

Delafloxacin: Rationale for EUCAST Clinical Breakpoints

Current version	1.2	17 January 2022
Previous versions	–	–

Foreword

EUCAST

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe.

Information on EUCAST and EUCAST breakpoints is available on the EUCAST website at https://www.eucast.org/publications_and_documents/rd/.

EUCAST rationale documents

EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

Availability of EUCAST documents

All EUCAST documents are freely available from the EUCAST website at <http://www.eucast.org>.

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This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Delafloxacin Rationale Document, version 1.2, 2022. <http://www.eucast.org/rd>."

Introduction

Delafloxacin *N*-methylglucamine salt, hereafter referred to as delafloxacin, is a novel anionic fluoroquinolone antibiotic with a broad spectrum of antibacterial activity. Delafloxacin is a dual-targeting fluoroquinolone and unlike other quinolones, such as ciprofloxacin, levofloxacin, and norfloxacin, which usually have a binding affinity for either DNA gyrase or topoisomerase IV, delafloxacin is equally potent against both enzymes. This dual targeting is believed to help reduce the selection of resistant mutants *in vitro* and *in vivo*.

Unlike other available fluoroquinolones which usually bind to either DNA gyrase or topoisomerase IV, delafloxacin equally binds to both enzymes. Delafloxacin is anionic in nature and uncharged at slightly acidic pH (≤ 5.5). At neutral pH, delafloxacin is highly potent against all *Staphylococcus aureus* strains regardless of resistance phenotype (including moxifloxacin-resistant strains) but acidic conditions (as found at infection sites) markedly enhance delafloxacin's activity against both extracellular and intracellular forms of *S. aureus* and explain delafloxacin's greater accumulation in bacteria, bacteria-infected eukaryotic cells and biofilms. In contrast, moxifloxacin is zwitterionic at pH > 5.5 and is a cation at pH < 5.5 leading to decreased activity at low pH levels.

The presence of a hetero-aromatic substituent at position 1 (which greatly influences antibacterial activity), a weak polarity associated with the presence of a chlorine molecule at position 8 (which confers the most potent antibacterial activity on the fluoroquinolone molecule) and a lack of basic group in position 7 are three unique features of delafloxacin that, in conjunction, are thought to explain the increased activity of delafloxacin against quinolone-resistant Gram-positive bacteria.

Like other fluoroquinolones, spontaneous delafloxacin-resistant mutants could be selected *in vitro* but at very low frequencies ($< 10^{-9}$) at $\geq 4X$ the MIC. In both laboratory-derived mutants and clinical isolates, the predominant mutation in *S. aureus* was in Ser84-Leu in *gyrA*/Ser80-Tyr or Ser80-Phe in *griA*. Double mutations in *gyrB* and *gyrA* resulted in elevated delafloxacin MIC values but such isolates had decreased fitness *in vitro*.

Delafloxacin has been developed as a sterile 0.3 g lyophilized Captisol[®]-containing formulation for IV administration as well as a 0.45 g compressed tablet formulation for oral use. For intravenous infusion, 0.3 g is given over 60 minutes every 12 hours for a total duration of 5 to 14 days. A switch to the delafloxacin 0.45 g tablet orally every 12 hours for a total duration of 5 to 14 days is possible at the discretion of the physician. For oral administration, the 0.45 g tablet is taken every 12 hours for a total duration of 5 to 14 days. The 0.45 g oral dose provides an equivalent AUC exposure to the 0.3 g IV dose.

Delafloxacin is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections. EMA approval for community-acquired pneumonia was granted in June 2021.

1. Dosage

EMA

Most common dose	0.3 g x 2 iv over 60 minutes 0.45 g oral x 2
Maximum dose schedule	0.3 g x 2 iv over 60 minutes 0.45 g oral x 2
Available formulations	iv, oral

2. MIC distributions and epidemiological cut-off (ECOFF) values

MIC distributions and ECOFFs can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

