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CHMP assessment report on extension of indication variation

Quofenix

International non-proprietary name: delafloxacin

Procedure No. EMEA/H/C/004860/II/0003

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

ABBREVIATION	DEFINITION
ABSSSI	acute bacterial skin and skin structure infections
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AM	alveolar macrophages
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC:MIC	area under the mean concentration-time curve to minimum inhibitory
AUC ₀₋₁₂	area under the concentration-time curve from time 0 to 12 hours
AUC _∞	area under the concentration-time curve from time zero to infinity
BAL	bronchoalveolar lavage
BCRP	Breast cancer resistant protein
BID	every 12 hours
BMI	body mass index
BSA	body surface area
CAP	community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CE	clinically evaluable
CFU	colony-forming unit
CI	confidence interval
CL	total clearance
CL _d	mean dialysate clearance
C _{max}	maximum (peak) mean plasma drug concentration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DRESS	drug reaction with eosinophilia and systemic symptoms
ECG	electrocardioGram
ECR	Early Clinical Response
ELF	epithelial lining fluid
EMA	European Medicines Agency
EOT	End of Treatment
ESBL	extended-spectrum β-lactamase
ESRD	end-stage renal disease
fAUC ₂₄ /MIC	free delafloxacin area under the mean concentration-time curve from time 0 to 24 hours
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
IDSA/ATS	Infectious Diseases Society of America/American Thoracic Society
ITT	intent-to-treat
IV	intravenous
MDRSP	multiple drug-resistant <i>Streptococcus pneumoniae</i>
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MIC ₉₀	minimum inhibitory concentration required to inhibit the growth of 90% of
MITT	microbiological intent-to-treat

MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MRSP	macrolide-resistant <i>Streptococcus pneumoniae</i>
MSSA	methicillin-susceptible <i>Staphylococcus aureus</i>
NDA	New Drug Application
NMDA	N-methyl-D-aspartate
PCR	polymerase chain reaction
PD	pharmacodynamics
PFGE	pulsed-field gel electrophoresis
P-gp	P-glycoprotein
PISP	penicillin-intermediate <i>Streptococcus pneumoniae</i>
PK	pharmacokinetic(s)
popPK	population pharmacokinetic
PORT	Pneumonia Patient Outcomes Research Team
PRSP	penicillin-resistant <i>Streptococcus pneumoniae</i>
PT	preferred term
Q12h	every 12 hours
QD	once daily
QRDR	quinolone-resistance determining region
QTcF	corrected QT interval using Fridericia's correction
SAE	serious adverse event
SAP	statistical analysis plan
SBECD	sulfobutylether- β -cyclodextrin
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	standard deviation
SMQ	Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query
sNDA	supplemental New Drug Application
SOC	system organ class
SPA	Special Protocol Assessment
t _{1/2}	elimination half-life
TEAE	treatment-emergent adverse event
TOC	Test of Cure
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States
USPI	United States package insert
V _{max}	maximum rate of Michaelis-Menten elimination from the central component
WBC	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, A. Menarini - Industrie Farmaceutiche Riunite - s.r.l. submitted to the European Medicines Agency on 11 March 2020 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of community-acquired pneumonia (CAP) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections, for Quofenix 450 mg tablets and 300 mg powder for concentrate for solution for infusion; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0125/2019 on the granting of a product-specific waiver for delafloxacin (EMA-001080-PIP03-18).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	11 Mar 2020
Start of procedure	28 Mar 2020
CHMP Rapporteur Assessment Report	20 May 2020
CHMP Co-Rapporteur Assessment Report	25 May 2020
PRAC Rapporteur Assessment Report	29 May 2020
PRAC members comments	03 Jun 2020
Updated PRAC Rapporteur Assessment Report	05 Jun 2020
PRAC endorsed relevant sections of the assessment report ³	11 Jun 2020
CHMP members comments	15 Jun 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 Jun 2020
Request for supplementary information (RSI)	25 Jun 2020
Timetable extension request adopted	17 Sep 2020
Submission of responses	26 Jan 2021
Restart of procedure	27 Jan 2021
PRAC Rapporteur Assessment Report	1 Feb 2021
PRAC members comments	3 Feb 2021
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	10 Feb 2021
PRAC outcome	11 Feb 2021
CHMP members comments	15 Feb 2021
Updated CHMP Assessment Report	18 Feb 2021
Opinion	25 Feb 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease and epidemiology

Community-acquired pneumonia (CAP) is one of the most common causes of hospital admissions and death worldwide (Tejada 2018). It is the most infectious cause of sepsis globally with approximately 50% of intensive care unit (ICU) admissions due to CAP being associated with septic shock (Cilloniz 2019; Rello 2008; Tejada 2018). Given that the global population is aging, it is expected that CAP will continue increasing as an outstanding public health problem (Tejada 2018). CAP incidence in Europe varies from 20.6 – 79.9 per 10,000 person-years depending on country (Ferreira-Coimbra 2020).

State the claimed therapeutic indication

Quofenix is indicated for the treatment of the following infections in adults:

- acute bacterial skin and skin structure infections (ABSSSI)
- community-acquired pneumonia (CAP)

when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections (see sections 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

It should be considered that the second line indication CAP applied for is in line with the approved indication of moxifloxacin and levofloxacin.

Aetiology and pathogenesis

While *S. pneumoniae* remains the most common causative pathogen in CAP, other pathogens cause CAP including the atypical pathogens (*L. pneumophila*, *M. pneumoniae* and *C. pneumoniae*), *S. aureus* and Gram-negative bacteria, especially *H. influenzae*, *P. aeruginosa* and *K. pneumoniae* (Cilloniz 2019; Tejada 2018). The main problem concerning the treatment of Gram-negative bacterial infections is their related antibiotic resistance (Cilloniz 2019).

Clinical presentation and diagnosis

Clinical presentation of CAP typically includes fever, productive cough, purulent sputum, dyspnea, and chest pain. A diagnosis of CAP is based on findings of tachypnea and rales, in case of consolidation including increased tactile fremitus, bronchial breath sounds, and possibly egophony. Empyema or parapneumonic effusion may cause decreased tactile fremitus and dullness on chest percussion (Baer, 2019).

