

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208610Orig1s000

208611Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Subject	Division Director Summary Review
NDA #s	NDA 208610 and 208611
Applicant	Melinta Therapeutics, Inc.
Date of Submission	October 19, 2016
PDUFA Goal Date	June 19, 2017
Proprietary Name / Non-Proprietary Name	Baxdela (delafloxacin)
Dosage Form(s) / Strength(s)	Tablets, 450 mg and Powder for injection, 300 mg/vial
Applicant Proposed Indication(s)/Population(s)	Acute bacterial skin and skin structure infections in adults
Recommended Action for NME:	Approval
Recommended Indication/Population(s)	Acute bacterial skin and skin structure infections in adults

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Caroline Jjingo MD MPH
Statistical Review	Janelle Charles PhD
Pharmacology Toxicology Review	Amy Nostrandt DVM PhD and Wendelyn Schmidt PhD
OPQ ATL Review	Balajee Shanmugam PhD
Microbiology Review	Jalal Sheikh PhD
Clinical Pharmacology Review	Kunyi Wu PharmD
OPDP	Puja Shah PharmD
OSI	Bei Yu PhD
CDTL Review	Thomas Smith MD
OSE/DMEPA	Sevan Kolejian PharmD
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OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK= Division of Risk Management
 DMPP=Division of Medical Policy Programs
 ATL= Application Technical Lead

1. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Summary and Assessment

The Applicant has provided adequate evidence to support the safety and efficacy of delafloxacin for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI), at a dose of 300 mg every 12h administered over 60 minutes via intravenous infusion or 450 mg orally every 12h for a total duration of 5 to 14 days. The efficacy of delafloxacin was demonstrated in two adequate and well-controlled noninferiority trials comparing delafloxacin to vancomycin plus aztreonam. The key characteristics of the two trials were consistent with the recommendations in the ABSSSI guidance, including infection type, lesion size, use of prior effective antibacterial drugs, and endpoints.¹ Noninferiority (NI) was demonstrated in both trials for the primary endpoint of a 20% reduction in lesion size at the 48-72 hour timepoint post-randomization; the pre-specified noninferiority margin of 10% was met in both trials. Treatment effect was also seen at later time points including the end of therapy and the follow up visits.

While other approved therapies are available for the treatment of ABSSSI, it is beneficial to have different therapeutic options. Resistance to available therapies is continuing to increase and hence having a variety of treatment options is always optimal. Also, it is important to have antibacterial drugs with different safety profiles to ensure that patients who are allergic or have safety issues with certain drugs or classes of drugs have treatment options. There are other approved therapies for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA), an important cause of ABSSSI; however, there are few oral treatment options for patients with infections due to MRSA. As the spectrum of activity of delafloxacin includes MRSA and certain Gram-negative bacteria, it provides another oral option for patients for the treatment of ABSSSI.

From a safety standpoint, no significant safety concerns emerged in the safety database of 1682 delafloxacin-exposed subjects (varying doses and durations) that included 741 patients in the two Phase 3 trials. The common adverse reactions reported in the clinical trials included nausea, diarrhea, headache, transaminase elevations and vomiting. As delafloxacin is a member of the fluoroquinolone class of antibacterial drugs, it is possible that safety findings related to the drug will become evident postmarketing when a larger number of patients are exposed to the drug. Labeling for this product will include safety-related information that is applicable to the fluoroquinolone class of antibacterial drugs. Safety information regarding myasthenia gravis and disabling and potentially irreversible serious adverse reactions that have occurred together, including, tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects will be included in the Boxed Warning. The Warnings and Precautions section will include class labeling language including, disabling and potentially irreversible serious adverse reactions, tendinitis and tendon rupture, peripheral neuropathy, central nervous system effects, exacerbation of myasthenia gravis, and hypersensitivity reactions. Also, consistent with other fluoroquinolones, labeling will include a Medication Guide to convey important safety information to patients. Delafloxacin is not recommended for use in patients with End Stage Renal Disease (ESRD) (eGFR <15 mL/min including hemodialysis) as there are no observed data in patients with ESRD receiving delafloxacin tablets and the concerns with accumulation of sulfobutylether-beta-cyclodextrin (SBECD) in ESRD patients receiving the intravenous formulation. Continued

¹ FDA guidance for industry *Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment* (October, 2013)

pharmacovigilance postmarketing will help identify any emerging safety signals once the product is approved and used more widely.

Pediatric studies were waived as the risks with fluoroquinolones outweigh the benefits for the indication of ABSSSI. This information will be included in the Pediatric Use section of the prescribing information.

I agree with the recommendations by the review team and the CDTL that these NDAs be approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	ABSSSI is a serious bacterial infection and includes conditions such as cellulitis, wound infections and abscesses.	ABSSSI is a serious bacterial infection that if left untreated can cause significant morbidity and lead to death in some circumstances.
Current Treatment Options	There are many approved antibacterial drugs for the treatment of ABSSSI or complicated skin and skin structure infections. Some of these drugs are available only as intravenous formulations and some are available as both oral and intravenous formulations. Most approved therapies cover the common Gram-positive bacteria that cause ABSSSI, including <i>S. aureus</i> and <i>Streptococcus pyogenes</i> . Some approved therapies are more broad-spectrum and have activity against Gram-negative bacteria as well. Approved antibacterial drugs including, linezolid, daptomycin, telavancin, ceftaroline, dalbavancin, tedizolid, and oritavancin also have activity against MRSA. Of these, only linezolid and tedizolid are available in oral formulations.	There are many approved antibacterial drugs for the treatment of ABSSSI/complicated skin and skin structure infections. Approved therapies are available as either intravenous or intravenous and oral formulations.
Benefit	The efficacy of delafloxacin in the treatment of ABSSSI has been demonstrated in two adequate and well-controlled NI trials in which delafloxacin was noninferior to the comparator (vancomycin plus aztreonam) in the intent to treat population. The efficacy of delafloxacin was demonstrated for the primary endpoint of clinical response assessed at 48-72 hours from treatment initiation. Clinical response was also sustained at later time points including the end of therapy and at follow up on Day 14 ± 1. Efficacy findings were consistent across different analysis populations and in different subgroups. Patients enrolled in these trials had a variety of skin	Delafloxacin was demonstrated to be noninferior to an acceptable comparator regimen in two adequate and well-controlled trials. Delafloxacin offers the advantage of being available as parenteral and oral formulations and so patients do not need to be switched to a different therapy for oral step-down. It also provides for another oral treatment option for MRSA and can also be useful for the treatment of mixed infections due

