CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208610Orig1s000
208611Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 16, 2017
From	Thomas Smith, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	208610 (tablets); 208611 (injection)
Applicant	Melinta Therapeutics, Inc.
Date of Submission	October 19, 2016
PDUFA Goal Date	June 19, 2017
Proprietary Name / Non-Proprietary Name	Baxdela™/Delafloxacin
Dosage forms / Strengths	Tablets: 450 mg; Injection: 300 mg single-use vials
Applicant Proposed Indication/Population	Acute bacterial skin and skin structure infections in adults
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	Acute bacterial skin and skin structure infections in adults

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Delafloxacin (Baxdela) is a fluoroquinolone antimicrobial which has been developed in tablet (NDA 208610) and injection (NDA 208611) dosage forms by Melinta Therapeutics, Inc., for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of designated gram-positive and gram-negative bacteria. The recommended regulatory action is approval.

ABSSSIs include cellulitis and erysipelas, wound infection, and major cutaneous abscess. Pathogens include *Staphylococcus aureus*, *Streptococcus pyogenes*, other streptococcal species, *Enterococcus faecalis*, and Gram-negative bacteria. In recent years, methicillin-resistant *S. aureus* (MRSA) infections have become more common. These infections may be serious and are occasionally life-threatening. Several classes of antimicrobial agents are approved for the treatment of ABSSSI or complicated skin and skin structure infections. Oral therapies for ABSSSIs due to MRSA are limited.

The applicant conducted two pivotal trials of delafloxacin for the treatment of ABSSSI. Both trials compared delafloxacin with vancomycin plus aztreonam; one trial was with intravenous (IV) delafloxacin and the other was with IV delafloxacin with a mandatory switch to oral delafloxacin after six doses. Clinical response rates were 78.2% for delafloxacin and 80.9% for vancomycin plus aztreonam in the first trial and 83.7% for delafloxacin and 80.6% for vancomycin plus aztreonam in the second trial; both trials met the prespecified noninferiority margin of -10%. Efficacy findings were consistent across demographic subgroups and analysis populations.

The most common adverse reactions in patients treated with delafloxacin were nausea, diarrhea, headache, transaminase elevations, and vomiting. Adverse events of special interest (AESIs) for fluoroquinolone antimicrobials that were assessed included myopathy, *Clostridium difficile* diarrhea, convulsions, peripheral neuropathy, tendon disorder, QT prolongation, phototoxicity, allergic reactions, dysglycemia, and hepatic-related events. No major safety concerns were identified in the limited clinical trial database. Use in patients under 18 years of age is not recommended. Pediatric studies were not conducted because risk-benefit considerations do not support the use of delafloxacin for ABSSSI in this population. Fluoroquinolones cause arthropathy in juvenile animals.

Delafloxacin is effective in the treatment of adult patients with ABSSSI, and the safety information provided supports its use. Labeling will contain the fluoroquinolone class-specific Boxed Warning about tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbations of myasthenia gravis, as well as information in the Warnings and Precautions section about other potentially serious adverse reactions. As with other fluoroquinolones, a Medication Guide will be provided with delafloxacin prescriptions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ABSSSIs include cellulitis and erysipelas, wound infection, and major cutaneous abscess. Pathogens include *S. aureus*, *S. pyogenes*, other streptococcal species, *E. faecalis*, and gram-negative bacteria. In recent years, methicillin-resistant *S. aureus* (MRSA) infections have become more common. • ABSSSIs may be serious, often requiring hospitalization, and they are occasionally life-threatening.	ABSSSIs include cellulitis and erysipelas, wound infection, and major cutaneous abscess. These infections may be serious and are occasionally life-threatening.
Current Treatment Options	• Approved therapies for the treatment of ABSSSI or complicated skin and skin structure infections include several classes of antimicrobial agents. • Most approved therapies are active against *S. aureus* and *S. pyogenes*; there are differences in activity against MRSA and gram-negative bacteria. • Therapies are available in intravenous or oral formulations; the only	Several classes of antimicrobial agents are approved for the treatment of ABSSSI or complicated skin and skin structure infections. Oral therapies for ABSSSIs due to MRSA are limited.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	oral formulations approved for the treatment of ABSSSI due to MRSA are linezolid and tedizolid.	
Benefit	• The applicant conducted two pivotal trials of delafloxacin for the treatment of ABSSSI. • Study RX-3341-302 (Study 302) compared the efficacy and safety of intravenous (IV) delafloxacin with that of vancomycin plus aztreonam in the treatment of ABSSSI in adults. A total of 660 patients were randomized to receive delafloxacin, 300 mg IV q12h, or vancomycin, 15 mg/kg IV q12h plus aztreonam, 2 g q12h. The duration of treatment was 5 to 14 days. The primary endpoint was objective response of >20% reduction in area of 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. Objective clinical response rates were 78.2% for the delafloxacin group and 80.9% for the vancomycin plus aztreonam group. The treatment difference of -2.6% met the prespecified noninferiority margin of -10%. • Study RX-3341-303 (Study 303) compared the efficacy and safety of IV and oral delafloxacin with that of vancomycin plus aztreonam in the treatment of ABSSSI in adults. A total of 850 patients were randomized to receive delafloxacin, 300 mg IV q12h for 6 doses, followed by a mandatory switch to oral delafloxacin, 450 q12h, or vancomycin, 15 mg/kg IV q12h plus aztreonam, 2 g q12h. The duration of treatment was 5 to 14 days. The primary endpoint was objective response of >20% reduction in area of 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.	The data submitted meet the evidentiary standard for approval of IV and oral delafloxacin for the treatment of ABSSSIs in adults. Delafloxacin is effective against the major gram-positive and gram-negative causes of ABSSSI, including MRSA. The availability of IV and oral formulations is an advantage.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Objective clinical response rates were 83.7% for the delafloxacin group and 80.6% for the vancomycin plus aztreonam group. The treatment difference of 3.1% met the prespecified noninferiority margin of -10%. • The design of the trials, including the primary efficacy analysis, was consistent with recommendations in FDA's guidance for industry on ABSSSIs. • Efficacy findings were consistent across demographic subgroups and analysis populations.	
Risk	• The delafloxacin clinical 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). Across all studies, 2658 subjects received delafloxacin. The primary data used to evaluate the safety profile of delafloxacin are from the integrated phase 3 ABSSSI trials. • The most common adverse reactions in patients treated with delafloxacin were nausea, diarrhea, headache, transaminase elevations, and vomiting. • Adverse events of special interest (AESIs) for fluoroquinolone antimicrobials that were assessed included myopathy, *Clostridium difficile* diarrhea, convulsions, peripheral neuropathy, tendon disorder, QT prolongation, phototoxicity, allergic reactions, dysglycemia, and hepatic-related events. • No major safety concerns were identified in the limited clinical trial database. • Use in patients under 18 years of age is not recommended. Pediatric studies were not conducted because risk-benefit considerations do not support the use of delafloxacin for ABSSSI in this population. Fluoroquinolones cause arthropathy in juvenile animals.	The safety information provided supports the use of delafloxacin for the treatment of ABSSSI in adult patients. No major safety concerns were identified in the limited clinical trial database. Fluoroquinolone-specific warnings will be included in labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• Labeling will contain the fluoroquinolone class-specific Boxed Warning about tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbations of myasthenia gravis, as well as information in the Warnings and Precautions section about other potentially serious adverse reactions. As with other fluoroquinolones, a Medication Guide will be provided with delafloxacin prescriptions.	Labeling will contain fluoroquinolone class-specific warnings. A Medication Guide will be provided with delafloxacin prescriptions. Routine postmarketing safety monitoring is sufficient at this time.