Management

Empiric treatment of CAP is based on an array of factors, including likely pathogens and the possibility of resistance, patient comorbidities, the pharmacokinetic (PK) properties and safety profiles of antibiotics, and treatment setting. Fluoroquinolones are recognized as established treatment options for CAP, both in the outpatient setting as well as in the hospital, by the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases (ERS / ESCMID) management guidelines (Woodhead et al. 2011) as well as the Infectious Diseases Society of America / American Thoracic Society (IDSA / ATS) Guidelines (Metlay et al. 2019).

The emergence and spread of respiratory pathogens resistant to macrolides, β -lactams, and other classes of antibiotics are a global public health concern and have begun to limit therapeutic options for CAP (Asche et al. 2008; File 2004; Niederman 2004; Pfaller et al. 2018). Antibiotic resistance among *S. pneumoniae*, the most prevalent CAP pathogen and the leading pathogen associated with mortality from CAP, poses a major therapeutic challenge. The commonly used macrolide class of antibiotics has increasingly been associated with high levels of pneumococcal resistance, approaching 50% in areas of North America and greater than 70% in China (Kim et al. 2012; Pfaller et al. 2018) and up to greater than 35% in some European countries (ECDC 2018).

Delafloxacin does not address an unmet need but would increase the availability of treatment options in face of rising antimicrobial resistance.

2.1.2. About the product

Delafloxacin is approved in the European Union (EU) and the United States (US) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults (in the EU as second line indication in line with other fluoroquinolones) and in the US it is also approved for community-acquired bacterial pneumonia (CAP). It is available as a sterile 300 mg lyophilized Captisol®-containing formulation for intravenous (IV) administration as well as a 450 mg tablet formulation for oral use.

For this application, the MAH submitted data related to CAP indication. Furthermore, the MAH is referring to the prior data in the ABSSSI MAA (EMA/H/C/004860/0000) of the oral and IV delafloxacin formulations.

In addition, ADRs reported in CAP are pooled and analysed with ABSSSI data with the aim to update Section 4.8 of the SmPC.

2.1.3. General comments on compliance with GCP

GCP

The MAH has provided statements that clinical trials were conducted in accordance with GCP.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH will submit a joint ERA (ABSSSI + CAP) within 2 months as part of a post authorisation measure (REC) already included in the Letter of Recommendations.

2.2.2. Discussion on non-clinical aspects

See above.

2.2.3. Conclusion on the non-clinical aspects

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points are recommended for further investigation:

A joint ERA (ABSSSI + CAP) will be submitted within 2 months as part of a post authorisation measure (REC) already included in the Letter of Recommendations.

2.3. *Clinical aspects*

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of submitted clinical studies relevant for the indication CAP; for clinical studies submitted and assessed for the indication ABSSSI, please refer to the EPAR.

Table 1 Tabular overview of submitted clinical studies relevant for the indication CAP

Location of the study report	Study Identifier Type of Study	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Analysis set
5.3.3.1	ML-3341-119 Phase I	Primary: PK (the steady-state intrapulmonary disposition) Secondary : PK, safety	Open-label, multi-dose, single-center study	Delafloxacin solution / 300 mg Q12h/IV (7 doses total)	30 enrolled 30 completed	Healthy male and female adult subjects	4 days	Non-integrated study
5.3.5.4	M01-344 Safety, efficacy Phase IIb	<u>Primary:</u> Dose-finding, safety, efficacy	Phase IIb, multi-center, double-blind, randomized, parallel group study	Delafloxacin capsule / 100, 200, 400 mg QD on Days 1 - 7 / Oral Placebo capsule/QD on Days 1 - 7 / Oral	309 enrolled 275 completed	Male and female subjects with CAP	7 days	Non-integrated study
5.3.5.1	ML-3341-306 Efficacy, safety Phase III	Primary: Efficacy in subjects with CABP Secondary: Efficacy, safety, tolerability, PK in subjects with CABP	Randomized, double-blind, multi-center, active-controlled study	Delafloxacin solution / 300 mg BID (every 12 hours) / IV (at least 6 doses); followed by delafloxacin tablet / 450 mg BID / Oral plus placebo moxifloxacin QD (every 24 hours) / Oral (10 - 20 active doses total) Moxifloxacin solution / 400 mg QD / IV alternating with IV placebo to maintain blind for BID (at least 6 doses); followed by moxifloxacin tablet / 400 mg QD / Oral plus placebo delafloxacin BID / Oral (5 - 10 active doses total) Optional alternative therapy for MRSA (moxifloxacin group only): linezolid solution / 600 mg BID / IV	859 enrolled 783 completed	Male and female adult subjects with CABP	5 - 10 days	Non-integrated study

2.3.2. Pharmacokinetics

Absorption

The absorption of delafloxacin was described and assessed during procedure EMEA/H/C/004860/0000.

Distribution

Study ML-3341-119

This was a Phase 1, single-center, open-label study to assess the intrapulmonary disposition of delafloxacin in 30 healthy adult male and female subjects. Each subject received 300 mg delafloxacin IV as a 1-hour infusion every 12 h for a total of 7 doses over 4 days. Blood samples were collected on Day 4 pre-dose and at 0.5, 1, 1.25, 1.5, 2, 4, 6, 8, 12 and 24 h after the start of administration of the seventh dose of delafloxacin. Each subject underwent a single bronchoscopy and BAL at 1 of 5 specified time points (6 subjects per time point): 0.5, 1.5, 4, 8 and 12 h after the start of the infusion of the seventh dose. Pooled lavage samples of each subject were centrifuged to separate AM (cell pellet) and ELF (supernatant). In addition, a blood sample to determine plasma urea concentration was collected just prior to scheduled bronchoscopy. Aliquots of BAL fluid were obtained to determine urea concentrations and differential cell count in BAL.

Results:

- PK of delafloxacin in plasma

PK parameter of delafloxacin in plasma at steady state are shown in Table 2 and are comparable to results of previous studies in healthy adults.