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>infections, including abscesses, wound infections, and cellulitis. The etiologic agents also varied and included the common Gram positive organisms (e.g., <i>S. aureus</i> (both methicillin-susceptible and resistant), <i>S. pyogenes</i>) and Gram-negative bacteria (e.g. <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>). No specific concerns with regard to efficacy were noted for any of the organisms for which the product will be indicated.</p>	<p>to its activity against the common Gram-positive and Gram-negative bacteria that cause ABSSSI.</p>
<p>Risk</p>	<p>The clinical development program for delafloxacin includes healthy volunteers and patients exposed to varying doses and durations of treatment. The safety database at the proposed dose and duration (oral/intravenous) in the Phase 3 trials was 741. The common adverse reactions reported in the clinical trials included nausea, diarrhea, headache, transaminase elevations and vomiting. As delafloxacin is a member of the fluoroquinolone class of antibacterial drugs, it is possible that safety findings related to the fluoroquinolone class will become evident postmarketing when a larger number of patients are exposed to the drug.</p>	<p>As delafloxacin is a member of the fluoroquinolone class of antibacterial drugs, there are safety concerns that should be taken into consideration. Although no major safety signals were identified in the database so far, it is important to note that the safety database at this time is rather small. As with other fluoroquinolones, it is possible that the safety signals will emerge postmarketing and will need to be closely monitored.</p>
<p>Risk Management</p>	<p>Labeling for this product will include safety-related information that is applicable to the fluoroquinolone class of antibacterial drugs. Safety information regarding myasthenia gravis and disabling and potentially irreversible serious adverse reactions that have occurred together, including, tendinitis and tendon rupture, peripheral neuropathy, and central nervous system effects will be included in the Boxed Warning. The Warnings and Precautions section will include class labeling language including, disabling and potentially irreversible serious adverse reactions, tendinitis and tendon rupture, peripheral neuropathy, central nervous system effects, exacerbation of myasthenia gravis, and hypersensitivity reactions. Also, consistent with other fluoroquinolones, labeling will include a Medication Guide to convey important safety information to patients. Continued pharmacovigilance postmarketing will help identify emerging safety signals once the product is approved and used more widely.</p>	<p>Routine postmarketing surveillance activities will suffice at this point. There are no safety signals/potential for safety issues that require a Risk Evaluation and Mitigation Strategy (REMS) at this time. Labeling for the product, including the Medication Guide adequately conveys the safety concerns.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Pediatric studies were waived as the risks with fluoroquinolones outweigh the benefits for the indication of ABSSSI. Fluoroquinolones cause arthropathy in juvenile animals. This information will be included in the Pediatric Use section of the prescribing information.</p>	

2. Background

Melinta Therapeutics, Inc. submitted NDAs 208610 and 208611, for delafloxacin, a new fluoroquinolone antibacterial drug 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 (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*),

(b) (4)

(b) (4)

(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*. The Applicant is seeking approval of two formulations of delafloxacin (intravenous and tablets). The proposed dosing regimen is 300 mg every 12h administered over 60 minutes via intravenous infusion or 450 mg orally every 12h for a total duration of 5 to 14 days.

FDA guidance on ABSSSI defines ABSSSI as cellulitis and erysipelas, wound infection, and major cutaneous abscess and recommends enrollment of patients with a minimum lesion size of 75 cm² of redness, edema, or induration.¹ The IDSA treatment guidelines for skin and soft tissue infections provide recommendations for choice of empiric antimicrobial therapies, in addition to incision and drainage and surgical wound management, based on type of infection and etiologic agent.²

IND 62772 was filed by Abbott Laboratories on June 21, 2001, for ABT-492, the oral formulation of delafloxacin. The IND was transferred to Rib-X Pharmaceuticals on June 9, 2006. IND 76096 was filed by Rib-X Pharmaceuticals on March 20, 2007, for RX-3342, the IV formulation of delafloxacin. On October 7, 2013, FDA was notified that the Sponsor's name was changed to Melinta Therapeutics, Inc. The clinical development program included 30 completed studies: 23 Phase 1 studies, 4 Phase 2 trials (2 in ABSSSI and 2 in respiratory indications), and 3 Phase 3 trials (2 in ABSSSI and 1 in uncomplicated urogenital gonorrhea).

Special protocol agreements were reached for both ABSSSI trials, one on February 7, 2013, for the IV-only protocol (RX-3341-302) and on August 19, 2013, for the IV-to-oral protocol (RX-3341-303). FDA agreed to a modification of the latter protocol on July 1, 2015.

Qualified infectious disease product (QIDP) designation was granted for the ABSSSI indication on September 8, 2012, and fast track designation was granted on December 18, 2012. Based on the QIDP designation, both NDAs received a priority review.

² Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014;59:e10-52.

3. Product Quality

Balajee Shanmugam, Ph.D., is the Application Technical Lead (ATL) for these NDAs.

Drug Substance

Delafloxacin meglumine drug substance is polymorphic and is manufactured by (b) (4). (b) (4) was used in the clinical trials and stability studies. The Applicant has provided assurance that the desired polymorphic form, (b) (4) will be controlled and produced consistently in the drug substance manufacturing process. The drug substance specifications were considered adequate by the drug substance reviewer. Stability data support a retest period of (b) (4).

Drug Products

Delafloxacin Tablet

The tablet drug product manufactured by (b) (4) is an immediate release, modified capsule-shaped beige to mottled beige (b) (4) tablet. Each tablet contains 450 mg delafloxacin (equivalent to 649 mg delafloxacin meglumine) and the inactive ingredients, citric acid, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, sodium bicarbonate, and sodium phosphate monobasic monohydrate. The product specifications for the tablets were considered adequate. Stability data support the proposed shelf life of 36 months when stored at 20 to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).

The biopharmaceutics review found the proposed dissolution method and acceptance criterion acceptable. The clinical studies used a scored tablet while the commercial product is unscored. The bridging study between the scored and unscored tablets was acceptable.

The drug substance and drug product manufacturing facilities and the packaging and testing facilities were found to be acceptable.

The Office of Pharmaceutical Quality (OPQ) review team recommends approval of NDA 208610 from a product quality perspective. The Applicant has agreed to the CMC-related PMCs as noted in Section 13 of this review.

Delafloxacin for Injection

The manufacturer of the IV drug product is (b) (4). Delafloxacin for injection is a sterile, lyophilized powder containing 300 mg delafloxacin (equivalent to 433 mg delafloxacin meglumine) in a single-dose vial which must be reconstituted and further diluted with sterile 5% dextrose solution or 0.9% saline solution prior to intravenous infusion. Inactive ingredients include meglumine, sulfobutylether-β-cyclodextrin (SBECD), edetate sodium, (b) (4). Specifications for the injection formulation were considered adequate. The lyophilized cake may have variations in appearance (b) (4), which does not affect drug product quality. Stability data support an expiration date of 30 months when stored at 20 to 25°C (68°F to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F). The reconstituted powder may be stored

for up to 24 hours under refrigerated or controlled room temperature and then further diluted for intravenous infusion. The reconstituted solution in the infusion bag may be stored under refrigerated or controlled room temperature conditions for up to 24 hours.

