CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208610Orig1s000
208611Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

Division of Anti-Infective Products
Clinical Microbiology Review

NDA: 208610 (450 mg oral Tablets) & 208611 (300 mg/vial IV infusion)

Date Company Submitted: 10/18/2016
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Reviewer: **Jalal Sheikh, Ph.D.**

NAME AND ADDRESS OF APPLICANT:
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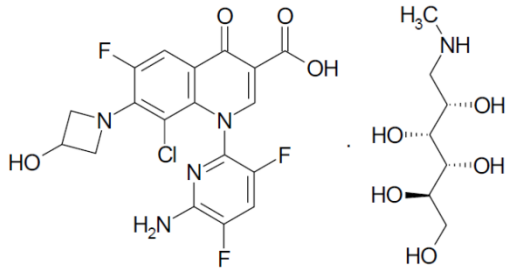
DRUG PRODUCT:
Proprietary Name: Baxdela
Code Name: RX-3341; WQ-3034, ABT-492, ABT-319492
Established Name: Delafloxacin
Chemical Name: 1-deoxy-1- (methylamino)-D-glucitol, 1-(6-amino-3,5-difluoro-2-pyrdinyl)-8-chloro-6-fluoro-7-(3- hydroxy-1-azetidinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate

MOLECULAR FORMULA: $C_{18}H_{12}ClF_3N_4O_4$

MOLECULAR WEIGHT: 440.764 g/mol (free acid); 635.977 g/mol (meglumine salt)

STRUCTURAL FORMULA:



DRUG CATEGORY: Antibacterial

PROPOSED DOSAGE FORM, STRENGTH, ROUTE OF ADMINISTRATION AND DURATION OF TREATMENT:

Dosage Form:	Tablet	Injectable
Route of Administration:	Oral	IV infusion
Dose Strength:	450 mg	300 mg
Frequency:	Every 12 hours	Every 12 hours
Duration:	5 to 14 days	5 to 14 days

DISPENSED: Prescription product (Rx)

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

RELATED DOCUMENTS:
IND-62772
IND-76096

TYPE OF SUBMISSION:
New Drug Application (NDA)

PURPOSE OF SUBMISSION: Original Application; 505(b)(1)

SUMMARY AND RECOMMENDATIONS:
The applicant has submitted two NDAs: NDA 208610 (Baxdela Tablets formulation, 450 mg) and NDA 208611 (Baxdela IV formulation, 300 mg/vial) for the treatment of ABSSSI in adults caused by susceptible isolates of the following Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, (b) (4) *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (b) (4), (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*.

Two randomized, double-blind, active-controlled multi-center phase 3 studies were conducted to support the efficacy and safety of delafloxacin and indication for ABSSSI in adult patients [***RX-3341-302*** *(IV delafloxacin 300 mg to comparator IV vancomycin (15 mg/kg actual body weight) with IV aztreonam (2 g) in 660 subjects with ABSSSI) and* ***RX-3341-303*** *(IV delafloxacin, 300 mg Q12h for 6 doses stepped down to 450 mg Q12h orally, to comparator IV vancomycin (recommended 15 mg/kg actual body weight) with IV aztreonam (1 to 2 g) Q12h in 850 subjects with ABSSSI)*]. The study populations of the Phase 2 and Phase 3 studies consisted of adult male and female subjects of ≥ 18 years of age with a diagnosis of ABSSSI. The key comparators in the 2 Phase 3 studies were vancomycin + aztreonam combination therapy based on their respective activity against gram-positive and gram-negative pathogens.

From a clinical microbiology perspective, both NDAs 208610 and 208611 are approvable, pending the applicant accepting the changes in the MICROBIOLOGY subsection of the Package Insert recommended by the reviewer as shown below.

MICROBIOLOGY SUBSECTIONS OF THE PACKAGE INSERT
This Reviewer recommends the following changes to the Microbiology section of the label. All additions and deletions (strikethrough) are marked as red.

Reviewer's comment: To be consistent with the current Division practice and the FDA's draft guidance document: "Microbiological Data for Systemic Antibacterial Drug Products-Development, Analysis and Presentation", minor changes were made to the formatting of the microbiology section of the labeling.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BAXDELA is an antibacterial drug [*see Microbiology (12.4)*].

12.4 Microbiology

Mechanism of Action

(b) (4) Delafloxacin belongs to the fluoroquinolone class of antibacterial drugs and is anionic in nature. The antibacterial activity of (b) (4) delafloxacin is due to the inhibition of both bacterial topoisomerase IV and DNA gyrase (topoisomerase II) enzymes which are required for bacterial DNA replication, transcription, repair, and recombination. (b) (4) Delafloxacin exhibits a (b) (4) concentration-dependent bactericidal activity against (b) (4) gram-positive and (b) (4) gram-negative bacteria in vitro. (b) (4)

(b) (4)

Reviewer's comment: To be consistent with other fluoroquinolone labeling and to make it more precise, I have proposed this modification.

(b) (4) -Resistance

Resistance to fluoroquinolones, including (b) (4) delafloxacin, can occur due to mutations in defined regions of the target bacterial enzymes topoisomerase IV and DNA gyrase referred to as Quinolone-Resistance Determining Regions (QRDRs), or through altered efflux.

Fluoroquinolones, including (b) (4) delafloxacin, have a different chemical structure and mechanism of action relative to other classes of antibacterial compounds (e.g. aminoglycosides, macrolides, β-lactams, glycopeptides, tetracyclines, and oxazolidinones) (b) (4)
(b) (4)

(b) (4)

In vitro resistance to delafloxacin develops (b) (4) by multiple step mutations in the QRDRs of gram-positive and gram-negative bacteria. Delafloxacin-resistant mutants were selected in vitro at a (b) (4) -frequency (b) (4) of $<10^{-9}$.

Although cross-resistance between (b) (4) and other fluoroquinolone-class antibacterial agents has been observed, some isolates resistant to other fluoroquinolone-class antibacterial agents may be susceptible to BAXDELA.

Reviewer's comment: This section has been modified to indicate that resistance occurs in the QRDR region of gram-positive and –negative bacteria.

Interaction With Other Antimicrobials

In vitro drug combination studies with (b) (4) and aztreonam, ceftazidime, colistin, daptomycin, linezolid, meropenem, tigecycline, trimethoprim/sulfamethoxazole, and vancomycin demonstrated neither synergy nor antagonism.

Antimicrobial Activity

BAXDELA has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections, [*see Indications and Usage (1)*].

(b) (4)

(b) (4) Gram-positive bacteria

Staphylococcus aureus (including methicillin-resistant strains)

Staphylococcus haemolyticus

(b) (4)

Staphylococcus lugdunensis

Streptococcus pyogenes

Streptococcus agalactiae

Streptococcus anginosus Group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*)

(b) (4)

Enterococcus faecalis

Reviewer's comment: Among the proposed gram-positive pathogens, I recommend excluding (b) (4) *from the 1st list.* (b) (4) *are considered normal flora and hence not recommended to be included in either 1st or 2nd list. The clinical experience for* (b) (4) *was not adequately established in Phase 3 trials. I recommend moving* (b) (4) *into the 2nd list by considering that the proposed susceptible BPs of similar genus will have activity against >90% of the isolates.*

(b) (4) Gram-negative bacteria

Escherichia coli

Klebsiella pneumoniae

(b) (4)

Enterobacter cloacae

Pseudomonas aeruginosa

Reviewer's comment: The clinical data for (b) (4) *were not adequate in the*

Phase 3 trials. Therefore, I do not recommend including these isolates in the 1st list. Both organisms are included in the 2nd list considering that the proposed susceptible BPs of similar genus will have activity against ≥90% of these isolates.

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint (b) (4) delafloxacin against isolates of similar genus or organism group. However, the efficacy of BAXDELA in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic bacteria

Gram-positive bacteria
Streptococcus dysgalactiae

Gram-negative bacteria
Enterobacter aerogenes
Haemophilus parainfluenzae
Klebsiella oxytoca
Proteus mirabilis

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative reports of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid in the selection of an appropriate antibacterial drug for treatment.

Dilution Techniques
Quantitative methods are used to determine (b) (4) (b) (4) MICs. These MICs (b) (4) provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs (b) (4) should be determined using a standardized (b) (4) test method[1,3] (broth and/or agar). The MIC values should be interpreted according to (b) (4) criteria provided in Table (b) (4) 5.

Diffusion Techniques
Quantitative methods that require measurement of zone (b) (4) (b) (4) diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size (b) (4) should be determined using a standardized test method[2,3] (b) (4)

(b) (4)

(b) (4) This procedure uses paper disks impregnated with 5 mcg of (b) (4) delafloxacin to test the susceptibility of bacteria to (b) (4) delafloxacin.

(b) (4)

(b) (4)

(b) (4)

(b) (4) -The disk diffusion breakpoints are provided in Table 5.

Table (b) (4) 5 Susceptibility Test Interpretive Criteria for (b) (4) Delafloxacin

(b) (4)	Minimum Inhibitory Concentrations (b) (4) mcg/mL)			Disk Diffusion ((b) (4) zone (b) (4) diameter in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	≤ (b) (4) 0.25	(b) (4) 0.5	≥ (b) (4) 1	≥ (b) (4) 23	(b) (4) (b) (4) 20-22	≤ (b) (4) 19
Staphylococcus haemolyticus	≤ (b) (4) 0.25	(b) (4) 0.5	≥ (b) (4) 1	≥ (b) (4) 24	(b) (4) (b) (4) 21-23	≤ (b) (4) 20
(b) (4)						
Streptococcus pyogenes[a]	≤ (b) (4) .06	-	(b) (4)	≥ (b) (4) 20	-	(b) (4)
Streptococcus agalactiae	≤ (b) (4) .06	0.12	≥ (b) (4) 0.25	(b) (4)	-	(b) (4)
(b) (4)						
Streptococcus anginosus Group[a,b]	≤ (b) (4) .06	-	(b) (4)	≥ (b) (4) 25	-	(b) (4)
(b) (4)						
Enterococcus faecalis	≤ (b) (4) 0.12	(b) (4) 0.25	≥ (b) (4) 0.5	≥ 21	(b) (4) (b) (4) 19-20	≤ (b) (4) 18
Enterobacteriaceae[c]	≤0.25	0.5	≥1	≥22	19-21	≤18
(b) (4)						

(b) (4)	Minimum Inhibitory Concentrations ((b) (4) mcg/mL)			Disk Diffusion ((b) (4) zone (b) (4) diameter in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
(b) (4)						
Pseudomonas aeruginosa	≤ 0.5	(b) (4) 1	≥ 2	≥23	20-22	≤ 19

S = susceptible; I = intermediate; R = resistant

[a] The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.

[b] includes: S. anginosus, S. constellatus and S. intermedius

(b) (4)

[c] includes: E. coli, K. pneumoniae, and E. cloacae only.

Reviewer's comment: Based on the available data, the Agency revised and recommended the following MIC and disk diffusion BPs:

S. aureus: The MIC_{90} of delafloxacin against S. aureus isolates from both clinical and surveillance studies is 0.25 mcg/ml. Based on the data from in vitro MIC, clinical trials, and PK-PD, the Agency recommends a revised MIC BPs for susceptible (S)/intermediate (I)/resistant (R) as ≤0.25/0.5/≥1 mcg/mL.

Based on the revised MIC BPs and to minimize error-rates, the Agency recommends a revised S/I/R disk diffusion BPs of ≥23/20-22/≤19 mm.

S. haemolyticus: Similar to S. aureus, the Agency recommends a revised MIC BPs of S/I/R as ≤0.25/0.5/≥1 mcg/mL for S. haemolyticus.

Based on the revised MIC BPs and to minimize error-rates, the Agency recommends a revised susceptible/intermediate/resistant disk diffusion BP of ≥24/21-23/≤20 mm.

(b) (4)

S. pyogenes: No nonclinical PK-PD data are available for S. pyogenes. Based on in vitro MIC data from clinical and surveillance isolates and clinical outcome data the Agency recommends a susceptible only MIC BP of ≤0.06 mcg/mL for S. pyogenes. Based on the revised MIC BPs and to keep the acceptable error-rates to a minimum, the Agency recommends a revised susceptible disk

diffusion BP of ≥20 mm.

The current absence of resistant isolates from clinical and surveillance studies preclude defining any results other than "Susceptible".

S. agalactiae: No nonclinical PK-PD data are available for S. agalactiae. Based on in vitro MIC data from clinical and surveillance isolates and clinical outcomes experience the Agency recommends a revised MIC BPs of S/I/R as ≤ 0.06/0.12/≥ 0.25 mcg/mL for S. agalactiae.

The Agency does not recommend disk diffusion BPs at this time due to the absence of S. agalactiae-specific disk-diffusion data. The scatterplots provided by the Applicant include isolates of S. agalactiae along with other beta-hemolytic streptococci. Moreover, S. agalactiae isolates with increased MICs were seen in recent surveillance studies. The Agency can revisit the disk diffusion BPs once more data will be available from post marketing studies.

S. anginosus: No nonclinical PK-PD data are available for S. anginosus. Based on in vitro MIC data from clinical and surveillance isolates and clinical outcomes the Agency recommends an MIC susceptibility BP of 0.06 mcg/mL for S. anginosus Group.

The current absence of resistant isolates from clinical and surveillance studies preclude defining any results other than "Susceptible".

Based on the revised MIC BPs and to minimize error-rates, the Agency recommends a revised susceptible disk diffusion BP of ≥25 mm.

E. faecalis: In absence of pre-clinical PK-PD data and limited clinical data for E. faecalis, the Agency recommends MIC BPs of S/I/R as ≤ 0.12/ 0.25/ ≥ 0.5 mcg/mL. The agency accepts the Applicant-provided recalculation of disk diffusion BPs of S/I/R as ≥ 21/19-20/≤ 18 mm for E. faecalis.

Enterobacteriaceae (E. coli, K. pneumoniae, and E. cloacae only): The Agency recommends using Enterobacteriaceae as a group for E. coli, K. pneumoniae, and E. cloacae isolates since all of them have identical MIC and disk diffusion BPs.

The Agency accepts the Applicant-provided recalculation of disk diffusion S/I/R BPs as ≥ 22/19-21/≤ 18 mm for Enterobacteriaceae.

A report of (b) (4) *Susceptible (S)* indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of (b) (4) *Intermediate (I)* indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a

high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of (b) (4) *Resistant (R)* indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls (b) (4) to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test (b) (4) [1,2,3]. Standard (b) (4) delafloxacin powder should provide the following range of MIC values noted in Table (b) (4) 5. For the diffusion technique using the 5 mcg (b) (4) delafloxacin disk, (b) (4) (b) (4) the criteria in Table (b) (4) 6 should be achieved (b) (4).

Table (b) (4) 6 Acceptable Quality Control Ranges for (b) (4) Delafloxacin

	Minimum Inhibitory Concentrations (mcg/mL)	**Disk Diffusion (zone diameters in mm)**
Staphylococcus aureus ATCC 29213	0.001–0.008	Not applicable
Staphylococcus aureus ATCC 25923	(b) (4) Not applicable	(b) (4) 32-40
Enterococcus faecalis ATCC 29212	0.015–0.12	Not applicable
Streptococcus pneumoniae ATCC 49619	0.004–0.015	29–36
Escherichia coli ATCC 25922	0.008–0.03	28–35
Pseudomonas aeruginosa ATCC 27853	0.12–0.5	23–29
Haemophilus influenzae ATCC 49427	0.00025–0.001	40–51

ATCC = American Type Culture Collection

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Tenth Edition.* CLSI document M07-A10. Wayne, PA: Clinical and Laboratory Standards Institute; 2015

2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Susceptibility Tests, Approved Standard – Twelfth Edition.* CLSI document M02-A12. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.

3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing* – 27th ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.

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EXECUTIVE SUMMARY

I. IN VITRO INFORMATION

MECHANISM OF ACTION

Delafloxacin is an antibacterial drug that belongs to fluoroquinolone class of antibacterial drugs. It exerts its antibacterial activity by inhibiting DNA gyrase and topoisomerase IV. In gram-positive organisms, delafloxacin has a higher affinity for DNA gyrase while in gram-negative organisms, the inhibition of DNA gyrase and topoisomerase IV is nearly equivalent.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Delafloxacin has demonstrated in vitro activity against a wide range of clinically-relevant gram-positive, gram-negative, and anaerobic organisms. The in vitro activity of delafloxacin was evaluated in preclinical profiling and surveillance studies by determining MIC_{50}, and MIC_{90} against a diverse collection of isolates.

Delafloxacin showed higher in vitro susceptibility against gram-positive pathogens compared to fluoroquinolone comparators. Levofloxacin MIC_{50}/MIC_{90} values were higher than delafloxacin against all tested gram-positive isolates. For example, against 2,606 *S. aureus* delafloxacin demonstrated an overall MIC_{50}/MIC_{90} of ≤ 0.004/0.25 mcg/mL (≤ 0.004/0.015 mcg/mL against MSSA, and 0.12/1 mcg/mL against MRSA). Levofloxacin had MIC_{50}/MIC_{90} values of 0.25/>4 mcg/mL against *S. aureus* (0.25/1 mcg/mL against MSSA, and 4/>4 mcg/mL against MRSA). Delafloxacin had an overall MIC_{50}/MIC_{90} of ≤ 0.015/0.5 mcg/mL compared to 0.25/>4 mcg/ml for levofloxacin against a total of 744 coagulase-negative *S. aureus* (CoNS) isolates. Similarly, delafloxacin had an overall MIC_{50}/MIC_{90} of ≤ 0.008/0.015 mcg/mL compared to 0.5/1 mcg/ml for levofloxacin against a total of 902 *S. pyogenes* isolates.

Against 4,659 Enterobacteriaceae isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.12/4 mcg/mL compared to ≤ 0.12/ > 4 mcg/mL and ≤ 0.03/ > 4 mcg/mL for ciprofloxacin and levofloxacin, respectively. Against 302 *P. aeruginosa* isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.25/>4 mcg/ml compared to 0.5/>4 mcg/ml for levofloxacin.

RESISTANCE

Delafloxacin resistant mutants were selected in vitro at frequencies ranging from $<10^{-9}$ to $<10^{-12}$ for both gram-positive and gram-negative bacteria. Isolates that are resistant to delafloxacin commonly acquired mutations in the quinolone-resistance determining region (QRDR) relative to the parent isolates. Elevated delafloxacin MIC values typically associated with isolates having acquired mutations in *gyr A*, *gyrB* and *parC/grlA* genes.

ANTIMICROBIAL INTERACTION STUDIES

Delafloxacin showed no antagonism or synergy when tested in combination with daptomycin, linezolid, meropenem, ceftazidime, trimethoprim/sulfamethoxazole, vancomycin, tigecycline, colistin, and aztreonam against *S. aureus*, *S. pyogenes*, *S. pneumoniae*, *E. faecalis, E. coli* and *P. aeruginosa*.

EFFECTS OF MISCELLANEOUS FACTORS ON ACTIVITY

Delafloxacin protein binding ranged between 75- 84%. Intracellular accumulation studies indicate that delafloxacin accumulates within the cytosol of monocytes and macrophages and this accumulation was shown to be pH dependent; higher cytosolic accumulation occurred at lower pH. Studies investigating biofilm activity suggest that delafloxacin inhibited the formation of biofilm in *S. aureus*. Post-antibiotic effect (PAE) of delafloxacin against *S. aureus* ranged from 0.5 to 1 hour at 2X MIC, 0.75 to 1.75 hours at 4X MIC and 0.75 to 2.25 hours at 8X MIC. Against *S. pyogenes* ATCC 19615 strains, a PAE of 2hr was observed at 2X and 4X MIC and 2.25 hours at 8X MIC.

BACTERICIDAL ACTIVITY

Similar to other fluoroquinolones, delafloxacin exhibited bactericidal activity against both gram-positive and gram-negative pathogens. Delafloxacin MBC:MIC ratios against tested gram-positive and gram-negative pathogens were typically ≤ 2 which is indicative of bactericidal activity.

II. ANIMAL DISEASE MODELS

Delafloxacin activity was studied in vivo using experimental animal disease models including systemic infection, soft-tissue infection, pulmonary infections, murine pyelonephritis, and rat granuloma pouch abscess models. In these models, efficacy was evaluated against both gram-positive and gram-negative pathogens including *S. aureus* (methicillin and quinolone-resistant strains), *S. pneumoniae* (including fluoroquinolone- or macrolide resistant strains), *E. faecalis*, *E. coli*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *H. influenzae*. In systemic lethal infections, delafloxacin was efficacious in infections caused by *S. aureus* and *S. pneumoniae*, regardless of the route of drug administration, and was similar in efficacy to trovafloxacin but more active than levofloxacin. In systemic lethal infections caused by *E. coli* or *P. aeruginosa*, delafloxacin was approximately 2-fold less active orally than either ciprofloxacin or trovafloxacin. In contrast, delafloxacin showed similar or higher activity compared to the comparators when administered by the subcutaneous route. Overall, the efficacy of delafloxacin was found to be similar or more active than the comparators.

PHARMACOKINETIC / PHARMACODYNAMIC STUDIES

The Applicant used neutropenic murine lung or thigh infection models to determine the PK/PD parameters for delafloxacin. Similar to other fluoroquinolones, the PK/PD target, *f*AUC24/MIC ratio was determined to be the PK parameter most closely associated with delafloxacin efficacy. Monte Carlo simulations were performed for delafloxacin dosing regimens of 300 mg q12h IV and 450mg q12h PO to estimate the probability of target attainment for stasis and 1-$\log_{10}$ kill against *S. aureus*, *E. coli*, and *P. aeruginosa*.

The percent probabilities of PK/PD target attainment were estimated as 96.5% for net bacterial stasis for all *S. aureus* isolates at an MIC value of 0.5 mcg/mL (the MIC_{90} for the MRSA distribution) and 99% for 1-$\log_{10}$ kill at an MIC value of 0.25 mcg/ml.

The percent probabilities of PK/PD target attainment were estimated as ≥ 98% for net bacterial stasis against *E. coli* at an MIC value of 0.25 mcg/mL and ≥ 99.3% for 1-$\log_{10}$ kill at an MIC value of 0.12 mcg/ml. At the proposed dosing regimen, only 66.6% of all *E. coli* isolates (N=1031 from surveillance studies) will be covered. However, this dosing regimen is predicted to cover 96.2% (N=711) of levofloxacin susceptible *E. coli* isolates.

For *P. aeruginosa* the percent probabilities of PK/PD target attainment were estimated as ≥ 97.3% for net bacterial stasis at an MIC value of 1 mcg/mL and 100% for 1-$\log_{10}$ kill at an MIC value of 0.5 mcg/ml.

III. CLINICAL TRIALS

The Applicant conducted two Phase 3 clinical studies, RX-3341-302 and RX-3341-303 in adult patients (≥ 18 years of age) with ABSSSI to determine the safety and efficacy of delafloxacin. The Phase 3 studies were the primary data sources in support of the efficacy of delafloxacin in the treatment of patients with ABSSSI. The comparators in both Phase 3 studies were vancomycin + aztreonam combination therapy based on their respective activity against gram-positive and gram-negative pathogens. A total of 1510 subjects were enrolled and analyzed in both Phase 3 studies.

Gram-positive target pathogens constituted approximately 90% of the total baseline isolates from both Phase 3 studies. While gram-negative target pathogens were encountered less frequently, most of them were predominantly associated with gram-positive pathogens as part of polymicrobial infections.

Among the proposed gram-positive target pathogens, this Reviewer recommends excluding (b) (4) (b) (4) (b) (4) from the 1st list; thus, no breakpoints (BPs) are recommended for these pathogens. The removal (b) (4) is based on the fact that these bacteria are considered normal skin flora. Although, microbiological success for (b) (4) (b) (4) was 88.9% (8/9), the clinical experience was not adequately established in ≥ 10 clinical infections; therefore, (b) (4) has been recommended to be included into the 2nd list.

Microbiological success rates of 100% were reported for (b) (4) however, their clinical experiences were not adequately established in ≥ 10 clinical infections This Reviewer recommends placing these isolates in the 2nd list.

Only a susceptible MIC BP of ≤ (b) (4) mcg/ml and disk diffusion zone diameter of ≥ (b) (4) mm is proposed for *S. pyogenes* and *S. anginosus* Group. No resistant BP is proposed since clinical and surveillance data for these isolates indicate the absence or rare occurrence of resistant isolates. Therefore, isolates above the susceptible breakpoint should be reported as non-susceptible.

Based on scatterplot analysis of 110 clinical and surveillance *E. faecalis* isolates, the Applicant proposed MIC BPs of ≤ (b) (4) mcg/ml and disk diffusion BPs of ≥21 (b) (4) mm. However, in absence of pre-clinical PK-PD data and limited clinical data for *E. faecalis*, this Reviewer is recommending the following MIC of ≤ 0.25(S)/ 0.5(I)/ ≥ 1.0(R) mcg/ml. The disk diffusion BPs will remain same.

Based on data from the Phase 3 clinical trials, PK/PD, and in the vitro microbiology surveillance studies, this Reviewer recommends the following MIC break points:

The Agency Recommended and Applicant Agreed Susceptibility Interpretive Criteria for Delafloxacin

Table 1 Susceptibility Test Interpretive Criteria for Delafloxacin

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (Zone Diameter in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	≤ 0.25	0.5	≥ 1	≥ 23	20-22	≤ 19
Staphylococcus haemolyticus	≤ 0.25	0.5	≥ 1	≥ 24	21-23	≤ 20
Streptococcus pyogenes[a]	≤ 0.06	-	-	≥ 20	-	-
Streptococcus agalactiae	≤ 0.06	0.12	≥ 0.25	-	-	-
Streptococcus anginosus Group[a, b]	≤ 0.06	-	-	≥ 25	-	-
Enterococcus faecalis	≤ 0.12	0.25	≥ 0.5	≥ 21	19-20	≤ 18
Enterobacteriaceae[c]	≤ 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] The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results other than “Susceptible” should be submitted to a reference laboratory for further testing.

[b] includes: *S. anginosus*, *S. constellatus* and *S. intermedius*

[c] *E. coli*, *K. pneumoniae*, and *E. cloacae* only.

INTRODUCTION

The subject of this NDA is Baxdela (delafloxacin), a new member of the fluoroquinolone class of antibacterial drugs for the treatment of ABSSSI in adults. The proposed dose is delafloxacin administered every 12 hours (Q12h) either orally (450 mg tablet) or intravenously over 60 minutes as 300mg/vial after reconstitution. The Applicant is seeking indication for susceptible isolates of the following bacteria:

Gram-positive organisms:
Staphylococcus aureus (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates),
Staphylococcus haemolyticus,
(b) (4)
Staphylococcus lugdunensis,
Streptococcus agalactiae,
Streptococcus anginosus Group,
(b) (4)
Streptococcus pyogenes, and
Enterococcus faecalis

Gram-negative organisms:
Escherichia coli,
Enterobacter cloacae,
(b) (4)
Klebsiella pneumoniae,
(b) (4) and
Pseudomonas aeruginosa.

Regulatory History

Delafloxacin was originally developed by Wakunaga Pharmaceutical Company in Japan and then transferred to Abbott Laboratories (ABT-492) for the development of an oral formulation. The IND was then transferred to the Rib-X Pharmaceuticals for the development of the oral formulation (IND#62,772) and for an intravenous formulation (IND# 76,096). Delafloxacin is available as a sterile 300 mg lyophilized formulation for intravenous administration as well as a 450 mg capsule for oral administration. The clinical development of delafloxacin is owned by Melinta Therapeutics, Inc. On September 8, 2012, delafloxacin was granted QIDP designation for the treatment of ABSSSI and community-acquired bacterial pneumonia (CABP). On December 18, 2012, delafloxacin was granted Fast Track Designation for the same indications. The FDA has determined that the tradename BAXDELA is conditionally acceptable on May 29, 2015.

The Applicant, Melinta Therapeutics submitted NDA 208610 for 450 mg oral tablets and NDA 208611 for 300 mg/vial IV infusion on October 19, 2016. All preclinical, pharmacology,

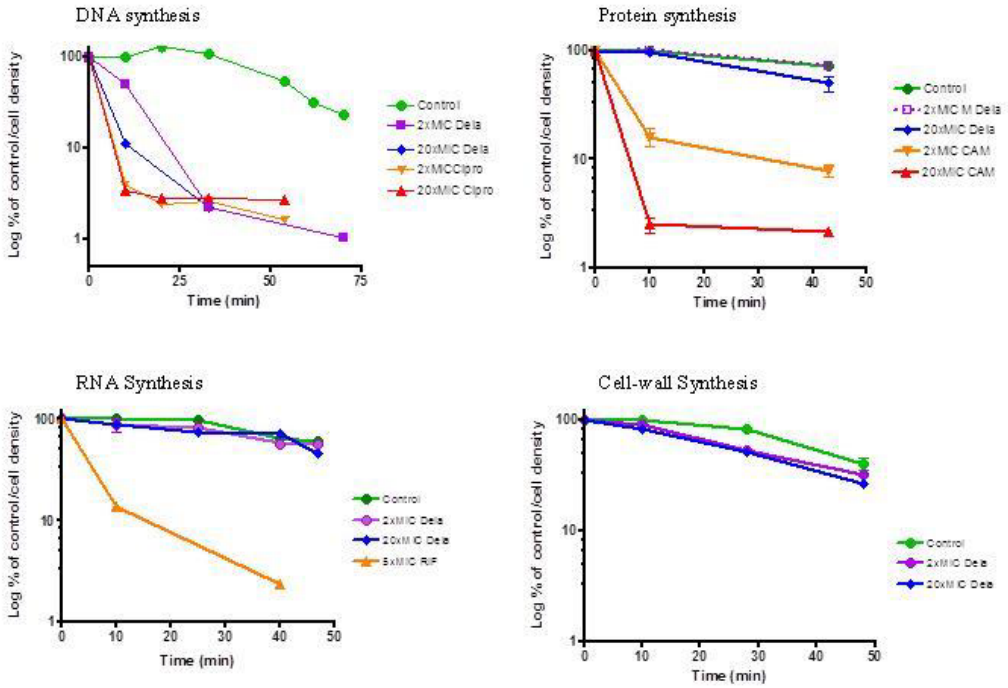
pharmacokinetics (PK), safety and efficacy data for both formulations were submitted under NDA 208610. Chemistry, Manufacturing, and Controls (CMC) and Quality Overall Summary data are submitted under NDA 208611 which cross references NDA 208610 for other sections.

IN VITRO INFORMATION

MECHANISM OF ACTION

Delafloxacin is an antibacterial drug that belongs to the fluoroquinolone class of antibacterial agents. Similar to other fluoroquinolones, it exerts its antibacterial activity by inhibiting DNA synthesis by targeting bacterial type II isomerases i.e., DNA gyrase and topoisomerase IV. In gram-positive organisms, delafloxacin inhibits DNA gyrase slightly more than topoisomerase IV while in gram-negative organisms, the inhibition of DNA gyrase and topoisomerase IV is nearly equivalent. In contrast, other fluoroquinolones e.g., ciprofloxacin and trovafloxacin showed preference for the inhibition of topoisomerase IV in *S. aureus* and DNA gyrase in *E. coli*. Delafloxacin was shown to inhibit DNA synthesis similar to ciprofloxacin (FIG 1) and no impact on protein, RNA or cell-wall synthesis was observed.

Figure 1. Effects of Delafloxacin and Comparators on de novo Macromolecular Synthesis in *E. coli* 25922



Dela = delafloxacin; Cipro = ciprofloxacin; CAM = chloramphenicol; RIF = rifampin
Minimum-inhibitory concentrations, in mcg/mL, against *E. coli* ATCC 25922 were 0.03 for both fluoroquinolones, 32 mcg/mL for rifampin and 8 mcg/mL for chloramphenicol. Source: MB-3341-040 Figures 3, 4, 5, 6

In another study, the specificity of delafloxacin to bacterial DNA gyrase or topoisomerase IV in

both *S. aureus* and *E.coli* was investigated. The data indicate that delafloxacin shows marked specificity for the bacterial enzymes and not for human type II topoisomerase (Table 1).

Table 1. Concentrations of Delafloxacin and Comparators Resulting in DNA Cleavage

Species	DNA topoisomerase	Delafloxacin (µg/mL)	Ciprofloxacin (µg/mL)	Trovafloxacin (µg/mL)
S. aureus	DNA gyrase	0.57	3.5	1.6
	topoisomerase IV	1.7	0.18	0.19
E. coli	DNA gyrase	0.8	0.24	0.43
	topoisomerase IV	1.1	1.8	4.5
Human	topoisomerase II	> 100	> 100	> 100

For bacterial topoisomerases, results are reported as the drug concentration causing half maximal DNA cleavage (maximal cleavage was determined based on the cleavage observed in the presence of a large amount of ciprofloxacin [100 µg/mL]); for human topoisomerase, the results are reported as the drug concentration causing 7% more DNA cleavage than that seen without drug treatment.
Source: RD-01-296 Table 5

ANTIMICROBIAL SPECTRUM OF ACTIVITY

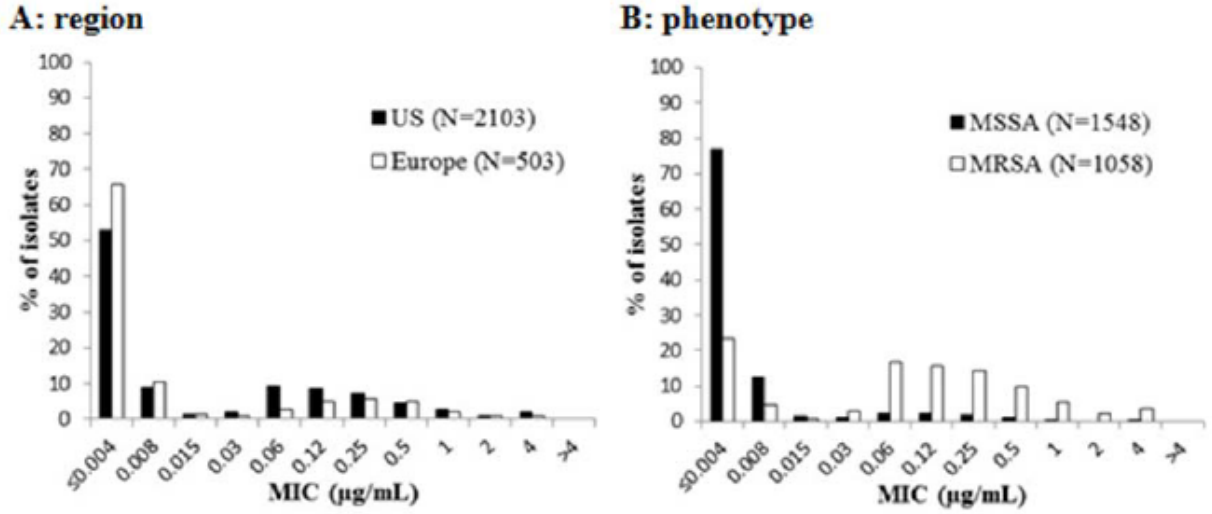
Delafloxacin has demonstrated in vitro activity against a wide range of clinically-relevant gram-positive, gram-negative, and anaerobic organisms. The in vitro activity of delafloxacin was evaluated by determining MIC_{50} and MIC_{90} against a diverse collection of clinically important isolates in preclinical profiling (Table A-1 and Table A-2 in Appendix-A) and surveillance studies (Table A-3 and Table A-4 in Appendix-A). All in vitro studies were conducted using broth microdilution method (b) (4) by following the CLSI guidelines[1, 2, 20]. The activity of delafloxacin was comparable in both studies; however, more recent isolates were analyzed in surveillance studies.

This review will focus primarily on the (b) (4) pathogens pertinent to (b) (4) this NDA. The in vitro spectrum of activity of delafloxacin was analyzed against the following bacteria: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, *Staphylococcus hominis*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group, *Streptococcus dysgalactiae*, *Streptococcus mitis* Group, *Streptococcus pyogenes*, and *Enterococcus faecalis*, and against the following gram-negative organisms: *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.

The in vitro activity of delafloxacin was evaluated against US and European isolates collected between 2014 and 2015and no significant variations in delafloxacin susceptibilities were observed. The overall activity of delafloxacin and levofloxacin against gram-positive isolates from 2014 to 2015 surveillance studies are summarized in Table A-3 in Appendix-A.

Against 2,606 *S. aureus* isolates (including 40.6% MRSA), delafloxacin had an overall MIC_{50}/MIC_{90} of ≤ 0.004/0.25 mcg/mL compared to 0.25/>4 for levofloxacin. Against MSSA, delafloxacin MIC_{50}/MIC_{90} values were ≤ 0.004/0.015 mcg/mL compared to 0.25/1 mcg/ml for levofloxacin. Against MRSA, the delafloxacin MIC $_{50}/MIC_{90}$ values were 0.12/1 mcg/mL compared to 4/>4 mcg/ml against levofloxacin. The delafloxacin MIC distribution against MSSA and MRSA overall is shown in Figure 2.

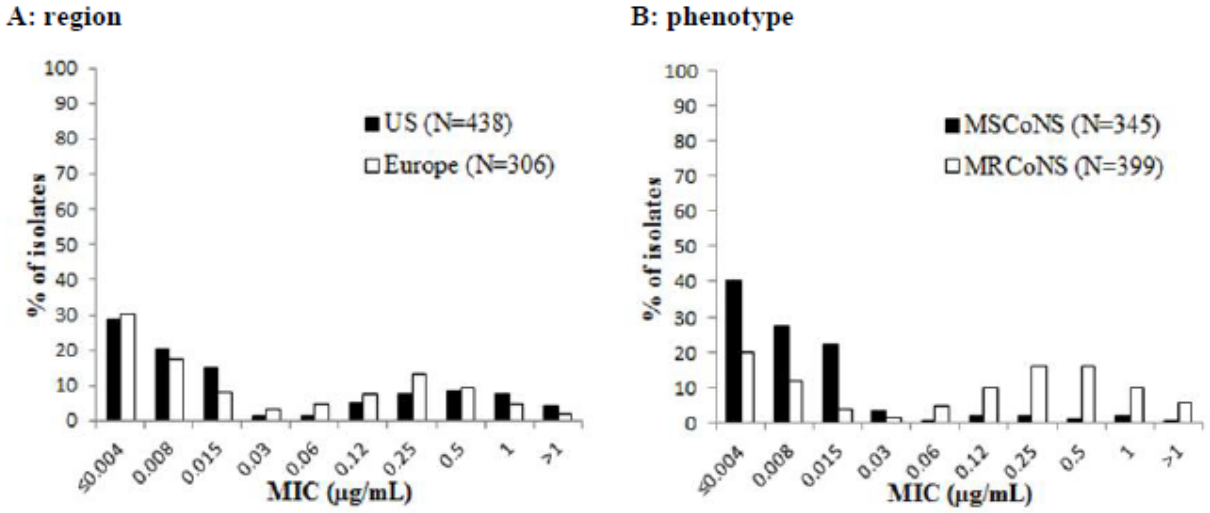
Figure 2. Delafloxacin MIC Distribution Against *S. aureus* From 2014-2015 Surveillance by Region and by Phenotype



MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*;MSSA = methicillin-susceptible *S. aureus*
Source: Surveillance Studies Appendix 2.1

A total of 744 coagulase-negative staphylococci (CoNS) isolates were evaluated during surveillance studies [345 isolates were methicillin-susceptible coagulase-negative staphylococci (MSCoNS) and 399 were methicillin-resistant coagulase-negative staphylococci (MRCoNS)]. The following species were included in this group: *Staphylococcus auricularis* (1), *S. capitis* (30), *S. caprae* (5), *S. condimenti* (2), *S. epidermidis* (290), *S. haemolyticus* (100), *S. hominis* (120), *S. lugdunensis* (128), *S. pasteuri* (1), *S. pettenkoferi* (3), *S. pseudintermedius /intermedius / delphini* (3), *S. saprophyticus* (15), *S. sciuri* (1), *S. simulans* (32), and *S. warneri* (13). Delafloxacin had an overall MIC_{50}/MIC_{90} of 0.015/0.5 mcg/mL against CoNS, 0.008/0.03 mcg/mL against MSCoNS, and 0.12/1 mcg/mL against MRCoNS. Levofloxacin MIC_{50}/MIC_{90} values against all categories of CoNS isolates were higher than delafloxacin. The overall MIC distribution of delafloxacin against CoNS from 2014 to 2015 surveillance is shown by geographic region in Figure 3.

Figure 3. Delafloxacin MIC Distribution Against Coagulase-negative Staphylococci From 2014-2015 Surveillance by Region and by Phenotype



MIC = minimum inhibitory concentration; MRCoNS = methicillin-resistant coagulase-negative staphylococci; MSCoNS = methicillin-susceptible coagulase-negative staphylococci
Source: Surveillance Studies Appendix 2.2

Against 672 *E. faecalis* isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.12/1 mcg/mL. Levofloxacin MIC_{50}/MIC_{90} values against these isolates were higher (1/>4) than delafloxacin.

Against 902 *Streptococcus pyogenes* isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.008/0.015 mcg/mL. Levofloxacin MIC_{50}/MIC_{90} values against these isolates were higher (0.5/1) than delafloxacin.

Against 477 *S. agalactiae* isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.015/0.03 mcg/mL. Levofloxacin MIC_{50}/MIC_{90} values against these isolates were higher (0.5/1) than delafloxacin.

Against 477 *S. dysgalactiae* isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.008/0.015 mcg/mL. Levofloxacin MIC_{50}/MIC_{90} values against these isolates were higher (0.5/1) than delafloxacin.

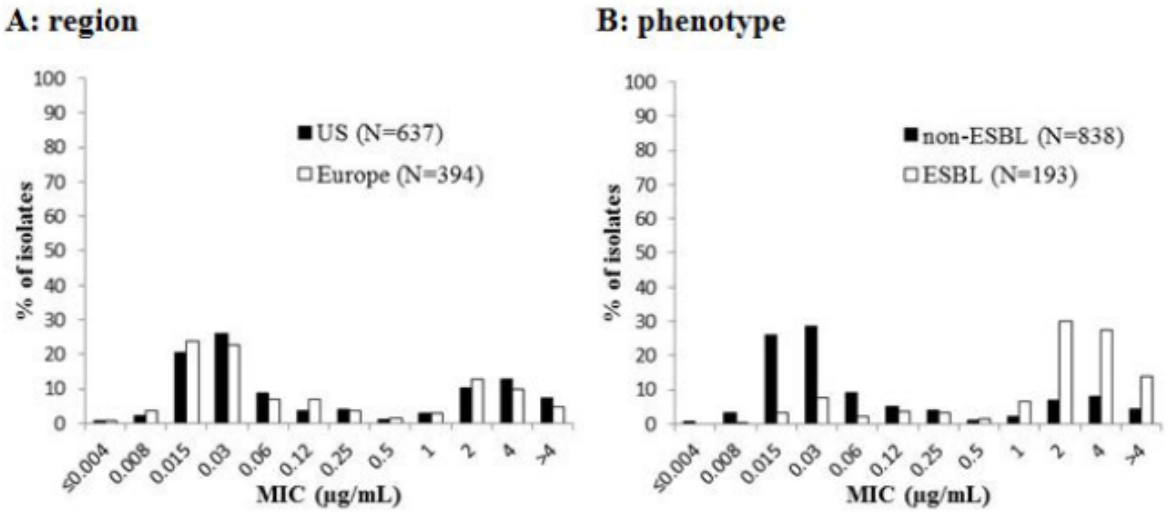
A total of 625 Viridans Group Streptococci isolates were evaluated during surveillance studies. The following species were included in this group: *S. anginosus* (131), *S. anginosus* group (20), *S. australis* (5), *S. bovis* group (2), *S. constellatus* (40), *S. cristatus* (8), *S. equinus* (1), *S. gallolyticus* (22), *S. gordonii* (13), *S. infantarius* (1), *S. infantis* (6), *S. intermedius* (22), *S. lutetiensis* (4), *S. massiliensis* (1), *S. mitis* (21), *S. mitis* group (26), *S. mitis/oralis* (111), *S. mutans* (9), *S. oralis* (90), *S. parasanguinis* (37), *S. salivarius* (17), *S. salivarius* group (13), *S. sanguinis* (21), *S. vestibularis* (4). Delafloxacin had an overall MIC50/MIC90 of 0.015/0.06 mcg/mL. Levofloxacin overall MIC_{50}/MIC_{90} values against these isolates were higher (1/2) than delafloxacin.

The Applicant analyzed and submitted a large collection of gram-negative isolates from the US and European surveillance studies. The activity of delafloxacin and comparator levofloxacin against these surveillance isolates are summarized in Table A-4 in Appendix-A.

Against 1031 *E. coli* isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.06/4 mcg/mL. Levofloxacin and ciprofloxacin MIC_{50}/MIC_{90} values against these isolates were ≤ 0.12/> 4 mcg/mL and 0.03/4 mcg/mL, respectively.

