region, n (%)						
North America	268 (81.0%)	274 (83.3%)	202 (47.8%)	196 (45.9%)	470 (62.3%)	470 (62.2%)
Europe	63 (19.0%)	55 (16.7%)	165 (39.0%)	173 (40.5%)	228 (30.2%)	228 (30.2%)
Asia	0 (0.0%)	0 (0.0%)	9 (2.1%)	14 (3.3%)	9 (1.2%)	14 (1.9%)
Latin American	0 (0.0%)	0 (0.0%)	47 (11.1%)	44 (10.3%)	47 (6.2%)	44 (5.8%)
BMI (kg/m²)						
n	331	329	423	427	754	756
Mean (SD)	28.4 (6.4)	27.9 (6.4)	30.4 (7.4)	30.7 (7.5)	29.5 (7.1)	29.5 (7.2)
Median	27.2	26.7	29.7	30.0	28.8	28.3
Min, Max	16.5, 52.0	17.3, 52.8	15.3, 65.8	17.3, 68.0	15.3, 65.8	17.3, 68.0
BMI Categories (kg/m²)						
<18.5 kg/m ²	6 (1.8%)	3 (0.9%)	6 (1.4%)	2 (0.5%)	12 (1.6%)	5 (0.7%)
18.5 - 24.9 kg/m ²	107 (32.3%)	122 (37.1%)	97 (22.9%)	102 (23.9%)	204 (27.1%)	224 (29.6%)
25-29.9 kg/m ²	98 (29.6%)	110 (33.4%)	109 (25.8%)	109 (25.5%)	207 (27.5%)	219 (29.0%)
30-39.9 kg/m ²	101 (30.5%)	77 (23.4%)	170 (40.2%)	169 (39.6%)	271 (35.9%)	246 (32.5%)
≥ 40 kg/m ²	19 (5.7%)	17 (5.2%)	41 (9.7%)	45 (10.5%)	60 (8.0%)	62 (8.2%)
CrCl (mL/min)						
n	321	323	409	421	730	744
Mean (SD)	128.5 (44.1)	128.6 (45.2)	141.3 (56.3)	144.9 (53.9)	135.7 (51.7)	137.8 (50.9)
Median	125.0	125.0	136.0	142.0	129.5	136.0
Min, Max	10, 278	30, 324	30, 333	18, 330	10, 333	18, 330

Table 37: Subject Demographics and Baseline Characteristics (ITT Population)

	Trial 302		Trial 303		Pooled Phase 3 Trials	
	Delaflox	Vancom	Delaflox	Vancom	Delaflox	Vancom
Baseline CrCl Categories (mL/min), n/N (%)						
CKD Stage 1 Normal or high (≥ 90)	268 (81.0%)	269 (81.8%)	341 (80.6%)	354 (82.9%)	609 (80.8%)	623 (82.4%)
CKD Stage 2 Mild (60-89)	39 (11.8%)	36 (10.9%)	43 (10.2%)	48 (11.2%)	82 (10.9%)	84 (11.1%)
CKD Stage 3 Moderate (30-59)	12 (3.6%)	18 (5.5%)	25 (5.9%)	17 (4.0%)	37 (4.9%)	35 (4.6%)
CKD Stage 4 Severe (15-29)	1 (0.3%)	0 (0.0%)	0 (0.00%)	2 (0.5%)	1 (0.1%)	2 (0.3%)
CKD Stage 5 Kidney Failure (<15)	1 (0.3%)	0 (0.0%)	0 (0.00%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Missing	7 (2.1%)	6 (1.8%)	12 (2.8%)	6 (1.4%)	19 (2.5%)	12 (1.6%)
eGFR (mL/min/1.73 m²)						
n	321	323	409	421	730	744
Mean (SD)	98.9 (29.9)	100.2 (30.4)	107.2 (37.9)	108.7 (37.4)	103.5 (34.9)	105.0 (34.8)
Median	95.3	99.6	104.9	105.2	101.1	102.7
Min, Max	9.0, 189.7	24.6, 225.6	14.4, 316.8	12.3, 309.8	9.0, 316.8	12.3, 309.8
Baseline eGFR (mL/min/1.73 m²), n/N (%)						
CKD Stage 1 Normal or high (≥ 90)	197 (61.3%)	201 (62.2%)	263 (64.3%)	280 (66.5%)	460 (63.0%)	481 (64.7%)
CKD Stage 2 Mild (60-89)	98 (30.5%)	98 (30.3%)	118 (28.9%)	110 (26.1%)	216 (29.6%)	208 (28.0%)
CKD Stage 3 Moderate (30-59)	23 (7.2%)	20 (6.2%)	25 (6.1%)	26 (6.2%)	48 (6.6%)	46 (6.2%)
CKD Stage 4 Severe (15-29)	2 (0.6%)	4 (1.2%)	2 (0.5%)	4 (1.0%)	4 (0.5%)	8 (1.1%)
CKD Stage 5 Kidney Failure (<15)	1 (0.3%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (0.1%)
Diabetes Status, n (%)						
No	301	302	370	373	671	675

Table 37: Subject Demographics and Baseline Characteristics (ITT Population)

	Trial 302		Trial 303		Pooled Phase 3 Trials	
	Delaflox	Vancom	Delaflox	Vancom	Delaflox	Vancom
	(90.9%)	(91.8%)	(87.5%)	(87.4%)	(89.0%)	(89.3%)
Yes	30 (9.1%)	27 (8.2%)	53 (12.5%)	54 (12.6%)	83 (11.0%)	81 (10.7%)
Bacteremia, Baseline, n (%)						
No	325 (98.2%)	320 (97.3%)	412 (97.4%)	419 (98.1%)	737 (97.8%)	739 (97.8%)
Yes	6 (1.8%)	9 (2.7%)	11 (2.6%)	8 (1.9%)	17 (2.3%)	17 (2.3%)

Source: ISE Population. ADSL data set.

Medical Reviewer's Comments:

As **Table 37** illustrates the mean age of subjects in Trial 302 was 46.3 years of age and 55.4 years of age in the delafloxacin and the comparator arm, respectively. Subjects in Trial 303 were slightly older, with the mean ages of subjects in the delafloxacin and comparator arms being 51.2 and 50.2 years old, respectively. By age category, most subjects in both Trials 302 and 303, across both treatment arms, were between the ages of 45 and 64. This is followed by subjects in the 18 to 44 age category. However, in each of these trials, there were fewer numbers of subjects aged 65 and older, with Trial 302 having comparatively fewer subjects in this age category than Trial 303. As **Table 37** demonstrates, Trial 302 had 17 of 331 (5.1%) and 9 of 331 (2.7%) subjects aged 65 to 74 years old and ≥ 75 years old in the delafloxacin arm, respectively; whereas, the comparator arm had 10 of 329 subjects (3.0%) aged 65 to 74 years old and aged ≥ 75 years old each. Trial 303 had slightly more older subjects; however the overall numbers and percentages of subjects by all age categories were comparable across treatment arms with slight differences between treatment arms.

When considering gender, race, and ethnicity across trials and treatment arms, most subjects were white, non-Hispanic males. Females accounted for near similar proportion of subjects across both treatment arms in each trial, with females accounting for anywhere between 35-38% of all subjects. Collectively, non-whites accounted for 10% of all subjects across treatment arms in Trial 302; whereas, in Trial 303 non-whites accounted for slightly less than 20% of all subjects in the delafloxacin arm (17.7%) and in the vancomycin comparator arm (16.8%).

Overall, 83 of 754 (11%) and 81 of 756 (10.7%) subjects in the pooled delafloxacin and vancomycin (\pm aztreonam) comparator arms, respectively, were diabetics. With regards to baseline bacteremia (2.3%) or a total of 17 subjects in each treatment arm were bacteremic.

When evaluating the proportion of subjects by BMI category, nearly a third of subjects in either treatment arm were overweight (BMI 25-29 kg/m²) in Trial 302 and nearly 25% of subject were overweight in Trial 303. In Trial 302, obese subjects (BMI 30-39 kg/m²) accounted for slightly more subjects in the delafloxacin arm (30.5%) compared with the vancomycin comparator arm (23.4%). In Trial 303, approximately 40% of all subjects were obese, as was pre-specified in the protocol. Morbidly obese subjects (BMI ≥ 40 kg/m²) accounted for nearly 5% and 10% of all subjects across both treatment arms in Trials 302 and 303, respectively.

The percentage of subjects by baseline renal function was evaluated according to both the Cockcroft-Gault equation (for CrCl) and the modified diet in renal disease (MDRD) equation (for eGFR) since the applicant originally proposed dosing adjustments based on renal function. The mean CrCl and eGFR in Trials 302 and 303 across both treatment arms were ≥ 90 mL/min/1.73 m² and ≥ 60 mL/min/1.73 m², respectively. Approximately 80% of all subjects in each arm of each trial had baseline renal function the equivalent of CKD Stage 1 (normal) according to CG (for CrCl). However, fewer numbers of subjects in either trial had baseline impaired renal function due to protocol eligibility exclusion criteria (please refer to Section 6 for details). In the delafloxacin arm alone, 39 subjects (11.8%) in Trial 302 and 43 subjects (10.2%) in Trial 303 had mild renal impairment (CKD Stage 3 CrCl of 60 to 89 mL/min); 12 subjects (3.6%) and 25 subjects (5.9%) of subjects in Trials 302 and 303, respectively, had moderate renal impairment (CKD Stage 3, CrCl of 30 to 50 mL/min); one subject (0.3%) in Trial 302 and no subjects in Trial 303 had severe renal impairments (CKD Stage 4, CrCl of 15 to 29 mL/min) or kidney failure (CKD Stage 5, CrCl <15). Likewise, in the vancomycin (\pm aztreonam) comparator arm, 36 subjects (10.9%) in Trial 302 and 48 subjects (11.2%) in Trial 303 had mild renal impairment (CKD Stage 3 CrCl of 60 to 89 mL/min); 18 subjects (5.5%) and 17 subjects (4.0%) of subjects in Trials 302 and 303, respectively, had moderate renal impairment (CKD Stage 3, CrCl of 30 to 50 mL/min); no subjects (0.0%) in Trial 302 and two subjects (0.5%) in Trial 303 had severe renal impairments (CKD Stage 4, CrCl of 15 to 29 mL/min); and no subjects in either trial had kidney failure (CKD Stage 5, CrCl <15). As with baseline CrCl, few subjects across in either of the pivotal Phase 3 studies had baseline moderate, severe or kidney failure in either the delafloxacin or the vancomycin (\pm aztreonam) comparator arms according to the MDRD equation.

Clinical Efficacy at the Primary FDA Endpoint for Key Demographic Subgroups

Although neither of the Applicant's Phase 3 trials was powered to detect differences in treatment rates by key demographic subgroups, **Table 38** below, illustrates clinical efficacy rates by such variables as age, sex, race, diabetes status, renal impairment, in addition to other variables. As stated earlier, Trial 303 was enriched for subjects with BMIs ≥ 30 kg/m². The reviewer notes that calculations found below were not adjusted for multiple comparisons, but provide a general overview of efficacy by key subject features.

Table 38: Clinical Response at 48 to 72 hours for Key Demographic Sub-groups, (ITT Population)				
	Trial 302		Trial 303	
	Delafloxacin	Vancomycin (\pm Aztreonam)	Delafloxacin	Vancomycin (\pm Aztreonam)
AGE CATEGORIES, n/N (%)				
18-64				
N	305	309	338	346
Cure, n (%)	242 (79.3%)	253 (81.9%)	287 (84.9%)	285 (82.4%)
Failure, n (%)	63 (20.7%)	56 (18.1%)	51 (15.1%)	61 (17.6%)
Difference (95%CI)	-2.5 (-8.8, 3.7)		2.5 (-3.0, 8.3)	
65-74				
N	17	10	42	48
Cure, n (%)	13 (76.4%)	4 (40.0%)	34 (81.0%)	33 (68.8%)

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Failure, n (%)	4 (23.6%)	6 (60.0%)	8 (19.1%)	15 (31.2%)
≥75				
N	9	10	43	33
Cure, n (%)	4 (44.4%)	9 (90.0%)	33 (76.7%)	26 (78.8%)
Failure, n (%)	5 (55.6%)	1 (10.0%)	10 (23.3%)	7 (21.2%)
SEX, n/N (%)				
Male				
N	206	209	262	276
Cure, n (%)	159 (77.2%)	171 (81.8%)	222 (84.7%)	226 (81.9%)
Failure, n (%)	47 (22.8%)	38 (18.2%)	40 (15.3%)	50 (18.1%)
Difference (95%CI)	-4.6 (-12.5, 3.2)		2.9 (-3.5, 9.2)	
Female				
N	125	120	161	151
Cure, n (%)	100 (80.0%)	95 (79.2%)	132 (82.0%)	118 (78.2%)
Failure, n (%)	25 (20.0%)	25 (20.8%)	29 (18.0%)	33 (21.8%)
Difference (95%CI)	0.8 (-9.3, 11.1)		3.8 (-5.1,12.8)	
RACE, n/N (%)				
White				
N	297	304	348	355
Cure, n (%)	231 (77.8%)	247 (81.3%)	299 (85.9%)	290 (81.7%)
Failure, n (%)	66 (22.2%)	57 (18.7%)	49 (14.1%)	65 (18.3%)
Difference (95%CI)	-3.5 (-10.0, 3.0)		4.2 (-1.2, 9.7)	
Black or African American				
N	27	19	13	18
Cure, n (%)	23 (85.2%)	15 (78.9%)	9 (69.2%)	18 (100.0%)
Failure, n (%)	4 (14.8%)	4 (21.1%)	4 (30.8%)	0 (0.0%)
Difference (95% CI)	6.2 (-22.6, 34.5)		-30.8 (-61.4, 4.5)	
ETHNICITY, n/N (%)				
Hispanic or Latino				
N	101	103	132	99
Cure, n (%)	85 (84.2%)	90 (87.4%)	116 (87.9%)	80 (80.8%)
Failure, n (%)	16 (15.8%)	13 (12.6%)	16 (12.1%)	19 (19.2%)
Non-Hispanic or Non-Latino				
N	230	226	291	328
Cure, n (%)	174 (75.7%)	176 (77.9%)	238 (81.8%)	264 (80.5%)
Failure, n (%)	56 (24.3%)	50 (22.1%)	53 (18.2%)	64 (19.5%)
BMI (kg/m²), n/N (%)				
< 25				
N	113	125	103	104

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Cure, n (%)	89 (78.7%)	104 (83.2%)	81 (78.6%)	76 (73.0%)
Failure, n (%)	24 (21.3%)	21 (16.8%)	22 (21.4%)	28 (26.9%)
Difference (95%CI)	-4.4 (-14.7, 5.6)		5.6 (-6.2, 17.2)	
25-29.9 kg/m ²				
N	98	110	109	109
Cure, n (%)	80 (81.6%)	92 (83.6%)	97 (89.0%)	94 (86.2%)
Failure, n (%)	18 (18.4%)	18 (16.4%)	12 (11.0%)	15 (13.8%)
Difference (95%CI)	-2.0 (-12.7, 8.4)		2.8 (-6.2, 11.9)	
30-39.9 kg/m ²				
N	101	77	170	169
Cure, n (%)	78 (77.2%)	59 (76.6%)	146 (85.9%)	138 (81.7%)
Failure, n (%)	23 (22.8%)	18 (23.4%)	24 (14.1%)	31 (18.3%)
≥ 40 kg/m ²				
N	19	17	41	45
Cure, n (%)	12 (63.2%)	11 (64.7%)	30 (73.2%)	36 (80.0%)
Failure, n (%)	7 (36.8%)	6 (35.3%)	11 (26.8%)	9 (20.0%)
Baseline CrCl Categories (mL/min), n/N (%)				
CKD Stage 1: Normal or high (CrCl ≥90)				
N	274	271	344	356
Cure, n (%)	218 (79.1%)	219 (80.8%)	295 (85.8%)	294 (82.6)
Failure, n (%)	56 (20.9%)	52 (19.2%)	49 (14.2%)	62 (17.4%)
Difference (95%CI)	-6.2 (-25.1, 13.3)		3.2 (-2.7, 8.6)	
CKD Stage 2: Mild (CrCl 60-89)				
N	39	36	44	48
Cure, n (%)	29 (74.4%)	29 (80.6%)	36 (81.8%)	35 (72.9%)
Failure, n (%)	10 (25.6%)	7 (19.4%)	8 (18.2%)	13 (27.1%)
Difference (95%CI)	-6.2 (-25.1, 13.3)		8.9 (-8.6, 25.9)	
CKD Stages 3-5: Moderate (CrCl <60))				
N	14	19	25	19
Cure, n (%)	11 (78.6%)	15 (78.9%)	17 (68.0%)	13 (68.4%)
Failure, n (%)	3 (21.4%)	4 (21.1%)	8 (32.0%)	6 (31.6%)
Difference (95%CI)	-0.4 (-33.4, 33.4)		-0.4 (-27.2, 27.7)	
Diabetes Status, n/N (%)				
Non-Diabetics				
N	301	302	370	373
Cure, n (%)	238 (79.1%)	246 (81.5%)	312 (84.3%)	301 (80.7%)
Failure, n (%)	63 (20.9%)	56 (18.5%)	58 (15.7%)	72 (19.3%)

Difference (95%CI)	-2.4 (-8.8, 4.0)		3.6 (-1.9, 9.1)	
Diabetics				
N	30	27	53	54
Cure, n (%)	21 (70.0%)	20 (74.1%)	42 (79.2%)	43 (79.6%)
Failure, n (%)	9 (30.0%)	7 (25.9%)	11 (20.8%)	11 (20.4%)
Difference (95%CI)	-4.1 (-27.0, 19.7)		-0.4 (-16.1,15.2)	
Bacteremia Baseline, n/N (%)				
No				
N	325	320	412	419
Cure, n (%)	255 (78.5%)	260 (81.3%)	346 (84.0%)	340 (81.2%)
Failure, n (%)	70 (21.5%)	60 (18.7%)	66 (16.0%)	79 (18.8%)
Yes				
N	6	9	11	8
Cure, n (%)	4 (66.7%)	6 (66.7%)	8 (72.7%)	4 (50.0%)
Failure, n (%)	2 (33.3%)	3 (33.3%)	3 (27.3%)	4 (50.0%)
<i>Source: ISE Population. ADSL and ADEFF data sets. 95% CI, where provided, were calculated by statistical reviewer, Dr. Janelle Charles</i>				

Medical Reviewer Comments:

There were no major discrepancies in clinical efficacy by key demographic sub-groups (i.e., race, gender). A limited number of subjects aged 65 years and older and those with severe renal impairment made additional efficacy assessment in these patients difficult.

7.3 Integrated Assessment of Effectiveness

The results from Phase 3 Trials 302 and 303 establish delafloxacin’s non-inferiority to the comparator vancomycin ± aztreonam in the treatment of ABSSSIs. Overall, no differences in efficacy were observed among subjects in key demographic sub-groups (i.e., race, sex). However, limited numbers of subjects aged 65 years and older and those with severe renal impairment (CKD Stage 4, CrCl 15-29 min/mL) made efficacy assessments in these patient sub-groups difficult.

In Trial 302, the first of two Phase 3 pivotal trials, evaluating the safety and efficacy of twice daily IV delafloxacin 300-mg over a 5 to 14 day treatment course, delafloxacin was found to be non-inferior (NI), at the 10 % NI margin, to the comparator vancomycin (± aztreonam), with 78.2% of subjects in the delafloxacin arm achieving an objective clinical response at the 48 to 72 hours in the ITT population (FDA primary endpoint) versus 80.9% in the comparator arm. Likewise, delafloxacin was found to be non-inferior at the 10% NI margin in Trial 303, the mandatory IV to oral switch trial, whereby an objective clinical response was demonstrated in 83.7% of subjects in the delafloxacin arm versus 80.6% of subjects in the vancomycin (± aztreonam) comparator arm in the ITT population at the 48 to 72 hour FDA primary efficacy endpoint.

8 Review of Safety

8.1 Safety Review Approach

The delafloxacin safety database was **primarily** comprised of the 1,492 subjects included in the Applicant's two pivotal Phase 3 clinical trials (RX-3341-302 and RX-3341-303). By definition, the safety analysis population consisted of all enrolled subjects who received *at least* one dose of study drug. Of the 741 subjects randomized to the delafloxacin arm, 324 subjects were from RX-3341-302 and 417 subjects from RX-3341-303. Safety events occurring in all subjects in the pivotal Phase 3 trials were pooled to provide a broader overview of delafloxacin safety.

In addition, the safety data collected from the 348 subjects who comprised the safety population in the Applicant's two Phase 2 clinical trials (RX-3341-201 and RX-3341-202) were analyzed. Due to differences in comparators and trial design, the subjects in these studies were evaluated separately from each other and from subjects in the Phase 3 trials. As previously stated, RX-3341 201 evaluated two IV dosages of delafloxacin: 300-mg IV and 450-mg IV against a single comparator tigecycline; whereas RX-3341 202 evaluated delafloxacin 300-mg IV against two comparators, linezolid 600-mg IV and vancomycin IV. Please refer to **Section 6 Review of Relevant Individual Trials Used to Support Efficacy** for a more detailed overview of each of the Applicant's Phase 2 trials.

The Applicant's safety program also included safety data from 20 of their 23 Phase 1 trials. These Phase 1 trials provided safety information for various IV and oral doses administered to healthy adult volunteers involved in delafloxacin's early clinical development program. Data from a total of 814 subjects from these Phase 1 studies were pooled according to dose and dose formulation and relative to the proposed commercial dosing and were categorized as follows: (a) for oral delafloxacin, dosing safety was evaluated in subjects receiving <400-mg, those receiving 400-500 mg, and those receiving >500-mg and (b) for IV delafloxacin dosing, where safety was evaluated according to subjects receiving ≤300-mg IV and those receiving > 300-mg IV (Source: Summary of Clinical Safety).

Delafloxacin belongs to the fluoroquinolone (FQ) antibacterial class and since FQs are required to carry boxed warnings for certain AEs, the Applicant's two Phase 2 and two Phase 3 studies were evaluated for FQ specific adverse events of special interest (AESI), namely: convulsions/seizures, episodes of dysglycemia (both hypoglycemia and hyperglycemia); peripheral neuropathies (i.e., paresthesias, hypoesthesia, dysethesias, weakness); tendinitis and potential tendon disorders; central nervous system effects (i.e., nervousness, agitation, insomnia, anxiety etc); myopathies; phototoxic events; episodes of *C. difficile*; episodes of QT prolongation, in addition to hepatic-related events and hypersensitivity reactions.

The Applicant used MedDRA version 16.1 to code all AEs. This clinical reviewer analyzed all safety data using JReview software versions 9.0 and 11.0 and MAED.

8.2 Review of the Safety Database

8.2.1 Overall Exposure

In total, the Applicant conducted 24 studies which collectively contributed to delafloxacin's composite safety profile. **Table 39** below provides an overview of delafloxacin's overall safety database which included: two Phase 3 trials (Trials 302 and 303); two Phase 2 trials (Trials 201 and 202); and 20 completed Phase 1 studies (which collectively included 814 healthy volunteers). A combined 868 subjects received delafloxacin in the Applicant's Phase 2 and 3 trials. A combined 972 subjects were treated with various comparator drugs in the Phase 2 and 3 trials.

Table 39: Safety Population, Size and Denominators Primary Safety Database for Delafloxacin		
Clinical Trial Groups	Pooled Delafloxacin	Pooled Comparators
Phase 1: Safety Analysis Set (Healthy Volunteers)	814	N/A
Phase 2: ABSSSI Subjects	127	221
Phase 3: ABSSSI Subjects	741	751

8.2.2 Relevant Characteristics of the Safety Population

Table 40, obtained from the Applicant's Summary of Clinical Safety, provides an overview of key demographic characteristics and baseline features of all subjects enrolled in the Applicant's Phase 2 and 3 safety population.

Table 40: Demographic Characteristics of Subjects in Applicant's Pooled Phase 2 and 3 Trials						
	Pooled Phase 3 Skin		Pooled Phase 2 Skin		All Skin Studies	
	Delafloxacin N=741	Vancomycin (±Aztreonam) N=751	Delafloxacin N=127	Pooled Comparators N=221	Delafloxacin N=868	All Comparators N=972
AGE						
n	741	751	127	221	868	972
Mean (SD)	49.2 (15.32)	48.2 (15.54)	41.0 (14.67)	43.7 (14.90)	48.0 (15.49)	47.2 (15.50)
Median	49.0	48.0	40.0	44.0	48.0	47.0
Min, Max	18, 94	19, 93	19, 83	18, 91	18, 94	18, 93

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AGE Categories (year), n (%)						
≤ 65	640 (86.4)	656 (87.4)	119 (93.7)	202 (91.4)	759 (87.4)	858 (88.3)
> 65	101 (13.6)	95 (12.6)	8 (6.3)	19 (8.6)	109 (12.6)	114 (11.7)
SEX, n (%)						
Male	459 (61.9)	483 (64.3)	77 (60.6)	136 (61.5)	536 (61.8)	619 (63.7)
Female	282 (38.1)	268 (35.7)	50 (39.4)	85 (38.5)	332 (38.2)	353 (36.3)
RACE, n (%)						
Asian	12 (1.6)	16 (2.1)	0	4 (1.8)	12 (1.4)	20 (2.1)
Black	38 (5.1)	36 (4.8)	16 (12.6)	38 (17.2)	54 (6.2)	74 (7.6)
Native American or Alaska Native	16 (2.2)	9 (1.2)	6 (4.7)	4 (1.8)	22 (2.5)	13 (1.3)
Native Hawaiian or Other Pacific Islander	3 (0.4)	4 (0.5)	3 (2.4)	1 (0.5)	6 (0.7)	5 (0.5)
White	636 (85.8)	656 (87.4)	100 (78.7)	169 (76.5)	736 (84.8)	825 (84.9)
Other	36 (4.9)	30 (4.0)	2 (1.6)	5 (2.3)	38 (4.4)	35 (3.6)
ETHNICITY, n (%)						
Hispanic or Latino	231 (31.2)	201 (26.8)	36 (28.3)	54 (24.4)	267 (30.8)	255 (26.2)
Non Hispanic or Latino	510 (68.8)	550 (73.2)	91 (71.7)	167 (75.6)	601 (69.2)	717 (73.8)
REGION, n(%)						
Asia	9 (1.2)	14 (1.9)	0	0	9 (1.0)	14 (1.4)
Europe	225 (30.4)	228 (30.4)	0	0	225 (25.9)	228 (23.5)
Latin America	46 (6.2)	43 (5.7)	0	0	46 (5.3)	43 (4.4)
North	461 (62.2)	466 (62.1)	127 (100.0)	221 (100.0)	588 (67.7)	687 (70.7)

America						
Body Mass Index (BMI) (kg/m³)						
n	741	751	127	220	868	971
Mean (SD)	29.6 (7.10)	29.5, (7.20)	28.9 (6.52)	29.2 (6.61)	29.5 (7.02)	29.4 (7.07)
Median	28.8	28.3	27.2	28.0	28.6	28.2
Min, Max	15.9, 65.8	17.3, 68.0	15.4, 51.9	17.1, 52.5	15.4, 65.8	17.1, 68.0
Body Mass Index Ranges (kg/m²)						
BMI <30	414 (55.9)	445 (59.3)	83 (65.4)	133 (60.2)	497 (57.3)	578 (59.5)
BMI ≥30	327 (44.1)	306 (40.7)	44 (34.6)	87 (39.4)	371 (42.7)	393 (40.4)
Missing	0	0	0	1 (0.5)	0	1 (0.1)
Diabetes, n (%)	84 (11.3)	83 (11.1)	9 (7.1)	25 (11.3)	93 (10.7)	108 (11.1)
Baseline Renal Impairment, n (%)	121 (16.3)	121 (16.1)	18 (14.2)	36 (16.3)	139 (16.0)	157 (16.2)
Patients with a History of Hepatitis B or C, n (%)	216 (29.1)	217 (28.9)	17 (13.4)	14 (6.3)	233 (26.8)	231 (23.8)
<i>Source: Adapted from Applicant's Module 2.7.4 Summary of Clinical Safety. Table 6 Demographics and Other Baseline Characteristics</i>						

Medical Reviewer's Comment: Over half of all subjects comprising the safety population in both Phase 3 trials were white, males, aged 18 to <65, and were recruited from the United States. The demographic distribution of subjects in both Phase 2 studies was similarly reflective of those subjects in the Phase 3 trials. Persons 65 and older comprised less than 15% of the integrated summary of safety (ISS) population. Subjects with BMIs of ≥ 30 accounted for approximately 40 % of all subjects in the Applicant's Phase 3 trials. An evaluation of all subjects by salient baseline disease characteristics, such as diabetes mellitus, is also displayed in **Table 40**. It is also noted that, for both Phase 3 trials, subjects with CKD Staging of 3 (moderate renal impairment) and 4 (severe renal impairment) collectively accounted for less than 5% of all subjects (see **Table 37**). Despite IV drug use being a risk factor for ABSSSIs and IV drug abusers accounted for a significant proportion of U.S. subjects, interestingly, the Applicant did not collect data on the exact numbers of IV drug users (typically heroin and/or methamphetamine) enrolled in their trials.

8.2.3 Adequacy of the Safety Database

Representing over 2000 subjects, the Applicant's safety database was sufficiently comprehensive to provide a relatively well-informed assessment of delafloxacin's overall safety profile according to proposed indication and commercial dosing, duration of treatment, patient demographic features and disease characteristics. The safety population adequately reflects the general U.S. population. A safety database of this size is compliant with, the 2013 FDA ABSSSI Guidance for Industry that recommends a preapproval safety database of approximately 700 patients or more.

While the Applicant originally sought a dosing claim for "patients with severe renal impairment (eGFR of 15-29 mL/min/1.73 m²) (b)(4)", and posed recommendations that dosing in these populations "should be decreased to 200-mg IV (b)(4) or (b)(4) the Applicant's safety database failed to include sufficient numbers of subjects with moderate to severe renal impairment. Delafloxacin is partially renally cleared; therefore, **Section 8.6 Safety Analyses by Demographic Sub-groups** of this review closely evaluated any potential concerning safety signals among subjects with moderate to severe renal impairments.

8.3 Adequacy of Applicant's Clinical Safety Assessments

8.3.1 Issues Regarding Data Integrity and Submission Quality

No significant data quality or data integrity issues were identified during this review of safety. Case report forms and subject narratives were reviewed and compared against the Applicant's data sets and assessments for all deaths, SAEs, and treatment discontinuations due to AEs for Phase 2 and 3 studies. It is noted that the Applicant failed to account for one death in their safety assessments. In addition, there were several, minor discrepancies between the Applicant's and this reviewer's assessment in the frequency counts of several AEs, however such differences were minor and did not preclude overall evaluation of delafloxacin's safety.

8.3.2 Categorization of Adverse Events

The Applicant's definitions for adverse events (AEs) and serious adverse events (SAEs) were written in compliance with the CFR and ICH Guidelines. Likewise, the Applicant's definition of treatment emergent adverse events (TEAEs) was appropriately defined. Adverse events were assessed with adequate frequency and were documented and reported within the appropriate timeframes. The Applicant states that all AEs were elicited using non-directed questioning. All AEs and TEAEs contained in the ISS were coded according to MedDRA version 16.1 and were subsequently grouped according to MedDRA hierarchy. While the Applicant did not utilize a standardized toxicity grading scale to classify AE severity, AEs/TEAS were categorized as mild, moderate and severe. The investigator assessed the severity intensity and causality for all study AEs/TEAEs.

Because all FQs are now required to contain a boxed warning highlighting several FQ associated AEs, the Applicant identified several AEs of special interest (AESIs) for which they planned to conduct detailed safety reviews. This reviewer observed several instances of splitting of AEs at the preferred terms (PT) level when conducting her safety evaluations. These are addressed in the body of this safety review.

8.3.3 Routine Clinical Tests

Routine safety assessments were conducted at pre-specified time points throughout both Phase 3 trials, namely: pre-treatment/screening, during the treatment period (on pre-specified days); the end of treatment (EOT) visit (Study Day 5-14); the follow-up (FU) visit (Study Day 14 ± 1); the late follow-up (LFU) (Study Day 21-28); and otherwise, when indicated, at unscheduled visits. The following safety assessments were conducted: targeted physical examinations and vital signs; clinical laboratory testing (including hematology, serum chemistry, and urinalysis labs); and the reporting of all adverse events. Subject safety data was collected upon the signing of the informed consent form (ICF) and AEs were elicited throughout the study period, up through the follow-up telephone contact call made 30 days after receipt of the final dose of study drug. A single ECG was collected at Screening. Afterwards ECGs were only obtained when deemed necessary by the study investigator. Due to a FQ class associated concern for dysglycemia, subjects, diabetic and non-diabetic alike, were periodically assessed for hypoglycemia via laboratory chemistry, during Phase 3 trials. Overall, the frequency and scope of safety assessments was deemed adequate. For further description of routinely collected safety procedures, the reader is referred to **Section 6 Review of Relevant Individual Trial Used in Support Efficacy**.

8.4 Safety Results

Phase 1 Trials

The sponsor conducted a total of 23 Phase 1 clinical studies, 20 of which were included in the Phase 1 Safety analysis set and three studies (the hepatic impairment, renal impairment and photosensitizing potential) are discussed separately in **Section 8.7 Safety Specific Studies**. The 20 Phase 1 studies consisted of a total of 814 subjects all of whom either received *at least* one dose of a single or multiple doses of IV or oral delafloxacin. Oral delafloxacin doses in Phase 1 studies ranged from 50 to 1,600-mg and IV delafloxacin doses ranged from 50 to 1,200 mg. **Table 41** below provides a tabular display of the various treatment dose groups comprising the Phase 1 safety population.

Table 41: Treatment Dose Groups Comprising the Phase 1 Safety Population.					
Phase 1 Oral Delafloxacin			Phase 1 Intravenous (IV) Delafloxacin		Combined Phase 1 Delafloxacin Studies
< 400 mg (50, 100, 200, 250, and 300 mg) N=235	400 to 500 mg (400, 450, 475, and 500 mg) N=288	> 500 mg (800, 900, 1200, and 1600 mg) N=152	≤ 300 mg (50, 100, 150, 200, and 300 mg) N=232	> 300 mg (400, 450, 600, 750, 900, and 1200 mg) N=111	All doses and regimens N=814

Source: Adapted from Applicant Module 2.5 Clinical Overview

The most consistently reported treatment-emergent adverse reactions in the Phase 1 oral and IV delafloxacin safety population were coded under the Gastrointestinal (GI) disorders and Nervous System disorders SOCs and included: diarrhea, nausea, headache, dizziness, abdominal

pain/abdominal discomfort . In addition, non-GI related PTs such as infusion site pain and syncope/pre-syncope were commonly observed. In most cases, the incidence of adverse reactions increased as both oral and IV delafloxacin dosages increased. **Table 42** below provides a summary, by SOC and PT terms of **key**, as well as, frequently reported TEAEs and/or AESIs, found in the Applicant's Phase 1 oral, IV and combined trials.

Table 42: Treatment-Emergent Adverse Events by System Organ Class and Preferred Terms in Phase 1 Safety Analysis Set						
System Organ Class/Preferred Term	Phase 1 Oral Delafloxacin			Phase 1 IV Delafloxacin		Combine Phase 1 Delafloxacin Studies
	< 400 mg N=235 n (%)	400-500 mg N=288 n (%)	>500 mg N=152 n (%)	≤ 300 mg N=232 n(%)	>300 mg N=111 n(%)	All Doses and Regimens N=814 n(%)
Total number of TEAEs	137	163	217	209	130	856
Subjects with at least one TEAE	76 (32.3)	81 (28.1)	79 (52.0)	74 (31.9)	58 (52.3)	346 (42.5)
Gastrointestinal Disorders	31 (13.2)	52 (18.1)	61 (40.1)	30 (12.9)	38 (34.2)	204 (25.1)
Diarrhea	18 (7.7)	39 (13.5)	33 (21.7)	14 (6.0)	6 (5.4)	108 (13.3)
Nausea	5 (2.1)	7 (2.4)	29 (19.1)	12 (5.2)	32 (28.8)	83 (10.2)
Vomiting	3 (1.3)	1 (0.3)	8 (5.3)	3 (1.3)	21 (18.9)	36 (4.4)
Abdominal Pain/Abdominal Discomfort	9 (3.9)	14 (4.8)	13 (8.6)	8 (3.4)	2 (1.8)	45 (5.5)
Nervous System Disorders	34 (14.5)	22 (7.6)	21 (13.8)	31 (13.4)	13 (11.7)	118 (14.5)
Headache	23 (9.8)	19 (6.6)	13 (8.6)	18 (7.8)	4 (3.6)	76 (9.3)
Dizziness	4 (1.7)	1 (0.3)	6 (3.9)	15 (6.5)	6 (5.4)	32 (3.9)
Presyncope/Syncope	1 (0.4)	2 (0.7)	4 (2.0=7)	1 (0.4)	2 (1.8)	10 (1.3)
Dysgeusia	0	0	1 (0.7)	4 (1.7)	0	5 (0.6)
Somnolence	3 (1.3)	1 (0.3)	0	0	1 (0.9)	5 (0.6)
Paraesthesia/Hypoesthesia	2 (0.8)	1 (0.3)	0	2 (0.9)	1 (0.9)	6 (0.7)

General Disorders and Administration Site Pain	5 (2.1)	5 (1.7)	9 (5.9)	28 (12.1)	26 (23.4)	72 (.8.8)
Infusion site pain/Injection site pain	1 (0.4)	0	0	14 (6.0)	20 (18.0)	34 (4.2)
Infusion site phlebitis	0	0	0	11 (4.7)	0	11 (1.4)
Skin and Subcutaneous Tissue Disorders	8 (3.4)	7 (2.4)	13 (8.6)	18 (7.8)	4 (3.6)	49 (6.0)
Pruritus/Pruritus, generalized	0	3 (1.0)	1 (0.7)	6 (2.6)	1 (0.9)	11 (1.3)
Rash/Rash, macular/Rash, maculopapular/Rash, pruritic/ Rash papular	6 (2.5)	2 (0.6)	8 (5.4)	1 (0.4)	0	17 (2.1)
Dermatitis, contact/Dermatitis	0	0	0	8 (3.4)	0	8 (1.0)
Urticaria	1 (0.4)	0	0	0	0	1 (0.1)
Musculoskeletal and Connective Tissue Disorders	4 (1.7)	12 (4.2)	5 (3.3)	10 (4.3)	2 (1.8)	33 (4.1)
Myalgia	0	5 (1.7)	2 (1.3)	5 (2.2)	2 (1.8)	14 (1.7)
Arthralgia	0	2 (0.7)	1 (0.7)	0	0	3 (0.4)
Infections and Infestations	2 (0.9)	7 (2.4)	4 (2.6)	9 (3.9)	1 (0.9)	22 (2.7)
Vulvovaginal Candidiasis	1 (0.4)	2 (0.7)	0	1 (0.4)	0	4 (0.5)
<i>Clostridium difficile</i> colitis	0	1 (0.3)	0	0	0	1 (0.1)
Investigations	5 (2.1)	2 (0.7)	1 (0.7)	0	0	8 (1.0)
ALT increased	4 (1.7)	2 (0.7)	0	0	0	6 (0.7)
AST increased	1 (0.4)	0	0	0	0	1 (0.1)
Blood creatinine increased	0	0	1 (0.7)	0	0	1 (0.1)
Psychiatric Disorders	1 (0.4)	1 (0.3)	0	0	0	2 (0.2)
Abnormal Dreams	0	1 (0.3)	0	0	0	1 (0.1)

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Immune System Disorders	0	0	0	1 (0.4)	0	1 (0.1)
Hypersensitivity	0	0	0	1 (0.4)	0	1 (0.1)
<i>Source: Adapted from Applicant's Summary of Summary of Clinical Safety for Delafloxacin Table 14.3.1.2.2. Treatment-Emergent Adverse Events by System Organ Class and Preferred Terms in Phase 1 Safety Analysis Set</i>						

8.4.1 Deaths

Five deaths occurred in the delafloxacin development program, including one death in the delafloxacin arm and four deaths in the comparator arm. All deaths occurred in the Phase 3 trials. Two of the decedents were aged ≥ 65 years; whereas the other two were aged <65 years old. All decedents had multiple co-morbid conditions.

One death (Subject 303/233-440-3865) in the vancomycin arm was not reported by the Applicant; however, this death was discovered during the safety review. This death occurred on post treatment day 33 (or 47 days after treatment initiation).

There were no reported deaths in any of the Phase 1 and 2 trials.

Table 43 provides a tabular summary of all the Phase 3 subject deaths, including the death uncovered during this review of safety. Each of these deaths are subsequently discussed in brief accompanying narratives.

Table 43 Treatment-Emergent and Non-treatment Emergent Deaths, ISS Population							
Unique Subject Identifier	Age/Sex	Country	Actual Treatment	System Organ Class	Cause of Death by Dictionary Derived Term	Study /Post treatment Day on which Death occurred	Duration of Study Treatment
RIBX302/376-081-0724	89/M	Israel	Delafloxacin 300-mg IV	Infections and Infestations	Septic Shock	Study Day 20/ Post-treatment Day 6	14 days
RIBX302/784-063-0539	64/F	Ukraine	Vancomycin + Aztreonam	Respiratory, Thoracic, and Mediastinal Disorders	Pulmonary Embolism	Study Day 24/ Post-treatment Day 13	11 days
MEL303/100-435-3845	59/M	Bulgaria	Vancomycin + Aztreonam	Cardiac Disorder	Myocardial Infarction	Study Day 17/ Post-treatment Day 3	14 days

MEL303/ 233-440- 3865	67/F*	Estonia	Vancomycin + Aztreonam	Infections and Infestations	*Septic Arthritis	Post- treatment Day 33	14 days
MEL303/ 604-405- 3613	85/M	Peru	Vancomycin + Aztreonam	Gastrointestinal Disorders	Intestinal Ischemia	Study Day 30/ Post- treatment Day 15	14 days
<i>Source: ISS Population. ADSL and ADAE data sets. Table generated by the clinical reviewer. * Indicates the death that was unreported by the Applicant.</i>							

Death Narratives

RIBX302/376-081-0724: Subject 376-081-0724 was an 89 year old white male with multiple co-morbid conditions, including congestive heart failure; ischemic heart disease, hypertension; diabetes mellitus type 2; atrial fibrillation; mild peripheral vascular disease; bilateral leg edema; and chronic renal failure, for which he was taking multiple medications. On (b) (6) (Study Day 1), he enrolled in Protocol 302 and was randomized to receive delafloxacin for the treatment of a left leg cellulitis/erysipelas. He received no antibacterials prior to receipt of delafloxacin. ABSSSI site and blood cultures remained negative for growth. No surgical procedures were performed during the study period. Subject received daily dressing changes (a permitted adjunctive therapy) during the study period. He experienced several TEAEs during the study period, most notably what was reported as a “hypoglycemic episode” with a glucose of 72 mg/dL on (b) (6) (Study Day 4). He completed delafloxacin treatment on (b) (6) (Study Day 14). He was deemed a clinical failure for having required additional antibacterial therapy after 28 doses of study treatment. The subject was reportedly transferred to a rehabilitation center on (b) (6) (Study Day 18) and afterwards was admitted to another hospital for septic shock (fever 39, heart rate 110) on (b) (6) (Study Day 19). He died the following day on (b) (6) (Study Day 20). The Applicant reports that an autopsy was not performed. However, the subject’s death certificate stated he died from cardio-pulmonary arrest. This event was graded by the investigator as being a serious intensity SAE that was deemed unrelated to the study treatment.

Medical Reviewer’s Comments: Subject 376-081-0724 was a chronically ill elderly man with multiple co-morbid conditions. This reviewer agrees that the subject was a clinical treatment failure and that his death from septic shock was most likely a consequence of an ineffectively treated infection in a subject who was already immunocompromised due to advanced age and multiple medical conditions.

RIBX302/784-063-0539: Subject 784-063-0539 was a 64 year old white female with a history of morbid obesity (BMI 43.7). Other notable baseline medical conditions included hypertension, ischemic heart disease, and a partial thyroid resection presumptively for a thyroid nodule. She received no antibacterial therapies prior to study enrollment. On (b) (6) (Study Day 1), she was randomized into Protocol 302 for a right leg cellulitis/erysipelas and began treatment with vancomycin that same day. Her final day of study treatment was (b) (6) (Study Day 11). Baseline ABSSSI and blood cultures remained negative throughout the study period.

No surgical procedures for her ABSSSI were performed during her study enrollment period. She experienced several TEAEs during the study period, including abdominal discomfort. This TEAE was deemed unrelated to study treatment. Her final dose of study drug was administered on [REDACTED] (b) (6) (Study Day 11). She was evaluated by the investigator as being a clinical cure at EOT. The CRF indicated that on [REDACTED] (b) (6) (Study Day 20), 10 days post-therapy, the patient complained of acute abdominal pain for which she underwent an emergent laparotomy for suspicion of an acute abdomen. She was discovered to have a perforated gastric ulcer and liver cirrhosis (both coded as SAEs). She subsequently received several antibacterial agents for the treatment of a post-surgical peritonitis (levofloxacinum 500-mg IV daily cefoperazon + sulbactam 2-grams twice daily and Ornidazolium 100-ml). This patient reportedly sustained a pulmonary embolism (PE) and died on [REDACTED] (b) (6) (Study Day 24). This event was assessed by the investigator to be a serious SAE that was deemed unrelated to the study treatment.

Medical Reviewer's Comments: *This subject's prolonged hospitalization (and likely resulting immobility from this hospitalization), recent surgery, and history of morbid obesity, placed her at greater risk for venous thromboembolic events (VTE) events. Furthermore, it is unclear if this subject was administered DVT prophylaxis during her hospitalization. Hence, it is conceivable that the cause of death is related to these underlying conditions as opposed to a causal relationship with the study drug.*

MEL303/100-435-3845: Subject 100-435-3845 was a 59 year old white male with a baseline medical history noted for hypertension, atherosclerosis, COPD, and morbid obesity (BMI of 51.4). His home medication regimen consisted of several anti-hypertensives, namely lisinopril dehydrate/hydrochlorothiazide, torazemide (a loop diuretic) and bisoprolol fumarate. Subject was enrolled into Protocol 303 and was subsequently randomized to treatment with vancomycin for a right leg cellulitis/erysipelas on [REDACTED] (b) (6) (Study Day 1). He received no previous antibacterial agents prior to study entry. While enrollment blood cultures remained negative, cultures of the ABSSSI site grew *Staphylococcus haemolyticus*. No surgical procedures were performed during the study period. The patient received his final dose of treatment with vancomycin (± aztreonam) on [REDACTED] (b) (6) (Study Day 14) and was assessed by the investigator to be a clinical responder at the 48 to 72 hour FDA primary endpoint. The patient completed the study treatment on [REDACTED] (b) (6) (Study Day 15). He was assessed as clinically improved at the EOT visit, also Study Day 15. Two days post-therapy, on [REDACTED] (b) (6) (Study Day 17), he was documented as having died from a myocardial infarction. This SAE was deemed a severe intensity event that was unrelated to the study treatment.