3. Breakpoints prior to harmonisation (mg/L)

Not applicable

4. Pharmacokinetics (PK)

Dosage	0.3 g x 2 iv	0.45 g x 2 oral		
C _{max} (mg/L)	10.7	6.12		
C _{min} (mg/L)	–	–		
Total body clearance (L/h)	12.5	–		
T _{1/2} (h), mean (range)	10.9	14.1		
AUC ₀₋₁₂ (mg.h/L)	25.7	21.2		
AUC ₀₋₂₄ (mg.h/L)	–	–		
AUC _{0-∞} (mg.h/L)	26.7	24.2		
Fraction unbound (%)	16	16		
Volume of distribution _{ss} (L)	34.2	–		
Comments	<ul style="list-style-type: none"> • Protein binding determined <i>in vitro</i> using equilibrium dialysis methodology. • The median ELF/plasma Ratio of Delafloxacin AUC₀₋₁₂ following administration of delafloxacin 0.3 g IV Q12h for 7 Doses was 0.102 based on total concentration in plasma and 0.638 based on unbound concentration in plasma 			
References	<ul style="list-style-type: none"> • Hoover R, Lawrence L, Benedict M, Gunda S, Li D, Sun E, Cammarata S. 54st ICAAC Washington DC, 2014; Poster A-682 • Hoover R, Hunt T, Benedict M, Paulson SK, Lawrence L, Cammarata S, Sun E. <i>Clin Ther.</i> 2016; 38:53-65 			

5. Pharmacodynamics (PD)

Index	Neutropenic Mouse Thigh			Neutropenic Mouse Lung			
	<i>S. aureus</i> (n=5) ^{a,b}	<i>P. aeruginosa</i> (n=3) ^{a,c}	<i>E. coli</i> ^d (n=3) ^a	<i>S. aureus</i> (n=4) ^e	<i>S. pneumoniae</i> (n=4) ^f	<i>K. pneumoniae</i> (n=12) ^g	<i>P. aeruginosa</i> (n=5) ^h
fAUC/MIC for bacteriostasis (Median, Range)	9.3	3.8	14.5	1.42 (<1.05-3.12)	0.56 (<0.26-2.28)	28.6 (3.08-155)	5.66 (3.41-24.8)
fAUC/MIC for 1-log ₁₀ reduction (Median, Range)	14.3	5	26.2	7.92 (6.61-10.8)	3.36 (0.39-10.3)	64.1 (5.47-321)	14.3 (9.82-51.6)
fAUC/MIC for 2-log ₁₀ reduction Not available	–	–	–	–	–	–	–
Comments	<p>Values shown are median (range) values.</p> <p>As <i>H. influenzae</i> is not able to grow sufficiently well in mouse lungs, a one-compartment in vitro infection model was used to determine the pharmacodynamic target. The median (range) fAUC/MIC for bacteriostasis and a 1 log reduction from baseline in bacterial burden at 24 hours was 23.5 (17.4-35.5) and 28.7 (21.7-40.7), respectively.</p> <p>The ELF/plasma ratio in mice was 9.8-16.3. Since delafloxacin is highly protein bound (97.6%) in mice, ratios of >10 are unlikely to reflect passive diffusion from plasma to ELF and, therefore, such a high pulmonary distribution seems unlikely, unless other methods of transport and/or diffusion are involved. As it is unclear what mechanism(s) could deliver delafloxacin ELF concentrations at such an extreme multiple above free plasma values this finding does not appear to be physico-chemically or biologically plausible.</p> <p>a. Number of isolates included in determination b. 2 MSSA and 3 MRSA. Delafloxacin MIC range 0.004 – 0.8 mg/L. c. 2 reference strains and 1 recent surveillance isolate. Delafloxacin MIC range 0.25 – 2 mg/L. d. One ESBL-positive strain and 2 recent surveillance isolates. Delafloxacin MIC range 0.016 – 2 mg/L. e. MSSA and 3 MRSA. Delafloxacin MIC range 0.004 – 0.008 mg/L. f. 1 PSSP and 3 PRSP. Delafloxacin MIC range 0.016 – 0.125 mg/L. g. 1 WT, 3 ESBL-positive strains and 8 recent surveillance isolates from HCAP patients. Delafloxacin MIC range 0.06 – 4 mg/L. h. 3 WT, 1 FQ-R and 1 recent surveillance isolate from an HCAP patient. Delafloxacin MIC range 0.12 – 4 mg/L.</p>						

References

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- Lepak A, Andes D. Antimicrob Agents Chemother. 2016;60(8):4764-9.
- VanScoy BD, Conde H, McCurdy SP, Keedy K, Ambrose PG and Bhavnani SM. ASM-ESCMID 2019, Boston, MA. September 3-6, 2019. Poster No. T-10.