The product quality microbiology review concluded that the Applicant has adequately mitigated drug product sterility and endotoxin risks. The Applicant will submit sterility test requalification data from the process validation batches as a CBE-30 supplement.

The Office of Process and Facilities has found the manufacturing and testing sites for both NDAs to be acceptable.

The OPQ review team recommends approval of both NDAs from a product quality perspective. The team has recommended postmarketing commitments as outlined in Section 13 of this review.

The ATL for these NDAs, Dr. Shanmugam, agrees with the OPQ review team and recommends approval of these NDAs.

4. Nonclinical Pharmacology/Toxicology

Wendelyn Schmidt PhD and Amy Nostrandt, DVM PhD are the pharmacology/toxicology reviewers for these NDAs.

In the 3-month repeat dose toxicology studies of delafloxacin in rats and dogs, the most prominent effects after both IV and oral dosing were gastrointestinal effects (abnormal stool, dilated cecum, and decreased food intake and/or body weights in rats; and emesis, salivation, and abnormal stool/diarrhea in dogs). Additional findings in rats included increased cholesterol, noisy respiration and epithelial hyperplasia and interstitial inflammation in the lungs. In dogs, the decrease in red blood cell parameters and increase in serum ALT and cholesterol were reversible. In one of the three high dose females in the only toxicology study of the tablet formulation in dogs, articular cartilage degeneration was noted. Studies performed to evaluate the effects of delafloxacin formulated with sulfobutylether-beta-cyclodextrin (Captisol®, SBECD) were consistent with earlier studies, with the exception of vacuolation in the kidney, a reversible finding known to occur with SBECD.

No adverse effects on fertility or early embryonic development were seen with IV delafloxacin in rats at exposures up to 5 times the human exposure. In embryo-fetal development studies, oral administration of delafloxacin to pregnant rats during the period of major organogenesis resulted in maternal toxicity and reduced fetal body weights at the highest dose (1600 mg/kg/day) and fetal ossification delays at all doses. No malformations were reported. The lowest dose in rats, 200 mg/kg/day, would be approximately 2.5 times the estimated human plasma exposure based on AUC. In a pre-postnatal development study in rats of IV delafloxacin, dams at the highest dose tested (120 mg/kg/day) exhibited slightly lower body weights and slightly longer gestation length than control animals (exposure estimated to be approximately 5 times human plasma exposure based on AUC). Effects on pups at that dose included increased mortality during lactation, small stature, and lower body weights, but no

changes to functional or developmental landmarks or reproductive performance were reported. The No Adverse Effect Level (NOAEL) for maternal toxicity and pup development in that study was 60 mg/kg/day, slightly lower than the equivalent clinical IV dose.

No concerns were identified in the genetic toxicology studies. The Applicant has agreed to two postmarketing requirements; one to further evaluate the distribution of the drug substance to the reproductive tract and developing fetus with the oral and IV formulations and the second to conduct an embryo-fetal developmental toxicology study in pregnant rats treated during the period of organogenesis with the IV formulation if the results of the tissue distribution studies demonstrate greater exposure of the fetus/maternal reproductive tract to delafloxacin with the IV formulation to assess any potential effects of delafloxacin with the excipient SBECD.

Dr. Nostrandt recommends approval of these NDAs and I agree with her assessment.

5. Clinical Pharmacology

Kunyi Wu, PharmD is the clinical pharmacology reviewer for these NDAs.

The AUC of a single 450 mg oral dose of delafloxacin is similar to that achieved with a single 300 mg IV dose. Under fasted conditions, peak plasma concentrations were achieved an hour after oral administration. The absolute bioavailability of a single dose of delafloxacin 450 mg oral tablet was 58.8%. The plasma protein binding of delafloxacin ranged from 80-84% in those with severe renal impairment and healthy subjects, respectively. The steady state volume of distribution of delafloxacin is 30-48 L. The estimated mean half-life was 3.7 hours and 4.2 to 8.5 hours following a single IV administration and multiple oral administration of delafloxacin, respectively. Following a single 300 mg IV dose of delafloxacin, the mean clearance (CL) of delafloxacin was 16.3 L/h; renal clearance (CL_r) accounts for 35-45% of the total clearance. Glucuronidation of delafloxacin is the primary metabolic pathway. There are no significant circulating metabolites in humans. After a single intravenous dose of ¹⁴C-labeled delafloxacin, 65% of the radioactivity is excreted in urine as unchanged delafloxacin and glucuronide metabolites and 28% is excreted in feces as unchanged delafloxacin. Following a single oral dose of ¹⁴C-labeled delafloxacin, 50% of the radioactivity is excreted in urine as unchanged delafloxacin and glucuronide metabolites and 48% is excreted in feces as unchanged delafloxacin.

The oral only delafloxacin dosing regimen has not been evaluated in any clinical studies in patients with ABSSSI. In a clinical study (Study RX-3341-115), the overall systemic exposure (AUC_{0-t} and AUC_{0-inf}) of delafloxacin were comparable between delafloxacin 450 mg tablet and IV delafloxacin (300 mg infused over 1 hour) after a single dose in healthy subjects. Taking together the results from Study RX-3341-115 and comparison of overall systemic exposure (AUCs) of delafloxacin across pharmacokinetic (PK) studies using the to-be-marketed IV and oral formulations, Dr. Wu concludes that the 450 mg oral tablet achieves comparable delafloxacin exposure to 300 mg administered IV. Also, based on results from studies using IV delafloxacin formulations (with or without SBECD), SBECD did not appear to alter delafloxacin PK. Based on the information provided by the Applicant and the FDA's independent population PK analyses, it appears that the disease state of ABSSSI is not likely

to alter the PK, specifically the absorption, of delafloxacin for the oral tablet formulation. Therefore, the proposed oral only dosing regimen 450 mg q12h for 5-14 days was found to be acceptable.

Dr. Wu agrees with the Applicant's proposed dosing regimen of 300 mg every 12 hours administered by IV infusion over 60 minutes or 450 mg q12h orally (with or without food) for a total duration of 5 to 14 days in patients with normal renal function. For patients with severe renal impairment (b) (4) the Applicant proposed a dose of 200 mg IV 12h or (b) (4) (b) (4). Dr. Wu does not agree with the proposed oral dosing in patients with severe renal impairment and the use of IV and oral delafloxacin in patients with ESRD.

In a PK study in subjects with renal impairment, following a single 300 mg IV dose, the AUC for the mild, moderate, and severe renal impairment groups were 1.3, 1.6, and 1.8 fold higher, respectively than that in subjects with normal renal function. In ESRD subjects on dialysis, following a single 300 mg IV dose, the AUC values of delafloxacin were 2.1 and 2.6 fold higher when on- and off-dialysis, respectively, than in subjects with normal renal function. Following a single 400 mg oral dose, the AUC values of delafloxacin for the mild, moderate, and severe renal impairment groups were 1.1, 1.5, and 1.6 fold higher, respectively, than the corresponding exposure in subjects with normal renal function. In patients with moderate renal impairment (n=37) in Phase 3 trials who received the proposed dose, the safety profile was similar to that of the overall safety population.