Medical Reviewer's Comments: *Subject 100-435-3845 had several cardiac risk factors including being a male >45 years of age, hypertension, morbid obesity, and a documented history of atherosclerosis. From his CRF, it is unclear if he had any additional coronary artery disease (CAD) risk factors (RF). Based on the provided information, this reviewer agrees that the subject's underlying RFs, as opposed to the study drug, could have contributed to his death.*

MEL303/604-405-3613: Subject 604-405-3613 was an 85 year old Peruvian male who was randomized into Trial 303 on [REDACTED] (b) (6) (Study Day 1) for trauma to his left arm resulting in a left arm cellulitis/erysipelas. His past medical history was noted for hypertension with

resultant hypertensive nephropathy (baseline Scr 0.9 mg/dL; CrCL 49 min/mL), and for being overweight (BMI of 27.3). He was administered his first dose of study drug on [REDACTED] (b) (6) (Study Day 1), the day of randomization. His last dose of study drug was administered on [REDACTED] (b) (6) (Study Day 15). Baseline microbiologic cultures from the primary ABSSI site grew *Escherichia coli* and *Staphylococcus aureus*. However, baseline blood cultures remained with no growth. No surgical procedures were performed during the study period, but he received twice daily dressing changes throughout the entire study duration. He was documented as having several SAEs including a nosocomial pneumonia beginning on Study Day 15 (Start date/End date: [REDACTED] (b) (6)) for which he was treated with imipenem 500-mg every 8 hours and vancomycin. This event was assessed as an SAE requiring prolongation of his hospitalization. He sustained a second severe intensity SAE, coded to the PT term subdural hematoma on (Study Day 21) (Start date/End date: [REDACTED] (b) (6)). This event was also assessed as being unrelated to study treatment.

In addition, this subject experienced several AEs of special interest including: a contact dermatitis (Study Day 17); “renal failure, acute” (Study Day 24) which was deemed by the investigator to be a moderate intensity event unrelated to study treatment; “AST increased” (Study Day 21/moderate intensity and unrelated). His final and fatal SAE, began on Study Day 30, and was coded as “intestinal ischemia” (Start/End dates: [REDACTED] (b) (6)). This event resulted in the subject undergoing an emergent laparotomy after which he sustained “systemic compromise.” He died 2 hours after surgery. An autopsy was not conducted; however, the cause of death was assessed as unrelated to study treatment.

Medical Reviewer’s Comments: *Based on the submitted details, the patient’s age and comorbidities, this reviewer agrees that the subject’s cause of death was unrelated to study drug.*

MEL303/233-440-3865: Subject 233-440-3865 was a 67 year old white female with a cellulitis/erysipelas of the right leg and a medical history noted for diabetes; renal insufficiency (baseline Cr 3.7 mg/dL/CrCl 23 min/mL); obesity (BMI 35.6); hypertension; and COPD. She was randomized and begun on treatment with vancomycin (± aztreonam) as an inpatient on [REDACTED] (b) (6). She completed 14 days of treatment (Treatment end date: [REDACTED] (b) (6)). At the EOT visit, the subject was deemed a clinical failure, because she required an unplanned surgical intervention. On [REDACTED] (b) (6) (Study Day 1) and [REDACTED] (b) (6) (Study Day 5), the subject had bedside I&Ds with the expression of purulent secretions. On [REDACTED] (b) (6) (Study Day 9), she went to the operating room for a repeat I&D after a new collection of pus was discovered. On [REDACTED] (b) (6) (Study Day 15), subject was reported as having septic arthritis. This was deemed an SAE that resulted in the prolongation of her hospitalization. On [REDACTED] (b) (6) (Study Day 47), 33 days after her last dose of study drug, subject was reportedly found unconscious with no spontaneous cardiac activity. A death certificate was completed. Autopsy revealed acute heart failure as the immediate cause of death.

Medical Reviewer’s Comments: *The above-described non-treatment emergent death, occurred 33 days after the subject received her final dose of study drug. This subject experienced an SAE coded to the PT term “arthritis, bacterial” which resulted in the prolongation of her hospitalization and complications which ultimately led to her death. This subject was deemed a treatment failure, as she required additional antibacterial therapy post study treatment and*

because she underwent an unplanned surgical procedure (I&D and a subsequent crural amputation) for worsening of a non-resolving “purulent talcrural arthritis.” This reviewer agrees with the site investigator that the patient’s surgical interventions and subsequent death resulted from ineffectiveness of therapy and related complications of her underlying ABSSSI. The Applicant did not flag this event as a study death since it occurred 47 days after she was initially randomized to Trial 303.

8.4.2 Serious Adverse Events (SAEs)

Phase 3 Trials: RX-3341-302 and RX-3341-303 (ISS Population)

Treatment emergent SAEs occurred relatively infrequently in both treatment arms of the Applicant’s pivotal Phase 3 trials. During this evaluation of treatment emergent SAEs, this reviewer closely reviewed all subject eCRFs and Applicant narratives and verified the information contained in these documents against the data contained in the appropriate ISS data sets.

A total of 26 (3.5%) of 741 subjects in the pooled delafloxacin Phase 3 safety population experienced at least one treatment emergent SAE- 11 subjects in Trial 302 and 16 subjects in Trial 303. Near equal numbers of subjects in the vancomycin (± aztreonam) comparator arm experienced SAEs: 9 and 17 subjects in Trial 302 and Trial 303, respectively, for a total of 27 (3.6%) of 751 subjects. There were a total of 31 SAEs in the delafloxacin arm and 37 SAEs in the vancomycin arm.

Table 44 below provides a tabular summary of all reported Phase 3 treatment-emergent SAEs by treatment arm, system organ class (SOC), and dictionary derived term (also referred to as preferred term [PT]).

Table 44: Pooled Phase 3 Trials Serious Treatment Emergent Adverse Events				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (± Aztreonam) N=751
Primary System Organ Class	Dictionary Derived Term	Delafloxacin 300 mg IV	Delafloxacin 300 mg IV-450 mg	Vancomycin (± Aztreonam)
Cardiac Disorders	Myocardial Infarction ^a	0 (0.0%)	0 (0.0%)	1 (0.1%)
Gastrointestinal Disorders	Colitis (infectious)	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Diarrhea	1 (0.1%)	0 (0.0%)	0 (0.0%)
	Gastric ulcer perforation	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Intestinal Ischemia ^a	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Nausea	0 (0.0%)	0 (0.0%)	1 (0.1%)
General Disorders and Administration Site Conditions	Pyrexia	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Systemic Inflammatory Response Syndrome	0 (0.0%)	0 (0.0%)	1 (0.1%)
Heptobiliary Disorders	Hepatic Cirrhosis	0 (0.0%)	0 (0.0%)	1 (0.1%)
Infections and	Abscess Limb	0 (0.0%)	1 (0.1%)	0 (0.0%)

Infestations	Septic Arthritis (Bacterial) ^a	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Cellulitis/Erysipelas/Skin Infection	4 (0.5%)	6 (0.8%)	7 (0.9%)
	Hepatitis C	1 (0.1%)	0 (0.0%)	0 (0.00%)
	Osteomyelitis	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Peritonitis	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Pneumonia	0 (0.0%)	1 (0.1%)	1 (0.1%)
	Sepsis/Septic Shock ^a	2 (0.3%)	0 (0.0%)	1 (0.1%)
	Soft Tissue Necrosis (Necrotizing Fasciitis)	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Surgical Wound, Infected	0 (0.0%)	0 (0.0%)	2 (0.3%)
Injury, Poisoning and Procedural Complications	Overdose	0 (0.0%)	0 (0.0%)	1 (0.13%)
	Stab wound	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Subdural hematoma	0 (0.0%)	1 (0.1%)	1 (0.1%)
	Toxicity to various agents (drug intoxication)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Investigations	Liver Function Test Abnormalities ALT/AST Increased	0 (0.0%)	1 (0.1%)	0 (0.0%)
Musculoskeletal and Connective Tissue Disorders	Rheumatoid Arthritis	0 (0.0%)	0 (0.0%)	1 (0.1%)
Neoplasms Benign, Malignant, and unspecified (including cysts and polyps)	Adenocarcinoma of colon	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Neoplasm Malignant	0 (0.0%)	0 (0.0%)	1 (0.1%)
Psychiatric Disorders	Major Depression	1 (0.1%)	0 (0.0%)	0 (0.0%)
	Polysubstance Dependence	1 (0.1%)	0 (0.0%)	0 (0.0%)
	Schizophrenia	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Suicidal Ideation/Substance-induced mood disorder	1 (0.1%)	0 (0.0%)	1 (0.1%)
Renal and Urinary Disorders	Renal Failure (Acute)	0 (0.0%)	0 (0.0%)	3 (0.4%)
Respiratory, Thoracic and Mediastinal Disorders	Acute Respiratory Failure	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Chronic Obstructive Pulmonary Disease	1 (0.1%)	0 (0.0%)	0 (0.0%)
	Pulmonary Embolism ^a	0 (0.0%)	2 (0.3%)	1 (0.13%)
Skin and Subcutaneous Tissue Disorders	Pyoderma Gangrenosum	1 (0.1%)	0 (0.0%)	0 (0.0%)
	Rash/Dermatitis (drug-induced)	0 (0.0%)	0 (0.0%)	2 (0.3%)
	Urticaria	0 (0.0%)	1 (0.1%)	0 (0.0%)
Vascular Disorders	Peripheral Vascular Disorder	0 (0.0%)	0 (0.0%)	1 (0.1%)
Total # of Subjects		26 (3.5%)		27 (3.6%)
<i>Source: ISS Population. ADSL and ADAE data sets. ^aIndicates a fatal serious adverse event occurred in a subject coded to PT term. In all there were a total of 4 subjects who sustained a fatal SAE (See Section 8.4.1 for details). *A total of 10 subjects had more than one SAE.</i>				

Table 45 below provides a tabular summary of all reported Phase 3 treatment-emergent serious adverse reactions by treatment arm, system organ class (SOC), and dictionary derived term (also referred to as preferred term [PT]).

Table 45: Pooled Phase 3 Serious Treatment Emergent Adverse Reactions Study Treatment				
System Organ Classification/Dictionary Derived Term		Delafloxacin N=741		Vancomycin (± Aztreonam) N=751
Primary System Organ Class	Dictionary Derived Term	Delafloxacin 300 mg IV	Delafloxacin 300 mg IV-450 mg	Vancomycin (± Aztreonam)
Gastrointestinal Disorders	Diarrhea	0 (0.0%)	1 (0.1%) [†]	0 (0.0%)
	Nausea	0 (0.0%)	0 (0.0%)	1 (0.1%)
Investigations	Liver Function Test Abnormalities ALT/AST Increased*	1 (0.1%)	0 (0.0%)	0 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	Pulmonary Embolism	0 (0.0%)	2 (0.3%)	1 (0.13%) [‡]
Renal and Urinary Disorders	Renal Failure (Acute)	0 (0.0%)	0 (0.0%)	3 (0.4%)
Skin and Subcutaneous Tissue Disorders	Rash/Dermatitis (drug-induced)	0 (0.0%)	0 (0.0%)	2 (0.3%)
	Urticaria	1 (0.1%)	0 (0.0%)	0 (0.0%)
Total # of Subjects (filtered)		5 (0.7%)		6 (0.9%)

*Source: ISS Population. ADSL and ADAE data sets. * A single patient had more than one serious adverse reaction.*
[†]Although diarrhea is typically considered an adverse reaction associated with delafloxacin treatment, this subject had diarrhea in the setting of opiate withdrawal. [‡]Although included in this table, the single subject in the vancomycin arm with a pulmonary embolus had multiple risk factors which predisposed this subject to developing a PE. This was a case of a fatal SAE and was discussed in Section 8.4.1

Altogether, there were ten subjects (3 in the delafloxacin arm and 7 in the vancomycin comparator arm) who were reported as having multiple SAEs. Four of the five aforementioned subject deaths were treatment emergent SAEs

When considering treatment-emergent adverse reactions, only 5 subjects (0.7%) in the delafloxacin arm and 6 (0.8%) in the vancomycin arm had treatment emergent serious adverse reactions that were considered, by this reviewer, to be related to study treatment. Among all listed SAEs, the following PT terms were considered delafloxacin specific adverse reactions:

liver function tests increased (inclusive of both ALT and AST); dermatitis/rash, pulmonary embolism, urticaria, and the GI-related terms and diarrhea.

There were a total of six subjects, two in the delafloxacin (2/741; 0.3%) arm and four (4/751; 0.5%) in the vancomycin (± aztreonam) arm, in whom a total 7 of non-treatment emergent SAEs were reported. This notably included a single subject (Subject 303/840-313-3655) in the vancomycin (± aztreonam) arm in whom two non-treatment emergent SAEs were reported (PT terms: clavicle fracture and laceration) and a 31 year old woman randomized to the delafloxacin arm who was reported as having a spontaneous abortion. This SAE is discussed in greater detail in **Section 8.8.2 Human Reproduction and Pregnancy**. Both subjects experiencing non-treatment emergent SAEs in the delafloxacin arm were in Protocol 302. There were no non-treatment emergent SAEs occurring in Protocol 303's delafloxacin arm.

Medical Reviewer's Comments:

Most SAEs were assessed by site investigators as being unrelated to the study treatment. In most instances this reviewer concurred with the investigators' assessments. A total of ten subjects experienced multiple SAEs, this included three delafloxacin treated subjects (Subjects 302/840-014-0684, 303/840-322-3179, and 303/840-302-3113), all of whom had an active history of drug use.

FQs carry a boxed warning stating that FQs have been associated with central nervous system effects (i.e. hallucinations, anxiety, depression, and insomnia). Subject 302/840-014-0684, a 47 year old white male with a history of hepatitis C and heroin abuse and no reported psychiatric history, was coded as having a total of 3 SAEs two of which were coded under the Psychiatric Disorders (PTs: major depression and substance-induced mood disorder-suicidal ideation); however, this reviewer did not consider these SAEs, which occurred 4 days post-therapy and required an inpatient hospitalization, to be precipitated by delafloxacin therapy. Instead the reviewer considered these events to be part of the sequelae of the subject's ongoing heroin addiction.

Subject 303/840-322-3179, also in the delafloxacin treatment arm, was reported as having two treatment emergent SAEs (PT: ALT increased and AST increased); however, this reviewer assessed these SAEs to be an illustration of splitting of PT terms. The reviewer considered that these events would more appropriately be coded under the single PT transaminase elevations. Subject 303/840-322-3179 is discussed in greater detail below.

At the SOC level, SAEs coded under the Infections and Infestations SOC were the most frequently cited among subjects of each treatment arms. As assessed by this reviewer, a total of 30 SAEs were coded under this SOC. There was considerable splitting at the PT level observed under the Infections and Infestations SOC, with most splitting involving ABSSSI-related SAEs, and included the following preferred terms: cellulitis (7), infection (4), skin infection (4), abscess limb (1), erysipelas(1), skin bacterial infection (1). In most instances these skin related SAEs involved: (a) a worsening of or relapse of the primary infection site or (b) re-infection with a secondary ABSSSI site that either required retreatment with another antibacterial therapy and/or rehospitalization. There were 11 such subjects in the pooled delafloxacin arm (11/741;

1.5%) and 10 such subjects within the vancomycin (\pm aztreonam) comparator arm (10/751; 1.3%).

Other notable infections coded under the Infections and Infestations SOC included: pneumonia (2); arthritis bacterial (1); osteomyelitis (1); and sepsis-related terms (3), including the PTs staphylococcus sepsis and septic shock. It was noted that subject RIBX302/840-014-0396 who was randomized into the vancomycin (\pm aztreonam) arm with a cellulitis/erysipelas experienced an SAE that, at the PT level was coded as “soft tissue necrosis” under the Musculoskeletal and Connective Tissue Disorders SOC. In this reviewer’s assessment this SAE appears to have evolved into a necrotizing fasciitis that required two bedside I&Ds and an unplanned trip to the operating room (OR) for debridement of necrotic tissue and the removal of infected tissue down to the fascia. Given this history, this SAE would have more appropriately been coded under the Infections and Infestations SOC.

The SOC with the second highest incidence of SAEs (both fatal and non-fatal) was the Respiratory, Thoracic and Mediastinal Disorders SOC. The SAEs under this SOC occurred in four subjects randomized to the pooled delafloxacin arm and in one from the pooled vancomycin (\pm aztreonam) comparator arm. It is worth noting that two of the four subjects in the delafloxacin arm with SAEs under this SOC had pulmonary emboli, one of which resulted in study drug withdrawal and premature discontinuation from both the study and the study treatment. The other case of PE occurred post-therapy. Given the potentially fatal consequences of PEs, a brief discussion of these events is merited and brief narratives of these events are described below.

- **Subject 303/840-307-3915 (Delafloxacin):** A 31 year old man with no past medical history, aside from an X-ray documented healed ankle fracture 2 months prior. The first dose of delafloxacin was administered for a right leg cellulitis on 23 Nov 2015 (Study Day 1). Concomitant medications at the time of treatment initiation included povidone-iodine, lidocaine, acetaminophen/codeine, and ibuprofen. On 24 Nov 2015 (Study Day 2), 11 hours after administration of the initial dose of delafloxacin, this subject developed left sided flank pain upon deep inspiration. This pain worsened the following day prompting the investigator to obtain a computed tomography (CT) which subsequently demonstrated a pulmonary embolus. Delafloxacin treatment was discontinued as a result of this finding on, 24 November 2015 (Study Day 2). On 27 Nov 2015, three days after the final dose of delafloxacin, the subject was noted to have a right leg deep vein thrombosis. Investigator deemed both of these events as unrelated to study drug.
- **Subject 303/840-327-3667 (Delafloxacin):** This 41 year old man with a history of obesity (BMI of 36.8 kg/m²) and diabetes, for which he was taking insulin glargine and Humalog mix, was randomized to delafloxacin therapy for a right leg cellulitis. He began study treatment on 2 Sept 2015 (Study Day 1). Subject received a total of 6 infusions of IV delafloxacin and 20 oral doses of delafloxacin with the final dose of delafloxacin received on 15 Sep 2015 (Study Day 14). On 21 Sept 2015 (Study Day 20), 6 days post-therapy, the subject presented to the ER with shortness of breath and chest pain. After a negative ER work-up which included an ECG and blood work, the study sub-investigator

obtained a CT which demonstrated a PE. Investigator deemed event unrelated to study drug.

In both of the above described SAEs, it is this reviewer's assessment that neither subject had any compelling known medical conditions nor circumstances that would predispose either subject to a venous thromboembolic event (VTE) (i.e., malignancy, prolonged hospitalization or travel, recent surgery etc.). According to the Applicant, both subjects were treated as outpatients, hence suggesting a certain amount of mobility in each of these subjects at baseline. The Applicant's narratives emphasized that one of the two subjects had sustained an ankle injury two months prior to study drug initiation, however according to the Geneva criteria this is outside the one month period that is generally accepted that a fracture would be considered a predisposing factor for a PE.

In the absence of a known biologically plausible relationship, there is, however, a temporal association between the study drug and the onset of these VTE events. Although there is no general consensus on the incidence of first time unprovoked VTE events in the general population, several population based studies report VTE rates of 1.05 to 1.43 per 1,000 persons, particularly in white males (Goldhaber SZ, Lancet 2012); hence neither chance nor exposure to delafloxacin could be excluded as a cause of these events. Upon review of other FDA approved fluoroquinolones, namely ciprofloxacin, levofloxacin, and moxifloxacin, none appear to have documented VTE events in their pre- or post-marketing experience. Ultimately, this reviewer's concern emerged from the fact that in a Phase 3 safety population of 1492 subjects, there were two subjects with no strong risk factors for VTE events who were diagnosed with a potentially life threatening medical event during or soon after receipt of study drug..

*This reviewer raised these concerns with the reviewer's supervisor, Dr. Thomas Smith, and the entire review team. This reviewer sent two information requests (IR) for clarification on these two cases of PE in the delafloxacin arm. In response to these IRs, the Applicant confirmed that a hypercoagulability work-up **was not** conducted in Subject 303/840-307-3915, the 31 year old patient, and neither was a hematology consult obtained. Furthermore, the Applicant could not confirm in which ankle the initial fracture occurred. The fact that the DVT in Subject 303/840-307-3915 was discovered **after** the PE makes it more difficult to establish a biologically plausible relationship between the DVT and the PE, as in most instances the DVT precedes the PE. Furthermore, evidence of a DVT was an exclusion criterion for eligibility for study participation, so it is presumed that this subject would have been evaluated for DVT prior to study enrollment or on Screening exam was assessed not to have concern for a DVT.*

The Applicant confirmed that a hematology consult was obtained in Subject 303/840-327-3667, the 41 year old patient with a PE. In his consult, the hematologist documented that the patient had no personal history of thromboembolism, "no family history suggestive of thrombophilia," and had a negative hypercoagulable work-up. Bilateral venous dopplers obtained on (b) (6) (b) (4) (two days post-therapy) showed no evidence of DVT in either leg. Although hematology consult documented that this subject was "restricted in physically strenuous activity, . . . he was ambulatory and able to carry out work of a light or sedentary nature."

Based on the above-assessed histories and the temporal nature between the two documented events and the study drug, this reviewer remains of the opinion that one cannot exclude, a possible association between the study drug and the two documented PEs. Nevertheless, it is noted that upon discussion with pharmacology toxicology reviewer, there were no cases of thrombosis in delafloxacin's non-clinical animal studies. The one subject (302/784-063-0539) in the vancomycin (± aztreonam) comparator arm who experienced a fatal PE had multiple VTE risk factors, including a prolonged hospitalization and recent surgery.

Briefly, there were no obvious investigator-assessed causal relationships between delafloxacin and SAEs that would be considered of special interest to the FQ class such as: (a) Renal and Urinary Disorders/renal failure where all such events occurred in the comparator arm; (b) Psychiatric Disorders, the three subjects from Trial 302 with psychiatric oriented SAEs occurred in persons with a known history of drug abuse and one of whom had pre-existing psychiatric diagnoses; (c) Investigations SOC, the single subject with observed elevations in his ALT and AST was an active IV drug abuser who recently seroconverted to HCV (as described above and below); and (d) a hypersensitivity reaction with urticaria that is described below. Although TEAEs from the GI SOC were the most frequently cited within the delafloxacin safety profile, there was only one subject (RIBX302/840-014-0684) in the delafloxacin arm with diarrhea. This SAE occurred in Subject 302/840-014-0684 who as mentioned earlier had a history of active IVDA and who was undergoing opiate withdrawal. Therefore, like the study investigator, this reviewer did not consider this SAE as being causally related to the study drug.

As indicated in **Table 46** below, the Applicant considered only six of the treatment emergent SAEs to be **related** to the study drug: two in the pooled Phase 3 delafloxacin arm (2/741; 0.3%), and four in the pooled Phase 3 vancomycin +aztreonam arm (4/751; 0.53%). The two subjects in the pooled delafloxacin arm were from Trial 303; there were no such subjects from Trial 302.

Brief descriptions of the two subjects in the pooled Phase 3 delafloxacin arm with investigator-assessed non-fatal, treatment emergent SAEs **related** to study treatment are discussed below. Upon review of the four SAEs in the comparator arm with an investigator-assessed causal relationship to the study treatment, three belonged to the renal and urinary disorders SOC (PT: renal failure/renal failure, acute) and one belonged to the skin and subcutaneous tissue disorders SOC (PT: rash). Given vancomycin's safety profile, such adverse reactions would not be unexpected.

Table 46: Treatment Emergent Serious Adverse Drug Reactions					
Unique Subject Identifier	Primary System Organ Class	Dictionary Derived Term	Analysis Causality	Delafloxacin	Vancomycin (Aztreonam)
RIBX302/376-040-0571	Renal and Urinary Disorders	Renal Failure, Acute	Related	0 (0.0%)	1 (0.1%)

MEL303/840-322-3179	Investigations	Aspartate Aminotransferase (AST) Increased	Related	1 (0.2%)	0 (0.0%)
	Investigations	Alanine Aminotransferase (ALT) Increased			0 (0.0%)
MEL303/100-435-3602	Renal and Urinary Disorders	Renal Failure	Related	0 (0.0%)	1 (0.1%)
MEL303/840-323-3299	Renal and Urinary Disorders	Renal Failure	Related	0 (0.0%)	1 (0.1%)
MEL303/233-443-3693	Skin and Subcutaneous Tissue Disorders	Urticaria	Related	1 (0.2%)	0 (0.0%)
MEL303/410-339-3178	Skin and Subcutaneous Tissue Disorders	Rash	Related	0 (0.0%)	1 (0.1%)
			Subjects(filtered)	2 (0.3%)	4 (0.5%)
			Overall Subjects	741 (100.0%)	751 (100.0%)

Source: ISS Population. ADSL and ADSAE data sets

Delafloxacin Subject 303/840-322-3179/ SAE “ALT and AST Increased”: A 32 year old white Hispanic male who was randomized into the delafloxacin arm for a left arm major cutaneous abscess. His baseline medical history was significant for IV heroin and methamphetamine addiction, depression and anxiety. He reportedly had a negative baseline history of Hepatitis B and C. He received no prior antibacterial drugs before study treatment initiation. He received the first dose of delafloxacin on 3 Jan 2015 for a total of 11 doses. His last day of study treatment was on 8 January 2015 (Study Day 6). On 23 January (Study Day 21), 16 days post-therapy, the subject’s was observed to have elevations in his ALT and AST that were observed to be, 859 IU/L and 442 IU/L, respectively, despite baseline ALT and AST values of 21 IU/L (within normal range). On 9 Feb 2015, he was diagnosed with acute Hepatitis C. The investigator assessed these elevations as “possibly related” to the study drug; whereas, the Applicant assessed these elevations as being “unlikely related” to the study drug given the change in his hepatitis antibody testing.” This reviewer concludes that there is a greater likelihood that the observed event occurred due to an infectious hepatitis as opposed to being a delafloxacin induced hepatitis.

Medical Reviewer’s Comment: *This subject has a history of active drug use which does place him at risk for HCV. Although the onset of this SAE was 16 days post-therapy, this reviewer believes that the subject’s active, ongoing drug use coupled with the seroconversion of his HCV antibody provides a more compelling explanation for this elevation in his LFTs than his*

exposure to study drug. It is unclear if a HCV RNA viral load was obtained which would have provided additional evidence in support of this diagnosis.

Delafloxacin 303/233-443-3693/SAE Urticaria: Subject 303/233-443-3693 was a 66 year old female who was randomized to delafloxacin on 7 September 2015 (Study Day 1) for treatment of a left leg cellulitis. On Day 7 of treatment (13 September 2015), she developed an urticarial rash on her neck and trunk which was described as erythematous and pruritic. This rash developed 7 hours after her 7th dose of oral delafloxacin. Her last dose of delafloxacin was on Study Day 7 (13 September 2015) following onset of this urticarial reaction. The subject received a total of 6 IV infusions and 8 oral doses of delafloxacin. The subject was treated with intramuscular steroids the day after the urticaria. This urticarial rash resolved on 27 September 2015 (Study Day 21).

Medical Reviewer’s Comment: *Based on the description of this SAE and the temporal nature between onset of this SAE and receipt of the study drug, this reviewer concurs with the investigator’s assessment that the above-described SAE constitutes a drug-induced urticarial hypersensitivity reaction.*

Phase 2 Trials: RX-3341-201 and RX-3341-202 (ISS Population)

Due to differences in delafloxacin dosing and/or comparator arms, this reviewer conducted separate reviews of safety for each of the Applicant’s Phase 2 trials. A discussion of all SAEs occurring in these Phase 2 trials is found below.

Trial 1 3341-202

Twelve subjects experienced a total of 21 treatment emergent SAEs during Trial 202: 4 (5.1%) of 78 subjects in the delafloxacin 300-mg IV arm; 2 of 75 (2.7%) subjects in the linezolid arm; and 6 (6.3%) of 96 subjects in the vancomycin arm. All SAEs were assessed by study investigators to be unrelated to study treatment irrespective of treatment arm.

Table 47 below summarizes all SAEs by SOC.

Table 47: Trial RX-3341-202 Serious Treatment Emergent Adverse Events				
Body System or Organ Class	Preferred Term	IV Delafloxacin, 300 mg N=78	IV Linezolid, 600 mg N=75	IV Vancomycin N=96
Blood and lymphatic system disorders				
	Anemia	0 (0.0%)	0 (0.0%)	1 (1.0%)
Cardiac disorders				
	Cardiac Failure Congestive	1 (1.3%)	0 (0.0%)	1 (1.0%)
Gastrointestinal disorders				
	Abdominal	0 (0.0%)	1 (1.3%)	1 (1.0%)

Table 47: Trial RX-3341-202 Serious Treatment Emergent Adverse Events				
Body System or Organ	Preferred	IV	IV Linezolid,	IV
	Pain			
	Diarrhea	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Nausea	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Vomiting	0 (0.0%)	0 (0.0%)	1 (1.0%)
General disorders and administration site conditions				
	Chest Pain	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Pyrexia	1 (1.3%)	0 (0.0%)	1 (1.0%)
Infections and infestations				
	Abscess	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Bacteremia	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Cellulitis	1 (1.3%)	1 (1.33%)	1 (1.0%)
	Infection	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Osteomyelitis	0 (0.0%)	0 (0.0%)	1 (1.0%)
Metabolism and nutrition disorders				
	Dehydration	0 (0.0%)	0 (0.0%)	1 (1.0%)
Nervous system disorders				
	Convulsion	1 (1.3%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders				
	Renal Failure Acute	0 (0.0%)	0 (0.0%)	1 (1.0%)
Total # of Subjects in each Treatment Arm		4 (5.1%)	2 (2.7%)	6 (6.3%)
Treatment Arm DENOMINATOR		78 (100.0%)	75 (100.0%)	96 (100.0%)
<i>Source: ISS Population. SDTM demographics and adverse events data sets. Four subjects have more than one SAE. There were two subjects with convulsions in Trial 202, however, in one of these two subjects the convulsions were not considered treatment emergent or a serious adverse event.</i>				

Medical reviewer's comments: Approximately 6% or less of subjects in each treatment arm experienced an SAE. As in the Applicant's pivotal Phase 3 trials, the most frequently cited SOCs in Trial 202, irrespective of treatment arm, belonged to the Infections and Infestation SOC. As in the Phase 3 trials, in most instances, these events were relapses of or re-infection with another ABSSSI.

A total of six treatment emergent SAEs occurred in four subjects in the delafloxacin arm and there was one subject with a non-treatment emergent SAE. Although there were two subjects in this arm who experienced AEs of special interest, namely convulsion, only one of these events

was considered a treatment emergent SAE; whereas the other was not. These two events are briefly summarized below:

- **RX-3341-202-11008-022 (Delafloxacin):** A 23-year old man with a past medical history significant for anxiety, insomnia, seizure disorder, and IV heroin abuse. Concomitant medications were oxycodone and alprazolam. Subject underwent an incision and drainage (I&D) for a “wound” on treatment day 1 with cultures from the ABSSSI site growing methicillin-resistant *Staphylococcus aureus*. He began treatment with delafloxacin for a right arm wound infection on (b) (6) (Study Day 1). The subject experienced abnormal dreams on days 1 through 14 of treatment. His final day of study drug treatment was (Study Day 6). He began methadone maintenance for his heroin addiction on Study Day 18. On Study Day 36, the subject was hospitalized for an SAE coded to the PT of convulsion (verbatim term: seizure). He was also documented as having a non-serious AE of headache and hypokalemia (baseline potassium of 3.2 and FU and LFU visits 4.7 and 4.1, respectively). The subject’s seizure, for which he received phenytoin, resolved the following day (Study Day 37). The investigator assessed the seizure to be unrelated to the study drug. The investigator did, however, consider the abnormal dreams to be “possibly related to study drug.” Although this subject’s seizure was considered an SAE, it was graded as a mild intensity, **non-TEAE** as it occurred after completion of the study drug.

***Medical reviewer’s comments:** Although FQs have been associated with convulsions, this subject with a prior history of seizure disorders and active IV drug use has multiple competing risk factors for seizure onset, including taking such concomitant methadone, oxycodone, and alprazolam, the latter two which have the potential for abuse and can result in seizures in the setting of drug overdose or withdrawal. Regarding any temporal associations between the event and the receipt of delafloxacin, this SAE occurred a little over a month post therapy. This reviewer agrees with the investigator that this event is unrelated to the study drug.*

- **RX-3341-202-11012-043 (Delafloxacin):** A 46 year old man with a prior medical history noted for convulsions. His concomitant medications included phenytoin, lidocaine and tramadol. He was enrolled into the study for treatment of a left leg cellulitis/erysipelas. Cultures from the ABSSSI site grew *Pseudomonas aeruginosa*. He received no previous systemic antibacterial drugs prior to enrollment into this study. He received his first dose of delafloxacin on (b) (6) (Study Day: 1). He received 8 days of study treatment and on the final day of treatment (b) (6) (Study Day 8), the subject was hospitalized for a “mild convulsion” which was assessed to be an SAE. He was treated with both diazepam and phenytoin and his seizure resolved the following day on Study Day 9 ((b) (6) This SAE was assessed by the study investigator as being unrelated to study drug treatment. This subject also had a second TEAE of muscle spasm.

***Medical reviewer’s comments:** This patient with a known history of seizures for which he was on standing phenytoin (but for whom baseline medication compliance is*

unknown) developed a seizure on the final day of his study treatment. This event is temporally related to study drug and hence this reviewer considers this SAE as being possibly related to study drug. However, the history is confounded by the fact that the subject has a known seizure history and is taking concomitant medications also associated with convulsions. One cannot exclude the possibility that delafloxacin may have lowered the seizure threshold in this subject.

- RX-3341-202-11022-008 (Delafloxacin):** A 44 year old woman with multiple co-morbid conditions including drug abuse with heroin, Hepatitis A, B and C; anxiety; depression; insomnia; and bipolar disorder with no documented history of prior VTE events. Concomitant medications included diazepam, hydromorphone. She was enrolled in Trial 202 for treatment of a left leg major cutaneous abscess for which she was begun on delafloxacin on (b) (6) (Study Day 1) as an outpatient. Culture of her ABSSSI site grew multiple pathogens. A blood culture from Study Day 11 grew *Stenotrophomonas maltophilia* and *Staphylococcus epidermidis*. On Study Day 13 she experienced two SAEs with PT terms pyrexia and bacteremia for which she was hospitalized. She was also documented as having several non-serious adverse events including a deep vein thrombosis in her right upper arm which was also assessed as a non-serious AE. Study drug was discontinued in light of the pyrexia and bacteremia. She was begun on piperacillin/tazobactam, linezolid, sutamicillin, gentamicin, and tobramycin. The investigator determined that all AEs, serious and non-serious alike, were unrelated to the study drug.

Medical reviewer’s comment: *This is another case of a VTE in the delafloxacin arm. Given the potential for fatalities associated with DVT (should it embolize to the lungs), this reviewer considers the presence of a DVT a medically important event and considers this to be an SAE. As an IVDA, however, this subject had a well-known predisposing risk factor for the development of a DVT.*

Phase 2 Trial RX- 3341-201

Trial 201 was the only one of the Applicant’s treatment trials that evaluated delafloxacin’s safety at the 450-mg IV dose. All AEs and SAEs were treatment emergent. No deaths and very few treatment emergent SAEs occurred across any treatment arm in Trial 201. A total of 8 SAEs occurred in 7 individuals: 1 (2.0%) in the delafloxacin 300-mg IV arm; 3 (5.9%) in delafloxacin 450-mg IV arm, and 3 (6.0%) in the tigecycline comparator arm.

Table 48 provides a summary of all SAEs by SOC and PT term.

Table 48: Trial RX-3341-201 Serious Treatment Emergent Adverse Events				
System Organ Class	Preferred Term	Delafloxacin 300 mg twice daily N=49	Delafloxacin 450 mg twice daily N=51	Tigecycline N=50
Cardiac Disorders	<i># of subjects, (%)</i>	0 (0.0%)	1 (2.0%)	0 (0.0%)
	Bradycardia	0 (0.0%)	1 (2.0%)	0 (0.0%)
Gastrointestinal	<i># of subjects, (%)</i>	0 (0.0%)	0 (0.0%)	1 (2.0%)

disorders	Duodenal ulcer hemorrhage*	0 (0.0%)	0 (0.0%)	1 (2.0%)
Infections and infestations	# of subjects, (%)	0 (0.0%)	1 (2.0%)	1 (2.0%)
	Cellulitis	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Osteomyelitis	0 (0.0%)	1 (2.0%)	0 (0.0%)
Injury, poisoning and procedural complications	# of subjects, (%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
	Femoral neck fracture	1 (2.0%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	# of subjects, (%)	0 (0.0%)	1 (2.0%)	1 (2.0%)
	Cerebellar infarction	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Convulsion	0 (0.0%)	1 (2.0%)	0 (0.0%)
Vascular disorders	# of subjects, (%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Subclavian vein thrombosis*	0 (0.0%)	0 (0.0%)	1 (2.0%)
Total # of Subjects (filtered)		1 (2.0%)	3 (6.0%)	4 (8.0%)
<i>Source: ISS Population. SDTM demographic and adverse event data sets and Applicant's Table 26 found in Trial RX-3341-201 clinical study report (CSR). *A single subject had more than 1 SAE.</i>				

All subject SAEs but one, the SAE for Subject 201-215-0055 (PT: convulsion), were determined by site investigators to be unrelated to the study treatment. Upon reviewing subject narratives, this reviewer concurred with the investigators' assessments. A brief description of the single SAE assessed by a site investigator as being "possibly related" to the study drug is found below.

- RX-3341-201-215-0055 (Delafloxacin):** Subject 201-215-0055 was a 53 year old white man with a history of undiagnosed ongoing seizure-like activity prior to study enrollment. He was only formally diagnosed with seizures on Study Day 3. The subject notified the study staff of what "may have been undiagnosed partial seizures prior to beginning study." However, he had never received a formal evaluation or diagnosis of a seizure disorder. Other relevant medical history included HCV, addiction to pain medications, and lumbar stenosis. His only concomitant medication was methadone. He had never received any prior anti-seizure medications. He received his first dose of IV delafloxacin 450-mg on (b) (6) and received his final dose on (b) (6). On Day 3 of study treatment (b) (6) subject experienced a sub-investigator witnessed seizure with an observed loss of consciousness, generalized stiffness and shaking of the upper body. A head CT was normal. Subject CRF provided the following description "Patient with increasing frequency and intensity of presumed generalized seizure activity. . . . Due to increasing intensity and frequency of episodes, patient was withdrawn from the study." Subject was subsequently evaluated by a neurologist whose working diagnosis, per case narrative, was peripheral vestibular dysfunction versus cardiogenic near syncope. Study drug was permanently discontinued on (b) (6) due to the subject's continued seizures while on treatment. Subject was also withdrawn from study. Seizure work-up included a negative electroencephalogram

and a negative MRI. The investigator-assessed that the subject’s seizures were possibly related to the study drug.

Medical reviewer’s comments: Subject appears to have been experiencing seizures prior to study enrollment and continued to have seizures throughout his study enrollment. It is very possible that subject would have continued to have seizures in the absence of study drug. It is also foreseeable that study drug quite possibly precipitated further seizures by lowering the seizure threshold. In this reviewer’s opinion, one cannot fully exclude the possibility that the study drug contributed to the worsening of the subject’s ongoing seizures given the temporal association between study drug and the events and the association between seizures and the FQ class. This event may indicate that at higher doses, in this case delafloxacin 450-mg, delafloxacin may lower the seizure threshold in subjects with a known seizure history. However, given the subject’s history of previous (yet formally undiagnosed seizures) it is clearly evident that delafloxacin was not the sole cause of this subject’s seizures. In addition, given the subject’s history of pain medication addiction, one cannot exclude the possibility that subject may not have been forthcoming with his concomitant medication use and/or that he may have been withdrawing from illicitly acquired pain medications (i.e. opiates or even benzodiazepines).

8.4.3 Dropouts and/or Discontinuations Due to Adverse Events

Phase 3 Trials: RX-3341-302 and RX-3341-303 (ISS Population)

Discontinuations of study treatment due to AEs occurred infrequently in the Applicant’s pivotal Phase 3 trials. A combined total of 39 subjects in the Phase 3 trials ISS population experienced a total of 40 TEAEs resulting in study drug discontinuation: a total of 13 subjects (13/741; 1.8%); in the delafloxacin arm, 3 from Trial 302 and 10 from Trial 303, discontinued the study treatment due to treatment emergent AEs (TEAEs); whereas, double the number of subjects in the pooled vancomycin comparator arm, 26 subjects (26/751; 3.5%) experienced TEAEs that resulted in study drug discontinuations- with one subject experiencing two such TEAEs. Several subjects who experienced treatment-emergent SAEs were also discontinued from the study treatment. Twenty-five study treatment discontinuation TEAEs (6 in the delafloxacin arm and 19 in the vancomycin arm) were assessed by study investigators as being **related** to the study treatment. This is compared with 15 study drug discontinuations which were deemed by investigators to be **unrelated** to the study drug. This reviewer carefully reviewed all subject narratives and CRFs of those subjects who discontinued the study treatment.

A tabular summary of TEAE study discontinuations is summarized in **Table 49** below.

Table 49: Pooled Phase 3 Trials Treatment Emergent Adverse Events Resulting in Discontinuation of Study Treatment		
System Organ Classification/Dictionary Derived Term (PT Term)	Delafloxacin N=741	Vancomycin (±Aztreonam) N=751

Primary System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg by mouth every 12 hours	Vancomycin (±Aztreonam)
Gastrointestinal Disorders	# of subjects, (%)	1 (0.1%)		0 (0.0%)
	Vomiting	0 (0.0%)	1 (0.1%)	0 (0.0%)
General Disorders and Administration Site Conditions	# of subjects, (%)	1 (0.1%)		2 (0.3%)
	Infusion Site Extravasation	0 (0.0%)	1 (0.1%)	2 (0.3%)
Immune System Disorders	# of subjects, (%)	2 (0.3%)		2 (0.3%)
	Hypersensitivity	1(0.1%)	1(0.1%)	2 (0.3%)
Infections and Infestations	# of subjects, (%)	2 (0.3%)		6 (0.8%)
	Cellulitis/Skin Infection/Infection	1(0.1%)	1 (0.1%)	3 (0.4%)
	Erythema†	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Sepsis	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Soft Tissue Necrosis†	0 (0.0%)	0 (0.0%)	1 (0.1%)
Injury, Poisoning, and Procedural Complications	# of subjects, (%)	1 (0.1%)		0 (0.0%)
	Subdural Hematoma	0 (0.0%)	1 (0.1%)	0 (0.0%)
Investigations	# of subjects, (%)	0 (0.0%)		1 (0.1%)
	Liver Function Test Abnormal	0 (0.0%)	0 (0.0%)	1 (0.1%)
Metabolism and Nutrition Disorders	# of subjects, (%)	0 (0.0%)		1 (0.1%)
	Hypoglycemia	0 (0.0%)	0 (0.0%)	1 (0.1%)
Musculoskeletal and Connective Tissue Disorders	# of subjects, (%)	0 (0.0%)		1 (0.1%)
	Muscle Spasm	0 (0.0%)	0 (0.0%)	1 (0.1%)
Nervous System Disorders	# of subjects, (%)	0 (0.0%)		1 (0.1%)
	Convulsion	0 (0.0%)	0 (0.0%)	1 (0.1%)
Psychiatric Disorders	# of subjects, (%)	0 (0.0%)		1 (0.1%)
	Agitation	0 (0.0%)	0 (0.0%)	1 (0.1%)
Renal and Urinary Disorders	# of subjects, (%)	0 (0.0%)		1 (0.1%)
	Renal Failure, Acute	0 (0.0%)	0 (0.0%)	1 (0.1%)

Table 49: Pooled Phase 3 Trials Treatment Emergent Adverse Events Resulting in Discontinuation of Study Treatment				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
Primary System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg by mouth every 12 hours	Vancomycin (±Aztreonam)
Respiratory, Thoracic, and Mediastinal Disorders	# of subjects, (%)	2 (0.3%)		0 (0.0%)
	Acute Respiratory Failure	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Pulmonary Embolism	0 (0.0%)	1 (0.1%)	0 (0.0%)
Skin and Subcutaneous Tissue Disorders	# of subjects, (%)	4 (0.5%)		10 (1.5%) (with a total of 11 TEAEs)
	Dermatitis Allergic	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Pruritus/Pruritus Generalized*	0 (0.0%)	0 (0.0%)	2 (0.3%)
	Pyoderma Gangrenosum	1 (0.1%)	0 (0.0%)	0 (0.0%)
	Rash	0 (0.0%)	0 (0.0%)	4 (0.5%)
	Urticaria*	0 (0.0%)	2 (0.3%)	5 (0.7%)
	Total # of Subjects (filtered)	10 (1.4%)	3 (0.4%)	26 (3.5%)
DENOMINATOR		741 (100.00%)		751 (100.00%)
Source: ISS ADAE data set and Table 12 of Module 2.7.4 Summary of Clinical Safety (p.41-45). * <i>A single subject had more than 1 TEAE that resulted in discontinuation of the study drug. † Erythema and Soft Tissue Necrosis were originally coded under the Skin and Subcutaneous Tissue Disorders SOC and Musculoskeletal and Connective Tissue Disorders SOC, respectively. However, upon review of subject narratives this event was re-adjudicated to the Infections and Infestations SOC.</i>				

Medical Reviewer’s Comments: The majority of TEAEs resulting in study drug discontinuation belonged to the Skin and Subcutaneous Tissue Disorders SOC. Of the 14 subjects experiencing TEAEs under this SOC, the majority of subjects, 10 (10/751; 1.3%) were from the pooled vancomycin comparator arm, including a single subject who experienced two such events leading to discontinuation of treatment; whereas the remaining four subjects (4/741; 0.5%) were from the pooled delafloxacin arm. In both treatment arms, observed events under this SOC, were coded to the following PT terms: urticaria (7), rash (4), dermatitis allergic (1), erythema (1), pyoderma gangrenosum (1; in a patient with inflammatory bowel disease), pruritus generalized (1). Two subjects, one in each of the two pooled treatment arms, experienced hypersensitivity reactions.

Pooled Delafloxacin Arm: Among the 13 subjects in the delafloxacin arm with TEAEs resulting in treatment discontinuations, six were assessed by the investigator as being related to the study drug treatment, of these 6 subjects: 3 subjects had events coded under the Skin and Subcutaneous Disorder SOC (PT terms: urticarial and dermatitis allergic); two subjects had events coded under the Immune System Disorders SOC (PT term: hypersensitivity) and one had an event coded under the Gastrointestinal Disorders (PT term: vomiting). Upon review of subject CRFs and narratives, this reviewer agrees that there was a temporal and biologically plausible causal linkage between the above-described events and the study drug. Subject 303/840-307-3915 who sustained a PE that resulted in an SAE as well as a withdrawal from delafloxacin therapy has been discussed previously.