The overall MIC distribution of delafloxacin against *E. coli* is shown by geographic region in Figure 4A. The delafloxacin MIC distribution was bimodal. It indicates the high fluoroquinolone resistance rates among *E.coli*, in particular ESBL isolates. The delafloxacin MIC distribution against ESBL and non-ESBL isolates from 2014 to 2015 surveillance is shown in Figure 4B.

Figure 4. Delafloxacin MIC Distribution Against *E. coli* From 2014-2015 Surveillance by Region and by Phenotype



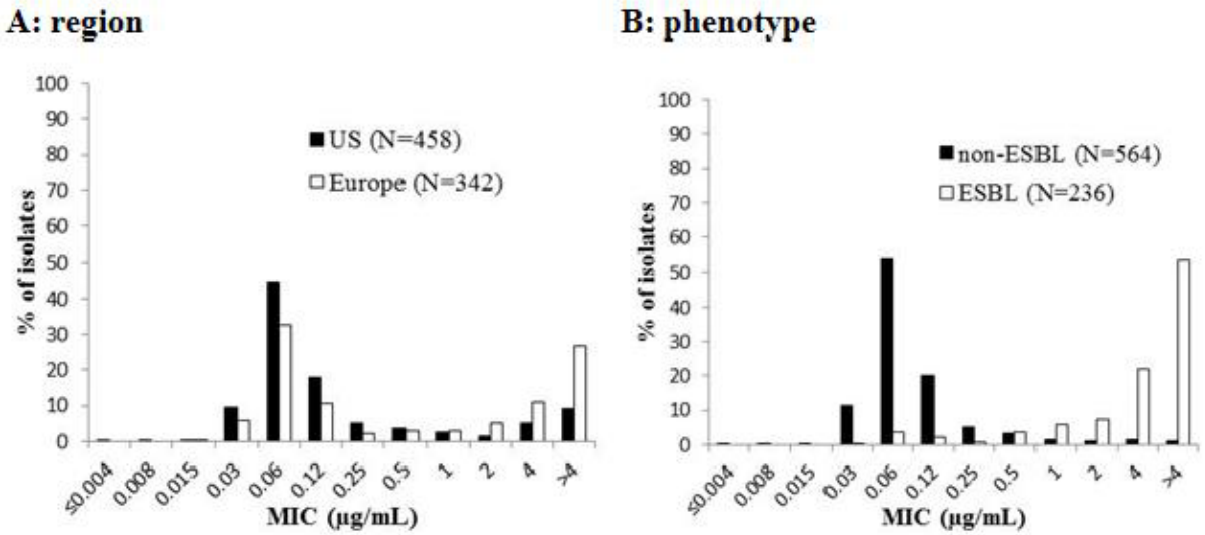
ESBL = phenotypically screen-positive for extended-spectrum beta-lactamases; MIC = minimum inhibitory concentration; non-ESBL = phenotypically screen-negative for extended-spectrum beta-lactamases
Source: Surveillance Studies Appendix 2.9

Against 800 *K. pneumoniae* isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.12/>4 mcg/mL. Levofloxacin and ciprofloxacin MIC_{50}/MIC_{90} values against these isolates were ≤0.12/> 4 mcg/mL and ≤0.03/> 4 mcg/mL respectively.

The overall MIC distribution of delafloxacin against *K. pneumoniae* is shown by geographic region in Figure 5A. The delafloxacin MIC distribution against ESBL and non-ESBL isolates from 2014 to 2015 surveillance is shown in Figure 5B. The difference in delafloxacin MIC

distribution against ESBL relative to non-ESBL isolates reflects the MIC_{50}/MIC_{90} data with ESBL isolates having higher delafloxacin MIC values relative to non-ESBL isolates.

Figure 5. Delafloxacin MIC Distribution Against *K. pneumoniae* From 2014-2015 Surveillance by Region and by Phenotype

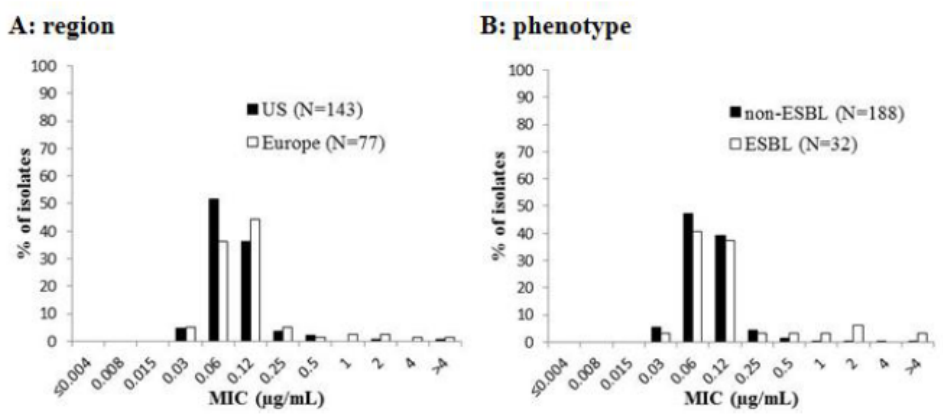


ESBL = phenotypically screen-positive for extended-spectrum beta-lactamases; MIC = minimum inhibitory concentration; non-ESBL = phenotypically screen-negative for extended-spectrum beta-lactamases
Source: Surveillance Studies Appendix 2.10.1

Against 220 *K. oxytoca* isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.06/0.12 mcg/mL. Levofloxacin and ciprofloxacin MIC_{50}/MIC_{90} values against these isolates were ≤0.12/ ≤ 0.12 mcg/mL and ≤ 0.03/0.06 mcg/mL respectively.

The overall MIC distribution of delafloxacin against *K. oxytoca* is shown by geographic region in Figure 6A. The delafloxacin MIC distribution against ESBL and non-ESBL isolates from 2014 to 2015 surveillance is shown in Figure 6B.

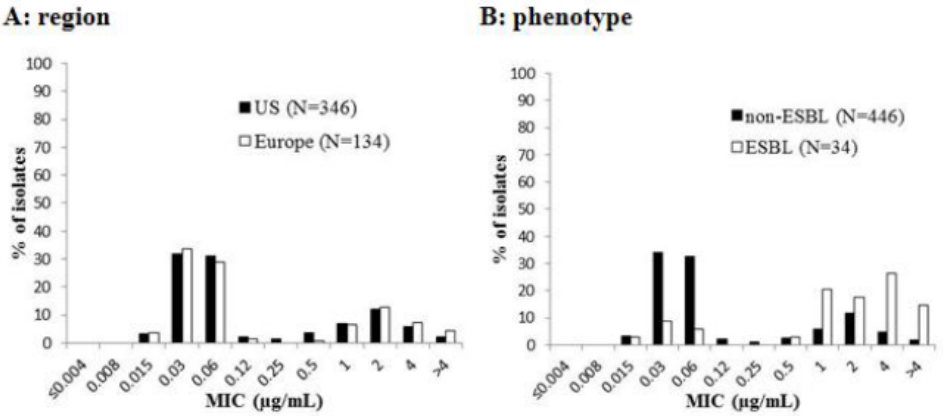
Figure 6. Delafloxacin MIC Distribution Against *K. oxytoca* From 2014-2015 Surveillance by Region and by Phenotype



ESBL = phenotypically screen-positive for extended-spectrum beta-lactamases; MIC = minimum inhibitory concentration; non-ESBL = phenotypically screen-negative for extended-spectrum beta-lactamases
Source: Surveillance Studies Appendix 2.10.2

Against 480 *P. mirabilis* isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.06/2 mcg/mL. Levofloxacin and ciprofloxacin MIC_{50}/MIC_{90} values against these isolates were ≤0.12/> 4 mcg/mL and ≤ 0.03/ > 4 mcg/mL respectively. The overall MIC distribution of delafloxacin against *P. mirabilis* is shown by geographic region in Figure 7A. The delafloxacin MIC distribution was bimodal. It reflects the high fluoroquinolone resistance rates among *P. mirabilis*. The delafloxacin MIC distribution against ESBL and non-ESBL isolates from 2014 to 2015 surveillance is shown in Figure 7B.

Figure 7. Delafloxacin MIC Distribution Against *P. mirabilis* From 2014-2015 Surveillance by Region and by Phenotype



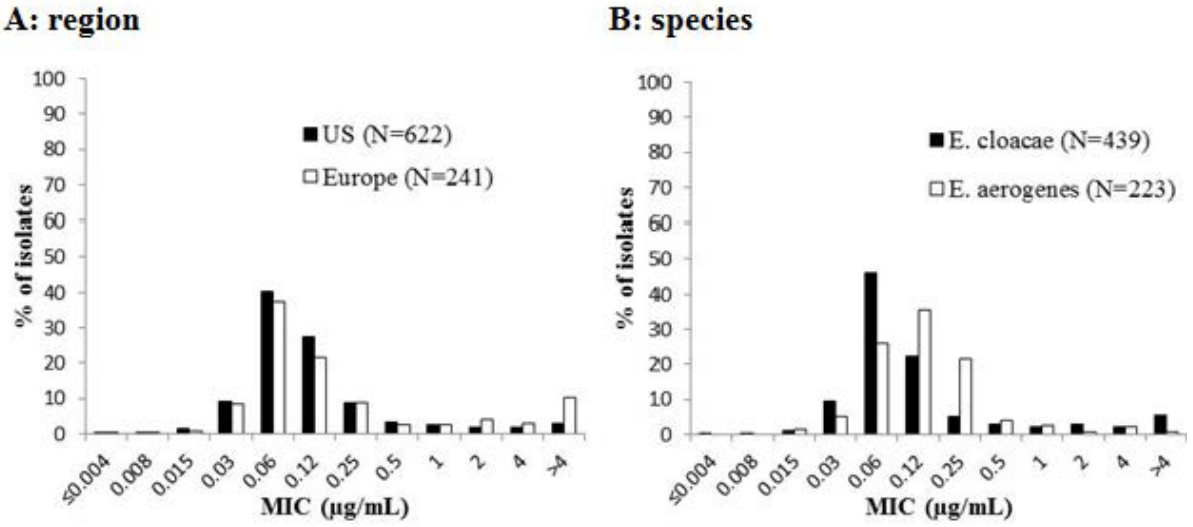
ESBL = phenotypically screen-positive for extended-spectrum beta-lactamases; MIC = minimum inhibitory concentration; non-ESBL = phenotypically screen-negative for extended-spectrum beta-lactamases
Source: Surveillance Studies Appendix 2.11

Against 863 *Enterobacter* spp. isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.06/1 mcg/mL. Levofloxacin and ciprofloxacin MIC_{50}/MIC_{90} values against *Enterobacter* spp. isolates were ≤0.12/0.5 mcg/mL and ≤ 0.03/ 0.5 mcg/mL respectively.

Against 439 *E. cloacae* isolates, delafloxacin had an MIC_{50}/MIC_{90} of 0.06/2 mcg/mL compared to that of ≤ 0.12/0.5 mcg/mL for levofloxacin and ≤ 0.03/0.5 mcg/mL for ciprofloxacin.

The overall MIC distribution of delafloxacin against *Enterobacter* spp. is shown by geographic region in Figure 8A. The delafloxacin MIC distribution against *E. cloacae* and *E. aerogenes* isolates from 2014 to 2015 surveillance is shown in Figure 8B.

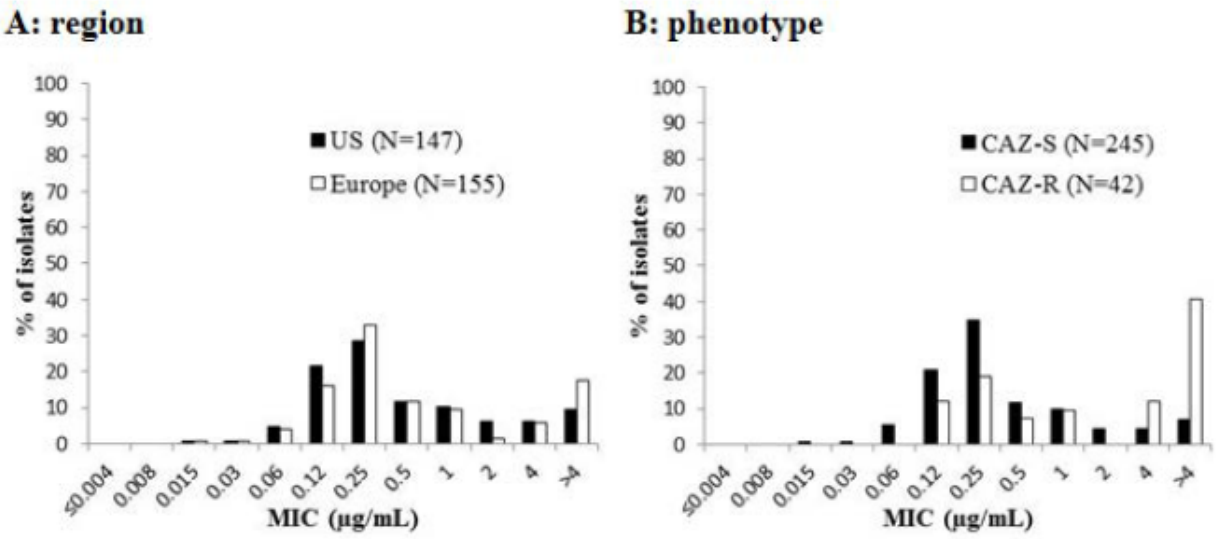
Figure 8. Delafloxacin MIC Distribution Against *Enterobacter* spp. From 2014-2015 Surveillance by Region and by Species



MIC = minimum inhibitory concentration
Source: Surveillance Studies Appendix 2.13

Against 302 *P. aeruginosa* isolates, delafloxacin had an overall MIC_{50}/MIC_{90} of 0.25/ >4 mcg/mL. Levofloxacin and ciprofloxacin MIC_{50}/MIC_{90} values against *P. aeruginosa* isolates were 0.5/ > 4 mcg/mL and 0.12/ > 4 mcg/mL respectively. The overall MIC distribution of delafloxacin against *P. aeruginosa* is shown by geographic region in Figure 9A. The delafloxacin MIC distribution against ceftazidime-susceptible and -resistant isolates from 2014 to 2015 surveillance is shown in Figure 9B. The difference in delafloxacin MIC distribution against ceftazidime-resistant relative to ceftazidime-susceptible isolates reflects the MIC_{50}/MIC_{90} data with ceftazidime-resistant isolates having higher delafloxacin MIC values relative to non-ESBL isolates.

Figure 9. Delafloxacin MIC Distribution Against *P. aeruginosa* From 2014-2015 Surveillance by Region and by Phenotype



CAZ-R = ceftazidime-resistant; CAZ-S = ceftazidime-susceptible; MIC = minimum inhibitory concentration; US = United States
Source: Surveillance Studies Appendix 2.18

RESISTANCE STUDIES

The applicant evaluated the potential for delafloxacin resistance development in both gram-positive and gram-negative organisms. Spontaneous mutation frequencies were determined in single-step resistance selection studies (Study RD-03-006 and MB-3341-008A1). Delafloxacin resistant mutants were generated and analyzed in step-wise serial passage studies on agar (RD-03-541) and in broth (for *S. aureus* only; MB-3341-026). The organisms included fluoroquinolone-susceptible and fluoroquinolone–resistant *S. aureus, E. faecalis, S. pneumoniae, E. coli, K. pneumoniae*, *P. aeruginosa*, and *H. influenzae* isolates. The isolates were genetically-characterized with pre-existing mutations in quinolone resistance-determining region (QRDR). Increased MIC values were commonly associated with the acquisition of mutations within target genes, *gyrA, gyrB* and *grlA/parC*. Based on QRDR sequence data, the mutations in target genes for delafloxacin serial passage mutants were similar to those observed in delafloxacin mutants selected during spontaneous mutation resistance studies.

For both gram-positive and gram-negative bacteria, delafloxacin MIC increased by several folds after 2-7 serial passages. However, delafloxacin mutations occurred more frequently in gram-positive bacteria with less serial passages compared to gram-negative which required a higher number of serial passages to acquire mutations in the QRDR region.

The results from spontaneous mutation studies with fluoroquinolone-susceptible and fluoroquinolone-resistant *S. aureus* isolates are shown in Table B-1 Appendix-B. Against *S. aureus* isolates, the resistance frequency was determined to be $< 10^{-9}$ for fluoroquinolone-

susceptible isolates and 10^{-8} to 10^{-9} for fluoroquinolone-resistant isolates. Mutations were found in *gyrA* (Ser84-Leu) in addition to the existing mutation in *grlA* (Ser80Phe) at baseline for fluoroquinolone-resistant *S. aureus* isolates. Delafloxacin MIC values of these mutants increased from 0.004 mcg/mL to 0.03 - 0.06 mcg/mL and from 0.015 to 1 mcg/mL for fluoroquinolone-susceptible and fluoroquinolone-resistant isolates respectively. Against 4 fluoroquinolone-resistant MRSA isolates (MB-3341-008A1), resistance frequencies determined to be $< 4.3 \times 10^{-12}$ to $< 1.4 \times 10^{-10}$. For fluoroquinolone-susceptible *S. aureus* isolate ATCC 25923, delafloxacin MIC increased 16-fold from ≤ 0.008 mcg/mL to 0.12 mcg/mL after 4 passages. This MIC increase was accompanied by the acquisition of mutations in both *gyrB* and *grlA*. For fluoroquinolone-resistant *S. aureus* isolate 5589, delafloxacin MIC values increased 32-fold from 0.015 mcg/mL to 0.5 mcg/mL after 2 passages. This MIC increase was accompanied by the acquisition of a mutation in *gyrA* in addition to the pre-existing mutation in *grlA*. The results from the serial passage study, RD-03-541for *S. aureus* are summarized in Table B-7 in Appendix-B of this review.

Against fluoroquinolone-susceptible *E. faecalis* isolate (study RD-03-066), the spontaneous mutation frequency of delafloxacin was determined to be $< 5.2 \times 10^{-9}$ and shown in Table B-2 in Appendix-B of this review. No mutations were identified in the QRDR region of delafloxacin-selected mutants and the delafloxacin MIC of mutants increased from 0.06 mcg/mL to 0.25 mcg/mL.

The spontaneous mutation frequency of delafloxacin against fluoroquinolone-susceptible and fluoroquinolone-resistant *S. pneumoniae* isolates was evaluated in study RD-03-066 and shown in Table B-3 in Appendix-B of this review. The mutation frequencies determined to be $<3.3 \times 10^{-9}$ to $< 8 \times 10^{-9}$. Delafloxacin MIC values increased with the acquisition of mutations and double mutations in *gyrA* and *parC*. Delafloxacin MIC values increased from 0.008 mcg/mL to 0.03 to 0.06 mcg/mL for *gyrA* single mutants (Ser81-Leu). Delafloxacin-selected mutants acquired additional mutations in *gyrA*, *gyrB* and *parE* and delafloxacin MIC values increased for these isolates from 0.03 to 0.06 mcg/mL to 0.5 to 2 mcg/mL. For fluoroquinolone-susceptible *S. pneumonia*e isolate ATCC 6303, delafloxacin MIC values increased 4-fold from ≤ 0.015 mcg/mL to 0.06 mcg/mL only after 2 passages. This MIC increase was accompanied by the acquisition of a mutation in *parC*. For fluoroquinolone-resistant isolate 7215, delafloxacin MIC values increased 32-fold from 0.03 mcg/mL to 1 mcg/mL after 7 passages. This MIC increase was accompanied by the acquisition of mutations in *gyrA* and *gyrB* in addition to the pre-existing mutation in *parC*. Results from serial passage study, RD-03-541for *S. pneumoniae* are summarized in Table B-8 in Appendix-B of this review.

The spontaneous mutation frequency of delafloxacin against fluoroquinolone-susceptible and fluoroquinolone-resistant Enterobacteriaceae was evaluated for 4 isolates of *E. coli* and 1 isolate of *K. pneumoniae* in study RD-03-066 and shown in Table B-4 in Appendix-B of this review. Against 3 fluoroquinolone-susceptible *E. coli* isolates, the mutation frequencies determined to be $< 9.1 \times 10^{-9}$. Delafloxacin mutation frequency was low for fluoroquinolone-resistant *E. coli* isolate, ≤ 10^{-9}. Against *K. pneumoniae* strain 7651, the mutation frequency was 8.97×10^{-8} to <

7.75×10^{-9}. For fluoroquinolone-susceptible *E. coli* isolates (n = 3), delafloxacin MIC values were increased in delafloxacin-selected mutants from 0.015 - 0.03 mcg/mL to 0.12 - 1 mcg/mL.

For fluoroquinolone-susceptible *E. coli* strain ATCC 25922, delafloxacin MIC values increased 8-fold from ≤ 0.015 mcg/mL to 0.12 mcg/mL after 5 passages. No mutations were detected in the QRDR of these mutants and no further increases in MIC were observed following 31 subsequent passages. Results from serial passage study, RD-03-541for *E. coli* are summarized in Table B-9 in Appendix-B of this review.

The spontaneous mutation frequency of delafloxacin against fluoroquinolone-susceptible *P. aeruginosa* strain ATCC 27853 was evaluated in study RD-03-066 and shown in Table B-5 in Appendix-B of this review. Mutation frequency was determined to be 4.22×10^{-10} to 6.02×10^{-11}. No mutations were observed at 2X MIC in *gyrA* or *parC* of the parent isolate. However, at 4X and 8X MIC mutation occurred in *gyrA* (Ser83-Ile) with an increase in delafloxacin MIC value from 0.25 mcg/ml to 2 - 8 mcg/mL.

The spontaneous mutation frequency of delafloxacin against fluoroquinolone-susceptible and fluoroquinolone-resistant *H. influenzae* isolates was evaluated in study RD-03-066 and shown in Table B-6 in Appendix-B of this review. Delafloxacin mutation frequency was $\leq 10^{-9}$ at 4X the MIC and above. Against fluoroquinolone-susceptible *H. influenzae* strain ATCC 49247, the acquisition of mutations at Ala120 in *gyrA* resulted in higher delafloxacin MIC values. Delafloxacin MIC values increased from 0.00025 mcg/ml to 0.002 - 0.004 mcg/mL. For the fluoroquinolone non-susceptible strain 7567, pre-existing mutations observed in both *gyrA* (Ser84-Leu) and *parC* (Ser84-Arg). The evaluated delafloxacin-selected mutant acquired an additional mutation in *gyrA* (Asp88-Tyr) and delafloxacin MIC increased from 0.12 mcg/ml to 0.5 mcg/mL for this strain.

For fluoroquinolone-susceptible *H. influenzae* strain ATCC 49247, delafloxacin MIC values increased 8-fold from 0.0005 mcg/mL to 0.004 mcg/mL after 2 passages. This MIC increase was accompanied by a 4 amino acid deletion in GyrB. No further increases were observed over 9 subsequent passages. For fluoroquinolone-non-susceptible strain 7567, delafloxacin MIC values increased 4-to 8-fold from 0.25 mcg/mL to 1 to 2 mcg/mL. The increase in the delafloxacin MIC was not accompanied by the acquisition of additional mutations beyond the pre-existing mutations in *gyrA* and *parC*. No further increases in delafloxacin MIC were observed over 16 subsequent passages. Results from serial passage study, RD-03-541for *H. influenzae* are summarized in Table B-10 in Appendix-B of this review.

ANTIMICROBIAL INTERACTION STUDIES

The antimicrobial interaction of delafloxacin was evaluated against approved antimicrobial drugs (daptomycin, linezolid, meropenem, ceftazidime, trimethoprim/sulfamethoxazole, vancomycin, tigecycline, colistin, and aztreonam) to determine the potential of synergistic or antagonistic interactions. The potential for synergy or antagonism between agents was evaluated by FIC values in vitro using a broth microdilution "checkerboard" panel, in which the combination

agents were tested alone and together at varying concentration ratios[10, 11]. The activity of delafloxacin and other combination agents when tested alone and in combination against the evaluated isolates is shown in Table C-1 and Table C-2 in the Appendix-C of this review.

Delafloxacin showed no antagonism or synergy when tested in combination with these agents in vitro against both gram-positive (*S. aureus*, *S. pyogenes*, *S. pneumoniae*, and *E. faecalis*) and gram-negative (*E. coli* and *P. aeruginosa*) isolates. There were no antagonistic or synergistic interactions for delafloxacin in combination with other antimicrobial drugs based on the evaluation of fractional inhibitory concentrations.

METABOLITES

Delafloxacin and its metabolite profiling were measured using a mass spectrometry method incorporating a full scan and multiple reaction monitoring (MRM) to confirm the presence of parent drug and any drug-related components. The data indicate that delafloxacin has four metabolites designated as M3, M5, M6A, and M7. Metabolites, M3 and M5 have been identified as ester glucuronide metabolites and M6A has been identified as an ether glucuronide of the parent drug, delafloxacin. The identity of M7 could not be confirmed.

The distribution of these metabolites varies in plasma, urine, and feces. Based on 1-12 hours pooled sample analysis, the major delafloxacin metabolite, M3 is present in plasma and urine as ≤10% and 26.36% respectively. No metabolites were present in feces. No activity has been identified for delafloxacin metabolites. The results of the metabolite profiling with MRM of plasma and urine are summarized in Table C-3 in the Appendix-C of this review.

EFFECTS OF MISCELLANEOUS FACTORS ON ACTIVITY

I. PROTEIN BINDING

Protein binding of delafloxacin was evaluated by analyzing human plasma samples obtained from healthy volunteers in Phase 1 study, RX-3341-107. Plasma protein binding was approximately 84% (ranged from 71.07% to 84.62%) in healthy volunteers, and no significant differences were seen in patients with renal impairment. In a study with renal impairment (RX-3341-110), protein binding of delafloxacin ranged from 80% for the severe renal impairment group, while the lowest binding of 75% observed in end stage renal disease (ESRD) group. In vitro, the percentage of delafloxacin bound to plasma protein, albumin, and α_1-acid glycoprotein is shown in Table C-4 in the Appendix-C of this review.

II. INTRACELLULAR ACTIVITY

The intracellular activity of delafloxacin against *S. aureus* was assessed in human THP-1 (monocytes) and J774 (macrophage) cell lines[12]. Delafloxacin accumulated in both THP-1 and J774 macrophage cell lines, and intracellular accumulation increased in cells grown in media at acidic pH relative to neutral pH. Subcellular localization data showed that delafloxacin accumulated mainly in the soluble fraction, suggesting that it is present primarily in the cytosol. Additionally, delafloxacin activity against *S. aureus* within J774 cells was dose-dependent and this accumulation within human macrophage cell lines was enhanced at acidic pH.

In another study, the intracellular accumulation of delafloxacin and comparator, moxifloxacin, was evaluated in human THP-1 cells both at physiological pH and decreasing pH (pH 5.5 to 7.4) over 30 minutes.[13] Delafloxacin accumulated 2- to 3-fold in THP-1 cells at physiological pH as measured by the ratio of the cellular concentration (Cc) to the extracellular concentration (Ce), compared to an approximately 7-fold intracellular accumulation observed for moxifloxacin. When cells were exposed to delafloxacin or comparator moxifloxacin for 30 minutes in media with decreasing pH, the intracellular delafloxacin accumulation increased 10 to12-folds at pH 5.5 to 6.0 relative to the accumulation seen at physiological pH. However, the impact of decreasing pH on increasing accumulation was not observed with moxifloxacin. The cellular concentrations of both agents are shown in Figure 10 below.

Source: Lemaire 2011[13]

The subcellular distribution of delafloxacin and moxifloxacin was evaluated in J774 murine macrophages. Briefly, the macrophages were exposed to 100 mcg/mL of either agent for 2 hours, then the soluble, granule/membrane, and nuclear fractions were recovered via centrifugation. The concentrations of delafloxacin and moxifloxacin in each fraction were quantitated and expressed relative to cell protein within the respective fractions. Subcellular localization of delafloxacin was evaluated in media at both physiological and acidic pH and for moxifloxacin from media at neutral pH.

Incubation of J774 cells in media with low pH resulted in an approximately marked increase in accumulation of delafloxacin relative to incubation of cells at physiological pH. The subcellular distribution of delafloxacin and moxifloxacin was similar and was not altered based on medium pH. These data indicated that both delafloxacin and moxifloxacin were primarily localized within the soluble fraction of the cell cytosol (Figure 11).

Source: Lemaire 2011[30]

The data above indicated that delafloxacin accumulated within the cytosol. Another study was conducted in THP-1 cells to determine if the intracellular antimicrobial activity of delafloxacin against *S. aureus* was pH dependent. The data indicated that the antibacterial activity under the above conditions was dependent on pH. Delafloxacin was more active at acidic pH relative to physiological pH. The change in log10 CFU after treatment with delafloxacin and moxifloxacin at both physiological and acidic pH for 24 hours relative to 0 hours is shown below in Figure 12.

Source: Lemaire 2011[30]

III. ACTIVITY AGAINST BIOFILMS

A study was conducted by Bauer et al[14] to determine the activity of delafloxacin against *S.*

aureus biofilms (both MSSA and MRSA). Biofilms were developed in 96-well plates by incubating 6 hours for young biofilms and 24 hours for mature biofilms. Both biofilms were exposed to 0.5 to 512X MIC of delafloxacin and other antimicrobial drugs including daptomycin for 24 hours and 48 hours. The effect on biofilm mass and viability were examined by confocal microscopy. Among all tested antimicrobial drugs, delafloxacin and daptomycin reduced the viability and biofilm depth by more than 50% in *S. aureus* biofilms.. In addition, antibiotic activity against biofilms was dependent on biofilm maturation and biofilm matrix produced by individual bacterial isolates.

IV. POST ANTIBIOTIC EFFECT (PAE)

The post-antibiotic effect (PAE) of a drug is the suppression of bacterial growth in response to the exposure to supra-inhibitory drug concentrations and its subsequent removal. The sub-inhibitory MIC effect (SME) is an evaluation of the suppression of bacterial growth during exposure to sub-inhibitory concentrations of the drug. The post-antibiotic sub-inhibitory MIC effect (PA-SME) is measured as the suppression of bacterial growth for bacteria initially exposed to supra-inhibitory concentrations of drug followed by prolonged exposure to sub-inhibitory concentrations of drug.

The observed PAE, SME, and PA-SME of delafloxacin relative to levofloxacin are summarized in Table C-5 in the Appendix-C of this review. PAE of delafloxacin against *S. aureus* ranged from 0.5 to 1 hour at 2X MIC, 0.75 to 1.75 hours at 4X MIC and 0.75 to 2.25 hours at 8X MIC. For *S. pyogenes* ATCC 19615 strains, the PAE of 2hr was observed at 2X, and 4X MIC; and 2.25 hours at 8X MIC. Levofloxacin had a comparable PAE of 2.25 hours at 2X MIC.

There was little to no apparent SME with either delafloxacin or levofloxacin against the evaluated *S. aureus* isolates. Against *S. pyogenes*, SME of 1.5 hours and 1.25 hours was apparent with delafloxacin and levofloxacin, respectively, at 0.25X MIC value.

The PA-SME of delafloxacin against *S. aureus* after initial exposure to 2X MIC value and subsequent exposure to 0.25X MIC value was 0.25 to 1.5 hour which is longer than the observed PAE at 2X MIC value. For *S. pyogenes*, the PA-SME of delafloxacin was 0.75 hour longer than the PAE following initial exposure to 2X MIC value and subsequent exposure to 0.12X and 0.25X MIC value of drug.

BACTERICIDAL ACTIVITY

Similar to other members of the fluoroquinolone class of antibacterial drugs,[3] delafloxacin exhibited bactericidal activity against both gram-positive and gram-negative pathogens. The Applicant demonstrated the bactericidal activity of delafloxacin by conducting both minimum bactericidal concentration (MBC) assays and time-kill kinetic assays by following the CLSI guidelines.[15]

An MBC assay is an extension of the broth microdilution assay, where aliquots from concentrations at and above the MIC are plated to evaluate viable growth. The MBC is the

concentration at which a 99.9% or greater (> 3 $\log_{10}$ CFU/mL) decrease in viable bacteria is observed relative to the concentration of the starting inoculum. An agent is considered bactericidal if the observed MBC values are ≤ 4-fold higher than the observed MIC values.

In time-kill assays, viable bacteria are quantitated at baseline and during exposure to multiples of the MIC. Agents are generally considered bactericidal if a 99.9% or greater (> 3 $\log_{10}$) decrease in viable bacteria relative to the initial inoculum is achieved at or before 24 hours and is maintained without evidence of regrowth.

I. MINIMUM BACTERICIDAL CONCENTRATION STUDIES

MBC determinations for delafloxacin and fluoroquinolone comparators were conducted in separate studies (Study RD-01-296, Study MB-3341-054 and Study MB-3341-016) against clinically prevalent gram-positive and gram-negative pathogens. Delafloxacin MBC: MIC ratios against tested gram-positive and gram-negative pathogens were typically ≤ 2 indicative of bactericidal activity.

II. TIME-KILL STUDIES

Delafloxacin time-kill studies were conducted against a variety of gram-positive and gram-negative organisms according to the CLSI guidelines. A reduction of ≥3 $\log_{10}$ of initial inoculum and no regrowth at 24 hours, was observed against quinolone-susceptible and –resistant isolates of *S. pneumoniae* (n = 4), *S. aureus* (n = 5), *H. influenzae* (n = 5), and *E. coli* (n = 5); quinolone-susceptible *E. faecalis* (n = 1) and *P. aeruginosa* (n = 1); and quinolone resistant *K. pneumoniae* (n = 1).

HUMAN AND ANIMAL STUDIES

ANIMAL DISEASE MODELS

The activity of delafloxacin was studied in vivo using experimental animal models including systemic infection models, soft-tissue infection models, pulmonary infections, murine pyelonephritis, and rat granuloma pouch abscess model. In these experimental animal models, efficacy was studied against both gram-positive and gram-negative pathogens including *S. aureus* (methicillin and quinolone-resistant strains), *S. pneumoniae* (including fluoroquinolone- or macrolide resistant strains), *E. faecalis*, *E. coli*, *K. pneumoniae*, *A. baumannii, P. aeruginosa,* and *H. influenzae*.

Systemic Infection Models

Oral or subcutaneous (SC) administration of delafloxacin showed activity in systemic lethal infections in mice induced by both gram-positive and gram-negative bacteria including MSSA, MRSA, *S. pneumoniae*, *E. coli*, and *P. aeruginosa* isolates (Study report: RD-01-134, EF-3341-001A1, EF-3341-004). The efficacy was compared with other fluoroquinolone. Mice were inoculated intraperitoneally (IP) and delafloxacin or comparator drugs were administered at 1 and 5 hours post-infection, either by the oral or subcutaneous route. For gram-positive organisms (*S. aureus* and *S. pneumoniae*) comparators were levofloxacin and trovafloxacin, or linezolid; for

gram-negative organisms (*E. coli* and *P. aeruginosa*), comparators were ciprofloxacin and trovafloxacin. Survival was monitored over 7 days, and then the mean ED_{50} was calculated.

Delafloxacin demonstrated activity against *S. aureus* and *S. pneumoniae* and was similar in efficacy to trovafloxacin; however, it was more active than levofloxacin or linezolid. In infections caused by *E. coli*, delafloxacin was approximately 2-fold less active orally than either ciprofloxacin or trovafloxacin. Against *P. aeruginosa*, delafloxacin had similar activity to ciprofloxacin and trovafloxacin. The study results are summarized in Table E-1 in the Appendix-E of this review.

Against MRSA isolates 67-0 (MICs for both delafloxacin and linezolid were 4 mcg/mL), 11512 (MICs for delafloxacin and linezolid were 0.5 mcg/mL and 4 mcg/mL, respectively), and 2926 (MICs for delafloxacin and linezolid were 0.03 mcg/mL and 2 mcg/mL, respectively), delafloxacin PD_{50} range for < 0.781, 42.5, and < 1.56 mg/kg respectively compared to PD_{50} of <50 mg/kg for levofloxacin against all isolates The study results are shown in Table E-2 in the Appendix-E of this review.

Soft-Tissue infection Models: Neutropenic Thigh Infection Models

The neutropenic thigh infection model is a localized model of skin and soft tissue infection where mice or rat are pre-treated with cyclophosphamide to induce neutropenia before inoculation with bacteria[16]. As a result, any reduction of bacterial burden would be attributed directly to the action of the drug. The activity of delafloxacin was evaluated against following gram-positive and gram-negative organisms using this model:

1. Neutropenic Thigh Infection Model in Mice with *S. aureus* (MRSA, FQ-RSA)
2. Neutropenic Thigh Infection Model in Mice with *S. pneumoniae* (QSSP and QRSP)
3. Neutropenic Thigh Infection Model in Mice with *E.coli*
4. Neutropenic Thigh Infection Model in Mice with *K. pneumoniae*
5. Neutropenic Thigh Infection in Rats with *S. pneumoniae* (FQ-SSP and FQ-RSP)

1. Neutropenic Thigh Infection Model with *S. aureus* (MRSA, FQ-RSA) in Mice

The efficacy of delafloxacin was assessed against clinically relevant *S. aureus* isolates. Delafloxacin demonstrated efficacy against the MSSA Smith strain and *S. aureus* ATCC 29213 in a dose-dependent fashion when administered SC. Against infections caused by FQ-RSA/MRSA strains 11540, 2926 and 11512, delafloxacin demonstrated > 2 log10 CFU reductions in bacterial burdens in thighs compared to untreated controls at the start of therapy. The study results are summarized in Table E-3 in the Appendix-E of this review.

2. Neutropenic Thigh Infection Model with *S. pneumoniae* (QSSP and QRSP) in Mice

In this model delafloxacin was tested against *S. pneumoniae* 6303, a fluoroquinolone, penicillin, and macrolide susceptible isolate; *S. pneumoniae* 5649, a macrolide-resistant, penicillin-intermediate isolate; and 6 FQ-RSP clinical isolates (*S. pneumoniae* 7215, 7247, 7250, 7257, 7260, and 7261). A >3-log_{10} decrease in CFU counts compared to vehicle-treated control was

reported except animals infected with *S. pneumoniae* 7215 and *S. pneumoniae* 7250, delafloxacin treatment resulted in a 2-$\log_{10}$ CFU reduction. The results are shown in Table E-4 in the Appendix-E of this review.

3. Neutropenic Thigh Infection Model with *E.coli* in Mice

The efficacy of delafloxacin was evaluated against *E. coli* isolates (*E. coli* 1705874, an ESBL-positive, MDR strain, MIC 2 mcg/mL; *E. coli* 1705884, MIC 0.016 mcg/mL; and *E. coli* 255010, MIC 0.25 mcg/mL). Tigecycline and ciprofloxacin was used as a comparator.

Delafloxacin demonstrated efficacy against *E. coli* 1705884, resulting in > 2-$\log_{10}$ CFU reduction and >1 $\log_{10}$ CFU reduction against *E. coli* 255010; treatment with ciprofloxacin resulted in a 2.5 to 2.6 $\log_{10}$ CFU reduction against these two isolates. However, delafloxacin was not efficacious in reducing bacterial burden against the ESBL-positive, MDR *E. coli* strain 1705874 (delafloxacin MIC 2 mcg/mL and ciprofloxacin MIC > 128 mcg/mL). Tigecycline administration resulted in a 1.67 $\log_{10}$ reduction in CFU against this isolate after 24 hours of treatment. Results are shown in Table E-5 in the Appendix-E of this review.

4. Neutropenic Thigh Infection Model with *K. pneumoniae* in Mice

Delafloxacin activity against *K. pneumoniae* isolates was studied in this model (Report: EF-3341-008). Briefly, neutropenia was induced in female CD-1 mice -4and -1 day prior to infection. The following isolates were used in this model: *K. pneumoniae* 1705966 and *K. pneumoniae* 17059571 (ESBL-positive, imipenem-resistant strain) with delafloxacin MIC values of 0.125 mcg/mL and 2 mcg/mL, respectively. Mice were intramuscularly inoculated with bacteria and treatment with delafloxacin was administered at 2 and 9 hours post infection. For *K. pneumoniae* 1705966, delafloxacin was administered subcutaneously (SC) and orally (PO) at 100 mg/kg while ciprofloxacin was administered SC at 25 mg/kg. For *K. pneumoniae* 17059571, delafloxacin was administered SC at 50, 100, and 160 mg/kg while tigecycline was administered SC at 50 mg/kg. The change in bacterial burden in tissues was determined 24 hours after therapy initiation as compared to the bacterial burden of control animals at the onset of treatment.

Delafloxacin showed varying degree of efficacy against tested isolates in a dose-dependent fashion and also based on the MIC of the isolates. Against *K. pneumoniae* 1705966 isolate, delafloxacin administered at 100 mg/kg SC and PO reduced the bacterial burden to -2.19 $\log_{10}$ CFU and -1.70 log10 CFU respectively. Ciprofloxacin produced a 2.5 to 3.0 $\log_{10}$ CFU reduction against this isolate. Delafloxacin had a static effect on mice infected with *K. pneumoniae* 17059571 and tigecycline demonstrated a 1.03-$\log_{10}$ CFU reduction in thigh burdens of this isolate. The results are shown in Table E-6 in the Appendix-E of this review.

5. Neutropenic Thigh Infection with *S. pneumoniae* in Rats

In this model delafloxacin activity was studied against fluoroquinolone-susceptible and fluoroquinolone-resistant *S. pneumoniae* (FQ-SSP and FQ-RSP) isolates (Study RD-01-334). Briefly, male CD rats were rendered neutropenic on Day -4 prior to initiation of infection. The following pneumococcal isolates were used in this study: *S. pneumoniae* 6303 (FQ-SSP,

delafloxacin, levofloxacin, and trovafloxacin MICs were 0.002, 1, and 0.25 mcg/mL respectively) and *S. pneumoniae* 7257 (FQ-RSP, delafloxacin, levofloxacin, and trovafloxacin MICs were 0.03, 8, and 2 mcg/mL respectively). Thighs were inoculated with 10^2 CFU on day 0 and the therapy was initiated PO after 1 and 8 hours post-inoculation. Thigh muscles were aseptically removed 12 hours after the last treatment. ED_{50} or 50% effective dose value for producing a 3-log reduction was calculated to the vehicle-treated control arm.

Delafloxacin demonstrated higher activity against both *S. pneumoniae* isolates (FQ-SSP and FQ-RSP) compared to fluoroquinolone comparators. Against the fluoroquinolone susceptible isolate, delafloxacin was more efficacious than trovafloxacin, and levofloxacin. The comparator quinolones were both less active against the FQ-RSP strain. The results are summarized in Table E-7 in the Appendix-E of this review.

Reviewer's comments: In neutropenic thigh infection models, treatment with delafloxacin achieved a 2- to 3-log_{10} CFU reduction against S. aureus including FQ-RSA/MRSA isolates. Delafloxacin was efficacious in mice and rats infected with S. pneumoniae resulting in a 2-3-log_{10} CFU reduction compared to vehicle treated controls Delafloxacin was shown to be efficacious in mice thighs infected with E. coli; a 1- 2-log_{10} CFU reduction was observed. Delafloxacin also showed efficacy in a dose- dependent manner against K. pneumoniae 1705966 (change in bacterial burden of + 1.53 to -2.58 log10 as the dose ranged from 10 to 160 mg/kg/day, MIC = 0.125 mcg/mL), and static activity against the ESBL-positive strain K. pneumoniae 17059571 (delafloxacin MIC of 2.0 mcg/mL), in the murine neutropenic thigh infection model.

Pulmonary Infections Model

Delafloxacin activity was studied in both rats and in mice against lung infections caused by different *S. pneumoniae* isolates.

1. Mouse Pulmonary Infection

The efficacy of delafloxacin was studied in a mouse lung infection model induced by *S. pneumoniae* D39 isolate (Study: EF-3341-006); ciprofloxacin and telithromycin were used as comparators. In this model, survival was monitored for 7 days and delafloxacin showed comparable protective efficacy to telithromycin in treating lung infections and also in reducing bacterial burden. Ciprofloxacin had no protective effect in this study. The results are summarized in Table E-8 in the Appendix-E of this review.

2. Rat Pulmonary Infection

Delafloxacin activity was also studied in a rat lung infection model induced with *S. pneumoniae* and *H. influenzae* isolates associated with pulmonary infections and was compared with ciprofloxacin, trovafloxacin, and levofloxacin (RD-01-135). Oral therapy with delafloxacin, levofloxacin, or trovafloxacin (in sterile water) was administered once daily on Day 1 and Day 2, beginning 18 hours post-infection.

The effective dose values for the 50% of the animals challenged (ED_{50}) representing a 2-log10 CFU reduction in bacteria compared to the vehicle-treated control mean was calculated. Delafloxacin was shown to be more efficacious against lung infections in rats caused by different *S. pneumoniae* isolates, compared to levofloxacin and trovafloxacin. Delafloxacin, levofloxacin, and trovafloxacin were equally efficacious against *H. influenzae*. The results are summarized in Table E-9 in the Appendix-E of this review.

Murine Pyelonephritis Model

The activity of delafloxacin was studied in an experimental pyelonephritis models in mice against MRSA, *E. coli*, *E. faecalis*, and *P. aeruginosa* isolates.