Table 2: Mean (%CV) Plasma Pharmacokinetic Parameters of Delafloxacin on Day 4 after Administration of Delafloxacin 300 mg IV Q12 h for 7 Doses

Parameter	Value (N = 30)
AUC ₀₋₁₂ (µg•h/mL)	26.3 (25.9)
Unbound AUC ₀₋₁₂ (µg•h/mL)	4.21 (25.9)
C _{min} (mg/L)	0.233 (62.1)
C _{max} (mg/L)	9.87 (20.1)
T _{max} (h) ^a	1.00 (0.97, 1.27)
t _{1/2} (h)	4.03 (18.1)
CL (L/h)	12.1 (23.1)
V _{ss} (L)	39.0 (22.0)

Abbreviations: AUC₀₋₁₂ = area under the concentration-time curve from time 0 to the dosing interval at steady state; CL = total clearance at steady state; C_{max} = maximum observed plasma concentration during a dosing interval at steady state; C_{min} = minimum observed plasma concentration at the 12-hour sampling time during a dosing interval at steady state; CV = coefficient of variation; IV = intravenous; N = number of subjects; Q12h = every 12 hours; T_{max} = time to achieve maximum observed plasma concentration at steady state; t_{1/2} = terminal elimination half-life at steady state;

V_{ss} = volume of distribution at steady state.

^a. Median (minimum, maximum)

Source: ML-3341-119 End-of-Text Table 14.2.2.1.

- PK of delafloxacin in ELF and AM

Following the IV infusion, delafloxacin was taken up rapidly in ELF and AM with detectable levels at 0.5 h after start of the infusion. Mean concentrations in ELF and AM 0.5 h after start of infusion were 0.833 µg/ml and 0.542 µg/ml, respectively, and remained detectable in ELF for 4 subjects and in AM for half of

the subjects over the dosing interval of 12 h. For the first 4 h after dosing the estimated delafloxacin concentrations were higher in ELF than in AM (Table 3).

Table 3: Mean (%CV) Concentrations of Delafloxacin in Plasma, Alveolar Macrophages and Epithelial Lining Fluid on Day 4 after Administration of Delafloxacin 300 mg IV Q12 h for 7 Doses

Time after Dose	Plasma		AM		ELF	
	N	Delafloxacin (mg/L)	N	Delafloxacin (mg/L)	N	Delafloxacin (mg/L)
0.5 hour	30	6.44 (24.1)	6	0.542 (22.3)	6	0.833 (59.9)
1.5 hour	30	6.41 (24.0)	6	0.413 (50.4)	6	0.727 (35.3)
4 hour	30	2.36 (31.6)	6	0.191 (49.8)	6	0.225 (76.8)
8 hour	30	0.660 (56.4)	6	0.437 (170.5)	6	0.0774 (57.5)
12 hour ^a	30	0.232 (62.1)	3	0.135 (144.9)	4	0.0322 (9.1)

Abbreviations: AM = alveolar macrophages; BLQ = below the limit of quantitation; CV = coefficient of variation; ELF = epithelial lining fluid; IV = intravenous; N = number of observations; Q12h = every 12 hours.

^a Missing values at 12 hours were BLQ. The summary statistics are based upon samples with measurable concentrations.

Note: The high mean and variability at the 8-hour time point for AM values are due to one exceptionally high concentration (1.93 mg/L).

Source: ML-3341-119 End-of-Text Table 14.2.1.1 and Table 14.2.1.3.

At steady state, based on AUC₀₋₁₂ ratios, the exposure of delafloxacin in ELF and AM was at least 50% of the unbound exposure in plasma over the dosing interval, whether estimated based on the mean or the median concentrations of BAL samples at each specific sampled time point. For ELF, the relative exposure was approximately 65% of unbound plasma exposure whether based on the mean or the median concentrations. For AM, the exposure based on mean concentrations was approximately 83% of unbound plasma exposure, but AM exposure based on median concentrations was approximately 51% of unbound plasma exposure (

Table 5). The difference between relative AM exposures appeared to be related to higher variability in individual AM concentrations at the 8-hour time point and below the limit of quantitation results at the 12-hour time point (Table 4). Based on the results of previous studies it was assumed that 16% of delafloxacin in plasma is unbound.

Relative to total plasma delafloxacin concentrations, penetration ratios for exposure in ELF and AM over the 12-hour dosing interval based on median concentrations were 0.102 and 0.082, respectively (Table 5).

Table 4: Mean (%CV) Penetration Ratios of Delafloxacin by Timepoint in Alveolar Macrophages and Epithelial Lining Fluid on Day 4 after Administration of Delafloxacin in 300 mg IV Q12 h for 7 Doses

Time after Dose	Alveolar Macrophages			Epithelial Lining Fluid		
	N	Penetration Based upon Total Plasma Concentrations	Penetration Based upon Unbound Plasma Concentrations	N	Penetration Based upon Total Plasma Concentrations	Penetration Based upon Unbound Plasma Concentrations
0.5 hour	6	0.0765 (20.2)	0.479 (20.0)	6	0.115 (52.2)	0.719 (52.2)
1.5 hour	6	0.0617 (41.7)	0.387 (41.5)	6	0.107 (30.9)	0.671 (30.9)
4 hour	6	0.0848 (49.0)	0.531 (48.7)	6	0.0850 (49.3)	0.533 (49.1)
8 hour	6	0.524 (151.2)	3.27 (151.2)	6	0.101 (39.1)	0.633 (39.2)
12 hour	3	0.338 (134.0)	2.12 (134.0)	4	0.105 (23.2)	0.656 (23.0)

Abbreviations: CV = coefficient of variation; IV = intravenous; N = number of observations; Q12h = every 12 hours.

Source: ML-3341-119 End-of-Text Table 14.2.2.2.

Table 5: Penetration Ratios of Delafloxacin AUC₀₋₁₂ Values in Epithelial Lining Fluid and Alveolar Macrophages after Administration of Delafloxacin 300 mg IV Q12 h for 7 Doses

Comparison	Ratios of AUC ₀₋₁₂ Values by Means	Ratios of AUC ₀₋₁₂ Values by Medians
ELF vs Total Plasma	0.105	0.102
ELF vs Unbound Plasma	0.653	0.638
AM vs Total Plasma	0.132	0.0818
AM vs Unbound Plasma	0.827	0.511

Abbreviations: AM = alveolar macrophages; AUC₀₋₁₂, area under the concentration-time curve from time 0 to the dosing interval at steady state; ELF = epithelial lining fluid; IV = intravenous; Q12h = every 12 hours.

Source: ML-3341-119 End-of-Text Table 14.2.2.5.

Total exposures (AUC₀₋₁₂) of delafloxacin in ELF based on mean or median ELF concentrations were 2.82 h*µg/ml and 2.68 µg/ml, respectively. Total exposures (AUC₀₋₁₂) of delafloxacin in AM based on mean and median ELF concentrations were 3.58 h*µg/ml and 2.15 h*µg/ml, respectively (Table 6).