Several unrelated TEAEs resulting in discontinuation of the study drug belonged to the Infections and Infestations SOC and were more appropriately assessed as failures in treatment efficacy.

Pooled Vancomycin (± aztreonam) Comparator Arm: Similarly, the majority of subjects in the vancomycin (± aztreonam) arm (12/751; 1.6%) with documented treatment related discontinuations had events coded under the Skin and Subcutaneous Disorders SOC and the Immune System Disorders SOC (with one subject sustaining two PTs under the Skin Disorders SOC). TEAEs were coded under the following PT terms: rash (4), urticaria (5), hypersensitivity (2); pruritus/pruritus generalized (2), and erythema (1). Events coded under the Infections and Infestations were the next most cited TEAEs resulting in discontinuation of vancomycin (± aztreonam) treatment. Other TEAEs assessed by the study investigators as being related to vancomycin (± aztreonam) treatment were coded under the following PT terms: convulsion (1), muscle spasms (1), hypoglycemia (1), and liver function test abnormal (1).

Table 50 below summarizes all treatment **adverse reactions** that resulted in discontinuation of the study drug in the Applicant’s Phase 3 trials.

Table 50: Pooled Phase 3 Treatment Emergent Adverse Reactions Resulting in Discontinuation of Study Treatment				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
System Organ Class	Dictionary Derived /PT Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg by mouth every 12 hours	Vancomycin (±Aztreonam)
Gastrointestinal Disorders	<i># of subjects, (%)</i>	1 (0.1%)		0 (0.0%)
	Vomiting	0 (0.0%)	1 (0.1%)	0 (0.0%)
General Disorders and Administration Site Conditions	<i># of subjects, (%)</i>	1 (0.1%)		2 (0.3%)
	Infusion Site Extravasation	0 (0.0%)	1 (0.1%)	2 (0.3%)

Table 50: Pooled Phase 3 Treatment Emergent Adverse Reactions Resulting in Discontinuation of Study Treatment				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
System Organ Class	Dictionary Derived /PT Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg by mouth every 12 hours	Vancomycin (±Aztreonam)
Immune System Disorders	<i># of subjects, (%)</i>	2 (0.3%)		2 (0.3%)
	Hypersensitivity	1(0.1%)	1(0.1%)	2 (0.3%)
Investigations	<i># of subjects, (%)</i>	0 (0.0%)		1 (0.1%)
	Liver Function Test Abnormal	0 (0.0%)	0 (0.0%)	1 (0.1%)
Metabolism and Nutrition Disorders	<i># of subjects, (%)</i>	0 (0.0%)		1 (0.1%)
	Hypoglycemia	0 (0.0%)	0 (0.0%)	1 (0.1%)
Musculoskeletal and Connective Tissue Disorders	<i># of subjects, (%)</i>	0 (0.0%)		1 (0.1%)
	Muscle Spasm	0 (0.0%)	0 (0.0%)	1 (0.1%)
Nervous System Disorders	<i># of subjects, (%)</i>	0 (0.0%)		1 (0.1%)
	Convulsion	0 (0.0%)	0 (0.0%)	1 (0.1%)
Psychiatric Disorders	<i># of subjects, (%)</i>	0 (0.0%)		1 (0.1%)
	Agitation	0 (0.0%)	0 (0.0%)	1 (0.1%)
Renal and Urinary Disorders	<i># of subjects, (%)</i>	0 (0.0%)		1 (0.1%)
	Renal Failure, Acute	0 (0.0%)	0 (0.0%)	1 (0.1%)
Respiratory, Thoracic, and Mediastinal Disorders	<i># of subjects, (%)</i>	1 (0.1%)		0 (0.0%)
	Pulmonary Embolism	0 (0.0%)	1 (0.1%)	0 (0.0%)
Skin and Subcutaneous Tissue Disorders	<i># of subjects, (%)</i>	3 (0.4%)		10 (1.3%)
	Dermatitis Allergic	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Pruritus/Pruritus Generalized*	0 (0.0%)	0 (0.0%)	2 (0.3%)
	Rash	0 (0.0%)	0 (0.0%)	4 (0.5%)
	Urticaria*	0 (0.0%)	2 (0.3%)	5 (0.7%)
Total # of Subjects (filtered)		1 (0.1%)	7 (1.0%)	21 (2.8%)
DENOMINATOR		741 (100.00%)		751 (100.00%)

Table 50: Pooled Phase 3 Treatment Emergent Adverse Reactions Resulting in Discontinuation of Study Treatment				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
System Organ Class	Dictionary Derived /PT Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg by mouth every 12 hours	Vancomycin (±Aztreonam)
<i>Source: ISS ADAE data set and Table 12 of Module 2.7.4 Summary of Clinical Safety (p.41-45).</i>				
<i>*A single subject had more than 1 TEAE that resulted in discontinuation of the study drug.</i>				

Phase 2 Trial RX-3341-202

Trial 1 202 had few TEAE treatment discontinuations. A total of 9 subjects across all 3 treatment arms experienced treatment related study withdrawals: 1 subject each in the delafloxacin 300-mg IV and linezolid 600-mg IV arms and a total of 7 subjects in the vancomycin IV arm. Three subjects experienced more than one TEAE: two in the vancomycin arm and one in the delafloxacin 300-mg IV arm).

Table 51 provides a tabular summary of all TEAEs that led to the subjects' study drug discontinuation.

Table 51: Trial RX-3341-202 Treatment Emergent Adverse Events Resulting in Discontinuation of Study Treatment				
System Organ Class (SOC)/ Preferred Term (PT)		RX-3341-202		
System Organ Class	Preferred Term	Delafloxacin, 300 mg IV N=78	Linezolid, 600 mg IV N=75	Vancomycin, 15 mg/kg IV N=96
Cardiac Disorders	<i># of subject, (%)</i>	0	0	1
	Cardiac Failure Congestive	0 (0.0%)	0 (0.0%)	1 (1.0%)
General Disorders and Administration Site Conditions	<i># of subject, (%)</i>	1	0	0
	Pyrexia*	1 (1.3%)	0 (0.0%)	0 (0.0%)
Infections and Infestations	<i># of subject, (%)</i>	0	0	3
	Abscess Limb	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Bacteremia*	1 (1.3%)	0 (0.0%)	0 (0.0%)

	Infection (worsening cutaneous abscess) [†]	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Osteomyelitis	0 (0.0%)	0 (0.0%)	1 (1.0%)
Psychiatric Disorders	<i># of subject, (%)</i>	0	0	3
	Aggression*	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Agitation*	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Psychotic Disorder*	0 (0.0%)	0 (0.0%)	1 (1.0%)
Skin and Subcutaneous Tissue Disorders	<i># of subject, (%)</i>	0	1	2
	Pruritus*	0 (0.0%)	0 (0.0%)	2 (2.1%)
	Rash	0 (0.0%)	1 (1.3%)	0 (0.0%)
Vascular Disorders	<i># of subject, (%)</i>	0	0	1
	Flushing*	0 (0.0%)	0 (0.0%)	1 (1.0%)
Total # of Subjects (filtered)		1 (1.3%)	1 (1.3%)	7 (7.3%)

Source: ISS Population. SDTM demographic (DM) and adverse events (AE) data sets and Table 37 of Trial 202 clinical study report (CSR).

**Three (3) subjects had more than 1 TEAE that resulted in the discontinuation of study drug, as indicated by the PT with an *. [†]Infection refers to the worsening of the primary infection, a major cutaneous abscess. This subject was withdrawn from treatment at the investigator's discretion.*

Delafloxacin 300-mg IV: Subject 202-11022-008 was the single subject in the delafloxacin arm who experienced a treatment related SAE that resulted in her withdrawal from the delafloxacin arm. This subject was a 44 year old woman with multiple co-morbid conditions including heroin abuse, Hepatitis A, B and C; anxiety; depression; insomnia; and bipolar disorder. This subject experienced two investigator assessed treatment emergent SAEs, coded under the PT terms pyrexia and bacteremia which resulted in her hospitalization on Study Day 13 with pyrexia and bacteremia. Delafloxacin was discontinued on Study Day 13 as a result of these events. This case was previously discussed in Section 8.4.2

Comparators

Linezolid 600-mg IV: Subject RX-3341-202-11008-013 was the sole subject in the linezolid comparator arm to experience a TEAE leading to the withdrawal of linezolid. The documented event was for a non-serious TEAE that occurred on Study Day 2. The TEAE was coded to the PT term rash. This drug-related rash was described as occurring on bilateral arms and abdomen (no further details provided) and resolved on Study Day 4 following linezolid discontinuation. The reviewer considers this event to be a drug induced rash.

Vancomycin IV: The seven subjects experiencing TEAEs that resulted in discontinuation of vancomycin (± aztreonam) had events coded under the following SOCs: the Infections and Infestations SOC (3); the Psychiatric Disorders SOC (1 subject with 3 separate PT terms); the Skin and Subcutaneous Disorders SOC (2 subjects, with one subject experiencing another TEAE coded under the Vascular SOC); the Cardiac Disorders SOC (1); and the Vascular Disorders (subject with TEAE cross-referenced under the Skin SOC).

Phase 2 Trial RX-3341-201

Ninety percent of all subjects (135/150) in RX-3341-201 completed the study: 93.9% (46/49) in the delafloxacin 300-mg twice daily arm; 92.2% (47/51) in the delafloxacin 300-mg twice daily arm; and 84% (42/50) in the tigecycline arm. The most common reasons for study discontinuation were lost to follow-up and adverse events. A total of five subjects experienced 7 treatment discontinuations due to TEAEs. **Table 52** below, summarizes the reasons for study discontinuations by SOC and PT terms

Table 52: Trial RX-3341-201 Treatment Emergent Adverse Events Resulting in Discontinuation of Study Treatment				
System Organ Class/Dictionary Derived Term		Delafloxacin		Tigecycline
System Organ Class	Dictionary Derived Term	RX-3341 300 mg BID N=49	RX-3341 450 mg BID N=51	Tigecycline N=50
Gastrointestinal disorders	<i># of subject, (%)</i>	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Constipation*	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Nausea*	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Vomiting*	0 (0.0%)	0 (0.0%)	1 (2.0%)
Investigations	<i># of subject, (%)</i>	0 (0.0%)	1 (2.0%)	1 (2.0%)
	Electrocardiogram abnormal	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Liver function test abnormal	0 (0.0%)	1 (2.0%)	0 (0.0%)
Nervous system disorders	<i># of subject, (%)</i>	0 (0.0%)	1 (2.0%)	1 (2.0%)
	Cerebellar infarction	0 (0.0%)	0 (0.0%)	1 (2.0%)
	Convulsion	0 (0.0%)	1 (2.0%)	0 (0.0%)
Total # of Subjects (filtered)		0 (0.0%)	2 (3.9%)	3 (2.0%)
<i>Source: ISS SDTM adverse event data set. * A single subject in the tigecycline arm had 3 TEAEs resulting in study discontinuation.</i>				

As illustrated in **Table 52** above, while no subjects in the delafloxacin 300-mg twice daily arm experienced any TEAEs resulting in study discontinuation, two subjects in the delafloxacin 450-mg twice daily arm discontinued the study due to a TEAE. Brief narrative summaries of these TEAE are provided below:

RX-3341-201-206-0075 (Delafloxacin 450-mg): Subject 3341-201-206-0075 was a 29 year old man with a history of MRSA skin infections. He received an initial dose of delafloxacin 450-mg IV on (b) (6) (Study Day 1) for “an abscess on the right hand.” The last dose of delafloxacin was administered on (b) (6) (Study Day 13). Baseline LFTs were within normal limits, with an alkaline phosphatase of 115 IU/L, an ALT of 28 IU/L and an AST of 21 IU/L. On Study Days 4 and 5 elevations in his ALT and AST occurred, with values rising to 200 U/L and 84 U/L, respectively. Bilirubin levels remained within normal limits and alkaline

phosphatase rose to 151 U/L. The subject's case report form documented that the subject failed to complete treatment due to an adverse event, with case narrative further confirming "study drug was discontinued on [REDACTED] (b) (6) (Study Day 13) as a consequence of "elevated liver function tests" and the "patient was withdrawn from the study." This subject required a surgical exploration for a presumed osteomyelitis. Antimicrobial therapy with vancomycin IV was begun on [REDACTED] (b) (6). On [REDACTED] (b) (6) (Study Day 16), the subject was hospitalized for "an osteomyelitis of right thumb" (AE term) where his right thumb, subcutaneous tissue and bone were debrided. A purulent abscess with necrotic tissue was discovered at that time. The investigator considered this event to be a medically important event and hence categorized it as an SAE.

Medical Reviewer's Comment: *CRF and case narratives were reviewed. Based on available data, it is noted that the investigator assessed the osteomyelitis to be unrelated to study drug and "related to disease progression." This reviewer concurs with the investigator's assessment and determined that this event was consistent with a failure in treatment efficacy. Delafloxacin was reportedly discontinued due to the non-serious TEAE of "elevated liver function test." However, it is this reviewer's assessment, that given the timing of vancomycin administration, it appears as though delafloxacin was discontinued for both LFT elevations and a presumed treatment failure resulting in an osteomyelitis.*

RX-3341-201-215-0055 (Delafloxacin 450 mg): A 53 year old man with a history of recently diagnosed seizures who began delafloxacin treatment on [REDACTED] (b) (6) (Study Day 1) for an abscess on his left chest. On Study Day 3 [REDACTED] (b) (6), he experienced a treatment emergent SAE described at the verbatim term level as "recurrent generalized seizure activity." This SAE was resolved on [REDACTED] (b) (6) and the subject was withdrawn from the study. This subject has previously been discussed in **Section 8.4.2 Serious Adverse Events**. Please refer to **Section 8.4.2** for full details and reviewer comments.

Comparator (Tigecycline)

The three subjects in the tigecycline arm who discontinued tigecycline therapy did so for the following reasons: one subject sustained a cerebellar infarction that was evaluated by the study investigator as being unrelated to the study drug; one subject experienced, what was evaluated as tigecycline associated constipation and vomiting; and another subject experienced a PT term coded as an "ECG abnormal."

8.4.4 Significant Adverse Events

The Applicant graded adverse event severity as either mild, moderate or severe. The definition for each AE severity category is found below:

- **Mild:** These events required minimal or no treatment and did not interfere with the patient's daily activities.
- **Moderate:** These events resulted in a low level of inconvenience or concern with the therapeutic measures. Moderate events may have caused some interference with functioning.
- **Severe:** These events interrupted a patient's usual daily activity and may have required systemic drug therapy or other treatment.

Severity grading of subject AEs was assessed by the study investigator or by designated study personnel.

Section 8.4.4 describes investigator-assessed TEAEs categorized as moderate or severe in the Applicant’s Phase 3 trials. Some of these events were SAEs and were previously discussed in Section 8.4.2 **Serious Adverse Events** of this review. Only pertinent delafloxacin related TEAEs will be discussed for the Phase 2 Trials 201 and 202.

Phase 3 Trials RX-3341-302 and RX-3341-303 Significant TEAEs, (ISS Population)

A total of 136 subjects (136/741; 18.4%) in the pooled delafloxacin arm had an investigator-assessed moderate or severe TEAE: 62 subjects (62/741; 8.4%) from Trial 302 and 74 subjects (74/741; 10.0%) from Trial 303. In comparison, a total of 152 (152/751; 20.2%) subjects had either moderate or severe TEAEs in the pooled Phase 3 vancomycin arm. Several subjects had more than 1 documented moderate or severe TEAEs; however, overall a total of 128 (128/741; 17.3%) and 26 (26/741; 3.5%) subjects had an investigator graded moderate or severe TEAE, respectively, in the pooled delafloxacin arm. Whereas, a total of 142 (142/751; 18.9%) and 21 (21/751; 2.8%) subjects had an investigator graded moderate or severe TEAE, respectively, in the pooled vancomycin arm.

Considerable splitting of terms at the PT level was observed among PT terms associated with liver transaminase elevations (PT: ALT increased, AST increased, hepatic enzyme increased, transaminases increased) hypersensitivity reactions (PT: hypersensitivity and drug hypersensitivity), infusion site reactions (PT: infusion site erythema, infusion site extravasation, infusion site pain, infusion site phlebitis, injection/infusion site swelling), and rash (rash, dermatitis, dermatitis allergic).

The most frequently cited moderate and severe TEAEs in the pooled Phase 3 trials, irrespective of investigators’ assessment of causality, are summarized in **Table 53** below.

Table 53: Pooled Phase 3 Significant Treatment Emergent Adverse Events				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg by mouth every 12 hours	Vancomycin (±Aztreonam)
Blood and Lymphatic System Disorders	# of subjects, (%)	3 (0.4%)		4 (0.5%)
	Anemia	0 (0.0%)	3 (0.4%)	4 (0.5%)
Gastrointestinal Disorders	# of subjects, (%)	39 (5.3%)		33 (4.4%)
	Abdominal Pain	1 (0.1%)	2 (0.3%)	5 (0.7%)
	Constipation	1 (0.1%)	2 (0.3%)	5 (0.7%)

Table 53: Pooled Phase 3 Significant Treatment Emergent Adverse Events				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg by mouth every 12 hours	Vancomycin (±Aztreonam)
	Diarrhea	5 (0.7%)	9 (1.2%)	8 (1.1%)
	Nausea	6 (0.8%)	8 (1.1%)	9 (1.2%)
	Vomiting	3 (0.4%)	2 (0.3%)	6 (0.8%)
General Disorders and Administration Site Conditions	<i># of subjects, (%)</i>	14 (1.9%)		17 (2.3%)
	Infusion Site Reactions	6 (0.8%)	3 (0.4%)	5 (0.7%)
	Pyrexia	2 (0.3%)	3 (0.4%)	12 (1.6%)
Immune System Disorders	<i># of subjects, (%)</i>	3 (0.4%)		2 (0.3%)
	Drug Hypersensitivity/Hypersensitivity	1 (0.1%)	2 (0.3%)	2 (0.3%)
Infections and Infestations	<i># of subjects, (%)</i>	43 (5.8%)		38 (5.1%)
	Abscess/Abscess Limb	1 (0.1%)	4 (0.5%)	7 (0.9%)
	Cellulitis/Skin bacterial Infection/Skin Infection	3 (0.4%)	7 (0.9%)	9 (1.2%)
	Infection/Localized Infection	13 (1.8%)	8 (1.1%)	20 (2.7%)
	Sepsis/Septic Shock/Staphylococcal Sepsis	2 (0.3%)	1 (0.1%)	1 (0.1%)
	Genital Infection Fungal/Vulvovaginal Candidiasis	1 (0.1%)	3 (0.4%)	1 (0.1%)
Investigations	<i># of subjects, (%)</i>	13 (1.8%)		9 (1.2%)
	Blood alkaline phosphatase	0 (0.0%)	2 (0.3%)	1 (0.1%)

Table 53: Pooled Phase 3 Significant Treatment Emergent Adverse Events				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg by mouth every 12 hours	Vancomycin (±Aztreonam)
	increased			
	Blood creatine phosphokinase elevated	2 (0.3%)	0 (0.0%)	2 (0.3%)
	Blood pressure increased	1 (0.1%)	2 (0.3%)	1 (0.1%)
	Transaminase Elevations	3 (0.4%)	3 (0.4%)	5 (0.7%)
Nervous System Disorders	# of subjects, (%)	12 (1.6%)		15 (2.0%)
	Dizziness	0 (0.0%)	2 (0.3%)	2 (0.3%)
	Headache	5 (0.7%)	5 (0.7%)	13 (1.7%)
Psychiatric Disorders	# of subjects, (%)	3 (0.4%)		4 (0.5%)
	Anxiety	1 (0.1%)	2 (0.3%)	4 (0.5%)
Renal and Urinary Disorders	# of subjects, (%)	2 (0.3%)		8 (1.1%)
	Renal failure,acute/Renal failure/Renal Impairment	1 (0.1%)	1 (0.1%)	8 (1.1%)
Skin and Subcutaneous Tissue Disorders	# of subjects, (%)	7 (0.9%)		25 (3.3%)
	Pruritus	1 (0.1%)	1 (0.1%)	11 (1.5%)
	Rash/Dermatitis/Allergic Dermatitis	1 (0.1%)	1 (0.1%)	8 (1.1%)
	Urticaria	2 (0.3%)	1 (0.1%)	6 (0.8%)
<i>Source: ISS Population. SDTM demographics and adverse events data sets.</i>				

Table 54 provides a tabular summary of all moderate and severe treatment-emergent adverse drug reactions, Phase 3 Trials ISS Population (Irrespective of Relationship to Study Drug)

Table 54: Pooled Phase 3 Trials Moderate and Severe Treatment-emergent Adverse Drug Reactions				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
Primary System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg po every 12 hours	Vancomycin (±Aztreonam)
Cardiac Disorders	<i>Total # of subjects, (%)</i>	1 (0.1%)		2 (0.3%)
	<i>Moderate</i>			
	<i># of subjects, (%)</i>	1 (0.1%)		1 (0.1%)
	Palpitations	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Tachycardia	0 (0.0%)	1 (0.1%)	0 (0.0%)
	<i>Severe</i>			
	Tachycardia (Supraventricular Tachycardia)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Gastrointestinal Disorders	<i>Total # of subjects, (%)</i>	36 (4.9%)		28 (3.7%)
	<i>Moderate</i>			
	<i># of subjects, (%)</i>	12 (1.6%)		18 (2.4%)
	Diarrhea	4 (0.5%)	9 (1.2%)	8 (1.1%)
	Nausea	6 (0.8%)	8 (1.1%)	8 (1.1%)
	Vomiting	3 (0.4%)	2 (0.3%)	4 (0.5%)
	Abdominal Pain/Abdominal Discomfort	1 (0.1%)	2 (0.3%)	5 (0.7%)
	Dyspepsia	0 (0.0%)	0 (0.0%)	1 (0.1%)
	<i>Severe</i>			
	<i># of subjects, (%)</i>	1 (0.1%)		2 (0.3%)
	Diarrhea	1 (0.1%)	0 (0.0%)	0 (0.0%)
	Nausea	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Vomiting	0 (0.0%)	0 (0.0%)	1 (0.1%)
	General Disorders and Administration Site	<i>Total # of subjects, (%)</i>	8 (1.1%)	

Conditions	(%)			
	Moderate			
Infusion site extravasation	2 (0.3%)	1 (0.1%)	3 (0.4%)	
Infusion site phlebitis	0 (0.0%)	2 (0.3%)	1 (0.1%)	
Infusion/Injection site swelling	1 (0.1%)	0 (0.0%)	1 (0.1%)	
Infusion site erythema	1 (0.1%)	0 (0.0%)	0 (0.0%)	
Infusion site pain	1 (0.1%)	0 (0.0%)	0 (0.0%)	
Immune System Disorders	Total # of subjects, (%)			
	3 (0.4%)			
	Moderate			
	Hypersensitivity/Drug Hypersensitivity	1 (0.1%)	1 (0.1%)	2 (0.3%)
	Severe			
Hypersensitivity	0 (0.0%)	1 (0.1%)	0 (0.0%)	
Infections and Infestations	Total # of subjects, (%)			
	5 (0.7%)			
	Moderate			
	Vulvovaginal Candidiasis/Genital Infection Fungal	1 (0.1%)	3 (0.4%)	1 (0.1%)
Fungal Infection	1 (0.1%)	0 (0.0%)	0 (0.0%)	
Investigations	Total # of subjects, (%)			
	19 (2.6%)			
	Moderate			
	# of subjects, (%)	16 (2.1%)		
	ALT increased	3 (0.4%)	0 (0.0%)	1 (0.1%)
	AST increased	3 (0.4%)	0 (0.0%)	2 (0.3%)
	Hepatic enzyme increased	0 (0.0%)	1 (0.1%)	1 (0.1%)
	Hypertransaminasaemia	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Transaminase increased	0 (0.0%)	1 (0.1%)	2 (0.3%)
	Blood alkaline phosphatase increased	0 (0.0%)	2 (0.3%)	1 (0.1%)

	Blood creatine phosphokinase increased	1 (0.1%)	0 (0.0%)	2 (0.3%)
	Blood creatinine increased	1 (0.1%)	0 (0.0%)	2 (0.3%)
	Blood pressure increased	1 (0.1%)	2 (0.3%)	1 (0.1%)
	<i>Severe</i>			
	# of subjects, (%)	3 (0.4%)		0 (0.0%)
	ALT increased	0 (0.0%)	1 (0.1%)	0 (0.0%)
	AST increased	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Blood creatine phosphokinase increased	1 (0.1%)	0 (0.0%)	0 (0.0%)
Metabolism and Nutrition Disorders	Total # of subjects, (%)	1 (0.1%)		2 (0.3%)
	<i>Moderate</i>			
	# of subjects, (%)	0 (0.0%)		2 (0.3%)
	Hyperglycemia	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Hypoglycemia	0 (0.0%)	0 (0.0%)	1 (0.1%)
	<i>Severe</i>			
	# of subjects, (%)	1 (0.1%)		0 (0.0%)
	Hyperglycemia	1 (0.1%)	0 (0.0%)	0 (0.0%)
Nervous System Disorders	Total # of subjects, (%)	13 (1.8%)		18 (2.4%)
	<i>Moderate</i>			
	# of subjects, (%)	12 (1.6%)		18 (2.4%)
	Headache	4 (0.5%)	5 (0.7%)	13 (1.7%)
	Dizziness	0 (0.0%)	2 (0.3%)	2 (0.3%)
	Syncope	1 (0.1%)	0 (0.0%)	0 (0.0%)
	Dysgeusia	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Hypoesthesia	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Peripheral neuropathy	0 (0.0%)	0 (0.0%)	1 (0.1%)
	<i>Severe</i>			
	# of subjects, (%)	1 (0.1%)		0 (0.0%)
Headache	1 (0.1%)	0 (0.0%)	0 (0.0%)	
Psychiatric Disorders				

	Total # of subjects, (%)	13 (1.8%)		18 (2.4%)
	<i>Moderate</i>			
	# of subjects, (%)	12 (1.6%)		18 (2.4%)
	Anxiety	1 (0.1%)	2 (0.3%)	4 (0.5%)
	Insomnia	1 (0.1%)	0 (0.0%)	0 (0.0%)
Renal and Urinary Disorders	Total # of subjects, (%)	13 (1.8%)		18 (2.4%)
	<i>Moderate</i>			
	# of subjects, (%)	12 (1.6%)		18 (2.4%)
	Renal Failure/Renal Failure, Acute	0 (0.0%)	1 (0.1%)	6 (0.8%)
	Renal Impairment	1 (0.1%)	0 (0.0%)	0 (0.0%)
	<i>Severe</i>			
	# of subjects, (%)	1 (0.1%)		0 (0.0%)
	Renal Failure/Renal Failure, Acute	0 (0.0%)	0 (0.0%)	2 (0.3%)
Skin and Subcutaneous Tissue Disorders	Total # of subjects, (%)	13 (1.8%)		18 (2.4%)
	<i>Moderate</i>			
	# of subjects, (%)	6 (0.8%)		25 (3.3%)
	Pruritus/Pruritus Generalized	1 (0.1%)	1 (0.1%)	11 (1.5%)
	Rash (Erythematous, Generalized, Macular, Papular, Maculo-Papular, Vesicular)	1 (0.1%)	0 (0.0%)	7 (0.9%)
	Urticaria	1 (0.1%)	1 (0.1%)	6 (0.8%)
	Dermatitis, allergic	0 (0.0%)	1 (0.1%)	1 (0.1%)
	<i>Severe</i>			
	# of subjects, (%)	1 (0.1%)		0 (0.0%)
	Urticaria	0 (0.0%)	1 (0.1%)	0 (0.0%)
Vascular Disorders	Total # of subjects, (%)	13 (1.8%)		18 (2.4%)
	<i>Moderate</i>			
	# of subjects, (%)	6 (0.8%)		25 (3.3%)
	Flushing	0 (0.0%)	1 (0.1%)	0 (0.0%)

	Hypertension	0 (0.0%)	2 (0.3%)	1 (0.1%)
	Hypotension	1 (0.1%)	0 (0.0%)	0 (0.0%)
	Phlebitis	0 (0.0%)	0 (0.0%)	6 (0.8%)
	<i>Severe</i>			
	# of subjects, (%)	1 (0.1%)		0 (0.0%)
	Pulmonary Embolism	0 (0.0%)	2 (0.3%)	1 (0.1%)
	Hypotension	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Total # of subjects with moderate ADRs	34 (4.6%)	36 (4.9%)	78 (10.4%)
	Total # of subjects with severe ADRs	3 (0.4%)	5 (0.7%)	6 (0.8%)
	Total # of Subjects (filtered)	78 (10.5%)		84 (11.2%)
	DENOMINATOR	741	741	751
<i>Source: ISS population. ADSL and ADAE data sets. Several subjects may have had more than one moderate and/or severe treatment emergent adverse drug reactions.</i>				

Medical Reviewer’s Comments:

Although moderate and severe TEAEs were relatively infrequent across both pooled treatment arms of the Phase 3 ISS population, the GI-related events nausea and diarrhea emerged as the most frequently cited treatment emergent reactions of moderate or severe intensity, with slightly more of these events occurring in the delafloxacin arm versus the comparator arm as is reflected in the delafloxacin label. This is followed by the Investigations and Nervous System Disorders SOCs, respectively, as the second and third most frequently cited SOCs. Although significant numbers of PT terms coded under the Infections and Infestations SOC were identified as severe or moderate TEAEs, they are largely reflective of treatment failures and are not considered related to the study drug.

Phase 2 Trial RX-3341-202 Significant TEAEs, (ISS Population)

Few subjects in the three treatment arms of Trial 202 experienced moderate or severe TEAEs. A table of significant TEAEs in the delafloxacin arm and the two comparator arms is found below.

Table 55 displays all Investigator-Assessed Moderate and Severe Related TEAEs Reported in 2 or More Subjects for Trial 202.

Table 55: Protocol 202 Investigator-Assessed Moderate and Severe Related Treatment-emergent Adverse Reactions				
Primary System Organ Class	Dictionary Derived Term (PT Term)	Delafloxacin 300 mg IV N=78	Linezolid 600-mg IV N= 75	Vancomycin N=96
	<i>Total # of subjects, (%)</i>	9 (11.5%)	6 (8.0%)	5 (5.2%)
Gastrointestinal Disorders	<i>Moderate</i>			
	# of subjects, (%)	9 (11.5%)	5 (6.7%)	5 (5.2%)
	Diarrhea	3 (3.8%)	1 (1.3%)	1 (1.0%)

Table 55: Protocol 202 Investigator-Assessed Moderate and Severe Related Treatment-emergent Adverse Reactions					
Primary System Organ Class	Dictionary Derived Term (PT Term)	Delafloxacin 300 mg IV N=78	Linezolid 600-mg IV N= 75	Vancomycin N=96	
	Vomiting	3 (3.8%)	2 (2.7%)	1 (1.0%)	
	Nausea	2 (2.6%)	2 (2.7%)	1 (1.0%)	
	Dyspepsia	1 (1.3%)	0 (0.0%)	0 (0.0%)	
	Abdominal pain/Abdominal pain, upper	0 (0.0%)	0 (0.0%)	2 (2.1%)	
	<i>Severe</i>				
	Nausea	0 (0.0%)	1 (1.3%)	0 (0.0%)	
General disorders and administration site conditions	# of subjects, (%)	1 (1.3%)	2 (2.7%)	1 (1.0%)	
	<i>Moderate</i>				
	Infusion site phlebitis	1 (1.3%)	0 (0.0%)	2 (2.1%)	
Infection and Infestations	Total # of subjects, (%)	1 (1.3%)	1 (1.3%)	2 (2.1%)	
	<i>Moderate</i>				
	Fungal infection/Fungal skin infection	1 (1.3%)	1 (1.3%)	2 (2.1%)	
	Vulvovaginal candidiasis	0 (0.0%)	1 (1.3%)	0 (0.0%)	
Investigations	Total # of subjects, (%)	1 (1.3%)	0 (0.0%)	1 (1.0%)	
	<i>Moderate</i>				
	# of subjects, (%)	1 (1.3%)	0 (0.0%)	1 (1.0%)	
	Liver function test abnormal	1 (1.3%)	0 (0.0%)	0 (0.0%)	
	Blood creatinine increased	0 (0.0%)	0 (0.0%)	1 (1.0%)	
Musculoskeletal and connective tissue disorders	Total # of subjects, (%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	
	<i>Moderate</i>				
	Myalgia	0 (0.0%)	0 (0.0%)	1 (1.0%)	
Nervous System Disorders	Total # of subjects, (%)	0 (0.0%)	2 (2.7%)	0 (0.0%)	
	<i>Moderate</i>				
	# of subjects, (%)	0 (0.0%)	1 (1.3%)	0 (0.0%)	

Table 55: Protocol 202 Investigator-Assessed Moderate and Severe Related Treatment-emergent Adverse Reactions				
Primary System Organ Class	Dictionary Derived Term (PT Term)	Delafloxacin 300 mg IV N=78	Linezolid 600-mg IV N= 75	Vancomycin N=96
	Headache	0 (0.0%)	1 (1.3%)	0 (0.0%)
	<i>Severe</i>			
	<i># of subjects, (%)</i>	<i>1 (1.3%)</i>	<i>1 (1.3%)</i>	<i>0 (0.0%)</i>
	Convulsion	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Headache	0 (0.0%)	1 (1.3%)	0 (0.0%)
Psychiatric disorders	Total # of subjects, (%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
	<i>Moderate</i>			
	Anxiety	0 (0.0%)	0 (0.0%)	1 (1.0%)
Renal and urinary disorders	Total # of subjects, (%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
	<i>Severe</i>			
	<i># of subjects, (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>1 (1.0%)</i>
	Renal failure, acute	0 (0.0%)	0 (0.0%)	1 (1.0%)
Skin and Subcutaneous Tissue Disorders	Total # of subjects, (%)	3 (3.8%)	1 (1.3%)	8 (8.3%)
	<i>Moderate</i>			
	<i># of subjects, (%)</i>	<i>3 (3.8%)</i>	<i>1 (1.3%)</i>	<i>5 (5.2%)</i>
	Pruritus	1 (1.3%)	0 (0.0%)	4 (4.2%)
	Rash	2 (0.7%)	1 (1.3%)	1 (1.0%)
	<i>Severe</i>			
	<i># of subjects, (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>3 (3.1%)</i>
	Pruritus	0 (0.0%)	0 (0.0%)	2 (2.1%)
Rash	0 (0.0%)	0 (0.0%)	1 (1.0%)	
Vascular Disorders	Total # of subjects, (%)	1 (1.3%)	1 (1.3%)	2 (2.1%)
	<i>Moderate</i>			
	<i># of subjects, (%)</i>	<i>1 (1.3%)</i>	<i>1 (1.3%)</i>	<i>1 (1.0%)</i>
	Hypertension	1 (1.3%)	1 (1.3%)	0 (0.0%)
	Hypotension	0 (0.0%)	0 (0.0%)	1 (1.0%)
	<i>Severe</i>			
	<i># of subjects, (%)</i>	<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>1 (1.0%)</i>
Flushing	0 (0.0%)	0 (0.0%)	1 (1.0%)	

Source: SS, population. SDTM adverse events and demographic data sets. Moderate and severe ADRs as graded by site investigators.

Medical Reviewer's Comments:

Few moderate or severe treatment emergent adverse reactions occurred in the three treatment arms of Trial 202. Similar to the pooled Phase 3 trials, the most commonly cited moderate and severe treatment emergent adverse reactions in Trial 202 occurred under the GI SOC and were coded to the PT terms diarrhea, vomiting, and nausea. Most of these events occurred among delafloxacin treated subjects.

Phase 2 Trial RX-3341-201 Significant Treatment-emergent Adverse Reactions, (ISS Population)

Table 56 summarizes Trial 201 Investigator-Assessed Moderate and Severe Related TEAEs

Table 56: Trial 201 Treatment Emergent Moderate and Severe Treatment Emergent Adverse Events, Investigator -Assessed				
Primary System Organ Class	Dictionary Derived Term	RX-3341 300 mg BID (N=49)	RX-3341 450 mg BID (N=51)	Tigecycline (N=50)
Moderate				
Gastrointestinal disorders	Total # of events	0	5	16
	Diarrhea, n/N (%)	0 (0.0%)	3 (5.9%)	1 (2.0%)
	Nausea, n/N (%)	0 (0.0%)	1 (2.0%)	7 (14.0%)
	Vomiting, n/N (%)	0 (0.0%)	1 (2.0%)	4 (8.0%)
	Constipation	0 (0.0%)	0 (0.0%)	3 (6.0%)
	Abdominal discomfort, n/N (%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
General disorders and administration site conditions	Total # of events	0	2	0
	Catheter site related reaction, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
	Pyrexia, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Infections and Infestations	Fungal infection, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Investigations	Total # of events	3	1	0
	Alanine aminotransferase increased, n/N (%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
	Liver function test abnormal, n/N (%) [†]	0 (0.0%)	1 (2.0%)	0 (0.0%)
	Blood creatinine increased, n/N (%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
	Blood glucose increased, n/N (%)	1 (2.0%)	0 (0.0%)	0 (0.0%)

Nervous system disorders	Total # of events	0	2	2
	Headache, n/N (%)	0 (0.0%)	1 (2.0%)	2 (4.0%)
	Tremor, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Psychiatric disorders	Insomnia, n/N (%)	1 (2.0%)	1 (0.67%)	1 (2.0%)
Total # of Subjects with Moderate AEs (filtered)		3 (6.1%)	8 (15.7%)	9 (18.0%)
Severe				
Gastrointestinal Disorders	Nausea, n/N (%)	0 (0.0%)	0 (0.0%)	2 (4.0%)
Metabolism and nutrition disorders	Hypokalemia, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Nervous Systems Disorders	Total # of events	0	1	1
	Convulsion, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
	Headache, n/N (%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Total # of Subjects (filtered)		0 (0.0%)	1 (2.0%)	1 (2.0%)
<p>Source: ISS population. Table derived from SDTM adverse events and demographic data sets. *Several subjects had multiple ADRs. †Resulted in discontinuation of study drug.</p>				

Medical Reviewer's Comments:

All 150 subjects receiving study treatment were included in the safety population, subject counts were as follows: 49 subjects received delafloxacin 300-mg IV; 51 subjects received delafloxacin 450-mg IV; and 50 subjects received vancomycin.

The most frequently endorsed TEAEs belonged to the GI SOC and occurred with greatest frequency in the tigecycline arm. The most cited PT terms under the GI SOC were nausea and diarrhea. Diarrhea was the most frequently reported moderate TEAE and ADR in the delafloxacin 450-mg IV arm with three subjects being assessed by investigators as having moderate diarrhea. A single subject had a treatment emergent AE coded each to nausea and vomiting in the delafloxacin 450-mg IV arm. The second most endorsed SOC under the 450-IV arm occurred under the General Disorders and Administration Site Conditions SOC and the Nervous System Disorders SOC, where a single Subject RX-3341-201-215-0055, who had been discussed previously, had an event coded to the PT convulsion. Otherwise, no clear pattern of TEAEs emerged in these latter two SOC.

In Trial 201, there were **no subjects in either of the delafloxacin arms** who were reported as having an investigator **graded severe adverse drug reaction (ADR)**. Three subjects (3/49; 8.1%)

in the delafloxacin 300-mg arm were reported as having moderately graded ADRs, including one subject (Subject 201-205-0134), a 40 year old Native American/Alaska Native male with a history of heroin abuse and hepatitis C who was enrolled for a right buttock wound infection, and who had two ADRs each coded under the PT terms “blood creatinine increased” and “ALT increased.” Subject 201-205-0134 had a baseline Cr of 0.9 mg/dL (80 µmol/L) which peaked to 3.9 mg/dL (345 µmol/L) also on Study Day 23, 18 days post-therapy. In addition, this subject, who had baseline elevated ALT (89 U/L) and AST (84 U/L) values, likely due to his ongoing HCV infection (for which he was apparently not receiving treatment), was observed to have a steady increase in his ALT during treatment. His ALT peaked to 146 U/L on Study Day 23; whereas, his AST peaked to 126 U/L on Study Day 6. By Study Day 29 his AST and Cr returned to baseline levels, 80 U/L and 1.0 mg/dL (88 µmol/L), respectively, while his ALT remained slightly elevated at 100 U/L. There was insufficient information to determine the etiology this subject’s creatinine elevation. Since Cr elevations occurred post treatment they were unlikely to be due to delafloxacin. No subjects with moderately graded ADRs in the delafloxacin 300-mg arm were withdrawn from the trial.

The delafloxacin 450-mg treatment arm had a total of 8 subjects (8/51; 15.7%) with an investigator moderate investigator graded ADR. Three of these 8 subjects had >1 ADR and one subject (Subject 201-206-0075) a 29 year old white male enrolled into the study with a right hand abscess, was withdrawn from study treatment for an SAE coded as an osteomyelitis. However, this patient was also coded as having a non-serious ADR of “liver function test abnormal.” Despite having baseline normal ALT and AST values, this subject’s ALT, AST, and alkaline phosphatase peaked to 200 U/L, 84 U/L, and 151 U/L, respectively, on Study Day 5 of a 13 day treatment course.

In comparison, 9 subjects (9/51; 18.0%) in the tigecycline comparator arm had moderate ADRs, 5 of whom had >1 ADR. A single subject (Subject 201-215-0131), a 38 year old black male was reported as having a total of 5 investigator assessed moderate PTs (penile swelling, constipation, headache, nausea and vomiting). There were three subjects in the tigecycline arm who were assessed as having severe ADRs (PT: nausea and headache).

8.4.5 Treatment Emergent Adverse Events and Adverse Reactions

Phase 3 Trials 302 and-303 (ISS Population)

This section focuses on the most commonly observed TEAEs and treatment emergent adverse reactions in the pooled Phase 3 ISS population. Collectively, the treatment emergent adverse reactions will be used to support delafloxacin’s safety profile.

Table 57 illustrates all TEAEs accounting for ≥ 2% of all observed treatment emergent events, irrespective of investigator assessed causality or severity grade.

Table 57: Treatment Emergent Adverse Events Irrespective of Investigator assessed Causality or Severity Grade		
Dictionary Derived Term (PT Term)	Delafloxacin N=741	Vancomycin (± Aztreonam) N=751

Dictionary Derived Term	Delafloxacin	Vancomycin (± Aztreonam)
Diarrhea	58 (7.8%)	24 (3.2%)
Nausea	56 (7.6%)	47 (6.3%)
Infection	44 (5.9%)	38 (5.1%)
Infusion site extravasation	41 (5.5%)	54 (7.2%)
Headache	24 (3.2%)	41 (5.5%)
Transaminase Elevations	22 (3.0%)	28 (3.7%)
Pyrexia	17 (2.3%)	17 (2.3%)
Vomiting	17 (2.3%)	18 (2.4%)

Source: ISS Population. ADAE data sets.

Medical Reviewer’s Comments:

The most commonly reported investigator assessed treatment emergent adverse events in the Phase 3 trials were the GI related terms nausea and diarrhea. Additionally, TEAEs coded under the PT term infections were commonly observed, however, these were believed to be from treatment failure or relapse of infection. Near equal numbers of subjects in both the delafloxacin and vancomycin (aztreonam) comparator arms experienced treatment emergent headaches.

As stated earlier, there was significant splitting of several TEAEs at the PT level, thereby serving to potentially mask treatment-related events. For example, under the Investigations SOC there were several approaches to the coding of transaminase elevations and included such PT terms as: AST increased, ALT increased, transaminases increased, hypertransaminasaemia, hepatic enzyme increased, and liver function test abnormal. This was similarly true of PT terms that could be collectively considered infusion site reactions. Such PT terms as infusion site phlebitis, infusion site swelling, infusion site pain, infusion site erythema, infusion site extravasation, infusion site discomfort, and injection site swelling were coded separately. However, infusion site extravasation was the most commonly observed of these PT terms, most likely from high rates of drug abuse in this trial. (b) (4)

However, (b) (4) there were other study drug related TEAEs that were encountered more frequently (b) (4).

Table 58 provides an overview of **treatment emergent adverse reactions** which occurred in the Applicant’s pivotal Phase 3 trials.