Delafloxacin efficacy was compared with vancomycin and telithromycin in a murine pyelonephritis model in mice induced with MRSA 11540 (USA 300) isolate (EF-3341-007). The reduction in kidney CFU counts after treatment for 48 hours was compared to CFU counts in vehicle-treated control animals at the start of therapy. Delafloxacin demonstrated efficacy in a dose-dependent fashion in this model. Results are summarized in Table E-10 in the Appendix-E of this review.

In a similar study (RD-01-332), the efficacy of delafloxacin was compared with ciprofloxacin, trovafloxacin, and levofloxacin in a murine model of pyelonephritis induced with gram-negative (*E. coli* 1289, *P. aeruginosa* 5007) and gram-positive (*E. faecalis* 1967) pathogens associated with renal infections. Delafloxacin was equivalent in efficacy to trovafloxacin against *E. coli*, *E. faecalis*, and *P. aeruginosa* in this murine pyelonephritis model and demonstrated ED_{50} values of 1.1, 28.9 and 8.8 mg/kg/day against these organisms respectively. Delafloxacin and ciprofloxacin were both efficacious against *P. aeruginosa* and demonstrated ED_{50} values of 8.8 vs. 14.9 mg/kg/day, respectively. Results are summarized in Table E-11 in the Appendix-E of this review.

Abscess Model: Rat Granuloma Pouch[17, 18]

The rat granuloma pouch model is a chronic, localized model of infection and inflammation that allows continuous sampling from infection site and thereby ability to monitor both bacterial burden and drug concentrations at the infection site over time. Delafloxacin activity was evaluated with comparators ciprofloxacin for *E. coli*, *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* isolates and vancomycin for *S. aureus* isolates (EF-3341-003).

Briefly, granuloma pouch infections were established in male SD rats with 1 mL of bacterial culture following six days of post-granuloma formation. Delafloxacin, ciprofloxacin, or vancomycin (*S. aureus* only) were dosed via subcutaneous administration beginning 4 to 6 hours (*S. aureus* and *P. aeruginosa*) or 24 hours (*E. coli*, *K. pneumoniae* and *A. baumannii*) post-infection and continuing once (*E. coli*, *A. baumannii*, *P. aeruginosa* and *K. pneumoniae*) or twice (*S. aureus*) daily for 2 days. MIC values are shown for each organism in Table E-12 in the Appendix-E of this review.

Figures G8, G9, G10, G11, and G12 in the Appendix F show the mean change in $\log_{10}$ CFU following the inoculation of each bacterial isolate over time and treated animals were compared with a vehicle-treated control. These figures also indicate the time points when the drug levels stayed above the MIC levels for specific organism. Delafloxacin level remained above the MIC for *S. aureus* isolate MRSA 11540 throughout the study, although the final dose was given at 54 hours post-infection (Figure G9 in the Appendix F). The MIC values of delafloxacin and vancomycin are similar against MRSA 11540. Please note that the plasma and pouch levels of vancomycin were not determined in this study.

Delafloxacin level remained above the MIC for *A. baumannii* through 72 hours, and CFU levels remained low until 96 hours without rebound; final dose was given at 48 hours post-infection. Ciprofloxacin levels decreased in the pouch to below MIC after 72 hours, and this decrease corresponded to an apparent increase in bacterial load at that time point (Figure 68 in the Appendix F).

Delafloxacin levels in the *E. coli*-infected pouch remained steady, and the bacterial load continued to decrease even after therapy (final dose was given at 48 hours post-infection). However ciprofloxacin levels after the 72-hour time point decreased to near MIC level in experimental pouches, and ciprofloxacin-treated bacterial loads plateaued as the drug levels decreased (Figure G10 in the Appendix F).

Delafloxacin pouch levels remained steadily below MIC against *P. aeruginosa* throughout the study (final dose was given 48 hours post -infection), and this corresponded to a reduction of bacterial load. The bacterial load reduction observed with delafloxacin was similar to what was observed with ciprofloxacin (Figure G11 in the Appendix F).

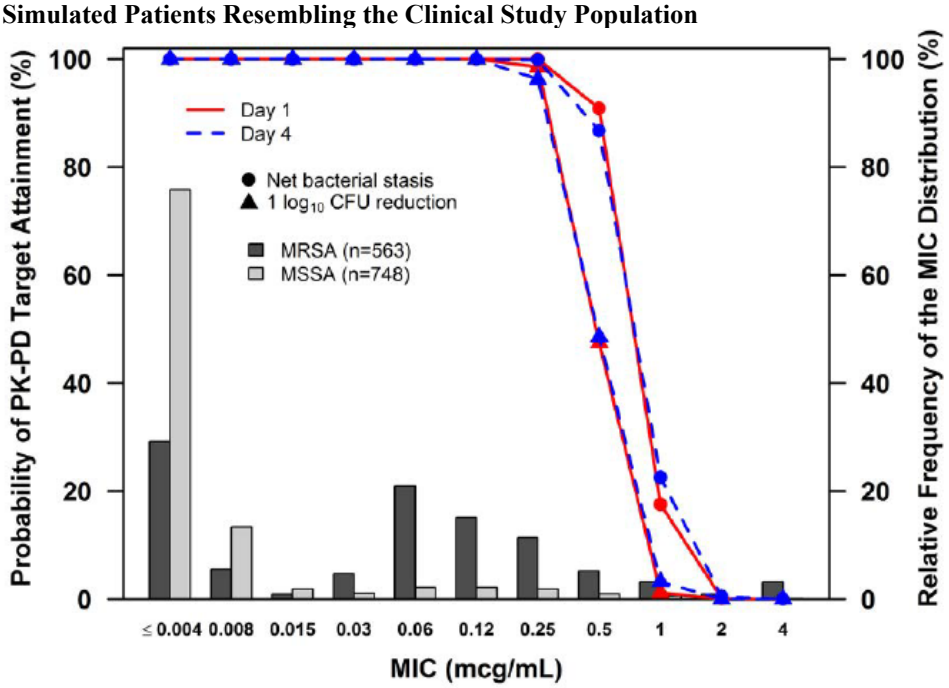
Delafloxacin levels remained above the MIC against *K. pneumoniae* 1705966 isolate throughout the study (final dose was given at 48 hours post-infection and the final time point was at 96 hours). Although, ciprofloxacin was 7.5 times more active than delafloxacin against this isolate (MIC 0.008 vs. MIC 0.06), an approximately 2.5-log10 CFU reduction (compared to the start of therapy) was observed in the pouch exudates for both drugs. Pouch levels of ciprofloxacin fell below the limit of detection 32 hours after the final dose was given (Figure G12 in the Appendix F).
Reviewer's comments: Delafloxacin was shown to be efficacious in different murine infection models; including systemic lethal infections, soft-tissue infections, pneumonia, pyelonephritis, and experimental abscess infections (rat granuloma pouch infection). Efficacy was observed against gram-positive and gram-negative pathogens and in most studies the efficacy of delafloxacin was found to be similar to or more active than the quinolone and non-quinolone comparators.

PHARMACOKINETIC / PHARMACODYNAMIC STUDIES
The Applicant used experimental neutropenic murine lung or thigh infection models to determine the PK/PD parameters for delafloxacin. Similar to other fluoroquinolones, the PK/PD target,

*f*AUC24/MIC ratio was determined to be the PK parameter most closely associated with delafloxacin efficacy. Monte Carlo simulations were performed for delafloxacin dosing regimens of 300 mg q12h IV and 450mg q12h PO to estimate the probability of target attainment for stasis and 1-$\log_{10}$ kill against *S. aureus*, *E. coli*, and *P. aeruginosa*.

The percent probabilities of PK/PD target attainment were estimated as 96.5% for net bacterial stasis for all *S. aureus* isolates at an MIC value of 0.5 mcg/mL (the MIC_{90} for the MRSA distribution) and 99% for 1-$\log_{10}$ kill at an MIC value of 0.25 mcg/mL. Percent probabilities of PK/PD target attainment by MIC distributions for MRSA and MSSA isolates are shown in Figure 13.

Figure 13. Percent Probabilities of PK/PD Target Attainment by MIC distributions for *S. aureus* isolates on Day 1 for Delafloxacin Dosed at 300 mg IV Q12h (Days 1 – 3) Followed by 450 mg Oral Q12h (Day 4) Among Simulated Patients Resembling the Clinical Study Population

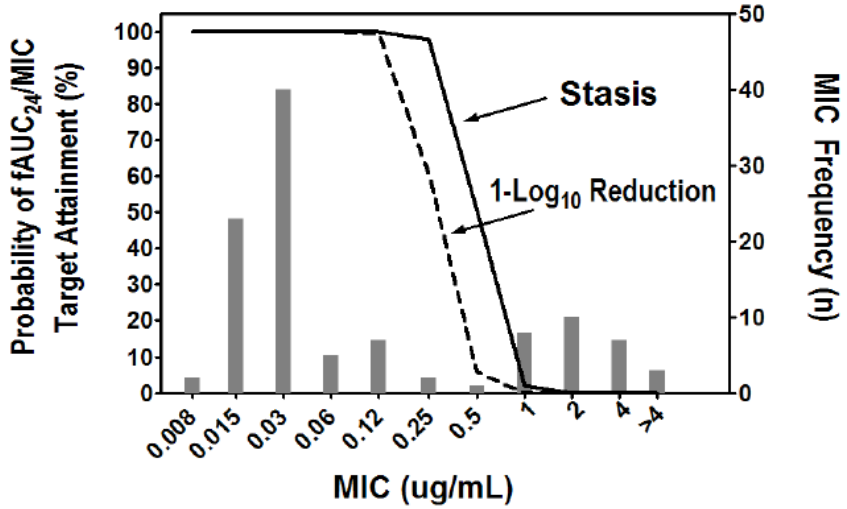


ABSSSI = acute bacterial skin and skin structure infection; CFU = colony-forming unit; MIC = Minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *S. aureus*; PK/PD = pharmacokinetic/pharmacodynamic

Source: PK-3341-015 Figure 9

The percent probabilities of PK/PD target attainment were estimated as ≥98% for net bacterial stasis against *E. coli* at an MIC value of 0.25 mcg/mL and ≥99.3% for 1-$\log_{10}$ kill at an MIC value of 0.12 mcg/mL. At the proposed dosing regimen, only 66.6% of all *E. coli* isolates (N=1031 from surveillance studies) will be covered. However, this dosing regimen is predicted to cover 96.2% (N=711) of levofloxacin susceptible *E. coli* isolates. Percent probabilities of PK/PD target attainment for *E. coli* isolates are shown in Figure 14.

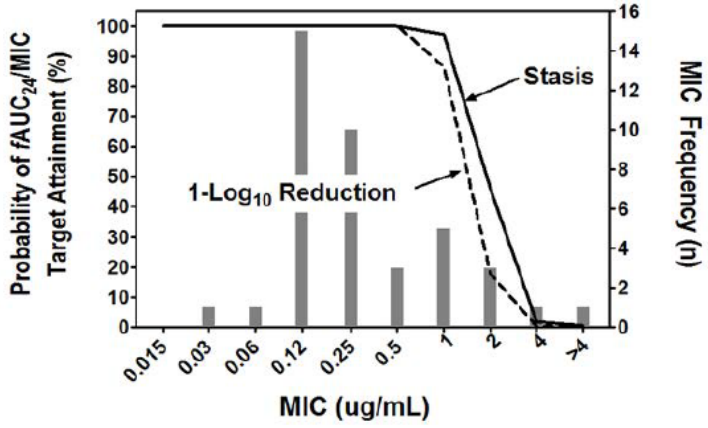
Figure 14. Probability of Target Attainment in Humans Based on Monte Carlo Simulations, and the MIC Distribution for *E. coli* Skin and Soft Tissue Isolates From Delafloxacin North American Surveillance



Solid Line: Probability (%) of $fAUC_{24}$/MIC target attainment for stasis (14.5)
Dashed Line: Probability (%) of $fAUC_{24}$/MIC target attainment for 1-log kill (26.2)
Grey Bars: MIC Frequencies for *E. coli* skin and soft tissue isolates from 2014-2015 delafloxacin surveillance (n = 108)
Source: PK-3341-011 Figure 13

For *P. aeruginosa* the percent probabilities of PK/PD target attainment were estimated as ≥ 97.3% for net bacterial stasis at an MIC value of 1 mcg/mL and 100% for 1-$\log_{10}$ kill at an MIC value of 0.5 mcg/mL. Percent probabilities of PK/PD target attainment for *P. aeruginosa* clinical isolates are shown in Figure 15.

Figure 15. Probability of Target Attainment in Humans Based on Monte Carlo Simulations, *P. aeruginosa* *f*AUC24/MIC Ratios, and the MIC Distribution for *P. aeruginosa* Skin and Soft-Tissue Isolates From Delafloxacin North American Surveillance



Solid Line: Probability (%) of $fAUC_{24}$/MIC target attainment for stasis (3.81)
Dashed Line: Probability (%) of $fAUC_{24}$/MIC target attainment for 1-$\log_{10}$ CFU reduction (5.02)
Grey Bars: MIC Frequencies for *P. aeruginosa* skin and soft-tissue isolates from 2014-2015 delafloxacin surveillance (n = 40)
Source: PK-3341-020, Figure 8

Please see clinical pharmacology review for in depth analysis of all studies conducted for pharmacokinetics and pharmacodynamics of delafloxacin.

CLINICAL STUDIES
SUMMARY OF CLINICAL STUDIES

The Applicant conducted two Phase 3 clinical studies, RX-3341-302 and RX-3341-303 among adult patients (≥ 18 years of age) with ABSSSI to determine the safety and efficacy of delafloxacin. The Phase 3 studies were the primary data sources to support the efficacy of delafloxacin in the treatment of patients with ABSSSI. The comparators in both Phase 3 studies were vancomycin + aztreonam combination therapy based on their respective activity against gram-positive and gram-negative pathogens.

A total of 1510 subjects were enrolled and analyzed in both Phase 3 studies. Approximately 85% of subjects in each treatment group completed the studies. A summary of Phase 2 and Phase 3 clinical studies is shown in Table F-1 in the Appendix-F of this review.

- RX-3341-302 was a randomized, double-blind, Phase 3, active-controlled study comparing the efficacy of IV delafloxacin 300 mg Q12h to comparator IV vancomycin (15 mg/kg actual body weight) with IV aztreonam (2 g) in 660 subjects. All subjects were randomized and dosed BID for 5 to 14 days.
- RX-3341-303 was a randomized, double-blind, Phase 3 study comparing the efficacy of IV delafloxacin, 300 mg Q12h for 6 doses stepped down to 450 mg Q12h orally, to comparator IV vancomycin (recommended 15 mg/kg actual body weight) with IV aztreonam (1 to 2 g) Q12h in 850 subjects with ABSSSI including infections caused by MRSA. All subjects were randomized and dosed BID for 5 to 14 days in a double-blind fashion.

According to the Applicant, the following different analysis sets were used to analyze the clinical response and the microbiological response in both Phase 3 clinical studies.

- ITT (Intent-to-treat) Analysis Set: Includes all subjects who were randomly assigned to treatment.
- MITT (Microbiological ITT) Analysis Set: Includes all subjects in the ITT analysis set who had a baseline bacterial pathogen identified by the Sponsor that was known to cause ABSSSI.
- CE (Clinically evaluable) Analysis Sets: There are 6 CE analysis sets, each based on the type of assessment (investigator-assessed or objective) and timing of the assessment (48 to 72 hours, end of treatment [EOT], FU (Follow-up) or LFU (Late follow-up) visits). Includes all subjects in the ITT analysis set who had an ABSSSI, received their assigned treatment, received ≥ 80% of study drug, had required clinical assessments within appropriate window, did not receive systemic antibacterial therapy with activity against the causative pathogen through the time period in question, and had no protocol deviations that would have affected efficacy assessments through the time period in question. Subjects were analyzed according to their assigned treatment.

- ME (Microbiologically evaluable) Analysis Sets: The ME analysis sets include all patients in the MITT analysis set who also met the criteria for the corresponding CE (CE72O, CEFUI, CELFI) analysis set as follows:
    - ME72O: ME at 48 to 72 hours (± 2 hours) for the objective response
    - MEFUI: ME at FU for the investigator-assessed response
    - MELFI: ME at LFU for the investigator-assessed response

Microbiological response for patients in the ME and MITT analysis sets were based on results of the baseline and post-baseline cultures (FU and LFU Visits) and susceptibility testing, together with the clinical response assigned by the investigator. Microbiological responses were generated at each of the FU and LFU visits at the pathogen level. For summary analyses, eradicated included documented and presumed eradicated while persistent included documented and presumed persisted.

- Documented eradicated - The baseline pathogen was absent in cultures of the original site of infection at the post-baseline visit.
- Presumed eradicated - There was no material available for culture or no culture was done and the patient had an investigator-assessed response of success.
- Documented persisted - The baseline pathogen was present in cultures of the original site of infection at the visit.
- Presumed persisted - There was no material available for culture or no culture was done and the patient had an investigator-assessed response of failure (where failure included investigator assessment of failure + indeterminate or the assessment was missing).

The primary endpoint of both Phase 3 studies was the objective response (≥ 20% reduction of erythema area,) rate at 48 to 72 hours. Delafloxacin was non-inferior to vancomycin + aztreonam in objective response after initiation of study drug in the both pivotal Phase 3 studies. The proportion of subjects who were responders at 48 to 72 hours after initiation of study drug was similar between the 2 treatment groups in each pivotal Phase 3 studies. Similar results were observed in the other analysis sets (MITT, CE at 48 to 72 hours, and ME at 48 to 72 hours) which is presented in the following Table 2.

Table 2. Summary of Objective Response at 48 to 72 hours

Type Analysis Set	RX-3341-302		RX-3341-303		Pool 1	
	Responder Rate (%)[a]	Difference (95% CI)[b,c]	Responder Rate (%)[a]	Difference (95% CI)[b,c]	Responder Rate (%)[a]	Difference (95% CI)[b,c]
ITT	78.2, 80.9	−2.6 (−8.8, 3.6)	83.7, 80.6	3.1 (−2.0,8.3)	81.3, 80.7	0.8 (−3.2, 4.7)
MITT	81.1, 83.8	−2.7 (−9.5, 4.0)	87.6, 82.3	5.3 (−0.7, 11.4)	84.6, 83.0	1.8 (−2.7, 6.3)
CE72O	85.0, 86.5	−1.5 (−7.2, 4.2)	87.6, 84.5	3.1 (−1.8, 8.0)	86.5, 85.4	1.2 (−2.6, 4.9)
ME72O	86.4, 88.4	−2.1 (−8.4, 4.2)	89.0, 86.4	2.6 (−3.1, 8.4)	87.8, 87.4	0.5 (−3.8, 4.7)

CE72O = clinical efficacy at 48 to 72 hours (± 2 hours) for the objective response; CI = confidence interval; ITT = intent-to-treat; ME72O = microbiologically evaluable at 48 to 72 hours (± 2 hours) for objective response; MITT = microbiological intent-to-treat
[a] Responder rate for delafloxacin and vancomycin + aztreonam treatment groups, respectively
[b] Difference in rates (delafloxacin group minus vancomycin + aztreonam group).
[c] Confidence intervals were calculated using the Miettinen Nurminen method without stratification.
Source: Section 2.7.3 Appendix 1

Baseline Microbiology

In both Phase 3 studies, a baseline culture of the primary infection site was obtained from all patients at screening. Additional specimens for microbiologic culture and gram-stain were collected from the ABSSSI site before initiation of any rescue therapy, and/or if the patient was a clinical failure. All specimens were sent to a local laboratory for Gram-stain and culture and were processed according to the local standard operating procedures (SOP). The Gram-stain slide of the specimen, performed at the local study site, was retained by the local microbiology laboratory. Isolates were forwarded to the central microbiology laboratory, (b) (4) (b) (4) for confirmation of identity, antimicrobial susceptibility testing, and any further molecular or phenotypic characterization (e.g., polymerase chain reaction for Panton Valentine leukocidin, PFGE, etc.). A duplicate frozen sample of any isolate(s) submitted to the central microbiology laboratory was also maintained by the local laboratory. In addition, all of the final isolates from these studies are maintained frozen at the central laboratory.

Overall, there were no differences in baseline pathogens between the 2 studies in the MITT analysis set. As expected for ABSSSI, gram-positive pathogens constituted the majority of pathogens recovered during in the Phase 3 studies. The predominant species isolated at baseline was *S. aureus*, in both delafloxacin and comparator treatment arms at rates of 61.6% and 61.8%, respectively. Overall, MRSA rates were between 43 to 45% among all recovered *S. aureus* isolates with the vast majority of MRSA isolated from patients in North America.

Beta-hemolytic streptococci were isolated at rates of 8.8% and 7.8% for the delafloxacin and comparator treatment arms, respectively, with *S. pyogenes* being the most common (4.4% and 3.4%, respectively). *S. anginosus* Group isolates were also commonly observed at baseline in 12.7% and 12.8% of patients from the delafloxacin and comparator treatment arms, respectively.

Other gram-positive cocci including a variety of coagulase-negative staphylococci including *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. lugdunensis*, and *S. simulans* were isolated at baseline followed by a smaller overall proportion of *S. mitis* Group isolates and *E. faecalis*.

Gram-negative pathogens were also isolated among patients at baseline including a variety of Enterobacteriaceae. *K. pneumoniae* was the most prevalent and isolated at 4.2% and 4.4% in the delafloxacin and comparator treatment arms, respectively, followed by *E. coli*, *E. cloacae*, *P. mirabilis*, and *K. oxytoca*.

In addition, *P. aeruginosa* was isolated among 2.1% and 2.3% of patients in the delafloxacin and comparator arms, respectively. A small number of *H. parainfluenzae* were encountered at baseline at 1.2% and 1.3% in the delafloxacin and comparator arms, respectively.

The distributions of baseline gram-positive and gram-negative pathogens in the MITT populations are summarized in Table F-2 and Table F-3 in the Appendix-F of this review respectively.

Monomicrobial and Polymicrobial Infections
The presence of monomicrobial gram-positive and gram-negative, polymicrobial gram-positive and gram-negative infections and mixed (gram-positive and gram-negative; aerobe and anaerobe) infections are summarized in Table F-4 in the Appendix-F of this review for both the MITT and ME at FU (MEFUI) populations. In the MITT and MEFUI populations, respectively in the pooled delafloxacin arm, 65.4% [339/518] and 65.9% [270/410] of subjects had a monomicrobial gram-positive infection. In the MITT and MEFUI populations in the pooled delafloxacin arm, 3.3% (17/518) and 3.9% (16/410) had monomicrobial gram-negative infections, 14.1% (73/518) and 13.2% (54/410) had polymicrobial mixed gram-negative and – positive infections and 5.4% (28/ 518) and 4.6% (19/410) had mixed aerobic and anaerobic infections.

Reviewer's comment: There were ≤ 10 cases of monomicrobial infections caused by individual target gram-negative pathogens. Gram-negative pathogens were mostly recovered predominantly with gram-positive ABSSSI pathogens from cases with polymicrobial infections.

In vitro activity of Delafloxacin against Target Pathogens at Baseline (MICs and disk diffusion zone diameters)
The MICs of delafloxacin against key baseline target gram-positive and gram-negative pathogens from the MITT analysis set for both treatment arms from both Phase 3 studies are summarized in Table F-5 and Table F-6 in the Appendix-F of this review.

Delafloxacin had activity against target gram-positive pathogens overall by MIC_{50} and MIC_{90} as shown in Table F-5 in the Appendix-F. The activity of delafloxacin against isolates from Europe and North America was similar by MIC_{50} and MIC_{90} with the exception of *S. aureus* which is likely due to the lower prevalence of MRSA isolates from Europe and also to the higher degree of pre-existing levofloxacin non-susceptible MSSA isolates from North America relative to Europe. Overall, the percentages of levofloxacin non-susceptible isolates were highest among *S. aureus* and *S. haemolyticus*. Levofloxacin-non-susceptible *S. aureus* isolates were associated primarily with the MRSA subpopulation.

Delafloxacin was active against target gram-negative pathogens overall by MIC_{50} and MIC_{90} as shown in Table F-6 in the Appendix-F. The MIC_{50} and MIC_{90} values of delafloxacin against gram-negative clinical study isolates were similar to those observed in surveillance studies. The percentage of levofloxacin non-susceptible isolates was highest among *P. aeruginosa* and *P. mirabilis*.

The zone diameter summary statistics (minimum, maximum, median, mean [standard deviation]) for delafloxacin as determined by disk diffusion against key target pathogens at baseline are summarized for gram-positive and gram-negative pathogens in Table F-7 and Table F-8, respectively in the Appendix-F of this review (MITT-both treatment arms, Pool 1).

MIC Distribution – Clinical vs. Surveillance

The Applicant provided histograms showing the MIC distribution of delafloxacin against target pathogens isolated in clinical studies (MITT-Delafloxacin and Comparator Treatment Arms, Pool 1) relative to recent surveillance. Overall, the delafloxacin MIC distribution from clinical study isolates was similar to that observed during recent surveillance isolates.

Against 685 *S. aureus* clinical isolates, delafloxacin overall MIC_{range} and MIC_{50}/MIC_{90} were 0.002-4 mcg/mL and 0.008/0.25 mcg/mL, respectively. The MIC_{range} and MIC_{50}/MIC_{90} were 0.002-0.5 mcg/mL and 0.008/0.03 mcg/mL for MSSA and 0.002-4 mcg/mL and 0.12/0.25 mcg/mL, respectively for MRSA isolates. Delafloxacin MIC distributions are shown for *S. aureus* isolates in Figure G1 in Appendix F.

Against 186 coagulase-negative staphylococci (CoNS) clinical isolates, delafloxacin overall MIC_{range} and MIC_{50}/MIC_{90} were 0.002-8 mcg/mL and 0.004/0.5 mcg/mL respectively. Delafloxacin MIC distributions are shown for coagulase-negative staphylococci overall and by species in Figure G2 in Appendix F.

Against 215 β-hemolytic and other streptococci clinical isolates, delafloxacin overall MIC_{range} and MIC_{50}/MIC_{90} were ≤0.004-0.12 mcg/mL and ≤0.004/0.06 mcg/mL, respectively. Against 27 *E. faecalis* isolates, delafloxacin overall MIC_{range} and MIC_{50}/MIC_{90} were ≤0.004-2 mcg/mL and 0.12/1 mcg/mL, respectively. Delafloxacin MIC distributions are shown for β-hemolytic streptococci overall and by species in Figure G3, *S. anginosus* Group overall and by species in Figure G4, *E. faecalis* in Figure G5 in Appendix F.

Against 133 Enterobacteriaceae clinical isolates, delafloxacin overall MIC_{range} and MIC_{50}/MIC_{90} were 0.008-8 mcg/mL and 0.06/4 mcg/mL, respectively. Against 24 *P. aeruginosa* clinical isolates, delafloxacin overall MIC_{range} and MIC_{50}/MIC_{90} were 0.012-8 mcg/mL and 0.25/4 mcg/mL, respectively. Delafloxacin MIC distributions are shown for Enterobacteriaceae overall and by species in Figure G6, and *P. aeruginosa* in Figure G7 in Appendix F.

Overall Per-Pathogen Response

Microbiological success by baseline pathogen was similar between the 2 Phase 3 studies for both treatment groups at the FU and LFU visits in the ME analysis sets which are presented in Table F-9 and Table F-10 in the Appendix-F of this review. For the ME population at FU, the overall favorable microbiologic response rates were: 98.4% for *S. aureus* (98.1% for MRSA), 100% for target species of coagulase negative staphylococci (excluding *S. epidermidis*), 100% for *S. anginosus* Group, 94.7% for *S. pyogenes*, 100% for *S. agalactiae*, *S. dysgalactiae*, and *S. mitis* Group, 90.0% for *E. faecalis*, 100% for target Enterobacteriaceae excluding *E. cloacae* where a rate of 91.7% was observed, and 100% for *P. aeruginosa* and *H. parainfluenzae*.

Correlation of Broth Microdilution and Agar Dilution MIC Values
Broth microdilution MIC values and agar dilution MIC values were compared in the study MB-3341-052. A total of 117 clinical isolates including *S. aureus* (n = 33), *Streptococcus* spp. (n = 29), and Enterobacteriaceae (n = 55) were evaluated concurrently by broth microdilution and agar dilution in accordance with CLSI guidelines.

Delafloxacin agar dilution MIC values exhibited 89.7% (105/117) correlation with an overall essential agreement with broth microdilution MIC values[19]. Essential agreements of 96.9% and 94.6% were observed for *S. aureus* and Enterobacteriaceae, respectively. However, there was poor correlation between delafloxacin agar and broth microdilution MIC values for *S. pneumoniae*, with an essential agreement rate of 50.0% and a large proportion of isolates (6/12; 50.0%) with agar dilution MIC values at least 4-fold lower than those observed by broth microdilution. Excluding *S. pneumoniae*, the overall essential agreement observed between delafloxacin agar dilution MIC values and broth microdilution values was 94.3% (99/105). These results demonstrated the equivalence of delafloxacin MIC values as determined by agar dilution relative to broth microdilution for *S. aureus*, streptococcus spp. (non-*pneumoniae*), and Enterobacteriaceae. In contrast, delafloxacin MIC values as determined by agar dilution for *S. pneumoniae* did not correlate with broth microdilution MIC values and, as such, agar dilution susceptibility testing of delafloxacin for *S. pneumoniae* is not recommended. The results are summarized in Table F-11 in the Appendix-F of this review.

DISK DIFFUSION METHODS

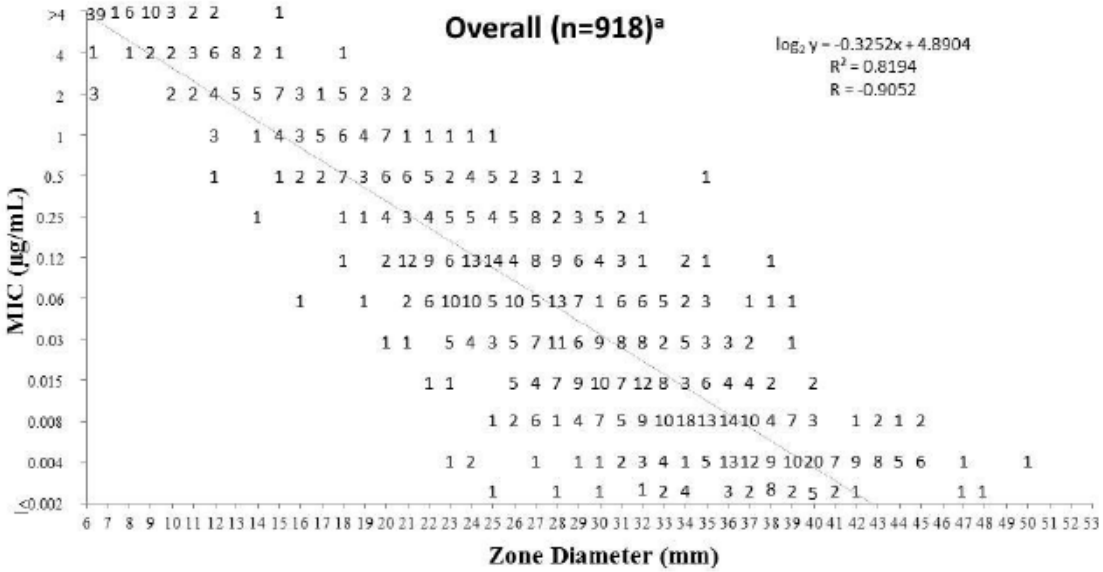
Disk Content Studies
Study MB-3341-012 was conducted to determine the appropriate disk mass for use in disk diffusion testing of delafloxacin against target pathogens. Delafloxacin susceptibility was determined by disk diffusion testing using a 5-µg disk for target pathogens, based on the overall correlation between disk diffusion zone sizes and broth microdilution MIC values.

The majority of the fluoroquinolones (e.g. levofloxacin, moxifloxacin, and ciprofloxacin) have an approved disk mass of 5 mcg for susceptibility testing. Investigational delafloxacin disk masses tested included 2, 5, 10, and 15 mcg. A negative linear correlation was observed for all evaluated disk masses against the test isolates with R-values of -0.8953, -0.9140, -0.9109, and -0.9124 for disk masses of 2, 5, 10, and 15 mcg, respectively. The Applicant tested 10 independent replicates of ATCC quality control strains which resulted in stable and reproducible zone sizes for all evaluated disk masses (MB-3341-012).[1, 19]

The correlation of disk diffusion zone sizes to broth microdilution MIC values for delafloxacin was further evaluated using a large volume of isolates and commercially-manufactured disks containing 5-µg delafloxacin in 2 separate studies (MB-3341-028-A1; MB-3341-064). The resulting scatterplots illustrating the negative linear correlation of delafloxacin disk zones to broth microdilution MIC values overall and by organism group are shown below. Overall, a

strong negative linear correlation was observed for evaluated isolates with an R-value of -0.9052 which is shown in Figure 16.

Figure 16. Overall Broth MIC Value Versus Disk Zone Diameter Correlation for Delafloxacin (5 mcg) Against Evaluated Target Pathogens



MIC = minimum inhibitory concentration
[a] *H. influenzae* (30) and *M. catarrhalis* (20) excluded due to the majority of isolates having undefined MIC values of ≤ 0.002
Source: MB-3341-028-A1; MB-3341-064 Figure 1 to 5

Isolates with delafloxacin MIC values ≥ 2 mcg/mL typically had zone sizes < 15 mm and isolates with delafloxacin MIC values ≤ 0.5 mcg/mL typically had zone sizes > 20 mm demonstrating the potential for discrimination between likely delafloxacin-susceptible and -resistant populations when testing with the 5-µg disk. Delafloxacin disk (5 mcg) performance was further evaluated in accordance with CLSI testing guidelines by error-rate bounding using the proposed broth microdilution and disk diffusion interpretive criteria.

Disk Stability

Disk stability studies were conducted to evaluate the stability or shelf-life of delafloxacin 5 mcg disks from three batches manufactured by (b) (4). The three batches were packaged in the final format in sealed containers, and stored at various temperatures (-20°C, 4°C, RTR- Intended to simulate usage or transport followed by return to refrigerated storage, RT- Room Temperature - to be 25°C, 37˚C, and 50˚C). Each batch was tested at intervals of 0, 6, 12, 15, 18 and 24 months and there are no signs of deterioration of the disks. The disks demonstrated acceptable stability up to 24 months. All 3 batches were reported to be within acceptable specification ((b) (4) (b) (4) of label content). Disk performance was also evaluated according to CLSI recommendations against a panel of ATCC organisms and was found within respective limits for

all organisms. All 3 batches were within specification (within 3 mm) indicating no intra-batch or inter-batch variability.

QUALITY CONTROL STUDIES

Development of Quality Control (QC) Ranges

To establish the QC ranges for the in vitro susceptibility testing of delafloxacin, broth microdilution MIC and disk diffusion zone diameters studies were performed in accordance with CLSI guidelines.

Broth Microdilution MIC Testing Quality Control

QC ranges for the broth microdilution testing of delafloxacin against relevant ATCC quality control isolates were determined in a multicenter study consisting of 9 laboratories according to CLSI M23 Tier 2 QC guidelines[19]. Frozen broth microdilution panels containing delafloxacin and levofloxacin (control agent) were used by participating laboratories. Each panel contained delafloxacin in the standard CLSI test media for the testing of that particular organism (cation-adjusted Mueller-Hinton broth [CAMHB] for non-fastidious aerobes, CAMHB supplemented with lysed horse blood for streptococci, and Haemophilus Test Medium for *Haemophilus* spp.). Three separate lots of media from 3 separate manufacturers were used to assess potential variation by media lot. Standard ATCC QC isolates including *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *H. influenzae* ATCC 49247 were evaluated. Data were compiled and analyzed in accordance with CLSI guidelines and using the Rangefinder Method of Turnidge and Bordash.

A summary of the Tier 2 QC ranges for broth dilution susceptibility testing is shown in the following Table 3.

Table 3. Summary of QC Ranges for the Testing of Delafloxacin Based on Results From a 9-Laboratory Tier 2 Study

Organism	QC Range (µg/mL)	Total N	N (%) in Range
S. aureus ATCC 29213	0.001 - 0.008	270	268 (99.3)
E. faecalis ATCC 29212	0.015 - 0.12	270	270 (100)
S. pneumoniae ATCC 49619	0.004 - 0.015	270	267 (98.9)
E. coli ATCC 25922	0.008 - 0.03	270	260 (96.3)
P. aeruginosa ATCC 27853	0.12 - 0.5	270	269 (99.7)
H. influenzae ATCC 49247	0.00025 - 0.001	270	270 (100)[a]

ATCC = American Type Culture Collection; CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; QC = quality control
[a] A total of 11 replicate inocula resulted in delafloxacin MIC values of ≤ 0.00025 during the Tier 2 study
Source: Adapted from CLSI M100-S26[48]; MB-3341-011Table VI

Disk Diffusion Testing Quality Control

QC ranges for the disk diffusion testing of delafloxacin against relevant ATCC QC isolates were established in a multicenter study consisting of 8 laboratories according to CLSI M23 Tier 2 QC guidelines[19]. Two separate lots of commercially-manufactured delafloxacin 5-µg disks (b) (4) (b) (4) were tested alongside levofloxacin 5-µg disks (b) (4) (b) (4) tested as the control agent. Each disk was tested using standard CLSI test medium for the testing of that particular organism (Mueller-Hinton Agar [MHA] for non-fastidious aerobes, MHA with lysed sheep blood for streptococci, and Haemophilus Test Medium [HTM] for *Haemophilus* spp.). Three separate lots of media from 3 separate manufacturers were used to assess potential variation by medium lot. Standard ATCC QC isolates including *S. aureus* ATCC 25923, *S. pneumoniae* ATCC 49619, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *H. influenzae* ATCC 49247 were evaluated. Data were compiled and analyzed in accordance with CLSI guidelines using the Gavan statistic and the Rangefinder Method of Turnidge and Bordash. A summary of the Tier 2 QC ranges for disk diffusion susceptibility testing is shown in the following Table 4.

Table 4. Summary of QC Ranges for the Testing of Delafloxacin Based on Results From Tier 2 M23 Studies

Organism	QC Range (mm)	Total N	N (%) in Range
S. aureus ATCC 25923	32 - 40	414[a]	409 (98.8)
S. pneumoniae ATCC 49619	28 - 36[b]	480[c]	478 (99.6)
E. coli ATCC 25922	28 - 35	480	480 (100)
P. aeruginosa ATCC 27853	23 - 29	480	476 (99.2)
H. influenzae ATCC 49247	40 - 51	478[d]	462 (96.7)

ATCC = American Type Culture Collection; CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; QC = quality control
[a] A total of 60 results from lab 1 (outlier) and 6 results from lab 8 (out of QC for control) were removed from analysis
[b] Based on data from MB-3341-047A1; a range could not be established for *S. pneumoniae* ATCC 49619 based on data available from MB-3341-043A1
[c] A total of 60 results from lab 4 (outlier) were removed from analysis
[d] A total of 2 results from lab 2 were removed from analysis due to an issue with test media (agar dislodged from the provided test plates during shipping)
Source: adapted from CLSI M100-S26[48]; MB-3341-043A1Table VII; MB-3341-047A1 Table VI

PROVISIONAL SUSCEPTIBILITY TESTING INTERPRETIVE CRITERIA

Proposed Interpretive Criteria

The Applicant has proposed the delafloxacin interpretive breakpoints presented in Table 5. The Applicant stated that these proposed breakpoints are based on several components including the data from the MIC distribution patterns in surveillance and clinical studies, PK/PD measure of $fAUC_{24}$/MIC ratio, and the correlation of clinical response to the MIC from clinical studies.

Table 5. Proposed Broth Microdilution and Disk Diffusion Susceptibility Test Criteria for Delafloxacin

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	(b) (4)	
S. haemolyticus *S. hominis* *S. lugdunensis*		
S. pyogenes *S. agalactiae* *S. dysgalactiae*		
S. anginosus Group (*S. anginosus, S. intermedius,* and *S. constellatus)*		
S. mitis Group (*S. cristatus, S. gordonii, S. mitis, S. oralis,* and *S. sanguinis)*		
E. faecalis		
E. coli *K. pneumoniae* *K. oxytoca* *E. cloacae* *P. mirabilis*		
P. aeruginosa		

MIC = minimum inhibitory concentration; NA = not applicable
[a] Delafloxacin 5-µg disk

Broth MIC versus Disk Correlation and Error-Rate Bounding Analysis

The broth dilution MIC versus disk diffusion correlation of delafloxacin against indicated pathogens were evaluated in accordance to CLSI guidelines M23-A3[19]. The CLSI guideline for acceptable discrepancy rates with intermediate ranges and without intermediate ranges are shown below in Table 6.

Table 6. Acceptable Discrepancy Rates (With Intermediate Ranges)

MIC Range		Discrepancy Rates		
1-dilution Intermediate Range	No Intermediate Range	Very Major	Major	Minor
≥ I+2	≥ R+1	< 2%	NA	< 5%
I+1 to I-1	R+S	< 10%	< 10%	< 40%
≤ I-2	≤ S-1	NA	< 2%	< 5%

CLSI = Clinical and Laboratory Standards Institute; I = intermediate; R = resistant; S = susceptible; Very Major = false susceptible by disk; Major = false resistant by disk; MIC = minimum inhibitory concentration; Minor = false intermediate by disk or broth; NA = not applicable;
Source: CLSI M23-A3[62]

Broth versus disk correlation scatterplots and error-rate bounding analysis were conducted for *S. aureus* (Figure G13 in the Appendix F), MSSA (Figure G14 in the Appendix F), MRSA (Figure G15 in the Appendix F), coagulase-negative staphylococci (Figure G16 in the Appendix F), β-hemolytic streptococci (Figure G17 in the Appendix F), *S. anginosus* Group (Figure G18 in the Appendix F), *E. faecalis* (Figure G19 in the Appendix F), Enterobacteriaceae (Figure G20 in the Appendix F), and *P. aeruginosa* (Figure G21 in the Appendix F).

Rationale for the Applicant-Proposed Breakpoints by Pathogen

The Applicant-proposed breakpoints for delafloxacin are summarized below by each target ABSSSI pathogens. According to the Applicant, the proposed breakpoints are based on MIC distribution, available PD modeling data including probability of target attainment analysis, and resulting clinical study outcomes as they correlate to delafloxacin MIC. The disk diffusion breakpoints were based on minimizing categorical error rates in accordance to CLSI M23 guidelines[19].

Staphylococcus aureus

The Applicant proposed the following breakpoints for *S. aureus,* including MRSA and MSSA isolates:

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
S. aureus (methicillin-resistant and methicillin-susceptible isolates)	(b) (4) Susceptible (b) (4) Intermediate (b) (4) Resistant	(b) (4) Susceptible Intermediate Resistant

MIC=minimum inhibitory concentration
[a] Delafloxacin 5-µg disk

The following rationale was provided by the Applicant:

- A susceptible breakpoint of ≤ (b) (4) mcg/mL is predicted to cover 94.9% of contemporary *S. aureus* isolates and 96.4% of contemporary *S. aureus* isolates from skin and soft-tissue infections.

- A susceptible breakpoint of ≤ (b) (4) mcg/mL is predicted to cover 88.7% of contemporary MRSA isolates and 92.7% of contemporary MRSA isolates from skin and soft-tissue infections.
- Delafloxacin MICs are bimodal for *S. aureus* isolates and MRSA isolates presumably due to the existing resistance to levofloxacin. However, delafloxacin maintains activity against fluoroquinolone-resistant *S. aureus* and exhibited high rates of clinical success and microbiological eradication for fluoroquinolone-resistant isolates during Phase 3 clinical studies. The first mode (MIC values of 0.002-0.03 mcg/mL) had 98.2% (166/169) microbiological response rates in the MEFUI population. The second mode (MIC range of 0.06 to 4 mcg/mL) had similar efficacy rates of 98.7% (78/79).
- For subjects with *S. aureus* clinical isolates that were non-susceptible to levofloxacin, 98.8% (80/81) efficacy was observed. For subjects with MRSA isolates, similar efficacy (98.6% [70/71]) was observed in the MEFUI population.
- For *S. aureus* clinical isolates, the predominant mutation observed was Ser84-Leu in *gyrA*/Ser80-Phe in *parC*. The delafloxacin MIC_{90} for isolates with this mutation was 0.25 mcg/mL whereas the MIC_{90} for levofloxacin and ciprofloxacin was 8 and > 8 mcg/mL. The microbiological response rate for isolates with this mutation was 98.8% (83/84).
- Based on achieving the PK/PD target, delafloxacin MIC value of (b) (4) mcg/mL was predicted to be associated with 95% and 100% target attainment for IV 300 mg Q12h and IV 450 mg Q12h, respectively.
- The percent probability of target attainment associated with net bacterial stasis was 96.5% for all *S. aureus* isolates including 92.8% and 99.2% for MRSA and MSSA isolates, respectively. The percent probabilities of PK/PD target attainment for *S. aureus* at an MIC value of (b) (4) mcg/mL were 90.8% and 86.7% on treatment Days 1 and 4, respectively.
- The Applicant has proposed an intermediate MIC BP of (b) (4) mcg/ml for *S.aureus* and related species. However, no isolate was recovered with this MIC-level in clinical studies; therefore efficacy information is not available at this time.