2. Background

Delafloxacin is a new fluoroquinolone antimicrobial which has been developed in tablet (NDA 208610) and injection (NDA 208611) dosage forms. The proposed indication is 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 proposed dosing regimen is 300 mg q12h administered over 60 minutes for intravenous infusion or 450 mg orally q12h for a total duration of 5 to 14 days.

Acute bacterial skin and skin structure infections

FDA's guidance for industry on ABSSSIs[1] defines ABSSSI as cellulitis and erysipelas, wound infection, and major cutaneous abscess. Pathogens include *S. aureus*, *S. pyogenes*, other streptococcal species, *E. faecalis*, and gram-negative bacteria; in recent years, MRSA infections have become more common. Numerous antimicrobial agents, including ciprofloxacin, levofloxacin, and moxifloxacin, are approved for the treatment of ABSSSI, skin and skin structure infections, or complicated skin and skin structure infections (indications formerly granted). The only oral formulations approved for the treatment of ABSSSI due to MRSA are linezolid and tedizolid. Current treatment guidelines for skin and soft tissue infections[2] recommend the following empiric antimicrobial therapies, in addition to incision and drainage and surgical wound management:

- Cellulitis and erysipelas: vancomycin plus piperacillin/tazobactam for severe infections; penicillin, ceftriaxone, cefazolin, or clindamycin for moderate infections
- Wound infections (primarily surgical site infections): cefazolin or vancomycin; a cephalosporin plus metronidazole, levofloxacin plus metronidazole, or a carbapenem; or penicillin and clindamycin, depending on clinical presentation and location of infection
- Cutaneous abscesses: vancomycin, daptomycin, linezolid, telavancin, or ceftaroline for severe infections; trimethoprim/sulfamethoxazole for moderate infections.

The ABSSSI guidance[1] recommends a minimum lesion size of 75 cm^2 of redness, edema, or induration for enrollment in clinical trials. Methods for measurement of lesion size include

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

manual measurement (length times perpendicular width), digital planimetry, or computer-assisted tracings. Noninferiority trials are acceptable for this indication. Patients with major cutaneous abscesses should be limited to no more than 30 percent of the trial population because of the effect of incision and drainage procedures on clinical outcomes. Pretrial antimicrobial therapy, if initiated, should be limited to a single dose of a short-acting agent within 24 hours of enrollment in no more than 25 percent of the population; enrollment of patients with objective documentation of clinical progression of an ABSSSI while on therapy or of patients who receive surgical antimicrobial prophylaxis and subsequently develop an ABSSSI is acceptable. Concomitant antimicrobial should be avoided; if necessary, it should not have overlapping antibacterial activity with the investigational drug. Adjunctive therapies, including surgical interventions planned at the initiation of treatment, should be specified in the protocol. The recommended primary efficacy endpoint is lesion response at 48 to 72 hours, with clinical response defined as ≥20 percent reduction in lesion size compared with baseline. The intent-to-treat (ITT) population is the recommended primary analysis population. For noninferiority trials for this indication, a margin of 10 percent for the primary endpoint can be supported by historical evidence.

Regulatory history

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 phase 3 clinical development plan for the ABSSSI indication was discussed at an end-of-phase 2 meeting on April 14, 2010. FDA agreed that two successful noninferiority trials, one with IV therapy only and the other with an IV-to-oral switch, could support an ABSSSI indication. The proposed trials were submitted for special protocol assessments, and agreements were reached 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.

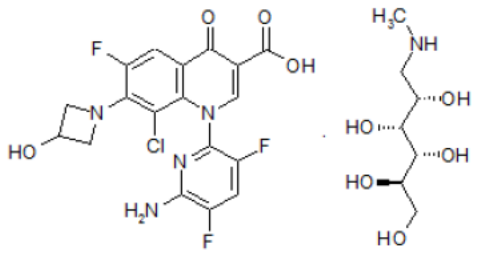
Qualified infectious disease product (QIDP) designation was granted for the ABSSSI indication on September 8, 2012, and fast track designation was granted on December 18, 2012. The NDAs were submitted on October 19, 2016, and qualified for priority review.

The clinical 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).

3. Product Quality

Bala Shanmugam, Ph.D., was the application technical lead for the product quality assessment team. The team's findings are summarized below.

Delafloxacin meglumine (1-Deoxy-1-(methylamino)-D-glucitol, 1-(6-amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-hydroxyazetidin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (salt)) has a molecular formula of $C_{18}H_{12}ClF_3N_4O_4 \cdot C_7H_{17}NO_5$. The meglumine salt has a molecular weight of 635.97 g/mol, and the molecular weight of delafloxacin free acid is 440.76 g/mol. The meglumine salt has the following chemical structure:



Delafloxacin meglumine drug substance is manufactured by (b) (4). The manufacturing process (b) (4) (b) (4) (b) (4) The applicant 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 include tests and acceptance criteria for appearance, identification, assay, impurities, water, residual solvents, residue on ignition, particle size, total aerobic microbial count, total yeast and mold count, and bacterial endotoxin and were considered adequate. Stability data support a retest period of (b) (4).