Table 58: Pooled Phase 3 Treatment Emergent Adverse Reactions Irrespective Assessed Causality or Grade, ISS Population				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
Primary System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg po every 12 hours	Vancomycin (±Aztreonam)

Table 58: Pooled Phase 3 Treatment Emergent Adverse Reactions Irrespective Assessed Causality or Grade, ISS Population				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
Primary System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg po every 12 hours	Vancomycin (±Aztreonam)
Cardiac Disorders	<i># of subjects, (%)</i>	6 (0.8%)		6 (0.8%)
	Bradycardia	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Palpitations	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Tachycardia (Atrial tachycardia, Sinus tachycardia, Supraventricular tachycardia)	3 (0.4%)	1 (0.1%)	6 (0.8%)
Ear and Labyrinth Disorders	<i>Total # of subjects, (%)</i>	4 (0.5%)		1 (0.1%)
	Tinnitus	1 (0.1%)	1 (0.1%)	1 (0.1%)
	Vertigo	0 (0.0%)	2 (0.3%)	0 (0.0%)
Eye Disorders	<i>Total # of subjects, (%)</i>	2 (0.3%)		3 (0.4%)
	Vision blurred	2 (0.3%)	0 (0.0%)	3 (0.4%)
Gastrointestinal Disorders	<i>Total # of subjects, (%)</i>	147 (19.8%)		100 (13.3%)
	Diarrhea	27 (3.6%)	31 (4.2%)	24 (3.2%)
	Nausea	24 (3.2%)	32 (4.3%)	47 (6.3%)
	Vomiting	7 (1.0%)	10 (1.4%)	18 (2.4%)
	Abdominal Pain/Abdominal Discomfort	3 (0.4%)	7 (1.0%)	7 (0.9%)
	Dyspepsia	1 (0.1%)	5 (0.7%)	4 (0.5%)
General Disorders and Administration Site Conditions	<i>Total # of subjects, (%)</i>	70 (9.5%)		85 (11.3%)
	Infusion site extravasation	28 (3.8%)	13 (1.8%)	54 (7.2%)
	Infusion site pain	5 (0.7%)	5 (0.7%)	13 (1.7%)
	Infusion site phlebitis	2 (0.3%)	3 (0.4%)	5 (0.7%)

Table 58: Pooled Phase 3 Treatment Emergent Adverse Reactions Irrespective Assessed Causality or Grade, ISS Population				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
Primary System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg po every 12 hours	Vancomycin (±Aztreonam)
	Infusion site erythema	1 (0.1%)	2 (0.3%)	5 (0.7%)
	Infusion site swelling	3 (0.4%)	4 (0.5%)	6 (0.8%)
	Infusion site thrombosis	2 (0.3%)	1 (0.1%)	0 (0.0%)
	Catheter site bruise	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Infusion site irritation	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Infusion site discomfort	1 (0.1%)	0 (0.0%)	0 (0.0%)
Immune System Disorders	<i>Total # of subjects, (%)</i>	2 (0.3%)		5 (0.7%)
	Drug Hypersensitivity/ Hypersensitivity	1 (0.1%)	1 (0.1%)	5 (0.7%)
Infections and Infestations	<i>Total # of subjects, (%)</i>	15 (2.0%)		8 (1.1%)
	Vulvovaginal candidiasis/Genital Candidiasis/Genital Fungal Infection	5 (0.7%)	5 (0.7%)	6 (0.8%)
	Candida/Fungal Infection	1 (0.1%)	1 (0.1%)	1 (0.1%)
	Oral Candidiasis	1 (0.1%)	1 (0.1%)	1 (0.1%)
	<i>Clostridium difficile</i> infection	0 (0.0%)	1 (0.1%)	0 (0.0%)
Investigations	<i>Total # of subjects, (%)</i>	49 (6.6%)		59 (7.9%)
	ALT increased	12 (1.6%)	2 (0.3%)	14 (1.9%)
	AST increased	7 (1.0%)	3 (0.4%)	14 (1.9%)
	Hepatic enzyme increased	0 (0.0%)	2 (0.3%)	2 (0.3%)
	Hypertransaminasaemia	0 (0.0%)	2 (0.3%)	1 (0.1%)
	Transaminase increased	1 (0.1%)	2 (0.3%)	5 (0.7%)

Table 58: Pooled Phase 3 Treatment Emergent Adverse Reactions Irrespective Assessed Causality or Grade, ISS Population				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
Primary System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg po every 12 hours	Vancomycin (±Aztreonam)
	Blood alkaline phosphatase	0 (0.0%)	4 (0.5%)	2 (0.3%)
	Blood creatine phosphokinase increased	3 (0.4%)	5 (0.7%)	15 (2.0%)
	Blood creatinine increased	2 (0.3%)	0 (0.0%)	5 (0.7%)
	Blood pressure increased	2 (0.3%)	2 (0.3%)	1 (0.1%)
Metabolism and Nutrition Disorders	<i>Total # of subjects, (%)</i>	4 (0.5%)		5 (0.7%)
	Hyperglycemia	2 (0.3%)	0 (0.0%)	2 (0.3%)
	Hypoglycemia	2 (0.3%)	0 (0.0%)	3 (0.4%)
Musculoskeletal and Connective Tissue Disorders	<i>Total # of subjects, (%)</i>	1 (0.1%)		2 (0.3%)
	Myalgia	1 (0.1%)	0 (0.0%)	2 (0.3%)
Nervous System Disorders	<i>Total # of subjects, (%)</i>	45 (6.1%)		55 (7.3%)
	Headache	10 (1.4%)	14 (1.9%)	41 (5.5%)
	Dizziness	6 (0.8%)	5 (0.7%)	8 (1.1%)
	Dysgeusia	0 (0.0%)	2 (0.3%)	2 (0.3%)
	Hypoesthesia	1 (0.1%)	0 (0.0%)	1 (0.1%)
	Paresthesia	2 (0.3%)	2 (0.3%)	1 (0.1%)
	Peripheral neuropathy	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Pre-syncope	0 (0.0%)	1 (0.1%)	0 (0.0%)
	Syncope/Loss of consciousness	1 (0.1%)	1 (0.1%)	1 (0.1%)
Psychiatric Disorders	<i>Total # of subjects, (%)</i>	14 (1.9%)		9 (1.2%)
	Abnormal Dreams	0 (0.0%)	1 (0.1%)	1 (0.1%)

Table 58: Pooled Phase 3 Treatment Emergent Adverse Reactions Irrespective Assessed Causality or Grade, ISS Population				
System Organ Classification/Dictionary Derived Term (PT Term)		Delafloxacin N=741		Vancomycin (±Aztreonam) N=751
Primary System Organ Class	Dictionary Derived Term	Trial 302 Delafloxacin 300 mg IV every 12 hours	Trial 303 Delafloxacin 300 mg IV - 450 mg po every 12 hours	Vancomycin (±Aztreonam)
	Anxiety	4 (0.5%)	4 (0.5%)	5 (0.7%)
	Insomnia	3 (0.4%)	2 (0.3%)	3 (0.4%)
Skin and Subcutaneous Tissue Disorders	<i>Total # of subjects, (%)</i>	30 (4.1%)		67 (8.9%)
	Pruritus/Pruritus Generalized	6 (0.8%)	5 (0.7%)	39 (5.2%)
	Rash (Erythematous, Generalized, Macular, Papular, Maculo-Papular, Vesicular)	5 (0.7%)	4 (0.5%)	16 (2.1%)
	Urticaria	4 (0.5%)	2 (0.3%)	9 (1.2%)
	Dermatitis/Dermatitis, allergic	1 (0.1%)	3 (0.4%)	3 (0.4%)
Vascular Disorders	<i>Total # of subjects, (%)</i>	10 (1.4%)		10 (1.3%)
	Pulmonary Embolism	0 (0.0%)	2 (0.3%)	1 (0.1%)
	Flushing	0 (0.0%)	2 (0.3%)	3 (0.4%)
	Hypertension	0 (0.0%)	4 (0.5%)	6 (0.8%)
	Hypotension	1 (0.1%)	1 (0.1%)	0 (0.0%)
Total # of Subjects (filtered)		127 (17.1%)	118 (15.9%)	266 (35.4%)
DENOMINATOR		741	741	751
<i>Source: ISS population. ADSL and ADAE data sets. Several subjects may have had more than one treatment emergent adverse drug reaction.</i>				

Medical Reviewer's Comments:

Treatment emergent adverse reactions across both pooled treatment arms were relatively similar. However, as mentioned throughout this review, diarrhea and nausea were the most prominent of all delafloxacin related adverse reactions and occurred with greater frequency among delafloxacin treated subjects than among vancomycin subjects as illustrated in the table above. This reviewer accounted for apparent splitting of infusion site reaction related PT terms which are potentially indicative that infusion site reactions may be associated with the

delafloxacin arm. Headache and vomiting also remained among those TEAEs listed with a frequency of $\geq 2\%$

Phase 2 Trial RX-3341-202: Treatment-emergent Adverse Drug Reactions, ISS Population

Table 59 below displays all treatment emergent adverse reactions that occurred in Trial 202.

Table 59: Trial 3341-202 Treatment Emergent Adverse Reactions				
System Organ Class/Dictionary Derived Term (PT Term)		Delafloxacin	Linezolid	Vancomycin
System Organ Class	Dictionary Derived Term	Delafloxacin 300 mg IV N=78	Linezolid 600-mg IV N= 75	Vancomycin N=96
Cardiac Disorders	# of subjects, (%)	1 (1.3%)	2 (2.6%)	1 (1.0%)
	Palpitations	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Tachycardia	0 (0.0%)	2 (2.6%)	1 (1.0%)
Eye Disorders	# of subjects, (%)	1 (1.3%)	0 (0.0%)	1 (1.0%)
	Vision blurred	1 (1.3%)	0 (0.0%)	1 (1.0%)
Gastrointestinal Disorders	# of subjects, (%)	44 (5.9%)	30 (40.0%)	28 (29.2%)
	Nausea	17 (21.8%)	16 (21.3%)	13 (13.5%)
	Diarrhea	12 (15.4%)	5 (6.7%)	4 (4.2%)
	Vomiting	10 (12.8%)	6 (8.0%)	8 (8.3%)
	Abdominal pain/Abdominal discomfort	4 (5.1%)	2 (2.6%)	3 (3.1%)
	Dyspepsia	1 (1.3%)	1 (1.3%)	0 (0.0%)
General Disorders and Administration Site Conditions	# of subjects, (%)	8 (10.3%)	13 (22.7%)	10 (10.4%)
	Infusion site pain	4 (5.1%)	7 (9.3%)	5 (5.2%)
	Infusion site erythema	2 (2.6%)	0 (0.0%)	0 (0.0%)
	Infusion site phlebitis	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Infusion site swelling	1 (1.3%)	0 (0.0%)	4 (4.2%)
	Catheter site inflammation	0 (0.0%)	1 (1.3%)	0 (0.0%)
	Catheter site related reaction	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Infusion site extravasation	0 (0.0%)	1 (1.3%)	0 (0.0%)

Table 59: Trial 3341-202 Treatment Emergent Adverse Reactions

System Organ Class/Dictionary Derived Term (PT Term)		Delafloxacin	Linezolid	Vancomycin
System Organ Class	Dictionary Derived Term	Delafloxacin 300 mg IV N=78	Linezolid 600-mg IV N= 75	Vancomycin N=96
	Infusion site pruritus	0 (0.0%)	2 (2.7%)	0 (0.0%)
	Injection site irritation	0 (0.0%)	1 (1.3%)	0 (0.0%)
Immune System Disorders	# of subjects, (%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Hypersensitivity	0 (0.0%)	0 (0.0%)	1 (1.0%)
Infections and Infestations	# of subjects, (%)	6 (7.7%)	3 (5.3%)	4 (4.2%)
	Candida infection/ Fungal Infection	1 (1.3%)	1 (1.3%)	4 (4.2%)
	Fungal skin infection	1 (1.3%)	1 (1.3%)	0 (0.0%)
	Vulvovaginal candidiasis	4 (5.1%)	1 (1.3%)	0 (0.0%)
Investigations	# of subjects, (%)	3 (3.9%)	1 (1.3%)	7 (7.3%)
	ALT increased	0 (0.0%)	0 (0.0%)	1 (1.0%)
	AST increased	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Blood creatinine increased	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Blood glucose increased	0 (0.0%)	1 (1.3%)	2 (2.1%)
	Blood pressure systolic increased	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Hepatic enzyme increased	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Liver function test abnormal	2 (2.6%)	0 (0.0%)	1 (1.0%)
Metabolism and Nutrition Disorders	# of subjects, (%)			
	Hyperglycemia	2 (2.6%)	1 (1.3%)	2 (2.1%)
Musculoskeletal and Connective Tissue Disorders	# of subjects, (%)	3 (3.9%)	2 (2.7%)	1 (1.0%)
	Muscle spasms	1 (1.3%)	2 (2.7%)	0 (0.0%)
	Musculoskeletal pain/ Myalgia	2 (2.6%)	0 (0.0%)	1 (1.0%)
Nervous System Disorders	# of subjects, (%)	14 (18.0%)	7 (9.3%)	10 (10.4%)
	Headache	5 (6.4%)	5 (6.7%)	6 (6.3%)

Table 59: Trial 3341-202 Treatment Emergent Adverse Reactions

System Organ Class/Dictionary Derived Term (PT Term)		Delafloxacin	Linezolid	Vancomycin
System Organ Class	Dictionary Derived Term	Delafloxacin 300 mg IV N=78	Linezolid 600-mg IV N= 75	Vancomycin N=96
	Dizziness	5 (6.4%)	1 (1.3%)	1 (1.0%)
	Convulsion	2 (2.6%)	0 (0.0%)	0 (0.0%)
	Hypoaesthesia	1 (1.3%)	0 (0.0%)	1 (1.0%)
	Syncope	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Paraesthesia	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Somnolence	0 (0.0%)	1 (1.3%)	1 (1.0%)
	# of subjects, (%)	4 (5.1%)	2 (2.7%)	5 (5.2%)
Psychiatric Disorders	Abnormal dreams	1 (1.3%)	0 (0.0%)	0 (0.0%)
	Anxiety	1 (1.3%)	0 (0.0%)	1 (1.0%)
	Confusional state	0 (0.0%)	1 (1.3%)	1 (1.0%)
	Insomnia	2 (2.6%)	1 (1.3%)	3 (3.1%)
	# of subjects, (%)			
Renal and Urinary Disorders	Renal Failure/Renal Failure, Acute	0 (0.0%)	0 (0.0%)	2 (2.1%)
	# of subjects, (%)	10 (12.8%)	14 (18.7%)	31 (32.3%)
Skin and Subcutaneous Tissue Disorders	Pruritus/Pruritus Generalized	6 (7.7%)	7 (9.3%)	21 (21.9%)
	Rash (Generalized, Maculo-Papular, Papular)	2 (2.6%)	6 (8.0%)	5 (5.2%)
	Urticaria	0 (0.0%)	0 (0.0%)	1 (1.0%)
	Dermatitis, allergic/ Dermatitis, contact	2 (2.6%)	1 (1.3%)	4 (4.2%)
	# of subjects, (%)	2 (2.6%)	2 (2.7%)	5 (5.2%)
Vascular Disorders	Flushing	0 (0.0%)	0 (0.0%)	4 (4.2%)
	Hypertension	2 (2.6%)	2 (2.7%)	0 (0.0%)
	Hypotension	0 (0.0%)	0 (0.0%)	1 (1.0%)
Total # of subjects (filtered)		49 (62.8%)	38 (50.7%)	54 (56.3%)
DENOMINATORS		78 (100.0%)	75 (100.0%)	96 (100.0%)
<i>Source: ISS Population. ADSL and ADAE data sets. All treatment emergent adverse drug reactions</i>				

Medical Reviewer’s Comments: *As with the Phase 3 trials, the most common adverse reactions observed in Trial 202 occurred in the Gastrointestinal SOC, followed by the Nervous Systems Disorders and Skin and Subcutaneous Disorders SOCs.*

Phase 2 Trial RX-3341-201: Treatment emergent adverse events and Treatment emergent adverse drug reactions, (ISS Population)

In all, 87 of 150 (58.0%) subjects in Trial 201 had *at least* one or more TEAE, including: 21 of 49 (42.9%) subjects in the delafloxacin 300-mg arm, 31 of 51 (60.8%) subjects in the delafloxacin 450-mg arm, and 35 of 50 (70.0%) subjects in the tigecycline arm. Multiple subjects, 62 in total, had two or more TEAEs, with the majority of subjects experiencing >1 TEAE in the tigecycline arm. However, when comparing the two delafloxacin arms, slightly more subjects in the 450-mg dose arm had >1 TEAEs than subjects in 300-mg dose arm, with 23 of 51 subjects (45.1%) versus 17 of 49 subjects (34.7%), respectively, experiencing multiple TEAEs.

Irrespective of treatment arm, most TEAEs occurred in the GI disorders SOC, with most events coded under the PT terms nausea, vomiting and diarrhea. Considerable splitting of infusion site related PT terms was observed under the General Disorders and Administration Site Conditions SOC and included such terms as: catheter site erythema, catheter site edema/infusion site edema, infusion site swelling, catheter site related reaction/infusion site reaction/infusion related reaction, infusion site pain, infusion site phlebitis. This reviewer presumed that most, but definitely not all, PT terms coded under the Infections and Infestations SOC were related to exacerbations of the underlying ABSSSI infection. Splitting of PT terms was also observed under this Infections and Infestations SOC, with the use of such terms as abscess limb/ subcutaneous abscess, cellulitis/skin infection, and infection/localized infection. **Table 60** below provides further illustration of all TEAE occurring in 2 or more subjects in Trial 201.

Table 60: Trial 201 Treatment emergent adverse events occurring in 2 or more subjects*				
Primary System Organ Class	Dictionary Derived Term	RX-3341 300 mg BID (N=49)	RX-3341 450 mg BID (N=51)	Tigecycline (N=50)
Cardiac disorders	Tachycardia	0 (0.0%)	1 (2.0%)	1 (2.0%)
Gastrointestinal disorders	Total # of events	13	33	49
	Nausea, n/N (%)	6 (12.2%)	13 (25.5%)	23 (46.0%)
	Diarrhea, n/N (%)	5 (10.2%)	12 (23.5%)	5 (10.0%)
	Vomiting	0 (0.0%)	6 (11.8%)	14 (28.0%)
	Abdominal discomfort/ Abdominal pain, n/N (%)	1 (2.0%)	2 (3.9%)	3 (6.0%)
	Constipation, n/N (%)	1 (2.0%)	0 (0.0%)	4 (8.0%)
General disorders and administration site conditions	Total # of events	5	20	7
	Catheter site edema/ Infusion site swelling/ Infusion site edema, n/N (%)	1 (2.0%)	2 (3.9%)	0 (0.0%)

Table 60: Trial 201 Treatment emergent adverse events occurring in 2 or more subjects*				
Primary System Organ Class	Dictionary Derived Term	RX-3341 300 mg BID (N=49)	RX-3341 450 mg BID (N=51)	Tigecycline (N=50)
	Catheter site pain/ Infusion site pain, n/N (%)	2 (4.1%)	7 (13.7%)	1 (2.0%)
	Catheter site related reaction/Infusion site reaction/Infusion related reaction, n/N (%)	1 (2.0%)	1 (2.0%)	2 (4.0%)
	Infusion site phlebitis, n/N (%)	0 (0.0%)	2 (3.9%)	2 (4.0%)
	Catheter site erythema, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
	Chills, n/N (%)	1 (2.0%)	1 (2.0%)	1 (2.0%)
	Fatigue, n/N (%)	1 (2.0%)	4 (7.8%)	0 (0.0%)
	Pyrexia, n/N (%)	0 (0.0%)	2 (3.9%)	1 (2.0%)
	Total # of events	4	7	4
Infections and infestations	Abscess limb/ Subcutaneous abscess, n/N (%)	2 (4.1%)	4 (7.8%)	2 (4.0%)
	Cellulitis, n/N (%)	0 (0.0%)	1 (2.0%)	2 (4.0%)
	Fungal infection, n/N (%)	0 (0.0%)	2 (3.9%)	0 (0.0%)
	Infection/Localized Infection, n/N (%)	2 (4.1%)	0 (0.0%)	0 (0.0%)
	Total # of events	1	2	4
Injury, poisoning and procedural complications	Laceration, n/N (%)	0 (0.0%)	0 (0.0%)	3 (6.0%)
	Procedural headache, n/N (%)	0 (0.0%)	1 (2.0%)	1 (2.0%)
	Wound complication, n/N (%)	1 (2.0%)	1 (2.0%)	0 (0.0%)
	Total # of events	7	4	2
Investigations	Alanine aminotransferase increased, n/N (%)	3 (6.1%)	0 (0.0%)	0 (0.0%)
	Liver function test abnormal, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
	Blood creatinine increased, n/N (%)	2 (4.1%)	0 (0.0%)	0 (0.0%)
	Blood pressure increased, n/N (%)	0 (0.0%)	1 (2.0%)	2 (4.0%)
	Total # of events	7	4	2

Table 60: Trial 201 Treatment emergent adverse events occurring in 2 or more subjects*				
Primary System Organ Class	Dictionary Derived Term	RX-3341 300 mg BID (N=49)	RX-3341 450 mg BID (N=51)	Tigecycline (N=50)
	Hematocrit decreased/Hemoglobin decreased, n/N (%)	2 (4.1%)	2 (3.9%)	0 (0.0%)
Metabolism and nutrition disorders	Decreased appetite	0 (0.0%)	3 (5.9%)	2 (4.0%)
Nervous system disorders	Total # of events	3	6	11
	Dizziness, n/N (%)	0 (0.0%)	1 (2.0%)	4 (8.0%)
	Dysgeusia, n/N (%)	1 (2.0%)	1 (2.0%)	1 (2.0%)
	Headache, n/N (%)	2 (4.1%)	4 (7.8%)	6 (12.0%)
Psychiatric disorders	Insomnia, n/N (%)	2 (4.1%)	1 (2.0%)	2 (4.0%)
Respiratory, thoracic and mediastinal disorders	Dry throat, n/N (%)	1 (2.0%)	1 (2.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Total # of events	3	3	7
	Dermatitis contact, n/N (%)	2 (4.1%)	0 (0.0%)	0 (0.0%)
	Erythema, n/N (%)	1 (2.0%)	0 (0.0%)	1 (2.0%)
	Pruritus/ Pruritus generalized, n/N (%)	0 (0.0%)	1 (2.0%)	3 (6.0%)
	Rash, n/N (%)	0 (0.0%)	2 (3.9%)	3 (6.0%)
Total # of subjects		21 (42.9%)	31 (60.8%)	35 (70.0%)

*Source: ISS population. Table derived from SDTM adverse events and demographic data sets. *Overall, a total of 62 subjects had at least 2 or more treatment emergent adverse events.*

Table 61 below provides an overview of treatment emergent adverse drug reactions that occurred during Trial 201 in all three treatment arms. While fully acknowledging the challenges associated with determining causality for all reported events, this reviewer reviewed all available subject narratives, assessed AE start and stop dates in relation to treatment start and stop dates, and other available data in order to make the best determinations as to whether a reported event was causally linked either through a biologically plausible mechanism or via a temporal association with a reported event.

Table 61: Trial 201 Treatment Emergent Adverse Drug Reactions, Irrespective of Investigator Assessed Causality and Severity Grade*				
Primary System Organ Class	Dictionary Derived Term	RX-3341 300 mg BID (N=49)	RX-3341 450 mg BID (N=51)	Tigecycline (N=50)
Cardiac disorders	Total # of events	0	2	1
	Tachycardia, n/N (%)	0 (0.0%)	1 (2.0%)	1 (2.0%)
Ear and labyrinth disorders	Tinnitus, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Gastrointestinal disorders	Total # of events	13	33	49
	Nausea, n/N (%)	6 (12.2%)	13 (25.5%)	23 (46.0%)
	Diarrhea, n/N (%)	5 (10.2%)	12 (23.5%)	5 (10.0%)
	Vomiting, n/N (%)	0 (0.0%)	6 (11.8%)	14 (28.0%)
	Abdominal discomfort/ Abdominal pain, n/N (%)	1 (2.0%)	2 (3.9%)	3 (6.0%)
General disorders and administration site conditions	Total # of events	5	20	7
	Catheter site oedema/ Infusion site swelling/ Infusion site oedema, n/N (%)	1 (2.0%)	2 (3.9%)	0 (0.0%)
	Catheter site pain/ Infusion site pain, n/N (%)	2 (4.1%)	7 (13.7%)	1 (2.0%)
	Catheter site related reaction/Infusion site reaction/Infusion related reaction, n/N (%)	1 (2.0%)	1 (2.0%)	2 (4.0%)
	Infusion site phlebitis, n/N (%)	0 (0.0%)	2 (3.9%)	2 (4.0%)
	Catheter site erythema, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
	Fatigue, n/N (%)	1 (2.0%)	4 (7.8%)	0 (0.0%)
Infections and	Total # of events	2	2	0

Table 61: Trial 201 Treatment Emergent Adverse Drug Reactions, Irrespective of Investigator Assessed Causality and Severity Grade*				
Primary System Organ Class	Dictionary Derived Term	RX-3341 300 mg BID (N=49)	RX-3341 450 mg BID (N=51)	Tigecycline (N=50)
infections	<i>Clostridium difficile</i> colitis, n/N (%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
	Fungal infection, n/N (%)	0 (0.0%)	2 (3.9%)	0 (0.0%)
	Vulvovaginal mycotic infection, n/N (%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
Investigations	Total # of events	5	2	2
	Alanine aminotransferase increased, n/N (%)	3 (6.1%)	0 (0.0%)	0 (0.0%)
	Liver function test abnormal, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
	Blood creatinine increased, n/N (%)	2 (4.1%)	0 (0.0%)	0 (0.0%)
	Blood pressure increased, n/N (%)	0 (0.0%)	1 (2.0%)	2 (4.0%)
Metabolism and nutrition disorders	Hypoglycaemia, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	Arthralgia, n/N (%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Nervous system disorders	Total # of events	3	6	12
	Dizziness, n/N (%)	0 (0.0%)	1 (2.0%)	4 (8.0%)
	Dysgeusia, n/N (%)	1 (2.0%)	1 (2.0%)	1 (2.0%)
	Headache, n/N (%)	2 (4.1%)	4 (7.8%)	6 (12.0%)
	Hypoesthesia, n/N (%)	0 (0.0%)	0 (0.0%)	1 (2.0%)

Table 61: Trial 201 Treatment Emergent Adverse Drug Reactions, Irrespective of Investigator Assessed Causality and Severity Grade*				
Primary System Organ Class	Dictionary Derived Term	RX-3341 300 mg BID (N=49)	RX-3341 450 mg BID (N=51)	Tigecycline (N=50)
Psychiatric disorders	Total # of events	3	1	2
	Anxiety, n/N (%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
	Insomnia, n/N (%)	2 (4.1%)	1 (2.0%)	2 (4.0%)
Skin and subcutaneous tissue disorders	Total # of events	3	3	8 (16.0%)
	Dermatitis contact, n/N (%)	v	0 (0.0%)	
	Erythema, n/N (%)	1 (2.0%)	0 (0.0%)	1 (2.0%)
	Pruritus/ Pruritus generalized, n/N (%)	0 (0.0%)	1 (2.0%)	3 (6.0%)
	Rash, n/N (%)	0 (0.0%)	2 (3.9%)	3 (6.0%)
	Urticaria, n/N (%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
Total # of Subjects (filtered)		19 (38.8%)	28 (54.9%)	33 (66.0%)
<i>Source: ISS population. Table derived from SDTM adverse events and demographic data sets.</i>				
<i>*Several subjects had at least 2 or more treatment emergent adverse reactions.</i>				

Medical Reviewer’s Comments:

Analysis of TEAEs and ADRs across all treatments in Trial 201 demonstrated that GI-related events, primarily driven by diarrhea and nausea, occurred with the greatest frequency. This was particularly true of the tigecycline comparator arm. However, the incidence of GI-related events was approximately 2.5-fold higher in the delafloxacin 450-mg arm than in the delafloxacin 300-mg arm. This trend was also observed across both TEAEs and ADRs under the Nervous Systems Disorders SOC, where ADRs in the delafloxacin 450-mg arm were nearly doubled those in the 300-mg arm, with the most frequent events coded under the PT term headaches followed by dizziness. Infusion site related events (i.e. infusion site pain, infusion site phlebitis) were 5 times greater in the delafloxacin 450-mg than in the 300-mg arm. The higher incidence of TEAEs and ADRs in the higher dose delafloxacin arm along with similar efficacy results in each treatment arm, prompted the Applicant to pursue delafloxacin 300-mg dose as its to be marketed dose.

8.4.6 Laboratory Findings

Section 8.4.6 discusses treatment-emergent laboratory abnormalities occurring in the pooled Phase 3 ISS population. Severity grading was assessed according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.0)(November 2014). The following chemistry and hematologic parameters are discussed in this section: hepatic enzymes--alanine aminotransferase (ALT), aspartate aminotransferase

(AST), total bilirubin (Tbili); glucose; renal impairment as assessed by creatinine clearance using the Cockcroft-gault equation, and creatine phosphokinase (CPK).

Phase 3 Pivotal Trials: RX-3341-302 and RX-3341-303 (ISS Population)

Liver Function Tests

In post-marketing reports, several FQs have been associated with severe hepatotoxicity (including acute hepatitis and fatal events). Therefore, Section 5 Warnings and Precautions of several currently marketed FQs warn against the potential risk for hepatotoxicity. Given the potential for FQ associated hepatic related adverse reactions, this reviewer conducted a detailed review of any elevations in hepatic related laboratory findings.

Alanine Aminotransferase Elevations

In the pooled Phase 3 trials, a total of 677 subjects (91.4%; 677/741) in the delafloxacin arm and 667 subjects (88.8%; 667/751) in the pooled comparator arm had baseline ALT values. The majority of subjects in both treatment arms had Grade 0 baseline ALT values, although slightly more subjects in the pooled delafloxacin arm had Grade 0 baseline values: 525 (525/741; 70.9%) compared with 480 subjects (480/751; 63.9%) in the comparator arm. **Table 62** provides a tabular summary of baseline and maximal post-baseline ALT values.

Table 62: Alanine Aminotransferase (ALT) Baseline and Maximal Post-Baseline Shift Table				
PARAMETER	Baseline DAIDS Toxicity Grade	Maximal Post-Baseline DAIDS Toxicity Grade	Pooled Delafloxacin N=741	Pooled Vancomycin ± Aztreonam N=751
Alanine Aminotransferase (U/L)	Grade 0	Grade 0	525 (70.9%)	480 (63.9%)
		Grade 1 (Mild): 1.25 to <2.5 ULN	51 (6.9%)	83 (11.1%)
		Grade 2 (Moderate): 2.5 to <5.0 ULN	8 (1.1%)	15 (2.0%)
		Grade 3 (Severe): 5.0 to <10.0 ULN	0 (0.0%)	3 (0.4%)
		Grade 4 (Potentially Life Threatening): ≥10.0 x ULN	2 (0.3%)	1 (0.1%)
	Grade 1: Mild	Grade 0	33 (4.5%)	22 (2.9%)
		Grade 1 (Mild): 1.25 to <2.5 ULN	34 (4.6%)	39 (5.2%)
		Grade 2 (Moderate): 2.5 to <5.0 ULN	9 (1.2%)	5 (0.7%)

	Grade 2: Moderate	Grade 3 (Severe): 5.0 to <10.0 ULN	0 (0.0%)	1 (0.1%)
		Grade 0	0 (0.0%)	3 (0.4%)
		Grade 1 (Mild): 1.25 to <2.5 ULN	12 (1.6%)	6 (0.8%)
		Grade 2 (Moderate): 2.5 to <5.0 ULN	1 (0.1%)	8 (1.1%)
		Grade 3 (Severe): 5.0 to <10.0 ULN	1 (0.1%)	0 (0.0%)
	Grade 3: Severe	Grade 0	1 (0.1%)	0 (0.0%)
		Grade 3 (Severe): 5.0 to <10.0 ULN	0 (0.0%)	1 (0.1%)
Subjects (filtered)			677 (91.4%)	667 (88.8%)
Denominator			741 (100.0%)	751 (100.0%)
<i>Source: ISS population. ADSL and ADLB data sets. Table generated by the clinical reviewer using JReview.</i>				

Overall, post-baseline Grade 4 ALT elevations were rare. Across treatment arms, few subjects with baseline ALT values of Grades 0, 1, and 2 developed Grade 3 and 4 ALT/AST abnormalities post-baseline. There were only two subjects in the delafloxacin arm with baseline Grade 0 ALT values and one in the comparator arm who sustained maximal post-baseline ALT values characterized as Grade 4 severity. There were no subjects with baseline Grade 1, 2 and 3 ALT values who developed Grade 4 post-baseline ALT values. There was, however, a single subject with a baseline Grade 2 ALT value who developed a post-baseline maximal ALT value of Grade 3 severity following delafloxacin therapy. The two delafloxacin subjects with baseline Grade 0 ALT values that subsequently developed Grade 4 maximal post-baseline ALT values are briefly described below:

- Subject 303/604-404-3351:** A 29 year old man with no significant medical issues, including no reported history of hepatitis was begun on delafloxacin on 4 May through 15 May 2015 for a right leg cellulitis/erysipelas. Concomitant medications notably included terbinafine (05 May through 19 May 2015) and clotrimazole (26 May to 15 June 2015). Subject's baseline ALT and AST were 11 U/L and 15 U/L, respectively. These values peaked, on Day 12, to 669 U/L and 416 U/L, respectively. By Day 32 (04 June 2015) both ALT and AST had returned to normal. The study investigator concluded that, given the temporal relationship between the observed "hypertransaminasemia" and the study drug, that the event was "possibly related" to the study drug and/or related to terbinafine.

Medical Reviewer's Comment:

In this instance, the reviewer agrees with the investigator's assessment. It is noted that terbinafine, an oral antifungal used in the treatment of onychomycosis, has a safety profile that has been associated with hepatotoxicity, including liver failure.

- Subject 303/604-408-3313:** A 56 year old woman with neither a history of hepatitis nor any other issues of medical significance was treated with delafloxacin from 02 April (Study Day 1) to 15 April 2015 (Study Day 14) for a left leg cellulitis/erysipelas. Most notable concomitant medications included tramadol + acetaminophen (12 April to 14 April 2015). Baseline (Study Day 1) ALT, AST and alkaline phosphatase values were within normal limits at 31 U/L, 36 U/L and 159 U/L, respectively, with only slight elevations observed in the alkaline phosphatase. At the EOT visit (15 April 2015), her ALT, AST, and alkaline phosphatase rose to 814 U/L, 923 U/L, and 567 U/L. These values eventually declined and returned to normal ranges by Day 44. The investigator assessed this event as being “possibly” related to the study drug, given: a temporal relationship between the AE and delafloxacin administration; the AE being a FQ class associated adverse reaction; and due to improvement in the subject’s LFTs once delafloxacin was discontinued.

Medical Reviewer’s Comments: The reviewer finds the investigator’s assessment acceptable.

Aspartate aminotransferase Elevations

A total of 679 (679/741; 91.6%;) and 668 (668/751; 89.0%;) subjects, in the delafloxacin and vancomycin arms, respectively, had baseline AST values in the pivotal Phase 3 trials. Only two subjects in the delafloxacin arm with baseline Grade 0 AST values developed severity Grade 3 (Subject 303/604-404-3313) and Grade 4 (Subject 303/604-408-3351) AST elevations. Both of these subjects were described in the section above. Otherwise, across each treatment arm, there were few, and near equal numbers of subjects who sustained severity Grade 2 or higher AST elevations. **Table 63** summarizes baseline and maximal post-baseline shifts in AST values.

Table 63: Aspartate Aminotransferase (AST) Baseline and Maximal Post-Baseline Shift Table				
PARAMETER	DAIDS Baseline Toxicity Grade	Maximal Post-baseline DAIDS Toxicity Grade	Pooled Delafloxacin N=741	Pooled Vancomycin ± Aztreonam N=751
Aspartate Aminotransferase (U/L)	Grade 0	Grade 0	561 (75.7%)	542 (72.2%)
		Grade 1 (Mild): 1.25 to <2.5 x ULN	38 (5.1%)	52 (6.9%)
		Grade 2 (Moderate): 2.5 to <5.0 ULN	7 (0.9%)	7 (0.9%)
		Grade 3 (Severe): 5.0 to <10.0 ULN	1 (0.1%)	1 (0.1%)
		Grade 4 Potentially Life-Threatening: ≥10.0 x ULN	1 (0.1%)	0 (0.0%)
	Grade 1:	Grade 0	25 (3.4%)	24 (3.2%)

	Mild	Grade 1 (Mild): 1.25 to <2.5 x ULN	26 (3.5%)	26 (3.5%)
		Grade 2 (Moderate): 2.5 to <5.0 ULN	7 (0.9%)	5 (0.7%)
	Grade 2: Moderate	Grade 0	5 (0.7%)	2 (0.3%)
		Grade 1 (Mild): 1.25 to <2.5 x ULN	2 (0.3%)	2 (0.3%)
		Grade 2 (Moderate): 2.5 to <5.0 ULN	5 (0.7%)	6 (0.8%)
		Grade 3 (Severe): 5.0 to <10.0 ULN	1 (0.1%)	1 (0.1%)
Total # of Subjects (filtered)			679 (91.6%)	668 (89.0%)
DENOMINATOR			741 (100.0%)	751 (100.0%)
<i>Source: ISS population. ADSL and ADLB datasets. Table generated by the clinical reviewer using JReview.</i>				

Subject 302/840-001-0653 described below is the single subject in the delafloxacin arm who experienced an AST severity Grade 2 shift to a severity Grade 3 shift.

Subject 302/840-001-0653: A 45 year old man with a history of HCV was treated with delafloxacin from 12 March (Study Day 1) to 21 March 2014 (Study Day 10) for a right arm cellulitis/erysipelas. Concomitant medications included hydrochlorothiazide and potassium chloride begun on 14 May 2014 (Study Day 3). Baseline Day 1 (12 March) AST and ALT values were 117 U/L and 90 U/L, respectively. On Study Day 7 (18 March), AST and ALT were observed to increase to 175 U/L and 120 U/L, respectively. By the EOT visit on 21 March 2014 (Study Day 10), AST and ALT peaked to 331 U/L and 189 U/L, respectively. The subject was lost to follow-up and hence subsequent AST and ALT results were unavailable. Study drug was neither interrupted nor discontinued as a result of these elevations. The investigator assessed these findings to be “unrelated to study drug due to unspecified cause.”

Medical Reviewer’s Comments: *Subject 302/840-001-0653 had baseline elevations in his AST/ALT most likely in the setting of untreated HCV infection. In this reviewer’s assessment, given the temporal relationship between the observed superimposed LFT elevations that occurred during delafloxacin therapy, one cannot exclude the possibility that there was a causal linkage between the study drug and the observed event. This reviewer, therefore, does not agree with the investigator’s assessment of no causal relationship between the drug and the observed transaminase, namely AST, elevations. Unfortunately, due to the subject’s loss to follow-up we are unaware of ultimate outcome of this subject’s LFT.*

As **Table 64** illustrates, there were no post-baseline Grade 3 or 4 shift changes among subjects with baseline Grade 1 and 0 alkaline phosphatase or total bilirubin values.

Table 64: Alkaline Phosphatase (ALP) and Total Bilirubin Baseline and Maximal Post-Baseline Shift Table					
PARAMETER	Baseline DAIDS Toxicity Grade	Maximal Post-Baseline DAIDS Toxicity Grade	Pooled Delafloxacin N=741	Pooled Vancomycin ± Aztreonam N=751	
Alkaline Phosphatase U/L	Grade 0	Grade 0	609 (82.2%)	616 (82.0%)	
		Grade 1 (Mild): 1.25 to <2.5 x ULN	18 (2.4%)	14 (1.9%)	
	Grade 1: Mild	Grade 0	26 (3.5%)	17 (2.3%)	
		Grade 1 (Mild): 1.25 to <2.5 x ULN	18 (2.4%)	19 (2.5%)	
		Grade 2 (Moderate): 2.5 to <5.0 x ULN	5 (0.7%)	1 (0.1%)	
	Grade 2: Moderate	Grade 0	0 (0.0%)	1 (0.1%)	
		Grade 1 (Mild): 1.25 to <2.5 x ULN	2 (0.3%)	0 (0.0%)	
		Grade 2 (Moderate): 2.5 to <5.0 x ULN	0 (0.0%)	1 (0.1%)	
	Subjects (filtered)			678 (91.5%)	669 (89.1%)
	Denominator			741 (100.0%)	751 (100.0%)
PARAMETER	Baseline DAIDS Toxicity Grade	Maximal Post-Baseline DAIDS Toxicity Grade	Pooled Delafloxacin N=741	Pooled Vancomycin ± Aztreonam N=751	
Bilirubin (umol/L)	Grade 0	Grade 0	618 (83.4%)	601 (80.0%)	
		Grade 1 (Mild): 1.25 to <2.5 x ULN	2 (0.3%)	0 (0.0%)	
	Grade 1: Mild	Grade 0	17 (2.3%)	14 (1.9%)	
		Grade 1 (Mild): 1.25 to <2.5 x ULN	3 (0.4%)	0 (0.0%)	
	Grade 2: Moderate	Grade 0	4 (0.5%)	6 (0.8%)	
		Grade 1 (Mild): 1.25 to <2.5 x ULN	0 (0.0%)	1(0.1%)	
		Grade 2 (Moderate): 2.5 to <5.0 x ULN	1 (0.1%)	0 (0.0%)	
	Grade 3: Severe	Grade 0	1 (0.1%)	0 (0.0%)	
		Grade 1 (Mild): 1.25 to <2.5 x ULN	1 (0.1%)	1 (0.13%)	
		Grade 3 (Severe): 2.6 to <5.0 x ULN	1 (0.1%)	0 (0.0%)	
Subjects (filtered)			648 (87.5%)	623 (83.0%)	

Denominators	741 (100.0%)	751 (100.0%)
<i>Sources: ISS population. ADSL and ADLB datasets. Table generated by the clinical reviewer with JReview.</i>		

Medical Reviewer’s Comments: A single subject (Subject 604-406-3903) in the pooled Phase 3 delafloxacin arm was noted to have baseline severity Grade 3 elevations in total bilirubin (Tbili 74.4). This subject’s bilirubin remained elevated throughout study duration. There were no significant grade shifts among any subjects in either treatment arm for alkaline phosphatase.

Hy’s Law

According to the FDA Guidance on Drug Induced Liver Injury, Hy’s Criteria is characterized by drug induced hepatocellular injury manifested by 3-fold or greater elevations above the upper limit of normal (ULN) of ALT or AST; elevation of serum total bilirubin (TBL) to >2x ULN without evidence of cholestasis (elevated serum ALP), and no alternative explanation for these findings can be found. Although there were **no potential Hy’s Law cases**, there were (2) subjects, one in each treatment arm, whose ALT and AST values were initially *numerically* concerning for Hy’s law. Both cases are summarized below:

- Subject 302/840-001-0361 (Delafloxacin):** A 43 year old man with a history of alcohol and IV methamphetamine abuse and who additionally was HCV antibody (Ab) positive at screening (unaware if he had an accompanying HCV viral load at baseline). His baseline ALT, AST, ALP and Tbili were 71 U/L, 38 U/L, 78 U/L, and 0.5 mg/dL (8.2 µmol/L), respectively. He began treatment with delafloxacin for a right leg wound infection on 11 October 2013 (Study Day 1) and completed treatment on 16 October 2013 (Study Day 6). Relevant concomitant medications included: oxycodone (11 to 18 October 2013) and acetaminophen (11 to 18 October 2013). His EOT (Study Day 6) ALT, AST, ALP, and Tbili were mildly elevated at 115 U/L, 75 U/L, 71 U/L and 5.1 mg/dL (0.30 µmol/L), respectively. However, by Study Day 14, his ALT, AST, ALP, and Tbili values increased to 2335 U/L, 2360 U/L, 337 U/L and 7.4 mg/dL (127.2 µmol/L), respectively. He was documented as experiencing a moderate AE classified as “acute hepatitis C” on 15 October 2015 (Day 5). The subject also drank 80 ounces of alcohol the evening following treatment completion. On 28 October 2013 (Day 18), subject was documented as having a severe SAE coded as “worsening of acute HCV” with evidence of scleral icterus and jaundice on physical exam. HCV viral load obtained on was 47.4 million IU/mL. HAV and HBV core antibody were non-reactive. Acute cytomegalovirus, Epstein-Barr virus, and hepatitis E results were not reported. This subject completed the study.

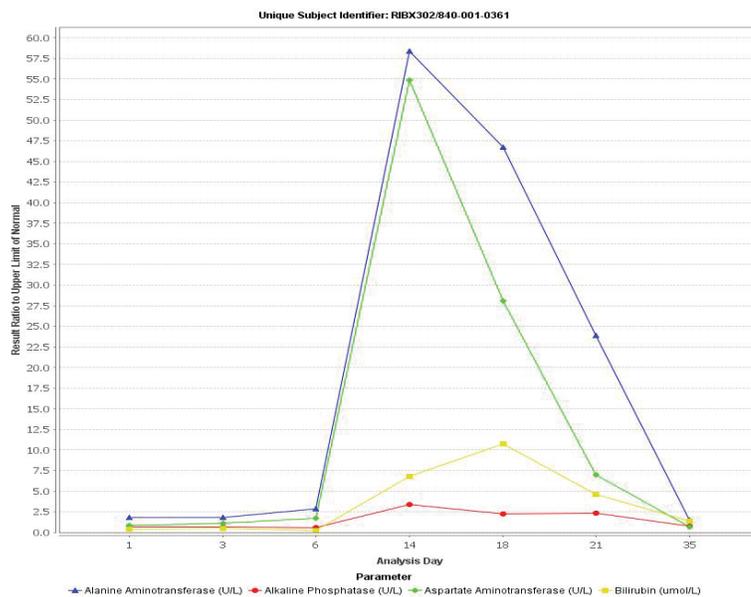


Figure 2 Subject 302/840-001-0361 LFT Elevations

Medical Reviewer’s Comments: *In this reviewer’s estimation, the above-described incident is most convincingly associated with a flare of HCV or acute hepatitis C infection in a known IV drug abuser with a superimposed history of alcohol abuse and concomitant medications of oxycodone and acetaminophen. While there may be a temporal association between delafloxacin therapy and the AE onset, this reviewer thinks a more compelling explanation for the observed transaminase elevations is the acute onset of HCV given the subjects high risk behavior of IV drug use.*

- Subject 303-840-491-3897 (Vancomycin):** A 44 year old woman being treated with vancomycin for a left leg major cutaneous abscess. She had a history of type 2 diabetes mellitus and GERD. Concomitant medications included glipizide and acetaminophen/codeine. LFTs were elevated at baseline and were as follows: ALT 95 U/L, AST 170 U/L, alkaline phosphatase 257 U/L and total bilirubin 2.5 mg/dL (41.9 μmol/L). She began treatment with vancomycin on 14 November 2015 (Day 1). Eleven hours after 3rd vancomycin dose LFTs peaked at 245 U/L, 218 U/L, 392 U/L and 1.3 mg/dL (21.7 μmol/L), respectively. Vancomycin was discontinued on Study Day 6 following this occurrence.

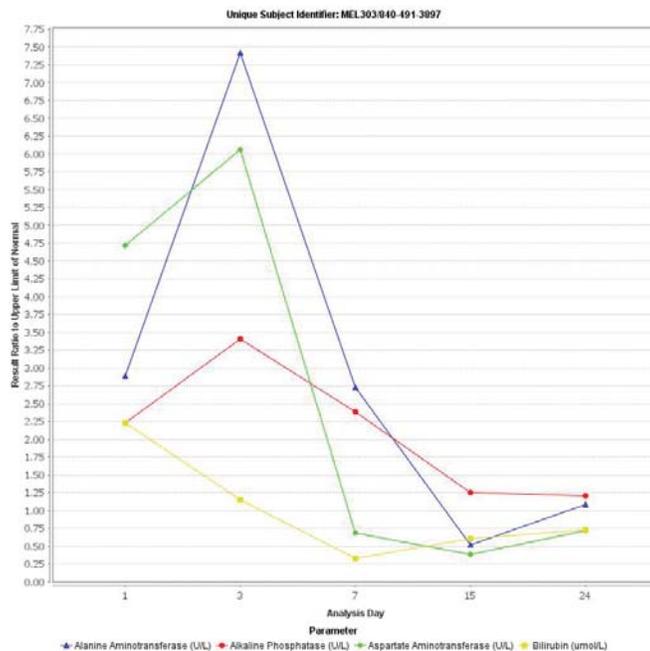


Figure 3 Subject 303/840-322-3179 LFT elevations

- **Subject 303/840-322-3179 (Delafloxacin):** A 32 year old male IV heroin and methamphetamine addict with a history of MRSA skin infections. Baseline HAV, HBV, and HCV screening were negative. Subject began a 6 day treatment course with delafloxacin for a major cutaneous abscess on 02 January 2015 (Study Day 1) and completed treatment on 08 January 2015 (Study Day 6). His baseline LFTs were as follows: ALT and AST were both 21 U/L, alkaline phosphatase was mildly elevated at 122 U/L, and total bilirubin was within normal limits (wnl) at 0.3 mg/dL (5.3 µmol/L). Tbili levels remained stable throughout the study duration. On Study Day 21, this subject developed substantial LFT elevations: ALT 859 U/L, AST 442 U/L, ALP 155 U/L. On Study Day 38 (09 February 2015), the subject was noted to be HCV Ab positive (a HCV viral load was not reported) and by Study Day 73 (16 March 2015), 67 days post-therapy, ALP (148 U/L) and ALT (46 U/L) levels remained mildly elevated, whereas, the AST returned to its baseline level of 21 U/L.