Dr. Wu agrees with the Applicant's proposal to reduce the IV dose to 200 mg q12h in patients with severe renal impairment. Based on simulations, the delafloxacin exposure is similar to that of normal subjects. Dr. Wu does not agree with the Applicant's proposal to (b) (4) (b) (4) in patients with severe renal impairment. Based on simulations, the mean AUC of delafloxacin is 30% lower compared to patients with normal renal function. Additionally, Probability of Target Attainment (PTA) analyses show that the oral dose of 450 mg (b) (4) administered to patients with severe renal impairment would result in a PTA of 65% at the proposed susceptible breakpoint of 0.5 mcg/mL for *S. aureus*. Dr. Wu recommends an oral dose of 450 mg q12h in patients with severe renal impairment. Simulation results show that at this dose, the mean AUC of delafloxacin is 48% higher than that in patients with normal renal function. Also, delafloxacin exposure at the 450 mg q12h oral dose is lower than that seen in patients who received 450 mg q12h IV in a Phase 2 study (Study RX-3341-201). No major safety concerns were identified in this study.

Dr. Wu does not recommend the use of oral or IV delafloxacin in patients with ESRD. No observed data are available in patients with ESRD receiving oral delafloxacin. In the dedicated renal impairment study, SBECd was found to accumulate extensively in subjects with severe renal impairment and ESRD subjects receiving hemodialysis. If the IV formulation is used in patients with severe renal impairment, routine monitoring of serum creatinine should be performed with consideration to changing to oral delafloxacin if increases in serum creatinine are observed.

The dosing recommendations are summarized in Table 1:

Table 1: Dosing Recommendations

Estimated Glomerular Filtration Rate (eGFR)(mL/min/1.73m ²) ^a	Recommended Dosage Regimen	
	Oral	Intravenous
30-89	No dosage adjustment	No dosage adjustment
15-29	No dosage adjustment	200 mg every 12 hours
ESRD (<15 including hemodialysis)	Not Recommended	
^a Estimate of GFR based on a Modification of Diet in Renal Disease (MDRD) equation. IV delafloxacin is administered over 60 minutes.		

In vitro studies to evaluate the potential of delafloxacin to induce or inhibit select cytochrome P450 isoforms and membrane transporters suggest a low potential for drug interactions. Delafloxacin was shown to be a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in vitro. The clinical relevance of co-administration of delafloxacin and P-gp or BCRP inhibitors is unknown.

In a randomized, positive- and placebo-controlled, thorough QT/QTc study, 51 healthy subjects received a single dose of delafloxacin 300 mg IV, delafloxacin 900 mg IV, oral moxifloxacin 400 mg, or placebo. Delafloxacin did not have any clinically relevant adverse effect on cardiac repolarization.

The Office of Clinical Pharmacology review team recommends approval of these NDAs from a clinical pharmacology perspective pending agreement on labeling. I agree with their assessment.

6. Clinical Microbiology

Jalal Sheikh, PhD, is the clinical microbiology reviewer for these NDAs.

Delafloxacin is an antibacterial drug that is bactericidal against Gram-positive and Gram-negative bacteria and acts by inhibiting bacterial DNA gyrase and topoisomerase IV. Resistance to fluoroquinolones, including delafloxacin, results from mutations in quinolone-resistance determining regions (QRDRs) of DNA gyrase and topoisomerase IV. Delafloxacin-resistant mutants were selected in vitro at frequencies of $<10^{-9}$ for Gram-positive and Gram-negative bacteria.

The activity of delafloxacin was assessed in animal models of systemic, pulmonary, urinary tract, and neutropenic thigh infections in mice and pulmonary infection and granuloma pouch abscess models in rats. In general, the activity of delafloxacin was similar or greater than that of comparators.

The in vitro activity of delafloxacin was evaluated against US and European isolates collected from surveillance studies. Against *S. aureus* isolates (including 41% methicillin-resistant), MIC50/MIC90 values for delafloxacin were $\leq 0.004/0.25$ mcg/mL. For methicillin susceptible *S. aureus*, the MIC50/MIC90 values were $\leq 0.004/0.015$ mcg/mL and for methicillin-resistant

S. aureus, the MIC₅₀/MIC₉₀ values were 0.12/1 mcg/mL. Against Enterobacteriaceae isolates, the MIC₅₀/MIC₉₀ of delafloxacin was 0.12/4 mcg/mL. Against *P. aeruginosa* isolates, the MIC₅₀/MIC₉₀ of delafloxacin was 0.25/>4 mcg/mL.

Delafloxacin resistant mutants were selected in vitro at frequencies ranging from $<10^{-9}$ - $<10^{-12}$ for both Gram-positive and Gram-negative bacteria. Isolates that are resistant to delafloxacin commonly acquired mutations in QRDR relative to the parent isolates. Elevated delafloxacin MIC values were generally associated with isolates having acquired mutations in *gyrA*, *gyrB* and *parC/grlA* genes. Delafloxacin showed no antagonism or synergy when tested in combination with several different antibacterial drugs.

Similar to other fluoroquinolones, fAUC₂₄/MIC of delafloxacin is the PK/PD parameter associated with activity. The percent probabilities of target attainment (PTA) at the proposed dose were estimated as 96.5% for net bacterial stasis for all *S. aureus* isolates at an MIC of 0.5 mcg/mL and 99% for 1-log₁₀ kill at an MIC of 0.25 mcg/mL. The PTA against *E. coli* was estimated as $\geq 98\%$ for net bacterial stasis at an MIC of 0.25 mcg/mL and $\geq 99.3\%$ for 1-log₁₀ kill at an MIC of 0.12 mcg/mL. For *P. aeruginosa*, the PTA was estimated as $\geq 97.3\%$ for net bacterial stasis at an MIC of 1 mcg/mL and 100% for 1-log₁₀ kill at an MIC of 0.5 mcg/mL.

In the two Phase 3 trials, approximately 90% of baseline isolates were Gram-positive organisms and over 60% were *S. aureus* (56% methicillin-susceptible and 44% methicillin-resistant). The predominant species isolated at baseline was *S. aureus* (62%). Beta-hemolytic streptococci were isolated at rates of 8.8% and 7.8% in the delafloxacin and comparator arms, respectively, with *S. pyogenes* being the most common. *S. anginosus* Group isolates were identified at baseline in ~13% of patients. Other Gram-positive cocci included a variety of coagulase-negative staphylococci, *S. mitis* Group isolates and *E. faecalis*.

Gram-negative pathogens isolated at baseline included a variety of Enterobacteriaceae; *K. pneumoniae* was most prevalent followed by *E. coli*, *E. cloacae*, *P. mirabilis*, and *K. oxytoca*. *P. aeruginosa* was isolated in ~ 2% of patients. Overall, the delafloxacin MIC distribution for the isolates in the clinical trials was similar to that observed among recent surveillance isolates. The majority of Gram-negative isolates were from polymicrobial infections that included Gram-positive organisms.