Delafloxacin tablet (NDA 208610)

The manufacturer of the tablet drug product is (b) (4). The delafloxacin 450 mg tablet is an immediate release, modified capsule-shaped (b) (4) beige to mottled beige tablet. Each tablet contains 450 mg delafloxacin (equivalent to 649 mg delafloxacin meglumine) and the following inactive ingredients: citric acid, crospovidone, magnesium stearate, microcrystalline cellulose, povidone, sodium bicarbonate, and sodium phosphate monobasic monohydrate. The drug product specifications for the tablet formulation include tests and acceptance criteria for appearance, identification, assay, impurities, dissolution, uniformity of dosage units, water, and microbial testing and were considered adequate. The drug product reviewer, Yushi Feng, Ph.D., recommended that control of the polymorphic form of the drug substance be instituted in the tablet drug product specifications through a postmarketing commitment (PMC). The tablets will be packaged as bottles of 20 tablets with a child-resistant closure and as unit dose blister packs containing 20 tablets (2 blister cards of 10 tablets each). Stability data support the proposed shelf life for both presentations of the tablet drug product 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 that the proposed dissolution method and acceptance criterion were acceptable. The clinical studies used a scored tablet and the commercial product is unscored. The bridging study between the scored and unscored tablets was acceptable.

The process and product quality microbiology review recommended a PMC (b) (4) (b) (4)

The drug substance and drug product manufacturing facilities and the packaging and testing facilities were found to be acceptable. The applicant will add a facility responsible for the x-ray powder diffraction testing that will be established as a PMC.

The Office of Pharmaceutical Quality review team recommended approval of the delafloxacin tablet NDA from a product quality perspective. PMCs are noted below:

1. Addition of the facility responsible for 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 [x-ray powder diffraction] 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. (b) (4) (b) (4)

Delafloxacin for injection (NDA 208611)

The manufacturer of the IV formulation 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 (b) (4), sulfobutylether-β-cyclodextrin (SBECD; Captisol®) (b) (4) (b) (4) (b) (4). Specifications for the injection formulation include tests and acceptance criteria for appearance, identity, reconstitution time, appearance of reconstituted solution, pH, assay, uniformity of dosage units, purity, bacterial endotoxin, sterility, particulate matter, and water content and 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 process review recommended approval. The applicant will submit process validation data to support more suitable in-process control limits at (b) (4) % of (b) (4) as a CBE-30 supplement.

The product quality microbiology review concluded that the applicant 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 drug substance manufacturing facility was found to be acceptable and did not require inspection. The drug product manufacturing facility was inspected in February, 2017, and found to be acceptable.

The Office of Pharmaceutical Quality review team recommended approval of the delafloxacin for injection NDA from a product quality perspective.

4. Nonclinical Pharmacology/Toxicology

Wendelyn Schmidt, Ph.D., and Amy Nostrandt, DVM, Ph.D., were the pharmacology/toxicology reviewers for these applications. Dr. Schmidt was the initial primary reviewer, and Dr. Nostrandt completed the review with edits and additions. Their findings and recommendations are summarized below.

Safety pharmacology studies in various species showed minimal or no effects of delafloxacin on central nervous, cardiovascular, respiratory, and gastrointestinal systems. At high doses, sedation, ptosis, and abnormal gait were observed. Emesis and diarrhea were observed at lower doses.

Repeated dose toxicology studies in mice, rats, and dogs revealed primarily gastrointestinal effects. Articular cartilage degeneration was observed in one of three female dogs administered a high dose (480 mg/kg/d for 28 days) of the tablet formulation; this is a known effect of fluoroquinolones.

Delafloxacin was not mutagenic in a bacterial reverse mutation (Ames) assay and was not clastogenic in a mouse bone marrow micronucleus assay. In an in vitro chromosomal aberration assay, it was clastogenic at the highest concentrations under cytotoxic conditions; this has been observed with other fluoroquinolones, and is believed to be due to inhibitory effects on eukaryotic topoisomerase. Carcinogenicity studies were not performed.

Delafloxacin did not affect fertility in male and female rats at exposures up to 5 times the human clinical exposure.

No malformations or fetal deaths were observed when delafloxacin was administered orally to rats during the period of organogenesis at up to 7 times the estimated human clinical exposure based on AUC. Maternal toxicity and reduced fetal body weights were observed at the highest dose (1600 mg/kg/d), and fetal ossification delays were observed at all doses. There were no adverse effects observed in offspring when delafloxacin was administered IV to rats in late

pregnancy and through lactation at exposures similar to the clinical IV exposure based on AUC. Delafloxacin is excreted in the breast milk of rats.

The reproductive and developmental toxicology studies did not include an excipient in the IV formulation, sulfobutylether-β-cyclodextrin (SBECD), which may alter exposure to delafloxacin. The potential reproductive and developmental effects of delafloxacin with the added SBECD are unknown. The pharmacology/toxicology team recommends a postmarketing requirement (PMR) for the applicant to conduct a tissue distribution study in pregnant rats treated during the period of organogenesis with the oral and the IV formulations of delafloxacin to assess the distribution of the drug substance to the reproductive tract and developing fetus. If the results of this study demonstrate greater exposure to delafloxacin with the IV formulation, the team recommends an additional PMR for the applicant to conduct an embryo-fetal developmental toxicology study in pregnant rats treated during the period of organogenesis with the IV formulation of delafloxacin to identify possible effects of delafloxacin with SBECD on fetal development during the period of organogenesis.

Dr. Nostrandt concluded that these applications were approvable from the pharmacology/toxicology perspective.

5. Clinical Pharmacology

Kunyi Wu, Pharm.D., was the primary clinical pharmacology reviewer for these applications. The Office of Clinical Pharmacology review team's findings and recommendations are summarized below.

The recommended dosing regimen for delafloxacin is 300 mg q12h administered by IV infusion over 60 minutes or 450 mg q12h orally at the discretion of the physician for a total duration of 5 to 14 days. Pharmacokinetic parameters are presented in Table 1.

Table 1: Mean (SD) Delafloxacin Pharmacokinetic Parameters Following Single and Multiple Oral and Intravenous Administration

	Tablet		**Intravenous Injection**	
Parameters	**Single Dose 450 mg**	**Steady State 450 mg q12h**	**Single Dose 300 mg**	**Steady State 300 mg q12h**
T_{max} (h)[a]	0.75 (0.5, 4.0)	1.00 (0.50, 6.00)	1.0 (1.0, 1.2)	1.0 (1.0, 1.0)
C_{max} (μg/mL)	7.17 (2.01)	7.45 (3.16)	8.94 (2.54)	9.29 (1.83)
AUC (μg•h/mL)[b]	22.7 (6.21)	30.8 (11.4)	21.8 (4.54)	23.4 (6.90)
CL or CL/F (L/h)[c]	20.6 (6.07)	16.8 (6.54)	14.1 (2.81)	13.8 (3.96)
CLr (L/h)	-		5.89 (1.53)	6.69 (2.19)
R_{ac}		1.36		1.1