Medical Reviewer's Comments: *It is the reviewer's determination that the above-described event is unrelated to this study drug but more likely due to infection with HCV.*

Overall Medical Reviewer's Comments: *The reviewer observed that in this ABSSSI trial many recruited patients had active substance abuse issues and/or a history hepatitis C. This led to considerable confounding when evaluating transaminase elevations as it was unclear if observed transaminase increases were a consequence of the underlying hepatitis C with or without superimposed increases from the drug itself. It was difficult to disentangle the two to make definitive conclusions on whether the witnessed transaminase elevations were **not** related to the*

drug. However, based on the safety data as reported by the Applicant, the reviewer did not observe episodes of hepatic failure due to delafloxacin in the Phase 3 safety population.

Hepatic Related TEAEs

By conducting customized MAED queries (CMQs) and standardized MAED queries (SMQs) and by analyzing HLT and PT terms for treatment emergent hepatic related AEs under the Hepatobiliary Disorders SOC or the Investigations SOC, this reviewer was able to assess the incidence of hepatic related TEAEs in the pivotal Phase 3 trials. There were several hepatic related TEAEs coded under the following PT terms: alanine aminotransferase increased; aspartate aminotransferase increased; hepatic enzymes increased; hypertransaminasaemia liver function test abnormal; and transaminases increased, all suggesting that there was considerable splitting at the PT level. The rates of hepatic related TEAEs were similar across both treatment arms: 23 subjects (23/741; 3.1%) with a total of 32 TEAEs, in the pooled Phase 3 delafloxacin arm compared with 28 subjects (28/751; 3.7%) with a total of 38 TEAEs in the pooled vancomycin arm.

Table 65: Hepatic Related Adverse Events by System Organ Class and Dictionary Derived Terms, Delafloxacin Arm Only

System Organ Class	Dictionary Derived Term(s)	Unique Subject Identifier	Baseline ALT	Peak ALT	Baseline AST	Peak AST	Rx Day	# of Rx Days
HEPATOBI LARY DISORDERS	Hypertransaminas aemia	MEL303/604- 404-3310	59	155	43	155	13	9
	Hypertransaminas aemia	MEL303/604- 404-3351	11	669	15	116	11	11.5
INVESTIGA TIONS	Transaminases Increased	MEL303/604- 408-3313	31	814	36	923	15	14
	Transaminases Increased	MEL303/840- 328-3657	18	113	17	230	13	5
	Transaminases Increased	RIBX302/840- 014-0508	94	126	78	92	5 to 12	5
	Hepatic Enzyme Increased	MEL303/158- 353-3377	21	146	26	117	9 and 14	9
	Hepatic Enzyme Increased	MEL303/498- 470-3403	13	80	15	39	14	7
	ALT Increased AST Increased	MEL303/840- 322-3179	21	859	21	442	20	5.5
	ALT Increased AST Increased	MEL303/840- 339-3242	23	65	19	45	2	5
	ALT Increased AST Increased	RIBX302/840- 001-0526	28	101	42	137	7 to 13	7
	ALT Increased AST Increased	RIBX302/840- 001-0653	90	189	117	331	2 to 9	9
	ALT Increased AST Increased	RIBX302/840- 002-0226	78	118	76	211	6	2.5

Table 65: Hepatic Related Adverse Events by System Organ Class and Dictionary Derived Terms, Delafloxacin Arm Only

System Organ Class	Dictionary Derived Term(s)	Unique Subject Identifier	Baseline ALT	Peak ALT	Baseline AST	Peak AST	Rx Day	# of Rx Days
	ALT Increased AST Increased	RIBX302/840-002-0329	101	201	55	117	21	5
	ALT Increased AST Increased	RIBX302/840-004-0097	35	162	24	101	14	6
	ALT Increased AST Increased	RIBX302/840-004-0161	126	224	50	166	22	6
	ALT Increased AST Increased	RIBX302/840-011-0610	65	102	78	114	21	7
	ALT Increased	RIBX302/784-065-0483	18	74	20	65	13	13
	ALT Increased	RIBX302/840-001-0361	71	2335	38	2360	13	5
	ALT Increased	RIBX302/840-004-0392	13	57	13	42	5	5
	ALT Increased	RIBX302/840-012-0196	19	118	40	65	12	9
	ALT Increased	RIBX302/840-012-0387	30	155	21	50	9 to 13	9
	AST Increased	MEL303/233-443-3354	20	47	30	55	2	10
	AST Increased	MEL303/840-305-3233	37	43	63	82	13	5
					# of Delafloxacin Subjects with hepatic related AEs		23	
	LFT Test Abnormal	MEL303/604-405-3947	55	76	42	42	6 to 14	13
		MEL303/840-491-3897	95	245	170	218	2 to 6	5
					# of Vancomycin Subjects with hepatic related AEs		28	

Source: ISS population. ADSL and ADAE data sets. Table generated by the clinical reviewer.

Of the 32 TEAEs occurring in the delafloxacin arm, 21 were assessed as mild, 9 as moderate, and 2 as severe (occurring in the same subject). Twenty-one events were assessed by the investigator as being related to the study drug, and 2 were SAEs (both occurring in the same subject). No hepatic related TEAEs resulted in discontinuation of delafloxacin. Similarly, of the 38 hepatic related TEAEs in the pooled vancomycin comparator arm: 32 were graded as mild, 6 as moderate; no events were graded as severe. Twenty-seven TEAEs (27/38 TEAEs; 71.1%) were assessed by the investigator as being related to vancomycin/aztreonam treatment. Subject 303/840-491-3897, who was treated in the vancomycin arm, experienced an AE coded under the

PT terms “liver function test abnormal” and was subsequently withdrawn from the study treatment.

Medical Reviewer’s Comments: As stated earlier, several fluoroquinolones carry warnings cautioning of the risk for hepatotoxicity. While there were no delafloxacin discontinuations, pooling of the most frequent hepatic PT demonstrated that 3.1% of all delafloxacin treated subjects experienced AST and/or ALT elevations. When accounting for the splitting of PT terms among subjects experiencing transaminase elevations in the pooled Phase 3 trials, this reviewer recommends that the delafloxacin label list “transaminase elevations” as adverse reactions occurring in $\geq 2\%$ of all subjects. The Applicant initially only proposed to include, under the

(b) (4)

Renal Function

This section focuses on changes in creatinine clearance (CrCl) as opposed to changes in serum creatine (S_{Cr}). Delafloxacin is partially renally excreted; therefore, the review team was interested in seeing if there was any association between delafloxacin and worsening renal impairment.

In its eligibility criteria, Trial 302 excluded individuals “with end-stage renal disease (ESRD) on hemodialysis or peritoneal dialysis (CKD Stage 5) **OR** a CrCl of ≤ 30 mL/minute” (CKD Stages 4 and 5) (as calculated by the Cockcroft-Gault equation); whereas, Trial 303 excluded individuals “with end-stage renal disease (ESRD) on hemodialysis or peritoneal dialysis **OR** CrCl of ≤ 15 mL/minute” (CKD Stage 5) (as calculated by the Cockcroft-Gault equation). Of the 741 subjects in the pooled Phase 3 delafloxacin arm, a total of 19 subjects (2.6%) had missing baseline S_{Cr} values. There were 12 of 751 subjects (1.6%) in the pooled vancomycin arm with missing baseline S_{Cr} values. Of the subjects with available data, 37 subjects (37/741; 5.0%) in the delafloxacin arm had moderate renal impairment (Stage 3 CKD; CrCl 30-59) (as calculated by the Cockcroft-Gault equation); whereas, there was one subject each with baseline severe renal impairment (CKD 4 staging; CrCl 15-29) and kidney failure (CKD 5 staging; CrCl <15). Both of these subjects were enrolled in Trial 302.

Medical Reviewer’s Comments: *The Applicant seeks a labeling claim for the use of delafloxacin in patients with severe renal impairment (CKD Stage 4) (b) (4). The originally proposed IV dosing recommendations for patients with CKD Stages 4 (b) (4) to reduce the delafloxacin dose from 300-mg IV (b) (4) as recommended for individuals with CKD Stage (b) (4) to 200-mg IV (b) (4). Original oral tablet dosing recommendations for patients with CKD Stages 4 (b) (4). Trial 302 excluded persons with CKD Stages ≥ 4 from study participation; nevertheless, one subject with CKD Stage 4 and 5 CKD staging, respectively, were inadvertently enrolled into Trial 302. Trial 303 had a total of 25 delafloxacin treated subjects with moderate renal impairment (CKD Stage 3). No subjects in Trial 303 had severe renal impairment (CKD Stage 4) or kidney failure (CKD Stage 5), despite eligibility criteria permitting the inclusion of subjects with severe renal impairment (CKD Stage 4). Renal function in the pivotal Phase 3 trials was calculated with the Cockcroft Gault equation (for CrCl). This was a departure from the population PK studies (Protocol 110), in which renal*

function was calculated using the MDRD equation to calculate eGFR (estimated glomerular filtration rate). No subjects with severe renal impairment (CKD Stage 4) and kidney failure (CKD Stage 5) were treated with oral delafloxacin 450-mg oral tablets in either of the Applica Phase 3 trials.

Subjects with Baseline CKD 4 and 5 (by Cockcroft Gault Equation)

Brief summaries of the clinical histories and the adverse event findings for the two subjects with severe renal impairment (CKD Stage 4) and ESRD (CKD Stage 5), in the delafloxacin are described below.

Subject 302/840-014-0347 (Delafloxacin/CKD Stage 5-Kidney Failure): Subject 302/840-014-0347 was a 59 year old white female who received delafloxacin treatment from 08 Oct 2013 (Study Day 1) through 12 October 2013 (Study Day 5) for a major cutaneous abscess. She received a total of 10 doses of delafloxacin, without interruption, during this 5 day period. Her baseline S_{Cr} was 4.93 mg/dL with a CrCl and eGFR of 10 min/mL and 8.99 mL/min/1.73 m², respectively. In addition to her diagnosis of kidney failure, she was also reported as having the following medically relevant conditions: hypertension; hyperlipidemia; chronic obstructive pulmonary disease (COPD); a history of right kidney cancer for which she was status post a right nephrectomy; and ongoing heroin addiction. Her relevant concomitant medications included salmeterol-fluticasone for COPD, benazepril for HTN; baby aspirin; lovastatin for hyperlipidemia; and methadone. Subject experienced several TEAEs assessed as mild in severity. These TEAEs were coded to the following PT terms: peripheral edema (October 8th, 11th, and 22nd); diarrhea (on Oct 8, 11, and 22nd); and blurred vision (on Oct 8th, 11th, and 22nd) and were all considered by the study investigator to be “possibly” related to delafloxacin.

Subject 302/428-041-0673 (Delafloxacin/CKD Stage 4-Severe Renal Impairment): Subject 302/428-041-0673 was a 78 year old Latvian, white female who was administered delafloxacin therapy from 25 March 2014 (Study Day 1) through 30 March 2014 (Study Day 6). She received a total of 10 doses of delafloxacin 300-mg IV for cellulitis of the leg. She reported a medical history most significant for chronic heart failure; atrial fibrillation; and cerebral hemorrhage. Her baseline S_{Cr} was 2.66 mg/dL with a CrCl and eGFR of 22 min/mL and 17 mL/min/1.73 m², respectively. Her concomitant medications included digoxin; furosemide; prestarium (for hypertension); preductal (for angina pectoris); orfarin (warfarin); spirix (ketorolac); concor (HTN/coronary artery disease); almiral (diclofenac an anti-inflammatory drug). Subject reportedly experienced a single AE coded to the PT “blood creatinine decreased,” (Start Date March 25) which was determined by the investigator to be of mild intensity and unrelated to the study therapy. This event did not result in delafloxacin being either interrupted or discontinued.

Medical Reviewer’s Comments: *The two delafloxacin-treated subjects with severe renal impairment and kidney failure sustained no SAEs, no moderate or severe TEAEs and did not discontinue delafloxacin due to a TEAE. Subject 302/428-041-0673 with severe renal impairment was described as having a decline in S_{Cr} which this reviewer would not consider an adverse event. Neither was subject 302/840-014-0347 with kidney failure observed to have any TEAEs that were uncommon or of greater severity than the population of subjects with normal, mild, or severe renal impairments.*

Subjects with Baseline CKD Stage 4 (by Estimated Glomerular Filtration)

In their population PK study, the Applicant used the estimated glomerular filtration rate (eGFR) as calculated by the MDRD equation, to determine subjects' renal function. In their label, the Applicant has proposed the use of eGFR as determined by the MDRD equation, (b) (4) in determining renal function. Please refer to **Table 37** in **Section 7.1.3 Subpopulations** for further details on the % of subjects with kidney failure and moderate and severe renal impairments in both pivotal Phase 3 trials. When renal function is calculated according to the MDRD, two subjects in Protocol 303 who were previously determined to have moderate renal impairment (CKD Stage 3) according to the CG equation were now determined to have baseline severe renal impairment (CKD Stage 4). These 2 subjects are briefly discussed below.

Subject 303/233-441-3350: A 72 year old white Estonian woman with a baseline S_{Cr} of 1.90 mg/dL and a CrCl and eGFR of 38 mL/min and 26 mL/min/1.73 m², respectively, was administered delafloxacin, from 3 May 2015 (Study Day 1) through 14 May 2015 (Study Day 12), for a leg cellulitis. Documented co-morbid conditions included HTN, obesity (BMI of 30), and a chronic skin ulcer. Notable concomitant medications included ketoprofen (non-steroidal anti-inflammatory), ibuprofen, zopiclone (a hypnotic agent), metoprolol succinate, omeprazole, and furosemide. On Study Day 2 (4 May 2015), subject experienced a single, mild intensity TEAE coded to the PT term "catheter site pain." This TEAE resolved on Study Day 3, 5 May 2015. The investigator assessed this event as being related to delafloxacin treatment. This TEAE was not an SAE and did not result in study drug interruptions or discontinuation.

Subject 303/233-441-3723: A 75 year old white woman and native of Estonia with a baseline S_{Cr} of 3.14 mg/dL and a CrCl and eGFR of 33 mL/min and 14 mL/min/1.73 m², respectively, began treatment with delafloxacin for a leg cellulitis on 14 September 2015 (Day 1). She completed her treatment on 27 September 2015 (Study Day 14). She received a total of 13 doses of delafloxacin during this 14 day treatment period. Pertinent recorded medical history included: chronic renal insufficiency; congestive heart failure; diabetes mellitus, type 2; morbid obesity (BMI of 51); atrial fibrillation; gout; and status post iliac arterial thrombosis. Notable concomitant medications included pentoxifylline (presumably for peripheral vascular disease); ketoprofen (non-steroidal anti-inflammatory); spironolactone; zopiclone (a hypnotic agent); dexketoprofen (non-steroidal anti-inflammatory); atorvastatin; metoprolol; rivaroxaban (anticoagulant); torasemide; Humalog mix insulin and lispro insulin. This subject had no documented TEAEs.

TEAEs in Subjects with Baseline Moderate Renal CKD Stage 3 (Moderate)(by Cockcroft Gault Equation)

A total of 72 subjects across both arms of the pooled Phase 3 safety population had baseline renal function corresponding to moderate renal impairment (CKD Stage 3), as calculated by the Cockcroft Gault equation (CrCl). Of those 72 subjects, there were 25 delafloxacin treated subjects (25/741; 3.4%;) in Protocol 303, with baseline moderate renal impairment who altogether sustained a total of 14 TEAEs. In contrast, Protocol 302 had a total of 12 delafloxacin treated subjects (12/741; 1.6%) with moderate renal impairment 11 of whom experienced a total of 13 TEAEs.

Medical Reviewer’s Comments: Across both treatment arms, there were few subjects with moderate renal impairment who sustained TEAEs. There were no SAEs or treatment discontinuations that occurred among delafloxacin subjects with moderate renal impairment. Only two subjects with moderate renal impairments had their delafloxacin infusions interrupted and in each instance it was coded under the PT term “infusion site extravasation.” Most delafloxacin treated subjects with moderate renal impairment had TEAEs which were assessed by study investigators to be of mild severity. There were only 4 subjects assessed with moderate grade TEAEs. No pattern of delafloxacin specific TEAEs emerged among delafloxacin treated subjects with moderate renal impairment Across both treatment arms, but among the delafloxacin arm in particular, TEAEs were similar to those subjects with normal (CKD Stage 1) and mildly decreased (CKD Stage 2) renal function. There were slightly more subjects receiving delafloxacin in whom GI events and infusion/catheter site reactions occurred when compared to the vancomycin arm.

Despite overall limited numbers of subjects with moderate and severe renal impairments and kidney failure in both Phase 3 trials, the pre-market safety profile of delafloxacin treated patients suggests that there is no increase in concerning safety signals in the sub-population of patients with renal impairment or kidney failure. It is anticipated that a more comprehensive safety profile for renally impaired patients will emerge in delafloxacin’s post-marketing phase.

Table 66 demonstrates all subjects in the delafloxacin arm with baseline and maximal post-baseline shifts in CrCl, at key study visits.

Table 66: Baseline versus Maximal Post-Baseline Creatinine Clearance Shift Table by Key Study Visit					
		Pooled Phase 3 Delafloxacin Treatment Arm			
Baseline Creatine Clearance (CrCl) mg/dL	Maximal Post-baseline Creatinine Clearance (CrCl)	3: Study Day 3	10: EOT	11: FU	12: Late FU
Baseline Stage 1: ≥ 90 (Normal or High)	Stage 2: 60 - 89 (Mild)	41 (5.6%)	51 (7.0%)	31 (4.3%)	15 (2.1%)
	Stage 3: 30 - 59 (Moderate)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Stage 4: 15 - 29 (Severe)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Stage 5: <15 or Dialysis (Kidney Failure)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Baseline Stage 2: 60 - 89	Stage 3: 30 - 59 (Moderate)	6 (0.8%)	12 (1.6%)	4 (0.6%)	5 (0.7%)

(Mildly Decreased)	Stage 4: 15 - 29 (Severe)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)
Baseline Stage 3: 30 - 59 (Moderately Decreased)	Stage 4: 15 - 29 (Severe)	1 (0.1%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
Subject Column Totals		48 (6.6%)	65 (8.9%)	36 (4.9%)	21 (2.9%)
Total # Subjects (Safety Denominator)		730 (100.0%)	730 (100.0%)	730 (100.0%)	730 (100.0%)
<i>Source: ISS Population. ADSL and ADLB data sets. Table generated by the clinical reviewer using JReview.</i>					

Several subjects in the delafloxacin arm with mild renal impairment (CKD Stage 2) experienced declines in renal function resulting in their being classified as having moderate renal impairment (CKD Stage 3). A single subject (Subject 303/840-011-0167) declined from mild renal impairment to severe renal impairment CKD Stage 4 (Severe) at the FU visit. No subjects with baseline mild renal impairment (CKD Stage 2) had observed declines in renal function resulting in their being classified as being severely renally impaired or as having kidney failure at the LFU visit. Only three subjects with moderate renal impairment dropped to CKD Stage 4 while receiving delafloxacin during the Study Day 3 or EOT visits. However, as **Table 66** indicates, no delafloxacin treated subjects with baseline normal, mild or moderated renal impairments were observed to have a drop in the CrCl consistent with severe renal impairment at the FU and LFU visits.

A total of 3 subjects had unscheduled visits where they were found to have declines in their baseline CKD staging: two subjects who went from normal (CKD Stage 1) to mild renal impairment (CKD Stage 2) and a single subject (Subject 303/840-011-0167) who went from a baseline mild renal impairment to severe renal impairment. This subject is discussed in greater detail below.

Medical Reviewer’s Comments: *Table 66 illustrates that in the Phase 3 pivotal trials, delafloxacin was not associated with significant worsening of renal function by study treatment visit. Although this information was not shown in the table above, the vancomycin comparator arm had substantially higher percentages of subjects with worsening renal function at various key study visits. The purpose of this shift table was to address any concerns that may arise, particularly in patients who may have baseline normal, mild and moderate renal impairment who during the course of delafloxacin therapy may require dose adjustments, based on Applicant proposed labeling, due to a decline in renal function during the recommended 5-14 day course of therapy. There were two delafloxacin treated subjects (Subject 303/100-434-3394 and Subject 303/233-440-3616)—both of whom were ≥ 75 years of age with multiple co-morbid conditions who were taking several concomitant medications and who had baseline moderate renal impairment whose CrCl declined to severe renal impairment at the EOT visit. Hence, a labeling recommendation to closely follow both Cr and eGFR levels in persons (particularly older ones) with baseline CKD Stage 3, with co-morbid conditions and concomitant medications that may place them at greater risk for worsening renal function while on delafloxacin is most likely justified.*

Creatine Phosphokinase (CPK) Laboratory Values

Using the DAIDS Table for Grading the Severity of AEs (Version 2.0), a shift table of baseline versus post-baseline maximal CPK values was constructed. This table is found below.

Table 67:Creatine Phosphokinase (CPK) Shift Table				
Parameter	Baseline CPK Category	Maximal Post Baseline CPK Category	Pooled Delafloxacin N=741	Pooled Vancomycin ± Aztreonam N=751
Creatine Phosphokinase (U/L)	Missing.	Grade 0: CPK	14 (1.9%)	12 (1.6%)
	Grade 0 (Normal): CPK		680 (91.8%)	696 (92.7%)
		Grade 1: CPK ≥3 -<6xULN	14 (1.9%)	20 (2.7%)
		Grade 3: CPK ≥10- <20xULN	3 (0.4%)	3 (0.4%)
		Grade 4: CPK ≥ 20xULN	2 (0.3%)	1 (0.1%)
	Grade 1 (Mild): CPK ≥ 3-<6x ULN	Grade 1: CPK ≥3 -<6xULN	15 (2.0%)	11 (1.5%)
	Grade 2 (Moderate): CPK ≥6 -<10x ULN	Grade 2: CPK ≥ 6 - <10xULN	0 (0.0%)	1 (0.1%)
	Grade 2 (Moderate): CPK ≥6 -<10x ULN	Grade 2: CPK ≥ 6 - <10xULN	7 (0.9%)	3 (0.4%)
	Grade 3 (Severe): CPK ≥ 10 - <20x ULN	Grade 3: CPK ≥ 10 - < 20xULN	0 (0.0%)	3 (0.4%)
	Grade 4 (Potentially Life-Threatening): CPK ≥ 20x ULN	Grade 4 : CPK ≥ 20xULN	2 (0.3%)	1 (0.1%)
Subjects			741 (100.0%)	751 (100.0%)

Source: ISS Population. ADSL and ADLB data sets. Table generated by the clinical reviewer using JReview.

Medical Reviewer's Comments: In the delafloxacin arm, there were total of two subjects with baseline normal CPK values who progressed to Grade 3 post-baseline maximal CPK values and 2 subjects who developed Grade 4 post-baseline maximal CPK values. There were no subjects with baseline normal CPK values in the vancomycin (± aztreonam) comparator arm who experienced any Grade 4 post-baseline maximal CPK values and only one subject who experienced a Grade 3 post-baseline maximal elevation in CPK values.

Subject Narratives for Delafloxacin Subjects with Grade 3 and Grade 4 Maximal Post-Baseline CPK Values

Subject 303/840-305-3233 (Delafloxacin/Grade 3 CPK elevations): A 53 year old male who was treated with delafloxacin from 11 Feb 2015 (Study Day 1) to 16 Feb 2015 (Study Day 6) for a right arm wound infection. His pertinent medical history included a history of HCV and prior cellulitis, HTN, and heroin addiction. Pertinent concomitant medications included oxycodone, bupirone hydrochloride, trazodone, and diamorphine (heroin). He received a total of 10 doses of delafloxacin with 2 infusion interruptions. On 27 April 2015 (Study Day 76), this subject experienced a severe grade elevation in CPK levels, with CPK peaking to 2,616 U/L from a slightly elevated baseline value of 239 U/L. In addition, he experienced mild elevations in AST and ALT with values of 172 U/L and 116 U/L, respectively. As this event occurred approximately 70 days post-treatment, the investigator assessed these events to be unrelated to study treatment.

***Medical Reviewer Comment:** Reviewer is in agreement with investigator's assessment that delafloxacin is unlikely to be responsible for the observed transaminases and CPK elevations in the above-described subject.*

Subject 303/840-322-3268 (Delafloxacin/Grade 3 CPK elevations): A 43 year old white man who was treated with delafloxacin from 7 March 2015 (Study Day 1) through 12 March 2015 (Study Day 6) for a wound infection. This subject had a relevant medical history significant for IV heroin and inhaled **methamphetamine** addiction. He received a total of 9 doses of delafloxacin. Baseline CPK was 136 U/L (wnl). CPK levels were elevated at 274 U/L and 368 U/L on Study Day 3 (9 March 2015) and at the FU visit (Study Day 13), respectively. Two weeks post-therapy, at the 27 March 2015 LFU visit (Study Day 21), this subject's CPK levels were observed to increase to 3255 U/L, this occurred alongside mild simultaneous elevations in ALT, AST and ALP of 75 U/L, 84 U/L, and 122 U/L, respectively. CPK levels collected during an unscheduled visit on Study Day 27 (02 April 2015), had returned to normal.

***Medical Reviewer Comment:** While the above-described subject's CPK increased slightly from normal baseline CPK levels during treatment, it is this reviewer's determination that the markedly elevated CPK values observed at the LFU visit, two weeks post-delafloxacin treatment, were most likely **unrelated** to treatment, but were most likely attributable to some unknown precipitant. The reviewer did ask for the accompanying subject eCRF but found the documented information uninformative.*

Subject 302/840-002-0226 (Delafloxacin/Grade 4 CPK elevations): A 48 year old male with a history of falls and a positive HCV Ab at screening was administered delafloxacin for a left leg major cutaneous abscess from 29 Aug 2013 (Study Day 1) through 01 September 2013 (Study Day 4). In addition to a positive HCV Ab, his medical history was also notable for anxiety and obsessive compulsive disorder. Relevant concomitant medications included gabapentin, fluoxetine hydrochloride, bupropion hydrochloride and lithium. His baseline screening CPK value was elevated at 510 U/L, however they peaked to 4,947 U/L on Day 7 (4 Sept 2013) of treatment at the EOT visit. On Day 7 (4 Sept 2013), the subject simultaneously experienced 2 other AEs—elevations in his previously elevated screening AST and ALT values, with both values peaking to 211 U/L and 118 U/L, respectively. Delafloxacin therapy was discontinued

early due to non-compliance with therapy. He had missed “6 consecutive doses of study drug and may have received non-study antibiotics.”

Subject 302/840-004-0161 (Delafloxacin/Grade 4 CPK elevations): A 26 year old male with a history of HCV, **methamphetamine** abuse, and a baseline normal CPK value of 175 U/L was treated with a 7 day course of delafloxacin for a left leg wound infection. He experienced a post-treatment (Day 23) elevation of CPK to 4,505 U/L with concurrent elevations in ALT (ALT 224 U/L) and AST (AST 166 U/L). Notable concomitant medications included gabapentin which has been associated with elevations in CPK, LFTs and rhabdomyolysis. No further details were given. CPK elevations reportedly resolved on Day 76. The Investigator assessed the event as being “possibly” related to the study drug “due to an unspecified cause.”

Medical Reviewer’s comments: All of the above described subjects had a history of substance abuse and several of them had a reported history of methamphetamine use. Methamphetamine is a known stimulant. Acute methamphetamine intoxication can result in rhabdomyolysis, in addition to hyperthermia and agitation. It is the reviewer’s opinion that since many of the observed elevations in CPK occurred several days post-treatment that the observed elevations could quite possibly be related the methamphetamine. There is likely confounding between the observed laboratory abnormalities, delafloxacin treatment and substance abuse behaviors.

Creatine Phosphokinase (CPK) Adverse Events

In reviewing delafloxacin’s safety profile, several subjects experienced TEAEs coded to the PT “blood creatine phosphokinase increased” in the Investigations SOC. This reviewer analyzed the safety database at both the SOC and PT levels to clarify the incidence of CPK elevations in the pooled Phase 3 delafloxacin arm relative to the comparator, as exhibited in the table below.

Dictionary Derived Term	Serious Event	Causality	Severity Intensity	Action Taken with Study Treatment	Protocol 303 300-mg IV 450-mg oral q12 hrs	Protocol 1302 300-mg IV	Pooled Vancomycin (± Aztreonam)
Blood Creatine Phosphokinase Increased	No	Unrelated	Mild	No Action Taken	4 (1.0%)	2 (0.6%)	6 (0.8%)
	No	Unrelated	Moderate	No Action Taken	0 (0.0%)	0 (0.0%)	2 (0.3%)
	No	Unrelated	Severe	No Action Taken	1 (0.2%)	0 (0.0%)	0 (0.0%)
	No	Possible	Mild	No Action Taken	0 (0.0%)	1 (0.3%)	7 (0.9%)
	No	Possible	Moderate	No Action Taken	0 (0.0%)	1 (0.3%)	0 (0.0%)
	No	Possible	Severe	No Action	0 (0.0%)	1	0 (0.0%)

	Not Taken	Not Assessed	Taken	(0.3%)
Total # Subjects with TEAE	5 (1.2%)	5 (1.5%)	15 (2.0%)	
Denominator	417 (100.0%)	324 (100.0%)	751 (100.0%)	

Source: ISS Population. ADSL and ADLB data sets. Table generated by the clinical reviewer using JReview.

Medical Reviewer’s Comments: CPK elevations occurred in nearly equal proportions of subjects across both treatment arms. A total of 10 subjects (10/741; 1.3%;) in the pooled delafloxacin arm, 5 from each Phase 3 trial, compared with 15 subjects (15/751; 2.0%) in the pooled comparator arm experienced TEAEs coded to CPK elevations. The majority of these events were assessed by the investigators as being mild in intensity and unrelated to study treatment, irrespective of treatment arm. There were no study discontinuations or SAEs resulting from the CPK elevations observed in either treatment arm.

Subject 302/784-060-0538, a 58 year old Ukrainian male treated with an 8-day course of delafloxacin (23 Dec 2013 [Day 1] to 30 Dec 2013 [Day 8]) for a major cutaneous abscess was assessed as having a severe causally related elevation in CPK. His baseline CPK value was normal at 23 U/L; however, on Study Day 8 his CPK increased to 1,889 U/L. No further details were given. The event resolved by Study Day 13 with his CPK returning to a value of 109 U/L (lab reference range: 24-207). Given the temporal relationship between the drug exposure and the CPK elevation, the investigator determined that there may be a causal association between the event and delafloxacin therapy.

A second subject (Subject 840-004-0161), a 26 year old male with a history of HCV, methamphetamine abuse, and a baseline normal CPK value of 175 U/L was treated with a 7 day course of delafloxacin for a left leg wound infection and was described above.

Based on the limited information which the Applicant has provided on these 2 subjects, the reviewer considers that a possible causal relationship between delafloxacin and CPK elevations cannot be excluded.

Glucose Related Adverse Events

This reviewer conducted an independent analysis of all Phase 3 hypoglycemic and hyperglycemic events based on shift tables created from Version 2.0 of the DAIDs toxicity grading table. The shift tables contain all subjects with baseline glucose evaluations, 412 (412/741; 55.6%) and 415 (415/751; 55.3%) subjects, in the pooled delafloxacin and vancomycin arms, respectively. This sub-section discusses all subjects in the delafloxacin arm with baseline Grade 0, Grade 1 (mild) and Grade 2 (moderate) glucose levels who developed Grade 3 (severe) or Grade 4 (life threatening) maximal post-baseline glucose laboratory values. **Glucose evaluations were non-fasting.** Nevertheless, it is noted that glycemic events were fairly balanced across treatment arms.

Table 69 and the majority of delafloxacin treated subjects had baseline Grade 0 glucose values. To better evaluate any causal linkages between delafloxacin and hypo-, hyper-glycemic episodes, a brief summary of each subject who experienced a Grade 3 or 4 glucose event is provided below.

Hyperglycemic Events

Table 69: Baseline versus Maximal Post-Baseline Glucose Shift Table (Hyperglycemic Events)				
Parameter	Baseline Glucose (High)	Maximal Post Baseline Glucose (Hyperglycemia)	Delafloxacin	Vancomycin (±Aztreonam)
Glucose (mmol/L)	Grade 0	Grade 0	122 (16.5%)	133 (17.7%)
		Grade 1 (Mild): 116 to 160 mg/dL or 6.44 to < 8.89 mmol/L	126 (17.0%)	143 (19.0%)
		Grade 2 (Moderate): >160 to 250 mg/dL or 8.89 to < 13.89 mmol/L	34 (4.6%)	28 (3.7%)
		Grade 3 (Severe): >250 to 500 mg/dL or 13.89 to <27.75 mmol/L	1 (0.1%)	3 (0.4%)
	Grade 1: Mild	Grade 0	20 (2.7%)	17 (2.3%)
		Grade 1 (Mild): 116 to 160 mg/dL or 6.11 to <6.95 mmol/L	37 (5.0%)	31 (4.1%)
		Grade 2 (Moderate): >160 to 250 mg/dL or 8.89 to < 13.89 mmol/L	18 (2.4%)	10 (1.3%)
		Grade 3 (Severe): >250 to 500 mg/dL or	2 (0.3%)	7 (0.9%)

		13.89 to <27.75 mmol/L		
		Grade 4 (Potentially Life Threatening): >500 mg/dL or ≥ 27.75 mmol/L	1 (0.1%)	0 (0.0%)
Grade 2: Moderate		Grade 0	1 (0.1%)	2 (0.3%)
		Grade 1 (Mild): 116 to 160 mg/dL or 6.11 to < 6.95 mmol/L	10 (1.4%)	8 (1.1%)
		Grade 2 (Moderate): >160 to 250 mg/dL or 8.89 to < 13.89 mmol/L	17 (2.3%)	12 (1.6%)
		Grade 3 (Severe): >250 to 500 mg/dL or 13.89 to <27.75 mmol/L	5 (0.7%)	5 (0.7%)
Grade 3: Severe		Grade 1 (Mild): 116 to 160 mg/dL or 6.11 to <6.95 mmol/L	1 (0.1%)	0 (0.0%)
		Grade 2 (Moderate): >160 to 250 mg/dL or 8.89 to < 13.89 mmol/L	6 (0.8%)	4 (0.5%)
		Grade 3 (Severe): >250 to 500 mg/dL or 13.89 to <27.75 mmol/L	9 (1.2%)	11 (1.5%)
		Grade 4 (Potentially Life Threatening): >500 mg/dL or ≥ 27.75 mmol/L	2 (0.3%)	1 (0.1%)
		Subjects(filtere	412 (55.6%)	415 (55.3%)

	d)		
	1stCollItemSubj ects	741 (100.0%)	751 (100.0%)
<i>Source: ISS Population. ADSL and ADLB data sets. Table generated by the clinical reviewer using JReview.</i>			

Subject 303/840-327-3850 (Delafloxacin): A 45 year old woman with a medical history most notable for interstitial cystitis, depression, anxiety, and obesity was administered delafloxacin for a right breast cellulitis from (b) (6) (Study Day 1) through (b) (6) (Study Day 9). She received a total of 16 doses of delafloxacin. Notable concomitant medications included citalopram, temazepam, and alprazolam. Her baseline glucose value was 95 mg/dL (5.27 µmol/L) but rose to 278 mg/dL (15.43 µmol/L) on Study Day 8. This event was categorized as a severe event (toxicity grade 3 event). This subject additionally developed an unrelated SAE coded under the PT term “community acquired pneumonia” which resulted in her being hospitalized on Study Day 18 (b) (6) 10 days post-delafloxacin treatment. The above-described hyperglycemic event was not coded as an AE by the site investigator.

Medical Reviewer’ Comments: In the absence of more information it is difficult to determine if this single episode of hyperglycemia in a non-diabetic woman is related to the study drug as this was a non fasting glucose level. However, since there is a temporal association between FQs with dysglycemia a causal linkage cannot be excluded. The subject is also, however, on citalapram which has been implicated in “abnormal glucose tolerance” and hypoglycemia.

Subject 303/428-460-3876 (Delafloxacin): A 51 year old Latvian man, with no prior medical history, who received a total of 18 doses delafloxacin from 2 November 2015 (Study Day 1) to 11 November 2015 (Study Day 10) for a cellulitis. His initial baseline and EOT (11 November 2015) glucose values were 156 mg/dL (8.66 µmol/L) and 55.0 mg/dL (3.05 µmol/L), respectively. On Study Day 25 (26 November 2015), approximately 15 days post-delafloxacin therapy, his glucose peaked to 270.1 mg/dL (14.99 mmol/L).

Medical Reviewer’ Comments: *The above-described hyperglycemic event occurred several days post-treatment and is unlikely to have been related to delafloxacin. It is noted, however, that this subject’s EOT glucose value was consistent with hypoglycemia.*

Subject 303/840-307-3886 (Delafloxacin) A 32 year old African American woman with non-insulin dependent diabetes, hypertension and a previous history of ABSSSI was treated with delafloxacin for a cellulitis. Pertinent medications included metformin, lisinopril and hydrochlorothizide. Subject was administered delafloxacin from 7 November 2015 (Study Day 1) through 16 November 2015 (Study Day 15) for a 10 day period and received a total of 19 doses of delafloxacin. Her baseline glucose value was 140 mg/dL (7.77 mmol/L) and peaked to 386 mg/dL (21.43 mmol/L) around study Day 6.

Medical Reviewer’ Comments: *The above-described hyperglycemic event occurred in a known diabetic. As this was a non-fasting glucose check in a known diabetic, this reviewer is more inclined to attribute this event to the subject’s known underlying medical condition than to the delafloxacin itself.*

Grade 2 to Grade 3 Hyperglycemia

There were a total of 5 subjects with baseline Grade 2 glucose elevations who experienced Grade 3 glucose elevations during the Applicant’s Phase 3 pivotal trials. Three of these 5 subjects had known histories of diabetes. Another subject had HCV cirrhosis and a documented history of hyperglycemia. Available information indicated that all of these subjects completed the study.

Hypoglycemic Events

Table 70: Baseline versus Maximal Post-Baseline Glucose Shift Table (Hypoglycemic Events)					
Parameter	Baseline Glucose (Low)	Maximal Post-Baseline Glucose_Low	Delafloxacin	Vancomycin (± Aztreonam)	
Glucose (mmol/L)	Missing	Grade 0	0 (0.0%)	1 (0.1%)	
	Grade 0	Grade 0	372 (50.2%)	373 (49.7%)	
		Grade 1 (Mild): 55 to 64 mg/dL or 3.05 to 3.55 mmol/L	12 (1.6%)	15 (2.0%)	
		Grade 2 (Moderate): 40 to <55 mg/dL or 2.11 to <2.78 mmol/L	6 (0.8%)	9 (1.2%)	
		Grade 3 (Severe): 30 to <40 mg/dL or 1.67 to <2.22 mmmol/L	1 (0.1%)	3 (0.4%)	
		Grade 4 (Potentially Life-Threatening): <30 mg/dL or <1.67	1 (0.1%)	0 (0.0%)	
	Grade 1: Mild	Grade 0	2 (0.3%)	3 (0.4%)	
		Grade 1 (Mild): 55 to 64 mg/dL or 3.05 to 3.55 mmol/L	1 (0.1%)	0 (0.0%)	
	Grade 2: Moderate	Grade 0	1 (0.1%)	0 (0.0%)	
		Grade 1 (Mild): 55 to 64 mg/dL or 3.05 to 3.55 mmol/L	1 (0.1%)	0 (0.0%)	
	Grade 3: Severe	Grade 2 (Moderate): 40 to <55 mg/dL or 2.11 to <2.78 mmol/L	0 (0.0%)	1 (0.1%)	
	Grade 4: Potentially Life Threatening	Grade 0	14 (1.9%)	9 (1.2%)	
		Grade 2 (Moderate): 40 to <55 mg/dL or 2.11 to <2.78 mmol/L	1 (0.1%)	1 (0.1%)	
	# of Subjects			412 (55.60%)	415 (55.26%)
	Denominator			741 (100.0%)	751 (100.0%)

Source: ISS population. ADSL and ADLB data sets.

As displayed in the hypoglycemia shift table, most subjects had baseline Grade 0 glucose levels and most of these subjects' maximal post-baseline glucose levels remained in this normal range. Only two subjects with baseline Grade 0 glucose levels developed Grade 3 and 4 hypoglycemic episodes. There were no other subjects, in either treatment arm, who sustained moderate (toxicity Grade 2) declines in blood glucose levels. These two subjects are discussed briefly below:

Subject 303/840-328-3541 (Delafloxacin): A 41 year old female who, from 5 August (Study Day 1) through 12 August 2015 (Study Day 8), was treated with delafloxacin for a major cutaneous abscess. She received a total of 14 doses of delafloxacin. Her medical history was noted for IV heroin abuse and previous skin infections. Her most notable concomitant medications included omeprazole and diamorphine (heroin). Her baseline glucose level was 78 mg/dL (4.33 µmol/L). On Study Day 8, her glucose dropped to 34 mg/dL (1.89 µmol/L). At the FU (Study Day 14) and LFU (Study Day 21) visits, glucose levels had normalized to 84 mg/dL (4.66 µmol/L) and 114 mg/dL (6.33 µmol/L), respectively.

Subject 303/840-328-3654 (Delafloxacin): A 54 year old American male with a history of HCV and IV heroin abuse. His only concomitant medication included diamorphine (heroin). He began delafloxacin treatment on 1 September 2015 (Study Day 1) and completed delafloxacin treatment 06 September 2015 (Study Day 6) for a wound infection. He received a total of 10 doses of delafloxacin. This subject had a baseline glucose level of 103 mg/dL (5.72 µmol/L) which on Study Day 6 dropped to 29 mg/dL (1.61 µmol/L). By the FU (Study Day 14) and LFU (Study Day 24) visits, glucose values had normalized to 178 mg/dL (9.88 µmol/L) and 97 mg/dL (5.38 µmol/L), respectively.

Medical Reviewer's Comments: *The details around the two above-described subject events are limited. Neither of the subjects were known diabetics or on medications implicated in lowering blood glucose levels. However, both of these subjects were IV heroin abusers and may have had poor baseline nutritional status and/or eating habits. Each of these reported hypoglycemic events occurred on the final day of treatment and was apparently self-limited. In each case, the subject completed delafloxacin treatment. Despite there being potentially confounding factors, in the absence of additional information, this reviewer cannot definitively exclude a relationship between the observed hypoglycemic episodes and delafloxacin given a temporal linkage between the event and receipt of study drug which is a member of a drug class associated with dysglycemias.*

8.4.7 Vital Signs

Heart Rate

Table 71 is a shift table comparing subjects' baseline heart rate (HR) values with their maximal post-baseline values. **Table 71** was created using data collected from the Applicant's Phase 3 safety populations' vital signs datasets. There were 716 subjects (716/741; 96.6%;) in the pooled Phase 3 delafloxacin arm and 718 subjects (718/751; 95.6%;) from the pooled vancomycin comparator arm with baseline HR data. Most subjects had baseline HRs which were within normal limits (HR between 60 and 100); and as **Table 71** indicates, the majority of delafloxacin treated subjects' HRs remained within normal range throughout the study duration.

The mean baseline heart rate for delafloxacin treated subjects was 84 beats/minute (median: 82 beats/min) on Study Day 1. There were no significant changes in the mean heart rate that were observed across study visits in the delafloxacin treatment group. The mean heart rate for delafloxacin treated subjects at the EOT, FU, and LFU visits were 76 beats/min, 78 beats/min and 78 beats/min, respectively.

Several subjects in both treatments arms had TEAEs coded under such PT terms as sinus tachycardia, tachycardia, atrial tachycardia, and supraventricular tachycardia. The majority of subjects in both treatment arms had normal baseline HRs. Few subjects' heart rates were observed to increase from normal baseline HR to a maximal, post-baseline HRs of >100. **Table 71** below illustrates shifts in baseline HR and maximal post-baseline HR in both treatment arms. Likewise, there were few delafloxacin and vancomycin treated subjects with normal baseline heart rates who experienced bradycardia during the Phase 3 trials.

Table 71: Baseline versus Maximal Post-Baseline Heart Rate Shift Table					
PARAMETER	Baseline Heart Rate Category	Maximal Post Baseline Heart Rate Category	Pooled Delafloxacin N=741	Vancomycin ± Aztreonam N=751	
Heart Rate (BEATS/MIN)	Low: < 60	Low	7 (0.9%)	9 (1.2%)	
		Normal	16 (2.2%)	14 (1.9%)	
	Normal: 60 - ≤100	Low	45 (6.1%)	48 (6.4%)	
		Normal	620 (83.7%)	648 (86.3%)	
		High	45 (6.1%)	54 (7.2%)	
	High: >100	Low	2 (0.3%)	0 (0.0%)	
		Normal	76 (10.3%)	50 (%)	
		High	23 (3.2%)	15 (6.7%)	
	Subjects (filtered):			716 (96.6%)	718 (95.6%)
	Denominator Subjects:			741 (100.0%)	751 (100.0%)
<i>Source: ISS Population. ADSL and ADVS data sets. Table generated by the clinical reviewer using JReview.</i>					

Systolic Blood Pressure (SBP)

Table 72 illustrates baseline versus maximal post-baseline changes in SBP among the 716 (716/741; 96.6%) subjects in the delafloxacin arm and the 718 subjects (718/751; 95.6%) in the vancomycin comparator arm with baseline systolic blood pressure values. As **Table 72** shows, most subjects started with SBPs within a normal range and maintained normal range systolic blood pressures throughout the study.

The mean baseline systolic blood pressure for delafloxacin treated subjects on Study Day 1 was 127 mm Hg (median 127 mm Hg). There were no significant changes in the mean systolic blood pressure that were observed across study visits in the delafloxacin treatment group. The mean systolic blood pressures for delafloxacin treated subjects at the EOT, FU, and LFU visits were 128 mmHg, 127 mmHg, and 127 mm Hg, respectively.

Although relatively infrequent in occurrence, a total of 17 subjects were recorded as having AEs associated with elevated blood pressures. The majority of these subjects had pre-existing histories of hypertension. Nearly equal numbers of subjects in both treatment arms of the Phase 3 safety population were either coded under the Investigations SOC or the Vascular Disorders SOC as having “blood pressure increased,” “hypertension,” or “prehypertension.” None of these AEs were SAEs. All of them were assessed as either mild or moderate in severity and none resulted in drug withdrawals. All but three cases were evaluated as being unrelated to the study treatment: 1 in the delafloxacin arm and 3 in the comparator arm.