In the Phase 3 ABSSSI trials, the microbiologic response rates by baseline organisms did not differ significantly between the delafloxacin and comparator arms.

The following susceptibility test interpretive criteria were established using MIC distribution data from surveillance studies, PK/PD analyses, and clinical data from the Phase 3 trials.

Table 2: Susceptibility Test Interpretive Criteria

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (Zone Diameter in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (methicillin-resistant and methicillin-susceptible isolates)	≤ 0.25	0.5	≥ 1	≥ 23	20-22	≤ 19
<i>Staphylococcus haemolyticus</i>	≤ 0.25	0.5	≥ 1	≥ 24	21-23	≤ 20
<i>Streptococcus pyogenes</i>	≤ 0.06	-	-	≥ 20	-	-
<i>Streptococcus agalactiae</i>	≤ 0.06	0.12	≥ 0.25		-	
<i>Streptococcus anginosus</i> Group	≤ 0.06	-	-	≥ 25	-	-
<i>Enterococcus faecalis</i>	≤ 0.12	0.25	≥ 0.5	≥ 21	19-20	≤ 18
<i>Enterobacteriaceae</i>	≤ 0.25	0.5	≥ 1	≥ 22	19-21	≤ 18
<i>Pseudomonas aeruginosa</i>	≤ 0.5	1	≥ 2	≥ 23	20-22	≤ 19

There were insufficient numbers of isolates of (b) (4) and hence these organisms will be included in labeling only in the second list. Dr. Sheikh did not find the Applicant's proposal to include (b) (4) acceptable as they are considered normal flora and unlikely ABSSSI pathogens. Susceptibility test interpretive criteria will not be provided for *S. lugdunensis* at this time only limited clinical data are available and there are no PK/PD data to support the use of the *S. aureus* PD target from the nonclinical studies.

Dr. Sheikh recommends that these NDAs be approved from a clinical microbiology perspective, pending agreement on labeling. I agree with Dr. Sheikh's assessment.

7. Clinical/Statistical-Efficacy

Caroline Jjingo, MD, MPH, is the clinical reviewer, and Janelle Charles, PhD, is the statistical reviewer for these NDAs. The clinical program included two Phase 2 and two Phase 3 trials.

Phase 2 trials

Study RX-3341-201 was a randomized, double-blind trial comparing two dosing regimens of delafloxacin (300 mg IV q12h and 450 mg IV q12h) with tigecycline for the treatment of complicated skin and skin structure infections. One hundred fifty patients were randomized (1:1:1). The primary endpoint was clinical response in the clinically evaluable population at the test of cure visit 14 to 21 days after the last dose of study drug. Clinical response rates were similar across arms.

Study RX-3341-202 was a randomized, double-blind trial comparing delafloxacin, 300 mg IV q12h with linezolid or vancomycin for the treatment of ABSSSI. Two hundred fifty-six patients were randomized, stratified by infection category; within categories, randomization was 1:1:1. The primary endpoint was clinical response at a follow-up visit on day 14.

Response rates were similar in the delafloxacin and linezolid arms and lower in the vancomycin arm.

Phase 3 trials

Study RX-3341-302 (Study 302) was a multicenter, randomized, double-blind trial in which the efficacy and safety of IV delafloxacin was compared to that of IV vancomycin plus aztreonam in the treatment of ABSSSI. This trial was conducted at sites in the US, Europe, and Israel. Study RX-3341-303 (Study 303) was a multicenter, randomized, double-blind trial in which the efficacy and safety of IV and oral delafloxacin was compared to that of IV vancomycin plus aztreonam in the treatment of ABSSSI. This trial was conducted at sites in North America, South America, Europe, and Asia.

In general, the protocols for these trials were consistent with those outlined in the FDA guidance on ABSSSI. In both trials, no more than 25% of enrolled patients could have a major cutaneous abscess. In Study 302, no more than 35% could have a wound infection, and in Study 303, no more than 30% could have a wound infection. Patients were excluded from enrollment if they received systemic antimicrobial therapy within the preceding 14 days with the following exceptions: receipt of at least 48 hours of therapy for ABSSSI and documentation of clinical progression; completion of a course of antimicrobial therapy within the preceding 7 days for an infection other than ABSSSI that was treated with an agent not active against ABSSSI pathogens; no more than 25% of patients could receive one dose of potentially effective short-acting (half-life ≤ 12 h) therapy or a short-acting regimen before enrollment. Digital photography was performed to determine objective clinical response. Unplanned incision and drainage and major debridement procedures were not allowed after enrollment.

In Study 302, patients were randomly assigned (1:1) to receive either delafloxacin, 300 mg IV q12h, or vancomycin, 15 mg/kg IV q12h plus aztreonam, 2 g q12h. Patients in the delafloxacin arm received placebo infusions instead of aztreonam to maintain the study blind. Placebo or aztreonam was to be discontinued if a Gram-negative pathogen was not identified in baseline cultures. Randomization was stratified by type of ABSSSI. Study 303 was similar in design to Study 302 with some differences. Patients randomized to receive IV delafloxacin were switched to oral delafloxacin after 6 doses of IV delafloxacin. Randomization was stratified by type of ABSSSI and by baseline body mass index (BMI < 30 and BMI ≥ 30); 40-50% of patients were to have BMI ≥ 30 . In both studies, duration of therapy was 5 to 14 days, as determined by the investigator.

In both trials, the primary endpoint was objective response of $\geq 20\%$ reduction in lesion erythema compared with baseline as determined by digital measurement of the leading edge at 48 to 72 hours (± 2 hours) after initiation of therapy, with no evidence of clinical failure. Clinical failure at this time point was defined as $< 20\%$ reduction in area of lesion erythema, administration of rescue therapy, need for unplanned surgical intervention, or death. The major secondary endpoint was investigator-assessed clinical response at the follow-up visit on study day 14 ± 1 , at least 12 hours after the last dose of study drug.

In both trials, the primary analysis population was the intent-to-treat (ITT) population. The microbiological intent-to-treat (MITT) population was defined as all patients in the ITT population who had a baseline pathogen identified that was known to cause ABSSSI. The clinically evaluable (CE) population was defined as all patients in the ITT population who had a diagnosis of ABSSSI; received the correct study drug based on assigned randomization; received at least 80% of the expected doses of study drug, or if a failure, at least 4 doses of study drug; had an investigator assessment of response at the follow-up visit or was a clinical failure; did not receive any concomitant potentially effective systemic therapy; and had no protocol deviations that would affect assessment of efficacy through the follow-up visit.