Table 6: Total Exposure (µg*h/ml) of Delafloxacin in Epithelial Lining Fluid, Alveolar Macrophages, and Plasma after Administration of Delafloxacin 300 mg IV Q12 h for 7 Doses

Matrix	AUC ₀₋₁₂ Values by Means	AUC ₀₋₁₂ Values by Medians
ELF	2.82	2.68
AM	3.58	2.15
Plasma	27.0	26.3
Unbound Plasma	4.33	4.20

Abbreviations: AM = alveolar macrophages; AUC₀₋₁₂, area under the concentration-time curve from time 0 to the dosing interval at steady state; ELF = epithelial lining fluid; IV = intravenous; Q12h = every 12 hours.

Source: ML-3341-119 End-of-Text Table 14.2.2.3.

Elimination

The elimination of delafloxacin was described and assessed during procedure EMEA/H/C/004860.

Dose proportionality and time dependencies

Dose proportionality and time dependencies of delafloxacin were described and assessed during procedure EMEA/H/C/004860.

Pharmacokinetics in target population

During studies RX-3341-303 in ABSSSI patients and ML-3341-306 in CAP patients, serial blood samples for PK analysis were obtained at selected investigative sites on Day 3 (± 1 day) of treatment within the 30 minutes before study drug administration and at 1.5 and 3 hours after the start of dosing. All time points had a ± 10-minute window. Subjects were to receive a minimum of 3 consecutive doses of study drug before the start of PK blood collection. Given that a sparse sampling approach was employed non-compartmental PK analysis was not performed. Summary statistics were calculated for the plasma concentration-time data including n, mean, SD, coefficient of variation (CV), median, minimum, maximum, and geometric mean for each planned time point regardless of which study day the sample was collected. These results were reported in Table 14.4.1 of the ML-3341-306 CSR. Summary statistics (geometric mean (CV%)) for individual, model-derived delafloxacin plasma exposure and secondary PK parameters by day for patients in study 303 with ABSSSI and patients in study 306 with CAP included in

the PK populations described in reports 00526-3 and 00593-1, respectively, are shown in Table 7.

Table 7 Model-derived delafloxacin geometric mean (geometric CV%) plasma exposure and secondary PK parameters for patients with ABSSSI and CAP from studies 303 and 306

Name	RX-3341-303			ML-3341-306		
	Study 303 Day 1	Study 303 Day 2	Study 303 Day 3	Study 306 Day 1	Study 306 Day 2	Study 306 Day 3
AGE (Y) (CV%)	46.3 (35.4%)	46.3 (35.4%)	46.3 (35.4%)	56.9 (34.1%)	56.9 (34.1%)	56.9 (34.1%)
AUC _{24_tot} (ug.h/mL) (CV%)	47.5 (35.1%)	46.3 (41.0%)	44.6 (45.2%)	59.5 (45.9%)	56.2 (46.4%)	56.3 (48.3%)
C _{MAX_tot} (ug/mL) (CV%)	7.64 (21.8%)	7.76 (22.8%)	7.82 (22.6%)	9.37 (28.2%)	9.42 (28.9%)	9.47 (29.4%)
V _c (L) (CV%)	24.7 (24.6%)	24.7 (24.6%)	24.7 (24.6%)	18.2 (31.2%)	18.2 (31.2%)	18.2 (31.2%)
V _{ss} (L) (CV%)	85.2 (13.1%)	85.2 (13.1%)	85.2 (13.1%)	77.7 (15.6%)	77.7 (15.6%)	77.7 (15.6%)
CL _{avg} (L/h) (CV%)	15.1 (33.3%)	12.0 (44.5%)	10.5 (45.7%)	13.3 (43.4%)	10.9 (49.6%)	10.5 (51.5%)
CL _{CR} (mL/min) (CV%)	84.4 (48.1%)	84.4 (48.1%)	84.4 (48.1%)	66.0 (44.3%)	66.0 (44.3%)	66.0 (44.3%)
T _{1/2 α avg} (h) (CV%)	0.284 (21.5%)	0.293 (21.7%)	0.296 (22.3%)	0.231 (26.7%)	0.238 (27.2%)	0.239 (27.6%)
T _{1/2 β avg} (h) (CV%)	2.24 (19.8%)	2.65 (24.5%)	2.90 (27.3%)	2.14 (19.6%)	2.44 (22.5%)	2.51 (24.3%)
T _{1/2 γ avg} (h)	23.3 (12.6%)	24.1 (13.0%)	24.5 (13.5%)	24.2 (12.8%)	25.0 (11.3%)	25.2 (11.2%)
WT/kg	80.7 (25.9%)	80.7 (25.9%)	80.7 (25.9%)	74.9 (22.7%)	74.9 (22.7%)	74.9 (22.7%)
BMI (kg/m ²)	27.5 (24.5%)	27.5 (24.5%)	27.5 (24.5%)	26.2 (20.4%)	26.2 (20.4%)	26.2 (20.4%)
Males N (CV%)	72 (65.5%)	-	-	178 (56.6%)	-	-
Females N (CV%)	38 (34.5%)	-	-	38 (34.5%)	-	-

Patients with CAP compared to patients with ABSSSI are older (mean age 56.9 versus 46.3 years, respectively), lighter (74.9 kg versus 80.7 kg, respectively), and have worse renal function (mean normalised creatinine clearance (CL_{CR}) 66.0 mL/min versus 84.4 mL/min). These differences are reflected in the higher observed exposures in the CAP patients. The values for T_{1/2} are similar for the 2 patient populations and the observed differences are probably not of clinical significance. While it cannot be ruled out that there exists a combination of physiologic factors in CAP patients that can explain the observed difference in V_c, one possible explanation is the fact that ABSSSI patients are more likely to experience significant oedema as a consequence of their infection, which could potentially account for the slightly higher V_c in those patients.

Population pharmacokinetic analyses

Updated population pharmacokinetic analyses

The objectives of the presented analyses are the following:

- To evaluate the previously-developed delafloxacin population PK model via incorporation of data from patients with CAP enrolled in Study 306;

and

- To qualify the resultant model for its ability to predict delafloxacin disposition in CAP patients and for use in PK-PD analyses for efficacy and simulations for PK-PD target attainment analyses.