Reviewer's comment: Against all S. aureus isolates (including both MRSA and MSSA) from clinical and surveillance studies, the MIC_{90} of delafloxacin was ≤0.25 mcg/mL. There were only 4 S. aureus (3 MRSA and 1 MSSA) isolates with an MIC 0.5 mcg/mL in the delafloxacin arm (319 subjects with baseline S. aureus isolates) in clinical studies. Among them, 3(75%) isolates were presumed eradicated and 1(25%) isolate persisted at the end of treatment.

The Applicant-proposed susceptible breakpoint of (b) (4) mcg/mL would be inappropriate as there is limited clinical data at this MIC. A susceptible breakpoint of 0.25 mcg/mL would be more appropriate based on in vitro MIC data, clinical experience and microbiological eradication at the end of treatment. The PK/PD target attainment data were also supportive in determining the S. aureus breakpoints. Monte Carlo simulation analysis predicted that almost 100% of simulated patients will achieve target attainment at an MIC value of 0.25 mcg/mL. This will allow setting the intermediate BP at 0.5 mcg/mL which will provide target attainment of >90% and will accommodate inter laboratory testing variability related with AST.

Based on in vitro MIC data, clinical experience and presumed microbiological eradication at the end of treatment, and PTA, this Reviewer recommends MIC BPs of S/I/R as ≤ 0.25/ 0.5 / ≥ 1 mcg/mL and disk diffusion BPs as ≥ 23/20-22/≤ 19 mm (Figure G13 in Appendix G).

Staphylococcus haemolyticus
The Applicant proposed the following breakpoints for *S. haemolyticus*:

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
S. haemolyticus	(b) (4) Susceptible (b) (4) Intermediate (b) (4) Resistant	(b) (4) Susceptible Intermediate Resistant

MIC = minimum inhibitory concentration
[a] Delafloxacin 5-µg disk

The following rationale was provided by the Applicant:

- A susceptible breakpoint of ≤ (b) (4) mcg/mL is predicted to cover 89.0% of contemporary *S. haemolyticus* isolates and 90.9% of contemporary *S. haemolyticus* isolates from skin and soft-tissue infections.
- When microbiological outcomes were tabulated by MIC for clinical study isolates (MEFUI population, Pool 1), 100% efficacy (12/12) of delafloxacin was observed for isolates up to and including a delafloxacin MIC of (b) (4) mcg/mL.
- The Applicant has proposed an intermediate BP of (b) (4) mcg/ml for *S. haemolyticus*. A single isolate with this MIC value was isolated which was eradicated and considered as success in clinical studies.

Reviewer's comment: The MIC_{90} for delafloxacin against coagulase negative S. haemolyticus from clinical (n=24) and surveillance studies (n=100) were 0.5 and 1.0 mcg/mL respectively. The MIC ranged from 0.008-8 mcg/mL in the clinical studies and ≤0.004->1.0 mcg/mL in the surveillance studies. Although clinical success and presumed microbiological eradication were achieved with all isolates, 12/15 (80%) isolates had delafloxacin MIC of 0.25 mcg/mL. The pre-clinical PK-PD was not available for S. haemolyticus. A susceptible breakpoint of 0.25 mcg/mL would be more appropriate. This will allow setting the intermediate BP at 0.5 mcg/mLl and resistant breakpoint at 1.0 mcg/mL.

Based on in vitro MIC data, clinical experience and microbiological eradication at the end of treatment, this Reviewer recommends MIC BPs of S/I/R as ≤ 0.25/ 0.5 / ≥ 1 mcg/mL and disk diffusion BPs as ≥ 24/21-23/≤ 20 mm (Figure G16 in Appendix G).

(b) (4)

(b) (4)

[redacted]

Streptococcus pyogenes

The Applicant proposed the following breakpoints for *S. pyogenes*:

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
S. pyogenes	(b) (4) Susceptible Resistant	(b) (4) Susceptible Resistant

MIC = minimum inhibitory concentration
[a] Delafloxacin 5-µg disk

The following rationale was provided by the Applicant:

- A susceptible breakpoint of ≤ (b) (4) mcg/mL is predicted to cover 100% of contemporary *S. pyogenes* isolates and 100% of contemporary *S. pyogenes* isolates from skin and soft-tissue infections.
- The highest delafloxacin MIC value among surveillance isolates of *S. pyogenes* was 0.06 mcg/mL.
- When microbiological outcomes were tabulated by MIC for clinical study isolates (MEFUI population, Pool 1), 94.7% efficacy (18/19) of delafloxacin was observed for isolates up to and including delafloxacin MIC values of 0.06 mcg/mL. Clinical study isolates with MIC values > 0.06 mcg/mL were not observed.

Reviewer's comment: The MIC_{90} for delafloxacin against S. pyogenes isolates from clinical (n=46) and surveillance studies (n=902) were 0.06 and 0.015 mcg/mL respectively. The MIC ranged from 0.008-0.06 mcg/mL in the clinical studies and ≤0.004-0.06 mcg/mL in the surveillance studies. The clinical success and presumed microbiological eradication were achieved in 21/23(91.3%) isolates up to and including delafloxacin MIC values of 0.06 mcg/mL. The pre-clinical PK-PD data were not available for S. pyogenes, however, the Applicant presumed that it would be similar to S. aureus.

In absence of pre-clinical PK-PD data, this reviewer relied on in vitro MIC data, clinical experience and presumed microbiological eradication at the end of treatment, to determine the breakpoints for S. pyogenes. The Agency recommends a susceptible only breakpoint at ≤ 0.06 mcg/mL for S. pyogenes. No resistant breakpoints are proposed since clinical and surveillance data for these isolates indicate the absence or rare occurrence of resistant isolates. Therefore, isolates above the susceptible breakpoint should be reported as non-susceptible. Thus, only a susceptible breakpoint has been recommended. This Reviewer recommends a susceptible only disk diffusion zone diameter of ≥ 20 mm (Figure G17 in Appendix G).

Streptococcus agalactiae

The Applicant proposed the following breakpoints for *S. agalactiae:*

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
S. agalactiae	(b) (4) Susceptible Resistant	(b) (4) Susceptible Resistant

MIC = minimum inhibitory concentration
[a] Delafloxacin 5-µg disk

The following rationale was provided by the Applicant:

- A susceptible breakpoint of ≤ (b) (4) mcg/mL is predicted to cover 99.4% of contemporary *S. agalactiae* isolates and 99.5% of contemporary *S. agalactiae* isolates from skin and soft-tissue infections.
- When microbiological outcomes were tabulated by MIC for clinical study isolates (MEFUI population, Pool 1), 100% efficacy (11/11) of delafloxacin was observed for isolates up to and including delafloxacin MIC values of 0.03 mcg/mL.

- No specific efficacy or PD studies were conducted with *S. agalactiae*. However, the Applicant believes that based upon PK/PD target attainment for *S. aureus*, both the IV (300 mg Q12h) and oral (450 mg Q12h) formulations, should provide sufficient exposure to cover *S. agalactiae* isolates with MIC values of ≤ (b) (4) mcg/mL.

Reviewer's comment: The MIC_{90} of S. agalactiae isolates from clinical (n=27) and surveillance studies (n=477) were 0.06 and 0.03 mcg/mL respectively. The MIC ranged from 0.015-0.06 mcg/mL in the clinical studies and ≤0.004->0.5 mcg/mL in the surveillance studies. The clinical success and presumed microbiological eradication were achieved with all (100%) isolates up to and including delafloxacin MIC values of 0.03 mcg/mL. Similar to S. pyogenes, the pre-clinical PK-PD data was not available for S. agalactiae, however the Applicant presumed that it would be similar to S. aureus.

Based on in vitro MIC data from clinical and surveillance isolates, clinical experience, and the absence of PK-PD data, the Agency recommends a revised MIC BPs of S/I/R as ≤ 0.06/0.12/≥ 0.25 mcg/mL for S. agalactiae.

The Agency does not recommend disk diffusion BPs at this time due to the absence of S. agalactiae-specific disk-diffusion data. The scatterplots provided by the Applicant included isolates of S. agalactiae and other beta-hemolytic streptococci. In addition, isolates existed with increased MICs in recent surveillance studies. The Agency can revisit the disk diffusion BPs, once more data are available from post marketing studies.

***Streptococcus anginosus* Group**
The Applicant proposed the following breakpoints for *S. anginosus* Group:

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
S. anginosus Group (*S. anginosus*, *S. intermedius*, and *S. constellatus*)	(b) (4) Susceptible Resistant	(b) (4) Susceptible Resistant

MIC = minimum inhibitory concentration
[a] Delafloxacin 5-µg disk

The following rationale was provided by the Applicant:

- A susceptible breakpoint of ≤ (b) (4) µg/mL is predicted to cover 100% of contemporary *S. anginosus* Group isolates and 100% of contemporary *S. anginosus* Group isolates from skin and soft-tissue infections.
- The highest delafloxacin MIC value among levofloxacin-resistant *S. anginosus* Group isolates is 0.12 mcg/mL suggesting the absence of resistance among these isolates.
- No non-clinical efficacy or PK-PD studies were conducted with *S. anginosus* Group organisms. However, the Applicant believes that based upon PK/PD target attainment for *S. aureus*, both the IV (300 mg Q12h) and oral (450 mg Q12h) formulations, should provide sufficient exposure to cover *S. anginosus* Group isolates with MIC values of ≤ (b) (4) mcg/mL.

Reviewer's comment: The MIC ranged from ≤0.004-0.06 mcg/mL in the clinical study isolates (n=90) and from ≤0.004 to 0.03 mcg/mL among 33 clinical isolates of S. anginosus Group in delafloxacin arm. No clinical experience was available for isolates with MIC >0.03 mcg/mL; therefore efficacy information is not available at this time. The MIC_{90} of delafloxacin against S. anginosus Group in clinical and surveillance studies were 0.03 and 0.015 mcg/mL respectively.

Based on in vitro MIC data, clinical experience and presumed microbiological eradication at the end of treatment, a susceptible only BP of ≤ 0.03 mcg/mL would be more appropriate. In a follow up communication with the Applicant dated 6/7/2017, the Applicant requested to consider a susceptible BP of ≤ 0.06 mcg/mL as using an MIC BP of 0.06 mcg/mL, the potential for a false susceptible disk result would decrease. Using the MIC BP of 0.03 mcg/mL, 2.2% of the evaluated isolates would have been interpreted as susceptible by disk and non-susceptible by broth microdilution. No such discordance would be observed using a broth microdilution breakpoint of 0.06 mcg/mL. The Agency accepted this rationale.

No resistant breakpoints are proposed since clinical and surveillance data for these isolates indicate the absence or rare occurrence of resistant isolates. Therefore, this reviewer recommends that isolates above the susceptible breakpoint should sent to the reference laboratory for further testing.

This Reviewer recommends the susceptible only MIC BP of 0.06 mcg/mL and the disk diffusion susceptible BP of ≥25 mm for S. anginosus Group (Figure G18 in Appendix G).

Enterococcus faecalis

The Applicant proposed following breakpoints for *E. faecalis*:

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
E. faecalis	(b) (4) Susceptible (b) (4) Intermediate (b) (4) Resistant	(b) (4) Susceptible Intermediate Resistant

MIC = minimum inhibitory concentration
[a] Delafloxacin 5-µg disk

The following rationale was provided by the Applicant:

- A susceptible breakpoint of ≤ (b) (4) mcg/mL is predicted to cover 84.4% of contemporary *E. faecalis* isolates and 80.6% of contemporary *E. faecalis* isolates from skin and soft-tissue infections.
- When microbiological outcomes were tabulated by MIC for clinical study isolates (MEFUI population, Pool 1), 90% efficacy (9/10) of delafloxacin was observed for isolates up to a delafloxacin MIC of 2 mcg/mL.

- No non-clinical efficacy or PK-PD studies were conducted with *E. faecalis*. However, based upon PK/PD target attainment for *S. aureus*, the Applicant believes that both the IV (300 mg Q12h) and oral (450 mg Q12h) formulations should provide sufficient exposure to cover *E. faecalis* isolates with MIC values of ≤ (b) (4) mcg/mL.

Reviewer's comment: In absence of pre-clinical PK-PD data and limited clinical data for E. faecalis, the proposed BPs were re-evaluated and adjusted.

The MIC_{90} of E. faecalis isolates from both clinical (n=27) and surveillance studies (n=672) was 1.0 mcg/mL. The MIC ranged from ≤0.004-2 mcg/mL in both clinical and surveillance studies. The clinical success and presumed microbiological eradication were achieved with 8/11(73%) isolates up to and including delafloxacin MIC values of 0.12 mcg/mL. One failure was associated with an isolate at 0.12 mcg/mL and one success was associated with isolate at 2.0 mcg/mL.

The Agency recommends MIC BPs of S/I/R as ≤ 0.12/ 0.25/ ≥ 0.5 mcg/mL would be more appropriate. In a follow up communication received from the Applicant on 6/7/2017, the Agency accepts the Applicant-provided recalculation of disk diffusion BPs of S/I/R as ≥ 21/19-20/≤ 18 mm (Figure G19 in the Appendix G).

Escherichia coli

The Applicant proposed the following breakpoints for *E. coli*:

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
E. coli	≤ 0.25 Susceptible 0.5 Intermediate ≥ 1 Resistant	(b) (4) Susceptible 19- (b) (4) Intermediate ≤ 18 Resistant

MIC = minimum inhibitory concentration
[a] Delafloxacin 5-µg disk

The following rationale was provided by the Applicant:

- A susceptible breakpoint of ≤ 0.25 mcg/mL is predicted to cover 66.6% of contemporary *E. coli* isolates and 68.2% of contemporary *E. coli* isolates from skin and soft-tissue infections.
- A susceptible breakpoint of ≤ 0.25 mcg/mL would be predicted to cover 20.2% of contemporary ESBL *E. coli* isolates and 15.6 % of contemporary ESBL *E. coli* isolates from skin and soft-tissue infections.
- Delafloxacin MIC distributions are bimodal for *E. coli* presumably due to existing resistance to levofloxacin via QRDR mutations and expression of efflux pumps along with frequently concomitant extended-spectrum beta-lactamases.
- However, clinical study data demonstrated that delafloxacin had 100% efficacy against ESBL-positive *E. coli* isolates with delafloxacin MIC values as high as 2 mcg/mL and 1 fluoroquinolone non-susceptible isolate. The proposed delafloxacin breakpoint of 0.25

mcg/mL is predicted to cover *E. coli* isolates in the first mode but would declare isolates in the second mode as delafloxacin-resistant, where isolates already resistant to fluoroquinolones or possible fluoroquinolone resistance concomitant with pre-existing ESBLs would be more likely to be encountered.

- When microbiological outcomes were tabulated by MIC for clinical study isolates (MEFUI population, Pool 1), 100% efficacy (11/11) of delafloxacin was observed for isolates up to a delafloxacin MIC of 2 mcg/mL.
- For *E. coli* clinical isolates, the distribution of isolates was bimodal. The first mode (MIC values of 0.008 to 0.06 mcg/mL) had 100% (9/9) microbiological response rates. The second mode (MIC range of 1 to 2 mcg/mL) had similar efficacy rates of 100% (2/2) (MEFUI population, Pool 1). Two of the isolates in the second mode were shown to be ESBL-positive and 1 isolate was levofloxacin non-susceptible.
- Efficacy of delafloxacin was demonstrated in a neutropenic mouse thigh model of infection with *E. coli* isolates with delafloxacin MIC values of 0.016 and 0.25 mcg/mL.
- The results suggested that bacterial stasis would be achieved at a *f*AUC24/MIC ratio of 14.5, and a 1-log10 bacterial reduction would be achieved at a *f*AUC24/MIC ratio of 26.2.
- The human PK of delafloxacin as determined in a Phase 3 study in patients with ABSSSI (RX-3341-302), was used to estimate the percent probability of *f*AUC24/MIC target attainment with delafloxacin 300 mg IV, BID, over a wide range of MIC values. The stasis target has been previously shown to be predictive of clinical efficacy in patients with ABSSSI. For bacterial stasis, the probability of mean target attainment was ≥ 97.8% for MIC values up to and including 0.25 mcg/mL.
- When microbiological outcomes were tabulated by MIC for clinical study isolates, 100% eradication (11/11) of delafloxacin was observed for *E. coli* isolates up to a delafloxacin MIC of 2 mcg/mL.
- The Applicant proposed an intermediate BP of 0.5 mcg/ml for *E. coli* and other Enterobacteriaceae. However, no *E. coli*, or *K. pneumoniae* isolate was recovered at this MIC-level in clinical studies.

Reviewer's comment: The clinical experience with E. coli and other indicated gram-negative pathogens was very limited in clinical studies. While E. coli was recovered at baseline from 14 subjects in delafloxacin arm in clinical studies, they were mostly associated with polymicrobial infections. The MIC_{90} of delafloxacin against E. coli isolates from both clinical and surveillance studies were 4 mcg/mL. The MIC ranged from 0.008-4 mcg/mL in clinical studies (n=35) and ≤ 0.004 - > 4 mcg/mL in surveillance studies (n=1031).

This Reviewer agrees with the Applicant proposed MIC BPs of ≤ 0.25(S)/0.5(I)/≥ 1.0(R) mcg/mL for E. coli. Data from surveillance studies, clinical studies, and PK/PD analysis together support this BPs.

In a follow up communication received from the Applicant on 6/7/2017, the Agency accepts the Applicant-provided recalculation of disk diffusion BPs of S/I/R as ≥ (b)(4)/19- (b)(4)/≤ 18 mm for

Enterobacteriaceae (E. coli, K. pneumoniae, and E. cloacae) (Figure G20 in the Appendix G).

Klebsiella pneumoniae

The Applicant proposed the following breakpoints for *K. pneumoniae*:

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
K. pneumoniae	≤ 0.25 Susceptible 0.5 Intermediate ≥ 1 Resistant	≥ (b) (4) Susceptible 19- (b) (4) Intermediate ≤ 18 Resistant

MIC = minimum inhibitory concentration
[a] Delafloxacin 5-µg disk

The following rationale was provided by the Applicant:

- A susceptible breakpoint of ≤ 0.25 mcg/mL is predicted to cover 66.5% of contemporary *K. pneumoniae* isolates and 64.5% of contemporary *K. pneumoniae* isolates from skin and soft-tissue infections.
- Delafloxacin MIC distributions are bimodal for *K. pneumoniae* isolates. The proposed delafloxacin breakpoint of 0.25 mcg/mL would cover *K. pneumoniae* isolates in the first mode but would be resistant to isolates in the second mode as delafloxacin-resistant, where QRDR mutations and ESBLs would more likely occur.
- When microbiological outcomes were tabulated by MIC for clinical study isolates (MEFUI population Pool 1), 100% efficacy (17/17) of delafloxacin was observed for isolates up to a delafloxacin MIC of 4 mcg/mL.
- For *K. pneumoniae* clinical isolates, the isolates were distributed between 0.03 to 4 mcg/mL and had 100% microbiological response rates (MEFUI population, Pool 1).
- Efficacy of delafloxacin was demonstrated in a neutropenic mouse thigh model of infection with *K. pneumoniae* isolates with delafloxacin MIC values of 0.06 to mcg/mL.
- Based upon PK/PD target attainment for *E. coli*, both the IV (300 mg Q12h) and oral (450 mg Q12h) formulations, should provide sufficient exposure to cover *K. pneumoniae* isolates with MIC values of ≤ 0.25 mcg/mL.
- When microbiological outcomes were tabulated by MIC for *K. pneumoniae* clinical isolates, 100% eradication (17/17) of delafloxacin was observed for isolates up to a delafloxacin MIC of 4 µg/mL.

Reviewer's comment: As mentioned earlier, the clinical experience with K. pneumoniae and other indicated gram-negative pathogens was very limited in clinical studies. While K. pneumoniae was recovered as baseline from 22 subjects in delafloxacin arm in clinical studies, they were mostly associated with polymicrobial infections. All of them were eradicated at the end of treatment. The MIC values for these clinical isolates were as follows: 4 at 0.03 mcg/mL; 3 at 0.06 mcg/mL; 11 at 0.12 mcg/mL; 3 at 0.25 mcg/mL; and 1 at 4 mcg/mL. The MIC_{90} of delafloxacin against K. pneumoniae in clinical and surveillance studies were 0.25 and >4

mcg/mL respectively. The MIC ranged from 0.03-4 mcg/mL in clinical studies (n=45) and ≤ 0.004 - > 4 mcg/mL in surveillance studies (n=800).

This Reviewer agrees with the Applicant proposed MIC BPs of ≤ 0.25(S)/0.5(I)/≥ 1.0(R) mcg/mL for E. coli. Data from surveillance studies, clinical studies, and PK/PD analysis together support this BPs.

In a follow up communication received from the Applicant on 6/7/2017, the Agency accepts the Applicant-provided recalculation of disk diffusion BPs of S/I/R as ≥ (b)(4)/19- (b)(4)/≤ 18 mm for Enterobacteriaceae (E. coli, K. pneumoniae, and E. cloacae) (Figure G20 in the Appendix G).

Enterobacter cloacae

The Applicant proposed the following breakpoints for *E. cloacae*:

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
E. cloacae	≤ 0.25 Susceptible 0.5 Intermediate ≥ 1 Resistant	≥ (b)(4) Susceptible 19- Intermediate ≤ 18 Resistant

MIC = minimum inhibitory concentration
[a] Delafloxacin 5-µg disk

The following rationale was provided by the Applicant:

- A susceptible breakpoint of ≤ 0.25 mcg/mL is predicted to cover 84.7% of contemporary. *E. cloacae* isolates and 89.6% of contemporary *E. cloacae* isolates from skin and soft-tissue infections.
- When microbiological outcomes were tabulated by MIC for clinical study isolates (MEFUI population, Pool 1), 91.6% efficacy (11/12) of delafloxacin was observed for isolates up to a delafloxacin MIC of 4 mcg/mL.
- Based upon PK/PD target attainment for *E. coli*, both the IV (300 mg Q12h) and oral (450 mg Q12h) formulations, should provide sufficient exposure to cover *E. cloacae* isolates with MIC values of ≤ 0.25 mcg/mL.
- When microbiological outcomes were tabulated by MIC for *E. cloacae* clinical study isolates, 91.6% eradication (11/12) of delafloxacin was observed for isolates up to a delafloxacin MIC of 4 µg/mL.

Reviewer's comment: As mentioned earlier, the clinical experience with E. cloacae and other indicated gram-negative pathogens was very limited in clinical studies. While E. cloacae was recovered at baseline from 14 subjects in delafloxacin arm in clinical studies, they were mostly associated with polymicrobial infections. All of them were presumed to be eradicated at the end of treatment. The MIC values for these clinical isolates were as follows: 1 at 0.03 mcg/mL; 4 at 0.06 mcg/mL; 6 at 0.12 mcg/mL; 1 at 0.5 mcg/mL; 1 at 2 mcg/mL; and 1 at 4 mcg/mL. The MIC_{90} of delafloxacin against E. cloacae in clinical and surveillance studies were 2 and 1

mcg/mL respectively. The MIC ranged from 0.03->8 mcg/mL in clinical studies (n=26) and ≤ 0.004 - > 4 mcg/ml in surveillance studies (n=439).

This Reviewer agrees with the Applicant proposed MIC BPs of ≤ 0.25(S)/0.5(I)/≥ 1.0(R) mcg/mL for E. cloacae. Data from surveillance studies, clinical studies, and PK/PD analysis together support this BPs.

In a follow up communication received from the Applicant on 6/7/2017, the Agency accepts the Applicant-provided recalculation of disk diffusion BPs of S/I/R as ≥ (b) (4)/19- (b) (4)/≤ 18 mm for Enterobacteriaceae (E. coli, K. pneumoniae, and E. cloacae) (Figure G20 in the Appendix G).

Enterobacteriaceae (E. coli, K. pneumoniae, and E. cloacae only): *The Agency recommends using Enterobacteriaceae as a group for E. coli, K. pneumoniae, and E. cloacae isolates since all of them have identical MIC and disk diffusion BPs.*

Pseudomonas aeruginosa

The Applicant proposed the following breakpoints for *P. aeruginosa*:

Organism	MIC (µg/mL)	Zone Diameter[a] (mm)
P. aeruginosa	≤ 0.5 Susceptible	≥ (b) (4) Susceptible
	1 Intermediate	(b) (4) Intermediate
	≥ 2 Resistant	≤ (b) (4) Resistant

MIC = mininum inhibitory concentration
[a] Delafloxacin 5-µg disk

The following rationale was provided by the Applicant:

- A susceptible breakpoint of ≤ 0.5 mcg/mL is predicted to cover 66.9% of contemporary *P. aeruginosa* isolates and 73.4% of contemporary *P. aeruginosa* isolates from skin and soft-tissue infections.
- When microbiological outcomes were tabulated by MIC for clinical study isolates (MEFUI population, Pool 1), 100% efficacy (11/11) of delafloxacin was observed for isolates up to a delafloxacin MIC of 4 mcg/mL.
- Dose-dependent efficacy of delafloxacin was demonstrated in a neutropenic mouse thigh model of infection with *P. aeruginosa* isolates with delafloxacin MIC values of 0.25 to 2.0 mcg/mL.
- Based upon PK/PD target attainment for *P. aeruginosa*, both the IV (300 mg Q12h) and oral (450 mg Q12h) formulations should provide sufficient exposure to cover *P. aeruginosa* isolates with MIC values of ≤ 0.5 mcg/mL.
- The Applicant proposed an intermediate BP of 1.0 mcg/mL for *P. aeruginosa*. A single isolate with this MIC value was isolated which was eradicated and considered as success in clinical studies. The delafloxacin MIC ranged from 0.12 to >8 mcg/mL and 0.015 to >4 mcg/mL in clinical and surveillance studies respectively. At the proposed intermediate

BP of 1.0 mcg/mL, the PTA analysis for *P. aeruginosa* predicted about 90% PK-PD target attainment in simulated patients.

Reviewer's comment: This Reviewer agrees with the Applicant proposed MIC breakpoints for P. aeruginosa. Data from surveillance studies, clinical studies, and PK/PD analysis together support delafloxacin interpretive criteria of ≤ 0.5(S)/1(I)/≥ 2(R) mcg/mL for P. aeruginosa.

This Reviewer recommends the disk diffusion BPs of S/I/R as ≥23/20-22/≤19 mm (Figure G21 in Appendix G).

LABELING
APPLICANT'S PROPOSED LABELING
Sections 1 and 12 of the package insert are shown below.

1 INDICATION AND USAGE

1.1 Acute Bacterial Skin and Skin Structure Infections
BAXDELA is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive organisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus,* (b) (4) *Staphylococcus lugdunensis, Streptococcus agalactiae*, *Streptococcus anginosus* Group (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) (b) (4)*,* and *Pseudomonas aeruginosa.*

12 CLINICAL PHARMACOLGY

12.1 Mechanism of Action
BAXDELA is an (b) (4) antibacterial (b) (4) [*see Clinical Pharmacology (12.4)*].

12.4 Microbiology
Mechanism of Action
(b) (4) belongs to the fluoroquinolone class of antibacterial drugs and is anionic in nature. The antibacterial activity of (b) (4) is due to the inhibition of bacterial topoisomerase IV and DNA gyrase (topoisomerase II), enzymes required for bacterial DNA replication, transcription, repair, and recombination. (b) (4) exhibits (b) (4) concentration-dependent bactericidal activity against (b) (4) Gram-positive and Gram-negative bacteria in vitro (b) (4)

(b) (4)

(b) (4) **Resistance**

Resistance to fluoroquinolones, including (b) (4), can occur due to mutations in defined regions of the target bacterial enzymes topoisomerase IV and DNA gyrase referred to as Quinolone-Resistance Determining Regions (QRDRs), or through altered efflux.

Fluoroquinolones, including (b) (4), have a different chemical structure and mechanism of action relative to other classes of antibacterial compounds (e.g. aminoglycosides, macrolides, β-lactams, glycopeptides, tetracyclines, and oxazolidinones) (b) (4)

(b) (4)

In vitro resistance to delafloxacin develops (b) (4) by multiple step mutations. (b) (4) (b) (4) delafloxacin-resistant mutants were selected in vitro at (b) (4) ($< 10^{-9}$) frequencies.

Although cross-resistance between (b) (4) and other fluoroquinolone-class antibacterial agents has been observed, some isolates resistant to other fluoroquinolone-class antibacterial agents may be susceptible to BAXDELA.

Interaction with Other Antimicrobial Compounds

In vitro drug combination studies with (b) (4) and aztreonam, ceftazidime, colistin, daptomycin, linezolid, meropenem, tigecycline, trimethoprim/sulfamethoxazole, and vancomycin demonstrated neither synergy nor antagonism.

(b) (4)

BAXDELA has been shown to be active against most isolates of the following (b) (4), both in vitro and in clinical infections, as described in *Indications and Usage (1)*.

(b) (4) **Gram-positive Bacteria**

Staphylococcus aureus (including methicillin-resistant strains)

Staphylococcus haemolyticus

(b) (4)

Staphylococcus lugdunensis

Streptococcus pyogenes

Streptococcus agalactiae

Streptococcus anginosus Group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*)

(b) (4)

Enterococcus faecalis

(b) (4) **Gram-negative Bacteria**

Escherichia coli

Klebsiella pneumoniae

(b) (4)

Enterobacter cloacae

Pseudomonas aeruginosa

The following in vitro data are available, but their clinical significance (b) (4). At least 90% of the following (b) (4) exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to (b) (4). However, the (b) (4) (b) (4) of BAXDELA in treating clinical infections (b) (4) not been established in adequate and well-controlled clinical trials.

Enterobacter aerogenes

Haemophilus parainfluenzae

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of (b) (4) in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas (b) (4) (b) (4) as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid (b) (4) antibacterial drug for treatment.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). (b) (4) (b) (4). The MIC (b) (4) should be determined using a standardized (b) (4) method (b) (4) (broth, agar, (b) (4) (b) (4) (b) (4) The MIC values should be interpreted according to the criteria provided in Table (b) (4)

Diffusion Techniques

Quantitative methods that require measurement of zone (b) (4) (b) (4) also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. Zone (b) (4) should be determined using a standardized (b) (4) (b) (4) (b) (4). This procedure uses paper disks impregnated with 5 mcg of (b) (4) to test the susceptibility of bacteria to (b) (4) (b) (4)

Table (b) (4) Susceptibility Test Interpretive Criteria for BAXDELA

(b) (4)	Minimum Inhibitory Concentrations (µg/mL)			Disk Diffusion Zone Diameter (mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	(b) (4)					
Staphylococcus haemolyticus						
Streptococcus pyogenes	(b) (4)	-		(b) (4)	-	(b) (4)

	Minimum Inhibitory Concentrations (µg/mL)			Disk Diffusion Zone Diameter (mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Streptococcus agalactiae					-	
Streptococcus anginosus Group[a]		-			-	≤ 20
Enterococcus faecalis						
Pseudomonas aeruginosa	≤ 0.5		≥ 2			

S = susceptible; I = intermediate; R = resistant

A report of "Susceptible" indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative drugs, the test should be repeated. This category implies possible clinical in body sites where the drug is physiologically concentrated. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory control to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test Standardized powder should provide the following range of MIC values noted in Table 5. For the diffusion technique using the 5 mcg disk,

Table (b) (4) Acceptable Quality Control Ranges (b) (4)

Quality Control Organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameter in mm)
Staphylococcus aureus ATCC 29213	0.001–0.008	Not applicable
Staphylococcus aureus ATCC 25923	(b) (4)	
Enterococcus faecalis ATCC 29212	0.015–0.12	Not applicable
Streptococcus pneumoniae ATCC 49619	0.004–0.015	29–36
Escherichia coli ATCC 25922	0.008–0.03	28–35
Pseudomonas aeruginosa ATCC 27853	0.12–0.5	23–29
Haemophilus influenzae ATCC 49427	0.00025–0.001	40–51

ATCC = American Type Culture Collection

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AGENCY'S PROPOSED LABELING

Based on the overall review, changes to the microbiology sections of labelling are proposed to the Applicant's package insert. The Agency's proposed labeling is shown on page 7 of this review.

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APPENDIX-A

Table A-1. Summary of Delafloxacin and Levofloxacin Activity Against Common Gram-positive Pathogens During Profiling Studies

Organism	Phenotype	Delafloxacin			Levofloxacin			
		N	MIC_{50}	MIC_{90}	N	MIC_{50}	MIC_{90}	% LVX-R
S. aureus	Overall	2609	0.12	0.5	2609	4	32	62.4
	MSSA	396	≤ 0.004	0.12	396	0.25	8	14.1
	MRSA	2174	0.12	1	2174	8	32	72.2
CoNS	Overall	289	0.015	1	265	0.5	> 32	45.7
	MSCoNS	87	0.008	0.25	80	0.25	8	21.3
	MRCoNS	152	0.25	1	135	8	> 32	64.4
E. faecalis	Overall	298	0.12	2	282	1	> 32	27.3
	VSE	107	0.12	2	91	2	> 32	33.0
	VRE	47	0.25	8	47	2	> 32	44.7
E. faecium	Overall	126	8	> 16	116	> 32	> 32	73.3
	VSE	50	4	> 16	40	> 32	> 32	70.0
	VRE	27	4	16	27	> 32	> 32	70.4
S. pneumoniae	Overall	334	0.008	0.12	331	1	16	19.6
	PSSP[a]	30	0.015	0.25	29	1	16	27.6
	PISP[a]	30	0.015	0.25	29	1	16	27.6
	PRSP[a]	42	0.015	0.25	41	1	16	34.1
S. pyogenes	Overall	189	0.015	0.03	189	0.5	1	0.5
S. agalactiae	Overall	166	0.015	0.06	109	1	2	3.7
S. anginosus Group	Overall	45	0.008	0.03	45	0.5	1	0.0
Viridans Group Streptococci (non-AGS)	Overall	28	0.03	0.06	28	1	2	3.6

AGS = anginosus group streptococci; CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; MIC_{50} = MIC against 50% of the isolates; MIC_{90} = MIC against 90% of the isolates; MRCoNS = methicillin-resistant coagulase-negative staphylococci; MRSA = methicillin-resistant *S. aureus*; MSCoNS = methicillin-susceptible coagulase-negative staphylococci; MSSA = methicillin-susceptible *S. aureus*; PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; PSSP = penicillin-susceptible *S. pneumoniae*; VRE = vancomycin-resistant enterococci; VSE = vancomycin-susceptible enterococci; % LVX-R = percent levofloxacin-resistant

[a] CLSI oral-penicillin breakpoints applied

Source: Preclinical Profiling Appendix 1

Table A-2. Summary of Delafloxacin and Levofloxacin Activity Against Common Gram-negative Pathogens During Profiling Studies

Organism	Phenotype	Delafloxacin			Levofloxacin			
		N	MIC_{50}	MIC_{90}	N	MIC_{50}	MIC_{90}	% LVX-R
E. coli	Overall	239	0.06	8	231	0.12	> 8	42.9
	Non-ESBL	41	0.06	8	40	0.12	> 8	32.5
	ESBL[a]	57	4	> 8	50	> 8	> 8	94.0
K. pneumoniae	Overall	150	0.12	8	150	0.25	> 32	33.3
	Non-ESBL	8	0.06	NA	8	0.12	NA	25.0
	ESBL	34	1	2	34	8	16	52.9
P. mirabilis	Overall	76	0.06	2	76	0.12	> 8	15.8
Enterobacter spp.	Overall	68	0.12	32	68	0.06	> 8	20.6
C. freundii	Overall	42	0.12	16	42	0.06	16	16.7
S. marcescens	Overall	98	1	8	98	0.5	8	12.2
P. aeruginosa	Overall	351	0.5	> 16	351	1	> 32	33.3
	CEPH-S	49	0.5	> 16	49	1	> 32	34.7
	CEPH-R	31	8	> 16	31	32	> 32	77.4
A. baumannii	Overall	61	2	16	61	8	32	55.7
H. influenzae	Overall	466	≤ 0.001	0.004	466	0.015	0.03	NA
H. parainfluenzae	Overall	90	0.008	0.03	90	≤ 0.06	≤ 0.06	NA

CEPH-R = resistant to either ceftazidime or ceftriaxone; CEPH-S = susceptible to either ceftazidime or ceftriaxone; ESBL = phenotypically screen-positive for extended-spectrum beta-lactamases; MIC = minimum inhibitory concentration; MIC_{50} = MIC against 50% of the isolates; MIC_{90} = MIC against 90% of the isolates; NA = not applicable; non-ESBL = phenotypically screen-negative for extended-spectrum beta-lactamases; % LVX-R = percent levofloxacin-resistant

[a] Isolates phenotypically screen-positive for ESBL had an MIC > 2 µg/mL for ceftazidime or ceftriaxone (CLSI M100-S26).

Source: Preclinical Profiling Appendix 1

Table A-3. Delafloxacin and Levofloxacin Activity Against Gram-positive 2014-2015 Surveillance Isolates

Organism	Type	N	Delafloxacin		Levofloxacin		
			MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	% LVX-R
S. aureus	Overall	2606	≤ 0.004	0.25	0.25	> 4	33.7
	MSSA	1548	≤ 0.004	0.015	0.25	1	9.1
	MRSA	1058	0.12	1	4	> 4	69.8
CoNS[a]	Overall	744	0.015	0.5	0.25	> 4	36.0
	MSCoNS	345	0.008	0.03	0.25	1	7.5
	MRCoNS	399	0.12	1	4	> 4	60.7
E. faecalis	Overall	672	0.12	1	1	> 4	27.5
	VSE	661	0.06	1	1	> 4	26.3
	VRE	11	0.5	1	> 4	> 4	100.0
E. faecium	Overall	373	> 4	> 4	> 4	> 4	80.2
	VSE	170	> 4	> 4	> 4	> 4	75.3
	VRE	203	> 4	> 4	> 4	> 4	100.0
S. pneumoniae	Overall	939	0.015	0.03	1	1	1.1
	PSSP[b]	606	0.015	0.03	1	1	0.5
	PISP[b]	245	0.008	0.015	1	1	2.0
	PRSP[b]	88	0.015	0.03	1	1	2.3
S. pyogenes	Overall	902	0.008	0.015	0.5	1	0.1
S. agalactiae	Overall	477	0.015	0.03	0.5	1	2.1
S. dysgalactiae	Overall	303	0.008	0.015	0.5	1	0.7
VGS[c]	Overall	625	0.015	0.06	1	2	5.1
S. anginosus Group[d]	Overall	213	0.008	0.015	0.5	0.5	0.9
S. mitis Group[e]	Overall	268	0.03	0.06	1	2	6.7

CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; MIC_{50} = MIC against 50% of the isolates; MIC_{90} = MIC against 90% of the isolates; MRCoNS = methicillin-resistant coagulase-negative staphylococci; MRSA = methicillin-resistant *S. aureus*; MSCoNS = methicillin-susceptible coagulase-negative staphylococci; MSSA = methicillin-susceptible *S. aureus*; PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; PSSP = penicillin-susceptible *S. pneumoniae*; VGS = Viridans Group streptococci; VRE = vancomycin-resistant enterococci; VSE = vancomycin-susceptible enterococci; % LVX-R = percent levofloxacin-resistant

[a] Includes *Staphylococcus auricularis* (1), *S. capitis* (30), *S. caprae* (5), *S. condimenti* (2), *S. epidermidis* (290), *S. haemolyticus* (100), *S. hominis* (120), *S. lugdunensis* (128), *S. pasteuri* (1), *S. pettenkoferi* (3), *S. pseudintermedius/intermedius/delphini* (3), *S. saprophyticus* (15), *S. sciuri* (1), *S. simulans* (32), *S. warneri* (13).

[b] CLSI oral-penicillin breakpoints were applied for interpretation of penicillin phenotype.

[c] Includes *S. anginosus* (131), *S. anginosus group* (20), *S. australis* (5), *S. bovis* group (2), *S. constellatus* (40), *S. cristatus* (8), *S. equinus* (1), *S. gallolyticus* (22), *S. gordonii* (13), *S. infantarius* (1), *S. infantis* (6), *S. intermedius* (22), *S. lutetiensis* (4), *S. massiliensis* (1), *S. mitis* (21), *S. mitis* group (26), *S. mitis/oralis* (111), *S. mutans* (9), *S. oralis* (90), *S. parasanguinis* (37), *S. salivarius* (17), *S. salivarius* group (13), *S. sanguinis* (21), *S. vestibularis* (4).

[d] Includes *S. anginosus* (131), *S. anginosus* group (20), *S. constellatus* (40), *S. intermedius* (22).

[e] Includes *S. australis* (5), *S. cristatus* (8), *S. infantis* (6), *S. massiliensis* (1), *S. mitis* (21), *S. mitis group* (26), *S. mitis/oralis* (111), *S. oralis* (90)

Source: Surveillance Studies Appendix 2.1 to 2.8; MB-3341-050 Table 10 to 11, Table 13 to 23,Table 25 to 28; MB-3341-051 Table 10 and 11, Table 13 to 23, Table 25 to 28; MB-3341-061 Table 11 to 12, Table 14 to 15, Table 22 to 27, Table 29, Table 34 and 35; MB-3341-062 Table 11 to 12, Table 14 to 15, Table 22 to 27, Table 29, Table 34 and 35

Table A-4. Delafloxacin and Levofloxacin Activity Against Gram-negative 2014-2015 Surveillance Isolates

Organism	Type	N	Delafloxacin		Levofloxacin		
			MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	% LVX-R
E. coli	Overall	1031	0.06	4	≤ 0.12	> 4	29.3
	Non-ESBL	838	0.03	4	≤ 0.12	> 4	18.9
	ESBL[a]	193	2	> 4	> 4	> 4	74.6
K. pneumoniae	Overall	800	0.12	> 4	≤ 0.12	> 4	19.6
	Non-ESBL	564	0.06	0.25	≤ 0.12	0.25	1.6
	ESBL	236	> 4	> 4	> 4	> 4	62.7
	CSE	720	0.06	> 4	≤ 0.12	0.25	11.7
	CRE	80	> 4	> 4	> 4	> 4	62.7
P. mirabilis	Overall	480	0.06	2	≤ 0.12	> 4	17.7
	Non-ESBL	446	0.06	2	≤ 0.12	> 4	13.5
	ESBL	34	2	> 4	> 4	> 4	73.5
Enterobacter spp.[b]	Overall	863	0.06	1	≤ 0.12	0.5	4.4
Citrobacter spp.[c]	Overall	370	0.06	2	≤ 0.12	0.5	3.2
Serratia spp.[d]	Overall	361	1	2	≤ 0.12	1	1.9
Providencia spp.[e]	Overall	127	0.5	2	0.5	> 4	10.2
M. morganii	Overall	204	0.12	4	≤ 0.12	> 4	12.7
P. aeruginosa	Overall	302	0.25	> 4	0.5	> 4	18.5
	CAZ-S	245	0.25	4	0.5	> 4	11.0
	CAZ-R	42	4	> 4	4	> 4	50.0
A. baumannii-calcoaceticus complex	Overall	129	4	> 4	> 4	> 4	69.0
H. influenzae	Overall	295	≤ 0.001	0.004	≤ 0.015	≤ 0.015	NA
H. parainfluenzae	Overall	44	0.004	0.015	0.03	0.12	NA

CAZ-R = ceftazidime-resistant; CAZ-S = ceftazidime-susceptible; CRE = carbapenem-resistant Enterobacteriaceae; CSE = carbapenem-susceptible Enterobacteriaceae; ESBL = ESBL phenotype screen-positive; MIC = minimum inhibitory concentration; MIC_{50} = MIC against 50% of the isolates; MIC_{90} = MIC against 90% of the isolates; N = number of isolates; NA = not applicable (resistance breakpoint not available; all isolates were susceptible to levofloxacin); non-ESBL = ESBL phenotype screen-negative

[a] Determination of ESBL-positive phenotype was based on isolates with MIC values > 2µg/mL for ceftazidime or ceftriaxone or aztreonam

[b] Includes *Cronobacter sakazakii* (2), *E. aerogenes* (223), *E. amnigenus* (2), *E. asburiae* (7), *E. cancerogenus* (1), *E. cloacae* (439), *E. cloacae* species complex (185), *E. gergoviae* (2), *E. kobei* (1), *E. radicincitans* (1).

[c] Includes *Citrobacter amalonaticus* (10), *C. amalonaticus/farmeri* (1), *C. braakii* (14), *C. freundii* (144), *C. freundii* species complex (56), *C. koseri* (139), *C. werkmanii* (2), *C. youngae* (4).

[d] Includes *Serratia liquefaciens* (11), *S. marcescens* (345), *S. odorifera* (3), *S. plymuthica* (1), *S. rubidaea* (1).

[e] Includes *Providencia rettgeri* (58), and *P. stuartii* (69).