In both trials, the pre-specified noninferiority margin was -10%. The sample size of 660 patients had at least 90% power to demonstrate NI of delafloxacin for the primary endpoint, assuming a clinical response rate of 78% for vancomycin plus aztreonam and an advantage over control of 3%, using a 1-sided significance level of 0.025. Based on an exploratory analysis in Study 302, the Applicant concluded that there was an improved cure rate at the late follow-up visit (day 21 to 28) in obese patients treated with delafloxacin. For Study 303, the sample size was increased to up to 850 patients to increase the robustness of an assessment of a secondary endpoint of investigator-assessed clinical cure at follow-up for patients with a baseline BMI ≥ 30 .

Results

In Study 302, 660 patients were randomized, 331 to IV delafloxacin and 329 to vancomycin plus aztreonam. The median age was 47 years, 62% of patients were male, and 90% were white; 82% were from North America. The majority of patients (~ 83%) completed the study. The most common reason for withdrawal from the study was loss to follow-up (7.3% in the delafloxacin arm and 8.8% in the control arm). The most common diagnosis was cellulitis/erysipelas (39%), followed by wound infection (35%), and major abscess (25%); 1% had burn infection. A baseline pathogen was isolated in 74% of patients; the most common pathogen isolated was *S. aureus* (66% of MITT population). At baseline, 15 (2.3%) patients were bacteremic.

In Study 303, 850 patients were randomized, 423 to IV/oral delafloxacin and 427 to vancomycin plus aztreonam. The median age was 51 years (20% ≥ 65 years), 63% of patients were male, and 83% were white; 47% were from North America. The most common reason for withdrawal from the study was loss to follow-up (5.9% in the delafloxacin arm and 5.8% in the control arm). The most common diagnosis was cellulitis/erysipelas (48%), followed by wound infection (26%), and major abscess (25%); 1% had burn infection. A baseline pathogen was isolated in 65% of patients; the most common pathogen was *S. aureus* (58% of MITT population). At baseline, 19 (2.2%) patients were bacteremic.

In general, the demographic characteristics were similar between the two arms in each trial. In Study 302, 7% of patients were ≥ 65 years of age and in Study 303, ~20% were ≥ 65 years of age. Less than 1% of patients had severe renal impairment. In Study 302, 16% of patients in the delafloxacin arm received prior antibacterial therapy within 14 days of study enrollment compared to 22% in the control arm; in Study 303, the percentages were 21% in the

delafloxacin arm and 26% in the control arm. In Study 302, 8% of patients in the delafloxacin arm and 13% in the control arm received a 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; in Study 303, the frequency was 14% in the delafloxacin arm and 19% in the control arm.

Table 3 shows the objective clinical response rates at the 48 to 72 hour assessment for Studies 302 and 303. In each trial, the lower limit of the 95% confidence interval for the treatment difference was greater than -10%, demonstrating that delafloxacin was noninferior to vancomycin plus aztreonam for the treatment of ABSSSI. The most common reason for failure in both trials was <20% reduction in the area of lesion erythema; missing data was the reason for failure in 7.9% patients in the delafloxacin arm and in 6.7% of patients in the control arm in Study 302 and for 4.7% and 4.9% in Study 303, respectively.

Table 3: Objective Clinical Response at 48 to 72 Hours (ITT Population)

	Study 302			Study 303		
	Delafloxacin IV N=331	Vancomycin + aztreonam N=329	Treatment difference ¹ (95% CI)	Delafloxacin IV/PO N=423	Vancomycin + aztreonam N=427	Treatment difference ¹ (95% CI)
Clinical response, n (%)	259 (78.2)	266 (80.9)	-2.6 (-8.8, 3.6)	354 (83.7)	344 (80.6)	3.1 (-2.0, 8.3)

¹ Treatment difference, expressed as percentages based on Mantel Haenszel methods to account for stratification by infection site in study 302, and for stratification by BMI and infection type in Study 303
CI = confidence interval

Adapted from FDA statistical review, Table 14

Similar findings were seen in the MITT population. In general, subgroup analyses by age, race, sex, and geographic region, type of infection, use of prior therapy, and presence of diabetes, or mild to moderate renal impairment were consistent with the primary analysis. There was insufficient evidence to evaluate the efficacy of delafloxacin in patients with severe renal impairment or ERSD. Results were also consistent in the sensitivity analyses performed by Dr. Charles.

In Study 302, clinical response rate at EOT in the ITT population was 88.8% in the delafloxacin arm and 91.8% in the control arm, treatment difference, -3.0%, 95% CI (-7.5%, 1.5%); in Study 303, the clinical response rate was 94.1% in the delafloxacin arm and 92.3% in the control arm, treatment difference of 1.8% with 95% CI (-1.6%, 5.2%). These findings suggest that the early clinical response observed was sustained at the end of treatment.

Table 4 shows the investigator-assessed response at the Day 14 follow-up assessment in the ITT population. Results for this time point were similar to that for the early response endpoint. There was no drop-off in efficacy between the early and late endpoints in any of the treatment arms.

Table 4: Investigator-Assessed Response at Follow-up (Day 14) (ITT Population)

	Study 302			Study 303		
	Delafloxacin IV	Vancomycin + aztreonam	Treatment difference ¹ (95% CI)	Delafloxacin IV/PO	Vancomycin + aztreonam	Treatment difference ¹ (95% CI)
Success ² n/N (%)	270/331 (81.6)	274/329 (83.3)	-1.7 (-7.6, 4.1)	369/423 (87.2)	362/427 (84.8)	2.5 (-2.2, 7.1)

¹ Treatment difference, expressed as percentage, and CI based on Miettinen and Nurminen method without stratification

² Success defined as cure (complete resolution) + improved (incomplete resolution but improvement such that no further antimicrobial therapy was necessary)

Adapted from CDTL Review, Table 4

While in Study 302, post-hoc analysis showed a higher cure rate at the late follow-up visit (day 21 to 28) in obese patients (BMI ≥ 30) in the delafloxacin arm compared to the control arm (71.7% vs. 57.5%, respectively), a similar finding was not seen in Study 303.

Six patients in the delafloxacin arm had *S. aureus* bacteremia at baseline; 5 were responders at 48-72 hours and successes at follow-up. Two patients in the delafloxacin arm had Gram-negative bacteremia (*K. pneumoniae*, *P. aeruginosa*) at baseline; both were responders at 48 to 72 hours and successes at follow-up.

Dr. Charles concluded that delafloxacin was noninferior to the comparator in both trials and provides evidence to support the efficacy of delafloxacin for the treatment of ABSSSI. Dr. Jjingo also concluded that the Applicant has provided adequate evidence for the efficacy of delafloxacin in ABSSSI. Dr. Smith, the CDTL for these NDAs, concurs that the Applicant has provided substantial evidence of effectiveness to support approval of delafloxacin for the treatment of ABSSSI in adult patients. I agree with their assessment.

8. Safety

Caroline Jjingo, MD, MPH, is the clinical reviewer for these NDAs.