C_{max} = maximum concentration; T_{max} = time to reach C_{max}; AUC = area under the concentration-time curve; CL = systemic clearance; CL/F = apparent oral clearance; CLr = renal clearance; R_{ac} = accumulation ratio

[a] Median (range)

[b] AUC is AUC_{τ} (AUC from time 0 to 12 hours) for single dose and multiple-dose administration

[c] CL is reported for intravenous injection. CL/F is reported for tablet

Adapted from draft prescribing information, Table 4

The absolute bioavailability of delafloxacin 450 mg oral tablet administered as a single dose was 58.8%. Delafloxacin exposure (area under the concentration-time curve; AUC) after administration of a single 450 mg oral dose was similar to that observed following a single 300 mg IV dose. Peak plasma concentrations (C_{max}) were reached within approximately 1 hour after oral administration under fasted conditions. Total exposure ($AUC_{0-\infty}$) was unchanged under fasted or fed conditions. Plasma protein binding was 84%, primarily to albumin, and was not significantly affected by renal impairment. The steady state volume of distribution was 30 to 48 L, approximating total body water. The estimated mean half-life of delafloxacin was 3.7 h after IV administration and 4.2 to 8.5 h after oral administration. Mean clearance of delafloxacin was 16.3 L/h after administration of a single 300 mg IV dose; renal clearance was 35-45% of total clearance. The primary metabolic pathway for delafloxacin is glucuronidation. Unchanged parent drug is the main component in plasma. There are no significant circulating metabolites. After a single IV dose of ^{14}C-labeled delafloxacin, 65% of radioactivity was excreted in urine as unchanged delafloxacin and glucuronide metabolites, and 28% was excreted in feces as unchanged delafloxacin. After a single oral dose of ^{14}C-labeled delafloxacin, 50% of radioactivity was excreted in urine as unchanged delafloxacin and glucuronide metabolites, and 48% was excreted in feces as unchanged delafloxacin.

After administration of a single 300 mg IV dose of delafloxacin to subjects with renal impairment, AUC values for subjects with mild (estimated glomerular filtration rate (eGFR) = 51-80 mL/min/1.73 m^2), moderate (eGFR = 31-50 mL/min/m^2), and severe (eGFR = 15-29 mL/min/m^2) impairment were 1.3-, 1.6-, and 1.8-fold greater, respectively, than for matched normal control subjects. In subjects with end-stage renal disease (ESRD; eGFR <15 mL/min/m^2) requiring dialysis, AUC values on and off dialysis were 2.1- and 2.6-fold greater, respectively, than for matched normal control subjects. After administration of a single 400 mg oral dose of delafloxacin to subjects with mild, moderate, or severe renal impairment, AUC values were 1.1-, 1.5-, and 1.6-fold greater than for matched normal control subjects.

The applicant proposed no dosing adjustment for patients with mild or moderate renal impairment. The safety profile in patients with mild or moderate renal impairment in the phase 3 trials was similar to that of the overall patient population, and the OCP review team agreed with the applicant's proposed dosing. For patients with severe renal impairment or ESRD, the applicant proposed modifying the dosing of delafloxacin to 200 mg IV q12h or (b) (4) (b) (4). The OCP review team agreed with the proposed IV dosing in patients with severe renal impairment because it provides exposure similar to that in normal subjects, based on simulation. The review team did not agree with the proposed oral dosing, (b) (4) (b) (4). They recommended (b) (4) (b) (4) in a phase 2 trial in which no major safety issues were noted. The review team also recommended against the use of delafloxacin in patients with ESRD because of lack of information to provide appropriate dosing.

The SBECD vehicle in the IV formulation accumulates in patients with renal impairment and may present a risk of nephrotoxicity. The OCP review team recommended that serum creatinine

levels be monitored in patients with severe renal impairment receiving IV delafloxacin and consideration given to changing to oral delafloxacin if creatinine increases.

Dose adjustments are not needed for patients with hepatic impairment or for geriatric patients.

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 coadministration 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.

For fluoroquinolone antimicrobials, the ratio of area under the concentration-time curve of free drug to minimal inhibitory concentration ($fAUC_{24}$/MIC) is the pharmacokinetic/pharmacodynamic (PK/PD) index most closely associated with activity. The applicant proposed susceptibility breakpoints of 0.5 µg/mL for *S. aureus*, 0.25 µg/mL for *E. coli*, and 0.5 µg/mL for *P. aeruginosa* based on $fAUC_{24}$/MIC ratios obtained for bacterial stasis and for 1-$\log_{10}$ bacterial kill in a murine neutropenic thigh model of infection. There are no relevant clinical pharmacology data for the other pathogens proposed by the applicant; these will be discussed in section 6.

The OCP pharmacometrics reviewer analyzed the probability of target attainment (PTA) in patients based on simulations using a population PK model with the PK/PD target for stasis and MIC distributions obtained from in vitro surveillance data. For the pathogens above, more than 90% of patients receiving the proposed IV and oral dosing regimens would achieve the PK/PD target associated with stasis at the proposed breakpoints across varying levels of renal function, except for patients with severe renal impairment receiving the proposed oral dosing regimen. For these patients, the OCP recommendation is to retain the 450 mg q12h dose, as noted above.

In the phase 3 ABSSSI trials, *S. aureus* was isolated from over 60% of patients. Almost all isolates had MICs $\leq$0.25 µg/mL; only 4 isolates had MICs of 0.5 µg/mL, and 1 isolate had an MIC of 4 µg/mL. Two of the 4 patients with *S. aureus* with MICs of 0.5 µg/mL were clinical responders on the primary endpoint. There were also few patients with *E. coli* or *P. aeruginosa* isolated. The clinical data are insufficient to support the applicant's proposed breakpoints.

Breakpoint determination is based on MIC distributions in clinical trials and surveillance programs, nonclinical PK/PD target attainment data, and clinical data. See section 6 for additional discussion of susceptibility criteria.

The OCP review team concluded that these applications were approvable from a clinical pharmacology perspective pending agreement on the dosing regimen and labeling.

6. Clinical Microbiology

Jalal Sheikh, Ph.D., was the clinical microbiology reviewer for these applications. His findings and recommendations are summarized below.

Delafloxacin is a fluoroquinolone antimicrobial that acts by inhibiting bacterial DNA gyrase and topoisomerase IV, which are required for DNA replication, transcription, repair, and recombination. It is bactericidal against gram-positive and gram-negative bacteria and has greater activity in vitro against gram-positive pathogens than other fluoroquinolones.

Resistance to fluoroquinolones, including delafloxacin, is due to mutations in quinolone-resistance determining regions (QRDRs) of DNA gyrase and topoisomerase IV. Delafloxacin-resistant mutations were selected at in vitro at frequencies of $<10^{-9}$ for gram-positive and gram-negative bacteria.