All data preparation and presentation were performed using SAS Version 9.3 software. The population PK analysis was conducted using NONMEM® Version 7.4.3 (ICON Development Solutions, Ellicott City, MD) implementing the first-order conditional estimation method with η - ϵ interaction, as facilitated by PerlSpeaks-NONMEM Version 4.7.0 and Pirana Version 2.9.9.

In study 306, approximately 860 male and female patients, 18 years of age and older with creatinine clearance (CL_{cr}) greater than 29 mL/min who had evidence of acute onset of CAP were enrolled and randomized 1:1 to receive either delafloxacin or moxifloxacin. Total duration of treatment was 5 to 10 days based on the investigator's judgment. Patients assigned to the delafloxacin arm received 300 mg IV every 12 hours (q12h) as 1-hour infusions for six doses with an option to switch to delafloxacin 450 mg orally q12h for the remaining doses. Blood samples for PK evaluation were collected at selected sites on Day 3 pre-dose (approximately 30 minutes prior to dose administration) and at 1.5 and 3 hours after the start of the infusion, producing a PK dataset consisting wholly of observations following IV administration.

A total of 316 individuals from Study 306 contributed an additional 946 plasma samples to the existing PK dataset, increasing the total number of individuals to 1,033 (30.6% CAP patients) and the total number of plasma samples to 13,407 (7.1% from CAP patients) across Phase 1-3 studies. Within Study 306, one plasma sample was BLQ, flagged as such, and excluded from PK analysis, with 13 additional plasma samples (1.4% of those available) determined to be significant outliers and also excluded. The final resultant dataset was thus comprised of 12,829 delafloxacin plasma concentrations (932 from Study 306 CAP patients) obtained from 1,029 individuals (316 CAP patients), with 96 of these individuals contributing 468 urine samples.

Summary statistics of baseline demographics stratified by patient population and for the total cohort of infected patients are provided in Table 8. The overall patient population (n = 1,029) was 58% male, with broad ranges of age (18 to 89 years), weight (39.2 to 170 kg), and renal function (4.00 to 244 mL/min/1.73 m²). CAP patients enrolled in Study 306 tended to be older and possessed lower renal function, though variability in demography was of similar extent as the ABSSSI patients.

Table 8: Summary statistics of patient demographics for the PK analysis population

Variable	Phase 1 Studies N = 301	ABSSSI patients N = 412	CAP patients N = 316	Total N = 1,029
	Median (Min. – Max.)	Median (Min. – Max.)	Median (Min. – Max.)	Median (Min. – Max.)
Age (yr)	34 (18 – 71)	46 (18 – 88)	63 (18 – 89)	47 (18 – 89)
Height (cm)	169 (148 – 198)	170 (137 – 198)	170 (146 – 203)	170 (137 – 203)
Weight (kg)	73.9 (44.3 – 140)	82.0 (41.9 – 170)	75.0 (39.2 – 160)	77.3 (39.2 – 170)
BSA (m ²)	1.85 (1.35 – 2.60)	1.96 (1.24 – 2.86)	1.85 (1.28 – 2.72)	1.89 (1.24 – 2.86)
BMI (kg/m ²)	26.3 (18.4 – 40.3)	28.0 (15.0 – 59.0)	26.2 (14.4 – 50.8)	26.6 (14.4 – 59.0)
CL _{cr} (mL/min/1.73 m ²)	99.2 (4.00 – 175)	95.5 (21.0 – 244)	67.8 (12.3 – 191)	89.6 (4.00 – 244)
Gender				
Male	160 (53%)	257 (62%)	178 (56%)	595 (58%)
Female	141 (47%)	155 (38%)	138 (44%)	434 (42%)
Race				
White	203 (67%)	359 (87%)	288 (91%)	850 (83%)
Black	92 (31%)	31 (8%)	21 (7%)	144 (14%)
Asian	3 (1%)	5 (1%)	5 (1%)	13 (1%)
Other	3 (1%)	17 (4%)	2 (1%)	22 (2%)

Note: Abbreviations are provided in the Abbreviation Listing.

Refinement of the delafloxacin population PK model occurred in two stages. First, a Bayesian estimation of individual PK parameters in Study 306 CAP patients and prediction-corrected visual predictive check (pc-VPC) was undertaken to externally validate the previously-developed population PK model (report 00526-3).

Goodness-of-fit plots did not show any significant bias, NPDEs further supported the suitability of the prior parameterization, centred around zero though with greater frequencies at the extremes than what would be observed under the standard normal distribution, consistent with a sparse sampling design in infected patients. The MAH concluded that these results suggest the previously-developed model provides an adequate prediction of delafloxacin disposition in this patient population. External validation via pc-VPC confirmed agreement of central tendency and of lower delafloxacin plasma concentrations, but an inability to capture the highest observations following repeated 300 mg IV dosing (Figure 1).

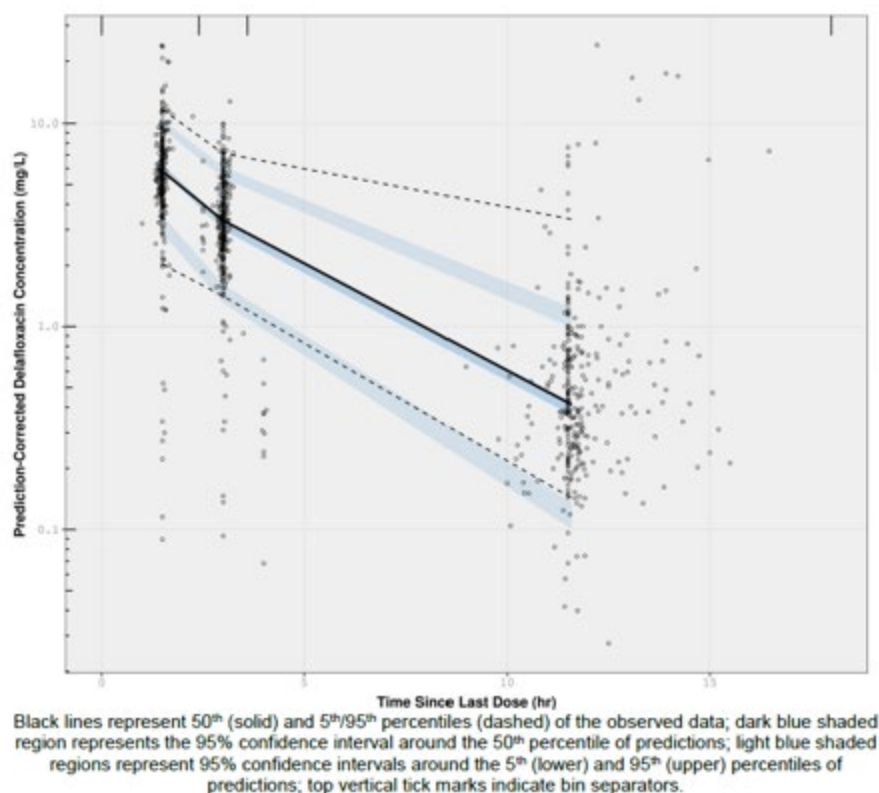


Figure 1: Prediction corrected visual predictive check of delafloxacin plasma data using the previously-developed population PK model