The clinical development program, includes 30 completed studies: 23 Phase 1 studies, 4 Phase 2 trials (2 in ABSSSI and 2 in respiratory indications), and 3 Phase 3 trials (2 in ABSSSI and 1 in uncomplicated urogenital gonorrhea). The primary data used to evaluate the safety profile of delafloxacin are from the two Phase 3 ABSSSI trials.

Phase 3 trials

In the pooled Phase 3 trials, 741 patients received delafloxacin, and 751 received vancomycin plus aztreonam. The duration of therapy in both studies was 5 to 14 days. The median duration of exposure to delafloxacin was 6 days (range, 0.5 to 14 days).

There were a total of five deaths, one in the delafloxacin arm and four in the comparator arm. The death in the delafloxacin arm was an 89-year-old patient with multiple comorbidities who

died of septic shock 5 days after completing a 14-day course of therapy; the clinical response at the end of treatment was failure.

Serious adverse events (SAEs) were reported by 27/741 (3.6%) patients in the delafloxacin arm and 26/751 (3.5%) patients in the comparator arm. SAEs that were reported in more than one delafloxacin-treated patient included, cellulitis/erysipelas/skin infection (n=4), sepsis/septic shock (n=2) and pulmonary embolism (n=2). The most common System Organ Class (SOC) in which SAEs were reported was Infection and Infestations and likely represents lack of efficacy.

In three patients, an SAE of pulmonary embolism was reported, two in the delafloxacin arm and one in the comparator arm. A 41-year-old delafloxacin-treated patient with cellulitis/erysipelas of the right leg, Type 2 diabetes, and obesity developed dyspnea and chest pain 6 days after completing a 14-day course of therapy and was diagnosed with a pulmonary embolism the following day. A 31-year-old patient with cellulitis/erysipelas of the right leg and lymphangitis developed a pulmonary embolism 11 hours after the first dose of study drug. Three days later, the patient was diagnosed to have deep vein thrombosis (DVT). He had a history of a healed ankle fracture, 2 months prior. One patient in the vancomycin plus aztreonam arm had a fatal pulmonary embolism. It appears that in both delafloxacin-treated patients who developed PE, there were risk factors for DVT. Both patients had cellulitis of the lower extremity, one was obese and the other had a history of ankle fracture 2 months prior to the PE developing. In the investigator’s assessment, the PE events were not study drug related. Dr. Jjingo notes that she does not completely exclude the possibility of these events being drug related as the patients did not have other risk factors for DVT/PE such as malignancy, prolonged hospitalization, recent surgery, prolonged travel, or history of exposure to concomitant medications. Dr. Jjingo also notes that thrombo-embolism was not noted in the nonclinical studies or with other members of the fluoroquinolone class. In my assessment, there are underlying medical conditions that might have predisposed these two patients to the thrombo-embolic events. At this time, these events do not specifically need to be included in labeling. However, if more events are noted postmarketing, labeling updates can be made at that time.

Table 5 shows a summary of the treatment-emergent adverse events (TEAEs) reported in the pooled Phase 3 trials. The incidence of TEAEs and serious adverse events (SAEs) was similar between treatment groups.

Table 5: Treatment-Emergent Adverse Events in the Pooled Phase 3 Trials

Type of Adverse Event	Delafloxacin (N=741)		Vancomycin + Aztreonam (N=751)	
	n	(%)	n	(%)
Any TEAE	334	(45.1)	358	(47.7)
Any SAE	27	(3.6)	26	(3.5)
Discontinuation due to TEAE	13	(1.8)	26	(3.5)
Death due to TEAE	1	(0.1)	3	(0.4)

N = number of patients in safety population; n = number of patients in category; TEAE = treatment-emergent adverse event; SAE = serious adverse event

Adapted from CDTL Memo, Table 6

Discontinuation of study drug due to TEAEs was reported in 13 (1.8%) patients in the delafloxacin arm and in 26 (3.5%) in the comparator arm. In the delafloxacin arm, two patients had urticaria and two had hypersensitivity, compared with five and two patients, respectively, in the comparator arm.

The most commonly reported TEAEs in delafloxacin-treated patients were diarrhea (7.8%), nausea (7.6%), infection (5.9%), infusion site extravasation (5.5%), headache (3.2%), vomiting (2.3%), and pyrexia (2.3%).

Phase 2 trials

There were no deaths in the Phase 2 trials. Seven SAEs were reported in five patients including pyrexia, femoral neck fracture, convulsion, and congestive cardiac failure. Delafloxacin was discontinued in one patient because of bacteremia and pyrexia. The most commonly reported TEAEs in the Phase 2 trials were similar to those reported in the Phase 3 trials.

Phase 1 studies

There were no deaths or SAEs in the Phase 1 studies. The most common TEAEs in subjects receiving delafloxacin were diarrhea, nausea, headache, vomiting, and infusion site pain. One subject developed *C. difficile* colitis.

Adverse Events of Special Interest (AESIs)

Adverse events of special interest (AESIs) for fluoroquinolones that were assessed include myopathy, *Clostridium difficile* diarrhea, convulsions, peripheral neuropathy, tendon disorder, QT prolongation, phototoxicity, allergic reactions, dysglycemia, and hepatic-related events.

One patient had an SAE of increased ALT/AST noted on Day 21, 15 days after the last dose of delafloxacin, with ALT 859 U/L and AST 442 U/L. Levels returned to normal or near-normal by Day 73. Two delafloxacin-treated patients with normal ALT at baseline had Grade 4 values post-baseline. Both patients were on concomitant medications and in both patients ALT levels returned to normal following discontinuation of study drug. The elevation in ALT was considered to be possibly related to study drug. There were no cases of Hy's law reported.

In the Phase 3 trials, blood glucose disturbances (coded to preferred terms hypoglycemia, hyperglycemia, or new onset diabetes) were similar between the treatment arms (10/741 in the delafloxacin arm and 10/571 in the comparator arms). Among the 10 patients in the delafloxacin arm, in three patients, the events (two hyperglycemia and one hypoglycemia) were considered as being possibly and definitely related to study drug. Dr. Jjingo performed a detailed review of all patients who had Grade 3 or 4 hypo/hyperglycemia and notes that a definite association with delafloxacin use cannot be established. Dysglycemic events will need to be monitored postmarketing to assess if there is a relationship between delafloxacin and dysglycemia as seen with some other fluoroquinolones.

Three patients in the pooled Phase 3 trials had four events related to tendinitis. No patients in the vancomycin comparator arm reported 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 in severity. 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 three patients had concomitant use of steroids, and one was over 60 years of age. All events occurred either at or around the end of treatment visit. Based on review of subject narratives and case report forms, Dr. Jjingo concluded that although there was a temporal relationship between the onset of the tendinitis and receipt of the study drug, the events were not related to delafloxacin therapy.