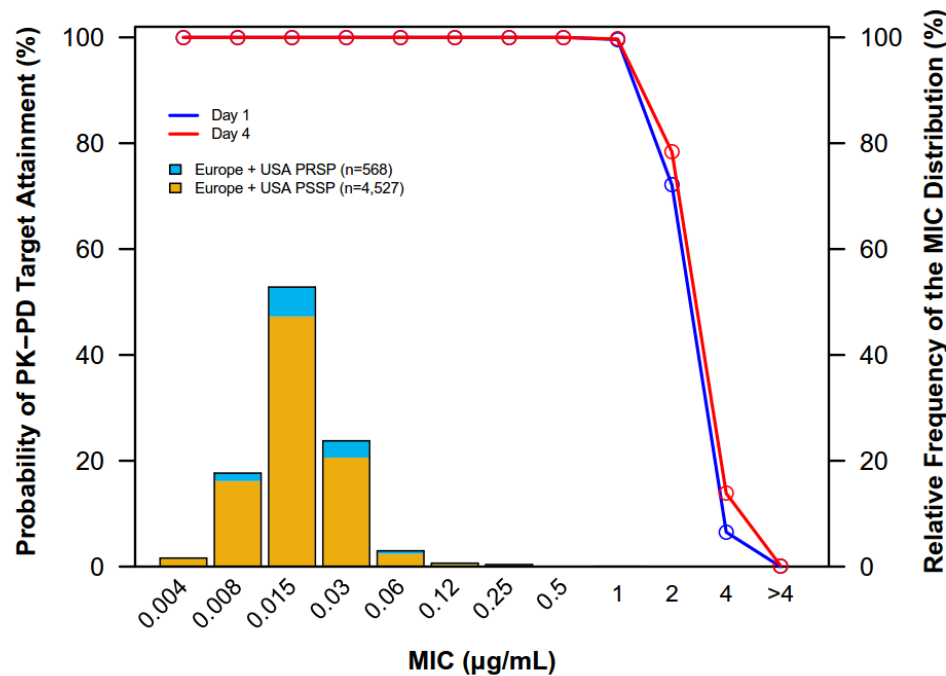
6. Monte Carlo simulations

Monte Carlo simulations were conducted using a population PK model developed for delafloxacin based on data from patients in the delafloxacin ABSSSI and CAP clinical studies. Percent probabilities of PK-PD target attainment (PTA) on Days 1 and 4 were determined for simulated patients using non-clinical AUC:MIC targets associated with a 1-log₁₀ CFU reduction from baseline against *S. pneumoniae*, *S. aureus*, *K. pneumoniae* and *P. aeruginosa* in a neutropenic murine-lung infection model and in a one-compartment in vitro infection model for *H. influenzae* shown in section 5.

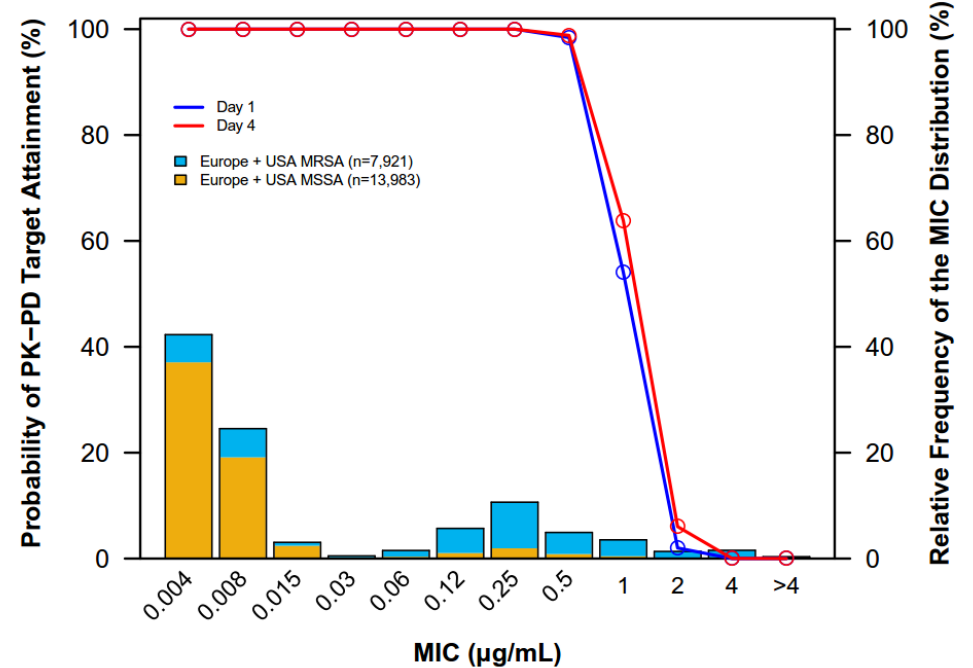
The PTA for 0.3 g x 2 iv in simulated patients with *S. pneumoniae*, *S. aureus*, *K. pneumoniae*, *P. aeruginosa* and *H. influenzae* are shown in Figures 1-6.