Delafloxacin was evaluated against a variety of pathogens in models of systemic, pulmonary, urinary tract, and neutropenic thigh infections in mice and pulmonary infection and abscess in rats. In general, delafloxacin was effective with similar or superior activity to comparators; it was less active than ciprofloxacin or trovafloxacin in systemic infections with *E. coli* in mice.

In the phase 3 trials, approximately 90% of baseline isolates were gram-positive; over 60% were *S. aureus* (56% MSSA, 44% MRSA). The majority of gram-negative isolates were from polymicrobial infections from which gram-positive organisms were also isolated. Delafloxacin MIC_{50}/MIC_{90} values were 0.008/0.03 µg/mL for MSSA and 0.12/0.25 µg/mL for MRSA. MIC_{50}/MIC_{90} values for most other gram-positive pathogens were similar to those for MSSA; for *E. faecalis*, MIC_{50}/MIC_{90} values were 0.12/1 µg/mL. For gram-negative pathogens isolated from at least 20 patients, MIC_{50}/MIC_{90} values ranged from 0.06/4 µg/mL for *E. coli* to 0.25/4 µg/mL for *P. aeruginosa*. The MIC distributions from of the clinical study isolates were generally similar to those from recent surveillance studies.

Microbiological outcomes were generally imputed in the phase 3 ABSSSI trials because few postbaseline isolates were obtained from patients. Microbiological response rates in the primary analysis population were similar to the clinical response rates. Clinical outcomes by pathogen are presented in section 7.

Clinical and microbiologic outcomes were correlated with MICs and disk diffusion zone diameters of baseline pathogens. Susceptibility interpretive criteria for delafloxacin were established using these data along with surveillance MIC distributions and PK/PD analyses. The criteria were discussed with the applicant and are presented in Table 2.

Table 2: Susceptibility Test Interpretive Criteria for Delafloxacin

	Minimum Inhibitory Concentrations (µg/mL)			**Disk Diffusion Zone Diameter (mm)**		
Pathogen	S	I	R	S	I	R
Staphylococcus aureus (MRSA and MSSA)	≤0.25	0.5	≥1	≥23	20-22	≤19
Staphylococcus haemolyticus	≤0.25	0.5	≥1	≥24	21-23	≤20

Streptococcus pyogenes	≤0.06	-	-	≥20	-	-
Streptococcus agalactiae	≤0.06	0.12	≥0.25	-	-	-
Streptococcus anginosus Group[a]	≤0.06	-	-	≥25	-	-
Enterococcus faecalis[b]	≤0.12	0.25	≥0.5	≥21	19-20	≤18
Enterobacteriaceae	≤0.25	0.5	≥1	≥22	19-21	≤18
Pseudomonas aeruginosa	≤0.5	1	≥2	≥23	20-22	≤19

S = susceptible; I = intermediate; R = resistant
[a] Includes *S. anginosus*, *S. constellatus*, and *S. intermedius*
[b] *E. coli*, *K. pneumoniae*, *E. cloacae* only

There were insufficient numbers of clinical infections with *S. dysgalactiae*, *K. oxytoca*, and *P. mirabilis* for these organisms (b) (4) they will therefore be added to the list of organisms for which data are available but efficacy has not been established. The applicant (b) (4) also included some organisms (b) (4) which are considered normal flora and unlikely ABSSSI pathogens. These will not be included in labeling.

Dr. Sheikh concluded that these applications were approvable from the clinical microbiology perspective, pending agreement on labeling.

7. Clinical/Statistical- Efficacy

Caroline Jjingo, MD, MPH, was the clinical reviewer, and Janelle Charles, PhD, was the statistical reviewer for these applications. The clinical program included two phase 2 and two phase 3 trials.

Phase 2 trials

Study RX-3341-201 was a randomized, double-blind study that compared two dosing regimens of delafloxacin (300 mg IV q12h and 450 mg IV q12h) with tigecycline, 100 mg initial dose followed by 50 mg q12h for the treatment of complicated skin and skin structure infections; treatment was administered for 5 to 14 days. 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. The analysis was exploratory. Study RX-3341-202 was a randomized, double-blind study that compared delafloxacin, 300 mg IV q12h with linezolid, 600 mg IV q12h, or vancomycin, 15 mg/kg q12h for the treatment of ABSSSI; treatment was administered for 5 to 14 days. 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. This analysis was also exploratory.

Phase 3 trials

FDA agreed that two successful noninferiority trials, one with IV therapy only and the other with an IV-to-oral switch, could support an ABSSSI indication. The proposed trials were submitted for special protocol assessments, and agreements were reached for both. The development

program was planned to support approval in the US and in Europe. The primary endpoints for the ABSSSI indication for FDA and for the skin and soft tissue infections (SSTI) indication for the European Medicines Agency (EMA) differ as described below.

Study RX-3341-302 (Study 302) was a multicenter, randomized, double-blind trial that compared the efficacy and safety of IV delafloxacin with that of vancomycin plus aztreonam in the treatment of ABSSSI. This trial was conducted at sites in the US, Europe, and Israel from 2013 to 2014. Study RX-3341-303 (Study 303) was a multicenter, randomized, double-blind trial that compared the efficacy and safety of IV and oral delafloxacin with that of vancomycin plus aztreonam in the treatment of ABSSSI. This trial was conducted at sites in North America, South America, Europe, and Asia from 2014 to 2016. The final versions of these protocols are described below.

Patients 18 years of age or older with one of the following types of ABSSSI were eligible:

- Cellulitis/erysipelas: a diffuse skin infection characterized by spreading areas of redness with a minimum surface area of 75 cm^2 (measured manually as length times perpendicular width)
- Wound infection: an infection characterized by purulent drainage from a traumatic or surgical wound with surrounding redness with a minimum surface area of 75 cm^2
- Major cutaneous abscess: an infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness with a minimum surface area of 75 cm^2
- Burn infection: an infection characterized by purulent drainage accompanied by redness with a minimum surface area of 75 cm^2; enrollment was restricted to burns of $\leq$10% of body surface area

For both studies, no more than 25% of enrolled patients could have a major cutaneous abscess; for Study 302, no more than 35% could have a wound infection, and for Study 303, no more than 30% could have a wound infection. Patients also had to have at least two of the following signs of systemic infection: lymph node enlargement due to the present infection; lymphangitis; documented fever $\geq$38°C orally (or equivalent depending on method of measurement); white blood cell (WBC) count $\geq$10,000 cells/μL within 48 hours before first dose of study drug; elevated C-reactive protein (>10 times upper limit of normal) within 48 hours before the first dose of study drug; or purulent or seropurulent drainage. 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; receipt of only one dose of potentially effective short-acting (half-life $\leq$12 h) therapy or a short-acting regimen before enrollment. Enrollment of patients receiving a single dose of a therapy or regimen was limited to no more than 25% of the randomized population. Specimens from the site of infection were to be collected for culture and Gram stain before the first dose of study drug; blood cultures were also collected. Digital photography was performed to determine objective clinical response. Daily dressing changes and minor debridement procedures were permitted. Topical solutions and antibacterial dressings were not permitted, with the exception of silver-containing dressings for burns. Unplanned incision and drainage and major debridement procedures were not allowed after enrollment. Hyperbaric oxygen therapy was not allowed.