Acknowledging the inclusion of likely outliers possibly related to incorrect timing of PK sampling or documentation of PK sampling (as determined by $|CWRES| > 5$), this process was repeated with such data excluded ($n=13$ plasma observations, as indicated in Table 1). This resulted in an improvement in goodness-of-fit, NPDEs, and pc-VPC, though an underprediction of the 95th percentile of observed data persisted.

In an attempt to improve model predictions of the highest observed delafloxacin plasma concentrations in CAP patients, reestimation of plasma residual error components was performed under the assumption of an increased probability of dose administration and sample collection recording errors within a Phase 3 setting. As this exercise produced insufficient improvement in the pc-VPC, the Study 306 CAP data was pooled with the remaining Phase 1 and Phase 2/3 ABSSSI data with all fixed and random effect parameters reestimated and addition of a third stratum of the preexisting central volume (V_c)-patient population covariate relationship to delineate ABSSSI from CAP patients. Introduction of the interindividual random effect for maximal intrinsic clearance ($CL_{int,max}$) into the previously derived covariance matrix (consisting of interindividual random effects for renal clearance [CLR], central volume of distribution [V_c], first distributional clearance [CL_{d1}], second peripheral volume [V_{p2}], absorption rate constant [k_a], and logit-transformed total bioavailability [F_{total} , logit]) resulted in significant improvement in model fit ($\Delta MVOF = -151.5$) without evidence of overparameterization (condition number, 161.2). Notably, such incorporation was not necessary to provide adequate capture of the previous ABSSSI patient PK data. This model produced an unbiased and precise fit, with a pc-VPC of Study 306 data providing better capture of the highest observed delafloxacin plasma concentrations in CAP patients (Figure 2).

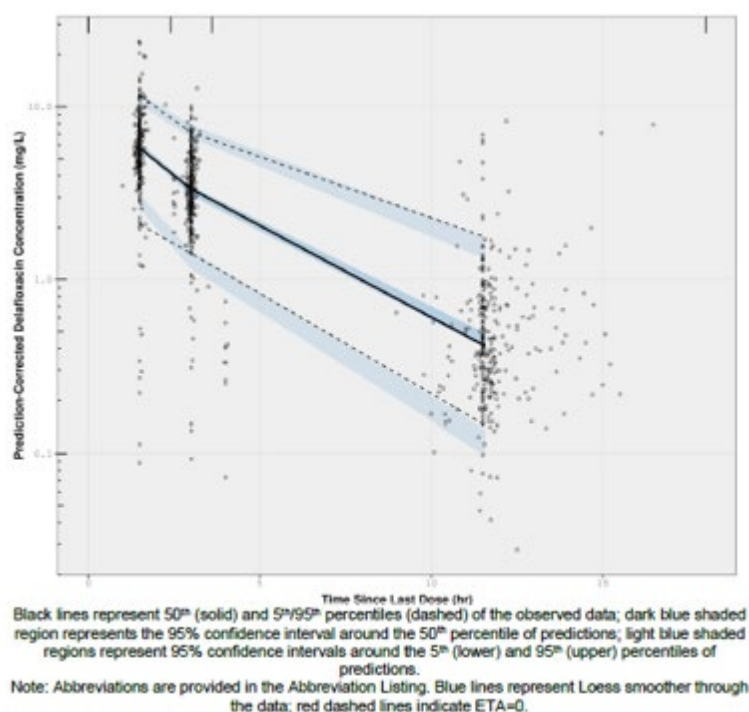


Figure 2: Prediction-corrected visual predictive check of delafloxacin plasma data in CAP patients using final pooled model

Final parameter estimates are provided in Table 9, demonstrating <10% change from those derived previously (Table 10) for all fixed effect parameters except the first peripheral volume (Vp1) [-19.8%] and the Vc-gender covariate effect (+17.8%). IIV was estimated to be larger for the majority of clearance and volume parameters than previously, with the exception of ω_2 -CLR, in line with the wider distribution of delafloxacin plasma concentrations observed in CAP patients following IV dosing. Given that reevaluation of univariate screening plots failed to reveal any significant trends, the MAH declared that the model was final and suitable for providing exposure predictions in CAP patients for use in PK-PD analyses for efficacy and simulation for PK-PD target attainment analyses. Explorations of age as a covariate for CL_{int}, max and Vc revealed parameter estimates reflective of null values with great imprecision (%RSEs >200), and thus were not included in the final model.

Table 9: Population pharmacokinetic parameter estimates for the final pooled delafloxacin PK model including Phase 1 healthy volunteers, Phase 2/3 ABSSSI patients, and Phase 3 CAP patients (Report 00593-1)