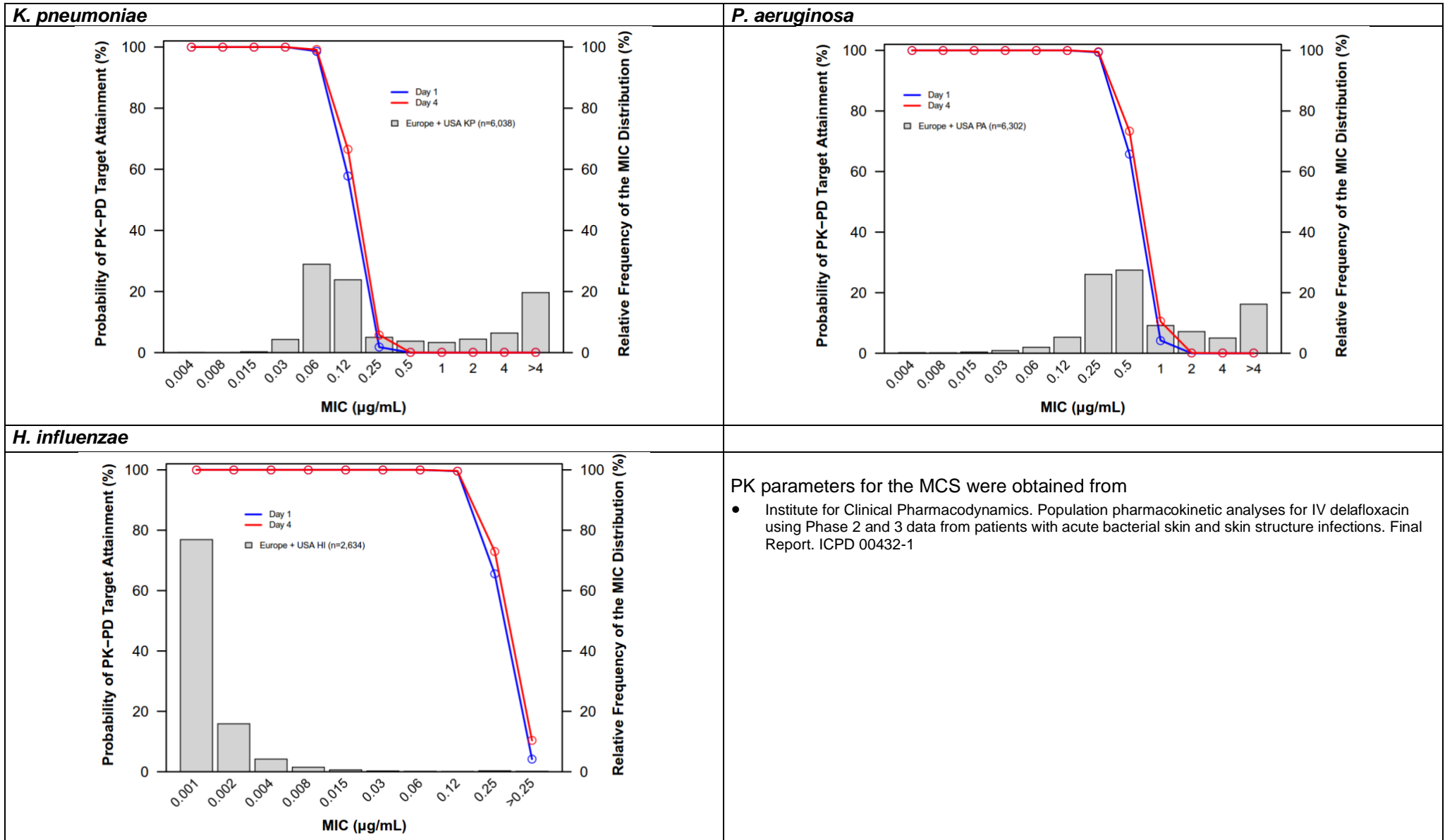
Results of PTA analysis with the 0.45 g oral dose every 12 hours demonstrate similar coverage.