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 group also 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. In Study 303, patients were randomly assigned (1:1) to receive either delafloxacin, 300 mg IV q12h for 6 doses, followed by a mandatory switch to oral delafloxacin, 450 q12h, or vancomycin, 15 mg/kg IV q12h plus aztreonam, 2 g q12h. Doses were adjusted for patients with creatinine clearances of 15-29 mL/min. Patients in the delafloxacin group also received placebo infusions instead of aztreonam, and patients in the vancomycin group received oral placebo to correspond with the switch to oral delafloxacin. IV 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 and by baseline body mass index (BMI <30 and BMI $\geq$30); 40% to 50% of patients were to have BMI $\geq$30. For both studies, duration of therapy was 5 to 14 days, as determined by the investigator.

The primary endpoint for both studies was objective response of $\geq$20% reduction in area of lesion erythema compared with baseline as determined by digital measurement of the leading edge at 48 to 72 hours ($\pm$2 hours) after initiation of therapy, with no evidence of clinical failure. Clinical failure at this time point was defined as <20% reduction in area of lesion erythema, administration of rescue therapy, need for unplanned surgical intervention, or death. The major secondary endpoint was investigator-assessed clinical response at the follow-up visit on study day 14$\pm$1, at least 12 hours after the last dose of study drug; this is the primary endpoint for EMA approval. For this endpoint, cure was defined as complete resolution of all baseline signs and symptoms of ABSSSI; if erythema was the only sign remaining at the follow-up visit and was absent at the late follow-up visit on day 21 to 28, the outcome was considered a cure. Improvement was defined as incomplete resolution, but improvement such that no further antimicrobial therapy was necessary. For analysis of this endpoint in this submission, success was defined as a response of cure or improved. Clinical failure was defined as administration of nonstudy antimicrobial therapy because of lack of efficacy after at least 4 doses of study drug, administration of nonstudy antimicrobial therapy because of a treatment-related adverse event, need for more than 28 doses of therapy, or need for an unplanned surgical intervention.

The primary analysis population was the intent-to-treat (ITT) population, which was all patients who were randomized. Secondary endpoint analyses were performed in the microbiological intent-to-treat (MITT) population, which was all patients in the ITT population who had a baseline pathogen identified that was known to cause ABSSSI. For evaluation of investigator-assessed clinical response at the day 14 follow-up visit, 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.

For both studies, noninferiority of delafloxacin to vancomycin plus aztreonam was concluded if the lower bound of the 95% confidence interval for the difference in clinical response rates (delafloxacin minus vancomycin/aztreonam) was greater than -10% in the ITT population. The applicant calculated that a sample size of 660 patients had at least 90% power to demonstrate noninferiority 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. In Study 302, based on an exploratory analysis, the applicant concluded that there was an improved cure rate at the late follow-up visit (day 21 to 28) for obese patients treated with delafloxacin. For Study 303, enrollment 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 $\geq$30. Enrollment of 340 to 425 obese patients had 60-70% power to demonstrate superiority on this endpoint, assuming a 12% difference between treatment arms.

In Study 302, 660 patients were randomized, 331 to IV delafloxacin and 329 to vancomycin plus aztreonam. The median age was 47 years (7% $\geq$65 years), 62% of patients were male, and 90% were white; 82% were from North America. The most common diagnosis was cellulitis/erysipelas (39%); 35% had wound infection, 25% had major abscess, and 1% had burn infection. A baseline pathogen was isolated in 74% of patients; the most common pathogen was *S. aureus* (66% of MITT patients). Bacteremia was present at baseline in 15 patients (2.3%).

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% $\geq$65 years), 63% of patients were male, and 83% were white; 47% were from North America. The most common diagnosis was cellulitis/erysipelas (48%); 26% had wound infection, 25% had major abscess, and 1% had burn infection. A baseline pathogen was isolated in 65% of patients; the most common pathogen was *S. aureus* (58% of MITT patients). Bacteremia was present at baseline in 19 patients (2.2%).

Table 3 shows the objective clinical response rates at the 48 to 72 hour assessment for Studies 302 and 303. In each study, the lower limit of the 95% confidence interval for the treatment difference was greater than-10%, and delafloxacin was noninferior to vancomycin plus aztreonam for the treatment of ABSSSI. The most common reason for failure in each study was <20% reduction in the area of lesion erythema; missing data was the reason for failure in 7.9% of delafloxacin patients and 6.7% of control patients in Study 302; for Study 303, data were missing for 4.7% and 4.9%, 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 percentage, and CI based on Miettinen and Nuriminen method without stratification
CI = confidence interval
Adapted from FDA statistical review, Table 14

In the analysis of this endpoint in the MITT population, response rates in Study 302 were 81.1% in the delafloxacin group and 83.8% in the vancomycin plus aztreonam group (treatment difference -2.7%, 95% CI (-9.5, 4.0)). Response rates in Study 303 were 87.6% in the delafloxacin group and 82.3% in the vancomycin plus aztreonam group (treatment difference 5.3%, 95% CI (-0.7, 11.4)).

Analyses by type of infection, use of prior therapy, and presence of diabetes or mild to moderate renal impairment were generally consistent with the primary analysis. There was insufficient evidence to evaluate the efficacy of delafloxacin in patients with severe renal impairment or end stage renal disease.

Subgroup analyses by age, race, sex, and geographic region were also consistent with the primary analysis.

In Study 302, the applicant reported that there was an improved cure rate at the late follow-up visit (day 21 to 28) for obese patients (BMI $\geq$30) treated with delafloxacin compared with control patients (71.7% vs. 57.5%, respectively). Response rates were similar for the 48 to 72 hour objective response assessment, however. The applicant enriched enrollment of obese patients in Study 303 to assess superiority of delafloxacin in a pre-specified subgroup analysis. Cure rates at the investigator-assessed late follow-up visit for patients with BMI $\geq$30 in Study 303 were 68.3% for delafloxacin patients and 71.0 % for control patients. The applicant's observation in Study 302 was not substantiated.