A total of 4/741 delafloxacin-treated patients and 3/751 comparator-treated patients reported peripheral neuropathy. All events in the delafloxacin arm were assessed as being mild in severity and one of the three patients in the comparator arm was assessed as having a moderate severity event which resulted in the study drug being interrupted, but not discontinued.

One delafloxacin-treated patient in a Phase 2 trial had an SAE of convulsion on Day 8, the last day of treatment. No delafloxacin-treated patients in the Phase 3 trials reported seizures; one patient in the comparator arm had a convulsion which resulted in withdrawal of the study drug. Four delafloxacin-treated patients experienced dizziness that was assessed by the investigator as being possibly related to delafloxacin. No patients were withdrawn from the delafloxacin arm due to dizziness; in one patient delafloxacin was temporarily interrupted. Five comparator-treated patients experienced dizziness which was assessed as possibly related to the drugs; all events were graded as mild to moderate in intensity.

In the Phase 3 trials, three delafloxacin-treated patients had syncope/pre-syncope and one in the comparator group had loss of consciousness. In the Phase 2 trials, one delafloxacin-treated patient experienced a syncopal episode.

There were no significant differences between the two treatment arms with respect to psychiatric AEs including depression/suicidal ideation, anxiety, hallucinations or paranoia.

One patient who received delafloxacin had an SAE of urticaria. Overall, immune and skin disorder TEAEs occurred more commonly in the comparator arm. One delafloxacin-treated patient in a Phase 2 trial had a photosensitivity reaction occurring 11 days after the end of therapy. No TEAEs of photosensitivity or phototoxicity were reported in the Phase 3 trials.

Two delafloxacin-treated patients had *C. difficile* colitis or infection vs. none in the comparator group. Neither was an SAE.

There were no cases of QT interval prolongation in the Phase 3 trials.

9. Advisory Committee Meeting

These NDAs were not discussed at an advisory committee meeting as there were no specific issues that required input from the committee.

10. Pediatrics

The Applicant's initial pediatric study plan (iPSP) proposing to request a full waiver of pediatric studies for ABSSSI was discussed with the Pediatric Review Committee (PeRC) on March 2, 2016. The proposal was based on safety concerns and failure to represent a meaningful therapeutic benefit over existing therapies and the likely lack of use in a substantial number of pediatric patients. PeRC concurred with the Division's assessment, and an agreed iPSP letter was issued on April 7, 2016. The agreed iPSP with request for full waiver was included in NDAs and presented to PeRC on May 17, 2017. PeRC concurred with the plan to grant a full waiver of pediatric studies for ABSSSI. The Pediatric Use section of the package insert will state the following:

Use in patients under 18 years of age is not recommended. Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Pediatric studies were not conducted because risk-benefit considerations do not support the use of Baxdela for ABSSSI in this population. Fluoroquinolones cause arthropathy in juvenile animals.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) Audits

Bei Yu, PhD, is the OSI reviewer for these NDAs. Four clinical investigator sites from the Phase 3 trials and the Applicant were inspected. The final classification of the inspections of two sites was No Action Indicated (NAI) and Voluntary Action Indicated (VAI) for two other sites. The preliminary classification of the inspection of the Applicant was NAI. Dr. Yu concluded that the data appeared acceptable to support the NDAs. The observations at the two sites that received a VAI classification do not appear to have significant impact on subject safety or efficacy assessment. Dr. Yu notes that the inspection observations are based upon preliminary communications with the ORA investigator. If a significant change in regulatory classification is determined after submission and review of the Establishment Inspection Report (EIR), an addendum will be provided.

12. Labeling

Recommendations from reviewers from OPDP, DMPP, and DMEPA were incorporated into labeling. The proposed proprietary name, Baxdela was found to be acceptable.

As delafloxacin is a member of the fluoroquinolone class of antibacterial drugs, safety issues related to the class will be included in relevant sections of labeling including the Boxed Warning and Warning and Precautions section. A Medication Guide is also being included as part of labeling to convey important safety information to patients. As this product will only be approved for the treatment of ABSSSI, information in other fluoroquinolone labeling regarding benefit-risk considerations for treatment of respiratory tract infections such as acute

bacterial sinusitis or uncomplicated urinary tract infections are not relevant to delafloxacin labeling.

13. Postmarketing

Till Olickal, PharmD, the Division of Risk Management (DRISK) reviewer notes that a REMS is not needed to ensure the benefits of delafloxacin outweigh its risks. Labeling, including the Medication Guide, routine pharmacovigilance, and postmarketing requirements were considered adequate to address the safety issues at this time.

The Applicant has agreed to the following postmarketing requirements (PMRs) and commitments (PMCs):

PMRs:

3220-1: Conduct US surveillance studies for five years from the date of marketing Baxdela to determine if resistance to delafloxacin has developed in those organisms specific to the indication in the label for ABSSSI.

Final protocol submission:	09/2017
First interim report:	07/2018
Second interim report:	07/2019
Third interim report:	07/2020
Fourth interim report:	07/2021
Fifth interim report:	07/2022
Study completion date:	09/2022
Final report submission date:	12/2022

3220-2: Conduct a tissue distribution study in pregnant rats treated during the period of organogenesis with the oral formulation and with the intravenous formulation of Baxdela with the excipient sulfobutylether beta-cyclodextrin (SBECD) to assess on the distribution of the drug substance to the reproductive tract and developing fetus.

Final Protocol Submission:	10/2017
Study Completion:	03/2018
Final Report Submission:	06/2018

3220-3: If the results of the tissue distribution studies from PMR 3220-2 demonstrate greater exposure of the fetus / maternal reproductive tract to delafloxacin with the intravenous formulation, conduct an embryo-fetal developmental toxicology study in pregnant rats treated during the period of organogenesis with the intravenous formulation of Baxdela to identify possible effects of delafloxacin with the excipient sulfobutylether beta-cyclodextrin (SBECD) on fetal development during the period of organogenesis.

Final Protocol Submission: 07/2018
Study Completion: 01/2019
Final Report Submission: 04/2019

The Applicant has also agreed to the following PMCs related to Chemistry Manufacturing and Controls:

1. Add the facility responsible for x-ray powder diffraction (XRPD) testing. The filing category should be selected based on FDA Guidance (See: Guidance for Industry Changes to an Approved NDA or ANDA).
2. Establish a validated XRPD limit test as part of product release. This information should be submitted as Changes Being Effected-30 Supplement.
3. Update drug product release specifications so commercial batches will have XRPD testing to confirm polymorphic form as a part of drug product final release testing. This information should be submitted as Changes Being Effected-30 Supplement.
4. Provide results from the on-going requalification of the sterility test method per USP <71>. Sponsor to provide data collected from on-going PV (process validation) runs at (b) (4)
5. Provide PV data to support a more suitable In-Process Control (IPC) limit at (b) (4) % of (b) (4) as a CBE-30 in lieu of the proposed specification ((b) (4) % of target, (b) (4) mg/mL) in NDA 208611.

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/s/

SUMATHI NAMBIAR
06/19/2017