Table 72: Baseline versus Maximal Post-Baseline Systolic Blood Pressure (SBP) Shift Table

Systolic Blood Pressure (mmHg)	Systolic Blood Pressure Baseline Category	Systolic Pressure Category	Pooled Delafloxacin N=741	Vancomycin + Aztreonam N=751
Systolic Blood Pressure (mmHg)	Low: <100: Low	Low	8 (1.1%)	6 (0.8%)
		Normal	19 (2.6%)	25 (3.3%)
		Stage 1	5 (0.7%)	3 (0.4%)
		Stage 2	2 (0.3%)	0 (0.0%)
	Normal: 100-139	Low	37 (5.0%)	33 (4.4%)
		Normal	568 (76.67)	569 (75.8%)
		Stage 1	161 (21.7%)	158 (21.0%)

		Stage 2	23 (3.1%)	34 (4.6%)
	Stage 1: 140-159	Low	0 (0.0%)	3 (0.4%)
		Normal	74 (10.0%)	66 (8.8%)
		Stage 1	66 (8.9%)	65 (8.7%)
		Stage 2	19 (2.6%)	21 (2.8%)
	Stage 2: ≥160	Normal	14 (1.9%)	16 (2.1%)
		Stage 1	19 (2.6%)	21 (2.8%)
		Stage 2	11 (1.5%)	13 (1.7%)
Subjects (filtered)			716 (96.6%)	718 (95.6%)
DENOMINATOR			741 (100.0%)	751 (100.00%)
<i>Source: ISS Population. ADSL and ADVS data sets. Table generated by the clinical reviewer using JReview.</i>				

Medical Reviewer's Comments

Several subjects under the Investigations SOC were coded to the PT term “increased blood pressure” of which there were 4 subjects (4/741; 0.5%) in the pooled delafloxacin arm and 2 (2/718; 0.3%) in the pooled vancomycin arm. Despite there being no drug withdrawals under this AE for either therapy, Subject 303/840-327-3064 in the delafloxacin arm had experienced multiple simultaneously occurring symptoms coded to the following PT terms: “BP elevated,” “dizziness,” “flushing,” and “headache” which resulted in an interruption of delafloxacin therapy. Briefly, Subject 303/840-327-3064 was a 77 year old man with a known history of hypertension (baseline BP was 158/96), coronary artery disease, and high cholesterol. This subject was assessed as having a moderate severity, investigator assessed TEAE coded to the PT “blood pressure increased.” The investigator considered this event as being “possibly” related to delafloxacin therapy. The event occurred on Study Day 7 of a total 7 day course of delafloxacin therapy. This subject’s peak post treatment BP was 162/105 (Study Day 19).

Eleven other hypertensive events occurred under the Vascular Disorders SOC and were coded to the PT term hypertension. There were 5 subjects (5/741; 0.7%) in the delafloxacin arm coded to this PT term and 6 subjects (6/751; 0.8%) in the vancomycin arm. Only two subjects coded to this AE in the vancomycin arm were assessed as being “possibly related” to study drug.

Two subjects, one in each treatment arm, were coded to the PT term hypotension. A single subject in the delafloxacin arm (Subject 302/428-044-0723) was documented as having a TEAE coded to the PT “hypotension.” This event was assessed as being of moderate severity and “possibly related” to delafloxacin. This subject was found at screening to have a BP of 89/49. All subsequent BPs were within normal limits.

Diastolic Blood Pressure (DBP)

As **Table 73** illustrates below, there were no significant differences between treatment groups in either baseline or post-baseline maximal DBP.

The mean baseline diastolic blood pressure for delafloxacin treated subjects on Study Day 1 was 77 mmHg (median: 78 mm Hg). There were no significant changes in the mean diastolic blood pressure that were observed across study visits in the delafloxacin treatment group. The mean diastolic blood pressures for delafloxacin treated subjects at the EOT, FU, and LFU visits were 77 mmHg, 77 mmHg, and 78 mmHg, respectively.

Table 73: Baseline versus Maximal Post-Baseline Diastolic Blood Pressure Shift Table				
Diastolic Blood Pressure (mmHg)	Baseline Diastolic Blood Category	Maximal Post-Baseline Diastolic Blood Category	Pooled Delafloxacin N=741	Pooled Vancomycin ± Aztreonam N=751
Diastolic Blood Pressure (mmHg)	Low: <60	Low	16 (2.2%)	17 (2.3%)
		Normal	33 (4.5%)	40 (5.3%)
		Stage 1	2 (0.3%)	2 (0.3%)
		Stage 2	1 (0.1%)	1 (0.9%)
	Normal: 60-89	Low	60 (8.1%)	66 (8.8%)
		Normal	575 (77.6%)	575 (76.6%)
		Stage 1	116 (15.7%)	115 (15.3%)
		Stage 2	19 (2.6%)	32 (4.3%)
	Stage 1: 90-99 (High)	Low	3 (0.4%)	0 (0.0%)
		Normal	78 (10.5%)	69 (9.2%)
		Stage 1	47 (6.3%)	51 (6.8%)
		Stage 2	15 (2.0%)	14 (1.9%)
	Stage 2: ≥100 (High)	Low	1 (0.1%)	2 (0.3%)
		Normal	13 (1.8%)	17 (2.3%)
		Stage 1	11 (1.5%)	14 (1.9%)
		Stage 2	7 (1.0%)	7 (0.9%)
Subjects (filtered)			716 (96.6%)	718 (95.6%)
DENOMINATOR SUBJECT			741 (100.0%)	751 (100.0%)

Source: ISS Population. ADSL and ADVS data sets. Table generated by the clinical reviewer using JReview.

Medical Reviewer’s Comments:

As **Table 73** illustrates, in each treatment arm, few subjects with baseline low (DBP<60) or normal (DBP 60-89) diastolic blood pressures had maximal post-baseline DBP increased to Stage 1 and Stage 2 blood pressures. No subjects had severe or life-threatening toxicity grade elevations in DBP.

8.4.8 Electrocardiogram

The majority of subjects in Trial 303 had baseline EKGs demonstrating a normal sinus rhythm: 342 (80.1%) in the delafloxacin arm and 350 (82.0%) in the comparator arm. There were 17 (4.0%) and 10 (2.0%) subjects in the delafloxacin and comparator arms, respectively, who were documented as having clinically significant EKGs at screening, with atrial fibrillation being the most commonly cited EKG abnormality, although there were few subjects in either arm exhibiting this rhythm. A single subject (303/428-460-3710) an 81 year old Latvian woman was recorded as having a screening EKG with a prolonged QT interval. She was randomized to and completed treatment with delafloxacin arm without incident.

As this reviewer did not find a data set with EKG results for Trial 302, in response to an information request sent by the reviewer, the Applicant referred the reviewer to Table 16.2.9.4 a listing of vital signs for Trial 302's analysis data set. A total of eight subjects in Trial 302 were noted to have clinically significant EKGs: five (5/331; 1.5%) of these subjects were in the delafloxacin arm and three (3/329; 0.9%) were in the vancomycin arm. The five subjects in the delafloxacin arm had the following clinically significant EKG findings atrial fibrillation, atrio-ventricular block, right bundle branch block, "non-Q changes of left ventricular wall, and tachycardia with ST depressions. Of the three subjects in the vancomycin arm with clinically significant findings on EKG, two subjects had atrial fibrillation and one was noted to have sinus tachycardia with a sinus arrhythmia.

8.4.9 QT

The Applicant conducted a thorough QT (TQT) study for delafloxacin under Trial 111. This TQT trial demonstrated that, unlike predecessor FQs, delafloxacin has little potential to induce QT prolongation. Please refer to **Section 8.7 Specific Safety Studies** for further discussion on Trial 111.

8.4.10 Immunogenicity

Delafloxacin is not a peptide. Therefore, its potential for immunogenicity was not anticipated and thus immunogenicity was not evaluated during the clinical trials.

8.5 Analysis of Submission-Specific Safety Issues

Section 8.5 addresses FQ-class specific safety issues. In 2008, 2013, and 2016, FDA issued drug safety communication warnings to healthcare professionals and the general public advising of potential FQ-associated side effects, namely tendinitis and tendon rupture, peripheral neuropathy, and central nervous system (CNS) disorders. FDA recommended against the use of FQs for several disease indications (i.e. acute bronchitis, acute sinusitis and uncomplicated urinary tract infections) whenever the risk of FQ-associated side effects outweighed the benefits of treatment. All drugs of the FQ class are required to carry boxed warnings cautioning that FQs have been associated with the aforementioned "disabling and potentially irreversible serious adverse reactions."

Moreover, in Section 5, the "Warnings and Precautions" section, most FQs contain warnings cautioning that FQs can lead to: tendon rupture and tendinitis; peripheral neuropathy; CNS effects, exacerbation of myasthenia gravis; QT prolongation; hepatotoxicity; development of drug resistant bacteria; *Clostridium difficile*-Associated Diarrhea; hypersensitivity reactions; blood glucose disturbances; photosensitivity/phototoxicity; and "other serious and sometimes

fatal reactions.” To address these safety concerns, the Applicant reported using MedDRA terminology and conducting standardized MedDRA queries (SMQs).

This reviewer independently conducted customized MedDRA queries (CMQ) as well as SMQs using MAED software, for both pivotal Phase 3 trials. The reviewer then compared these findings against the SMQs conducted by the Applicant for each Phase 3 trial. Using MedDRA, the reviewer also carefully assessed SOC, high level term (HLT) and PT terms for other AEs that may be related to delafloxacin. The sub-sections below address each of the above-mentioned FQ-associated AEs.

8.5.1 Tendinitis and Tendon Rupture

Tendinitis and tendon rupture are AEs of special interest associated with the FQ-class. This reviewer conducted an analysis for terms related to tendinitis under the Musculoskeletal and Connective Disorders SOC which yielded the following PT terms: tendinitis, tendinitis plantar, and arthralgia. Three subjects in the pooled Phase 3 trials sustained AEs coded to the PT term tendinitis/ tendinitis plantar. These three (3/741; 0.4%) subjects in the pooled delafloxacin arm experienced a total of four events. One subject was twice coded as having a TEAE under the PT term tendinitis plantar. No subjects (0%) in the vancomycin comparator arm were reported as having tendinitis.

Study investigators only assessed one of the four events coded to this PT term as moderate in severity; while the rest were graded as mild severity events. All events were determined by the study investigators to be unrelated to the study drug. None of these events resulted in delafloxacin being discontinued. None of the (3) subjects coded as having tendinitis/tendinitis plantar had concomitant use of steroids, and only one subject was over 60 years of age. All events occurred either at or around the end of treatment visit.

Medical Reviewer’s Comments:

Few subjects in the Applicant’s pivotal Phase 3 trials exhibited any AEs related to the terms tendinitis or tendon rupture. Based on review of subject narratives and eCRF, this reviewer finds it unlikely that the described events are related to delafloxacin therapy, even in spite of there being a temporal relationship between the onset of these tendinitis events and receipt of the study drug.

Table 1: Tendinitis Related Adverse Events

USUBID	Age	Sex	Medical History	History of Steroid Use	Infection Type/Site	Treatment	Treatment Start Date	AE Start Date/Day of Study	AE End Date/Day of Treatment	Adverse Event Term	SAE	Severity	Outcome	Causality
TENDINITIS														
MEL303-604-404-3292	57	M	Diabetes Mellitus	No	Cellulitis/Erysipelas	Delafloxacin	23 March 2015 (1)/02 Apr 2015 (11)	10 April 2015 (19)	29 April 2015 (38)	Tendinitis Plantar	No	Moderate	Recovered/Resolved	Unrelated
					Left Face/Right Foot		29 April 2015 (38)	02 May 2015 (41)	Tendinitis Plantar	No	Mild	Recovered/Resolved	Unrelated	
MEL303-604-404-3339	41	M	HIV	No	Cellulitis/Erysipelas Left Leg	Delafloxacin	22 April 2015 (1)/02 May 2015 (11)	1 May 2015 (10)	3 June 2015 (43)	Tendinitis	No	Mild	Recovered/Resolved	Unrelated
MEL303-604-404-3375	66	M	(+), but not significant	No	Cellulitis/Erysipelas Right Leg	Delafloxacin	18 May 2015 (1)/31 May 2015 (14)	28 May 2015 (11)	Unknown	Right Ankle Tendinitis	No	Mild	Recovered/Resolved	Unrelated

Source: ISS population, ADSL and ADAE data sets. Table generated by clinical reviewer using JReview and MAED.

Phase 2 Trials: RX-3341-201 and RX-3341-202

No subjects in the delafloxacin arm of the Applicant's Phase 2 trials sustained any TEAEs coded to the PT terms tendinitis/tendinopathy.

8.5.2 Peripheral Neuropathy

Similar to all other currently marketed FQs, the proposed delafloxacin label contains the following warning:

- (b) (4) cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons . . . have been reported in patients receiving fluoroquinolones.”

An analysis of peripheral neuropathy conducted under the Nervous System Disorders SOC yielded the following PT terms: paraesthesia, neuropathy peripheral, and hypoaesthesia. A total of 4 (4/741; 0.5%;) subjects in the pooled Phase 3 delafloxacin arm were reported as having a peripheral neuropathy. Three subjects (3/751; 0.4%) subjects in the pooled vancomycin comparator arm were reported as having a peripheral neuropathy. All events in the delafloxacin arm were assessed as being mild in severity. One of the three subjects in the comparator arm was assessed as having a moderate severity event (PT: hypoesthesia) which resulted in the study drug being interrupted, but not discontinued. The 4 subjects in the delafloxacin arm are briefly discussed below:

- **Subject 303-100-433-3906:** A 64 year old woman with a history of hypertension, developed “tingling in the toes” on Study Day 2 of an 11 day treatment course of delafloxacin for a left leg cellulitis. The investigator assessed this AE to be “possibly” related to the study drug. The event was not considered an SAE and it did not result in discontinuation of the study drug. The subject's symptoms were of mild severity intensity and self-limited in nature. The subject was later diagnosed with metastatic colon adenocarcinoma.

Medical Reviewer's Comments:

Based on the available data, it is this reviewer's assessment that the above-described event is most likely unrelated to the study drug. While there is a temporal relationship between the event and study drug administration, this medical reviewer cannot conclude with any certainty that these events are unrelated in this medically complicated subject.

Subject 302-840-004-0140: A 43 year old woman with a history of rheumatoid arthritis and hypokalemia received delafloxacin for a wound infection. She developed “numbness and tingling in right forearm” (assessed as two separate AEs) on Study Day 6 of an 8 day total course of delafloxacin treatment. The event was assessed as being unrelated to delafloxacin.

Medical Reviewer's Comments:

The onset of the AESI in question (PT: hypoesthesia and paresthesia) occurred on Day 6 of an 8 day treatment course. While the hypoesthesia was self-limited, the paresthesia had not resolved. Given the temporal relationship of AE to study drug, it cannot be excluded that the AE is possibly related to delafloxacin. However, it is also noted that the

subject has a history of hypokalemia which could also account for her reported paresthesias.

- **Subject 302-840-004-0160:** A 36 year old woman with a history of IV heroin abuse and methamphetamine inhalation was treated with delafloxacin for a left face wound infection. She developed left-sided paresthesias on Study Day 4 of a total of 8 day delafloxacin treatment. The event was not an SAE and did not result in discontinuation of study treatment.

Medical Reviewer's Comments:

The onset of the AESI in question (PT: paresthesia) occurred on Day 4 of treatment and resolved one day prior to study drug completion (Day 7). Hence, this reviewer disagrees with the investigator's assessment of no relationship between the AE onset and receipt of study drug, as it is conceivable that while on this drug a subject could develop paresthesias given the well-known side effect profile of FQs.

- **Subject 303/840-307-3592:** A 58 year old man with a history of hypertension was treated with delafloxacin for a left face cellulitis. He developed paresthesias on Study Day 30 after delafloxacin had been completed.

Medical Reviewer's Comments:

The onset of the AESI in question (PT: paresthesia) occurred 15 days post delafloxacin treatment and resolved 41 days post treatment. This reviewer agrees with the investigator's assessment that "the events were not reasonably temporally associated with study treatment administration."

Clinical Review
 Caroline J. Jjingo, MD, MPH
 NDA 208,610 and NDA 208,611
 BAXDELA™ (delafloxacin meglumine)

Table 75: Peripheral Neuropathy Related Treatment Emergent Adverse Events

USU BID	AGE	SEX	PERTINENT MEDICAL HISTORY	TYPE of INFECTI ON/SITE	TREATMENT ARM	Treatment Start Date	Treatment Stop Date	AE Start Date/ Day of Study	AE End Date/ Day of Study	Adverse Event Term	SAE	Severity	Outcome	Causality
PERIPHERAL NEUROPATHY														
MEL 303- 100- 433- 3906	64	F	Hypertension; Colon Cancer Chronic diarrhea	Cellulitis/ Erysipelas Left Leg	Delafloxacin	20 November 2015 (1)	30 November 2015 (11)	21 November 2015 (2)	Unknown	Paresthesia (tingling in the toes)	No	Mild	Recovered/ Resolved	Possible
MEL 303- 840- 307- 3592	58	M	Hypertension	Cellulitis/ Erysipelas Left face	Delafloxacin	18 August 2015 (1)	31 August 2015 (14)	16 September 2015 (30)	27 September 2015 (41)	Paresthesia	No	Mild	Recovered/ Resolved	Unrelated
MEL 302- 840- 004- 0140	43	F	Asthma, GERD, Rheumatoid Arthritis; hypokalemia; Hypertension	Wound Infection Right Leg secondary to bug/spider bite	Delafloxacin	25 July 2013 (1)	1 August 2013 (8)	30 July 2013 (6)	Blank	Numbness of Right Forearm	No	Mild	Recovered/ Resolved	Unrelated
								30 July 2013 (6)	Blank	Tingling Right Forearm	No	Mild	Not Recovered/ or Not resolved	Unrelated

Clinical Review
 Caroline J. Jjingo, MD, MPH
 NDA 208,610 and NDA 208,611
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MEL 302- 840- 004- 0160	36	F	IV drug abuse heroin; Smokes meth and cigarettes	Wound Infection Left face secondary to trauma	Delaflo xacin	3 August 2013 (1)	10 August 2013 (8)	6 August 2013 (4)	9 August 2013 (7)	Parast hesia Left Side	No	Mild	Recovered/ Resolved	Unrelated /Possible relationsh ip CJJ(revie wer)
RX3 341- 202- 1100 8- 023	27	M	Eczema (elbows); Psoriasis (shins)	Wound Infection Left Leg	Delaflo xacin	8 June 2011 (1)	13 June 2011 (6)	9 June 2011 (2)	9 June 2011 (2)	Numb ness in finger s, hands and feet	No	Mild	Recovered/ Resolved	Possible

Source: ISS Population. ADSL and ADAE data sets. Table generated by the clinical reviewer using JReview and MAED.

Phase 2 Trials: RX-3341-201 and RX-3341-202

As summarized above in **Table 75**, Subject 202-11008-023, was documented as experiencing a TEAE coded to the PT term hypoesthesia. Additional details are briefly summarized below:

Subject 202-11008-023: A 27 year old male with a history of eczema. He was treated with delafloxacin for a left leg wound infection. Initial onset of hypoesthesia was on Study Day 2 and this AE resolved on the same day. The event was self-limited and required no additional treatment. Concomitant medication included oxycodone. Following resolution of hypoesthesia, the subject had no recurrence of “tingling.” He completed delafloxacin therapy on Study Day 6.

***Medical Reviewer’s Comments:** Upon review of the accompanying narrative, since the onset of the above-described subject’s hypoesthesia begins soon after initiation of delafloxacin combined with the fact that FQs-are associated with peripheral neuropathy, the reviewer cannot exclude the possibility of a relationship between this event and delafloxacin. Although, the details in relation to this TEAE are somewhat limited, this reviewer agrees with investigator’s assessment that this event is “possibly related” to delafloxacin therapy.*

8.5.3 Blood Glucose Disturbances

Although the Applicant’s proposed label contains no information on blood glucose disturbances in Section 5 Warnings and Precautions, blood glucose disturbances are associated with the FQ drug class. Any observed cases of hypoglycemia, hyperglycemia and new onset diabetes AEs which occurred in the pivotal Phase 3 trials are briefly discussed in this section.

Despite being relatively rare events, equal numbers of subjects in both the delafloxacin (8/741; 1.1%) and comparator arms (9/751; 1.2%) experienced blood glucose disturbances which were coded under such PT terms as “hypoglycemia,” “hyperglycemia,” or “new onset diabetes”) during the Applicant’s Phase 3 trials. Among the 10 subjects in the delafloxacin arm found to have blood glucose abnormalities, three were assessed as having events causally linked (possibly and definitely related to study drug) to delafloxacin administration. Two of these events were coded under the PT term “hyperglycemia,” whereas, the latter event was coded under the PT term “hypoglycemia.” All other events were assessed by investigators as being causally unrelated to delafloxacin therapy. There were no reported SAEs or reports of premature discontinuation of delafloxacin due to these hyperglycemic and hypoglycemic episodes. Delafloxacin associated blood glucose events are discussed briefly below:

- **Subject 376-081-0724:** An 89 year old man with multiple medical issues most notably type 2 diabetes and chronic renal failure whose death was discussed earlier in Section 8.4.1. On Study Day 4, this subject developed a hypoglycemic episode with a blood glucose level of 72 mg/dL after receiving 8 units of insulin approximately 4 hours earlier. No action was taken with delafloxacin and the investigator assessed this as a mild intensity event that was unrelated to delafloxacin. The subject subsequently died on Study Day 20 from septic shock. Subject’s death was unrelated to the above-described event.

***Medical Reviewer’s Comments:** This reviewer agrees with the investigator’s assessment of causality as the administration of bedtime insulin in an elderly hospitalized patient was the likely*

precipitating factor of this event. It is also noted that a blood glucose of 72 mg/dL is not consistent with hypoglycemia which is defined as a blood glucose of <70 mg/dL.

- **Subject 302/784-060-0538:** A 58 year old man with a medical history of duodenal ulcers was administered delafloxacin for treatment of a left thorax major cutaneous abscess. Subject's primary concomitant medications included diazepam, ketamine, dextetoprofen tromatol (a non-steroidal pain killer), kedural C (ascorbic acid). His baseline pre-treatment glucose value was 98.0 mg/dL. Subject began treatment with delafloxacin on 23 December 2013 (Study Day 1). On Study Day 3, subject experienced a sharp peak in glucose from a pre-dose level of 76 mg/dL to a glucose of 507 mg/dL two hours post infusion. Serial glucose monitoring was performed. No action was taken with delafloxacin. The investigator's assessment was that this was a severe intensity event that was definitely related to delafloxacin.
- **Subject 302/840-002-0570:** A 57 year old man with a medical history significant for IV heroin abuse, COPD and bipolar disorder was enrolled in Trial 302 for treatment of a right arm cellulitis. He began treatment with delafloxacin on 10 Jan 2014 (Study Day 1) and completed treatment on 16 Jan 2014 (the final day of treatment). His baseline non-fasting glucose level was 92.0 mg/dL (5.11 µmol/L). The subjects experienced a mild AE of hypoglycemia (not reported) shortly prior to delafloxacin infusion. Investigator evaluated hypoglycemic event as "possibly related" to delafloxacin. Delafloxacin therapy was otherwise continued without interruption or discontinuation.
- **Subject 302/840-002-0048:** A 56 year old male IV heroin abuser with HCV and multiple secondary skin infections. Concomitant meds included oxycodone and diamorphine (heroin). He began delafloxacin for a wound infection on 21 May 2013 (Study Day 1) and completed treatment on Study Day 7 (27 May 2013). On Study Day 3 (23 May 2013) of treatment, subject was noted as being hyperglycemic to 145.1 mg/dL (8.05 µmol/L) prior to start of daily infusion. Serial glucose measurements were subsequently recorded. At his FU visit on Study Day 15 (4 Jun 2013), blood glucose level was 132 mg/d (7.33 µmol/L). The investigator evaluated this hyperglycemic episode as a mild intensity event that was "possibly related" to delafloxacin.

Medical Reviewer's Comments:

For the above-mentioned investigator assessed treatment related glycemic events, this reviewer agrees with the investigators' assessment of a possible causal linkage between delafloxacin and the observed toxicity grade 1 hyperglycemic AEs (a glucose of 145.1 mg/dL). However, this reviewer considers this a mild intensity event.

Subject 302/840-012-0281: A 54 year old man with no previous medical history received delafloxacin on 18 September 2013 (Day 1) for a left leg wound infection. His screening non-fasting glucose level was 308.1 mg/dL (17.1 µmol/L) (17 September 2013). On Study Day 3, subject's pre-dose blood glucose was elevated at 230.1 mg/dL

(12.77 µmol/L) peaking at 324.1 mg/dL two hours post infusion. Glucose levels continued to trend downwards. Subject was begun on metformin. Investigator considered this event of new onset Type 2 diabetes mellitus as being unrelated to study drug. The investigator graded this as a moderate severity event.

- **Subject 302/784-063-0708:** A 48 year old man with a past medical history of chronic bronchitis received delafloxacin for a right leg cellulitis/erysipelas. He received treatment from 28 April 2013 (Day 1) through 08 May 2013 (Day 11). Subject's screening /baseline non-fasting glucose was 334.1 mg/dL (18.54 µmol/L). On Study Day 3 (30 April 2013), subject's pre-infusion glucose was 328.1 mg/dL (18.2 µmol/L). His blood glucose continued to rise two hours post infusion peaking to 371 mg/dL (20.6 µmol/L) and gradually declined to 337.1 mg/dL (18.7 µmol/L) 12 hours post infusion. On Study Day 10 (07 May 2014), patient was begun on insulin.

Medical Reviewer's Comments:

It was clear from pre-treatment, baseline non-fasting blood glucose levels that subjects 302/840-012-0281 and 302/784-063-0708 most likely had undiagnosed diabetes prior to study enrollment, although it is unclear whether or not they harbored additional symptoms consistent with this diagnosis. Therefore, this reviewer agrees with the site investigators that delafloxacin was not responsible for these cases of new onset diabetes. The larger question is, in the absence of anti-hyperglycemic agents, does delafloxacin treatment contribute towards the worsening of baseline hyperglycemia. In evaluating 1 and 2 hour post infusion blood glucose levels, it can be argued that this may indeed be the case.

Overall Comments on Dysglycemia: Currently marketed FQs contain the following statement in their Warnings and Precautions section: “[D]isturbances in blood glucose, including symptomatic hyper- and hypoglycemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral anti-hyperglycemic agent or with insulin.” This reviewer would agree with investigators that for subjects with pre-treatment undiagnosed and untreated diabetes, delafloxacin was most likely not a contributor to the observed cases of new onset diabetes. Nevertheless, this reviewer recommends that the Applicant's complete label should alert such individuals that they are potentially at risk for experiencing dysglycemic events, with and possibly without the use of oral anti-hyper hypoglycemic agents or insulin. Otherwise, with the available information presented, it was difficult to fully ascribe a casual association between the event and the drug in several of the above described cases.

Phase 2 Trials: RX-3341-201 and RX-3341-202

There were a total of four glucose related events in the Applicant's two Phase 2 trials: two events were coded to the PT terms “increased blood glucose” and “hypoglycemia” under Protocol 201 and two events coded under the PT term “hyperglycemia” in Protocol 202. There were no cases of dysglycemia in the comparator arm:

Subject RX-202-11008-038: A 57 year white male with a history of heroin abuse and hepatitis (non-typed), and no prior history of diabetes, was treated with delafloxacin for an abdominal wound infection from 02 September 2011 (Study Day 1) through 07 September 2011 (Study Day

6). His baseline screening glucose value was 111.7 mg/dL (6.2 µmol/L). On Study Day 6, the subject was reported as having a non-fasting glucose level of 145 mg/dL (8.1 mmol/L). Concomitant medications at the time of event included: pantoprazole, methadone, and nicotine. Subsequent, non-fasting glucose values ranged from 93.7 mg/dL (5.2 µmol/L) (on Study Day 14 and was reported as resolved on 23 September 2011 (Day 22), with a final value of 97.3 (5.4 mmol/L). The investigator assessed this hyperglycemic event as being “possibly related” to delafloxacin.

Medical Reviewer’s Comments: *A non-fasting glucose value of 145 mg/dL would be consistent with a Grade 1 mild event, according to the DAIDs Toxicity Scale. Given the dearth of information on the portrayed event, this reviewer cannot make a definitive conclusion on the relatedness of this event to the study treatment. However, the reviewer notes, that given the association of several FQ with dysglycemia and the temporal association between the event and the administration of delafloxacin as a possible relationship between the two.*

Subject RX-202-11008-039: A 34 year old white male with a history of depression, headaches, insomnia, Wolff-Parkinson-White syndrome and bipolar disorder received delafloxacin 300-mg IV beginning on 06 September 2011 (Study Day 1) through 11 September 2011 (Study Day 6) for a left leg cellulitis/erysipelas for which he received a total of 9 doses of delafloxacin. According to the narrative, on treatment Day 1, the subject developed a non-serious mild, intensity event coded as hypoglycemia. Concomitant medications at the time of the event included lidocaine. Glucose levels were trended as follows: 109.9 mg/dL on Day 1; 169.4 mg/dL on Day 5, 160.4 mg/dL on Day 15, and 95.5 mg /dL on Day 24. This event resolved without intervention and was assessed by the investigator as “unrelated” to the study drug.

Medical Reviewer’s Comments: *This subject experienced mild to moderate non-fasting glucose elevations, according to the DAIDs toxicity scale. As with the antecedent case, this reviewer believes that an association between the event and the drug cannot be fully excluded given the timing of the event in relation to receipt of the study drug and FQ-class associations with blood glucose dysglycemia, this reviewer disagrees with the investigator and believes that there could be a possible association between the event (hyperglycemia) and receipt of the study drug.*

Subject RX-3341-201-202-0121: A 45 year old white male with a medical history notable only for hypercholesterolemia and a toe fracture was randomized to receive delafloxacin for a right foot wound infection. According to the subject narrative and applicant database, this subject had no known history of diabetes. He began delafloxacin therapy on 21 August 2008 (Study Day 1) and completed therapy on 28 August 2008 (Study Day 8), and received a total of 15 infusions. On Study Day 1, he was documented as having a glucose of 81 mg/dL (45.0 µmol/L) which subsequently rose to 198.0 mg/dL (11.0 µmol/L) by study Day 6.

On 26 August 2008 (Day 6 of study drug), he developed two AEs of special interest (AESI): (a) an increased ALT to 49 IU/L (b) a glucose elevation to 200 mg/dL (baseline value of 81 mg/dL) [AE term: increase glucose]. Episode of hyperglycemia was assessed by the investigator to be of moderate intensity AE for which no action was taken. The investigator assessed AE to be “unrelated” to the study drug. Event was not considered an SAE and the subject was not terminated from the study due to this AE. He experienced a concomitant rise in his ALT levels

from 29 U/L on Day 1 to 49 U/L on Day 6. Although this subject eventually voluntarily withdrew from the study, these events remained ongoing at time of his withdrawal. The investigator assessed the observed LFT elevation to be “possibly related” to delafloxacin; however he assessed the hyperglycemic event to be unrelated to the study drug.

Medical Reviewer’s Comments: *For the reasons cited in the two previous cases, this reviewer cannot exclude the possibility of a causal linkage between the above-described event and delafloxacin therapy.*

Subject RX-3341-201-215-0036: A 33 year old woman who began treatment with delafloxacin for a left arm abscess on 11 July 2008 (Study Day 1) and completed treatment on 17 July 2008 (Study Day 7). Her relevant medical history included hypothyroidism for which she was on levothyroxine and anxiety for which she was on fluoxetine. She had no reported history of diabetes. Her baseline glucose level was 87.0 mg/dL (4.83 µmol/L). On Day 6 (16 July 2008) of therapy, she was documented as having a hypoglycemic episode of 45.9 mg/dL (2.55 µmol/L). Subject, simultaneously, reported an AE coded to the PT term “decreased appetite” from 16 Jul-04 2008 through 04 August 2008 (Study Day 25). According to the narrative, no intervention was pursued and the event resolved on 18 July 2008 (Day 8), with a documented glucose of 101.1 mg/dL (5.61 µmol/L). The investigator assessed this event as being unrelated to delafloxacin.

Medical Reviewer’s Comments: *The investigator provided a credible alternative explanation (decreased appetite) to account for the above-described hypoglycemic event. This reviewer agrees with the investigator’s assessment.*

8.5.4 Central Nervous System (CNS) Effects

The Applicant has provided language in their proposed label addressing FQ-associated CNS effects. Their label states:

- “Fluoroquinolones have been associated with an increased risk of CNS reactions, including: convulsions and increased intracranial pressure (including pseudotumor cerebri) and toxic psychosis. Fluoroquinolones may also cause CNS reactions of nervousness, agitation, insomnia, anxiety, nightmares, paranoia, dizziness, confusion, tremors, hallucinations, depression, and suicidal thoughts or acts.”

Collectively, CNS effects is a broad category and therefore, the reviewer discussed CNS effects pertaining to the Psychiatric Disorders SOC (i.e., depression, suicidal ideation, anxiety etc) separately from other PTs relevant to this category.

Dizziness

A total of 12 (1.6%) subjects in the delafloxacin arm of the Phase 3 pivotal trials and 9 subjects (1.2%) in the comparator arm endorsed the PT term dizziness. Of the 12 subjects in the pooled delafloxacin arm who experienced dizziness, only four subjects were assessed by the investigator as being “possibly related” to delafloxacin. All other AEs were deemed unrelated to the study drug. There were no SAEs coded to this term. All AEs were graded as

either moderate or severe in intensity. No subjects were withdrawn from the delafloxacin arm due to dizziness, however, a single subject whose dizziness was assessed as a moderate intensity event and “possibly related,” delafloxacin was temporarily interrupted.

In comparison, five of the nine subjects in the pooled comparator arm experienced dizziness which was assessed as “possibly related” to vancomycin. All subjects with dizziness in the pooled vancomycin arm were graded as mild to moderate in intensity. There were neither any drug withdrawals nor discontinuations.

Convulsions

Protocol Phase 3

No subjects in the Phase 3 pooled delafloxacin arm experienced a convulsion or seizure; whereas a single subject in the comparator arm had a convulsion which resulted in withdrawal of the study drug.

Disturbance in Consciousness: Loss of Consciousness

Phase 3 Trials: RX-3341-302 and RX-3341-303

Three of 741 (3/741;1.4%) delafloxacin-treated subjects in the combined pivotal Phase 3 protocols experienced events coded to the PT terms syncope (2 subjects) and presyncope (1 subject), whereas, a single subject in the comparator arm experienced an event coded to the PT term loss of consciousness.

Phase 2 Trials: RX-3341-201 and RX-3341-202

A single subject in both of the Phase 2 trials experienced a syncopal episode.

Table 76 below describes these events.

Syncope/Pre-syncope/Seizure

Table 1: Syncope, Pre-Syncope and Loss of Consciousness Related Adverse Events

USUBID	AGE	SEX	Pertinent Medical History	Type of Infection/ Site	TREATMENT ARM	Treatment Start Date	AE Start Date/ Day of Study	AE End Date/ Day of Treatment	Adverse Event Term	Other Adverse Events	SAE	Severity	Outcome	Investigator Assessed Causality
302/840-002-0008	62	M	Hypertension	Major Cutaneous Abscess/	Delafloxacin	April 30 2013 (Day 1)	May 5 2013 (Day 6)	May 5 2013 (Day 6)	Syncope	None	No	Moderate	Resolved	Unrelated
303/840-302-3210	40	M	Heroin Abuse	Wound Infection/ Left leg	Delafloxacin	January 29 2015 (Day 1)	February 3 2015/ Day 6	February 3 2015/ Day 6	Syncope	Infection Site Extravasation	No	Mild	Resolved	Unrelated
303/840-307-3023	23	M	Attention Deficit Disorder; Tobacco Disorder	Cellulitis/ Erysipelas	Delafloxacin	July 23 2014 (Day 1)	July 23 2014 (Day 1)	July 24 2014 (Day 2)	Presyncope	Chills, Hyperhidrosis, nausea, vomiting, pyrexia	No	Mild	Resolved	Unrelated
303/840-322-3188	52	M	Heroin Abuse IV; Hepatitis C Virus; COPD/emphysema; Hypertension	Major Cutaneous Abscess/	Delafloxacin	January 8 2015 (Day 1)	January 12 2015 (Day 5)	January 12 2015 (Day 5)	Presyncope	Infection Site Extravasation	No	Mild	Resolved	Possibly Related

303/840-302-3099	28	M	Hepatitis C Virus; Heroin Abuse	Wound Infection/ Right arm	Vanco mycin (± Aztreo nam)	November 12 2014 (Day 1)	November 14 2014 (Day 3)	November 14 2014 (Day 3)	Loss of Consciousness (LOC)	Seizure (in setting of LOC)	No	Mild	Resolved	Possibly Related
202/11023-004	36	F	None	Major cutaneous abscess/ Left leg	Delafloxacin	June 17 2011 (Day 1)	June 18 2011/ Day 2	June 18 2011/ Day 2	Syncope	Convulsion (resulting from syncope event)	No	Mild	Resolved	Unrelated

SEIZURES

RX334	2	M	Seizure Disorder; IV drug abuse; Anxiety; Insomnia	Wound Infection Right arm	Delafloxacin	(1)	(6)	(36)	(37)	(b)(6)	Seizure	Yes	Severe	Recovered/ Resolved	Unrelated
1-202-11008-022	3	M	Seizures; HCV; Pain med addiction; Seizure (not dx'd until Day 3)	Cellulitis/ Erysipelas Left Leg	Delafloxacin	(1)	(7)	(8)	(9)	(b)(6)	Seizure	Yes	Mild	Recovered/ Resolved	Unrelated
RX334	4	M	HCV; Pain med addiction; Seizure (not dx'd until Day 3)	Abscess/ Left Chest	Delafloxacin 450-mg	(1)	(8)	(8)	(8)	(b)(6)	Convulsion; hypokalemia	Yes	Severe	Recovered/ Resolved	Possibly related

Psychiatric disorders—Anxiety, Hallucinations and Paranoia

In the Applicant's pivotal Phase 3 trials, there were substantial numbers of subjects with documented histories of baseline mental illness, including anxiety or depression, and/or substance abuse. Although few (8/741; 1.1%), near equal numbers of subjects in the Phase 3 pooled delafloxacin treatment arm experienced TEAEs coded under the PT term anxiety when compared to their counterparts in the vancomycin comparator group (5/751; 0.7%) in the pooled vancomycin arm. There were no anxiety related SAEs in either study arm. All AEs coded to the anxiety PT were determined by the investigator to be unrelated to either of the two study drugs. Irrespective of study arm, all anxiety AEs were assessed as either mild or moderate in severity. There was one subject in the delafloxacin arm with an unrelated, moderate severity, non-SAE anxiety event whose treatment was interrupted, but not withdrawn. This same subject (Subject 303/840-305-3208), who had a known history of anxiety and HCV as well as alcohol and IVDA, experienced two AEs coded under PT terms—*anxiety* and *psychomotor hyperactivity* (under the nervous system SOC). A single subject (Subject 302/840-014-0324) with a reported history of HCV, opioid dependence and anxiety endorsed PT terms coded to *anxiety* and another coded to *hallucinations*, the latter being assessed by the investigator as a moderate intensity event that was considered possibly related to delafloxacin therapy.

In the vancomycin arm, in addition to the 5 subjects who were coded to the PT term *anxiety*, there were two other subjects who were coded as having *agitation* and *affect lability*, respectively. The subject experiencing *agitation*, had a history of depression and IV heroin abuse, and was withdrawn from the study. Otherwise, no other subjects with *anxiety* in the vancomycin comparator arm had treatment interruptions or withdrawals.

One subject (Subject 302/840-001-0018) in the pooled Phase 3 delafloxacin arm was coded under the PT term *paranoia* for an event which resulted in delafloxacin being interrupted but not withdrawn. This subject had a history of multiple addictions, including heroin, methamphetamine, and alcohol. The event in question was graded as mild, assessed by the investigator as unrelated to delafloxacin, and was not an SAE. No other subjects in either treatment arm were documented as experiencing *paranoia*.

Psychiatric disorders—Depression/Suicidal Ideation

Few subjects in either arm experienced treatment related episodes of depression and/or suicidal ideation/actions. A single subject (1/741; 0.1%) (Subject 302/840-014-0684), in the pooled delafloxacin arm (treated from (b)(6)), who had a history of IV heroin abuse and HCV, experienced multiple AEs coded to three distinct PT terms: "*substance (heroin)-induced mood disorder*" ((b)(6)), which required an initial, 72-hour involuntary psychiatric hospitalization for "*depressed behavior and suicidal ideation*;" a second event coded as *major depression* ((b)(6)) required a second hospitalization; and a third event coded to the PT term *depression* ((b)(6)) required a hospitalization for opiate withdrawal and for suicidal statements. All events were assessed by the investigator as severe intensity SAEs which were unrelated to delafloxacin treatment.

Only two subjects (0.3%; 2/751) in the vancomycin arm experienced depressive related events (PT: depressed mood and suicidal ideation). While both of these events were assessed by their investigators as being unrelated to the study drug, the suicidal ideation event, occurred in a subject with a history of intermittent drug abuse, and was graded as a severe SAE.

Sleep Disturbances—Insomnia, Hypersomnolence, Abnormal Dreams

There were very few subjects in the Phase 3 pivotal trials who experienced sleep related disturbances. There were a total of 9 subjects: 6 (0.8%; 6/741) in the pooled delafloxacin arm and 3 (0.4%; 3/751) in the pooled vancomycin arm with AEs coded to the PT term insomnia. In most cases, these subjects endorsed a history of underlying medical illness (i.e. Alzheimer’s disease), mental illness (i.e. anxiety and/or depression), drug addiction (i.e. heroin and/or methamphetamine addiction), or insomnia. All events coded under this PT were investigator assessed as mild, unrelated, non-SAEs which required no drug interruptions or treatment withdrawals of subjects in either treatment arm.

Two subjects were coded to the PT phrase “abnormal dreams,” one in each of the two treatment arms. The subject in the delafloxacin arm (Subject 303/840-302-3149) had a history of anxiety, depression, IV heroin use and methamphetamine use and was assessed by the investigator as having a mild, non-SAE event that was unrelated to delafloxacin therapy and did not result in study drug withdrawal or interruption. Likewise, the subject in the vancomycin arm (Subject 302/840-014-0559) experiencing “abnormal dreams,” had a history of heroin addiction but also had a history of both insomnia and HCV.

Under the Nervous System Disorders, two subjects in the delafloxacin arm, sustained events coded to somnolence (Subject 303/840-328-3813) and hypersomnia (Subject 303/840-328-3509). Both of these subjects had substance abuse issues with IV heroin and crystal methamphetamine. Neither of these events was assessed as being related to delafloxacin or required any action to be taken with the study drug. Both events were considered mild and were not SAE.

8.5.5 Hypersensitivity Reactions

As with other FQs, SECTION 5. ^(b)₍₄₎ of the proposed delafloxacin label contains the following warning:

“Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving fluoroquinolone antibacterial drugs.”

To evaluate rates of hypersensitivity events in Protocols 302 and 303, this reviewer conducted MAED CMQs and SMQs and analyzed HLT and PT terms under the MedDRA Immune System Disorders SOC. . The reviewer read through available subject narratives and identified key PT terms which were assessed for causal and temporal linkages between the study drug and the reported AE. The following PT terms were considered under the Immune System Disorders SOC: dermatitis; allergic; dermatitis, atopic; dermatitis, contact; dermatitis; drug

hypersensitivity; hypersensitivity; swelling face (HLT: angioedemas); and urticaria. Overall, the incidence of hypersensitivity reactions across treatment arms was slightly more common with subjects in the vancomycin comparator arm than with those in the delafloxacin arm, irrespective of investigator assessed causality. A total of two delafloxacin subjects (2/741; 0.3%) had hypersensitivity reactions, and in each of these subjects the study drug was withdrawn. While none of these events were SAEs, two were graded as moderate in severity and one event was graded as severe. Likewise in the vancomycin arm, a total of six subjects developed six TEAEs coded as “hypersensitivity”. Two of these subjects were withdrawn from study treatment. Two events were graded as moderate intensity events, whereas the other was mild. All but one TEAE were assessed by the study investigators as being related to the study drug.

Six (0.8%) and nine (1.2%) subjects in the delafloxacin and vancomycin comparator arms, respectively, developed urticaria during the Phase 3 trials. The study drug was withdrawn from two of the six subjects in the delafloxacin arm due to the observed urticarial reactions. One subject was evaluated as having an SAE and severe intensity event in this setting. Five of the nine subjects in the vancomycin comparator arm with urticarial reactions were withdrawn from the study treatment and one had a treatment interruption.

Equal numbers of subjects in both treatment arms sustained either an allergic dermatitis, an atopic dermatitis, a contact dermatitis or a dermatitis. The seven subjects in the delafloxacin arm who had either a dermatitis or a contact dermatitis had these events assessed by the study investigator as being unrelated to delafloxacin arm. The one subject in the delafloxacin arm coded as having an allergic dermatitis related to the study drug was withdrawn from the study drug. Likewise, eight subjects in the vancomycin arm had TEAEs coded as a dermatitis or some variant of dermatitis. No subjects experiencing a dermatitis in the vancomycin arm was withdrawn from treatment and most of these events were assessed as being either mild or moderate in severity and unrelated to the study drug. **Table 77** below summarizes all immune and hypersensitivity reactions.