Source: Surveillance Studies Appendix 2.9-2.21, MB-3341-050 Table 31 to 35, Table 39 to 43, Table 45 to 47, Table 49, Table 51 to 52, Table 54 to 57; MB-3341-051 Table 31 to 35, Table 39 to 43, Table 45 to 47, Table 49, Table 51 to 52, Table 54 to 57; MB-3341-061 Table 37, Table 40, Table 42, Table 44 to 45, Table 47 to 49, Table 53 to 58, Table 60 to 63, Table 65 to 68; MB-3341-062 Table 37, Table 40, Table 42, Table 44 to 45, Table 47 to 49, Table 53 to 58, Table 60 to 63, Table 65 to 68

APPENDIX-B

Table B-1. Spontaneous Mutation Frequencies of Delafloxacin and Comparators against *S.aureus*

Isolate (mutation)	Phenotype	Selection	Inoculum (CFU)	Mutation Frequency			Source
				Delafloxacin	Ciprofloxacin or Levofloxacin[a]	Moxifloxacin	
S. aureus ATCC 25923	MSSA, FQ-S	2X MIC	1.41×10^{10}	TNTC	ND	1.08×10^{-7}	RD-03-066
		4X MIC	1.41×10^{10}	2.6×10^{-8}	1.42×10^{-10}	$< 1.41 \times 10^{-10}$	
		8X MIC	1.41×10^{10}	$< 1.41 \times 10^{-10}$	$< 1.41 \times 10^{-10}$	$< 1.41 \times 10^{-10}$	
		16X MIC	1.41×10^{10}	$< 1.41 \times 10^{-10}$	ND	ND	
S. aureus ATCC 29213	MSSA, FQ-S	2X MIC	3.6×10^{10}	TNTC	ND	TNTC	RD-03-066
		4X MIC	3.6×10^{10}	TNTC	1×10^{-8}	1.5×10^{-9}	
		8X MIC	3.6×10^{10}	2.35×10^{-7}	2.5×10^{-10}	7.5×10^{-10}	
		16X MIC	3.6×10^{10}	2×10^{-9}	ND	ND	
S. aureus 6/2926	MRSA; FQ-S	2X MIC	1.05×10^{10}	9.5×10^{-11}	2.0×10^{-8}	$< 9.5 \times 10^{-11}$	MB-3341-008A1, Remy, 2012
		4X MIC	1.05×10^{10}	$< 9.5 \times 10^{-11}$	$< 9.5 \times 10^{-11}$	$< 9.5 \times 10^{-11}$	
		8X MIC	1.05×10^{10}	$< 9.5 \times 10^{-11}$	$< 9.5 \times 10^{-11}$	$< 9.5 \times 10^{-11}$	
S. aureus 5589 [(*grlA* Ser80Phe)]	FQ-R	2X MIC	1.08×10^{11}	TNTC	ND	ND	RD-03-066
		4X MIC	1.08×10^{11}	1.3×10^{-8}	7×10^{-9}	7×10^{-9}	
		8X MIC	1.08×10^{11}	5×10^{-9}	$< 1.08 \times 10^{-11}$	9.6×10^{-10}	
		16X MIC	1.08×10^{11}	2×10^{-9}	ND	ND	
S. aureus 3384 [*gyrA* (Ser84Leu), *grlA* (Ser80Phe)]	FQ-R	2X MIC	2.37×10^{10}	TNTC	ND	5.25×10^{-8}	RD-03-066
		4X MIC	2.37×10^{10}	TNTC	ND	$< 2.37 \times 10^{-10}$	
		8X MIC	2.37×10^{10}	$< 2.37 \times 10^{-10}$	ND	$< 2.37 \times 10^{-10}$	
		16X MIC	2.37×10^{10}	$< 2.37 \times 10^{-10}$	ND	ND	

Isolate (mutation)	Phenotype	Selection	Inoculum (CFU)	Mutation Frequency			Source
				Delafloxacin	Ciprofloxacin or Levofloxacin[a]	Moxifloxacin	
S. aureus 7/14990 [*gyrA* (Ser84Val), *grlA* (Ser80Phe)]	MRSA; FQ-R	2X MIC	2.35×10^{11}	2.1×10^{-9}	$< 4.3 \times 10^{-12}$	$< 4.3 \times 10^{-12}$	MB-3341-008A1, Remy 2012
		4X MIC	2.35×10^{11}	$< 4.3 \times 10^{-12}$	$< 4.3 \times 10^{-12}$	$< 4.3 \times 10^{-12}$	
		8X MIC	2.35×10^{11}	$< 4.3 \times 10^{-12}$	$< 4.3 \times 10^{-12}$	$< 4.3 \times 10^{-12}$	
S. aureus 8/700699 [*gyrA* (Ser84Leu, Glu409Lys), *grlA* (Ser80Phe)]	MRSA; FQ-R	2X MIC	7×10^{9}	$< 1.4 \times 10^{-10}$	ND	5.7×10^{-10}	MB-3341-008A1, Remy 2012
		4X MIC	7×10^{9}	$< 1.4 \times 10^{-10}$	ND	$< 1.4 \times 10^{-10}$	
		8X MIC	7×10^{9}	$< 1.4 \times 10^{-10}$	ND	$< 1.4 \times 10^{-10}$	
S. aureus 9/14490 [*gyrA* (Ser84Leu), *grlA* (Ser80Tyr, Glu84Gly)]	MRSA; FQ-R	2X MIC	7×10^{9}	6.0×10^{-9}	ND	7.1×10^{-8}	MB-3341-008A1, Remy 2012
		4X MIC	7×10^{9}	$< 1.4 \times 10^{-10}$	ND	4.4×10^{-9}	
		8X MIC	7×10^{9}	$< 1.4 \times 10^{-10}$	ND	$< 1.4 \times 10^{-10}$	
S. aureus 10/ACH0231[b] [*gyrA* (Ser84Leu, Glu88Lys), *grlA* (Ser80Tyr, Glu84Gly)]	MRSA; FQ-R	2X MIC	2.75×10^{11}	$< 3.6 \times 10^{-12}$	ND	ND	MB-3341-008A1, Remy 2012
		4X MIC	2.75×10^{11}	$< 3.6 \times 10^{-12}$	ND	ND	
		8X MIC	2.75×10^{11}	$< 3.6 \times 10^{-12}$	ND	ND	
S. aureus ATCC 29213	MSSA; FQ-S	4X MIC	2.00×10^{9}	$< 5.00 \times 10^{-10}$	$< 5.00 \times 10^{-10}$	ND	MB-3341-074
		8X MIC	2.00×10^{9}	$< 5.00 \times 10^{-10}$	$< 5.00 \times 10^{-10}$	ND	
		16X MIC	2.00×10^{9}	$< 5.00 \times 10^{-10}$	$< 5.00 \times 10^{-10}$	ND	
S. aureus ATCC 25923	MSSA; FQ-S	4X MIC	1.80×10^{9}	$< 5.56 \times 10^{-10}$	$< 5.56 \times 10^{-10}$	ND	MB-3341-074
		8X MIC	1.80×10^{9}	$< 5.56 \times 10^{-10}$	$< 5.56 \times 10^{-10}$	ND	
		16X MIC	1.80×10^{9}	$< 5.56 \times 10^{-10}$	$< 5.56 \times 10^{-10}$	ND	

Isolate (mutation)	Phenotype	Selection	Inoculum (CFU)	Mutation Frequency			Source
				Delafloxacin	Ciprofloxacin or Levofloxacin[a]	Moxifloxacin	
S. aureus MMX 6500	MSSA; FQ-S	4X MIC	2.05×10^{9}	$< 4.88 \times 10^{-10}$	$< 4.88 \times 10^{-10}$	ND	MB-3341-074
		8X MIC	2.05×10^{9}	$< 4.88 \times 10^{-10}$	$< 4.88 \times 10^{-10}$	ND	
		16X MIC	2.05×10^{9}	$< 4.88 \times 10^{-10}$	$< 4.88 \times 10^{-10}$	ND	

CFU = colony-forming unit; FQ-R = fluoroquinolone-resistant; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin susceptible *S. aureus*, ND = not determined; TNTC = too numerous to count
[a] In RD-03-066, ciprofloxacin was used; in MB-3341-008A1 and MB-3341-074 levofloxacin was used.
[b] Reserpine was used during selection.
Source: RD-03-066 Table 1; MB-3341-008A1 Table 3; MB-3341-074 Table 2; Remy 2012[35]

Table B-2. Spontaneous Mutation Frequencies of Delafloxacin and Comparators Against *E. faecalis*

Isolate (mutation)	Phenotype	Selection	Inoculum (CFU)	Mutation Frequency		
				Delafloxacin	Ciprofloxacin	Moxifloxacin
E. faecalis ATCC 29212	FQ-S	2X MIC	5.2×10^9	2.74×10^{-7}	$< 5.2 \times 10^{-9}$	3.85×10^{-10}
		4X MIC	5.2×10^9	$< 5.2 \times 10^{-9}$	$< 5.2 \times 10^{-9}$	$< 5.2 \times 10^{-9}$
		8X MIC	5.2×10^9	$< 5.2 \times 10^{-9}$	$< 5.2 \times 10^{-9}$	$< 5.2 \times 10^{-9}$
		16X MIC	5.2×10^9	$< 5.2 \times 10^{-9}$	ND	ND

CFU = colony-forming unit; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration; ND = not determined
Source: RD-03-066 Table 1

Table B-3. Spontaneous Mutation Frequencies of Delafloxacin and Comparators Against *S. pneumoniae*

Isolate [mutation]	Phenotype	Selection	Inoculum (CFU)	Mutation Frequency		
				Delafloxacin	Ciprofloxacin	Moxifloxacin
S. pneumoniae ATCC 49619	FQ-S	1X MIC	3.3×10^9	3.3×10^{-9}	ND	ND
		2X MIC	3.3×10^9	$< 3.3 \times 10^{-9}$	ND	$< 3.3 \times 10^{-9}$
		4X MIC	3.3×10^9	$< 3.3 \times 10^{-9}$	$< 3.3 \times 10^{-9}$	$< 3.3 \times 10^{-9}$
		8X MIC	3.3×10^9	$< 3.3 \times 10^{-9}$	$< 3.3 \times 10^{-9}$	$< 3.3 \times 10^{-9}$
		16X MIC	3.3×10^9	$< 3.3 \times 10^{-9}$	ND	ND
S. pneumoniae 7215 [*parC* (Ser79-Phe)]	FQ-R	1X MIC	5.4×10^9	7.9×10^{-8}	ND	ND
		2X MIC	5.4×10^9	1.85×10^{-10}	ND	$< 5.4 \times 10^{-9}$
		4X MIC	5.4×10^9	$< 5.4 \times 10^{-9}$	$< 5.4 \times 10^{-9}$	$< 5.4 \times 10^{-9}$
		8X MIC	5.4×10^9	$< 5.4 \times 10^{-9}$	$< 5.4 \times 10^{-9}$	$< 5.4 \times 10^{-9}$
		16X MIC	5.4×10^9	$< 5.4 \times 10^{-9}$	ND	ND
S. pneumoniae 7257 [*gyrA* (Ser81-Phe), *parC* (Ser79-Phe)]	FQ-R	2X MIC	8.00×10^9	8.75×10^{-10}	ND	ND
		4X MIC	8.00×10^9	$< 8 \times 10^{-9}$	$< 8 \times 10^{-9}$	$< 8 \times 10^{-9}$
		8X MIC	8.00×10^9	$< 8 \times 10^{-9}$	$< 8 \times 10^{-9}$	$< 8 \times 10^{-9}$
		16X MIC	8.00×10^9	$< 8 \times 10^{-9}$	ND	$< 8 \times 10^{-9}$

CFU = colony-forming unit; FQ-R = fluoroquinolone-resistant; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration; ND = not determined
Source: RD-03-066 Table 1

Table B-4. Spontaneous Mutation Frequencies of Delafloxacin and Comparators Against *E. coli* and *K. pneumoniae*

Isolate (mutation)	Phenotype	Selection	Inoculum (CFU)	Mutation Frequency		
				Delafloxacin	Ciprofloxacin	Moxifloxacin
E. coli ATCC 25922	FQ-S	2X MIC	7.60×10^{9}	1.10×10^{-8}	$< 7.6 \times 10^{-9}$	$< 7.6 \times 10^{-9}$
		4X MIC	7.60×10^{9}	2.63×10^{-10}	$< 7.6 \times 10^{-9}$	$< 7.6 \times 10^{-9}$
		8X MIC	7.60×10^{9}	$< 7.6 \times 10^{-9}$	$< 7.6 \times 10^{-9}$	$< 7.6 \times 10^{-9}$
		16X MIC	7.60×10^{9}	$< 7.6 \times 10^{-9}$	ND	ND
E. coli 7528	FQ-S	2X MIC	5.90×10^{9}	9.0×10^{-8}	1.52×10^{-9}	1.02×10^{-9}
		4X MIC	5.90×10^{9}	4.41×10^{-9}	6.78×10^{-10}	$< 5.9 \times 10^{-9}$
		8X MIC	5.90×10^{9}	$< 5.9 \times 10^{-9}$	$< 5.9 \times 10^{-9}$	$< 5.9 \times 10^{-9}$
		16X MIC	5.90×10^{9}	$< 5.9 \times 10^{-9}$	ND	ND
E. coli 7529	FQ-S	2X MIC	9.10×10^{9}	3.30×10^{-10}	ND	$< 9.10 \times 10^{-9}$
		4X MIC	9.10×10^{9}	$< 9.10 \times 10^{-9}$	$< 9.10 \times 10^{-9}$	$< 9.10 \times 10^{-9}$
		8X MIC	9.10×10^{9}	$< 9.10 \times 10^{-9}$	$< 9.10 \times 10^{-9}$	$< 9.10 \times 10^{-9}$
		16X MIC	9.10×10^{9}	$< 9.10 \times 10^{-9}$	ND	ND
E. coli 5358 [*gyrA* (Ser83Leu)]	FQ-R	2X MIC	6.9×10^{10}	8.8×10^{-8}	ND	2×10^{-10}
		4X MIC	6.9×10^{10}	7×10^{-9}	4.3×10^{-11}	1.3×10^{-10}
		8X MIC	6.9×10^{10}	2.2×10^{-10}	2.9×10^{-11}	8.7×10^{-11}
		16X MIC	6.9×10^{10}	7.2×10^{-11}	ND	ND
K. pneumoniae 7651 [*gyrA* (Asp79[87]-Asn)]	FQ-S	2X MIC	7.75×10^{9}	ND	ND	ND
		4X MIC	7.75×10^{9}	8.97×10^{-8}	1.19×10^{-7}	1.67×10^{-7}
		8X MIC	7.75×10^{9}	$< 7.75 \times 10^{-9}$	$< 7.75 \times 10^{-9}$	4.77×10^{-9}
		16X MIC	7.75×10^{9}	$< 7.75 \times 10^{-9}$	ND	ND

CFU = colony-forming unit; FQ-R = fluoroquinolone-resistant; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration; ND=not determined
Source: RD-03-066 Table 1

Table B-5. Spontaneous Mutation Frequencies of Delafloxacin and Comparators Against *P. aeruginosa*

Isolate (mutation)	Phenotype	Selection	Inoculum (CFU)	Mutation Frequency		
				Delafloxacin	Ciprofloxacin	Moxifloxacin
P. aeruginosa ATCC 27853	FQ-S	2X MIC	1.66×10^{10}	TNTC	4.82×10^{-10}	$< 1.66 \times 10^{-10}$
		4X MIC	1.66×10^{10}	4.22×10^{-10}	$< 1.66 \times 10^{-10}$	$< 1.66 \times 10^{-10}$
		8X MIC	1.66×10^{10}	6.02×10^{-11}	$< 1.66 \times 10^{-10}$	$< 1.66 \times 10^{-10}$

CFU = colony-forming unit; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration; TNTC = too numerous to count
Source: RD-03-066 Table 1

Table B-6. Spontaneous Mutation Frequencies of Delafloxacin and Comparators Against *H. influenzae*

Isolate (mutation)	Phenotype	Selection	Inoculum (CFU)	Mutation Frequency		
				Delafloxacin	Ciprofloxacin	Moxifloxacin
H. influenzae ATCC 49247	FQ-S	2X MIC	7.40×10^{9}	1.66×10^{-8}	ND	ND
		4X MIC	7.40×10^{9}	2.70×10^{-9}	1.62×10^{-9}	1.76×10^{-9}
		8X MIC	7.40×10^{9}	2.03×10^{-9}	$< 7.4 \times 10^{-9}$	1.35×10^{-10}
H. influenzae 7567 [*gyrA* Ser84-Leu, *parC* Ser84-Arg]	FQ-R	2X MIC	1.95×10^{10}	1.00×10^{-9}	ND	TNTC
		4X MIC	1.95×10^{10}	8.21×10^{-10}	7.18×10^{-10}	1×10^{-9}
		8X MIC	1.95×10^{10}	9.74×10^{-10}	6.15×10^{-10}	4.10×10^{-10}

CFU = colony-forming unit; FQ-R = fluoroquinolone resistant; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration; ND = not determined; TNTC = too numerous to count
Source: RD-03-066 Table 1

Table B-7. Selection of Resistant *S. aureus* Isolates During Serial Passage With Delafloxacin

Isolate (Phenotype)	Selection (Fold initial MIC/ Number of Passes)[a]	Resulting Broth MIC (µg/mL) After Passage[b]			QRDR Results			
		Delafloxacin	Ciprofloxacin	Moxifloxacin	*gyrA*	*gyrB*	*grlA*	*grlB*
S. aureus ATCC 25923 (FQ-S)	NA - parent	≤ 0.008	0.5	0.06	WT	WT	WT	WT
	4/2,8/2,16/4	0.12	1	0.12	WT	Asp437-His	Ala116-Val	WT
	32/6	0.5	2	0.5	WT	Asp437-His	Ala116-Val	WT
	64/12	1	2	1	WT	Asp437-His	Ala116-Val	WT
S. aureus ATCC 29213 (FQ-S)	NA - parent	≤ 0.008	0.5	0.06	WT	WT	WT	WT
	4/**2**, 8/2	0.06	0.5	0.12 - 0.25	WT	WT	WT	WT
	16/16	0.12	2	0.5	WT	WT	WT	WT
S. aureus 5589 (FQ-R, MRSA)	NA - parent	0.015	4	0.25	WT	WT	Ser80-Phe	WT
	4/2, 8/**2**, 16/2, 32/1	0.5	8 - 64	1 - 8	Ser84-Leu	WT	Ser80-Phe	WT
	64/1	1	> 64	4	Ser84-Leu	WT	Ser80-Phe	WT
	1**28**/**2**, 256/3	2	64 - > 64	4 - 8	Ser84-Leu	WT	Ser80-Phe	WT
	512/10	8	> 64	16	Ser84-Leu	WT	Ser80-Phe	WT
S. aureus 3384 (FQ-R, MRSA)	NA - parent	1	> 64	4	Ser84-Leu	WT	Ser80-Phe	WT
	4/6, 8/**2**, 16/1, **32**/**2**	4	> 64	8	Ser84-Leu	WT	Ser80-Phe	WT

FQ-R = fluoroquinolone-resistant; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; NA = not applicable; QRDR = quinolone resistance-determining region; WT = wild-type strain
[a] The selection/pass in bold represents the first instance where the delafloxacin broth microdilution MIC value reported for each row was observed.
[b] MIC values reported correspond to instances where delafloxacin broth microdilution MIC values had increased at least 4-fold relative to the parental isolate; the first instance of the reported MIC corresponds to the selection condition at which it was first observed (shown in bold) and subsequent passes listed in each row.
Source: Adapted from RD-03-541 Table 1

Table B-8. Selection of Resistant *S. pneumoniae* Isolates During Serial Passage With Delafloxacin

Isolate (Phenotype)	Selection (Fold initial MIC/ Number of passes)[a]	Resulting Broth MIC (µg/mL) After Passage[b]			QRDR Results			
		Delafloxacin	Ciprofloxacin	Moxifloxacin	*gyrA*	*gyrB*	*parC*	*parE*
S. pneumoniae ATCC 6303 (FQ-S)	NA - parent	≤ 0.015	1	0.12	WT	WT	WT	WT
	2/2, **4/1**	0.06	16	1	WT	WT	Ser79-Phe	WT
	8/1, 16/2	0.12	64	2 - 4	WT	WT	Ser79-Phe	WT
	32/3	0.5	64	8	WT	WT	Ser79-Phe	WT
	64/4	1	> 64	8	WT	WT	Ser79-Phe	WT
S. pneumoniae ATCC 49619 (FQ-S)	NA - parent	≤ 0.015	1	0.25	WT	WT	WT	WT
	4/7, **8/1**	0.06	4	2	Ser81-Phe	WT	Ser79-Phe	WT
	16/1	0.25	32	8	Ser81-Phe	WT	Ser79-Phe	WT
	32/2	1	32	8	Ser81-Phe	Arg445-Cys	Ser79-Phe	WT
	64/2, **128/2**, 256/4	8 - 16	16 - 32	8 - 16	Ser81-Phe	Arg445-Cys	Ser79-Phe	WT
S. pneumoniae 7215 (FQ-R)	NA - parent	0.03	8	0.5	WT	WT	Ser79-Phe	WT
	4/7	1	16	4	Ser81-Tyr	Asp435-Asn	Ser79-Phe	WT
	8/1, 16/1	2	64	16 - 32	Ser81-Tyr	Asp435-Asn	Ser79-Phe	WT
	32/8	4	64	64	Ser81-Tyr	Asp435-Asn	Ser79-Phe	WT
S. pneumoniae 7257 (FQ-R)	NA - parent	0.12	16	2	Ser81-Phe	WT	Ser79-Phe	WT
	4/4	2	16	1	Ser81-Phe, Ala117-Val	WT	Ser79-Phe	WT
	8/1, 16/2	8	> 16 - 64	8	Ser81-Phe, Ala117-Val	WT	Ser79-Phe	WT

FQ-R = fluoroquinolone-resistant; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration; NA = not applicable; QRDR = quinolone resistance-determining region; WT = wild-type strain
[a] The selection/pass in bold represents the first instance where the delafloxacin broth microdilution MIC value reported for each row was observed.
[b] MIC values reported correspond to instances where delafloxacin broth microdilution MIC values had increased at least 4-fold relative to the parental isolate; the first instance of the reported MIC corresponds to the selection condition at which it was first observed (shown in bold) and subsequent passes listed in each row.
Source: Adapted from RD-03-541 Table 1

Table B-9. Selection of Resistant *E. coli* Isolates During Serial Passage With Delafloxacin

Isolate (Phenotype)	Selection (Fold initial MIC/ Number of passes)[a]	Resulting Broth MIC (µg/mL) After Passage[b]			QRDR Results			
		Delafloxacin	Ciprofloxacin	Moxifloxacin	*gyrA*	*gyrB*	*parC*	*parE*
E. coli ATCC 25922 (FQ-S)	NA - parent	≤ 0.015	≤ 0.015	≤ 0.015	WT	WT	WT	WT
	2/1, 4/3, **8/5**	0.12	≤ 0.03	0.06	WT	WT	WT	WT
E. coli 7529 (FQ-S)	NA - parent	0.015	≤ 0.008	0.03	WT	WT	WT	WT
	4/3, **8/2**	0.25	0.06	0.5	WT	WT	WT	WT
	16/1, 32/1	1 - 2	0.12	1 - 2	WT	WT	WT	WT
	64/1, 128/2, 256/1	8 - 16	1 - 2	4 - 8	Ser83-Leu	WT	WT	WT
	512/3	32	4	8	Ser83-Leu	WT	WT	WT
E. coli 5358 (FQ-S)	NA - parent	0.25	0.25	0.5	Ser83-Leu	WT	WT	WT
	2/3	1	1	1	Ser83-Leu	WT	WT	WT
	4/2, 8/10	2	1	1	Ser83-Leu	WT	WT	Glu370-Asp

FQ-R = fluoroquinolone-resistant; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration; NA = not applicable; QRDR = quinolone resistance-determining region; WT = wild-type strain
[a] The selection/pass in bold represents the first instance where the delafloxacin broth microdilution MIC value reported for each row was observed.
[b] MIC values reported correspond to instances where delafloxacin broth microdilution MIC values had increased at least 4-fold relative to the parental isolate; the first instance of the reported MIC corresponds to the selection condition at which it was first observed (shown in bold) and subsequent passes listed in each row.
Source: Adapted from RD-03-541 Table 1

Table B-10. Selection of Resistant *H. influenzae* Isolates During Serial Passage With Delafloxacin

Isolate (Phenotype)	Selection (Fold initial MIC/ Number of passes)[a]	Resulting Broth MIC (µg/mL) After Passage[b]			QRDR Results			
		Delafloxacin	Ciprofloxacin	Moxifloxacin	*gyrA*	*gyrB*	*parC*	*parE*
H. influenzae ATCC 49247 (FQ-S)	NA - parent	0.0005	0.015	0.03	WT	WT	WT	WT
	4/2	0.004	0.06	0.12	WT	WT	WT	WT
	8/2, 16/3, 32/1	0.03	0.06	0.5	WT	Δ 401-404	WT	WT
	64/1	0.06	0.06	0.5	WT	Δ 401-404	WT	WT
H. influenzae 1435 (FQ-S)	NA - parent	0.001	0.015	0.06	WT	WT	WT	WT
	4/2	0.004	0.06	0.12	WT	WT	WT	WT
	8/2	0.015	0.25	0.12	WT	WT	WT	WT
	16/1	0.06	1	0.5	WT	WT	WT	WT
	32/1, 64/2	0.12	1 - 2	0.5 - 1	WT	WT	WT	WT
H. influenzae 7567 (FQ-NS)	NA - parent	0.25	2	4	Ser84-Leu	WT	Ser84-Arg	WT
	2/4	1	4	8	Ser84-Leu	WT	Ser84-Arg	WT
	4/1, 8/1	1 - 2	16	16	Ser84-Leu	WT	Ser84-Arg	WT

FQ-NS = fluoroquinolone non-susceptible; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration; NA = not applicable; QRDR = quinolone resistance-determining region; WT = wild-type strain
[a] The selection/pass in bold represents the first instance where the delafloxacin broth microdilution MIC value reported for each row was observed.
[b] MIC values reported correspond to instances where delafloxacin broth microdilution MIC values had increased at least 4-fold relative to the parental isolate; the first instance of the reported MIC corresponds to the selection condition at which it was first observed (shown in bold) and subsequent passes listed in each row.
Source: Adapted from RD-03-541 Table 1

APPENDIX-C

Table C-1. Summary of the Activity of Delafloxacin and Combination Agents During Checkerboard Assays

Drug	MIC (µg/mL)									
	SAUR 0100/ ATCC 29213	SAUR 3884	SPYO 0404/ ATCC 19615	SPNE 1195/ ATCC 49619	EFAE 0101/ ATCC 29212	ECOL 0102/ ATCC 25922	ECOL 6098	PAER 0103/ ATCC 27853	PAER 6473	ABAU 6151
Delafloxacin[a]	0.008	0.5-1	0.015-0.03	0.008-0.015	0.06-0.12	0.03	8-16	0.25-0.5	32	0.06-0.12
Daptomycin	0.25	0.25	0.06	0.06	2	> 256	> 256	> 256	> 256	> 256
Linezolid	4	2	2	1	2	256	> 256	> 256	> 256	> 256
Meropenem	0.06	16	0.008	0.03	2	0.015	0.015	0.25	16	0.25
Ceftazidime	8	256	0.12	0.5	> 256	0.25	0.5	1	8	4
Trimethoprim/ Sulfamethoxazole	0.25/4.8	0.25/4.8	0.5/8.6	0.5/8.6	0.06/1.2	0.25/4.8	> 256/4864	32/608	64/4.8	0.5/8.6
Vancomycin	1	1	0.5	0.12	4	> 256	256	> 256	> 256	128
Tigecycline	0.25	0.25	0.03	0.03	0.12	0.12	0.5	16	32	0.25
Colistin	256	256	128	> 256	> 256	0.25	0.25	1	0.5	0.25
Aztreonam	>256	>256	8	256	> 256	0.12	0.12	4	64	16

ABAU = *A. baumannii*; ATCC = American Type Culture Collection; ECOL = *E. coli*; EFAE = *E. faecalis*; MIC = minimal inhibitory concentration; PAER = *P. aeruginosa*; SAUR = *S. aureus*; SPNE = *S. pneumoniae*, SPYO = *S. pyogenes*
[a] MIC range reported from 9 separate FIC checkerboard panels tested with the same inocula (delafloxacin was tested in combination with 9 other agents for each isolate).
Source: MB-3341-017 Table 2

Table C-2. Summary of Mean FICI Values for Delafloxacin in Combination With Other Agents During Checkerboard Assays

Combination Agent	Mean FICI									
	SAUR 0100/ ATCC 29213	SAUR 3884	SPYO 0404/ ATCC 19615	SPNE 1195/ ATCC 49619	EFAE 0101/ ATCC 29212	ECOL 0102/ ATCC 25922	ECOL 6098	PAER 0103/ ATCC 27853	PAER 6473	ABAU 6151
Daptomycin	1.96	1.19	1.25	1.13	0.75	1.20	1.29	1.23	1.19	1.29
Linezolid	1.46	1.39	1.32	1.07	1.38	1.10	1.29	1.23	1.19	1.38
Meropenem	1.29	0.92	1.00	1.13	0.75	0.87	0.83	0.93	0.84	0.86
Ceftazidime	1.29	1.00	1.00	1.13	0.97	0.82	0.71	0.94	0.89	1.13
Trimethoprim/ Sulfamethoxazole	1.29	1.09	1.25	1.13	0.96	1.10	1.29	1.09	1.19	1.29
Vancomycin	1.13	0.69	1.10	1.13	0.79	0.95	0.92	1.19	1.19	1.38
Tigecycline	1.29	1.19	1.25	1.13	1.38	1.20	1.29	0.94	1.19	1.38
Colistin	0.71	0.94	0.75	0.91	1.29	1.50	1.12	0.59	0.99	0.86
Aztreonam	1.04	1.98	1.20	0.88	1.38	1.03	1.24	1.04	0.74	1.38

ABAU = *A. baumannii*; ATCC = American Type Culture Collection; ECOL = *E. coli*; EFAE = *E. faecalis*; FICI = fractional inhibition concentration index; PAER = *P. aeruginosa*; SAUR = *S. aureus*; SPNE = *S. pneumoniae*; SPYO = *S. pyogenes*
Shaded cells indicate instances where one of the combination agents had an undefined MIC (e.g. > 256 µg/mL); in these instances the FIC for that agent was calculated using an MIC one doubling-dilution above the highest concentration tested (e.g. for an MIC of > 256 µg/mL, an MIC of 512 µg/mL was applied to determine the FIC of that agent)
Source: MB-3341-017 Table 3

Table C-3. Proportion of Radioactive Components in Plasma and Urine After IV Infusion of 300 mg [14C]-Delafloxacin to Healthy Male Volunteers (N = 6)

Component	Subject						
	001	002	003	004	005	006	Mean
	Plasma (% of sample radioactivity)						
Delafloxacin (1-12 h)	90.4	91.7	90.4	88.1	88.1	87.1	89.3
Delafloxacin glucuronide (1-12 h)	8.0	8.3	8.5	11.1	11.0	10.5	9.57
	Urine (% of administered dose)						
Delafloxacin (0-4 h)	37.62	38.49	29.66	25.60	31.59	22.94	31.0
Delafloxacin (4-24 h)	9.86	7.95	7.34	7.91	8.44	21.38	10.5
Delafloxacin (0-24 h)	47.48	46.44	37	33.51	40.03	44.32	41.5
Delafloxacin glucuronide (0-4 h)	13.77	13.78	14.22	13.78	11.84	6.63	12.3
Delafloxacin glucuronide (4-24 h)	7.26	6.16	8.06	9.39	6.67	8.72	7.71
Delafloxacin glucuronide (0-24 h)	21.03	19.94	22.28	23.17	18.51	15.35	20.0

IV = intravenous.

Note: Mean value was not calculated in the report but was the average value for the 6 subjects.

Source: RX-3341-107-03, Table 7, Table 8, and Table 9

Table C-4. Percent Binding of Delafloxacin to Human Plasma, Albumin, and α1-Acid Glycoprotein

Delafloxacin Concentration (µg/mL)	% Bound Plasma	% Bound Albumin	% Bound α_1-acid glycoprotein
0.1	83.98	84.89	3.68
1.0	84.54	84.48	2.40
5.0	83.44	84.09	4.49
10.0	82.98	83.93	2.57
25.0	83.82	84.21	1.12
50.0	83.56	84.98	3.24

Source: R&D/00/427 and R&D/00/428

Table C-5. Summary of PAE, PA-SME, and SME for Delafloxacin and Levofloxacin Against Evaluated Organisms

Organism	Drug	MIC (µg/mL)	PAE (hr)			PA-SME[a] (hr)			SME (hr)		
			2X MIC	4X MIC	8X MIC	0.06X MIC	0.12X MIC	0.25X MIC	0.06X MIC	0.12X MIC	0.25X MIC
S. aureus ATCC 29213	Delafloxacin	0.008	1.00	1.75	2.25	1.00	1.75	2.50	-0.25	-0.25	0.50
	Levofloxacin	0.25	1.50	NT	NT	1.50	2.00	2.50	-0.25	0.25	0.50
S. aureus MMX 3881[b]	Delafloxacin	0.015	0.50	0.75	0.75	0.25	0.50	0.75	0.00	0.00	0.25
	Levofloxacin	0.25	0.50	NT	NT	0.25	0.75	1.25	-0.25	-0.25	0.25
S. aureus MMX 3887[c]	Delafloxacin	0.5	0.75	0.75	1.00	0.25	0.50	1.25	0.00	0.00	0.00
	Levofloxacin	16	0.00	NT	NT	-0.25	0.00	0.25	0.00	0.00	0.00
S. pyogenes ATCC 19615	Delafloxacin	0.03	2.00	2.00	2.25	2.00	2.75	2.75	0.75	0.50	1.50
	Levofloxacin	0.5	2.25	NT	NT	1.75	2.00	3.00	0.00	0.50	1.25

ATCC = American Type Culture Collection; MIC = minimum inhibitory concentration; MMX = Micromyx isolate; NT = not tested; PAE = post-antibiotic effect; PA-SME = post-antibiotic sub-inhibitory effect; SME = sub-inhibitory effect
[a] PA-SME values determined after 1hr initial exposure to 2X the MIC of the test agent followed by continued exposure to sub-inhibitory concentrations as indicated
[b] MRSA, levofloxacin-susceptible isolate
[c] MRSA, levofloxacin-resistant isolate
Source: MB-3341-015 Table 2

APPENDIX-D

Table D-1. Summary of MBC:MIC Ratio for Delafloxacin and Levofloxacin at Neutral and Acidic pH Against Select Gram-positive Organisms

Organism	Drug	pH	Evaluable (n)[a]	% MBC:MIC ≤ 2	% MBC:MIC > 2
MSSA (n = 10)	Delafloxacin	7.2	10	90.0	10.0
		6.0	10	100.0	0.0
	Levofloxacin	7.2	10	100.0	0.0
		6.0	10	100.0	0.0
MRSA (n = 30)	Delafloxacin	7.2	30	100.0	0.0
		6.0	28	100.0	0.0
	Levofloxacin	7.2	29	100.0	0.0
		6.0	27	96.3	3.7
S. epidermidis (n = 10)	Delafloxacin	7.2	10	100.0	0.0
		6.0	8	100.0	0.0
	Levofloxacin	7.2	8	100.0	0.0
		6.0	8	100.0	0.0
Enterococci (n = 10)	Delafloxacin	7.2	10	80.0	20.0
		6.0	10	70.0	30.0
	Levofloxacin	7.2	4	100.0	0.0
		6.0	2	50.0	50.0
S. pneumoniae (n = 10)	Delafloxacin	7.2	10	90.0	10.0
		6.0	NA	NA	NA
	Levofloxacin	7.2	10	100.0	0.0
		6.0	NA	NA	NA
S. pyogenes (n = 5)	Delafloxacin	7.2	5	100.0	0.0
		6.0	NA	NA	NA
	Levofloxacin	7.2	5	100.0	0.0
		6.0	NA	NA	NA
S. agalactiae (n = 5)	Delafloxacin	7.2	5	100.0	0.0
		6.0	5	80.0	20.0
	Levofloxacin	7.2	5	100.0	0.0
		6.0	5	100.0	0.0

MBC = minimum bactericidal concentration; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; n = number of isolates; NA = not applicable
[a] Isolates where either the MIC or MBC endpoint was off-scale were not included for evaluation because it could not be determined whether the MBC:MIC ratio was ≤ 2 or > 2.
Source: MB-3341-016 Table 2

Table D-2. Summary of MBC:MIC Ratio for Delafloxacin and Levofloxacin at Neutral and Acidic pH Against Select Gram-negative Organisms

Organism	Drug	pH	Evaluable (n)[a]	% MBC:MIC ≤ 2	% MBC:MIC > 2
E. coli (n = 10)	Delafloxacin	7.2	10	80.0	20.0
		6.0	10	100.0	0.0
	Levofloxacin	7.2	10	100.0	0.0
		6.0	8	100.0	0.0
K. pneumoniae (n = 10)	Delafloxacin	7.2	9	100.0	0.0
		6.0	9	100.0	0.0
	Levofloxacin	7.2	8	100.0	0.0
		6.0	7	100.0	0.0
P. aeruginosa (n = 10)	Delafloxacin	7.2	10	100.0	0.0
		6.0	10	90.0	10.0
	Levofloxacin	7.2	10	100.0	0.0
		6.0	10	100.0	0.0
A. baumannii (n = 10)	Delafloxacin	7.2	10	100.0	0.0
		6.0	10	90.0	10.0
	Levofloxacin	7.2	10	100.0	0.0
		6.0	10	100.0	0.0

MBC = minimum bactericidal concentration; MIC = minimum inhibitory concentration; n = number of isolates; NA = not applicable
[a] Isolates where either the MIC or MBC endpoint was off-scale were not included for evaluation because it could not be determined whether the MBC:MIC ratio was ≤ 2 or > 2
Source: MB-3341-016 Table 4

Table D-3. MIC and MBC Values of Delafloxacin and Comparators Against S. aureus Including MRSA With Genetically Characterized Fluoroquinolone-Resistance

Organism (Phenotype/Genotype)	MIC/MBC (µg/mL)			
	Delafloxacin	Levofloxacin	Vancomycin	Daptomycin
S. aureus ATCC 29213 (MSSA; FQ-S)	0.004/0.008	0.25/0.25	1/2	0.5/1
S. aureus 110 (MRSA; FQ-S)	0.008/0.008	0.5/0.5	1/1	0.5/1
S. aureus (MRSA; FQ-R/ *gyr*A E88K, S84L; *parC* S80F)	0.5/0.5	8/8	1/1	0.5/1
S. aureus (MRSA; FQ-R/ *gyr*A E88K, S84L; *parC* E84G, S80Y)	4/8	> 32/ > 32	1/1	0.5/0.5

FQ-R = fluoroquinolone-resistant; FQ-S = fluoroquinolone-susceptible; MBC = minimum bactericidal concentration; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*
Source: MB-3341-054 Table 3

Table D-4. Summary of Delafloxacin and Levofloxacin MIC and Time to 3-log Kill in the Presence and Absence of 50% Human Serum[15]

Organism	Strain (Relevant Phenotype/ Genotype)	Drug	Human Serum	MIC (µg/mL)	Time to 3-log Kill (hr) at 8-fold the MIC
S. aureus	ATCC 29213 (FQ-S)	Delafloxacin	-	0.004	6
			+	0.004	6
		Levofloxacin	-	0.25	6
			+	0.25	6
	ATCC 25923 (FQ-S)	Delafloxacin	-	0.008	10
			+	0.008	10
		Levofloxacin	-	0.25	8
			+	0.25	10
	5589 (FQ-R, *grlA* Ser80-Phe)	Delafloxacin	-	0.015	6
			+	0.015	12
		Levofloxacin	-	2	8
			+	2	12
	3384 (FQ-R, *gyrA* Ser84-Leu, *grlA* Ser80-Phe)	Delafloxacin	-	1	6
			+	1	6
		Levofloxacin	-	32	8
			+	32	10

Organism	Strain (Relevant Phenotype/ Genotype)	Drug	Human Serum	MIC (µg/mL)	Time to 3-log Kill (hr) at 8-fold the MIC
S. pneumoniae	ATCC 49619 (FQ-S)	Delafloxacin	-	0.015	8
			+	0.015	12
		Levofloxacin	-	2	12
			+	2	10
	2486 (FQ-S)	Delafloxacin	-	0.015	6
			+	0.015	8
		Levofloxacin	-	1	10
			+	1	12
	7215 (FQ-R, *parC* Ser79-Phe)	Delafloxacin	-	0.06	12
			+	0.06	10
		Levofloxacin	-	4	12
			+	4	12
	7257 (FQ-R, *gyrA* Ser84-Phe, *parC* Ser79-Phe)	Delafloxacin	-	0.06	24
			+	0.06	24
		Levofloxacin	-	4	> 24
			+	4	> 24

Organism	Strain (Relevant Phenotype/ Genotype)	Drug	Human Serum	MIC (µg/mL)	Time to 3-log Kill (hr) at 8-fold the MIC
H. influenzae	ATCC 49247 (FQ-S)	Delafloxacin	-	0.00025	6
			+	0.001	6
		Levofloxacin	-	0.015	8
			+	0.015	10
	1435 (FQ-S)	Delafloxacin	-	0.004	8
			+	0.004	8
		Levofloxacin	-	0.015	8
			+	0.015	8
	7567 (FQ-R, *gyrA* Ser84-Leu)	Delafloxacin	-	0.06	10
			+	0.06	10
		Levofloxacin	-	2	12
			+	2	24
	7571 (FQ-R, *gyrA* Ser84-Phe)	Delafloxacin	-	0.002	6
			+	0.008	8
		Levofloxacin	-	0.06	6
			+	0.06	8
	7566 (FQ-R, *gyrA* Ser84-Leu, *parC* Ser84-Arg)	Delafloxacin	-	0.06	8
			+	0.12	10
		Levofloxacin	-	1	8
			+	4	10

Organism	Strain (Relevant Phenotype/ Genotype)	Drug	Human Serum	MIC (µg/mL)	Time to 3-log Kill (hr) at 8-fold the MIC
E. coli	ATCC 25922 (FQ-S)	Delafloxacin	-	0.03	6
			+	0.03	4
		Levofloxacin	-	0.015	2
			+	0.015	2
	7529 (FQ-S)	Delafloxacin	-	0.015	6
			+	0.015	8
		Levofloxacin	-	0.015	2
			+	0.015	2
	5358 (FQ-R, *gyrA* Ser 83-Leu)	Delafloxacin	-	0.5	4
			+	0.5	4
		Levofloxacin	-	2	4
			+	2	4
	7386 (QuinR, *gyrA* Ser83-Leu, Asp87-Asn, *parC* Ser80-Ile)	Delafloxacin	-	2	6
			+	2	10
		Levofloxacin	-	32	8
			+	32	8
K. pneumoniae	7651 (FQ-R, *gyrA* Asp79[87]-Asn)	Delafloxacin	-	1	6
			+	1	6
		Levofloxacin	-	1	8
			+	1	8
P. aeruginosa	ATCC 27853 (FQ-S)	Delafloxacin	-	0.5	8
			+	0.5	8
		Levofloxacin	-	8	8
			+	8	8

hr = hour; FQ-R = fluoroquinolone-resistant; FQ-S = fluoroquinolone-susceptible; MIC = minimum inhibitory concentration
Source: RD-02-532 Table 4

APPENDIX-E

Table E-1. Effective Dose$_{50}$ of Delafloxacin and Comparators Against Experimentally-Induced Systemic Lethal Infections in Mice

Organism	Bacterial Challenge (CFU/mouse)	Treatment Schedule	Study Drug Dose/Route	ED_{50} (95%CI)[a] Oral (mg/kg)	ED_{50} (95%CI) SC (mg/kg)	MIC[b] (µg/mL)
S. aureus 10649	1.0×10^6 IP in BHI plus 2% lysed sheep blood $158 \times LD_{50}$	1 and 5 h post-infection by oral or SC route	Delafloxacin	< 0.39	< 0.39	≤ 0.005
			Levofloxacin	12.71 (7.4–12.71)	2.52 (0.2–0.5)	0.2
			Trovafloxacin	0.82 (0.6–1.1)	0.33 (0.2–0.5)	0.02
S. pneumoniae 6303	1.3×10^2 IP in BHI plus 2% lysed sheep blood $126 \times LD_{50}$	1 and 5 h post-infection by oral or SC route	Delafloxacin	14.59 (11.8–18.0)	9.54 (7.5–12.1)	0.008
			Levofloxacin	104.33 (89.9–121.1)	40.62 (26.0–63.4)	0.5
			Trovafloxacin	25.04 (15.8–39.6)	12.51 (7.9–19.8)	0.06
E. coli JUHL	2.6×10^6 IP in BHI plus 2% lysed sheep blood $158 \times LD_{50}$	1 and 5 h post-infection by oral or SC route	Delafloxacin	11.28 (7.2–17.8)	1.80 (1.2–2.7)	0.02
			Ciprofloxacin	3.44 (2.3–5.2)	0.23 (0.1–0.4)	0.02
			Trovafloxacin	5.01 (3.2–7.9)	0.52 (0.3–0.8)	0.05
P. aeruginosa 5007	7.9×10^5 IP in BHI plus 2% lysed sheep blood $1000 \times LD_{50}$	1 and 5 h post-infection by oral or SC route	Delafloxacin	34.56 (22.7–52.7)	6.25 (4.0–9.9)	0.2
			Ciprofloxacin	28.24 (17.9–44.5)	2.42 (1.7–3.5)	0.39
			Trovafloxacin	16.50 (10.6–25.8)	12.51 (7.9–19.8)	0.1