Parameter	Population Mean		Magnitude of IIV (CV%)		
	Estimate	%SEM	Estimate	%SEM	%Shrinkage
CL _R (L/hr)	3.57	5.0	55.9	10.4	26.0
CL _{int,max} (L/hr)	11.1	2.9	38.1	8.9	13.6
K _m (mg/L)	14.9	8.1	---	---	---
V _c (L)	25.7	3.8	27.1	14.7	17.1
CL _{cr1} (L/hr)	1.25	3.6	46.2	11.5	42.5
V _{p1} (L)	38.6	1.9	---	---	---
CL _{cr2} (L/hr)	23.4	3.5	---	---	---
V _{p2} (L)	22.0	2.9	32.9	10.0	16.7
CL _{int,max} -SEXF	-0.231	11.9	---	---	---
CL _R -CLCRN	1.29	4.0	---	---	---
CL _R -WTKG	1.35	12.6	---	---	---
V _c -CAP	-0.184	26.0	---	---	---
V _c -HEALTHY	-0.369	6.7	---	---	---
V _c -SEXF	-0.199	14.4	---	---	---
V _c -WTKG	0.653	14.4	---	---	---
V _{p2} -SEXF	-0.218	11.1	---	---	---
V _{p2} -WTKG	0.554	12.2	---	---	---
V _{p2} -AGE	0.154	23.7	---	---	---
k _a (hr ⁻¹)	1.35	FIX	78.5	11.3	17.7
F _{total, logt} ^{a, b}	0.426	FIX	61.1	13.0	1.68
K _a -FOOD	0.253	FIX	---	---	---
F _{total, logt} -CAPSULE ^a	3.11	FIX	---	---	---
k _{sp} (hr ⁻¹)	8.41	FIX	92.1	FIX	21.4
Proportional RV (CV%)	25.7	0.6	---	---	7.9
Additive RV (mg/L)	0.00900	4.1	---	---	7.9
Condition number: 161.2					
Note: Abbreviations are provided in the Abbreviation Listing.					
Note: Parameters reflective of the ABSSSI population mean as remains predominant population in pooled dataset.					
Note: Full covariance matrix between CL _R , V _c , CL _{cr1} , V _{p2} , k _a , F _{total, logt} , and CL _{int,max} employed.					
Note: Oral parameters were fixed to their prior values where feasible as Study 306 PK data exclusively IV; random effects in k _a and F _{total, logt} estimated by virtue of inclusion in covariance matrix.					
a. Logit-transformed, equivalent to F _{total} = 0.605 for tablets, F _{total} = 0.790 for capsules.					
b. IOV in F _{total, logt} = 33.0% (20.2% RSE)					

Table 10: Population pharmacokinetic parameter estimates for the final pooled delafloxacin PK model (Phase 1-3 PO and IV data) from previous analysis (report 00526-3)

Parameter	Population Mean		Magnitude of IIV (CV%)		
	Estimate	%SEM	Estimate	%SEM	%Shrinkage
CL _R (L/hr)	3.51	5.4	62.5	13.0	22.1
CL _{int,max} (L/hr)	11.1	2.6	20.9	8.2	21.9
K _m (mg/L)	15.5	7.2	---	---	---
V _c (L)	25.9	4.0	18.7	16.0	28.8
CL _{cr1} (L/hr)	1.36	3.7	47.6	10.2	32.9
V _{p1} (L)	48.1	1.8	---	---	---
CL _{cr2} (L/hr)	22.2	4.1	---	---	---
V _{p2} (L)	21.9	3.2	7.1	14.3	23.1
CL _{int,max} -SEXF	-0.218	11.0	---	---	---
CL _R -CLCRN	1.28	4.2	---	---	---
CL _R -WTKG	1.36	12.0	---	---	---
V _c -ABSSSI	-0.355	7.1	---	---	---
V _c -SEXF	-0.169	16.2	---	---	---
V _c -WTKG	0.684	13.5	---	---	---
V _{p2} -SEXF	-0.216	10.6	---	---	---
V _{p2} -WTKG	0.646	11.9	---	---	---
V _{p2} -AGE	0.163	24.5	---	---	---
k _a (hr ⁻¹)	1.35	8.2	71.3	11.0	13.2
F _{total, logt} ^{a, b}	0.426	15.7	52.6	20.4	19.9
K _a -FOOD	0.253	2.2	---	---	---
F _{total, logt} -CAPSULE ^a	3.11	17.2	---	---	---
k _{sp} (hr ⁻¹)	8.41	9.4	92.1	12.6	19.6
Proportional RV (CV%)	25.6	0.7	---	---	6.5
Additive RV (mg/L)	0.00922	4.5	---	---	6.5
Condition number: 121.8					
Note: Abbreviations are provided in the Abbreviation Listing.					
Note: Covariance matrix and resultant standard errors are provided in run output file (Appendix 6).					
a. Logit-transformed, equivalent to F _{total} = 0.605 for tablets, F _{total} = 0.790 for capsules.					
b. IOV in F _{total, logt} = 33.0% (20.2% RSE)					

To assess the proposed final model's parameter precision, a sampling importance- resampling (SIR) procedure was performed. Here, the final model's covariance matrix is utilized as an initial proposal

distribution of parameter estimate values, generating a sufficiently large number of parameter vectors for evaluation against the analysis dataset. Each evaluation is then assigned a weight based on its MVOF in relation to that of the proposed final model, which collectively are used to resample parameter vectors closer to the true uncertainty distribution. This process is iteratively repeated for a user-defined number of times to arrive at parameter estimates and confidence intervals akin to those produced by a bootstrap resampling procedure. SIR results are considered final when the last two iterations' Δ MOF distributions overlap and fall below a reference χ -square distribution with degrees of freedom equal to the number of estimated model parameters. Additional diagnostics related to the adequacy of the proposal distribution and the adequacy of the sampling:resampling ratio provide information regarding how well the procedure captures the true uncertainty distribution for each parameter: in both cases, no trends should be observed. Initially, five iterations were employed, with the number of initial samples/number of importance resamples set at 1000/200, 1000/400, 1000/500, 2000/1000, and 2000/1000, respectively, to maximize efficiency; any additional iterations adopted a 2000/1000 ratio, to arrive at parameter point estimates and 95% confidence intervals based on 1000 sample vectors.

SIR results could be considered final after 7 iterations, without spatial or temporal trends to suggest deficiencies in capturing the true uncertainty distribution. As shown in Table 11, parameter means are aligned with those estimated during model development, with 95% confidence intervals consistent with the precision of the final model.