Dictionary Derived Term	Serious Event	Analysis Causality	Action Taken with Study Treatment	Severity Intensity	Delafloxacin	Vancomycin (± Aztreonam)
Hypersensitivity	No	Related	Drug Withdrawn	Moderate	1 (0.13%)	1 (0.13%)
Hypersensitivity	No	Related	Drug Withdrawn	Severe	1 (0.13%)	0 (0.00%)
Hypersensitivity	No	Related	Not Applicable	Moderate	1 (0.13%)	0 (0.00%)
Drug Eruption	No	Related	Not Applicable	Mild	1 (0.13%)	0 (0.00%)
Urticaria	Yes	Related	Drug Withdrawn	Severe	1 (0.13%)	0 (0.00%)
Urticaria	No	Related	Drug Withdrawn	Moderate	1 (0.13%)	4 (0.53%)

Urticaria	No	Related	Not Applicable	Mild	1 (0.13%)	0 (0.00%)
Urticaria	No	Related	Not Applicable	Moderate	1 (0.13%)	2 (0.27%)
Dermatitis Allergic	No	Related	Drug Withdrawn	Moderate	1 (0.13%)	0 (0.00%)
Dermatitis Allergic	No	Related	Not Applicable	Mild	0 (0.00%)	1 (0.13%)
Dermatitis Atopic	No	Related	Not Applicable	Mild	0 (0.00%)	1 (0.13%)
Hypersensitivity	No	Related	Drug Withdrawn	Mild	0 (0.00%)	1 (0.13%)
Hypersensitivity	No	Related	Not Applicable	Mild	0 (0.00%)	2 (0.27%)
Urticaria	No	Related	Drug Interrupted	Mild	0 (0.00%)	1 (0.13%)
Urticaria	No	Related	Drug Withdrawn	Mild	0 (0.00%)	1 (0.13%)
Unrelated						
Dermatitis Contact	No	Unrelated	Not Applicable	Mild	4 (0.54%)	3 (0.40%)
Dermatitis	No	Unrelated	Not Applicable	Mild	3 (0.40%)	0 (0.00%)
Urticaria	No	Unrelated	Not Applicable	Mild	2 (0.27%)	1 (0.13%)
Swelling Face	No	Unrelated	Not Applicable	Mild	1 (0.13%)	0 (0.00%)
Dermatitis	Yes	Unrelated	Not Applicable	Moderate	0 (0.00%)	1 (0.13%)
Dermatitis Allergic	No	Unrelated	Not Applicable	Moderate	0 (0.00%)	1 (0.13%)
Dermatitis Atopic	No	Unrelated	Not Applicable	Mild	0 (0.00%)	1 (0.13%)
Drug Hypersensitivity	No	Unrelated	Not Applicable	Moderate	0 (0.00%)	1 (0.13%)
				Subjects(filtered)	17 (2.29%)	22 (2.93%)
				1stCollItemSubjects	741 (100.00%)	751 (100.00%)
<i>Source: ISS Population. ADSL and ADAE data sets. Generated by the clinical reviewer with JReview.</i>						

The following PT terms were assessed under the Skin and Subcutaneous Tissue Disorders SOC: pruritus; pruritus, generalized; drug eruption; rash; rash erythematous; rash macular; rash macular popular; rash papular; and rash vesicular. A total of 9 of 741 subjects (9/741; 1.2%) in the delafloxacin arm were reported as having a rash; whereas, 16 of 751 subjects (16/751; 2.1%) in the vancomycin comparator arm developed a rash. As to be expected, a substantial number of subjects in the vancomycin arm, 39 of 751 (39/751; 5.2%) developed pruritus (coded as either pruritus or generalized pruritus); whereas 11 of 741 subjects (11/741; 1.5%) in the delafloxacin arm developed pruritus.

Overall Assessment: As noted previously, there was considerable splitting of TEAE PT terms. Potential hypersensitivity reactions were notably split across the Immune System SOC and Skin and Subcutaneous Tissue Disorder SOCs under various PT terms as explained above. This masks the numbers of TEAEs related to such PT terms as dermatitis, hypersensitivity, rash, and pruritus. (b) (4)

(b) (4)
Overall, the majority of immune and skin disorder TEAEs occurred in the vancomycin arm as opposed to in the delafloxacin arm. While there were no observed cases of anaphylaxis in either of the pivotal Phase 3 trials, there was a single subject in the delafloxacin arm (Subject 303/840-307-3050) who was reported as having “facial swelling” under the HLT angioedema and a separate event of “contact dermatitis” however, the former event was considered by the site investigator to be unrelated to delafloxacin and instead was attributed to his “living conditions.”

8.5.6 Prolongation of the QT Interval

Baseline EKGs alone were obtained for all subjects and were to be repeated in the setting of clinically significant findings. The Applicant reported that “no follow-up EKGs were performed for cause.” There were no cases of QT interval prolongation in the Phase 3 pivotal trials.

8.5.7 *Clostridium difficile*-Associated Diarrhea

A single case of *Clostridium difficile* infection (Subject 303/840-363-3931) occurred in the Phase 3 ISS population. The event occurred in a 56 year old man with a left face cellulitis who received a 10 day course of delafloxacin from 30 November 2015 (Study Day 1) through 09 December 2015 (Study Day 10). The subject was confirmed *C. difficile* positive 12 days post-therapy. This single case of *C. difficile* infection was assessed by the study investigator as mild in severity and “probably related” to the study drug. It was not considered an SAE. There were no cases of *C. difficile* in the vancomycin arm.

Phase 2 Trials: RX-3341-201 and RX-3341-202

There was a single case of *Clostridium difficile* colitis reported in the Phase 2 trials. There were no cases of *Clostridium difficile* colitis in any of the comparator arm. The event occurred in Protocol 201 and is described as follows:

Subject 201-203-0030: An 83 year old white female with a relevant past medical history of breast cancer, hypertension, glaucoma, hyperglycemia, hypothyroidism for which she was on several concomitant medications, including human insulin, for the treatment of these various conditions. The day prior to the start of delafloxacin, she had been on several other antibiotics including Augmentin 875-mg, amoxicillin 500-mg, and ceftriaxone. The subject was begun on delafloxacin 300-mg IV on 10 July 2008 (Day 1) and completed treatment on 21 July 2008 (Day 12) for a total of 22 infusions of delafloxacin. Sixteen days after her final dose of delafloxacin, the subject was reported as developing *Clostridium difficile* colitis. According to the accompanying narrative, “treatment was not given for the event,” “no action was taken with the study drug due to the event.” The event was reported as being resolved on study Day 39 (17 August 2008). The event was assessed by the study investigator as being “possibly related” to the study drug.

Medical Reviewer’s Comments: Section 5 “Warnings and Precautions” of currently marketed FQs warn that FQs have been reported to predispose individuals to *Clostridium difficile*-Associate diarrhea

(CDAD). This subject had several risk factors predisposing her to the development of CDAD, namely age, multiple co-morbid conditions, and receipt of antimicrobial agents associated with CDAD including Augmentin, amoxicillin and delafloxacin. This reviewer agrees that a causal link may exist between delafloxacin and the above-described episode of CDAD.

8.5.8 Photosensitivity/Phototoxicity Reaction

There were no photosensitivity or phototoxicity TEAEs in the pivotal Phase 3 trials.

Phase 2 Protocols

There were no described photosensitivity/phototoxicity reactions in Protocol 202. A single photosensitivity event occurred in Protocol 201 and is described below.

- RX-3341-201-215-0005 (Delafloxacin):** This is the case of a 57 year old construction contractor who received delafloxacin, from 05 July 2008 (Day 1) to 13 July 2008 (Day 9), a total of 17 infusions, for the treatment of a right axilla abscess. Pertinent medical history included diabetes mellitus and obesity. Prior to receipt of delafloxacin, the subject received doxycycline. His concomitant medications included insulin, vicodin, cyclobenzaprine and naproxen. The subject experienced the first of two AEs on Study Day 3 of treatment, a self-limited episode of contact dermatitis secondary to adhesive tape. However, on Study Day 20 (24 July 2008), 11 days after the completion of delafloxacin, the subject developed a photosensitivity reaction described by the investigator as “sun poison on face and lips.” The event was assessed by the investigator as being unrelated to delafloxacin and of moderate severity intensity. The event was still ongoing on 31 July 2008 at the test of cure visit.

Medical Reviewer’s Comment: Details of this AE are limited. The described subject works in construction field and presumably was exposed to significant sunlight given his line of work, particularly during the summer, when the above-described event occurred. With regards to temporality, this reaction occurred 11 days post-treatment, making the association between this event and the drug less likely.

8.5.9 Renal Treatment Emergent Adverse Events

Renal impairment/failure was an AE of special interest, particularly since the Applicant is proposing dosing adjustments for patients with Stage 4 ^{(b)(4)} kidney disease. By creating MAED CMQs and SMQs and by analyzing renal events at the SOC and PT terms, this reviewer found three subjects in the delafloxacin arm coded under the PT terms “Renal failure,” “Renal failure acute” and “Renal impairment.” There were more AEs coded to these PT terms in the vancomycin arm than in the delafloxacin arm. **Table 78** below provides a comparison of renal events by treatment arm.

Table 78: Treatment Emergent Renal Adverse Events

Primary System Organ Class	Serious Event	Investigator Analysis of Causality	Severity Intensity	Action Taken with Study Treatment	Delafloxacin 300-mg IV – 450-mg by mouth Q12H N=417	Delafloxacin 300 mg IV Q12H N=324	Vancomycin (±Aztreonam) N=751
Renal and Urinary Disorders							
Renal Failure, Acute	No	Related	Moderate	No Action	1 (0.1%)	0 (0.0%)	1 (0.1%)

				Taken			
	No	Unrelated	Moderate	No Action Taken	0 (0.0%)	0 (0.0%)	3 (0.4%)
	Yes	Related	Severe	Drug Withdrawn	0 (0.0%)	0 (0.0%)	1 (0.1%)
	No	Unrelated	Moderate	Drug Interrupted	0 (0.0%)	0 (0.0%)	1 (0.1%)
	No	Related	Mild	No Action Taken	0 (0.0%)	0 (0.0%)	1 (0.1%)
	No	Related	Mild	No Action Taken	1 (0.1%)	0 (0.0%)	1 (0.1%)
	Yes	Related	Severe	No Action Taken	0 (0.0%)	0 (0.0%)	1 (0.1%)
	Yes	Related	Moderate	No Action Taken	0 (0.0%)	0 (0.0%)	1 (0.1%)
	No	Unrelated	Mild	No Action Taken	0 (0.0%)	0 (0.0%)	1 (0.1%)
	No	Related	Moderate	No Action Taken	0 (0.0%)	1 (0.1%)	0 (0.0%)
# of SUBJECTS					2 (0.3%)	1 (0.1%)	11 (1.46%)
TOTAL # of SUBJECTS (SAFETY DENOMINATOR)					741 (100.0%)		751 (100.0%)
<i>Source: ISS Population. ADSL and ADAE data sets. Table generated by the clinical reviewer using JReview and MAED.</i>							

Subject 303/100-435-3891 (Delafloxacin): A 79 year old Bulgarian woman with a history of hypertension, coronary artery disease, and obesity (BMI=31.1) who was treated with delafloxacin for a left leg cellulitis. Pertinent concomitant medications at first dose of delafloxacin included isosorbide dinitrate, valsartan, nadroparin (anticoagulant/ low molecular weight heparin), and verapamil. Her baseline Cr was 1.0 mg/dL and her baseline eGFR and CrCl were 53 mL/min/1.73 m² and 50 min/mL, respectively, corresponding with moderate renal impairment (Stage 3 CKD; moderate). Delafloxacin therapy began on (b) (6) (Study Day 1) and ended on (b) (6) (Study Day 12), for a total of 23 doses. On (b) (6)

(b) (6) (Day 7), subject was observed to have a drop in her CrCl to 39 mL/min and an increase in her Cr to 1.30 (115 µmol/L). Her kidney function continued to worsen through Study Day 15, 3 days post-therapy, with her CrCl and Cr recorded as, 32 mL/min and 1.60 mg/dL, respectively. She was treated with sodium chloride and furosemide. This event was graded as a mild in intensity and possibly related to delafloxacin given the timing of the event and delafloxacin exposure.

Medical Reviewer's Comments: *The reviewer agrees with the investigator's causality assessment. However, it is dually noted that this subject is older with several co-morbid conditions and with a history of polypharmacy all of which make her particularly sensitive to any changes to Cr and renal function.*

Subject 303/604-408-3288 (Delafloxacin): A 52 year old Peruvian woman with a history of hypertension, subclinical hypothyroidism/hyperthyroidism, patent ductus arteriosus, and anxiety/depression. Pertinent concomitant medications included: amlodipine, captopril, enalapril, metamizole, tramadol, clonazepam, heparin, propranolol, and fluoxetine. Her baseline Cr, eGFR, and CrCl were 0.3 mg/dL, 233 mL/min/1.73 m², and 291 mL/min, respectively. She began treatment with delafloxacin for a right leg cellulitis on (b) (6) (Study Day 1) through (b) (6) (Study Day 13) and received a total of 24 doses of delafloxacin over a 13 day treatment period. On (b) (6) (Day 16) she developed what was coded as “acute renal failure” with a reported Cr of 0.50 mg/dL (44 µmol/L) and CrCl of 153 mL/min. She was also observed to have an exacerbation of her hypertension on (b) (6) (Study Day 6) through (b) (6) (Study Day 19) of the study, for which she was treated with propranolol, captopril, metamizole, sodium chloride, sodium bicarbonate and amlodipine. The acute renal failure event resolved on (b) (6) (Day 24). On (b) (6) (Study Day 28), subject was prematurely discontinued from the study due to a lack of efficacy.

The investigator considered the episode of acute renal failure to be “possibly” related to the delafloxacin due to a temporal association between the drug and the onset of this TEAE.

Medical Reviewer's Comments: *While this reviewer agrees that there is potentially a causal linkage between the study drug and the subject's slight worsening of renal function, there are several other features of this narrative that can confound this picture, such as an exacerbation of her hypertension and the addition of such concomitant medications as captopril. In the absence of full details, it is plausible that a constellation of events, including treatment with delafloxacin could have contributed to this event. However, it is also this reviewer's opinion that based on the (CrCl of ≥90 mL/min) there is not a significant insult to the subject's renal function.*

Subject 302/840-011-0167 (Delafloxacin): A 51 year white Hispanic American female with diabetes mellitus type 2, IV heroin abuse, and HCV. Pertinent concomitant medications included glipizide, insulin glargine, diamorphine (heroin). She began delafloxacin therapy for a major cutaneous abscess on 08 August 2013 (Day 1) through 12 August 2013 (Day 5). Her baseline Cr value was 0.6 mg/dL, with an eGFR and CrCl of 105 mL/min/1.73 m² and 74 mL/min, respectively. By Day 4/5 her Cr had increased to 0.80 mg/dL (71 µmol/L) and her CrCl had declined to 56 mL/min (eGFR 76 mL/min/1.73 m²). By study Day 19 (15 days post-treatment), her Cr had rose to 1.9 mg/dL (168 µmol/L) and her CrCl had further declined to 23 mL/min

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(eGFR of 28 mL/min/1.73 m²). There was no accompanying subject narrative for this subject, hence additional details are lacking.

Medical Reviewer's Comments: In the absence of additional information this reviewer cannot definitely state that there is a causal relationship between the event and delafloxacin exposure. However, what is apparent is that an observed decline in subject's CrCl occurred while she was still on therapy.

Overall compared with the comparator, delafloxacin had few renal related AEs. Among those subjects who experienced renal failure/impairment they were older and most importantly had comorbidities known to affect the kidneys (i.e., diabetes, HTN, heroin), hence Cr and eGFR should be closely monitoring during the duration of delafloxacin therapy in such subjects.

8.5.10 Infusion Site Reactions

This reviewer observed considerable splitting of multiple PT terms coded to the high level term infusion site reactions. **Table 79** provides a listing of all TEAEs subsumed under the infusion site reactions category.

Table 79: Infusion Site Reaction Related Adverse Events				
INFUSION SITE REACTIONS			Delafloxacin N=741	Vancomycin (± Aztreonam) N=751
Primary System Organ Class	High Level Term	Dictionary Derived Term	Pooled Site Reactions	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ADMINISTRATION SITE REACTIONS NEC	ADMINISTRATION SITE PAIN	0 (0.0%)	1 (0.1%)
	IMPLANT AND CATHETER SITE REACTIONS	CATHETER SITE PAIN	1 (0.1%)	2 (0.3%)

		CATHETER SITE BRUISE	0 (0.0%)	1 (0.1%)
	INFUSION SITE REACTIONS	INFUSION SITE PAIN	9 (1.2%)	10 (1.3%)
		INFUSION SITE ERYTHEMA	3 (0.4%)	5 (0.7%)
		INFUSION SITE SWELLING	5 (0.7%)	5 (0.7%)
		INFUSION SITE THROMBOSIS	3 (0.4%)	0 (0.0%)
		INFUSION SITE IRRITATION	0 (0.0%)	1 (0.1%)
		INFUSION SITE DISCOMFORT	1 (0.1%)	0 (0.0%)
		INFUSION SITE PHLEBITIS	5 (0.7%)	5 (0.7%)
		INFUSION SITE EXTRAVASATION	41 (5.5%)	54 (7.2%)
		INFUSION SITE OEDEMA	0 (0.0%)	1 (0.1%)
	INJECTION SITE REACTIONS	INJECTION SITE SWELLING	2 (0.3%)	0 (0.00%)
		# of Subjects(filtered)	63 (8.5%)	74 (9.9%)
		DENOMINATOR	741 (100.00%)	751 (100.00%)

Source: ISS Population. ADAE data sets. Table generated by the clinical reviewer using JReview.

Medical Reviewer’s Comments: Infusion site reactions, largely driven by infusion site extravasation, were noted in near equal numbers in both treatment arms. As substantial numbers of subjects in the Phase 3 trials were IV drug abusers many subjects experienced infusion site extravasation secondary to poor venous access. However, even when excluding the PT term infusion site extravasation >3% of subjects in each treatment arm had infusion site reactions coded to such PT terms as infusion site pain, infusion site bruising, infusion site erythema, and other PT terms as highlighted in the table above. The finding of infusion site reactions in human studies is quite similar to the experience found in animal studies, where venous irritation was observed in near equal numbers in the delafloxacin treated animals (rats and dogs) and vehicle treated animals. This could quite possibly be due to the vehicle SBEβCD which is contained in delafloxacin.

8.5.11 Cardiac Disorders—Bradycardia and Tachycardia

FQ-reported cardiac events were discussed during the 2015 FDA advisory committee on FQ safety. Therefore, this reviewer investigated the number of cardiac related PT events identified in the pivotal Phase 3 trials. A total of five subjects (5/741; 0.7%) in the delafloxacin arm and six subjects (6/751; 0.8%) in the delafloxacin arm had cardiac/heart rate related TEAEs coded under the Cardiac disorders SOC. A table briefly summarizing all delafloxacin subjects with reported cardiac related TEAEs is found below.

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Table 80: Treatment Emergent Renal Adverse Events

Primary System Organ Class	Dictionary Derived Term	Unique Subject Identifier	Age	Sex	Medical History	Serious Event	Severity Intensity	Outcome of Adverse Event	Causality	Date of First Exposure to Treatment	Start Date Time of Adverse Event	Datetime of Last Exposure to Treatment
CARDIA C DISORD ERS	Bradycardia	MEL303/ 152-394- 3228	61	M	No medical history	N	Mild	Recovered/Resolved	Possible	2015-02-10	2015-02-13	2015-02-16
	Palpitations	MEL303/ 840-327- 3667	41	M	Diabetes mellitus; Obesity	N	Moderate	Recovered/Resolved	Related	2015-09-02	2015-09-02	2015-09-15
	Sinus Tachycardia	RIBX302/ 840-001- 0100	30	M	Anxiety; Depression	N	Mild	Recovered/Resolved	Unrelated	2013-06-27	2013-07-01	2013-07-04
	Sinus Tachycardia	RIBX302/ 840-001- 0102	56	F	Anxiety; Asthma; COPD- Emphysema; Depression; Migraines Headaches; R shoulder tendinitis	N	Mild	Recovered/Resolved	Possible	2013-07-01	2013-07-05	2013-07-06
	Sinus Tachycardia	MEL303/ 840-302- 3113	57	F	Anemia; Depression; GERD; Hepatitis C; IVDA	N	Mild	Unknown	Unrelated	2014-11-21	2014-11-27	2014-11-26

Medical Reviewer's Comments: *All cardiac related events were assessed by study investigators as mild in severity and in most instances unrelated to delafloxacin. Only one subject who experienced a TEAE coded under the PT term "palpitations" was assessed as having a moderate severity event. None of the above-listed cardiac events were SAEs. Of all the subjects identified as having tachycardia, only Subject 302/840-014-0684 was recorded as having HRs consistent with tachycardia: a HR of 112 beats per minute at the EOT visit on Day 5 and a HR of 113 beats per minute at the LFU visit on Day 30. In this reviewer's estimation, all other subjects had no investigator documented evidence of tachycardia, defined by this reviewer as HRs >100 beats per minute. Subject 303/152-394-3228 was observed to have temporally associated bradycardia of 55 and 52 beats per minute, respectively, at the Day 5 and EOT visits. Based on the limited information, it is difficult to assess the relatedness of the events to the delafloxacin.*

Several cardiac PT terms such as myocardial infarction, myocardial ischemia and cardiac failure were identified in delafloxacin treated subjects; however, this reviewer determined that these events were unrelated to delafloxacin therapy.

8.5.12 Sensory Events

During the 2015 FQ advisory committee, reports of a potential relationship between certain sensory events and FQs were discussed. Consequently, this reviewer assessed for any emerging relationships between such sensory events as diminished and/or blurred vision and tinnitus, for example, and delafloxacin in the Applicant's Phase 3 trials. A total of 11 subjects in the delafloxacin arm (11/741; 1.5%) were reported as having 12 TEAEs coded under the Ear and Labyrinth Disorders and Eye Disorders SOCs. Nearly similar numbers of subjects in the vancomycin comparator arm, a total of 8 subjects (8/751; 1.1%) were reported as having a total of 9 TEAEs. Among delafloxacin treated subjects, most TEAEs coded under the above-mentioned SOCs, were assessed by site investigators as being mild in severity and unrelated to delafloxacin treatment. However, three of six subjects with events coded to the PT terms tinnitus, vertigo, and vision blurred were determined by site investigators as having TEAE that were potentially related to delafloxacin therapy. There were two subjects in the vancomycin arm with tinnitus and blurred vision whose TEAEs were assessed as being causally related to treatment.

8.5.13 Other AEs of Special Interest Associated with Currently Marketed FQ Crystalluria

Of the three presently marketed FQs, ciprofloxacin, levofloxacin, and moxifloxacin, the ciprofloxacin label carries, in Section 5 "WARNING and PRECAUTIONS," a warning pertaining to crystalluria (Section 5.17). The ciprofloxacin label states that "crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals." Such a warning is not included in the other two marketed FQ labels. In light of this ciprofloxacin warning, this reviewer conducted a search for subjects in the Applicant's Phase 2 and Phase 3 studies who had crystals in their urine.

Subject 303/840-327-3064 (Delafloxacin): A 77 year old white male with a history of vascular and cardiovascular disease. This subject also had a normal baseline CrCl of ≥ 90 min/mL (actual value of 147 min/mL) and Cr of 0.7 mg/dL (62 μ mol/L). Prior medical history was reported as hypertension, coronary artery disease, depression, high cholesterol, obesity (BMI = 34.4) and overactive bladder. His medication list included acetylsalicylic acid, amlodipine, atorvastatin, clopidogrel, eplerenone, ezetimibe, nadolol, nortriptyline, oxybutynin, ramipril, simvastatin. However, he apparently had not received these medications concurrently with delafloxacin. He received delafloxacin for a total of 8 days—22 October 2014 (Study Day 1) and 29 October 2014

(Study Day 8) and received a total of 14 doses of delafloxacin. On 24 October 2014 (Study Day 3) AE of “crystal urine present” was initially reported and was subsequently reported as resolved on 3 November 2014 (Study Day 13).

Urine studies showed on Study Day 3, 30-49 calcium oxalate crystals per high power field (HPF). All other crystals evaluated in the urine, including uric acid crystals, triple phosphate crystals, calcium carbonate crystals, calcium phosphate crystals, leucine crystals and cysteine crystals were notably absent at baseline, on Study Day 3 and on 3 November 2014 (Study Day 13). Day 3 urine pH was recorded as 6.0 (and within normal limits) and this was unchanged from baseline. Urine specific gravity on Day 3 appeared concentrated at 1.023 (normal range: 1.002-1.035) which was quite similar to the baseline value of 1.022

The study investigator assessed this AE as a mild intensity event and “possibly related” to the study treatment. Other AEs, all of which were graded as moderate intensity, namely blood pressure increased, dizziness, flushing and headache were short lived and occurred on 29 October 2014 (Day 8). Cr remained stable throughout the duration of the study at 0.9 mg/dL (80 µmol/L). All other electrolytes were within normal limits at baseline and remained within normal limits throughout the duration of his study enrollment.

Medical Reviewer’s Comment: *The above-mentioned subject is the sole subject in both Phase 3 trials with a PT term coded to “crystal urine present.” No other subjects were observed by this reviewer to have similar AE findings. In the absence of sufficient information, this reviewer found it difficult to make a causality determination for this AE. It does not appear as though urine was evaluated for delafloxacin crystals. However, calcium oxalate crystals were not present at the baseline urinalysis but were found on the Day 3 evaluation.*

However, given a temporal association between this AE and delafloxacin administration, the finding may possibly be related to delafloxacin, but in the absence of information it cannot be confirmed. There were no reported AEs coded to either “crystalluria” or “crystal urine present” in either of the Phase 2 studies. Per discussion with the pharmacology-toxicology reviewer, Dr. Amy Nostrandt there appears to be insufficient data collected from animal studies to confirm or disconfirm the presence of delafloxacin crystals in non-clinical animal studies.

8.6 Safety Analyses by Demographic Subgroups

In accordance with 21 CFR 314.50(d)(5)(vi)(a), this reviewer assessed the impact of age, gender, and race on the frequencies of TEAEs and SAEs for both treatment arms in each of the Applicant’s pivotal Phase 3 trials. In addition, the reviewer evaluated the impact of several other pertinent subgroups on AEs, namely: renal impairment, as delafloxacin is partially excreted renally; and BMI. This reviewer acknowledges that, while the pivotal trials were not powered to draw definitive safety conclusions such analyses were conducted to explore the impact of any potential interactions between these various subgroups and delafloxacin.

Overall, no one demographic subgroup was noted to be at a substantially higher risk for SAEs or TEAEs. The reviewer independently conducted her own demographic subgroup analyses and compared these findings against those presented by the Applicant in Tables 14.3.1.1.1 through 14.3.1.1.8 of the ISS. The sections below summarize the safety findings for each of the

subgroups articulated above. As this analysis did not account for multiple comparisons, no definitive conclusions can be made regarding safety among these various patient subgroups. This reviewer considers these analyses largely exploratory.

Age Categories

This reviewer compared the numbers of subjects with TEAEs and SAEs across treatments by those subjects <65 years of age and those ≥ 65 years of age. As **Table 81: TEAEs by AGE** below illustrates, the numbers of TEAEs/SAEs across treatments arms and **within** each of the (2) age categories were fairly comparable.

Table 81: TEAEs by AGE CATEGORY						
AGE CATEGORIES	Protocol 302 Delafloxacin 300-mg IV every 12 hours			Pooled Phase 3 Vancomycin (± Aztreonam)		
Any TEAEs						
	# of TEAEs	# of subjects		# of TEAEs	# of subjects	
		N	n (%)		N	n (%)
≤ 65 Years	704	640	297 (46.4%))	804	656	323 (49.2%))
> 65 Years	71	101	37 (36.6%))	75	95	35 (36.8%))
Any SAEs						
	# of SAEs	# of subjects		# of SAEs	# of subjects	
		N	n (%)		N	n (%)
≤ 65 Years	30	640	24 (3.8)	36	656	23 (3.5%)
> 65 Years	3	101	3 (3.0%)	6	95	3 (3.2%)

Source: Table 14.3.1.1.1.1 of Applicant's Summary of Clinical Safety

Study Discontinuations

Two subjects aged 65 and older discontinued the study drug due to AEs (urticaria and nausea/emesis) in the delafloxacin arm, whereas, a total of 5 subjects in the vancomycin arm who experienced AEs coded to PT terms: rash, sepsis, hypersensitivity, erythema, and muscle spasms, discontinued treatment in the vancomycin (± aztreonam) arm.

Moderate and Severe Events

A total of 25 subjects in the delafloxacin arm compared with 24 subjects in the vancomycin arm aged <64 were graded as having moderate to severe TEAEs. Approximately 20% percent (119/643) and 3.6% (23/643) of subjects aged <65 in the delafloxacin arm and 20.6% (135/655)

and 2.9% (19/655) of subjects aged <65 in the vancomycin were graded as having moderate and severe AE, respectively. In comparison, in the 65 to <75 age category, 5.1% (3/59) of subjects experienced severe and moderately graded investigator assessed TEAEs in the delafloxacin arm vs 13.8% (8/58) and 3.4% (2/58) subjects in this age category in the vancomycin arm experienced moderate and severe TEAEs, respectively. The percentages of subjects aged ≥75 assessed as having experienced moderate and severe TEAEs, in both delafloxacin and vancomycin were nearly equivalent (moderate: 13 vs 12; severe: 1 vs 3).

Most Frequent TEAEs

The most frequently observed TEAEs among subjects was analyzed by the following age categories: 18 to 44, 44 to 64, 65 to 74 and 75 years and older. Overall, nausea, diarrhea, infection, infusion site extravasation, and headache were among the most common TEAEs in subjects aged 18 to 44 and aged 45 to 64. Whereas in the 65 to 74 year old age category, diarrhea and catheter site pain were the most commonly encountered TEAEs; and in the 75 to 95 age group diarrhea, headache, delirium, and nausea were most commonly reported.

Medical Reviewer's Comments: *There were fewer numbers of subjects aged 65 to 74 and ≥75 than those aged 64 and younger. When taking the splitting of PT terms under several SOC/HLT into account, overall the most commonly observed TEAEs in the pivotal Phase 3 trials were: infusion site reactions, infections, and the GI related PT terms nausea, diarrhea, and less so vomiting. In the oldest age group, those subjects 75 and older, however, such PT terms as delirium which is most likely associated with ongoing medical issues unrelated to delafloxacin therapy were observed.*

Gender

Men accounted for 61.9% (459/741) and 64.3% (483/751) of all subjects in the delafloxacin and vancomycin arms, respectively in the Applicant's pivotal Phase 3 trials; whereas, women comprised 38.1% (282/741) and 35.7% (268/751) of all subjects in the delafloxacin and vancomycin arms, respectively, in Applicant's Phase 3 safety population. Of the five deaths that occurred in the Phase 3 trials, two occurred in women, none of whom received delafloxacin. The sole death occurring in a delafloxacin treated subject was that of an 89 year old Israeli man with multiple co-morbidities. This subject was previously discussed in Section 8.4.1. In the reviewer's assessment this death was unrelated to delafloxacin.

When accounting for splitting of several PT terms under certain SOCs, the following TEAEs accounted for ≥2% of all TEAEs among males: infusion site reactions (delafloxacin: 9.6% vs vancomycin 11.8%); infections (delafloxacin 9.6% vs vancomycin 10.1%); diarrhea (delafloxacin 7.8% vs vancomycin 3.3%); nausea (delafloxacin 7.0% vs vancomycin 5.8%); transaminase/LFT increases (5.2% in each treatment); pyrexia (delafloxacin 4.6% vs delafloxacin 2.7%) and lastly headaches (delafloxacin 3.1% vs vancomycin 4.8%). Among female subjects, infusion site reactions (delafloxacin 8.5% vs vancomycin 10.5%); nausea (delafloxacin 9.6% vs vancomycin 8.6%); infection (delafloxacin 8.9% vs vancomycin 6.3%); diarrhea (delafloxacin 8.2% vs vancomycin 3.4%); headache (delafloxacin 5.0% vs vancomycin 6.7%); vulvovaginal candidiasis (3.6% vs 1.9%); transaminase/LFT elevations (2.8% vs 4.9%);

vomiting (3.2% vs 3.7%); and pyrexia (2.1% vs 3.7%); were the most common TEAEs (when accounting for splitting of several PT terms).

Table 82: Treatment Emergent Adverse Events by Sex						
AGE CATEGORIES	Pooled Delafloxacin			Pooled Phase 3 Vancomycin (± Aztreonam)		
Any TEAEs						
	# of TEAEs	# of subjects		# of TEAEs	# of subjects	
		N	n (%)		N	n (%)
Male	461	459	207 (45.1%)	539	483	227 (47.0%)
Female	314	282	127 (45.0%)	340	268	131 (48.9%)
Any SAEs						
	# of SAEs	# of subjects		# of SAEs	# of subjects	
		N	n (%)		N	n (%)
Male	21	459	10 (3.3%)	23	483	17 (3.5%)
Female	10	282	9 (3.2%)	14	268	9 (3.4%)

Source: Table 14.3.1.1.1.1 of Applicant's Summary of Clinical Safety

Medical Reviewer's Comments: Among those subjects receiving delafloxacin, the incidence of TEAEs among both sexes was fairly similar in the Phase 3 pivotal trials and remained consistent with delafloxacin's overall safety profile. As detailed above, there were a few exceptions, such as slightly increased incidence of pyrexia occurring among male subjects than female subjects. In addition, vomiting and, for obvious reasons, vulvovaginal candidiasis were more commonly reported among females

Race

The majority of subjects in both treatment arms of the phase 3 trials were white: 85.8% (636/741) and 87.4% (656/751), in the delafloxacin and vancomycin arms, respectively. Similar to the aforementioned subgroups, among white subjects, the TEAEs accounting for ≥2% of all events in the delafloxacin and vancomycin treatment arms, respectively, were: infusion site reactions (8.8% vs 11.4%); infections (9.8% vs 8.8%); nausea (8.3% vs 6.7%); diarrhea (8.3% vs 3.1%); transaminases/LFTs increased (4.1% vs 4.4%); headache (3.9% vs 4.9%); pyrexia (3.5% vs 2.7%); and vomiting (2.4% vs 2.9%).

Among non-whites, blacks were the second most represented racial group, accounting for 5.1% (38/741) and 4.8% (4.8%) of all subjects in the delafloxacin and vancomycin arms, respectively. Infusion site reactions (delafloxacin 13.2% vs vancomycin 19.4%); infections (delafloxacin 10.5% vs 13.9%); nausea (7.9% vs 11.1%); and diarrhea (7.9% vs 5.6%) were reported in *at least* 2 or more black subjects in each treatment arm. Asians were 1.6% (12/741) and 2.1% (16/751) of all subjects in the delafloxacin and vancomycin arms of the Applicant's Phase 3 trials, respectively. The TEAEs pyrexia (delafloxacin 25% vs vancomycin 18.8%); and vomiting and nausea (delafloxacin 16.7% vs vancomycin 0.0%, each) were reported in 2 or more Asian subjects. Infusion site reactions, specifically infusion site extravasations were the most common occurring TEAEs among Native American subjects (delafloxacin 31.3% vs vancomycin 11.1%) who comprised 2.2% (16/741) and 1.2% (9/751) of all subjects in the delafloxacin and vancomycin safety populations respectively.

Medical Reviewer's Comments: *Delafloxacin's safety profile remained consistent across various racial categories, with infusion site reactions, infections, GI events (nausea, diarrhea, and vomiting) and transaminase/LFT elevations accounting, in most instances, accounting for the majority of TEAEs. This is relatively similar to other demographic subgroups.*

Obesity

The differences in the incidence of TEAEs among the various BMI categories in both treatment arms by BMI category were evaluated, particularly since Protocol 303 was enriched for subjects with BMIs of ≥ 30 . A review of TEAEs was conducted among the following BMI categories: 18.5 to <25 , 25 to <30 , 30 to <40 , and ≥ 40 . Irrespective of BMI, and similar to other subgroups, the most commonly reported TEAEs in, both treatment arms, but particularly among those subjects receiving delafloxacin included: GI related events, namely diarrhea, nausea and vomiting; followed by infections; infusion site reactions; transaminase/LFT elevations; headaches and pyrexia.

Medical Reviewer's Comments: *Delafloxacin's safety profile remained consistent across various BMI categories and relative to other demographic subgroups.*

8.7 Specific Safety Studies/Clinical Trials

Section 8.7 provides brief discussions of several Phase 1 studies conducted to evaluate delafloxacin's safety in specific subject populations or relative to certain FQ associated adverse events. This includes a discussion of the following a:

- Photosensitivity Study: Study M01-284
- Renal Impairment Study: RX-3341-110
- Cardiac Safety Study: RX-3341-111
- Hepatic Impairment Study: Study ML-3341-112

8.7.1 Study M01-284 “Effect of ABT-492 on Photosensitivity Levels in Healthy Male and Female Subjects”

Methods: A Phase 1, single-blind, placebo- and positive controlled, randomized, parallel-group study consisting of 52 health adult male and female volunteers aged 18 to 55, Study M01-284 was designed to evaluate the “photosensitizing potential and wavelength dependency (295-430 nm) of delafloxacin (formerly called ABT-492).” By inclusion criteria, subjects had to have skin types I-III in accordance with the Dermatology Scale of skin reactive types. The primary study endpoint was the “change in MED within subject/group comparing their baseline MED value with their MED while on study drug/placebo.” A secondary analysis, involving the calculation of the Phototoxic Index (PI), defined by the Applicant as the “baseline MED value/on-drug MED value for each subject and the median MED value for each group by the post-dose MED value,” was conducted. The maximum PI was indicative of the phototoxic potential of the study drug.

Fifty-two subjects (with 13 subjects assigned to each arm) were randomized in a 1:1:1:1 ratio to receive the following: ABT-492 200-mg daily (100-mg capsules x 2) for 6 days; 400-mg (100-mg capsules x 4) daily for 6 days; the positive control, lomefloxacin 400-mg (400-mg tablet x 1) for 6 days, and placebo for 6 days all under fasting conditions.

Prior to receipt of study drug, eligible subjects underwent baseline photosensitivity testing to ultraviolet A (UVA), ultraviolet B (UVB) and visible radiation (“by means of a standard monochromator technique”) over 3 days to determine the minimal erythema dose (MED). On Days 5-6 of the study, repeat phototesting was performed whereby each subject’s back was exposed to selected wavelengths of UVA, UVB and visible light. On Day 7 of the study, the exposed areas of each subject were assessed to determine the MED. Any subject demonstrating an “abnormal response” or a reduction in MED of >40% from baseline had repeat phototesting on Study Days 7-9 and remained in the clinical evaluation unit until any drug-induced photosensitivity had resolved. Safety assessments included the collection of 12-lead ECGs, performing physical examinations, vital signs and laboratory parameters and monitoring AE assessments.

Results: Forty-seven of the 52 originally enrolled subjects who were randomized to treatment completed *at least* 6-days of study drug and were included in the analysis. The Applicant reports that compared to subjects receiving the active comparator, lomefloxacin, subjects in both of the ABT-492 arms failed to demonstrate clinically significant evidence of phototoxicity at any of the tested wavelengths. No subjects in either of the two ABT-492 treatment arms or placebo demonstrated any statistically significant differences from “zero in percent change from baseline in MED” at any of the evaluated wavelengths (295 ± 5nm – 430 ±30 nm). However, those subjects receiving lomefloxacin demonstrated moderate evidence of phototoxicity at UVA wavelengths 335 and 365nm. At UVA wavelengths 335 nm and 365 nm, statistically significant differences in % change from baseline MED were observed in the lomefloxacin group when compared to both ABT dosing groups and the placebo group.

The Applicant reported that “no statistically significant differences in percent change from baseline in MED were observed at each wavelength tested within either ABT-492 dosing group or between the ABT-492 dosing groups and placebo group, using the monochromator or solar simulator.” No phototoxicity was observed in the placebo group. Based on these findings the

Applicant concluded that “ABT-492 at dosages of 200-mg and 400-mg daily failed to demonstrate a significant phototoxic effect. In particular, the classical pattern of FQ phototoxicity as detected in previous phototoxicity studies (i.e. UVA phenomenon maximal at 24 hours) was not seen.”

There were a total of 7 subjects who prematurely discontinued their enrollment in this study due to an AE, including: one in the ABT-492 200-mg arm; two subjects in the ABT-492 400-mg group; three subjects in the lomefloxacin group (2 subjects withdrew consent and 1 did not return for phototesting on Study Day 21); and 1 in the placebo group, a withdrawal due to an AE. All randomized subjects were white and the majority of them (65%) were male.

No subjects who received ABT-492 mg daily had an abnormal MED response on Study Day 7, whereas 2 subjects in the ABT-492mg group all 12 subjects in the lomefloxacin group and 1 subject in the placebo group had abnormal MED responses on Day 7 and underwent repeat phototoxic testing. However, any evidence of phototoxicity observed in these subjects subsided within 48 hours of discontinuing the study drug. With the exception of the lomefloxacin group at the 335 and 365 wavelengths, the mean and median phototoxic index values were similar in all groups at each of the wavelengths tested. Based on the PI scoring, all 11 subjects in the ABT-492 400 mg/day group had maximum PI scores of 1.4 to 2.1, indicating mild phototoxicity at all wavelengths tested with the exception of 295 nm and 430 nm which were <1.4 the equivalent of “absent phototoxicity.” In comparison, all subjects in the ABT-492 400-mg group had maximum PI scores of <1.4 at all wavelengths with the exception of 305, 335, and 365 nm where the maximum PI score were 1.4. The 12 subjects assigned to lomefloxacin had mild phototoxicity at the 300,304 and 400 nm wavelengths and severe phototoxicity at the 335 and 365 nm wavelengths.

Medical Reviewer’s Comments: *With regards to the primary endpoint, the ABT-492 400-mg group, along with the ABT-492 200-mg dosing group, demonstrated “no statistically significant differences in percent change from baseline in MED at all tested wavelengths within the ABT-492 dosing groups or between the two ABT-dosing groups and placebo.” In the secondary analysis all 11 subjects (11/11) administered the maximal 400-mg dosage demonstrated mild phototoxicity (PI 1.4 to 3.0) at nearly every wavelength, when the PI for this treatment group was evaluated. These findings were similar to those of the negative control and hence appeared to be acceptable. No subjects in the ABT-492 400-mg arm showed evidence of severe phototoxicity. In comparison more subjects assigned to the positive control group (lomefloxacin) exhibited both mild and severe phototoxicity (PI of >6.0) at various wavelengths; whereas, there was “absent phototoxicity” in the ABT-492 200-mg arm and placebo.*

The findings in this study appear to support that Applicant’s claim that delafloxacin has limited potential for phototoxicity.

8.7.2.RX-3341-110 A Phase I, Multicenter, Open-Label, Parallel-Group Crossover Study to Assess the Effect of Renal Impairment on the Single-Dose Pharmacokinetics and Safety of Oral and IV Delafloxacin (RX-3341) and IV Placebo

Methods: RX-3341-110 was a Phase 1, non-randomized, open-label, parallel-group, single-dose study with a planned enrollment of 40 subjects (5 groups of 8 subjects each) assigned to one of 5 groups, as follows:

- Group A: healthy subjects (estimated glomerular filtration rate [eGFR] of >80 mL/min/1.73 m²)
- Group B: subjects with mild renal impairment (eGFR >50-80 mL/min/1.73 m²)
- Group C: subjects with moderate renal impairment (eGFR >30-50 mL/min/1.73 m²)
- Group D: subjects with severe renal impairment (eGFR ≤30 mL/min/1.73 m²)
- Group E: subjects with end-stage renal disease (ESRD) on hemodialysis

The MDRD equation was used to calculate renal function. Healthy controls were matched by gender, mean age (± 10 years) and mean BMI (± 20%) to their renally impaired counterparts. The primary objective of this study was to compare the PK of delafloxacin dosed as a 400-mg oral dose and as a 300-mg IV infusion with Captisol in healthy adults subjects between the ages of 18 and 80 exhibiting either mild, moderate, and severe renal impairment. Persons on hemodialysis (HD) were to receive an IV infusion of delafloxacin 300-mg/IV Captisol.

Secondary endpoints included a comparison of safety and PK among the different subject groups.

For subjects in Groups A through D, the study was sub-divided into three treatment periods where subjects received a single dose of study drug separated by a washout period of at least 14 days. The treatment periods were as follows:

- Period 1: 300-mg delafloxacin/Captisol 1-hour IV infusion
- Period 2: placebo/Captisol 1-hour IV infusion
- Period 3: 400-mg oral delafloxacin (four 100-mg capsules)

Unlike subjects in Groups A through D, subjects in Group E participated in two treatment periods separated by at least 14 days. Subjects assigned to this group were administered a single dose of study drug as follows:

- Period 1: 300-mg delafloxacin/Captisol 1-hour IV infusion starting approximately 1 hour before initiation of the last hemodialysis session of the week
- Period 2: 300-mg delafloxacin/Captisol 1-hour IV infusion starting within 1 hour after completion of the last hemodialysis session of the week

Subjects in all groups were expected to fast 4 hours prior to the start of the treatment infusion and 4 hours afterwards. Blood and urine samples (and only if possible for subjects on HD) were collected for PK analyses of delafloxacin and Captisol concentrations. For subjects in Group E, PK samples were collected prior to dosing, before and during HD, and in Period 2 65 to 69 hours after dosing. The dialysate from subjects on HD were collected to determine the concentrations of delafloxacin and Captisol. All subjects were asked to return for a follow-up visit within 14 days (± 2 days) of the last dose after Period 3 if assigned to Groups A through D and after Period 2 for those subjects in Group E.

Disposition: A total of 44 subjects were enrolled into the study, with 42 (95.5%) of these subjects completing the study. The two subjects who discontinued the study did so due to the emergence of TEAEs: one subject in Group A (normal renal function) developed a severe case of *Clostridium difficile* on Day 4 of Period 2 (when he received placebo/Captisol IV infusion) and the second subject was in Group D received 300-mg delafloxacin/Captisol IV infusion in Period 1 and discontinued the drug 18 days later after developing left shoulder musculoskeletal pain.

The mean age of all enrolled subjects was 53.7 years old. More male subjects (56.8%) were enrolled in this study than female subjects (43.2%). There was equal representation of white and black subjects, with each racial category accounting for 47.7% of all subjects. The mean eGFR of enrolled subjects was 43.3 mL/min/1.73 m², with a range of 5-119 mL/min/1.73 m².

Results: Among all subject groups, peak plasma concentrations were achieved approximately 1 to 1.5 hours after the administration of oral delafloxacin. The sponsor observed that, following IV dosing, plasma concentrations were consistently lower among subjects with normal renal function than in renally impaired subjects, particularly those subjects in the ESRD group.

The sponsor observed the following findings after the dosing of 300-mg delafloxacin/Captisol IV (page 80 of 4479 in RX-3341-110 CSR):

:

- As the degree of renal impairment increased so too did the arithmetic mean total exposure (AUC_{0-t}) of delafloxacin increase with worsening renal impairment
- The mean AUC_{0-t} for the severe renal impairment group was 2.1-fold higher than the exposure observed for the healthy group. Mean AUC_{0-t} for the ESRD group without hemodialysis after dosing (Group E2) was 4.1-fold higher than the exposure observed for the healthy group.
- Peak exposure (C_{max}) was similar for the healthy group and the mild and moderate renal impairment groups. Arithmetic mean C_{max} values for the severe renal impairment group and the ESRD group without hemodialysis after dosing (Group E2) were 2.1-fold and 6.4-fold higher, respectively, than the corresponding value observed for the healthy group.”
- Only the severe renal impairment group and the ESRD group without HD after dosing (Group E2) were observed to have “meaningful” increases in t_{1/2}. “The mean t_{1/2} was 9.3 hours for the healthy group and increased to 15.0 hours for the ESRD group without HD after dosing (Group E2).”