S. pneumoniae



S. aureus





7. Clinical data

Acute Bacterial Skin and Skin Structure Infections

RX-3341-201 was a multicentre, double-blind, randomized, active-controlled study in 150 male and female subjects with complicated skin and skin structure infections (cSSSI) in US. The aim of the study was to assess the efficacy, safety and tolerability profiles of two different delafloxacin dosing regimens, 0.3 g and 0.45 g IV Q12h for 5 to 14 days, compared to IV tigecycline (100 mg followed by 50 mg Q12h for 5 to 14 days).

RX-3341-202 was a multicenter, double-blind, randomized, active-controlled study in 256 male and female subjects with ABSSSI in US. Enrolment was stratified by infection category and receipt of prior antibiotics. Delafloxacin 0.3 g IV Q12h was compared to vancomycin (15 mg/kg Q12h) and linezolid (600 mg IV Q12h). The aim of the study was to assess clinical efficacy using investigator assessment of clinical response.

RX-3341-302 was a randomized, double-blind, active-controlled study comparing the efficacy of IV delafloxacin 0.3 g to IV vancomycin (15 mg/kg/IV Q12h) with IV aztreonam (2 g IV Q12h) for 5 to 14 days in 660 subjects with ABSSSI. Subjects were stratified by infection type at enrolment.

RX-3341-303 was a randomized, double-blind, active-controlled study comparing the efficacy of IV delafloxacin, 0.3 g Q12h for 6 doses with a mandatory step down to 0.45 g Q12h orally, to IV vancomycin (recommended 15 mg/kg IV Q12h actual body weight) with IV aztreonam (1 to 2 g IV Q12h) in 850 subjects with ABSSSI. Subjects were stratified by infection type and body mass index (BMI) at enrolment (patients with BMI \geq 30 kg/m² were 50% of the population).

Study RX-3341-302: Delafloxacin iv versus Vancomycin+Aztreonam

Key Outcomes	DLX n/Total (%)	VAN n/Total (%)	Delta (95% CI)
Objective response 48-72 hours (ITT)	259/331 (78.2)	266/329 (80.9)	2.60 (-3.57, 8.78)
Investigator-assessed response at FU (ITT) (Cure)	172/331 (52.0)	166/329 (50.5)	-1.51 (-9.11, 6.11)
Investigator-assessed response at LFU (ITT) (Cure)	233/331 (70.4)	219/329 (66.6)	-3.83 (-10.89, 3.27)
Microbiological response at FU (ME) with MRSA infection	58/58 (100.0)	65/66 (98.5)	-1.52 (-8.14, 4.79)

Study RX-3341-303: Delafloxacin iv to oral versus Vancomycin+Aztreonam

Key Outcomes	DLX (n=423)	VAN/AZ (n=427)	DLX-VAN/AZ Delta (95% CI)
	n (%)	n (%)	
Objective Response at 48-72 hours	354 (83.7)	344 (80.6)	3.1 (-2.0,8.3)
Investigator-assessed response			
Cure at FU	244 (57.7)	255 (59.7)	-2.0 (-8.6,4.6)
Clinical success at FU	369 (87.2)	362 (84.8)	2.5 (-2.2,7.2)
Cure at LFU	287 (67.8)	303 (71.0)	-3.1 (-9.3,3.1)
Clinical success at LFU	353 (83.5)	351 (82.2)	1.3 (-3.8,6.3)

The *in vitro* activity of DLX and percent microbiological response in subjects infected with fluoroquinolone non-susceptible *S. aureus* isolates was determined from two global Phase 3 studies of DLX vs VAN/AZ in ABSSSI.