BHI = brain heart infusion broth; CFU = colony-forming units; ED_{50} = Effective dose 50%; HA-MRSA = hospital-associated MRSA; IP = intraperitoneal; LD_{50} = lethal dose 50%; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; SC = subcutaneous
[a] Effective dose 50 is the amount of drug (mg/kg/dose) required to cure 50% of infected animals (cure defined as survival).
[b] Minimum inhibitory concentration
Source: RD-01-134 Tables 1 and 2

Table E-2. Protective Dose$_{50}$ of Delafloxacin Against MRSA in Experimentally-Induced Systemic Lethal Infections in Mice

Organism	Bacterial Challenge (CFU/mouse)	Treatment Schedule	Study Drug Dose/ Route	PD_{50} (95%CI)[a] (mg/kg)	MIC[b] (µg/mL)
MRSA 67-0	2×10^8 IP 3% mucin	1 h post-infection IV in 5% DMSO/ 10% cyclodextrin/H_20	Delafloxacin 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.781/IV	< 0.781	4
			Linezolid 50/PO	< 50	4
MRSA 11512 (FQ-RSA[c], MRSA)	5×10^8 IP 3% mucin	1 h post-infection IV in 5% DMSO/ 10% cyclodextrin/H_20	Delafloxacin 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.781/IV	42.5 (28.32–64.02)	0.5
			Linezolid 50/PO	< 50	4
MRSA 2926 (HA-MRSA)	2.6×10^9 IP 3% mucin	1 h post-infection IV in 5% DMSO/ 10% cyclodextrin/H_20	Delafloxacin 100, 50, 25, 12.5, 6.25, 3.12, 1.56/IV	< 1.56	0.03
			Linezolid 50/PO	< 50	2

CFU = colony-forming units; DMSO = dimethylsulfoxide; FQ-RSA = fluoroquinolone-resistant *S. aureus*; h = hour; H_2O = water; HA-MRSA = hospital-associated MRSA; IP = intraperitoneal; IV = intravenous; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; PD_{50} = protective dose 50%; PO = oral administration
[a] Protective dose$_{50}$ is the amount of drug (mg/kg/dose) required to protect 50% of infected animals (protection defined as survival).
[b] Minimum inhibitory concentration
[c] Levofloxacin MIC = 16 µg/mL
Source: EF-3341-001 tables page 4, page 7, page 10

Table E-3. Delafloxacin in the Treatment of Experimentally-Induced Staphylococcal Soft-Tissue Infections in Neutropenic Mice

Organism Strain Resistance profile	Bacterial Challenge IM[a] CFU/mouse (log_{10})	Treatment Schedule Route	Study Drug (mg/kg) Dosing schedule	CFU/Thigh[b] (log_{10}) ± SEM	ΔCFU[c] (log_{10}) after 24 h	MIC (µg/mL)
S. aureus Smith ATCC13709 MSSA MLS-s	6.02	1) Pretreatment[d] cyclophosphamide 2) Study drugs administered SC 2 h postinfection as indicated 3) CFU count at start of therapy (2 h): 7.47 log_{10}	Delafloxacin			0.004
			20 QD	4.06 ± 0.28	-3.41	
			10 BID	3.93 ± 0.14	-3.54	
			5 QD	5.15 ± 1.37	-2.321	
			5 QID	3.68 ± 0.3	-3.79	
			2.5 BID	5.10 ± 0.43	-2.374	
			1.25 QD	7.86 ± 0.32	+0.388	
			1.25 QID	3.70 ± 0.26	-3.774	
			0.625 BID	7.18 ± 0.50	-0.294	
			0.313 QD	8.24 ± 0.38	+0.769	
			0.313 QID	5.72 ± 0.64	-1.748	
			0.15 BID	8.48 ± 0.17	+1.008	
			0.075 QID	8.36 ± 0.22	+0.89	
			Vehicle			
			NA	8.75 ± 0.17	+1.281	
S. aureus 11540 CA-MRSA USA300 FQ-RSA, Levo[R],CM[R]	5.80	1) Pretreatment[d] cyclophosphamide 2) Study drugs administered SC 2 h postinfection as indicated 3) CF count at start of therapy (2 h): 6.66 log_{10}	Delafloxacin			0.8[e]
			308 QD	6.91 ± 0.28	+0.258	
			308 BID	3.78 ± 0.14	-2.877	
			308 QID	3.80 ± 0.22	-2.850	
			160 QD	7.54 ± 0.33	+0.888	
			160 BID	5.31 ± 0.67	-1.347	
			160 QID	3.81 ± 0.20	-2.85	
			80 QD	8.01 ± 0.10	+1.355	
			80 BID	7.58 ± 0.22	+0.928	
			80 QID	5.16 ± 0.75	-1.501	
			40 BID	7.99 ± 0.08	+1.329	
			20 QID	7.56 ± 0.70	+0.907	
			Vehicle			

Organism Strain Resistance profile	Bacterial Challenge IM[a] CFU/mouse (log_{10})	Treatment Schedule Route	Study Drug (mg/kg) Dosing schedule	CFU/Thigh[b] (log_{10}) ± SEM	ΔCFU[c] (log_{10}) after 24 h	MIC (µg/mL)
			NA	8.47 ± 0.14	1.875	

Organism Strain Resistance profile	Bacterial Challenge IM[a] CFU/mouse (log_{10})	Treatment Schedule Route	Study Drug (mg/kg) Dosing schedule	CFU/Thigh[b] (log_{10}) ± SEM	ΔCFU[c] (log_{10}) after 24 h	MIC (µg/mL)
S. aureus 2926 HA-MRSA USA 100 FQ-RSA, CM[R]	6.09	1) Pretreatment[d] cyclophosphamide 2) Study drugs administered SC 2 h postinfection 3) CFU count at start of therapy (2 h): 6.57 log_{10}	Delafloxacin			0.016
			20 QD	4.39 ± 0.35	-2.177	
			5 QD	6.11 ± 0.17	-0.455	
			5 BID	5.02 ± 0.36	-1.55	
			5 QID	4.40 ± 0.35	-2.164	
			1.25 QD	6.86 ± 0.50	+0.295	
			1.25 BID	6.54 ± 0.68	-0.026	
			1.25 QID	5.24 ± 0.11	-1.324	
			0.313 QD	7.73 ± 0.08	+1.164	
			0.313 BID	7.09 ± 0.25	+0.52	
			0.313 QID	6.27 ± 0.47	-0.294	
			0.156 BID	7.70 ± 0.13	+1.134	
			Vehicle			
			NA	7.95 ± 0.04	+1.384	
S. aureus 11512 MRSA FQ-RSA	5.71	1) Pretreatment[d] cyclophosphamide 2) Study drugs administered SC 2 h postinfection 3) CFU count at start of therapy (2h): 6.06 log_{10}	Delafloxacin			0.8
			320 BID	4.37 ± 0.27	-1.688	
			160 BID	4.28 ± 0.21	-1.782	
			80 BID	6.60 ± 0.70	+0.044	
			40 BID	7.56 ± 0.27	+1.498	
			20 BID	8.70 ± 0.07	+2.641	
			Vancomycin			0.5
			50 BID	5.81 ± 1.23	-0.255	
			Vehicle			
			NA	8.83 ± 0.13	+2.772	

Organism Strain Resistance profile	Bacterial Challenge IM[a] CFU/mouse (log_{10})	Treatment Schedule Route	Study Drug (mg/kg) Dosing schedule	CFU/Thigh[b] (log_{10}) ± SEM	ΔCFU[c] (log_{10}) after 24 h	MIC (µg/mL)
S. aureus ATCC29213 MSSA	5.24	1) Pretreatment[d] cyclophosphamide 2) Study drugs administered SC2 h postinfection as indicated 3) CFU count at start of therapy (2 h): 5.12 log_{10}	Delafloxacin			0.006[e]
			100 BID	3.21 ± 0.21	-1.91	
			30 BID	3.46 ± 0.08	-1.658	
			10 BID	3.65 ± 0.11	-1.471	
			3 BID	4.07 ± 0.16	-1.043	
			Vancomycin			1—2
			25 BID	4.80 ± 0.39	-0.313	
			5 BID	8.08 ± 0.18	+2.963	
			Vehicle			
			NA	8.50 ± 0.12	+3.386	

ATCC = American Type Culture Collection; BID = twice daily; CA = community acquired; CFU = colony-forming units; CM-R = clindamycin resistant; h = hours; HA = hospital associated; FQ-RSA = fluoroquinolone-resistant *S. aureus*; h = hour; IM = intramuscular; Levo-R = levofloxacin resistant; MIC = minimum inhibitory concentration; MLS = Macrolide-Lincosamide-Streptogramin; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; NA = not applicable; QD = once daily; QID = 4 times daily; SC = subcutaneous administration; SEM = standard error of the mean; Vanc = vancomycin

[a] Intramuscular infection in both caudal thigh muscles

[b] CFU (log_{10} ± SEM) in both thighs harvested 24 hours after inoculation, aseptically homogenized then serial diluted on blood agar and incubated for 24 hours at 37°C in 5% CO_2

[c] Change in bacterial burden (ΔCFU) was defined as change in bacterial burden after 24 hours of treatment compared to bacterial burden at the onset of treatment (2 hours post-infection)

[d] Cyclophosphamide was administered on Day -4 (150 mg/kg) and on Day -1 (100 mg/kg) by the intraperitoneal route.

[e] Geometric means of replicates

Source: PK-3341-002 Appendix D; PK-3341-006 Table 1; PK-3341-005 Table 1 (MIC values)

Table E-4. Delafloxacin in the Treatment of Experimentally-Induced Pneumococcal Soft-Tissue Infections in Neutropenic Mice

Organism *S. pneumoniae* Strain Resistance profile	Bacterial Challenge IM[a] CFU/mouse (log_{10})	Treatment Schedule	Study Drug (mg/kg)	CFU/Thigh[b] (log_{10}) ± SEM	Δ CFU (log_{10}) after 24 h	MIC (µg/mL)
S. pneumoniae 6303 MLS-s	4.78	Cyclophosphamide: 150 mg/kg Day-4 100 mg/kg Day -1 IP Study Drug: 2 h post-inf Single Dose Oral	Delafloxacin			0.002
			20	4.71 ± 0.37	-3.21	
			5	7.22 ± 0.21	-0.70	
			Vehicle			
			NA	7.92 ± 0.17	--	
S. pneumoniae 5649 *mef*E, PenI	5.51		Delafloxacin			0.002
			20	2.16 ± 1.00	-4.36	
			5	5.20 ± 0.33	-1.32	
			Vehicle			
			NA	6.52 ± 0.89	--	
S. pneumoniae 6396 *erm*AM, PenS *erm*B,PenS	5.15		Delafloxacin			0.002
			20	1.18 ± 0.82	-6.67	
			5	3.94 ± 0.39	-3.90	
			Vehicle			
			NA	7.85 ± 0.13	--	
S. pneumoniae 7215 FQ-RSP	4.46		Delafloxacin			0.008
			20	4.88 ± 0.35	-2.03	
			5	5.74 ± 0.54	-1.17	
			Vehicle			
			NA	6.91 ± 0.17	--	

Organism *S. pneumoniae* Strain Resistance profile	Bacterial Challenge IM[a] CFU/mouse (log_{10})	Treatment Schedule	Study Drug (mg/kg)	CFU/Thigh[b] (log_{10}) ± SEM	Δ CFU (log_{10}) after 24 h	MIC (µg/mL)
S. pneumoniae 7247 FQ-RSP	5.81	Cyclophosphamide: 150 mg/kg Day-4 100 mg/kg Day -1 IP Study Drug: 2 h post-inf Single Dose Oral	Delafloxacin			0.03
			250	1.19 ± 0.82	-5.44	
			90	2.62 ± 1.27	-4.01	
			30	6.11 ± 0.62	-0.52	
			Vehicle			
			NA	6.63 ± 0.29	--	
S. pneumoniae 7250 FQ-RSP	6.8		Delafloxacin			0.06
			250	5.71 ± 0.36	-1.84	
			90	7.12 ± 0.22	-0.43	
			30	7.34 ± 0.42	-0.21	
			Vehicle			
			NA	7.55 ± 0.11	--	
S. pneumoniae 7257 FQ-RSP	4.38		Delafloxacin			0.03
			250	4.09 ± 0.15	-3.93	
			90	5.24 ± 0.33	-2.78	
			37.5	7.63 ± 0.16	-0.39	
			Vehicle			
			NA	8.02 ± 0.05	--	

Organism *S. pneumoniae* Strain Resistance profile	Bacterial Challenge IM[a] CFU/mouse (log_{10})	Treatment Schedule	Study Drug (mg/kg)	CFU/Thigh[b] (log_{10}) ± SEM	Δ CFU (log_{10}) after 24 h	MIC (µg/mL)
S. pneumoniae 7260 FQ-RSP	6.05	Cyclophosphamide: 150 mg/kg Day-4 100 mg/kg Day -1 IP Study Drug: 2 h post-inf Single Dose Oral	Delafloxacin			0.06
			250	0.95 ± 0.95	-6.61	
			90	1.91 ± 1.13	-5.65	
			30	5.84 ± 1.09	-1.72	
			Vehicle			
			NA	7.56 ± 0.59	--	
S. pneumoniae 7261 FQ-RSP	5.49		Delafloxacin			0.03
			250	1.62 ± 1.24	-4.45	
			90	5.64 ± 1.22	-0.43	
			30	6.03 ± 1.33	-0.04	
			Vehicle			
			NA	6.07 ± 0.95	--	

CFU = colony-forming units; FQ-RSP = fluoroquinolone-resistant *S. pneumoniae*; h = hour; IM = intramuscular; IP = intraperitoneal; MIC = minimum inhibitory concentration; MLS-s = macrolide-lincosamide-streptogramin-susceptible; NA = not applicable; PenI = penicillin intermediate; PenS = penicillin susceptible; post-inf = post-infection

[a] Intramuscular infection in the right hind thigh muscle

[b] CFU (log_{10} ± SEM) in thigh harvested 24 hours after inoculation, aseptically homogenized then serial diluted on Columbia CNA agar and incubated for 24 hours at 37°C in 5% CO_2.

Source: RD-01-333 Tables 1 to 10

Table E-5. Delafloxacin in the Treatment of Experimentally-Induced *E. coli* Soft-Tissue Infections in Neutropenic Mice

Organism[a] *E. coli* Strain	Bacterial Challenge IM[a] CFU/thigh(log_{10})	Treatment Schedule	Study Drug (mg/kg)	Δ CFU/thigh (log_{10})[b] after 24 h	MIC (µg/mL)
E. coli 1705874 ESBL+, MDR	5.63	Cyclophosphamide: 150 mg/kg Day-4 100 mg/kg Day -1 PO Study Drug: 2 h and 9 h post-infection SC	Delafloxacin		2
			160	+1.43	
			100	+2.27	
			50	+3.08	
			25	+3.25	
			Tigecycline		0.5–2
			50	-1.67	
			Vehicle		
			NA	+3.37	
E. coli 1705884	6.45	Cyclophosphamide: 150 mg/kg Day-4 100 mg/kg Day -1 PO Study Drug: 2 h and 9 h post-infection SC	Delafloxacin		0.016
			160	-2.84	
			100	-2.82	
			50	-2.22	
			25	-2.14	
			Ciprofloxacin		0.03–0.25
			50	-2.57	
			Vehicle		
			NA	+2.18	
E. coli 255010	5.25	Cyclophosphamide: 150 mg/kg Day-4 100 mg/kg Day -1 PO Study Drug: 2 h and 9 h post-infection SC	Delafloxacin		0.25
			160	-1.18	
			100	-0.91	
			50	-0.69	
			25	+0.41	
			Ciprofloxacin		0.016–0.06
			50	-2.52	
			Vehicle		
			NA	+2.65	

CFU = colony-forming units; ESBL+ = extended-spectrum beta-lactamase producing strain; h = hours; IM = intramuscular; MDR = multi-drug resistant, MIC = minimum inhibitory concentration; NA = not applicable; PO = oral
[a]Bacterial challenge was administered by Intramuscular infection in both caudal thigh muscles.
[b] Change in CFU (log_{10}) in thigh harvested 24 hours after inoculation, aseptically homogenized then serial diluted on blood agar and incubated for overnight and compared with bacterial burden in thighs at 2 hours post-challenge, when therapy was started.
Source: EF-3341-005 Table 4-1, Figure 4-1, Figure 4-2, Figure 4-3

Table E-6. Delafloxacin in the Treatment of Experimentally-Induced *K. pneumoniae* Soft-Tissue Infections in Neutropenic Mice

Organism[a] *K. pneumoniae* Strain	Bacterial Challenge IM[a] CFU/thigh(log_{10})	Treatment Schedule	Study Drug (mg/kg)/Route	ΔCFU/thigh (log_{10})[b] after 24 h	MIC (µg/mL)
K. pneumoniae 1705966	5.96	Cyclophosphamide: 150 mg/kg Day -4 100 mg/kg Day -1 PO Study Drug:[c] Post-infection SC or PO BID	Delafloxacin		0.060-0.125
			10/SC	+1.53	
			50/SC	-0.30	
			100/SC	-1.12	
			Ciprofloxacin		0.008
			25/SC	-2.52	
			Vehicle		
			NA	+1.94	
K. pneumoniae 1705966	5.80	Cyclophosphamide: 150 mg/kg Day -4 100 mg/kg Day -1 PO Study Drug:[c] Post-infection SC or PO BID	Delafloxacin		0.060–0.125
			50/SC	-0.57	
			100/SC	-1.53	
			160/SC	-2.58	
			Ciprofloxacin		0.008
			25/SC	-3.02	
			Vehicle		
			NA	+1.84	

Organism[a] *K. pneumoniae* Strain	Bacterial Challenge IM[a] CFU/thigh(log_{10})	Treatment Schedule	Study Drug (mg/kg)/Route	ΔCFU/thigh (log_{10})[b] after 24 h	MIC (µg/mL)
K. pneumoniae 1705966	6.12	Cyclophosphamide: 150 mg/kg Day -4 100 mg/kg Day -1 PO Study Drug:[c] Post-infection SC or PO BID	Delafloxacin		0.060–0.125
			100/PO	-2.56	
			100/SC	-1.80	
			Ciprofloxacin		0.008
			25/SC	-2.90	
			Vehicle		
			NA	+1.70	
K. pneumoniae 1705966	5.75	Cyclophosphamide: 150 mg/kg Day -4 100 mg/kg Day -1 PO Study Drug:[c] Post-infection SC or PO BID	Delafloxacin		0.060–0.125
			100/PO	-1.70	
			100/SC	-2.19	
			Ciprofloxacin		0.008
			25/SC	-2.87	
			Vehicle		
			NA	+2.00	

Organism[a] *K. pneumoniae* Strain	Bacterial Challenge IM[a] CFU/thigh(log_{10})	Treatment Schedule	Study Drug (mg/kg)/Route	ΔCFU/thigh (log_{10})[b] after 24 h	MIC (µg/mL)
K. pneumoniae 17059571 ESBL-positive, IMI[R]	4.70	Cyclophosphamide: 150 mg/kg Day -4 100 mg/kg Day -1 PO Study Drug:[c] Post-infection SC or PO BID	Delafloxacin		1-2.0
			160/SC	-0.08	
			100/SC	-0.33	
			50/SC	+0.11	
			Tigecycline		0.5-1.0
			50/SC	-1.03	
			Vehicle		
			NA	+4.06	

BID = twice daily; CFU = colony-forming units; ESBL = extended-spectrum beta-lactamase producing strain; IM = intramuscular; IMI[R] = imipenem- resistant; MIC = minimum inhibitory concentration; NA = not applicable; PO = oral administration; SC = subcutaneous
[a] Bacterial challenge was administered by intramuscular infection in both caudal thigh muscles.
[b] Change in CFU (log_{10}) in thigh harvested 24 hours after inoculation, aseptically homogenized then serial diluted on blood agar and incubated for overnight and compared with bacterial burden in thighs at 2 hours post-challenge, when therapy was started.
[c] In studies E1547 and E1553, the delafloxacin dose was titrated against *K. pneumoniae* 1705966; doses in these studies ranged from 10 mg/kg/dose SC to 160 mg/kg/dose SC. In studies E1577 and E1584, delafloxacin was dosed at 100 mg/kg/dose SC and PO and ciprofloxacin was dosed at 25 mg/kg/dose SC. In study E2110, the dose of delafloxacin was titrated from 50-160 mg/kg/dose against *K. pneumoniae* 17059571.
Source: EF-3341-008 Table 1, Figure 1, Figure 2, Figure 3

Table E-7. Delafloxacin in the Treatment of Experimentally-Induced Thigh Infections in Neutropenic Rats

Organism Strain Resistance profile	Bacterial Challenge IM[a] CFU/rat (log_{10})	Treatment Schedule	Study drug (mg/kg)	CFU/ thigh[b] (log_{10}) ± SEM 24 hours after last treatment	ED_{50} 95% CI[c] (mg/kg)	MIC (µg/mL)
S. pneumoniae 6303 MLS-s	1.36	Cyclophosphamide: Day-4: 150 mg/kg, IP Study Drugs: Day 0: 1 & 8 h post-inf Days 1 & 2 BID, oral	Delafloxacin 120, 80, 20	1.37 ± 0.60 to 3.26 ± 0.90	< 20	0.002
			Levofloxacin 240, 120, 60	0.94 ± 0.58 to 5.55 ± 0.18	120.1 (74.2-194.6)	1
			Trovafloxacin 80, 40, 20	1.54 ± 0.63 to 6.13 ± 0.27	46.6 (32.4-66.5)	0.25
			Vehicle	7.73 ± 0.10	-	
S. pneumoniae 7257 FQ-RSP	1.89	Cyclophosphamide: Day-4: 150 mg/kg, IP Study Drugs: Day 0: 1 & 8 h post-inf Days 1 & 2 BID, oral	Delafloxacin 120, 80, 20	1.46 ± 0.61 to 5.49 ± 0.63	36.0 (32.2-40.1)	0.03
			Levofloxacin 240, 160, 80	3.03 ± 0.12 to 6.48 ± 0.59	121.7 (99.4-149.1)	8
			Trovafloxacin 80, 20, 5	4.25 ± 0.18 to 7.08 ± 0.50	220.5 (170.7-284.8)	1-2
			Vehicle	7.74 ± 0.09	-	

BID = twice daily; CFU = colony-forming units; ED_{50} = effective dose 50%; IM = intramuscular; IP = intraperitoneal; MIC = minimum inhibitory concentration; MLS = macrolide-lincosamide-streptogramin-susceptible; Post-inf = post-infection; FQ-RSP = fluoroquinolone-resistant *S. pneumoniae*
[a] Intramuscular infection in the thigh muscle group
[b] Mean log_{10} CFU per thigh
[c] The ED_{50} is calculated based on a 3-log_{10} CFU reduction in bacterial burden compared to vehicle-treated control rats.
Source: RD-01-334 Table 1, Table 2, Table 3

Table E-8. Delafloxacin in the Treatment of Experimentally-Induced Pulmonary Infections in Mice

Organism Strain Resistance profile	Bacterial Challenge Intranasal[a] CFU/mouse (log_{10})	Treatment Schedule and Route of Administration	Study Drug[b] (mg/kg)	ΔCFU/ Lung[c] (log_{10}) 40 hours post-inf	Survival	MIC (µg/mL)
S. pneumoniae D39	6.71	18 and 24 h post-infection, SC	Delafloxacin			0.06
			50	-4.70	5/5	
			25	-4.76	3/5	
			10	-3.33	0/5	
			5	-3.11	0/5	
			1	-0.12	0/5	
		18 and 24 h post-infection, SC	Ciprofloxacin			0.5
			50	-1.82	0/5	
		18 and 24 h post-infection, Oral	Telithromycin			0.008
			100	-4.76[b]	5/5	
		18 and 24 h post-infection, SC	Vehicle			
			NA	+1.63	-	

CFU = colony-forming units; MIC = minimum inhibitory concentration; NA = not applicable; ND = not determined; post-inf = post-infection; PD_{50} = Protective Dose 50%; SC = subcutaneous
[a] PD_{50} = 44.03 (33.21 to 58.39)
[b] Delafloxacin was delivered in 5% dextrose in water (D5W), ciprofloxacin in saline, and telithromycin (5/5/90) in ethanol, Tween 80, and 0.5% methylcellulose.
[c] Limit of detection of the assay
Source: EF-3341-006 Figure 1

Table E-9. Delafloxacin in the Treatment of Experimentally-Induced Pulmonary Infections in Rats

Organism Strain Resistance profile	Bacterial Challenge intratrach[a] CFU/rat (log_{10})	Treatment Schedule	Study Drug (mg/kg)	CFU/ Lung[b] (log_{10}) ± SEM 24 h after last treatment	ED_{50} 95% CI[c] (mg/kg)	MIC (µg/mL)
S. pneumoniae 6303 MLS-s	5.78	18 h post-inf, Oral Days 1 & 2 QD	Delafloxacin 40, 10, 2.5	5.42 ± 0.06 to 6.94 ± 0.35	9.2 (5.9–14.4)	0.002
			Levofloxacin 240, 120, 60	2.86 ± 0.31 to 6.07 ± 0.55	86.0 (59.5–124.4)	1
			Trovafloxacin 40, 10, 2.5	5.16 ± 0.12 to 7.92 ± 0.03	31.9 (19.5–52.0)	0.25
			Vehicle	7.50 ± 0.25	–	
S. pneumoniae 5649 *mefE*, PenI	7.10	18 h post-inf, Oral Days 1 & 2 QD	Delafloxacin 80,20,5	2.23 ± 0.58 to 4.70 ± 0.15	< 5	0.002
			Levofloxacin 160, 40, 10	1.12 ± 0.70 to 5.04 ± 0.42	12.9 (8.9–18.6)	2
			Trovafloxacin 80, 20, 5	2.49 ± 0.11 to 5.38 ± 0.29	10.2 (6.3–16.5)	0.5
			Vehicle	6.88 ± 0.22	–	

Organism Strain Resistance profile	Bacterial Challenge intratrach[a] CFU/rat (log_{10})	Treatment Schedule	Study Drug (mg/kg)	CFU/ Lung[b] (log_{10}) ± SEM 24 h after last treatment	ED_{50} 95% CI[c] (mg/kg)	MIC (µg/mL)
S. pneumoniae 6396 *ermB*, PenS *ermAM*, PenS	5.54	18 h post-inf, Oral Days 1 & 2 QD	Delafloxacin 80, 20, 5, 1.25	0.88 ± 0.54 to 5.49 ± 0.71	5.0 (4.7–5.3)	0.004
			Levofloxacin 160, 40, 10	2.66 ± 0.31 to 5.89 ± 0.56	96.0 (90.8–101.5)	0.5
			Trovafloxacin 80, 20, 5, 1.25	2.54 ± 0.27 to 6.49 ± 0.39	34.3 (26.9–43.7)	0.06
			Vehicle	6.09 ± 0.17	–	
H. influenzae 1435	6.41	18 h post-inf, Oral Days 1 & 2 QD	Delafloxacin 10, 2.5,0.625	2.74 ± 0.09 to 3.92 ± 0.23	2.1 (0.8–5.7)	≤ 0.001
			Levofloxacin 10, 2.5,0.625	2.98 ± 0.17 to 5.47 ± 0.40	6.9 (4.0–11.7)	0.03
			Trovafloxacin 10, 2.5,0.625	2.83 ± 0.17 to 5.62 ± 0.62	5.9 (5.3–6.7)	0.03
			Vehicle	5.61 ± 0.20	–	

CFU = colony-forming units, CI = confidence interval, ED_{50} = Effective Dose 50%, h = hour; MIC = minimum inhibitory concentration; MLS_S = macrolide-lincosamide-streptogramin B-susceptible; PenI = penicillin-intermediate; PenS = penicillin-susceptible; post-inf = post-infection, QD = once daily

[a] Bacteria were introduced orally by feeding needle and delivered to the tracheal-bronchial interface.

[b] CFU (log_{10} ± SEM) in lung harvested 24 hours after the last treatment, aseptically homogenized then serial diluted on Columbia CNA agar (*S. pneumoniae*) or chocolate agar (*H. influenzae*) and incubated for 24 hours at 37°C in 5% CO_2.

[c] ED_{50} values are based on a dose calculated to reduce bacterial burden in the lung by 2-log_{10} CFU compared to vehicle-treated control rat

Source: RD-01-135 Table 1 to Table 6

Table E-10. Activity of Delafloxacin and Comparators Against an Experimentally-Induced MRSA Pyelonephritis in Mice

Organism	Bacterial Challenge CFU (log_{10}) /mouse	Treatment Schedule	Study Drug Doses (mg/kg)	Mean CFU After 48 hr (log_{10} ± SEM)	MIC (µg/mL)
MRSA 11540 CA-MRSA FQ-RSA, CM^R	7.66 via tail vein	4 h post-inf BID for 1 day	Delafloxacin (IV)		≤ 0.25
			150	-1.36	
			100	-1.29	
			50	-0.48	
			25	+2.49	
			Telithromycin (PO)		0.25
			100	-1.65[a]	
			Vancomycin		0.50
			100	-1.06	
			Vehicle		
			NA	3.73	

BID = twice daily; CA-MRSA=community-associated methicillin-resistant *S. aureus*; CFU = colony-forming units; CM^R = clindamycin resistant; FQ-RSA = fluoroquinolone resistant *S. aureus*; IV = intravenous; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; PO = oral; Post-inf = post-infection; SC = subcutaneous
[a] Limit of detection
Source: EF-3341-007

Table E-11. Effective Dose50 of Delafloxacin and Comparators Against an Experimentally-Induced Pyelonephritis in Mice

Organism	Bacterial Challenge CFU/mouse	Treatment Schedule	Study Drug Doses	ED_{50}[a] (95% C. I) mg/kg/day	Mean CFU at Day 3 (log_{10}) ± SEM	MIC (µg/mL)
E. coli 1289	3.6×10^6 IV in BHI broth	5 h post-inf BID on Days 1 & 2 Oral	Delafloxacin 10, 2.5, 0.63	1.1 (0.8–1.5)	1.42 ± 0.32 to 3.01 ± 0.63	0.008
			Levofloxacin	ND	-	0.03
			Trovafloxacin 10, 2.5, 0.63	1.6 (1.4–1.8)	0.99 ± 0.39 to 4.03 ± 0.97	0.008
			Ciprofloxacin	ND	-	0.004
			Vehicle	-	5.71 ± 0.65	
E. faecalis 1967	2.2×10^7 IV in BHI broth with 5% sheep blood	5 h post-inf BID on Days 1 & 2 Oral	Delafloxacin 150, 37.5, 9.38	28.9 (15.4–54.5)	3.51 ± 0.30 to 6.83 ± 0.15	0.03
			Levofloxacin 150, 37.5, 9.38	135.3 (72.8–251.3)	5.28 ± 0.34 to 7.57 ± 0.08	1
			Trovafloxacin 150, 37.5, 9.38	24.7 (16.3–37.6)	3.64 ± 0.18 to 7.02 ± 0.15	0.25
			Ciprofloxacin 150, 37.5, 9.38	> 150	6.10 ± 0.18 to 7.65 ± 0.07	0.5
			Vehicle	-	7.50 ± 0.06	
P. aeruginosa 5007	5.6×10^6 IV in BHI broth	17 h post-inf QD on Days 1 & 2	Delafloxacin 50, 12, 3.13	8.8 (6.0-13.0)	1.60 ± 0.49 to 6.88 ± 0.14	0.2
			Levofloxacin	ND	-	0.78
			Trovafloxacin 50, 12, 3.13	16.4 (11.5-23.6)	4.20 ± 0.48 to 7.62 ± 0.19	0.39
			Ciprofloxacin 50, 12, 3.13	14.9 (11.4-19.4)	3.08 ± 0.26 to 6.66 ± 0.14	0.39
			Vehicle	-	7.73 ± 0.13	

BHI = Brain heart infusion; BID = twice daily; CFU = colony-forming units; ED_{50} = Effective dose 50%; h = hours; IV = intravenous; MIC = minimum inhibitory concentration; ND = not done; post-inf = post-infection; QD = once daily; SEM = standard error of the mean; 95% CI = 95% Confidence Interval
[a] For *E. coli*, the ED_{50} is calculated based on a 3-log_{10} reduction in bacterial burden by linear regression analysis plotting the administered doses against the bacterial burden associated with those doses. For the other 2 organisms, ED_{50} was based on a 2-log_{10} reduction in bacterial burden.
Source: RD-01-332 Table 1 to Table 4

Table E-12. MIC values for Delafloxacin, Ciprofloxacin, and Vancomycin Against the Organisms used in the Rat Granuloma Pouch Infection Model

Strain	MIC (µg/mL)			Ratio[a]
	Delafloxacin	Ciprofloxacin	Vancomycin	Delafloxacin MIC/ Ciprofloxacin MIC
S. aureus MRSA 11540	0.65	128	0.6	1.1[b]
A. baumannii 1705943	0.25	0.25	NA	1
E. coli ATCC 25922	0.03	0.008	NA	3.75
P. aeruginosa PA01	0.25	0.12	NA	2
K. pneumoniae 1705966	0.06	0.008	NA	7.5

ATCC = American Type Culture Collection; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; NA = not applicable
[a]Ratio of delafloxacin MIC/ciprofloxacin MIC
[b]Ratio of delafloxacin MIC/vancomycin MIC
Source: EF-3341-003 Table 1

Table E-13. Single-Dose Pharmacokinetics for Delafloxacin in Mice and Rats

Species	Dose (mg/kg)	Route	C_{max} (µg/mL)	AUC_{∞} (µg·hr/mL)	Reference
Mouse	1.25	SC	0.65	0.81	PK-3341-002
	20		13.3	13.6	
	80		46.9	72.6	
	320		121.6	433.6	
	5	IV	-	7.18	M319492-12
	5	PO	4.57	3.88	
	20		13.42	15.38	
	30		19.57	17.14	
	90		26.49	56.32	
	250		47.09	127.41	
	2000		37.82	178.02	M319492-11
Rat	10	IV	21.5	11.15	PK-3341-001

Species	Dose (mg/kg)	Route	C_{max} (µg/mL)	AUC_{∞} (µg·hr/mL)	Reference
	5		-	11.74	MWQ3034-2
	5	PO		3.11	
	10		1.23	6.72	

AUC_{∞} = area under the concentration time curve from time 0 to infinity; C_{max} = maximum (peak) mean plasma drug concentration; IV = intravenous; PO = oral administration; SC = subcutaneous
Source: PK-3341-002 Table 1; PK-3341-001 Table 1; Abbott mouse reports M319492-11 Table 2 and M319492-12 Table 1; Abbott rat report MWQ3034-2 Table 1

Table E-14. *f*AUC_{24}/MIC Values for Bacterial Stasis and 1-log10 CFU Reduction for 5 *S. aureus* Strains

S. aureus Strain	MIC (µg/mL)	Free-Drug AUC:MIC Ratios Associated With Efficacy	
		Net Bacterial Stasis	1-log_{10} CFU↓
ATCC 13709	0.004	3.8	7.6
11540 (USA300)	0.8	9.3	14.3
2926 (USA100)	0.016	2.0	6.3
ATCC 29213	0.006	12.8	18.5
MRSA 11512	0.8	9.5	17.9
	Median	**9.3**	**14.3**
	Min., Max	2.0, 12.8	6.3, 18.5

AUC = area under the concentration-time curve; CFU = colony-forming unit; *f*AUC_{24}/MIC = ratio of free delafloxacin area under the mean concentration-time curve from time 0 to 24 hours to pathogen minimum inhibitory concentration; MIC = minimum inhibitory concentration
Source: PK-3341-005 Table 3

APPENDIX-F

Table F-1. Summary of Study Designs for Key Studies in Support of ABSSSI Indication

		RX-3341-201	RX-3341-202	RX-3341-302	RX-3341-303
Phase; Year Completed		Phase 2; 2008	Phase 2; 2011	Phase 3; 2014	Phase 3; 2016
Population		Adults with cSSSI (pre 2010 definition)	Adults with ABSSSI (required lesion size ≥ 75 cm^2) and at least 1 systemic sign of infection	Adults with ABSSSI (required lesion size ≥ 75 cm^2) and at least 2 systemic sign of infection	Adults with ABSSSI (required lesion size ≥ 75 cm^2) and at least 2 systemic sign of infection
Comparator (N)		Tigecycline (50)	Linezolid (77), Vancomycin (98) (optional aztreonam)	Vancomycin and aztreonam (329)	Vancomycin and aztreonam (427)
Delafloxacin Dose/Route (N)		300 mg IV Q12h (49), 450 mg IV Q12h (51)	300 mg IV Q12h (81)	300 mg IV Q12h (331)	300 mg IV Q12h for 6 doses with switch to 450 mg oral Q12h (423)
Duration of Therapy		5–14 d	5–14 d	5–14 d	5–14 d
Time points	**OR**	NA	48–72 h	48–72 h	48–72 h
	EOT	NA	NA	Assessment collected	Assessment collected
	FU	NA	Day 14	Day 14	Day 14
	LFU	NA	Day 21–28	Day 21–28	Day 21–28
	TOC	14–21 days post last dose	NA	NA	NA
Stratification Factors and Enrollment Limits at Randomization		Infection Type	Infection Type and Prior Antibiotics Enrollment limited to: Prior antibiotics – 30%, Abscesses – 30%	Infection Type Enrollment limited to: Prior antibiotics – 25%, Abscesses – 25%, Wounds – 35%	Infection Type and BMI (< or ≥ 30 kg/m^2). Enrollment limited to: Prior Antibiotics – 25%, Abscesses – 25%, Wounds – 30%, BMI ≥ 30 mg/kg^2 – ≤ 50%

	RX-3341-201	RX-3341-202	RX-3341-302	RX-3341-303
Primary Endpoint	Investigator outcome (traditional definition with complete or near resolution of signs and symptoms as cure)	Investigator assessment of cure only (similar to the Phase 3 studies, cure was classified as a success and all other responses were classified as failures [i.e., improved, failure, and indeterminate]).	Objective response at 48–72 h (at least 20% reduction in lesion size with no nonstudy med, major procedures or death)	Objective response at 48–72 h (at least 20% reduction in lesion size with no nonstudy med, major procedures or death)
Key Clinical Efficacy Secondary Endpoint	NA	Clinical success cessation: cessation of lesion spread at 48–72 h with resolution or absence of fever. Both must be sustained through 72 h. Clinical success reduction: reduction of lesion size (reported in 10% increments) at other time points including 48–72 h.	Investigator assessment of response of signs and symptoms of infection at the FU and LFU visit. Cure was the primary analysis.	Investigator assessment of response of signs and symptoms of infection at the FU and LFU visit. Cure was the primary analysis.