Following dosing of delafloxacin 400-mg orally, the sponsor reported the following findings (page 80 of 4479 in RX-3341-110 CSR):

- Group A (normal renal function) had nearly the same total exposure as observed following the 300-mg delafloxacin/Captisol IV dose, and demonstrated an arithmetic mean AUC_{0-t} of 23.64 µg•h/mL after IV dosing and 25.75 µg•h/mL after oral dosing.
- Subjects in Groups C and D (moderate and severe renal impairment, respectively) displayed mean AUC_{0-t} values which were approximately 1.5-fold higher than subjects in

Group A. “Mean C_{\max} varied little across the various renal function groups after oral dosing, with a slightly higher mean C_{\max} of 7.2 $\mu\text{g/mL}$ for the healthy group.”

Safety Analysis: Twenty-eight of the 44 subjects enrolled in RX-3341-110 experienced at least 1 TEAE. The sponsor reports a total of 83 TEAEs. The following numbers of subjects (per treatment group) experienced TEAEs following administration of IV 300-mg delafloxacin: 2 of 9 subjects (22.2%) in Group A (normal renal function); 5 of 8 subjects (62.5%) in Group B (the mild renal impairment group), 3 of 8 subjects (37.5%) in Group C (the moderate renal impairment group), and 5 of 9 subjects (55.6%) in Group D (the severe renal impairment group). Subjects in Group E (the ESRD group), reported the highest percentage of subjects with TEAEs, with 80% (8 of 10) of subjects reporting TEAEs when 300-mg delafloxacin/Captisol IV infusion was administered 1 hour before hemodialysis and 70% (7 of 10) of subjects reported TEAEs when administered 1 hour after HD.

When 400-mg oral delafloxacin was administered, the following numbers of subjects (per treatment group) reported TEAEs: no subjects in the healthy and mild renal impairment groups, 3 of 8 subjects (37.5%) in the moderate renal impairment group, and 2 of 8 subjects (25.0%) in the severe renal impairment group. “Treatment-emergent AEs were reported by 1 of 9 subjects (11.1%) in the healthy group, 4 of 8 subjects (50.0%) in the mild renal impairment group, 3 of 8 subjects (37.5%) in the moderate renal impairment group, and no subjects in the severe renal impairment group after the placebo/Captisol IV infusion.”

Most TEAEs were assessed as either being possibly related (22.7%) or probably related (15.9%) to the study drug. There were no deaths, SAEs, or AEs leading to study discontinuation. Most TEAEs were graded as mild severity, however 31 were graded as moderate and 1 as severe. The most frequently cited TEAEs occurred in the Gastrointestinal Disorders SOC and included diarrhea (in Groups B and C, and 1 subject in the Group D); nausea (reported by no subjects in Group A; reported by 2 subjects in Group B; and 1 subject each in Groups C and D). There were no reported cases of vomiting in any of the 4 groups. The Nervous System Disorders SOC was the second most frequently cited SOC, with the most commonly cited TEAEs in this SOC as follows: headache, with one subject in each group endorsing the PT, the exception being Group C which had 2 subjects with complaints of headache. This was followed by the PT term dizziness which was endorsed by 1 subject each in Groups A and C.

8.7.3 RX-3341-111 A Randomized, Crossover Study to Define the ECG Effects of Delafloxacin Using a Clinical and a Supratherapeutic Dose Compared with Placebo and Oral Moxifloxacin (a Positive Control) in Healthy Men and Women: A Thorough ECG Study

Methods: RX-3341-111 was a Phase 1, randomized, 4-period, single-center crossover study conducted to assess the ECG effects of a single administration of a therapeutic dose of delafloxacin (300-mg IV) and a supratherapeutic dose of delafloxacin (900-mg IV), in healthy male and female subjects. Secondary objectives included the evaluation of both safety and PK following single dose administration of either of these two doses. Moxifloxacin served as a

positive control and 5% dextrose in water was the placebo. All IV treatments were given over 60-minutes.

Fifty-two healthy subjects, aged 18 to 45, were assigned to one of 8 treatment sequences. ECGs were collected at various pre-specified time points, including at screening, pre-treatment (Day - 1), and on treatment (Days 1, 5, 9, and 13). On-treatment ECGs were obtained in triplicate prior to dosing (-45 minutes, -30 minutes, and -15 minutes), and a single safety ECG was obtained 1 hour following start of infusion. Afterwards, subjects were monitored on continuous 12-lead ECG digital recorder for 24 hours. Triplicate ECG readings were obtained and downloaded at an off-site ECG center and were collected at various time points before dosing, at 0.5 hours, and afterwards at multiple time points after the start of the infusion. Corresponding blood samples were collected for PK analysis on treatment days. “ECG extraction were time-matched to PK samples but were obtained before the actual plasma sampling time.”

Endpoints: RX-3341-111’s primary pharmacodynamics (PD) endpoint was “the time-matched QT interval correct for heart rate (HR) using Fridericia’s formula (QTcF) change from baseline corrected for placebo.” There were several secondary PD endpoints, including the QT interval corrected for HR using Bazett’s formula (QTcB), HR, PR, QRS, and QT intervals and any changes to ECG morphologic patterns.

Disposition: 51 of the 52 enrolled subjects completed the study. The one subject withdrew consent due to a family emergency. The majority of subjects were white (61.5%), and male (55.8%). A total of 23 subjects (44.2%) were female and 38.5% of all subjects were black. Subject mean age was 28.5, with a range of 18 to 43 years of age.

Safety Evaluation: All 52 enrolled subjects were included in the safety analysis. A total of 34 subjects (65.4%) reported a total of 118 TEAEs. The majority of TEAEs were reported among those subjects who were administered delafloxacin 900-mg. Across all treatment arms, most TEAEs occurred in the Gastrointestinal disorders SOC (44.2%), with the nausea (38.5%), vomiting (25.0%), abdominal pain (7.7%), and lastly diarrhea (5.8%) comprising the majority of TEAEs. The nervous system disorders SOC was the second most frequently endorsed SOC, with headache (19.2%) and dizziness (9.6%) being the most frequently cited PT terms. Subjects in the delafloxacin 300-mg arm had more headaches than those in the 900-mg arm. The PT infusion site pain, under the General disorders and administration site SOC was cited among 15.4% of all subjects, the majority of whom were in the delafloxacin 900-mg IV arm.

Sponsor’s Conclusions: Upon completion of this trial, the sponsor made the following conclusions regarding the PD endpoint:

- Delafloxacin failed to induce any cardiac repolarization using the QTcF interval.
- The sponsor reported there was no signal of significant effect on atrioventricular conduction or cardiac depolarization when measuring the PR and QRS interval durations. No clinically relevant morphologic changes were observed.

Medical Reviewer’s Comments: *The Division consulted with the QT-IRT team and requested that their team make an independent evaluation of the findings in the sponsor’s TQT study. The QT-IRT team’s overall conclusion was that there was “No significant QTc prolongation effect of*

delafloxacin (300 mg and 900 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between delafloxacin (300 mg and 900 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta QTcF$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated . . . , indicating that assay sensitivity was established". The findings of this TQT study were consistent with preclinical studies which found that delafloxacin did not block hERG currents or prolong QT in animals at concentration within range of the maximal tolerated dose in humans. For further details please also refer to Dr. Kunyi Wu's of clinical pharmacology's review.

QTc prolongation is an untoward event typically associated with drugs of the FQ class. However, based on review of the findings reported in Protocol RX-3341-111 and the findings from pre-clinical trials, it is safe to conclude that delafloxacin was not demonstrated to induce changes in the QTc. Subjects in this study were young, between the ages of 18 and 45, and healthy, experience of this drug in older populations, including in phase 3 trials is limited. It is noted that hypokalemia was observed in older populations so caution should still be exercised when using this drug in populations that may be prone to electrolyte imbalances (or in those who may experience diarrhea/vomiting who may be at a greater risk for electrolyte imbalances.)

As has been found in Phase 2 and 3 trials in support of this safety, the safety profile of subjects in this study, even among those in receipt of supratherapeutic doses of delafloxacin, remains consistent with what has been observed in Phase 2 and 3 trials conducted in support of this drug's safety, with the most common TEAES associated with the GI SOC such as nausea and diarrhea. No vomiting was observed in in this trial.

8.7.4 ML-3341-112 An Open-Label Evaluation of the Single-Dose Pharmacokinetics of Delafloxacin in Subjects With and Without Hepatic Impairment

Methods: ML-3341-112 was a Phase 1, multicenter, open-label, single-dose, PK study with the primary objective of evaluating the PK profile of a single IV dose of delafloxacin in normal healthy subjects and subjects with mild, moderate, and severe hepatic impairment. This study had a planned enrollment of 36 subjects each of whom were stratified into the following groups in accordance with their Child-Pugh classification:

- Group A: 6 subjects with mild hepatic impairment (Child-Pugh Class A)
- Group B: 6 subjects with moderate hepatic impairment (Child-Pugh Class B)
- Group C: 6 subjects with severe hepatic impairment (Child-Pugh Class C)
- Group D: 18 healthy subjects

Subjects, who were to be between the ages of 18 and 80, were enrolled sequentially, with subjects in Groups A and B (mild and moderate hepatic impairment) and matched healthy controls enrolled first followed by an interim analysis after which subjects with Group C (severe hepatic impairment) and their accompanying healthy controls with were enrolled. Healthy controls were matched by age (± 10 years), weight ($\pm 20\%$), gender, and where possible by alcohol and tobacco use with respect to their hepatically impaired counterparts. The study was divided into 4 phases (Screening, Check-in/Baseline, Treatment and Study Exit) and all subjects

on Day 1 of treatment received a single 1-hour IV infusion of delafloxacin 300 mg. Blood samplings for the PK analysis were collected over a 72 hour period post-dosing. In addition, safety assessments, inclusive of laboratory evaluations, ECG measurements, vital signs and physical examinations and AE reporting were performed.

Disposition: A total of 39 subjects received a single infusion of IV delafloxacin 300-mg, 36 (92.3%) of whom had evaluated PK data and were subsequently included in the PK analysis. The three subjects excluded from the study did so due to TEAEs resulting in study discontinuations. One subject was twice enrolled in the study (1st in the mild hepatic impairment group and then in the severe hepatic impairment group). Overall, the mean age of subjects in ML-3341-112 was 54.4 years, with a range of 42 to 68 years of age. Nearly 90% of all subjects were white, 10.3% were females, 79.5% were white, 17.9% were black, and the mean BMI for subjects was 29.7.

PK Analysis: Following a single, 1-hour infusion of delafloxacin 300-mg, the sponsor reported the following findings from their PK analysis (Page 78 of CSR):

- **Group A (mild hepatic impairment):** “Total (AUC_{0-t} and AUC_{0-inf}) and partial (AUC₀₋₁₂ and AUC₀₋₂₄) exposures for plasma delafloxacin were slightly increased by approximately 1.1-fold for subjects with mild hepatic impairment compared with healthy subjects.” Peak delafloxacin plasma exposures (C_{max}) were “not significantly different” between subjects in Group A compared with the matched controls and clearance was observed to be “slightly decreased”.
- **Group B (moderate hepatic impairment):** “Total (AUC_{0-t} and AUC_{0-inf}) and partial (AUC₀₋₁₂ and AUC₀₋₂₄) exposures for plasma delafloxacin were increased by approximately 1.1- to 1.2-fold for subjects with moderate hepatic impairment only when compared with the pooled healthy subject group.” Peak delafloxacin plasma exposures (C_{max}) were described as “slightly decreased” (by approximately 10%) in Group B subjects when compared with the (C_{max}) of their matched controls counterparts and the overall cohort of pooled healthy subjects. Clearance was noted to be decreased for subjects in Group B when compared with pooled healthy controls.
- **Group C (severe hepatic impairment):** “Total (AUC_{0-t} and AUC_{0-inf}) and partial (AUC₀₋₁₂ and AUC₀₋₂₄) exposures for plasma delafloxacin were increased by approximately 1.1- to 1.4-fold for subjects with severe hepatic impairment compared with healthy subjects.” Peak (C_{max}) exposure was slightly decreased for subjects with severe hepatic impairment only when compared with the pooled healthy subject group, as the C_{max} values for subjects with severe hepatic impairment were reduced by approximately 8% compared with C_{max} values for healthy subjects.” Observed decreases in delafloxacin clearance were noted in those subjects with severe hepatic impairment when compared with healthy subjects.

Safety Evaluation: Two of the three subjects who were discontinued from the study due to TEAEs, a subject from Group A and a matched healthy control for Group B) did so due to

developing hypersensitivity reactions. The third subject, a Group A matched healthy control, was discontinued from the study drug due a pre-syncopal TEAE.

Ten of the 39 enrolled subjects (25.6%) comprising the safety population reported *at least* 1 TEAE following receipt delafloxacin 300-mg IV dose. There were a total of 11 TEAEs reported in these 10 subjects. “Treatment-emergent AEs were reported by 1 of 7 subjects (14.3%) in the mild hepatic impairment group, no subjects in the moderate hepatic impairment group, 2 of 6 subjects (33.3%) in the severe hepatic impairment group, and 7 of 20 subjects (35.0%) overall in the healthy subjects group.” Of those subjects with treatment related TEAEs, most TEAEs were assessed as being probably (7.7%) or possibly (5.1%). No TEAEs were assessed as being definitely related to the study drug. Aside from the two TEAEs that were graded as severe intensity events, all other TEAEs were graded as mild in intensity.

As noted above, each of the six subjects comprising Groups B (moderate) and C (severe) did not experience any more TEAEs than their counterparts in Groups A (mild) and D (healthy controls). One of the two subjects in Group C reporting TEAE was coded to the PT term musculoskeletal pain under the Musculoskeletal and Connective Tissue Disorders SOC the other PT term was nasopharyngitis under the Infections and Infestations SOC. No subjects from Group B reported any TEAEs.

Medical Reviewer’s Comments: Overall, between 1.1-fold and 1.4-fold decreases in total and partial exposures of plasma delafloxacin were noted among subjects with mild, moderate, and hepatic impairment when compared with matched healthy controls in the Applicant’s dedicated hepatic impairment study (ML-3341-112). In their proposed label, the Applicant recommends “No dose adjustment is recommended in patients with hepatic impairment.”

Both the IV and oral formulations of delafloxacin are metabolized via glucuronidation and excreted in the urine and feces. Based on the reported findings in ML-3341-112 and the metabolism and excretion of this drug, including the decreased clearance noted in subject with hepatic impairment, this reviewer concludes this drug is presumed to be relatively safe in subjects with hepatic impairments. Although a limited number of subjects were evaluated in ML-3341, there was no observed increase in the incidence of TEAEs in subjects with mild, moderate and severe hepatic impairment.

8.8 Additional Safety Explorations

8.8.1 Human Carcinogenicity or Tumor Development

Delafloxacin is an antimicrobial product with a recommended treatment period of 5 to 14 days. The relatively short duration of therapy and treatment follow-up (up to 30 days) in the Phase 3 trials largely precluded a meaningful evaluation of oncologic events. Upon review of the Neoplasms Benign, Malignant and Unspecified SOC, a total of four subjects in the Phase 3 ISS population were identified as having a malignancy: 1 in the delafloxacin arm and 3 subjects in the vancomycin arm. The PTs included under the Neoplasms SOC in the ISS population included: malignant neoplasm (Subject 303/377-3609; vancomycin ± aztreonam); adenocarcinoma of colon (Subject 303/100-433-3906; delafloxacin); squamous cell carcinoma

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(Subject 303/840-327-3148; vancomycin ± aztreonam); and metastases to lymph node (Subject 302/044-0695; vancomycin ± aztreonam).

Subject 303/100-433-3906, the sole delafloxacin treated subject with documented malignancy was a 64 year old Bulgarian woman treated with a 11 days of delafloxacin who was reported as having adenocarcinoma of colon with ovarian, mesenteric, and peritoneal metastases, was discussed previously in in the SAE section. On Study Day 27, 16 days after the last dose of delafloxacin, Subject 303/100-433-3906 was incidentally found to have metastatic colorectal cancer when she underwent a planned hysterectomy for a suspected ovarian tumor.

Medical Reviewer's Comment: *The extent of the metastatic disease burden found in Subject 303/100-433-3906 during an elective surgical procedure leads this reviewer to conclude that Subject 303/100-433-3906's cancer evolved prior to her receipt of delafloxacin. Hence, it is this reviewer's determination that the above-described event is unrelated to delafloxacin therapy.*

8.8.2 Human Reproduction and Pregnancy

Pregnant and lactating women were excluded from eligibility in the Applicant's Phase 2 and Phase 3 trials. Nevertheless, the Applicant reports a single subject in the delafloxacin treatment arm, a 31 year woman, with a documented case of a spontaneous abortion. Subject 302/840-004-0263 was treated with delafloxacin for a left wrist wound infection, from 10 September 2013 (Day 1) to 15 September 2013 (Day 6), for a total of 11 doses of delafloxacin over this six day period. The subject had a medical history solely noted for drug dependence. The accompanying subject narrative reports the following:

- **Subject 302/840-004-0263** was documented as having an SAE of a spontaneous abortion in November 2013 (date not specified). The Applicant reports that their safety database recorded that the patient's last pre-treatment menstrual period was 15 August 2013 and that she had tested negative for pregnancy on both 9 September 2013 (Day -1) and 15 September 2013 (Day 6). However, on 23 September 2013 (Day 14), the subject was found to have a positive pregnancy test. On 10 October 2013 (Day 31), the subject expressed her decision to terminate the pregnancy. Despite multiple attempts on the study site's part to contact this subject, there were no additional contacts with the subject until 11 Jun 2014, when she reported that at approximately slightly less than 12 weeks gestation she believed herself to have had a spontaneous abortion with the passage of blood clots. According to the narrative, she neither sought prenatal care or follow-up with Planned Parenthood.

Medical Reviewer's Comment: *The Applicant reports a single event of a delafloxacin treated subject with a reported case of a spontaneous abortion. However due to a sustained period of no contact with the subject following report of the subject's pregnancy (approximately 8 months), the details surrounding this event remain spotty. No additional pregnancies were reported in the safety update report (SUR). What was known in this case is that the subject had a documented positive pregnancy test 9 days after the end of delafloxacin therapy. The negative pregnancy test on the last day of treatment could have been a true negative or a false negative report (as assay may not have been sensitive enough to pick up an early pregnancies). Although, the details of the event remain nebulous and it is known that spontaneous abortions are common in early*

pregnancy. A study authored by (Regan L, Rai R Best Pract Res Clin Obstet Gynaecol 2000 14(5):839) found that approximately 8 to 20% of women who know themselves to be pregnant, have a spontaneous abortion prior to 20 weeks gestation and that 80% of these events occur within the first 12 weeks of pregnancy. Therefore, it is not unlikely that this subject could have sustained a spontaneous abortion.

The Applicant conducted GLP embryo-fetal development studies with New Zealand White female rabbits (20/group), a species sensitive to delafloxacin and other antibiotics, where “Delafloxacin was noted not to be teratogenic in rabbits. In addition, there were no delafloxacin-related external, visceral, or skeletal malformations noted in pups at doses of up to 1.6-mg/kg/day, the maximum tolerated dose in pregnant rabbits. The NOAEL for maternal toxicity was 0.4-mg/kg/day. Embryo-fetal studies, in which oral delafloxacin was administered to pregnant Sprague-Dawley rats, demonstrated that “the period of major organogenesis resulted in maternal toxicity and reversible fetal ossification delays but no teratogenic effects up to the highest dose tested (approximately 7 times the estimated human plasm exposure based on AUC).”

Based on the non-clinical animal delafloxacin appears not to be teratogenic. However, as pre-pregnant women were not included in either the clinical Phase 2 or 3 trials, this reviewer can not make a definitive statement of the teratogenic potential of delafloxacin on fetuses.

8.8.3 Pediatrics and Assessment of Effects on Growth

Under Section 505B(a)(4)(A) of the Food, Drug and Cosmetic Act, the Applicant requested a *full product-specific waiver* from “generating clinical data in pediatric patients aged 0 to <18 years old with ABSSEI” for both oral and IV formulations of delafloxacin.

Invoking the Pediatric Research Equity Act (PREA), the Applicant based their request for a *full pediatric waiver* in accordance with the following exemptions:

1. The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.
2. The product fails to represent a meaningful therapeutic benefit over existing antimicrobials for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

Citing previous nonclinical canine data from earlier quinolones, which demonstrated damage to articular cartilage in weight-bearing joints of beagle dogs, and which consequently led to a boxed warning cautioning of “an increased risk for tendonitis and tendon rupture” (“*in all ages*”), the Applicant acknowledges that there are existing safety concerns related to the potential for fluoroquinolone-associated arthropathy in growing children. In conducting their own non-clinical studies in juvenile animals, the Applicant indicated that the potential for arthrototoxicities as seen in other quinolones, but to a lesser degree. The Applicant initially proposed the following language in the BAXDELA label regarding pediatric use of delafloxacin:

“Safety and effectiveness in pediatric patients below the age of 18 have not been established. Fluoroquinolones cause arthropathy in juvenile animals.”

The Applicant has cited that many alternative antimicrobial therapies available as first-line agents for the treatment of ABSSSIs, options which demonstrate a more favorable risk-benefit profile in pediatric populations than FQs.

Medical Reviewer’s Comment: *Delafloxacin has not been studied in pediatric patients less than 18 years of age, hence there are no pediatric data available for review in this application. Based on the class wide finding of FQ associated arthropathy in juvenile beagle dogs, the Applicant has sought a full pediatric waiver. This reviewer proposes the following language under SECTION 8.4 of the PI:*

“Clinical studies have not been conducted in pediatric patients less than 18 years of age. Therefore, the safety and effectiveness of BAXDELA has not been established in pediatric patients in this age category. Due to the lack of clinical experience with BAXDELA in pediatric patients less than 18 and the findings of FQ associated arthropathy in juvenile animal studies, BAXDELA is not recommended for use in children under 18 years of age.”

At the time of this review, a meeting is scheduled with the FDA PeRC to discuss the Applicant’s request for a full pediatric waiver in children <18 years of age.

8.8.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Delafloxacin is an antimicrobial agent with a recommended duration of treatment of 5-14 days. Although the potential for drug abuse, withdrawal, or rebound with delafloxacin was not evaluated in this application, the likelihood for abuse, withdrawal and/or rebound this is unexpected.

The Applicant reported five cases of subjects in whom there were overdosing errors during the Phase 3 studies. All subjects in whom these dosing errors occurred received doses lower than the maximum delafloxacin dose evaluated in the Phase 1 studies (single oral doses up to 1600-mg an multiple oral doses up to 1200 mg; single IV doses up to 1200mg).

Based on delafloxacin’s safety profile, in the setting of overdose, GI effects, such as nausea, diarrhea, and vomiting may most likely be expected. Supportive care should be considered for persons experiencing an intentional or unintentional overdose.

8.9 Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Delafloxacin is not currently marketed in the U.S or abroad, therefore the experience with delafloxacin is limited to its Phase 1, 2, and 3 clinical trial experience.

Medical Reviewer’s Comments: As a member of the FQ class, delafloxacin will carry a boxed warning found in currently marketed FQs which caution against FQ-associated serious adverse reactions, namely, “Tendinopathy, Peripheral Neuropathy or Central Nervous Effects.” However, as this review highlights, these constellation of serious events were not described

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together or separately (where the observed event was deemed to be in association with delafloxacin) in any of the Applicant's Phase 2 or 3 clinical trials.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety analyses and conclusions from this review were based upon evaluation of the data contained the Applicant's submitted Phase 2 and 3 trial populations. The eligibility criteria for these four pivotal trials may mitigate potential safety concerns that may be observed in the wider postmarket setting. At the time of this review, exploration of the presented safety data indicate that GI-related events are most likely to be encountered in patients receiving delafloxacin. In addition, one can anticipate that FQ-class related safety events may emerge in the postmarket setting. Emergence of any new safety events can be managed by routine pharmacovigilance surveillance.

8.10 Additional Safety Issues From Other Disciplines

Due to insufficient data precluding adequate characterization of potential safety signals (and efficacy) in patients with kidney failure in Phase 3 studies and Phase 2 trials, the Clinical Pharmacology team concluded that delafloxacin not be recommended in patients with kidney failure (CKD Stage 5)

8.11 Integrated Assessment of Safety

No major delafloxacin specific safety concerns were identified during the review of this product. As previously stated, the GI-related adverse reactions of nausea, diarrhea, and vomiting were the predominant findings associated with this drug. In addition, infusion site reactions and elevations in transaminases were frequently observed treatment emergent reactions. Although, this review assessed for any potential associations between delafloxacin and several FQ related AEs, it is this reviewer's assessment that, in the reviewed pre-market Phase 2 and 3 trials safety populations, delafloxacin does not appear to result in peripheral neuropathies, tendinopathies, or CNS effects. It is quite possible that in the post-marketing phase when larger numbers of persons are exposed to delafloxacin more FQ-associated AEs may emerge in greater numbers and frequency. However, based on pre-market data there were no such concerning safety signals.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this application.

10 Labeling Recommendations

10.1 Prescribing Information

At the time of this review, labeling negotiations are actively ongoing with the Applicant and the Agency. Major labeling recommendations or changes will be summarized, as needed, in an addendum to the clinical review.

1 INDICATIONS AND USAGE

This Section specifies that BAXDELA is indicated for use in adults with ABSSSI and the Gram positive and negative pathogens recommended for coverage.

2 DOSAGE AND ADMINISTRATION

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This Section recommends that neither the IV or oral formulations be used in patients with ESRD (including with and without HD).

3 DOSAGE FORMS AND STRENGTHS

This Section adds the wording “modified-capsule shaped tablets.”

4 CONTRAINDICATIONS

No major changes to this Section.

5 WARNINGS AND PRECAUTIONS

(b) (4)

6 ADVERSE REACTIONS

Table ^{(b) (4)} entitled “Selected Adverse Reactions Occurring in $\geq 2\%$ of Patients” has been updated to include “Transaminase Elevations,” ^{(b) (4)} and percentages have been updated to reflect adverse reactions irrespective of investigator’s assessed causality. Additional edits were made to the “Adverse Reactions Occurring in Less Than 2% of Patients” listing.

7 DRUG INTERACTIONS

No major changes were recommended for this Section.

8 USE IN SPECIFIC POPULATIONS

Updates more consistent with PLLR labeling were made to sub-sections 8.1 “Pregnancy” and 8.2 “Lactation.” Language in sub-section 8.4 “Pediatric Use” was updated to indicate that delafloxacin is not recommended for use in pediatric patients <18 years of age, due to the FQ class wide association of arthropathy in juvenile dogs. Sub-section 8.7 Renal Impairment was amended to reflect the Agency’s recommended dosage adjustments for subjects with severe renal impairments and those with ESRD.

10 OVERDOSAGE

No major changes were recommended to/for this Section.

11 DESCRIPTION

No major changes were recommended to/for this Section.

12 CLINICAL PHARMACOLOGY

No major changes were recommend to the content of this Section, aside from Sub-section 12.4 Microbiology where the Agency’s recommended updates to the pathogens with sufficient available data to merit coverage with this drug and Agency recommended changes to susceptibility MIC and disk diffusion diameter breakpoints.

13 NONCLINICAL TOXICOLOGY

Aside from a statement indicating that articular degeneration was observed in at least one dog that was administered the oral tablet formulation of the drug and additional details related to findings observed in rat fertility studies, no major changes were recommended to the content of this Section.

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14 CLINICAL STUDIES

Several recommended updates and corrections to the tables and information contained in this Section were incorporated.

16 HOW SUPPLIED/STORAGE AND HANDLING

No major content changes were recommended for this Section.

17 PATIENT COUNSELING INFORMATION

No major changes were recommended to the content of this Section, aside from the addition of a statement recommending that taking several specific medications, patients should wait at least 2 hour before or 6 hours after taking BAXDELA to then take these medications.

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Appendix

Clinical Investigator Financial Disclosures

Clinical Investigator Financial Disclosure

Application Number: NDA 208,610 and NDA 208,611

Submission Date(s): 18 October 2016

Applicant: Melinta Therapeutics, Inc.

Product: Delafloxacin

Reviewer: Caroline J. Jjingo MD, MPH

Date of Review: 13 June 2017

Covered Clinical Study (Name and/or Number): RX-3341-303, RX-3341-302;
 RX-3341-202; RX-3341-201

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators and sub-investigators identified: <u>674</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
<p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u></p> <p>Significant payments of other sorts: <u>N/A</u></p> <p>Proprietary interest in the product tested held by investigator: <u>1</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>N/A</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>2</u>		

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Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)
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Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Upon review of the submitted documents, this reviewer confirms that the applicant has adequately disclosed financial interests/arrangements with clinical investigators. Based on the submitted information, this reviewer does not believe that there are any financial interests/arrangements that would affect the approvability of the application.

¹ See [web address].

Table 83: Number of Subjects by Recruited by Geographic Region and Country						
GEOGRAPHIC LOCATION		PROTOCOL 302 N= 660		PROTOCOL 303 N=850		POOLED PHASE 3 TRIALS
Region	Country	Delafloxacin n=331	Vancomycin (± Aztreonam) n=329	Delafloxacin n=423	Vancomycin (± Aztreonam) n=427	All subjects
ASIA, # of subjects/n (%)	Korea (KOR)	0 (0.0%)	0 (0.0%)	8 (1.9%)	13 (3.0%)	21 (1.4%)
	Taiwan (TWN)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	2 (0.1%)
<i>Asia Sub-total</i>		<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>9 (2.1%)</i>	<i>14 (3.3%)</i>	<i>23 (1.5%)</i>
EUROPE, # of subjects/n (%)	Bulgaria (BGR)	0 (0.0%)	0 (0.0%)	45 (10.6%)	42 (9.8%)	87 (5.6%)
	Spain (ESP)	0 (0.0%)	2 (0.6%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
	Estonia (EST)	0 (0.0%)	0 (0.0%)	32 (7.6%)	40 (9.4%)	72 (4.8%)
	Georgia (GEO)	0 (0.0%)	0 (0.0%)	17 (4.0%)	14 (3.3%)	31 (2.1%)
	Croatia (HRV)	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)
	Hungary (HUN)	2 (0.6%)	1 (0.3%)	10 (2.4%)	16 (3.7%)	29 (1.9%)
	Israel (ISR)	12 (3.6%)	12 (3.7%)	0 (0.0%)	0 (0.0%)	24 (1.6%)
	Latvia (LVA)	16 (4.8%)	14 (4.3%)	29 (6.9%)	22 (5.2%)	81 (5.4%)
	Moldova (MDA)	0 (0.0%)	0 (0.0%)	9 (2.1%)	22 (5.2%)	31 (2.1%)
	Romania (ROU)	0 (0.0%)	0 (0.0%)	23 (5.4%)	17 (4.0%)	40 (2.7%)
	Ukraine (UKR)	31 (9.4%)	26 (7.9%)	0 (0.0%)	0 (0.0%)	57 (3.8%)
	<i>Europe Sub-total</i>		<i>63 (19.0%)</i>	<i>55 (16.7%)</i>	<i>165 (39%)</i>	<i>173 (40.5%)</i>
LATIN AMERICA, # of subjects/n (%)	Argentina (ARG)	0 (0.0%)	0 (0.0%)	4 (1.0%)	5 (1.2%)	9 (0.6%)
	Brazil (BRA)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1.2%)	5 (0.3%)
	Chile (CHL)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	2 (0.1%)
	Mexico (MEX)	0 (0.0%)	0 (0.0%)	8 (1.9%)	4 (0.9%)	12 (0.8%)
	Peru (PER)	0 (0.0%)	0 (0.0%)	34 (8.0%)	29 (6.8%)	63 (4.2%)
<i>Latin America Sub-total</i>		<i>0 (0.0%)</i>	<i>0 (0.0%)</i>	<i>47 (11.0%)</i>	<i>44 (10.3%)</i>	<i>91 (6.3%)</i>

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Table 83: Number of Subjects by Recruited by Geographic Region and Country						
GEOGRAPHIC LOCATION		PROTOCOL 302 N= 660		PROTOCOL 303 N=850		POOLED PHASE 3 TRIALS
Region	Country	Delafloxacin n=331	Vancomycin (± Aztreonam) n=329	Delafloxacin n=423	Vancomycin (± Aztreonam) n=427	All subjects
NORTH AMERICA, # of subjects/n (%)	USA	268 (81.0%)	274 (83.3%)	202 (47.8%)	196 (45.9%)	940 (62.3%)
	Subjects(filtered)	331 (100.0%)	329 (100.0%)	423 (100%)	427 (23.80%)	1510 (100.00%)
SOURCE: ADSL data set.						

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Table 84: Infection Type by Region and Country

			Protocol 302 N=660		Protocol 303 N=850	
Region	Country	Type of Infection	Delafloxacin N=331	Vancomycin (± Aztreonam) N=329	Delafloxacin N=423	Vancomycin ± Aztreonam N=427
Asia	Korea (KOR)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	8 (1.9%)	13 (3.0%)
	Taiwan (TWN)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)
EUROPE	Bulgaria (BGR)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	21 (5.0%)	22 (5.2%)
		Major Cutaneous Abscess	0 (0.0%)	0 (0.0%)	12 (2.8%)	11 (2.6%)
		Wound Infection	0 (0.0%)	0 (0.0%)	10 (2.4%)	8 (1.8%)
		Burn Infection	0 (0.0%)	0 (0.0%)	2 (0.5%)	1 (0.2%)
	Croatia (HRV)	Cellulitis/Erysipelas	2 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Estonia (EST)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	23 (5.4%)	25 (5.9%)
		Wound Infection	0 (0.0%)	0 (0.0%)	8 (1.9%)	11 (2.6%)
		Major Cutaneous Abscess	0 (0.0%)	0 (0.0%)	1 (0.2%)	4 (0.9%)
	Georgia (GEO)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	15 (3.6%)	12 (2.8%)
		Major Cutaneous Abscess	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)
		Wound Infection	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)
	Croatia (HRV)	Cellulitis/Erysipelas	2 (0.6%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Hungary (HUN)	Cellulitis/Erysipelas	2 (0.6%)	1 (0.30%)	10 (2.36%)	16 (3.75%)
	Israel (ISR)	Cellulitis/Erysipelas	11 (3.3%)	11 (3.34%)	0 (0.0%)	0 (0.0%)
		Major Cutaneous Abscess	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Wound Infection	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
	Latvia (LVA)	Cellulitis/Erysipelas	10 (3.02%)	11 (3.34%)	16 (3.78%)	10 (2.34%)
		Major Cutaneous Abscess	5 (1.51%)	3 (0.9%)	6 (1.42%)	7 (1.64%)
		Wound Infection	1 (0.30%)	0 (0.0%)	6 (1.42%)	4 (0.94%)

		Burn Infection	0 (0.0%)	0 (0.0%)	1 (0.24%)	1 (0.23%)
	Moldova (MVA)	Major Cutaneous Abscess	0 (0.0%)	0 (0.0%)	6 (1.42%)	12 (2.81%)
		Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	2 (0.47%)	6 (1.41%)
		Wound Infection	0 (0.0%)	0 (0.0%)	1 (0.24%)	4 (0.94%)
	Romania (ROU)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	13 (3.07%)	7 (1.64%)
		Major Cutaneous Abscess	0 (0.0%)	0 (0.0%)	4 (0.95%)	4 (0.94%)
		Wound Infection	0 (0.0%)	0 (0.0%)	5 (1.18%)	5 (1.17%)
		Burn Infection	0 (0.0%)	0 (0.0%)	1 (0.24%)	1 (0.23%)
	Spain (ESP)	Cellulitis/Erysipelas	0 (0.00%)	2 (0.6%)	0 (0.0%)	0 (0.0%)
	Ukraine (UKR)	Cellulitis/Erysipelas	28 (8.5%)	22 (6.7%)	0 (0.0%)	0 (0.0%)
		Wound Infection	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Major Cutaneous Abscess	2 (0.6%)	4 (1.2%)	0 (0.0%)	0 (0.0%)
Latin America	Argentina (ARG)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	4 (0.95%)	5 (1.2%)
	Brazil (BRA)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.9%)
		Wound Infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
	Chile (CHL)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	1 (0.24%)	1 (0.2%)
	Mexico (MEX)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	4 (1.0%)	3 (0.7%)
		Major Cutaneous Abscess	0 (0.0%)	0 (0.0%)	3 (0.7%)	0 (0.0%)
		Wound Infection	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)
Peru (PER)	Cellulitis/Erysipelas	0 (0.0%)	0 (0.0%)	30 (7.1%)	27 (6.3%)	
	Major Cutaneous Abscess	0 (0.0%)	0 (0.0%)	4 (1.0%)	2 (0.47%)	
		Wound Infection	114 (34.4%)	115 (35.0%)	79 (18.7%)	77 (18.0%)
North America	USA	Major Cutaneous Abscess	76 (23.0%)	76 (23.1%)	69 (16.3%)	65 (15.2%)
		Cellulitis/Erysipelas	75 (22.7%)	81 (24.6%)	54 (12.8%)	54 (12.7%)
		Burn Infection	3 (0.9%)	2 (0.6%)	0 (0.0%)	0 (0.0%)

Clinical Review
Caroline J. Jjingo, MD, MPH
NDA 208,610 and NDA 208,611
BAXDELA™ (delafloxacin meglumine)

		Subjects(filtered)	331 (100.0%)	329 (100.0%)	423 (100.0%)	427 (100.0%)
Source: ADSL data set in ISE population						

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Clinical Review
 Caroline J. Jjingo, MD, MPH
 NDA 208,610 and NDA 208,611
 BAXDELA™ (delafloxacin meglumine)

Key Target Gram Positive Pathogens by Polymicrobial vs Monomicrobial Infections, MITT Population (ABSSSI Source)	Delafloxacin	Vancomycin (± Aztreonam)
<i>Staphylococcus aureus, N</i>	319	323*
Monomicrobial Gram Positive Infections, n (%)	234 (73.4%)	248 (76.8%)
Polymicrobial Gram Positive Infections, n (%)	53 (16.6%)	36 (11.1%)
Polymicrobial Gram Mixed Infections, n (%)	32 (10.0%)	40 (12.4%)
<i>Staphylococcus aureus—MSSA, N</i>	177	183*
Monomicrobial Gram Positive Infections, n (%)	119 (67.2%)	127 (69.4%)
Polymicrobial Gram Positive Infections, n (%)	33 (18.6%)	26 (14.2%)
Polymicrobial Gram Mixed Infections, n (%)	25 (14.1%)	29 (15.9%)
<i>Staphylococcus aureus—MRSA, N</i>	144	141
Monomicrobial Gram Positive Infections, n (%)	118 (81.9%)	120 (85.1%)
Polymicrobial Gram Positive Infections, n (%)	19 (13.2%)	10 (7.1%)
Polymicrobial Gram Mixed Infections, n (%)	7 (4.9%)	11 (7.8%)
<i>Streptococcus anginosus Group</i>		
<i>Streptococcus intermedius, N</i>	28	30
Monomicrobial Gram Positive Infections, n (%)	15 (53.6%)	16 (53.3%)
Polymicrobial Gram Positive Infections, n (%)	7 (25.0%)	10 (33.3%)

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Polymicrobial Gram Mixed Infections, n (%)	6 (21.4%)	4 (13.3%)
<i>Streptococcus anginosus, N</i>	23*	23*
Monomicrobial Gram Positive Infections, n (%)	8	9
Polymicrobial Gram Positive Infections, n (%)	4	6
Polymicrobial Gram Mixed Infections, n (%)	12	10
<i>Streptococcus constellatus, N</i>	14	13
Monomicrobial Gram Positive Infections, n (%)	6 (42.9%)	2 (15.4%)
Polymicrobial Gram Positive Infections, n (%)	4 (28.6%)	5 (38.5%)
Polymicrobial Gram Mixed Infections, n (%)	4 (28.6%)	6 (46.2%)
<i>Streptococcus pyogenes, N</i>	23	17
Monomicrobial Gram Positive Infections, n (%)	11 (47.8%)	11 (64.7%)
Polymicrobial Gram Positive Infections, n (%)	10 (43.5%)	5 (29.4%)
Polymicrobial Gram Mixed Infections, n (%)	2 (8.7%)	1 (5.9%)
<i>Staphylococcus haemolyticus, N</i>	15	8*
Monomicrobial Gram Positive Infections, n (%)	5 (33.3%)	4
Polymicrobial Gram Positive Infections, n (%)	5 (33.3%)	4
Polymicrobial Gram Mixed Infections, n (%)	5 (33.3%)	

Clinical Review
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 BAXDELA™ (delafloxacin meglumine)

		1
<i>Streptococcus agalactiae, N</i>	14	12
Monomicrobial Gram Positive Infections, n (%)	3 (21.4%)	4 (33.3%)
Polymicrobial Gram Positive Infections, n (%)	6 (42.9%)	5 (41.7%)
Polymicrobial Gram Mixed Infections, n (%)	5 (35.7%)	3 (25.0%)
<i>Enterococcus faecalis, N</i>	11	16
Monomicrobial Gram Positive Infections, n (%)	1 (9.1%)	6 (37.5%)
Polymicrobial Gram Positive Infections, n (%)	6 (54.5%)	3 (18.8%)
Polymicrobial Gram Mixed Infections, n (%)	4 (36.4%)	7 (43.8%)
<i>Staphylococcus lugdunensis, N</i>	11*	9
Monomicrobial Gram Positive Infections, n (%)	5	3 (33.3%)
Polymicrobial Gram Positive Infections, n (%)	6	6 (66.7%)
Polymicrobial Gram Mixed Infections, n (%)	1	0 (0.0%)
(b) (4)		
Polymicrobial Gram Mixed Infections, n (%)	4 (66.7%)	3 (30.0%)

Clinical Review
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BAXDELA™ (delafloxacin meglumine)

Source: ADSL and ADMB data sets. Due to rounding final %s may not be exactly 100%.

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Table 85: Outcomes by Baseline Pathogen (Pooled across Trial 1 and Trial 2; MITT Population)				
	Clinical Response at 48-72 hours ^a		Clinical Investigator-Assessed Success ^b at Follow-Up	
	BAXDELA	Comparator	BAXDELA	Comparator
Pathogen	n/N (%)	n/N (%)	n/N (%)	n/N (%)
<i>Staphylococcus aureus</i>	271/319 (85.0)	269/324 (83.0)	275/319 (86.2)	269/324 (83.0)
Methicillin-susceptible ^c	149/177 (84.2)	148/183 (80.9)	154/177 (87.0)	153/183 (83.6)
Methicillin-resistant ^c	125/144 (86.8)	121/141 (85.8)	122/144 (84.7)	116/141 (82.3)
<i>Streptococcus pyogenes</i>	17/23 (73.9)	9/18 (50.0)	21/23 (91.3)	16/18 (88.9)
<i>Staphylococcus haemolyticus</i>	11/15 (73.3)	7/8 (87.5)	13/15 (86.7)	7/8 (87.5)
<i>Streptococcus agalactiae</i>	10/14 (71.4)	9/12 (75.0)	12/14 (85.7)	11/12 (91.7)
<i>Streptococcus anginosus</i> Group	59/64 (92.2)	55/61 (90.2)	54/64 (84.4)	47/61 (77.0)
<i>Staphylococcus lugdunensis</i>	8/11 (72.7)	6/9 (66.7)	10/11 (90.9)	8/9 (88.9)
<i>Enterococcus faecalis</i>	11/11 (100.0)	12/16 (75.0)	9/11 (81.8)	14/16 (87.5)
<i>Escherichia coli</i>	12/14 (85.7)	16/20 (80.0)	12/14 (85.7)	18/20 (90.0)
<i>Enterobacter cloacae</i>	10/14 (71.4)	8/11 (72.7)	12/14 (85.7)	10/11 (90.9)
<i>Klebsiella pneumoniae</i>	19/22 (86.4)	22/23 (95.7)	20/22 (90.9)	21/23 (91.3)
<i>Pseudomonas aeruginosa</i>	9/11 (81.8)	11/12 (91.7)	11/11 (100.0)	12/12 (100.0)

Source: Adapted from the delafloxacin label. ^aObjective clinical response was defined as a 20% or greater decrease in lesion size as determined by digital planimetry of the leading edge of erythema at 48 to 72 hours after initiation of treatment. ^bInvestigator-assessed success was defined as complete or near resolution of signs and symptoms, with no further antibacterial needed at Follow-up Visit (Day 14 ±1). ^cDiscrepancy in the total numbers is due to the total numbers is due to the multiple subjects having both MRSA and MSSA isolates.

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

/s/

CAROLINE J JJINGO
06/14/2017

THOMAS D SMITH
06/14/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 208,610 **Applicant:** Melinta Therapeutics **Stamp Date:** October 19, 2016
 & NDA208,611

Drug Name: Delafloxacin (Baxdela) **NDA/BLA Type:** 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm)	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			In Module 2.5.6
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:	X			There are multiple Phase 1 dose ranging studies in support of the recommended IV and oral dosing regimen for delafloxacin.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? <u>Pivotal Study #1</u> RX-3341-302 Phase 3, Multicenter, Randomized, Double-blind, Active-controlled Study to Evaluate the Efficacy and Safety of Delafloxacin Compared with Vancomycin + Aztreonam in Patients With Acute Bacterial Skin and Skin Structure Infections <u>Indication:</u> Acute Bacterial Skin and Skin Structure Infections (ABSSSI) <u>Pivotal Study #2</u> RX-3341-303 Phase 3, Multicenter, Randomized, Double-blind, Active-controlled Study to Evaluate the Efficacy and Safety of IV and Oral Delafloxacin Compared With Vancomycin + Aztreonam in Patients With Acute Bacterial Skin and Skin Structure Infections <u>Indication:</u> Acute Bacterial Skin and Skin Structure Infections	X			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		<u>Study 302:</u> 82% of all subjects are from North America and the remaining 18% are from Europe. <u>Study 303:</u> Nearly 50% of all subjects were from North America (including US and Mexico).
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			<u>RX-3341-111 TQT:</u> A Randomized, Crossover Study to Define the ECG Effects of Delafloxacin Using a Clinical and a Supratherapeutic Dose Compared With Placebo and Oral Moxifloxacin (a

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					Positive Control) in Healthy Men and Women: A Thorough ECG Study
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dosage (or dosage range) believed to be efficacious?		X		
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
25.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			Study 302: The sponsor submitted an AE coding dictionary for Study 302. Study 303: There was no AE coding dictionary for Study 303, however, verbatim terms can be mapped to preferred terms.
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry)	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?				
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Study 302: 82% of all subjects are from North America (the US) and the remaining 18% are from Europe. Study 303: Nearly 50% of all subjects were from North America (including US and Mexican clinical sites).
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			Module 1.3.4
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __ Yes _____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Caroline J. Jjingo
Reviewing Medical Officer

November 21, 2016
Date

Clinical Team Leader

Date

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

/s/

CAROLINE J JJINGO
11/28/2016

THOMAS D SMITH
11/28/2016