Baseline Organisms (MITT; both treatment arms)	Number of Isolates FQ-S/FQ-NS	DLX FQ-S MIC _{50/90} (µg/mL)	DLX FQ-S Range (µg/mL)	DLX FQ-NS MIC _{50/90} (µg/mL)	DLX FQ-NS Range (µg/mL)	Number of Subjects with FQ-S/FQ-NS isolates (ME Inv-Assessed Endpoint at Follow-Up)	Percent Micro Response for Subjects with FQ-NS isolates
<i>S. aureus</i> ¹	455/232	0.008/0.008	0.002-0.12	0.25/0.25	0.004-4	168/81	80/81 (98.8%)
MRSA	101/195	0.008/0.008	0.002-0.12	0.25/0.25	0.004-4	37/71	70/71 (98.6%)
MSSA	358/39	0.008/0.008	0.002-0.12	0.12/0.25	0.004-0.5	132/10	10/10 (100%)

Community-Acquired Pneumonia

The Phase 2 study (M01-344) was conducted to guide dose selection and provided additional data regarding clinical and microbiological efficacy. As this study was not active-controlled, data from this study were not integrated with data from the Phase 3 study (ML-3341-306).

Study ML-3341-306 was a Phase 3, double-blind, randomized, multi-center, active-controlled study evaluating the safety and efficacy of a 5-10 day course of IV/oral delafloxacin against IV/oral moxifloxacin in the treatment of adult patients with CAP. Subjects randomized to delafloxacin (n = 376) received IV delafloxacin, 0.3 g every 12 hours (BID) for at least 6 doses, with an option to switch to oral delafloxacin, 450 mg BID, for the remaining doses. Subjects randomized to moxifloxacin (n = 370) received IV moxifloxacin, 400 mg every 24 hours (QD) alternating with IV placebo QD to preserve the blind, for at least 6 active/placebo doses, with an option to switch to oral moxifloxacin, 400 mg QD, for the remaining doses. The primary efficacy endpoint was Clinical Outcome at Test of Cure (TOC) in the modified intention-to-treat (ModITT) population comprising all randomized subjects who received at least 1 dose of study drug and were classified as PORT Risk Class III through V. A number of pathogens were detected by PCR only, or predominantly, and there were few levofloxacin-resistant *S. pneumoniae*.

Study ML-3341-306: Delafloxacin in CAP Microbiological Eradication Rates

	Baseline MIC (mg/L)	N	Eradicated/Presumed Eradicated n/N (%)	Persisted/Presumed Persisted n/N (%)
<i>S. pneumoniae</i>		57	53	4
	0.004	2	2 (100)	0
	0.008	39	36 (92.3)	3 (7.7)
	0.015	15	14 (93.3)	1 (6.7)
	0.03	1	1 (100)	0
Penicillin-R	0.015	1	1 (100)	0
Macrolide-R		15	13	2
	0.008	13	11 (84.6)	2 (15.4)
	0.015	2	2 (100)	0
<i>S. aureus</i>		24	22	2
	0.001	5	5 (100)	0
	0.002	9	7 (77.8)	2 (22.2)
	0.004	9	9 (100)	0
	0.12	1	1 (100)	0
	Baseline MIC Value mg/L	N	Eradicated/Presumed Eradicated n/N (%)	Persisted/Presumed Persisted n/N (%)
<i>H. influenzae</i>		16	15	1
	0.00025	1	1 (100.0)	0
	0.0005	3	3 (100.0)	0
	0.001	12	11 (91.7)	1 (8.3)

	Baseline MIC Value mg/L	N	Eradicated/Presumed Eradicated n/N (%)	Persisted/Presumed Persisted n/N (%)
<i>K. pneumoniae</i>		14	12	2
	0.06	4	4 (100)	0
	0.12	7	5 (71.4)	2 (28.6)
	0.25	1	1 (100)	0
	2	1	1 (100)	0
	>256	1	1 (100)	0
<i>P. aeruginosa</i>		10	9	1
	0.008	1	1 (100)	0
	0.12	1	1 (100)	0
	0.25	3	3 (100)	0
	0.5	2	1 (50)	1 (50)
	1	1	1 (100)	0
	2	1	1 (100)	0
	4	1	1 (100)	0
	Baseline MIC Value mg/L	N	Eradicated/Presumed Eradicated n/N (%)	Persisted/Presumed Persisted n/N (%)
<i>M. pneumoniae</i>			7	0
	0.125	1	1 (100)	0
	0.25	4	4 (100)	0
	0.5	2	2 (100)	0
<i>L. pneumophila</i>		4	3	1
	0.00025	1	1 (100)	0
	0.0005	2	1 (50)	1 (50)
	0.001	1	1 (100)	0
<i>C. pneumoniae</i>		7	7	0
	0.125	1	1 (100)	0
	0.25	4	4 (100)	0
	0.5	2	2 (100)	0