Table 4 shows the investigator-assessed response at the day 14 follow-up assessment in the ITT and CE populations. This assessment suggests that the initial response to therapy is sustained. The assessment at this later time point also supports the efficacy of oral delafloxacin in Study 303, in which the switch from IV to oral therapy may not have taken place until after the 48 to 72 hour assessment.

Table 4: Investigator-Assessed Response at Follow-up (Day 14) (ITT and CE Populations)

	Study 302			**Study 303**		
	Delafloxacin IV	**Vancomycin + aztreonam**	**Treatment difference[1] (95% CI)**	**Delafloxacin IV/PO**	**Vancomycin + aztreonam**	**Treatment difference[1] (95% CI)**
ITT 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)
CE Success[2], n/N (%)	232/240 (96.7)	238/244 (97.5)	-0.9 (-3.9, 2.1)	339/353 (96.0)	319/329 (97.0)	-0.9 (-3.8, 2.0)

CI = confidence interval; ITT = intent to treat; CE = clinically evaluable

[1] Treatment difference, expressed as percentage, and CI based on Miettinen and Nuriminen 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 FDA statistical review, Table 19

The CE population used for evaluation of the investigator-assessed clinical response at the day 14 follow-up visit included 73% of the ITT population from Study 302 and 80% of the ITT population from Study 303. For both studies, the most common reasons for exclusion from the CE population were lack of assessment or indeterminate assessment in the follow-up window. Dr. Charles expressed concern about the applicant's imputation to account for missing data for one patient in Study 302, a delafloxacin patient who had an outcome imputed as "improved" at follow-up but who was considered a failure at late follow-up because additional therapy was required. She also cautioned about interpreting findings in the CE population because of potential bias due to exclusion of patients based on post-randomization factors that might be influenced by treatment.

Table 5 shows the clinical response rates at the 48 to 72 hour and day 14 follow-up assessments for the baseline pathogens (b) (4).

Table 5: Clinical Response Rates by Pathogen (MITT Population)

	Objective response at 48-72 hours		**Clinical success at follow-up**	
Pathogen	**Delafloxacin n/N (%)**	**Vancomycin + aztreonam n/N (%)**	**Delafloxacin n/N (%)**	**Vancomycin + aztreonam n/N (%)**
Gram-positive				
Staphylococcus aureus	271/319 (85.0)	269/324 (83.0)	275/319 (86.2)	269/324 (83.0)
Methicillin-susceptible	149/177 (84.2)	148/183 (80.8)	154/177 (87.0)	153/183 (83.6)
Methicillin-resistant	125/144 (86.8)	121/141 (85.8)	122/144 (84.7)	116/141 (82.3)
Staphylococcus haemolyticus	11/15 (73.3)	7/8 (87.5)	13/15 (86.7)	7/8 (87.5)
Staphylococcus hominis	11/11 (100)	10/13 (76.9)	10/11 (90.9)	12/13 (92.3)
Staphylococcus lugdunensis	8/11 (72.7)	6/9 (66.7)	10/11 (90.9)	8/9 (88.9)
Streptococcus pyogenes	17/23 (73.9)	9/18 (50.0)	21/23 (91.3)	16/18 (88.9)
Streptococcus anginosus Group[1]	59/64 (92.2)	55/61 (90.2)	54/64 (84.4)	47/61 (77.0)
Streptococcus agalactiae	10/14 (71.4)	9/12 (75.0)	12/14 (85.7)	11/12 (91.7)
Streptococcus dysgalactiae	7/9 (77.8)	8/11 (72.7)	8/9 (88.9)	10/11 (90.9)
Streptococcus mitis/oralis	12/13 (92.3)	5/5 (100)	12/13 (92.3)	4/5 (80.0)
Enterococcus faecalis	11/11 (100)	12/16 (75.0)	9/11 (81.8)	14/16 (87.5)
Gram-negative				
Klebsiella pneumoniae	19/22 (86.4)	22/23 (95.7)	20/22 (90.9)	21/23 (91.3)
Klebsiella oxytoca	5/6 (83.3)	4/5 (80.0)	6/6 (100)	5/5 (100)
Enterobacter cloacae	10/14 (71.4)	8/11 (72.7)	12/14 (85.7)	10/11 (90.9)
Escherichia coli	12/14 (85.7)	16/20 (80.0)	12/14 (85.7)	18/20 (90.0)
Pseudomonas aeruginosa	9/11 (81.8)	11/12 (91.7)	11/11 (100)	12/12 (100)
Proteus mirabilis	6/8 (75.0)	5/8 (62.5)	8/8 (100)	8/8 (100)

[1] Includes *Streptococcus anginosus*, *Streptococcus constellatus*, *Streptococcus intermedius*
Adapted from FDA statistical review, Tables 27 and 28

As noted in the previous section, there were insufficient numbers of clinical infections with *S. dysgalactiae*, *K. oxytoca*, and *P. mirabilis* for these organisms (b) (4) pathogens. The applicant (b) (4) also included some organisms (b) (4) (b) (4) which are considered normal flora and unlikely ABSSSI pathogens. These will not be included in labeling.

Six patients in the delafloxacin group had *S. aureus* bacteremia at baseline; 5 were responders at 48-72 hours and successes at follow-up. Two patients in the delafloxacin group had gram-

negative bacteremia (*K. pneumoniae*, *P. aeruginosa*) at baseline; both were responders at 48 to 72 hours and successes at follow-up.

Conclusions

Dr. Charles identified no major statistical issues with this application and concluded that the applicant provided adequate evidence for the efficacy of delafloxacin in ABSSSI. The treatment effect observed at the 48 to 72 hour assessment appears to be sustained at later time points. The assessment at later time points also supports the efficacy of oral delafloxacin in Study 303, in which the switch from IV to oral therapy may not have taken place until after the 48 to 72 hour assessment She recommended that labeling include only results obtained from the ITT population and not from the CE population because of concerns about exclusion of patients from the CE population due to post-randomization factors. She acknowledges that findings from CE populations have been included in labeling for other products approved for ABSSSI. Dr. Jjingo also concluded that the applicant provided adequate evidence for the efficacy of delafloxacin in ABSSSI. I concur that the phase 3 trials provide substantial evidence of effectiveness to support approval of delafloxacin for the treatment of ABSSSI in adult patients.

8. Safety

Caroline Jjingo, MD, MPH, performed the safety review for these applications.