ABSSSI = acute bacterial skin and skin structure infection; BMI = body mass index; cSSSI = complicated skin and skin-structure infections; EOT = End of Treatment; FU = Follow-up; h = hours; IV = intravenous; LFU = Late Follow-up; NA = not applicable; OR = objective response; Q12h = every 12 hours; TOC = Test of Cure
Source: Section 2.7.3 Table 1

Table F-2. Distribution of Gram-positive Target Pathogens From ABSSSI Site or Blood During Phase 3 Studies Overall and by Geographic Region (MITT-Pool 1)

MITT:	North America - n (%; n/N)		Europe - n (%; n/N)		Overall - n (%; n/N)	
Organism	Delafloxacin (N = 359)	Vancomycin (aztreonam) (N = 358)	Delafloxacin (N = 139)	Vancomycin (aztreonam) (N = 144)	Delafloxacin (N = 518)	Vancomycin (aztreonam) (N = 524)
Staphylococci						
S. aureus	246 (68.5)	250 (69.8)	60 (43.2)	61 (42.4)	319 (61.6)	324 (61.8)
MRSA	136 (37.9)	137 (38.3)	6 (4.3)	1 (0.7)	144 (27.8)	141 (26.9)
MSSA	113 (31.5)	113 (31.6)	54 (38.8)	60 (41.7)	178 (34.4)	183 (34.9)
S. epidermidis	24 (6.7)	23 (6.4)	22 (15.8)	25 (17.4)	47 (9.1)	50 (9.5)
S. haemolyticus	4 (1.1)	2 (0.6)	10 (7.2)	4 (2.8)	15 (2.9)	8 (1.5)
S. lugdunensis	8 (2.2)	6 (1.7)	3 (2.2)	3 (2.1)	11 (2.1)	9 (1.7)
S. hominis	6 (1.7)	2 (0.6)	5 (3.6)	11 (7.6)	11 (2.1)	13 (2.5)
S. simulans	5 (1.4)	3 (0.8)	1 (0.7)	3 (2.1)	6 (1.2)	7 (1.3)

MITT:	North America - n (%; n/N)		Europe - n (%; n/N)		Overall - n (%; n/N)	
Organism	Delafloxacin (N = 359)	Vancomycin (aztreonam) (N = 358)	Delafloxacin (N = 139)	Vancomycin (aztreonam) (N = 144)	Delafloxacin (N = 518)	Vancomycin (aztreonam) (N = 524)
Streptococci						
S. anginosus Group	64 (17.8)	64 (17.9)	2 (1.4)	1 (0.7)	66 (12.7)	66 (12.6)
S. intermedius	29 (8.1)	29 (8.1)	0	1 (0.7)	29 (5.6)	30 (5.7)
S. anginosus	23 (6.4)	22 (6.1)	0	0	23 (4.4)	23 (4.4)
S. constellatus	12 (3.3)	13 (3.6)	2 (1.4)	0	14 (2.7)	13 (2.5)
S. pyogenes	6 (1.7)	8 (2.2)	12 (8.6)	10 (6.9)	23 (4.4)	18 (3.4)
S. agalactiae	7 (1.9)	5 (1.4)	7 (5.0)	6 (4.2)	14 (2.7)	12 (2.3)
S. dysgalactiae	2 (0.6)	3 (0.8)	5 (3.6)	8 (5.6)	9 (1.7)	11 (2.1)
S. mitis Group[a]	18 (5.0)	7 (2.0)	2 (1.4)	3 (2.1)	22 (4.3)	10 (1.9)
Enterococci						
E. faecalis	5 (1.4)	2 (0.6)	6 (4.3)	13 (9.0)	11 (2.1)	16 (3.1)

ABSSSI = acute bacterial skin and skin structure infection; MITT = microbiological intent-to-treat; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; N = total number of patients; n = total number of patients with positive cultures at baseline from the primary infection site or blood for the indicated pathogen

[a] Includes *S. cristatus, S. gordonii, S. massiliensis, S. oralis, S. parasanguinis, S. mitis/oralis, S. mitis group,* and *S. sanguinis*

Source: SCM Table 14.1.10.4.1

Table F-3. Distribution of Gram-negative Target Pathogens From ABSSSI Site or Blood During Phase 3 Studies Overall and by Geographic Region (MITT - Pool 1)

MITT:	North America - n (%; n/N)		Europe - n (%; n/N)		Overall - n (%; n/N)	
Organism	Delafloxacin (N = 359)	Vancomycin (aztreonam) (N = 358)	Delafloxacin (N = 139)	Vancomycin (aztreonam) (N = 144)	Delafloxacin (N = 518)	Vancomycin (aztreonam) (N = 524)
Enterobacteriaceae						
K. pneumoniae	18 (5.0)	20 (5.6)	4 (2.9)	3 (2.1)	22 (4.2)	23 (4.4)
E. coli	4 (1.1)	5 (1.4)	10 (7.2)	11 (7.6)	14 (2.7)	20 (3.8)
E. cloacae	10 (2.8)	3 (0.8)	4 (2.9)	8 (5.6)	14 (2.7)	11 (2.1)
P. mirabilis	2 (0.6)	2 (0.6)	6 (4.3)	6 (4.2)	8 (1.5)	8 (1.5)
K. oxytoca	4 (1.1)	1 (0.3)	2 (1.4)	4 (2.8)	6 (1.2)	5 (1.0)
Non-Enterobacteriaceae						
P. aeruginosa	6 (1.7)	4 (1.1)	4 (2.9)	8 (5.6)	11 (2.1)	12 (2.3)
H. parainfluenzae	6 (1.7)	7 (2.0)	0	0	6 (1.2)	7 (1.3)

ABSSSI = acute bacterial skin and skin structure infection; MITT = microbiological intent-to-treat; N = total number of patients; n = total number of patients with positive cultures at baseline from the primary infection site or blood for the indicated pathogen

Table F-4. Monomicrobial and Polymicrobial Infections at Baseline by Treatment Group From ABSSSI Site or Blood (MITT and MEFUI Populations)

MITT	RX-3341-302		RX-3341-303		Pool 1	
	Delafloxacin N (%; N/N1)	Vancomycin (Aztreonam) N (%; N/N1)	Delafloxacin N (%; N/N1)	Vancomycin (Aztreonam) N (%; N/N1)	Delafloxacin N (%; N/N1)	Vancomycin (Aztreonam) N (%; N/N1)
All Infection Types, N1	243	247	275	277	518	524
Monomicrobial						
Gram-positive	168 (69.1)	172 (69.6)	171(62.2)	184 (66.4)	339 (65.4)	356 (67.9)
Gram-negative	6 (2.5)	10 (4.0)	11 (4.0)	19 (6.9)	17 (3.3)	29 (5.5)
Polymicrobial						
Gram-positive	35 (14.4)	32 (13.0)	47 (17.1)	36 (13.0)	82 (15.8)	68 (13.0)
Gram-negative	1 (0.4)	1 (0.4)	6 (2.2)	1 (0.4)	7 (1.4)	2 (0.4)
Gram-positive and -negative	33 (13.6)	32 (13.0)	40 (14.5)	37 (13.4)	73 (14.1)	69 (13.2)
Aerobe and anaerobe	16 (6.6)	13 (5.3)	12 (4.4)	17 (6.1)	28 (5.4)	30 (5.7)

MEFUI	RX-3341-302		RX-3341-303		Pool 1	
	Delafloxacin N (%; N/N1)	Vancomycin (Aztreonam) N (%; N/N1)	Delafloxacin N (%; N/N1)	Vancomycin (Aztreonam) N (%; N/N1)	Delafloxacin N (%; N/N1)	Vancomycin (Aztreonam) N (%; N/N1)
All Infection Types, N1	179	184	231	212	410	396
Monomicrobial						
Gram-positive	126 (70.4)	125 (67.9)	144 (62.3)	138 (65.1)	270 (65.9)	263 (66.4)
Gram-negative	6 (3.4)	10 (5.4)	10 (4.3)	16 (7.5)	16 (3.9)	26 (6.6)
Polymicrobial						
Gram-positive	24 (13.4)	23 (12.5)	41 (17.7)	28 (13.2)	65 (15.9)	51 (12.9)
Gram-negative		1 (0.5)	5 (2.2)	1 (0.5)	5 (1.2)	2 (0.5)
Gram-positive and -negative	23 (12.8)	25 (13.6)	31 (13.4)	29 (13.7)	54 (13.2)	54 (13.6)
Aerobe and anaerobe	9 (5.0)	11 (6.0)	10 (4.3)	11 (5.2)	19 (4.6)	22 (5.6)

ABSSSI = acute bacterial skin and skin structure infection; MEFUI = microbiologically evaluable at follow-up for the investigator-assessed response; MITT = microbiological intent-to-treat
Source: SCM Tables 14.1.10.7.1 and Table 14.1.10.7.2

Table F-5. Summary of Delafloxacin Activity by MIC Against Gram-positive Baseline Target Pathogens From ABSSSI Site or Blood Overall and by Geographic Region (MITT-Delafloxacin and Comparator Treatment Arms, Pool 1)

Organism	North America (N = 717)				Europe (N = 283)				Overall (N = 1042)			
	n	Range	$MIC_{50/90}$	% LVX-NS	n	Range	$MIC_{50/90}$	% LVX-NS	n	Range	$MIC_{50/90}$	% LVX-NS
Staphylococci												
S. aureus	511	0.002-4	0.008/0.25	44.4	145	0.002-0.5	0.004/0.008	2.8	685	0.002-4	0.008/0.25	33.7
MRSA	281	0.004-4	0.12/0.25	68.0	7	0.004-0.5	NA/NA	42.9	294	0.002-4	0.12/0.25	66.0
MSSA	234	0.002-0.5	0.008/0.12	15.8	138	0.002-0.12	0.004/0.008	0.7	395	0.002-0.5	0.008/0.03	9.6
S. epidermidis	52	0.002-1	0.008/0.12	11.5	51	0.004-0.5	0.008/0.12	13.7	106	0.002-2	0.008/0.12	14.2
S. haemolyticus	6	0.008-0.5	NA/NA	33.3	15	0.008-0.5	0.008/0.5	26.7	24	0.008-8	0.008/0.5	37.5
S. lugdunensis	13	0.008-0.03	0.015/0.03	0.0	6	0.015-0.03	NA/NA	0.0	19	0.008-0.03	0.015/0.03	0.0
S. hominis	8	0.002-0.008	NA/NA	0.0	16	0.002-1	0.004/0.008	6.3	24	0.002-1	0.004/0.008	4.2
S. simulans	8	0.002-0.25	NA/NA	12.5	4	0.002-0.008	NA/NA	0.0	13	0.002-0.25	0.004/0.03	7.7
Streptococci												
S. anginosus Group	88	≤ 0.004-0.06	0.008/0.03	0.0	1	0.015	NA/NA	0.0	90	≤ 0.004-0.06	0.008/0.03	0.0
S. intermedius	33	≤ 0.004-0.03	0.008/0.015	0.0	1	0.015	NA/NA	0.0	34	≤ 0.004-0.03	0.008/0.015	0.0
S. anginosus	43	≤ 0.004-0.06	0.015/0.03	0.0	0	NA	NA/NA	NA	44	≤ 0.004-0.06	0.015/0.03	0.0
S. constellatus	12	≤ 0.004-0.015	≤ 0.004/0.008	0.0	0	NA	NA/NA	NA	12	≤ 0.004-0.015	≤ 0.004/0.008	0.0
S. pyogenes	14	0.008-0.03	0.015/0.03	0.0	27	0.015-0.06	0.015/0.06	0.0	46	0.008-0.06	0.015/0.06	0.0
S. agalactiae	13	0.015-0.03	0.03/0.03	0.0	13	0.015-0.06	0.03/0.06	0.0	27	0.015-0.06	0.03/0.06	0.0
S. dysgalactiae	5	0.015-0.03	NA/NA	0.0	15	0.008-0.03	0.015/0.03	0.0	23	0.008-0.03	0.015/0.03	0.0
S. mitis Group[a]	22	≤ 0.004-0.12	0.03/0.06	0.0	5	0.015-0.12	NA/NA	0.0	29	≤ 0.004-0.12	0.03/0.06	0.0
Organism	**North America (N = 717)**				**Europe (N = 283)**				**Overall (N = 1042)**			
	n	**Range**	**$MIC_{50/90}$**	**% LVX-NS**	**n**	**Range**	**$MIC_{50/90}$**	**% LVX-NS**	**n**	**Range**	**$MIC_{50/90}$**	**% LVX-NS**
Enterococci												
E. faecalis	7	0.03-0.12	NA/NA	0.0	19	≤ 0.004-2	0.12/1	15.8	27	≤ 0.004-2	0.12/1	11.1

ABSSSI = acute bacterial skin and skin structure infection; MIC = minimum inhibitory concentration (µg/mL); MIC_{50} = MIC against 50% of the isolates; MIC_{90} = MIC against 90% of the isolates; MITT = microbiological intent-to-treat; N = total number of patients; n = total number of MIC values from isolates cultured at baseline from the primary infection site or blood; LVX = levofloxacin; NS = non-susceptible (intermediate plus resistant per CLSI M100-S25 interpretive criteria); NA = not applicable
[a] Includes *S. cristatus*, *S. gordonii*, *S. oralis*, *S. sanguinis*, *S. mitis/oralis*, *S. mitis group*, *S. massiliensis and S. parasanguis*
Source: SCM Tables 14.2.5.27.1 and 14.2.12.1; MB-3341-073 Tables 4 and 6; Microbiology Reviewer's Guide

Table F-6. Summary of Delafloxacin Activity by MIC Against Gram-negative Baseline Target Pathogens From ABSSSI Site or Blood Overall and by Geographic Region (MITT-Delafloxacin and Comparator Treatment Arms, Pool 1)

Organism	North America (N = 717)				Europe (N = 283)				Overall (N = 1042)			
	n	Range	$MIC_{50/90}$	% LVX-NS	n	Range	$MIC_{50/90}$	% LVX-NS	n	Range	$MIC_{50/90}$	% LVX-NS
Enterobacteriaceae												
K. pneumoniae	38	0.03-0.25	0.12/0.25	0.0	7	0.03-4	NA/NA	14.3	45	0.03-4	0.12/0.25	2.2
E. coli	9	0.03-0.06	NA/NA	0.0	21	0.008-4	0.06/1	4.8	35	0.008-4	0.06/4	5.7
E. cloacae	13	0.03-2	0.12/0.5	0.0	13	0.06-> 8	0.12/4	7.7	26	0.03-> 8	0.12/2	3.8
P. mirabilis	4	0.03-2	NA/NA	25.0	12	0.03-> 8	0.06/2	16.7	16	0.03-> 8	0.06/2	18.8
K. oxytoca	5	0.06-0.25	NA/NA	0.0	6	0.008-0.25	NA/NA	0.0	11	0.008-0.25	0.12/0.25	0.0
Non-Enterobacteriaceae												
P. aeruginosa	10	0.12-4	0.25/4	30.0	13	0.12-> 8	0.25/1	23.1	24	0.12-> 8	0.25/4	25.0
H. parainfluenzae	13	≤ 0.004-0.015	≤ 0.004/0.015	0.0	0	NA	NA/NA	NA	13	≤ 0.004-0.015	≤ 0.004/0.015	0.0

ABSSSI = acute bacterial skin and skin structure infection; MIC = minimum inhibitory concentration (µg/mL); MIC_{50} = MIC against 50% of the isolates; MIC_{90} = MIC against 90% of the isolates; MITT = microbiological intent-to-treat; N = total number of patients; n = total number of MIC values from isolates cultured at baseline from the primary infection site or blood; LVX = levofloxacin; NS = non-susceptible (intermediate plus resistant per CLSI M100-S25 interpretive criteria); NA = not applicable
Source: SCM Table 14.2.5.27.1 and 14.2.12.1

Table F-7. Summary of Delafloxacin Activity by Zone Diameter Against Gram-positive Baseline Target Pathogens From ABSSSI Site or Blood Overall and by Geographic Region (MITT-Delafloxacin and Comparator Treatment Arms, Pool 1)

Organism	North America (N = 717)				Europe (N = 283)				Overall (N = 1042)			
	n	Min, Max	Median	Mean (SD)	n	Min, Max	Median	Mean (SD)	n	Min, Max	Median	Mean (SD)
Staphylococci												
S. aureus	510	15, 45	33.0	32.5 (6.20)	145	24, 46	39.0	38.3 (4.25)	684	15, 46	35.0	34.0 (6.28)
MRSA	281	15, 43	27.0	29.5 (5.57)	7	24, 40	32.0	32.9 (6.31)	294	15, 43	28.0	29.8 (5.69)
MSSA	233	23, 45	37.0	36.1 (4.85)	138	26, 46	39.0	38.6 (3.95)	394	23, 46	38.0	37.1 (4.67)
S. epidermidis	52	22, 45	41.0	39.5 (4.78)	52	25, 49	38.0	37.9 (4.97)	107	17, 49	40.0	38.4 (5.40)
S. haemolyticus	6	25, 44	40.0	36.2 (8.42)	14	25, 50	42.0	39.1 (8.90)	23	10, 50	41.0	35.7 (10.62)
S. lugdunensis	14	36, 44	41.5	40.5 (2.18)	6	33, 41	35.0	36.2 (3.54)	20	33, 44	39.5	39.2 (3.27)
S. hominis	8	32, 45	39.0	38.8 (4.10)	15	18, 45	40.0	38.1 (6.91)	23	18, 45	39.0	38.3 (5.98)
S. simulans	8	24, 46	42.5	40.4 (6.91)	4	39, 50	42.5	43.5 (4.80)	13	24, 50	42.0	40.9 (6.24)
Streptococci												
S. anginosus Group	130	28, 50	39.0	39.4 (5.05)	3	33, 45	36.0	38.0 (6.24)	134	28, 50	39.0	39.3 (5.07)
S. intermedius	59	30, 50	42.0	41.8 (4.02)	1	45	45	45.0 (NA)	60	30, 50	42.0	41.9 (4.00)
S. anginosus	45	28, 49	36.0	35.4 (4.24)	0	NA	NA	NA	46	28, 49	36.0	35.3 (4.21)
S. constellatus	26	33, 49	41.0	40.8 (4.21)	2	33, 36	34.5	34.5 (2.12)	28	33, 49	41.0	40.3 (4.39)
S. pyogenes	14	25, 34	29.0	29.1 (2.07)	27	22, 37	27.0	28.3 (4.24)	46	22, 37	28.0	28.6 (3.50)
S. agalactiae	13	26, 36	30.0	29.8 (3.08)	13	25, 30	28.0	27.6 (1.61)	27	25, 36	28.0	28.7 (2.61)
S. dysgalactiae	5	26, 33	31.0	30.6 (2.88)	15	25, 33	29.0	29.1 (2.20)	23	25, 33	30.0	29.7 (2.34)
S. mitis Group[a]	26	30, 47	34.5	37 (5.5)	5	27, 44	31	32.2 (7.0)	33	27, 47	34.0	36.1 (5.8)
Enterococci												
E. faecalis	7	25, 33	26.0	27.9 (2.91)	19	15, 33	25.0	23.8 (4.15)	27	15, 33	25.0	24.8 (4.20)

ABSSSI = acute bacterial skin and skin structure infection; Max = maximum zone diameter; Min = minimum zone diameter; MITT = microbiological intent-to-treat; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = Methicillin-susceptible *Staphylococcus aureus*; n = total number of zone diameter values from isolates cultured at baseline from the primary infection site or blood; N = total number of patients; NA = not applicable; NS = non-susceptible (intermediate plus resistant per CLSI M100-S25 interpretive criteria); LVX = levofloxacin; SD = standard deviation
Zone diameter values shown in millimeters
Results are in mm.
[a] Includes *S. cristatus, S. gordonii, S. oralis, S. sanguinis, S. mitis group, S. parasanguis, S. mitis/oralis and S. massiliensis*
Source: SCM Table 14.2.14.1.1; MB-3341-073 Table 5 and Table 6

Table F-8. Summary of Delafloxacin Activity by Disk Against Gram-negative Baseline Target Pathogens From ABSSSI Site or Blood Overall and by Geographic Region (MITT-Delafloxacin and Comparator Treatment Arms, Pool 1)

Organism	North America (N = 717)				Europe (N = 283)				Overall (N = 1042)			
	n	Min, Max	Median	Mean (SD)	n	Min, Max	Median	Mean (SD)	n	Min, Max	Median	Mean (SD)
Enterobacteriaceae												
K. pneumoniae	38	22, 29	26.0	25.9 (1.55)	7	13, 27	26.0	24.3 (5.02)	45	13, 29	26.0	25.7 (2.41)
E. coli	9	27, 35	31.0	30.6 (2.70)	21	11, 32	28.0	26.3 (5.83)	35	6, 35	28.0	25.1 (7.95)
E. cloacae	13	16, 29	27.0	26.4 (3.28)	13	6, 30	27.0	24.3 (6.96)	26	6, 30	27.0	25.3 (5.43)
P. mirabilis	4	13, 33	31.0	27.0 (9.38)	12	6, 37	31.0	25.3 (11.06)	16	6, 37	31.0	25.8 (10.38)
K. oxytoca	5	24, 28	25.0	25.8 (1.64)	6	25, 31	27.0	27.5 (1.97)	11	24, 31	27.0	26.7 (1.95)
Non-Enterobacteriaceae												
P. aeruginosa	10	13, 30	27.0	23.6 (7.15)	13	6, 31	28.0	24.8 (6.78)	24	6, 31	27.5	24.4 (6.68)
H. parainfluenzae	13	24, 43	36.0	34.5 (6.08)	0	NA	NA	NA	13	24, 43	36.0	34.5 (6.08)

ABSSSI = acute bacterial skin and skin structure infection; Max = maximum; MIC = minimum inhibitory concentration; MIC_{50} = MIC against 50% of the isolates; MIC_{90} = MIC against 90% of the isolates; Min = minimum; MITT = microbiological intent-to-treat; n = total number of zone diameter values from isolates cultured at baseline from the primary infection site or blood; LVX = levofloxacin; N = total number of patients; NA = not applicable; NS = non-susceptible (intermediate plus resistant per CLSI M100-S25 interpretive criteria); SD = standard deviation
Results are in mm.
Source: SCM Table 14.2.14.1.1

Table F-9. Summary of Per-Pathogen Favorable Response Rates for Delafloxacin-Treated Patients With Gram-positive Baseline Pathogens and Delafloxacin MIC Values at Baseline

Organism	Per-Pathogen Rate of Response (n/N [%]) for the Indicated Outcomes and Populations (Pool 1)								
	Responder at 48-72 hr (Objective Response; ME72O)			Eradicated or Presumed Eradicated at FU (Microbiologic Response; MEFUI)			Eradicated or Presumed Eradicated at LFU (Microbiologic Response; MELFI)		
	North America	Europe	Overall	North America	Europe	Overall	North America	Europe	Overall
Staphylococci									
S. aureus	203/225 (90.2)	48/59 (81.4)	262/297 (88.2)	180/184 (97.8)	54/54 (100)	244/248 (98.4)	179/184 (97.3)	52/52 (100)	243/248 (98.0)
MRSA	113/128 (88.3)	5/6 (83.3)	120/136 (88.2)	101/103 (98.1)	4/4 (100)	106/108 (98.1)	99/102 (97.1)	4/4 (100)	105/108 (97.2)
MSSA	93/100 (93.0)	43/53 (81.1)	145/164 (88.4)	81/83 (97.6)	50/50 (100)	140/142 (98.6)	82/84 (97.6)	48/48 (100)	140/142 (98.6)
S. epidermidis	19/22 (86.4)	15/21 (71.4)	35/44 (79.5)	18/19 (94.7)	16/18 (88.9)	35/38 (92.1)	17/18 (94.4)	17/19 (89.5)	35/38 (92.1)
S. haemolyticus	3/3 (100)	7/10 (70.0)	11/14 (78.6)	3/3 (100)	8/8 (100)	12/12 (100)	3/3 (100)	8/8 (100)	12/12 (100)
S. lugdunensis	6/7 (85.7)	2/3 (66.7)	8/10 (80.0)	7/7 (100)	3/3 (100)	10/10 (100)	7/7 (100)	3/3 (100)	10/10 (100)
S. hominis	6/6 (100)	5/5 (100)	11/11 (100)	5/5 (100)	5/5 (100)	10/10 (100)	4/4 (100)	4/5 (80.0)	8/9 (88.9)
S. simulans	4/5 (80.0)	0/1 (0.0)	4/6 (66.7)	4/4 (100)	1/1 (100)	5/5 (100)	3/3 (100)	1/1 (100)	4/4 (100)

Organism	Per-Pathogen Rate of Response (n/N [%]) for the Indicated Outcomes and Populations (Pool 1)								
	Responder at 48-72 hr (Objective Response; ME72O)			Eradicated or Presumed Eradicated at FU (Microbiologic Response; MEFUI)			Eradicated or Presumed Eradicated at LFU (Microbiologic Response; MELFI)		
	North America	Europe	Overall	North America	Europe	Overall	North America	Europe	Overall
Streptococci									
S. anginosus Group	33/33 (100)	0/0 (NA)	33/33 (100)	26/26 (100)	0/0 (NA)	26/26 (100)	26/26 (100)	0/0 (NA)	26/26 (100)
S. intermedius	9/9 (100)	0/0 (NA)	9/9 (100)	8/8 (100)	0/0 (NA)	8/8 (100)	6/6 (100)	0/0 (NA)	6/6 (100)
S. anginosus	19/19 (100)	0/0 (NA)	19/19 (100)	14/14 (100)	0/0 (NA)	14/14 (100)	16/16 (100)	0/0 (NA)	16/16 (100)
S. constellatus	5/5 (100)	0/0 (NA)	5/5 (100)	4/4 (100)	0/0 (NA)	4/4 (100)	4/4 (100)	0/0 (NA)	4/4 (100)
S. pyogenes	5/6 (83.3)	8/12 (66.7)	17/23 (73.9)	3/3 (100)	12/12 (100)	18/19 (94.7)	4/4 (100)	12/12 (100)	20/21 (95.2)
S. agalactiae	5/6 (83.3)	5/7 (71.4)	10/13 (76.9)	5/5 (100)	6/6 (100)	11/11 (100)	6/6 (100)	5/6 (83.3)	11/12 (91.7)
S. dysgalactiae	2/2 (100)	3/5 (60.0)	7/9 (77.8)	2/2 (100)	3/3 (100)	7/7 (100)	2/2 (100)	4/4 (100)	8/8 (100)
S. mitis Group[a]	16/16 (100)	2/2 (100)	20/20 (100)	14/14 (100)	2/2 (100)	18/18 (100)	15/15	2/2 (100)	19/19 (100)
Enterococci									
E. faecalis	5/5 (100)	6/6 (100)	11/11 (100)	3/4 (75.0)	6/6 (100)	9/10 (90.0)	3/4 (75.0)	3/3 (100)	6/7 (85.7)

FU = follow-up; ME72O = microbiologically evaluable at 48 to 72 hours (± 2 hours) for the objective response; MEFUI = microbiologically evaluable at FU for the investigator-assessed response; MELFI = microbiologically evaluable at LFU for the investigator-assessed response; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; LFU = late follow-up; N = total number of patients with an eligible pathogen and a delafloxacin MIC at baseline; n = total number of patients with the indicated response; NA = not applicable

[a] Includes *S. cristatus*, *S. gordonii*, *S. mitis group*, *S. oralis*,*S. mitis/oralis* and *S. sanguinis*

Source: SCM Table 14.2.15.1.2, Table 14.2.16.1.2, and Table 14.2.16.1.3; MB-3341-073 Table 6

Table F-10. Summary of Per-Pathogen Favorable Response Rates for Delafloxacin Treated Patients With Gram-negative Baseline Pathogens and Delafloxacin MIC Values at Baseline

Organism	Per-Pathogen Rate of Response (n/N [%]) for the Indicated Outcomes and Populations (Pool 1):								
	Responder at 48-72 hr (Objective Response; ME72O)			Eradicated or Presumed Eradicated at FU (Microbiologic Response; MEFUI)			Eradicated or Presumed Eradicated at LFU (Microbiologic Response; MELFI)		
	North America	Europe	Overall	North America	Europe	Overall	North America	Europe	Overall
Enterobacteriaceae									
K. pneumoniae	15/16 (93.8)	3/4 (75.0)	18/20 (90.0)	13/13 (100)	4/4 (100)	17/17 (100)	14/14 (100)	4/4 (100)	18/18 (100)
E. coli	3/4 (75.0)	9/10 (90.0)	12/14 (85.7)	3/3 (100)	8/8 (100)	11/11 (100)	4/4 (100)	7/8 (87.5)	11/12 (91.7)
E. cloacae	8/10 (80.0)	2/4 (50.0)	10/14 (71.4)	7/8 (87.5)	4/4 (100)	11/12 (91.7)	8/9 (88.9)	4/4 (100)	12/13 (92.3)
P. mirabilis	1/1 (100)	5/6 (83.3)	6/7 (85.7)	2/2 (100)	5/5 (100)	7/7 (100)	2/2 (100)	4/4 (100)	6/6 (100)
K. oxytoca	4/4 (100)	1/2 (50.0)	5/6 (83.3)	4/4 (100)	2/2 (100)	6/6 (100)	4/4 (100)	2/2 (100)	6/6 (100)
Non-Enterobacteriaceae									
P. aeruginosa	4/6 (66.7)	4/4 (100)	9/11 (81.8)	6/6 (100)	4/4 (100)	11/11 (100)	6/6 (100)	3/3 (100)	10/10 (100)
H. parainfluenzae	6/6 (100)	0/0 (NA)	6/6 (100)	3/3 (100)	0/0 (NA)	3/3 (100)	3/3 (100)	0/0 (NA)	3/3 (100)

FU = follow-up; ME72O = microbiologically evaluable at 48 to 72 hours (± 2 hours) for the objective response; MEFUI = microbiologically evaluable at FU for the investigator-assessed response; MELFI = microbiologically evaluable at LFU for the investigator-assessed response; MIC = minimum inhibitory concentration; LFU = late follow-up; n = total number of patients with the indicated response; N = total number of patients with an eligible pathogen and a delafloxacin MIC at baseline; NA = not applicable
Source: SCM Table 14.2.15.1.2, Table 14.2.16.1.2, Table 14.2.16.1.3

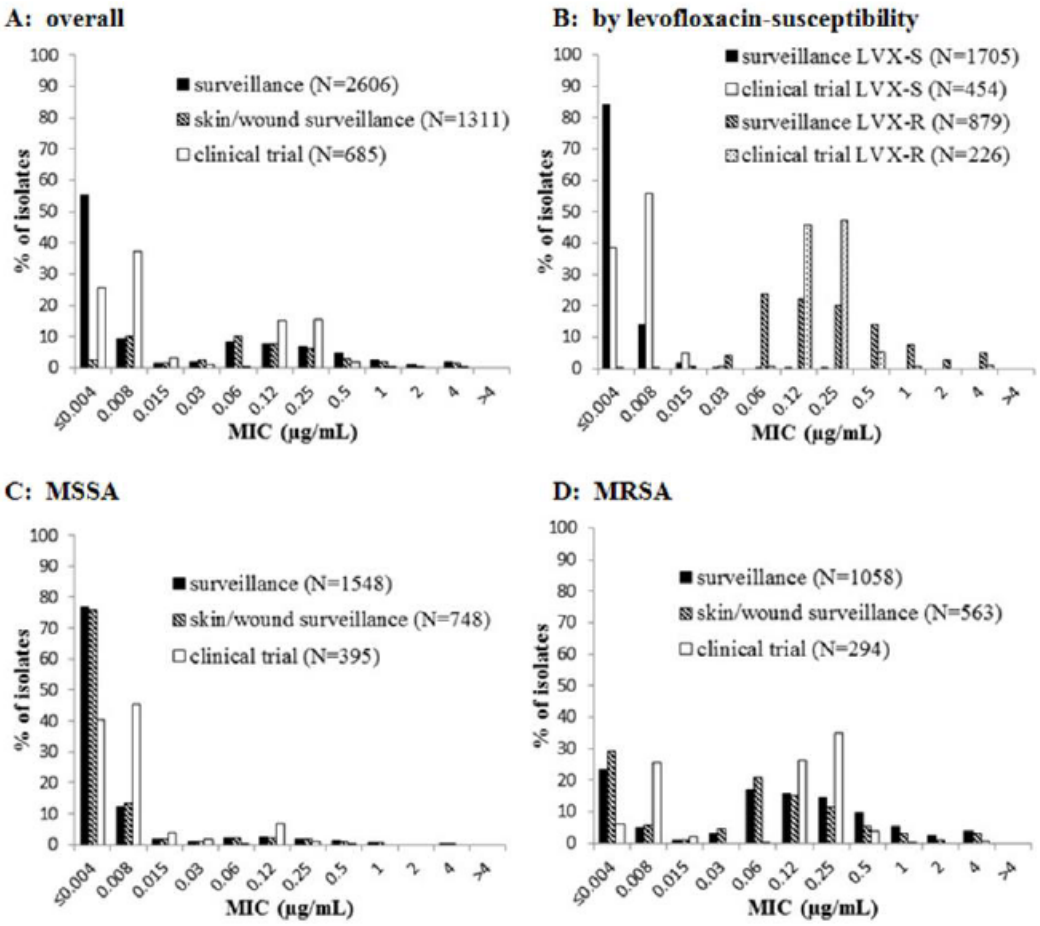
Table F-11. Summary of Agar: Broth Microdilution MIC Ratios Observed for Delafloxacin With Gram-positive and –negative Clinical Isolates

Organism	N[a]	Agar MIC:Broth MIC ratio (% of isolates)							% Essential Agreement
		≤ 0.12	0.25	0.5	1	2	4	≥ 8	
Staphylococcus aureus	33	3.0		51.5	45.4				96.9
Staphylococcus aureus (MSSA)	17	5.9		52.9	41.2				94.1
Staphylococcus aureus (MRSA)	16			50.0	50.0				100
Streptococcus spp.	29	3.4	24.1	55.2	17.2				72.4
Streptococcus pneumoniae	12	8.3	41.7	50.0					50.0
β-hemolytic streptococci[b]	10		10.0	60.0	30.0				90.0
Streptococcus anginosus Group[c]	7		14.3	57.1	28.6				85.7
Enterobacteriaceae	55		1.8	16.4	56.4	21.8			94.6[d]
Escherichia coli	17			11.8	70.6	17.6			100
Klebsiella pneumoniae	16		6.3	12.5	62.5	18.8			93.8
Other[e]	22			22.8	40.9	27.3			91.0[d]

MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*
[a] Isolates with agar and/or broth MICs which enabled an evaluation of essential agreement (defined as the percentage of isolates having an agar:broth MIC ratio of 0.5-2 [agar MIC was identical or within 2-fold of the broth microdilution MIC])
[b] *S. agalactiae* (5) and *S. pyogenes* (5)
[c] *S. anginosus* (6) and *S. constellatus* (1)
[d] Includes 1 isolate of *C. freundii* (1746) with an agar:broth ratio of < 0.5 and 1 isolate of *S. marcescens* (1433) with an agar:broth ratio of > 2
[e] *P. mirabilis* (2), *P. vulgaris* (4), *E. aerogenes* (3), *E. cloacae* (2), *C. freundii* (3), *C. koseri* (2), and *S. marcescens* (6)
Source: MB-3341-052 Table 1

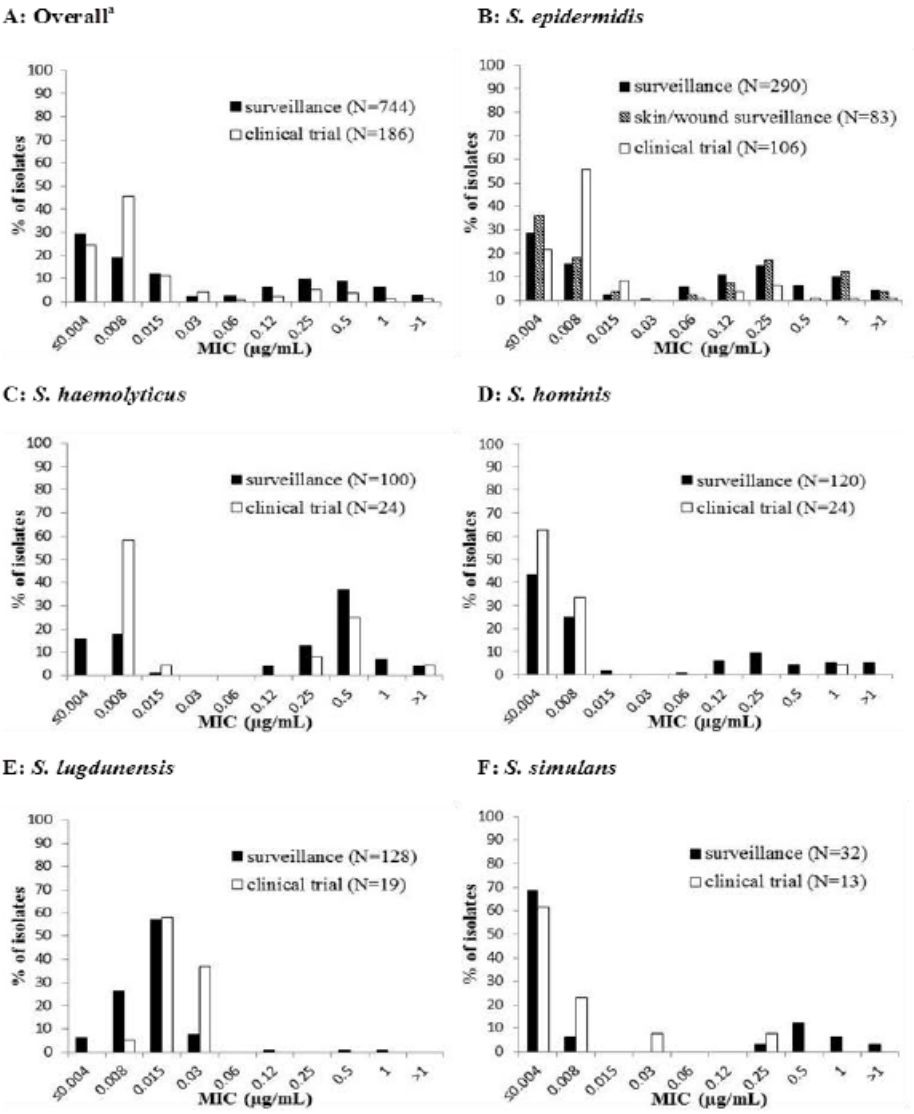
APPENDIX G

Figure G-1. MIC Distribution of Delafloxacin Against (A) *S. aureus* Overall, (B) by Levofloxacin Susceptibility Phenotype, (C) MSSA, and (D) MRSA as Observed During Phase 3 Clinical Studies (MITT at Baseline-Delafloxacin and Comparator Treatment Arms Pool 1) and Recent Surveillance



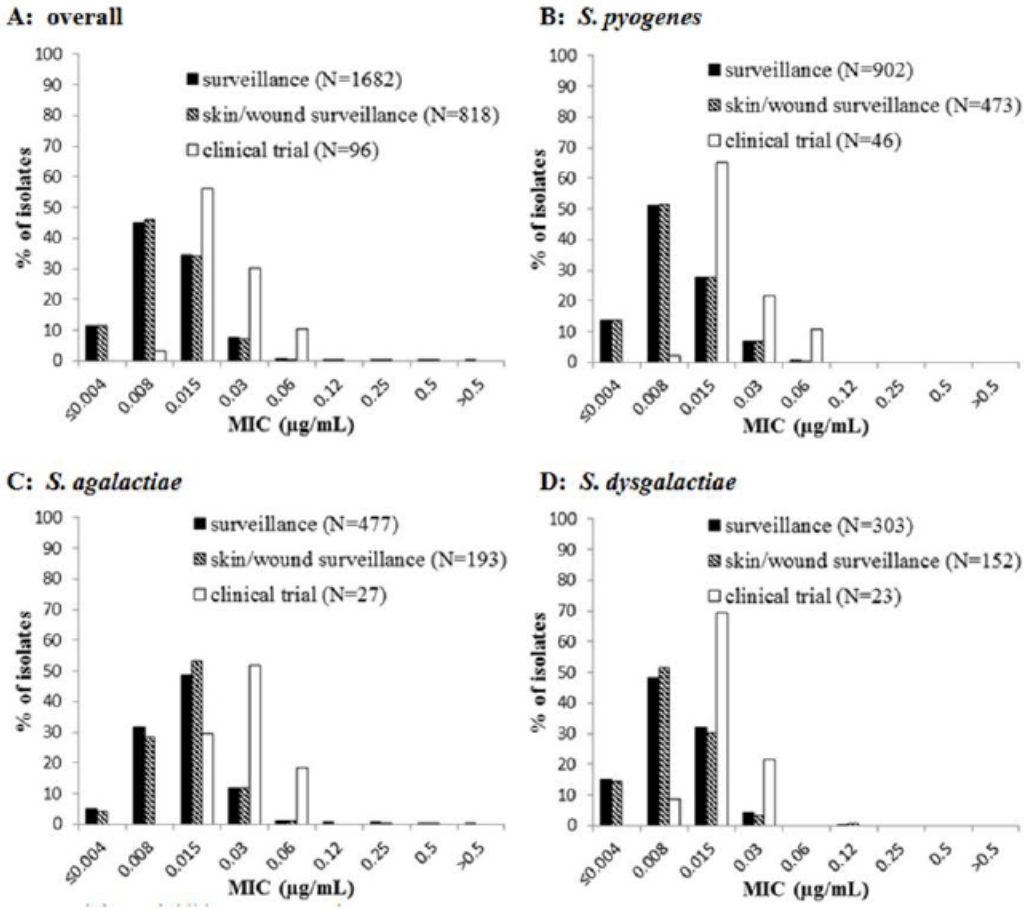
LVX = levofloxacin; MIC = minimum inhibitory concentration; MITT = microbiological intent-to-treat; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; N = number of subjects; R = resistant; S = susceptible
Skin/wound surveillance isolates are a subpopulation of overall surveillance isolates
Source: SCM Table 14.2.5.24.1; Surveillance Studies Appendix 2.1

Figure G2. MIC Distribution of Delafloxacin Against (A) CoNS Overall, (B) *S. epidermidis*, (C) *S. haemolyticus*, (D) *S. hominis*, (E) *S. lugdunensis*, (F) *S. simulans* as Observed During Phase 3 Clinical Studies (MITT at Baseline-Delafloxacin and Comparator Treatment Arms Pool 1) and Recent Surveillance



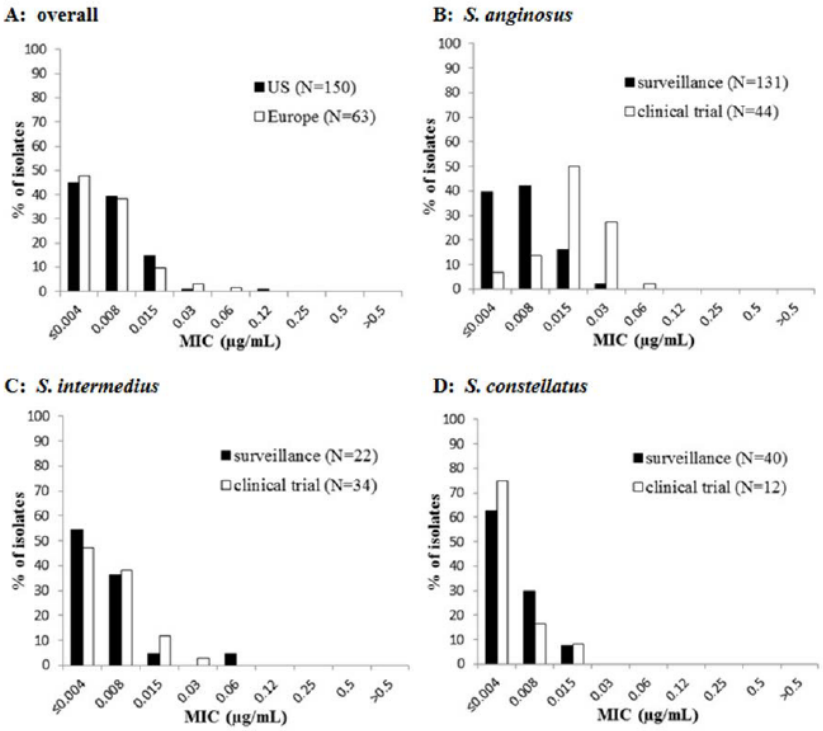
CoNS = coagulase-negative staphylococci; MIC = minimum inhibitory concentration; MITT = microbiological intent-to-treat; N = number of subjects
Skin/wound surveillance isolates are a subpopulation of overall surveillance isolates
[a] Surveillance isolates of CoNS overall include species other than target CoNS species for delafloxacin
Source: SCM Table 14.2.5.24.1; Surveillance Studies Appendix 2.2

Figure G3. MIC Distribution of Delafloxacin Against (A) β-hemolytic Streptococci Overall, (B) *S. pyogenes*, (C) *S. agalactiae*, and (D) *S. dysgalactiae* as Observed During Phase 3 Clinical Studies (MITT at Baseline-Delafloxacin and Comparator Treatment Arms Pool 1) and Recent Surveillance



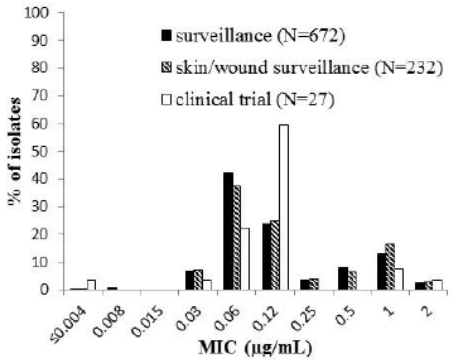
MIC = minimum inhibitory concentration; MITT = microbiological intent-to-treat; N = number of subjects
Skin/wound surveillance isolates are a subpopulation of overall surveillance isolates
Source: SCM Table 14.2.5.24.1; Surveillance Studies Appendix 2.6.1; Surveillance Studies Appendix 2.6.2; Surveillance Studies Appendix 2.6.3

Figure G4. MIC Distribution of Delafloxacin Against (A) *S. anginosus* Group Overall, (B) *S. anginosus*, (C) *S. intermedius*, and (D) *S. constellatus* As Observed During Phase 3 Clinical Studies (MITT at Baseline-Delafloxacin and Comparator Treatment Arms Pool 1) and Recent Surveillance



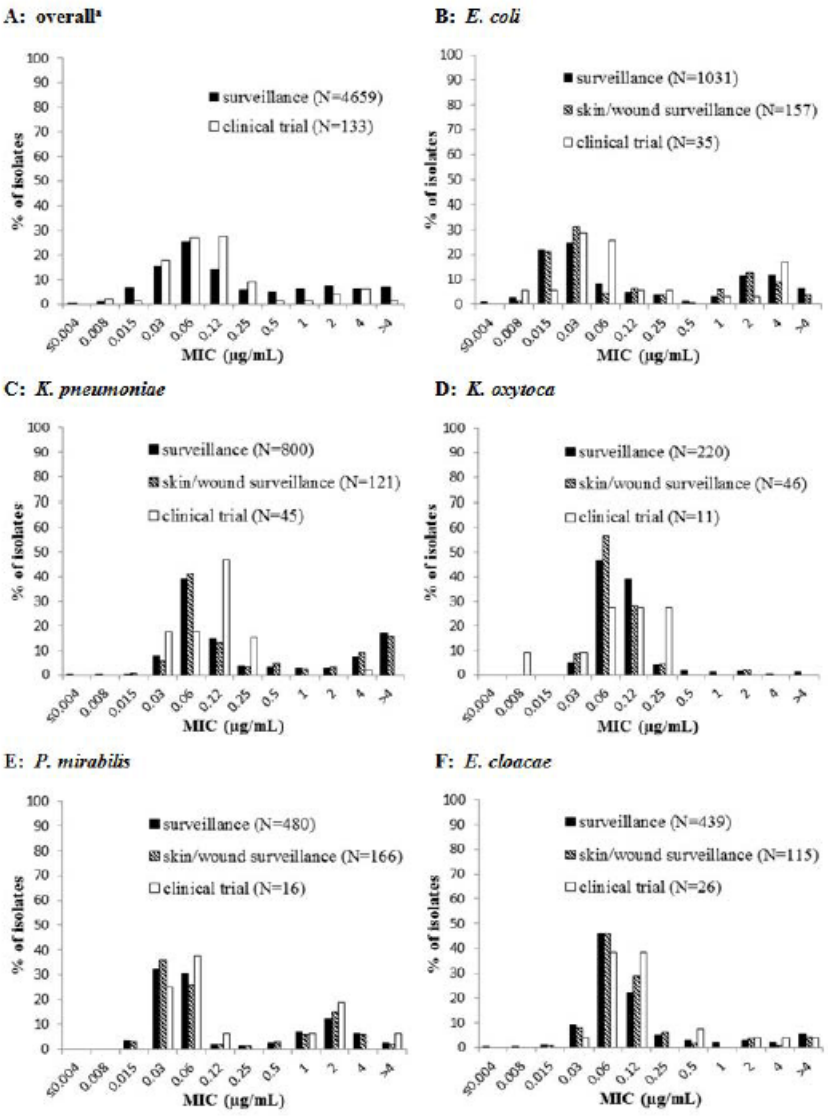
MIC = minimum inhibitory concentration; MITT = microbiological intent-to-treat; N = number of subjects;
US = United States
Skin/wound surveillance isolates are a subpopulation of overall surveillance isolates
Source: SCM Table 14.2.5.24.1; Surveillance Studies Appendix 2.7.1

Figure G5. MIC Distribution of Delafloxacin Against *E. faecalis* as Observed During Phase 3 Clinical Studies (MITT at Baseline Delafloxacin and Comparator Treatment Arms Pool 1) and Recent Surveillance



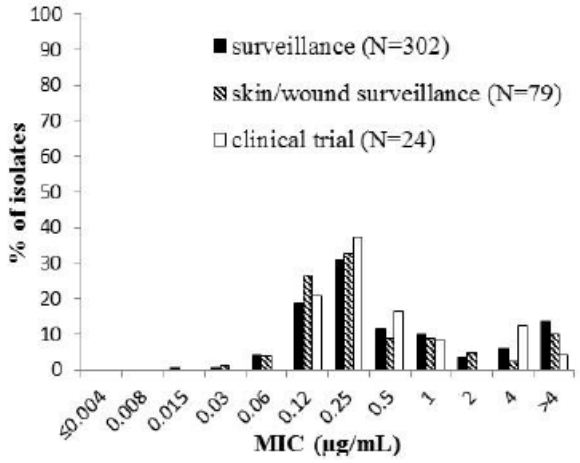
MIC = minimum inhibitory concentration; MITT = microbiological intent-to-treat; N = number of subjects
Skin/wound surveillance isolates are a subpopulation of overall surveillance isolates
Source: SCM Table 14.2.5.24.1; Surveillance Studies Appendix 2.3