References

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8. Clinical breakpoints (<http://www.eucast.org>)

PK/PD breakpoints (non-species related)	PK/PD breakpoints have been determined using PK/PD data and are independent of MIC distributions of specific species. They are for use only as a guide for organisms that do not have specific breakpoints. There is insufficient evidence to set PK/PD breakpoints, due principally to uncertainties about the mouse PK/PD model targets																																				
Species-related breakpoints	<table border="0"> <tr> <td><i>S. aureus</i></td> <td>S ≤0.25 mg/L</td> <td>R >0.25 mg/L</td> <td>(Acute bacterial skin and skin structure infections)</td> </tr> <tr> <td><i>S. aureus</i></td> <td>S ≤0.016 mg/L</td> <td>R >0.016 mg/L</td> <td>(Community-acquired pneumonia)</td> </tr> <tr> <td><i>S. pyogenes</i></td> <td>S ≤0.03 mg/L</td> <td>R >0.03 mg/L</td> <td></td> </tr> <tr> <td><i>S. dysgalactiae</i></td> <td>S ≤0.03 mg/L</td> <td>R >0.03 mg/L</td> <td></td> </tr> <tr> <td><i>S. agalactiae</i></td> <td>S ≤0.03 mg/L</td> <td>R >0.03 mg/L</td> <td></td> </tr> <tr> <td><i>S. anginosus</i> group</td> <td>S ≤0.03 mg/L</td> <td>R >0.03 mg/L</td> <td></td> </tr> <tr> <td><i>S. pneumoniae</i></td> <td>S ≤0.06 mg/L</td> <td>R >0.06 mg/L</td> <td></td> </tr> <tr> <td><i>H. influenzae</i></td> <td>S ≤0.004 mg/L</td> <td>R >0.004 mg/L</td> <td></td> </tr> <tr> <td><i>E. coli</i></td> <td>S ≤0.125 mg/L</td> <td>R >0.125 mg/L</td> <td></td> </tr> </table>	<i>S. aureus</i>	S ≤0.25 mg/L	R >0.25 mg/L	(Acute bacterial skin and skin structure infections)	<i>S. aureus</i>	S ≤0.016 mg/L	R >0.016 mg/L	(Community-acquired pneumonia)	<i>S. pyogenes</i>	S ≤0.03 mg/L	R >0.03 mg/L		<i>S. dysgalactiae</i>	S ≤0.03 mg/L	R >0.03 mg/L		<i>S. agalactiae</i>	S ≤0.03 mg/L	R >0.03 mg/L		<i>S. anginosus</i> group	S ≤0.03 mg/L	R >0.03 mg/L		<i>S. pneumoniae</i>	S ≤0.06 mg/L	R >0.06 mg/L		<i>H. influenzae</i>	S ≤0.004 mg/L	R >0.004 mg/L		<i>E. coli</i>	S ≤0.125 mg/L	R >0.125 mg/L	
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Species without breakpoints	There is insufficient evidence to set breakpoints for <i>Enterobacteriales</i> , <i>P. aeruginosa</i> , <i>Enterococcus</i> spp. and <i>M. catarrhalis</i>																																				
Clinical qualifications	Breakpoints for <i>S. pyogenes</i> , <i>S. dysgalactiae</i> , <i>S. agalactiae</i> , <i>S. anginosus</i> group and <i>E. coli</i> apply to acute bacterial skin and skin structure infections only Breakpoints for <i>S. pneumoniae</i> and <i>H. influenzae</i> apply to community-acquired pneumonia																																				
Dosage(s) linked to breakpoints	Standard dosage: 0.3 g x 2 iv over 60 minutes; 0.45 g x 2 oral. No High dosage.																																				
Additional comments	None																																				

9. Exceptions noted for individual national committees

None