The delafloxacin clinical program, conducted under INDs 62772 (tablet formulation) and 76096 (IV formulation), 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). Across all studies, 2658 subjects received delafloxacin. The primary data used to evaluate the safety profile of delafloxacin are from the integrated phase 3 ABSSSI trials.

Phase 3 trials

In the pooled phase 3 trials, 741 patients received delafloxacin, and 751 patients received vancomycin plus aztreonam. The duration of therapy in the trial protocols was 5 to 14 days. Patients in Study 303 received IV delafloxacin for 6 doses followed by a mandatory switch to oral delafloxacin. The median duration of exposure to delafloxacin was 6 days (range, 0.5 to 14 days). The median age of patients receiving delafloxacin was 49 years (range, 18 to 94 years); 62% were male, 86% were white, and 62% were from the U.S.

Table 6 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 6: Treatment-Emergent Adverse Events in the Pooled Phase 3 Trials

Type of Adverse Event	Delafloxacin (N=741) n	(%)	Vancomycin + Aztreonam (N=751) 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 Summary of Clinical Safety, Table 8

There were four deaths due to TEAEs in the pooled trials, one in the delafloxacin arm and three in the vancomycin plus aztreonam 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.

SAEs were reported in 27 (3.6%) patients treated with delafloxacin and in 26 (3.5%) patients treated with vancomycin plus aztreonam. SAEs that were reported in more than one patient treated with delafloxacin included skin infection (4 patients), cellulitis (3 patients), infection (2 patients), and pulmonary embolism (2 patients). Many of the SAEs were infection-related, and lack of efficacy of the study drug may be contributory. A 41-year-old 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. One patient in the vancomycin plus aztreonam arm had pulmonary embolism. Both of the patients in the delafloxacin arm had risk factors for deep vein thrombosis.

Discontinuation of study drug due to TEAEs was reported in 13 (1.8%) patients treated with delafloxacin and in 26 (3.5%) patients treated with vancomycin plus aztreonam. 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 recipients 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%). Rates of gastrointestinal events were similar in both studies (IV only and IV-to-oral switch). The applicant proposed a table of adverse drug reactions that was a subset of TEAEs based on frequency in the phase 3 trials and investigator assessments of relatedness to treatment. This list included only nausea, diarrhea, pruritus, and generalized pruritus. The division proposes to base the list on plausibly related reactions, not on investigator assessments of relatedness, and to include additional adverse reactions.

Adverse events of special interest (AESIs) for fluoroquinolone antimicrobials that were assessed using MedDRA terms and standard MedDRA queries included myopathy, *Clostridium difficile* diarrhea, convulsions, peripheral neuropathy, tendon disorder, QT prolongation, phototoxicity, allergic reactions, dysglycemia, and hepatic-related events. AESIs from the phase 3 and phase 2 ABSSSI trials are summarized below.

One patient who received delafloxacin 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. Another delafloxacin recipient had an SAE of hepatitis C infection. There were no other hepatic SAEs. Rates of hepatic-related events were similar in the delafloxacin and comparator groups. Dr. Jjingo recommended that rates of related hepatic events such as hypertransaminasemia, increased transaminases, and increased ALT and AST be combined in one term in labeling.

One patient in the delafloxacin group in a phase 2 trial had an SAE of convulsion on Day 8, the last day of treatment. One patient who received delafloxacin had an SAE of urticaria; rates of potential allergic reactions were lower in the delafloxacin group (4.0%) than in the comparator group (6.6%) in the combined phase 2 and phase 3 trials. Two patients in the delafloxacin group had *C. difficile* colitis or infection vs. none in the comparator group; both were considered of mild severity. Three patients in the delafloxacin group had syncope vs. one in the comparator group (loss of consciousness); these events were not classified as SAEs. Three patients in the delafloxacin group had tendinitis. One patient in the delafloxacin group had a photosensitivity reaction occurring 11 days after the end of therapy. Rates of dysglycemia, neuropathy, and myopathy were similar between groups, and there were no SAEs in these categories.

Phase 2 trials

There were no deaths in the phase 2 trials. Seven SAEs were reported in 5 patients who received delafloxacin. Three events were infection-related; the others were pyrexia (with bacteremia) and femoral neck fracture, convulsion (described above), congestive cardiac failure (with abscess). Delafloxacin was discontinued in one patient because of bacteremia and pyrexia (also SAEs). The most commonly reported TEAEs in the phase 2 trials were similar to those from phase 3.

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.

Conclusions

The safety information provided supports the use of delafloxacin for the treatment of ABSSSI in adult patients. Labeling will contain the fluoroquinolone class-specific Boxed Warning about tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbations of myasthenia gravis, as well as information in the Warnings and Precautions section about other potentially serious adverse reactions. As with other fluoroquinolones, a Medication Guide will be provided with delafloxacin prescriptions.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Melinta submitted an initial pediatric study plan (iPSP) on December 23, 2015, proposing to request a full waiver of pediatric studies for ABSSSI because of 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. The plan was discussed with the Pediatric Review Committee (PeRC) on March 2, 2016. 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 submitted with the 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 label 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

The Office of Scientific Investigations inspected four clinical investigator sites from the phase 3 trials and the applicant and concluded that the data appeared acceptable to support these applications. This conclusion was based on preliminary communications with the Office of Regulatory Affairs investigator for one of the clinical investigators and the applicant. The OSI reviewer, Bei Yu, Ph.D., stated that OSI would file an addendum if the conclusion changed following review of the final reports.

Melinta stated there were no clinical investigators who enrolled subjects and who had disclosable financial interests or arrangements. Melinta filed a Form 3455 for one investigator, (b) (6) (b) (6), whose spouse was employed by a company with distribution rights to delafloxacin in (b) (6) did not enroll subjects into the study for which he was an investigator.

12. Labeling

The Division of Medication Error Prevention and Risk Management of the Office of Surveillance and Epidemiology determined that the proposed proprietary name, Baxdela, was conditionally acceptable.

Recommendations from the Office of Prescription Drug Promotion, the Division of Medical Policy Programs, and the Division of Medication Error Prevention and Analysis were incorporated into labeling, including the Medication Guide.

13. Postmarketing Recommendations

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The applicant has agreed to the following 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: 09/30/2017

Study Trial Completion: 09/30/2022

Final Report Submission: 12/31/2022

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 the distribution of the drug substance to the reproductive tract and developing fetus

Final Protocol Submission: 10/2017

Study Trial Completion: 03/2018

Final Report Submission: 06//2018

3220-3: If the results of the tissue distribution studies from 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 Trial Completion: 01/2019

Final Report Submission: 04//2019

The applicant has also agreed to the following PMCs related to product quality:

1. Add the facility responsible for 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/

THOMAS D SMITH
06/16/2017