Figure G6. MIC Distribution of Delafloxacin Against (A) Enterobacteriaceae Overall, (B) *E. coli*, (C) *K. pneumoniae*, (D) *K. oxytoca*, (E) *P. mirabilis*, and (F) *E. cloacae* as Observed During Phase 3 Clinical Studies (MITT at Baseline-Delafloxacin and Comparator Treatment Arms Pool 1) and Recent Surveillance



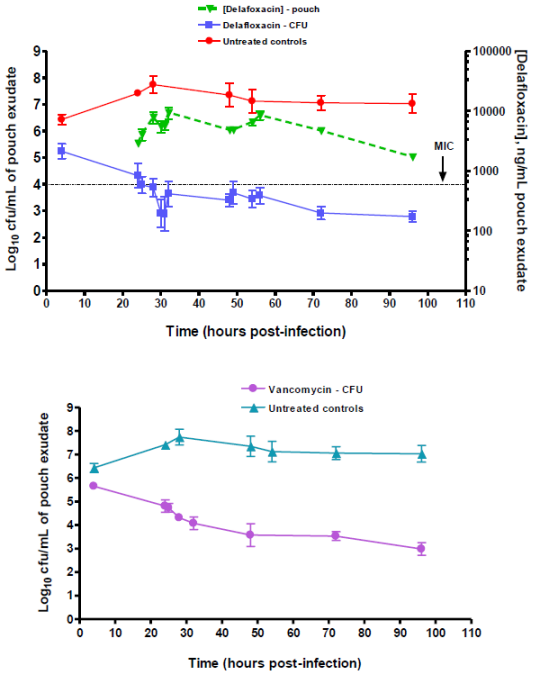
MIC = minimum inhibitory concentration; MITT = microbiological intent-to-treat; N = number of subjects
Enterobacteriaceae spp. for delafloxacin
Skin/wound surveillance isolates are a subpopulation of overall surveillance isolates
[a] Surveillance isolates of Enterobacteriaceae overall include species other than target
Source: SCM Table 14.2.5.24.1; Surveillance Studies Appendix 2.8; Surveillance Studies Appendix 2.9; Surveillance Studies Appendix 2.10.1; Surveillance Studies Appendix 2.10.2; Surveillance Studies Appendix 2.11; Surveillance Studies Appendix 2.13

Figure G7. MIC Distribution of Delafloxacin Against P. aeruginosa as Observed During Phase 3 Clinical Studies (MITT at Baseline-Delafloxacin and Comparator Treatment Arms Pool 1) and Recent Surveillance



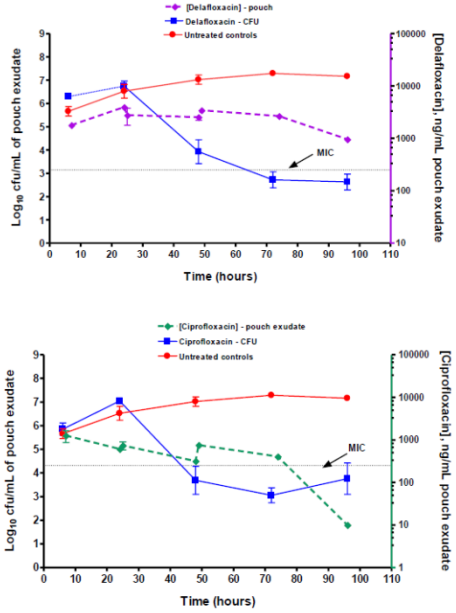
MIC = minimum inhibitory concentration; MITT = microbiological intent-to-treat; N = number of subjects
Skin/wound surveillance isolates are a subpopulation of overall surveillance isolates
Source: SCM Table 14.2.5.24.1; Surveillance Studies Appendix 2.18

Figure G8. MRSA 11540-infected Rat Granuloma Pouches Treated With Delafloxacin (50 mg/kg SC, top) and Vancomycin (75 mg/kg SC, bottom)



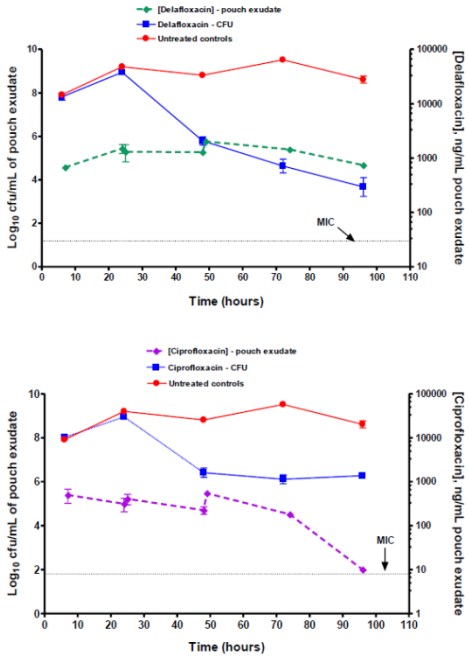
CFU = colony-forming unit; SC = subcutaneous
Source: EF-3341-003 Figure 1

Figure G9. *A. baumannii* 1705943-infected Rat Granuloma Pouches Treated With Delafloxacin (50 mg/kg SC, top) and Ciprofloxacin (50 mg/kg SC, bottom)



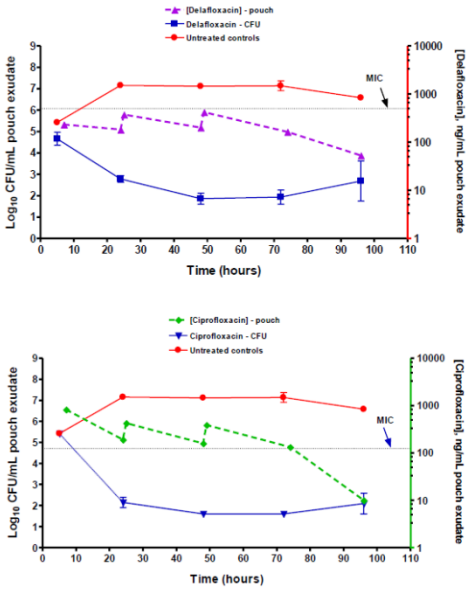
CFU = colony-forming unit; SC = subcutaneous
Source: EF-3341-003 Figure 2

Figure G10. *E. coli* 25922-infected Rat Granuloma Pouches Treated With Delafloxacin (25 mg/kg SC, top) and Ciprofloxacin (25 mg/kg SC, bottom)



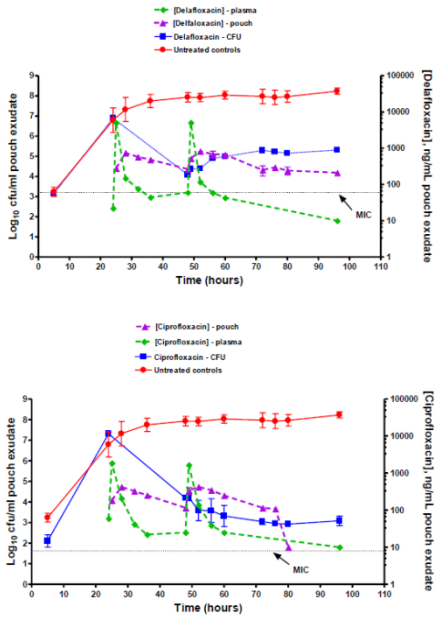
CFU = colony-forming unit; SC = subcutaneous
Source: EF-3341-003 Figure 3

Figure G11. *P. aeruginosa* PA01-infected Rat Granuloma Pouches Treated With Delafloxacin (15 mg/kg SC, top) and Ciprofloxacin (15 mg/kg SC, bottom)



CFU = colony-forming unit; SC = subcutaneous
Source: EF-3341-003 Figure 4

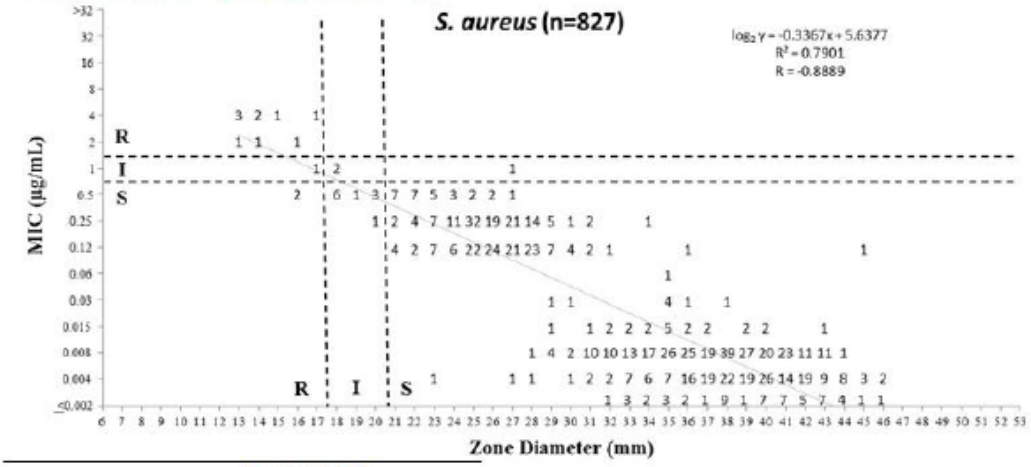
Figure G12. *K. pneumoniae* 1705966-infected Rat Granuloma Pouches Treated With Delafloxacin (10 mg/kg SC, top) and Ciprofloxacin (10 mg/kg SC, bottom)



CFU = colony-forming unit; SC = subcutaneous
Source: EF-3341-003 Figure 5

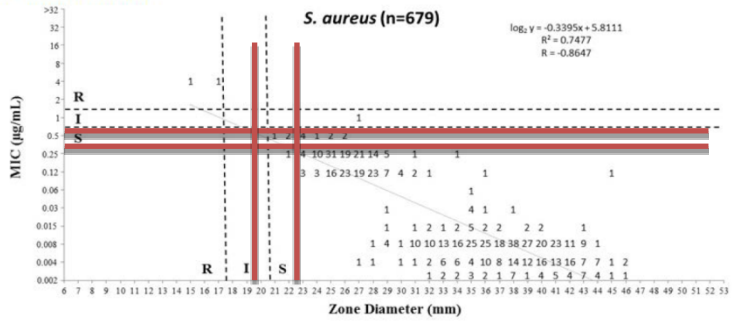
Figure G13. Broth Versus Disk Correlation and Error-rate bounding Analysis Based on Proposed Interpretive Criteria for Delafloxacin Against *S. aureus* (A) Overall (Profiling and Clinical Study Isolates) and (B) Clinical Study Isolates (MITT – Delafloxacin and Comparator Treatment Arms Pool 1)

A: Overall (Profiling and Clinical Trial Isolates)



MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ I−2	7	0	(0.0)		NA	0	(0.0)
I−1 to I-1	46	0	(0.0)	2	(4.3)	12	(26.1)
≤ I-2	774		NA	1	(0.1)	0	(0.0)
TOTAL	827	0	(0.0)	3	(0.4)	12	(1.5)

B: Clinical Trial Isolates



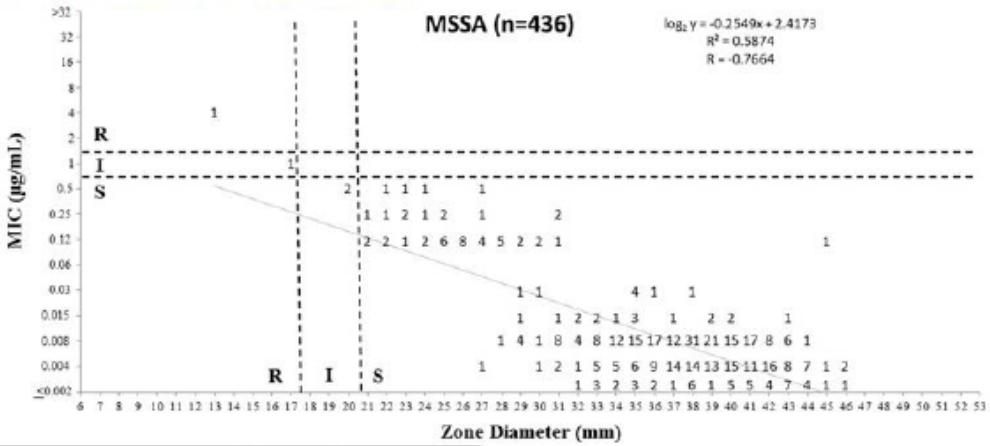
MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ I+2	2	0	(0.0)		NA	0	(0.0)
I+1 to I-1	13	0	(0.0)	0	(0.0)	1	(7.7)
≤ I-2	664		NA	0	(0.0)	0	(0.0)
TOTAL	679	0	(0.0)	0	(0.0)	1	(0.1)

MIC Range	N	Discrepancy Rates: Very Major, n (%)	Major, n(%)	Minor, n(%)
≥I+2	2	0 (0%)	NA	0 (0%)
I+1 to I-1	120	1(0.8%)	0 (0%)	10 (8.3%)
≤I-2	557	NA	0 (0%)	0 (0%)
Total	679	1 (0.1%)	0 (0%)	10 (1.5 %)

Recommended disk diffusion BPs:
≥23(S)/20-22(I)/≤19(R)

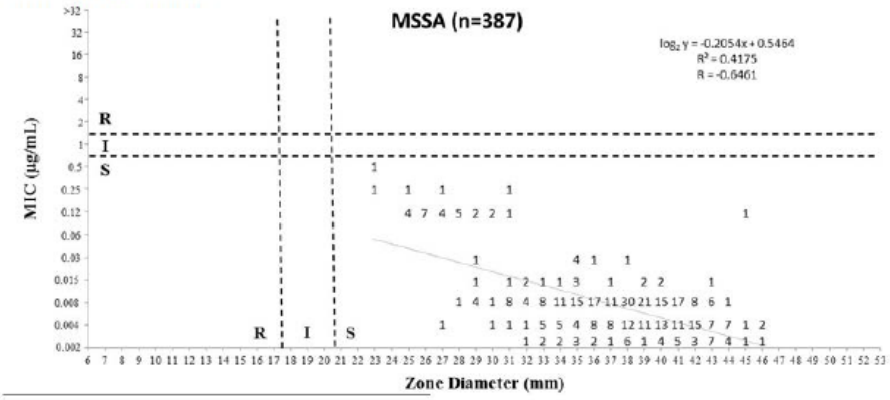
Figure G14. Broth Versus Disk Correlation and Error-rate bounding Analysis Based on Proposed Interpretive Criteria for Delafloxacin Against MSSA (A) Overall (Profiling and Clinical Study Isolates) and (B) Clinical Study Isolates (MITT – Delafloxacin and Comparator Treatment Arms Pool 1)

A: Overall (Profiling and Clinical Trial Isolates)



MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ I+2	1	0	(0.0)	NA		0	(0.0)
I+1 to I-1	7	0	(0.0)	0	(0.0)	3	(42.9)
≤ I-2	428	NA		0	(0.0)	0	(0.0)
TOTAL	436	0	(0.0)	0	(0.0)	3	(0.7)

B: Clinical Trial Isolates

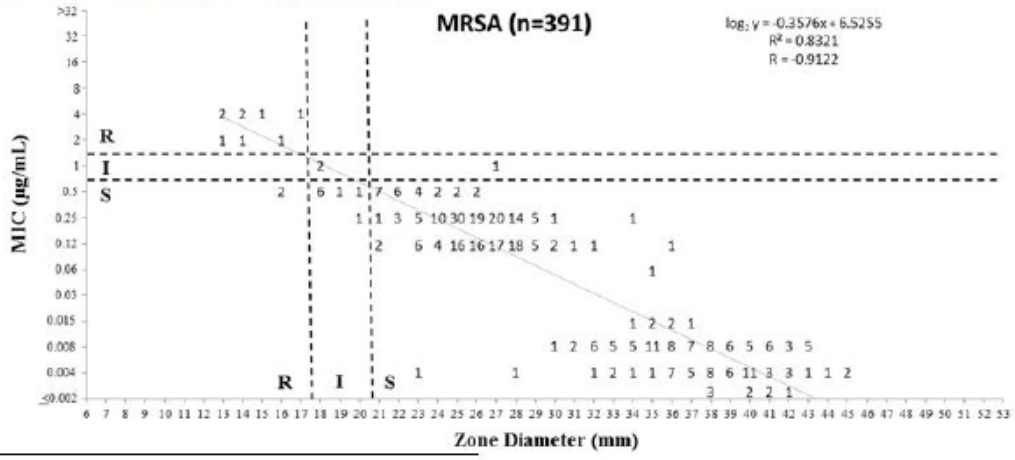


MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ I+2	0	0	(0.0)	NA		0	(0.0)
I+1 to I-1	1	0	(0.0)	0	(0.0)	0	(0.0)
≤ I-2	386	NA		0	(0.0)	0	(0.0)
TOTAL	387	0	(0.0)	0	(0.0)	0	(0.0)

I = intermediate; Major = false resistant by disk; MIC = minimum inhibitory concentration; mm = millimeter; Minor = false intermediate by disk or broth; MITT = microbiological intent-to-treat; MSSA = methicillin-susceptible *S. aureus*; n = number of isolates with indicated discrepancy between disk diffusion and broth microdilution interpretation based on proposed interpretive criteria; N = number of isolates in indicated MIC range; NA = not applicable; R = resistant; S = susceptible; Very Major = false susceptible by disk
Source: MB-3341-028-A1 Appendix; Microbiology Reviewer's Guide

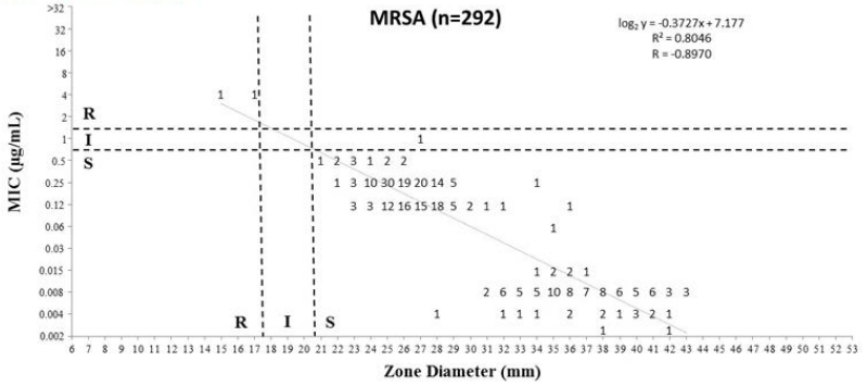
Figure G15. Broth Versus Disk Correlation and Error-rate bounding Analysis Based on Proposed Interpretive Criteria for Delafloxacin Against MRSA (A) Overall (Profiling and Clinical Study Isolates) and (B) Clinical Study Isolates (MITT – Delafloxacin and Comparator Treatment Arms Pool 1)

A: Overall (Profiling and Clinical Trial Isolates)



MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ I+2	6	0	(0.0)	NA		0	(0.0)
I+1 to I-1	39	0	(0.0)	2	(5.1)	9	(23.1)
≤ I-2	346	NA		0	(0.0)	1	(0.3)
TOTAL	391	0	(0.0)	2	(0.5)	10	(2.6)

B: Clinical Trial Isolates

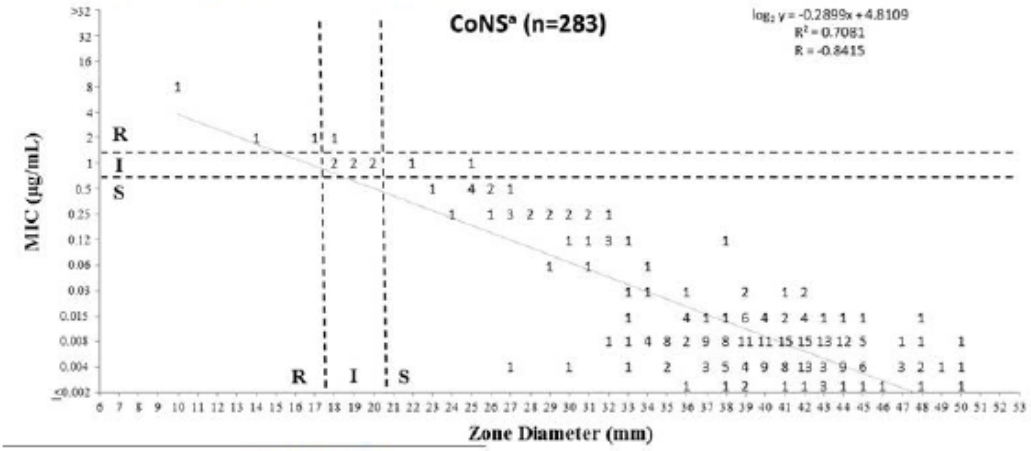


MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ I+2	2	0	(0.0)	NA		0	(0.0)
I+1 to I-1	12	0	(0.0)	0	(0.0)	1	(8.3)
≤ I-2	278	NA		0	(0.0)	0	(0.0)
TOTAL	292	0	(0.0)	0	(0.0)	1	(0.3)

I = intermediate; Major = false resistant by disk; MIC = minimum inhibitory concentration; Minor = false intermediate by disk or broth; MITT = microbiological intent-to-treat; mm = millimeter; MRSA = methicillin-resistant *S. aureus*; n = number of isolates with indicated discrepancy between disk diffusion and broth microdilution interpretation based on proposed interpretive criteria; N = number of isolates in indicated MIC range; NA = not applicable; R = resistant; S = susceptible; Very Major = false susceptible by disk
Source: MB-3341-028-A1 Appendix; Microbiology Reviewer's Guide

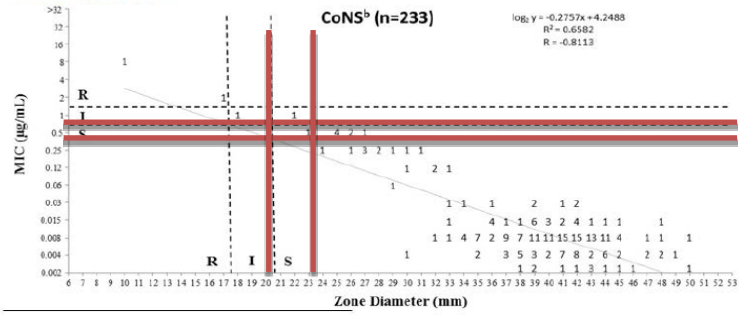
Figure G16. Broth Versus Disk Correlation and Error-rate bounding Analysis Based on Proposed Interpretive Criteria for Delafloxacin Against Coagulase-Negative Staphylococci (A) Overall (Profiling and Clinical Study Isolates) and (B) Clinical Study Isolates (MITT – Delafloxacin and Comparator Treatment Arms Pool 1)

A: Overall (Profiling and Clinical Trial Isolates)



MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ I+2	1	0	(0.0)		NA	0	(0.0)
I+1 to I-1	19	0	(0.0)	0	(0.0)	3	(15.8)
≤ I-2	263		NA	0	(0.0)	0	(0.0)
TOTAL	283	0	(0.0)	0	(0.0)	3	(1.1)

B: Clinical Trial Isolates



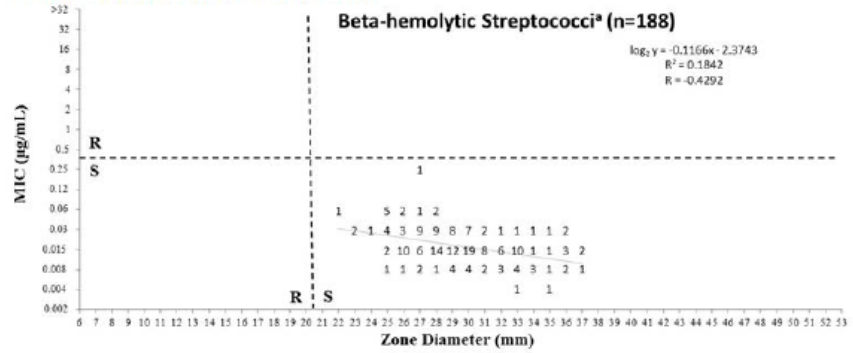
MIC Range	N	Discrepancy Rates: Very Major n(%)	Major n(%)	Minor n(%)
≥ I+2	1	0 (0.0)	NA	0 (0.0)
I+1 to I-1	11	0 (0.0)	0 (0.0)	1 (9.1)
≤ I-2	221	NA	0 (0.0)	0 (0.0)
TOTAL	233	0 (0.0)	0 (0.0)	1 (0.4)

MIC Range	N	Discrepancy Rates: Very Major, n (%)	Major, n(%)	Minor, n(%)
≥I+2	2	0 (0%)	NA	0 (0%)
I+1 to I-1	20	0 (0%)	0 (0%)	8 (40%)
≤I-2	211	NA	0 (0%)	0 (0%)
Total	233	0 (0%)	0 (0%)	8 (3.4 %)

Recommended disk diffusion BPs:
≥24(S)/21-23(I)/≤20(R)

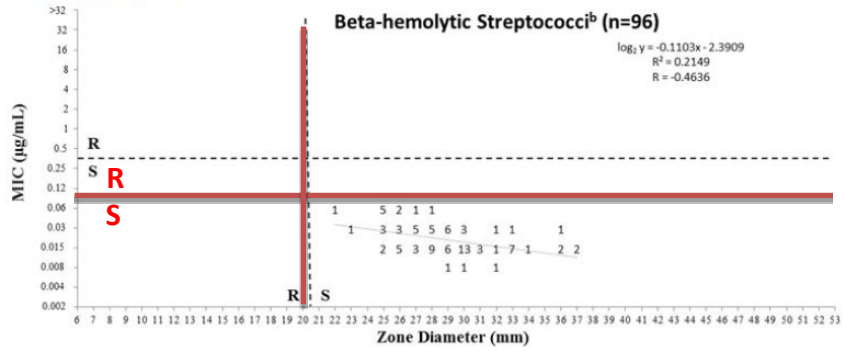
Figure G17. Broth Versus Disk Correlation and Error-rate bounding Analysis Based on Proposed Interpretive Criteria for Delafloxacin Against β-hemolytic Streptococci (A) Overall (Profiling and Clinical Study Isolates) and (B) Clinical Study Isolates (MITT – Delafloxacin and Comparator Treatment Arms Pool 1)

A: Overall (Profiling and Clinical Trial Isolates)



MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ R+1	0	0	(0.0)		NA	0	(0.0)
R+S	1	0	(0.0)	0	(0.0)	0	(0.0)
≤ S-1	187		NA	0	(0.0)	0	(0.0)
TOTAL	188	0	(0.0)	0	(0.0)	0	(0.0)

B: Clinical Trial Isolates



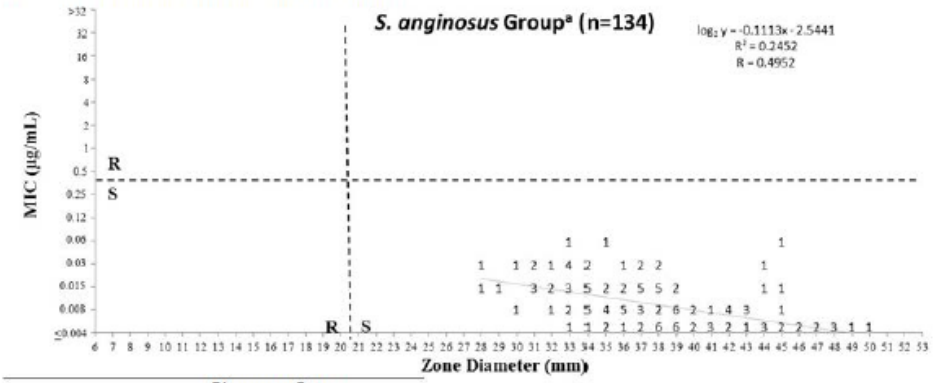
MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ R+1	0	0	(0.0)		NA	0	(0.0)
R+S	0	0	(0.0)	0	(0.0)	0	(0.0)
≤ S-1	96		NA	0	(0.0)	0	(0.0)
TOTAL	96	0	(0.0)	0	(0.0)	0	(0.0)

MIC Range	N	Discrepancy Rates: Very Major, n (%)	Major, n(%)	Minor, n(%)
≥R+1	0	0 (0%)	NA	0 (0%)
R+S	0	0 (0%)	0 (0%)	0 (0%)
≤S-1	96	NA	0 (0%)	0 (0%)
Total	96	0 (0%)	0 (0%)	0 (0%)

Recommended disk diffusion BPs:
≥20(S)/-/-

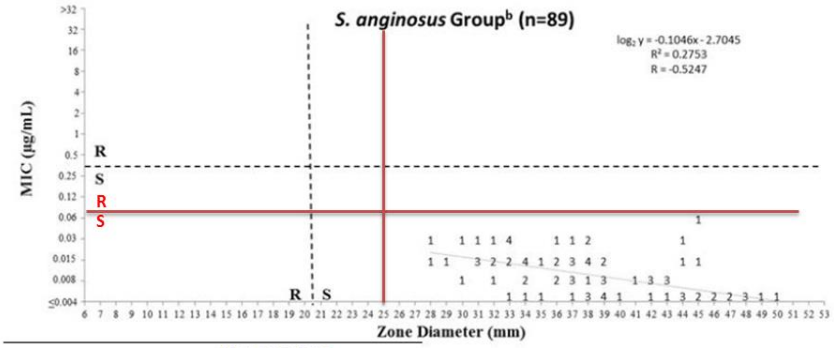
Figure G18. Broth Versus Disk Correlation and Error-rate bounding Analysis Based on Proposed Interpretive Criteria for Delafloxacin Against *S. anginosus* Group (A) Overall (Profiling and Clinical Study Isolates) and (B) Clinical Study Isolates (MITT – Delafloxacin and Comparator Treatment Arms Pool 1)

A: Overall (Profiling and Clinical Trial Isolates)



MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ R+1	0	0	(0.0)		NA	0	(0.0)
R+S	0	0	(0.0)	0	(0.0)	0	(0.0)
≤ S-1	134		NA	0	(0.0)	0	(0.0)
TOTAL	134	0	(0.0)	0	(0.0)	0	(0.0)

B: Clinical Trial Isolates

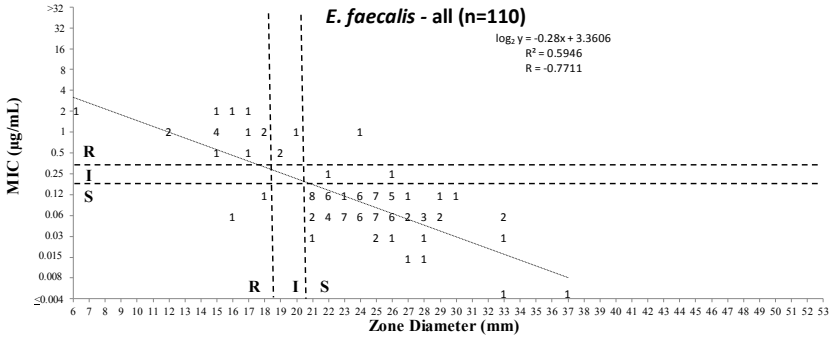


MIC Range	N	Discrepancy Rates: Very Major n	(%)	Major n	(%)	Minor n	(%)
≥ R+1	0	0	(0.0)		NA	0	(0.0)
R+S	0	0	(0.0)	0	(0.0)	0	(0.0)
≤ S-1	89		NA	0	(0.0)	0	(0.0)
TOTAL	89	0	(0.0)	0	(0.0)	0	(0.0)

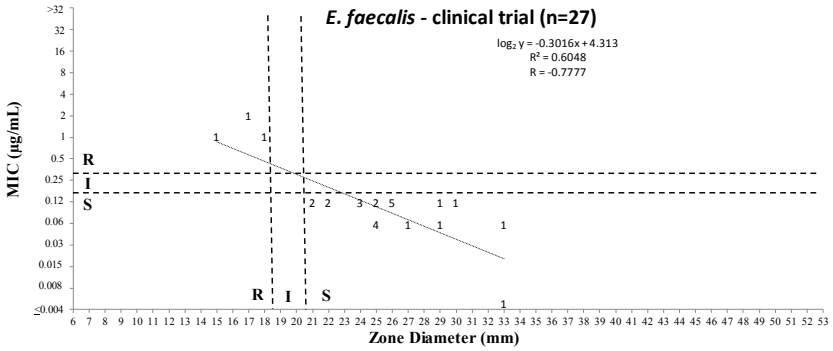
MIC Range	N	Discrepancy Rates: Very Major, n (%)	Major, n(%)	Minor, n(%)
≥R+1	0	0 (0%)	NA	0 (0%)
R+S	0	0 (0%)	0 (0%)	0 (0%)
≤S-1	89	NA	0 (0%)	0 (0%)
Total	89	0 (0%)	0 (0%)	0 (0%)

Recommended disk diffusion BPs:
≥25(S)/-/-

Figure G19. Broth Versus Disk Correlation and Error-rate bounding Analysis Based on Proposed Interpretive Criteria for Delafloxacin Against *E. faecalis* (A) Overall (Profiling and Clinical Study Isolates) and (B) Clinical Study Isolates (MITT – Delafloxacin and Comparator Treatment Arms Pool 1)

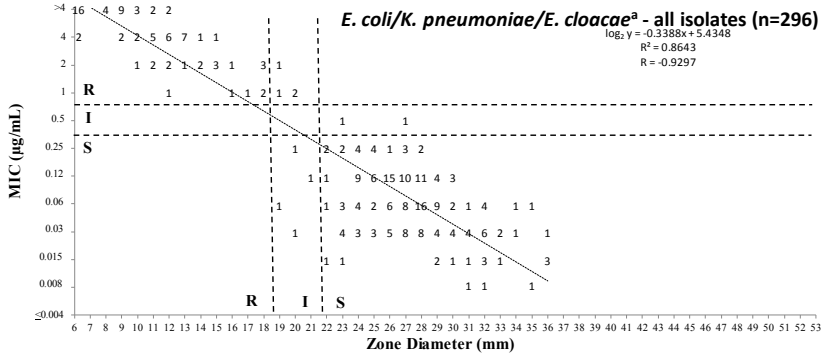


		Discrepancy Rates		
		Very Major	Major	Minor
MIC Range	N	n (%)	n (%)	n (%)
≥ I+2	15	1 (6.7)	NA	1 (6.7)
I+1 to I-1	43	0 (0.0)	1 (2.3)	4 (9.3)
≤ I-2	52	NA	1 (1.9)	0 (0.0)
TOTAL	110	1 (0.9)	2 (1.8)	5 (4.5)

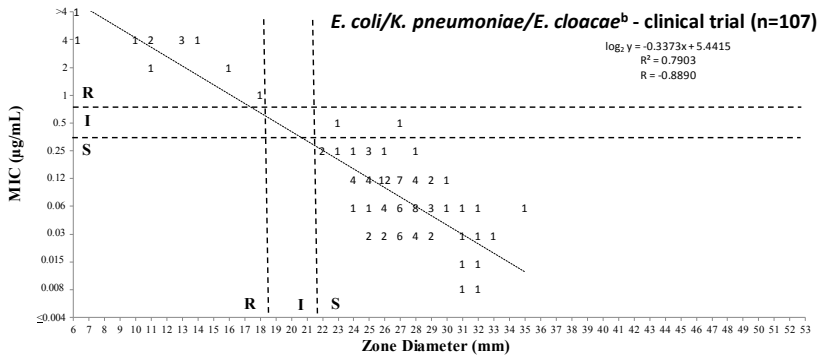


		Discrepancy Rates		
		Very Major	Major	Minor
MIC Range	N	n (%)	n (%)	n (%)
≥ I+2	3	0 (0.0)	NA	0 (0.0)
I+1 to I-1	16	0 (0.0)	0 (0.0)	0 (0.0)
≤ I-2	8	NA	0 (0.0)	0 (0.0)
TOTAL	27	0 (0.0)	0 (0.0)	0 (0.0)

Figure G20. Broth Versus Disk Correlation and Error-rate bounding Analysis Based on Proposed Interpretive Criteria for Delafloxacin Against Enterobacteriaceae (A) Overall (Profiling and Clinical Study Isolates) and (B) Clinical Study Isolates (MITT – Delafloxacin and Comparator Treatment Arms Pool 1)



		Discrepancy Rates		
		Very Major	Major	Minor
MIC Range	N	n (%)	n (%)	n (%)
≥ I+2	78	0 (0.0)	NA	1 (1.3)
I+1 to I-1	29	0 (0.0)	0 (0.0)	6 (20.7)
≤ I-2	189	NA	0 (0.0)	3 (1.6)
TOTAL	296	0 (0.0)	0 (0.0)	10 (3.4)

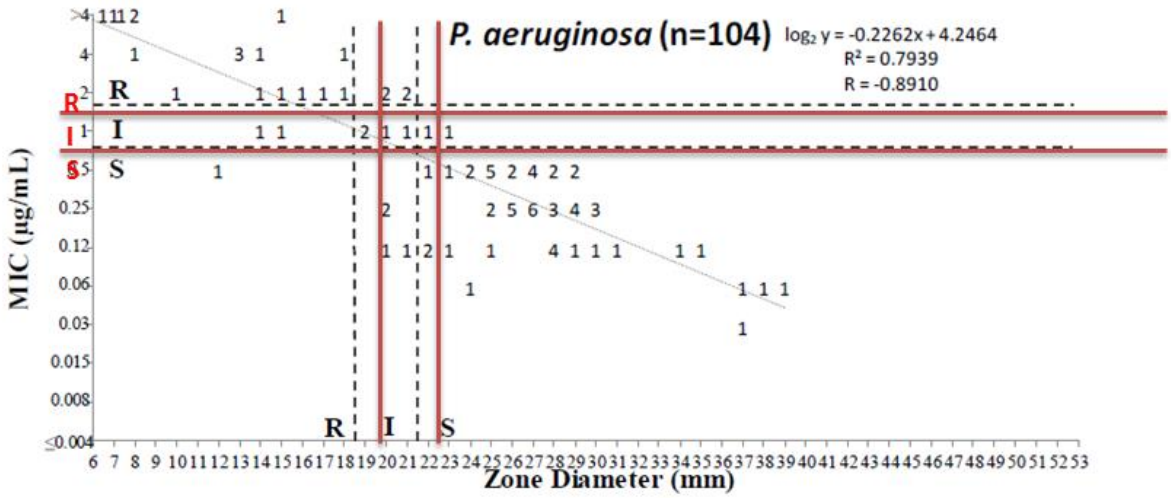


		Discrepancy Rates		
		Very Major	Major	Minor
MIC Range	N	n (%)	n (%)	n (%)
≥ I+2	11	0 (0.0)	NA	0 (0.0)
I+1 to I-1	12	0 (0.0)	0 (0.0)	2 (16.7)
≤ I-2	84	NA	0 (0.0)	0 (0.0)
TOTAL	107	0 (0.0)	0 (0.0)	2 (1.9)

[a] 115 *E. coli*, 123 *K. pneumoniae*, 57 *E. cloacae*, 1 *E. cloacae* species complex
[b] 35 *E. coli*, 45 *K. pneumoniae*, 26 *E. cloacae*, 1 *E. cloacae* species complex

Figure G21. Broth Versus Disk Correlation and Error-rate bounding Analysis Based on Proposed Interpretive Criteria for Delafloxacin Against *P. aeruginosa* (A) Overall (Profiling and Clinical Study Isolates) and (B) Clinical Study Isolates (MITT – Delafloxacin and Comparator Treatment Arms Pool 1)

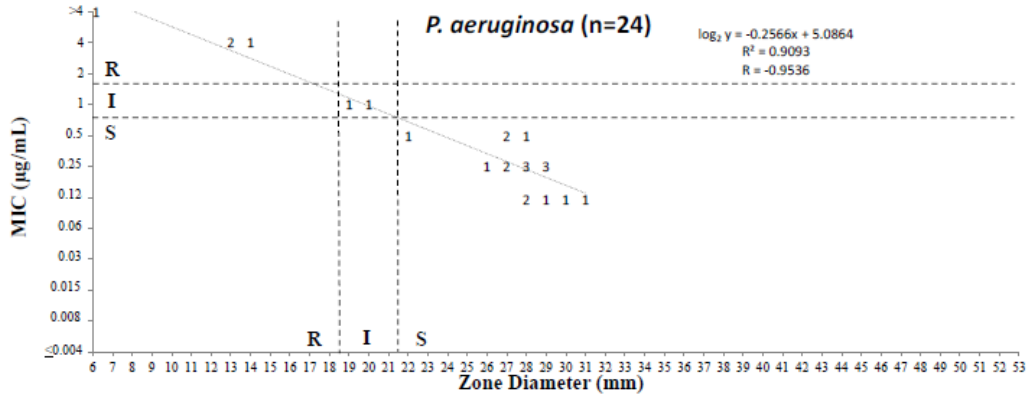
A: Overall: (Profiling and Clinical Study Isolates)



		Discrepancy Rates		
		Very Major	Major	Minor
MIC Range	N	n (%)	n (%)	n (%)
≥ I+2	21	0 (0.0)	NA	0 (0.0)
I+1 to I-1	38	0 (0.0)	1 (2.6)	8 (21.1)
≤ I-2	45	NA	0 (0.0)	4 (8.9)
TOTAL	104	0 (0.0)	1 (1.0)	12 (11.5)

		Discrepancy Rates		
MIC Range	N	Very Major, n(%)	Major, n (%)	Minor, n(%)
≥I+2	21	0 (0%)	NA	0 (0%)
I+1 to I-1	38	0 (0%)	0 (0%)	10 (26.3%)
≤I-2	45	NA	0 (0%)	6 (13.3%)
Total	104	0 (0%)	0 (0%)	16 (15.4%)

Recommended disk diffusion BPs:
≥23(S)/20-22(I)/≤19(R)



		Discrepancy Rates		
		Very Major	Major	Minor
MIC Range	N	n (%)	n (%)	n (%)
≥ I+2	4	0 (0.0)	NA	0 (0.0)
I+1 to I-1	15	0 (0.0)	0 (0.0)	3 (20.0)
≤ I-2	5	NA	0 (0.0)	0 (0.0)
TOTAL	24	0 (0.0)	0 (0.0)	3 (12.5)

I = intermediate; Major = false resistant by disk; MIC = minimum inhibitory concentration; Minor = false intermediate by disk or broth; MITT = microbiological intent-to-treat; mm = millimeter; n = number of isolates with indicated discrepancy between disk diffusion and broth microdilution interpretation based on proposed interpretive criteria; N = number of isolates in indicated MIC range; NA = not applicable; R = resistant; S = susceptible; Very Major = false susceptible by disk
Source: MB-3341-028-A1 Appendix; Microbiology Reviewer's Guide

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/s/

JALAL U SHEIKH
06/16/2017

DMITRI IARIKOV
06/16/2017

Clinical Microbiology: 45-Day Meeting – NDA Checklist for Filing

NDA and Drug Product: # 208610 & 208611; Delafloxacin 450 mg Tablet and IV 300 mg/vial (Baxdela)
Applicant: Melinta Therapeutics
Letter Date: 10/18/2016
Stamp Date: 10/19/2016

On **initial** overview of the NDA application for RTF:

No.	Item	Yes	No	Comments
1	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	✓		
2	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin?	✓		
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?	✓		
4	On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains/ isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	✓		
5	Has the applicant submitted draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	✓		
6	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓		
7	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?	✓		

Clinical Microbiology: 45-Day Meeting – NDA Checklist for Filing

NDA and Drug Product: # 208610 & 208611; Delafloxacin 450 mg Tablet and IV 300 mg/vial (Baxdela)
Applicant: Melinta Therapeutics
Letter Date: 10/18/2016
Stamp Date: 10/19/2016

8	Has the applicant submitted the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
9	Has the applicant submitted a clinical microbiology dataset in a format which intends to determine resistance development by correlating changes in the phenotype (such as *in vitro* susceptibility) and/or genotype (such as mutations) of the baseline relevant pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
10	Has the applicant used standardized methods or if non-standardized methods were used has the applicant included full details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	✓		
11	Is the clinical microbiology draft labeling consistent with 21 CFR Parts 201, 314, 601 and current Divisional policy.	✓		
12	FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? **IF NO, GIVE REASONS BELOW.**	✓		

Application Type: PDUFA V Application

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

Any Additional Clinical Microbiology Comments: There are no additional comments.

Jalal Sheikh, Ph.D.
Reviewing Clinical Microbiologist
DAIP

Tamara Feldblyum, Ph.D.
Acting Team Leader
Clinical Microbiology, DAIP

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/s/

JALAL U SHEIKH
11/17/2016

TAMARA V FELDBLYUM
11/17/2016