Table 11: Summary statistics of resampled population PK parameters in comparison to the final pooled PO and IV model parameter estimates

Parameter	Final model		Resample statistics (N=1000)			
	Final estimate	%RSE	Mean	Median	%RSE	95% CI
CL _R (L/hr)	3.67	5.0	3.68	3.67	3.7	[3.42, 3.94]
CL _{int,max} (L/hr)	11.1	2.9	11.1	11.1	2.3	[10.7, 11.7]
K _m (mg/L)	14.9	8.1	14.9	14.9	7.1	[12.8, 16.9]
V _c (L)	25.7	3.8	25.8	25.7	3.0	[24.3, 27.3]
CL _{d1} (L/hr)	1.25	3.6	1.25	1.25	3.0	[1.18, 1.33]
V _{p1} (L)	38.6	1.9	38.7	38.7	2.1	[37.2, 40.3]
CL _{d2} (L/hr)	23.4	3.5	23.3	23.3	2.9	[22.0, 24.7]
V _{p2} (L)	22.0	2.9	22.0	2.0	2.3	[21.0, 23.0]
CL _{int,max} -SEXF	-0.231	11.9	-0.231	-0.231	9.6	[-0.275, -0.187]
CL _R -CLCRN	1.29	4.0	1.29	1.29	3.8	[1.18, 1.38]
CL _R -WTKG	1.35	12.6	1.35	1.35	10.6	[1.05, 1.62]
V _c -CAP	-0.184	26.0	-0.185	-0.185	25.6	[-0.276, -0.0909]
V _c -HEALTHY	-0.369	6.7	-0.368	-0.369	4.7	[-0.402, -0.335]
V _c -SEXF	-0.199	14.4	-0.198	-0.199	12.0	[-0.245, -0.153]
V _c -WTKG	0.653	14.4	0.654	0.654	12.2	[0.488, 0.813]
V _{p2} -SEXF	-0.218	11.1	-0.219	-0.218	9.7	[-0.261, -0.175]
V _{p2} -WTKG	0.554	12.2	0.552	0.551	10.8	[0.437, 0.672]
V _{p2} -AGE	0.154	23.7	0.152	0.154	19.5	[0.0908, 0.208]
ω^2 -CL _R	0.312	10.4	0.311	0.311	8.8	[0.260, 0.363]
ω^2 -CL _{int,max}	0.145	8.9	0.144	0.144	5.9	[0.130, 0.162]
ω^2 -V _c	0.0736	14.7	0.0752	0.0748	14.9	[0.0550, 0.0988]
ω^2 -CL _{d1}	0.213	11.5	0.214	0.213	10.5	[0.173, 0.261]
ω^2 -V _{p2}	0.108	10.0	0.108	0.108	6.4	[0.0953, 0.122]
ω^2 -K _a	0.616	11.3	0.609	0.607	10.2	[0.489, 0.737]
ω^2 -F _{total, logit}	0.373	13.0	0.371	0.369	9.7	[0.304, 0.446]
σ^2 , Proportional	0.0660	0.6	0.0659	0.0659	0.7	[0.0649, 0.0667]
σ^2 , Additive	0.0000810	4.1	8.12e ⁻⁶	8.11e ⁻⁶	5.0	[7.32e ⁻⁶ , 8.96e ⁻⁶]

Note: Abbreviations are provided in the Abbreviation Listing.

Note: Parameters reflective of the ABSSSI population mean as remains predominant population in pooled dataset.

Note: Full covariance matrix between CL_R, V_c, CL_{d1}, V_{p2}, K_a, F_{total, logit}, and CL_{int,max} employed.

Note: Oral parameters were fixed to their prior values where feasible as Study 306 PK data exclusively IV; random effects in K_a and F_{total, logit} estimated by virtue of inclusion in covariance matrix.

The final population PK model described was used to derive the Bayesian PK exposures of patients with CAP after delafloxacin IV administration. The summary statistics for delafloxacin plasma exposure and key secondary PK parameters, stratified by treatment day, for the patients with CAP are provided in

Table 12 stratified by age category. Analogous estimates for ABSSSI patients, are provided in Table 13 and showed minimal deviation from values reported previously (report 00526-3).

Table 12: Summary statistics [geometric mean (CV%)] for individual, model-derived delafloxacin plasma exposure and secondary PK parameters by day for patients ≥ 65 years of age with CAP enrolled in Study 306 and included in the PK population stratified by age category

Parameter	65 – 74 years (n = 84)			75 – 84 years (n = 53)			≥ 85 years (n = 11)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
AUC ₀₋₂₄ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	63.6 (38.4)	61.4 (39.3)	62.5 (39.2)	88.0 (40.7)	82.7 (44.3)	83.5 (47.5)	83.0 (37.8)	81.9 (38.7)	85.1 (39.5)
C _{max} ($\mu\text{g}/\text{mL}$)	9.62 (25.7)	9.70 (26.4)	9.76 (26.8)	11.2 (27.0)	11.3 (27.9)	11.4 (28.7)	11.5 (23.4)	11.6 (24.9)	11.7 (25.1)
CL _{avg} (L/hr)	12.3 (39.4)	9.77 (40.0)	9.50 (41.9)	9.33 (37.4)	7.42 (44.3)	6.84 (45.3)	10.1 (31.5)	7.14 (37.0)	7.87 (47.8)
V _c (L)	18.1 (30.3)	18.1 (30.3)	18.1 (30.3)	15.9 (30.6)	15.9 (30.6)	15.9 (30.6)	15.0 (27.6)	15.0 (27.6)	15.0 (27.6)
V _{ss} (L)	77.8 (15.4)	77.8 (15.4)	77.8 (15.4)	73.2 (15.0)	73.2 (15.0)	73.2 (15.0)	71.5 (13.3)	71.5 (13.3)	71.5 (13.3)
t _{1/2α} , avg (hr)	0.235 (26.7)	0.243 (27.5)	0.244 (28.0)	0.215 (27.8)	0.220 (28.2)	0.222 (28.6)	0.204 (25.3)	0.212 (27.1)	0.208 (25.9)
t _{1/2β} , avg (hr)	2.26 (17.8)	2.66 (17.4)	2.71 (20.2)	2.41 (15.1)	2.82 (16.6)	2.98 (19.1)	2.20 (16.5)	2.79 (24.9)	2.59 (23.9)
t _{1/2pV} , avg (hr)	24.0 (10.7)	24.8 (9.61)	24.9 (9.76)	23.9 (9.98)	25.1 (8.73)	25.6 (9.11)	24.1 (16.1)	25.8 (12.1)	25.5 (11.6)

Table 13: Summary statistics [geometric mean (CV%)] for individual, model-derived delafloxacin plasma exposure and secondary PK parameters by day for patients ≥ 65 years of age with ABSSSI enrolled in Studies 302 and 303 and included in the PK population stratified by age category

Parameter	65 – 74 years (n = 15)			75 – 84 years (n = 12)			≥ 85 years (n = 3)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
AUC ₀₋₂₄ ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	57.9 (33.1)	60.4 (38.5)	58.3 (47.0)	71.1 (18.0)	71.7 (28.5)	74.5 (28.9)	80.9 (34.2)	83.6 (47.3)	80.0 (58.1)
C _{max} ($\mu\text{g}/\text{mL}$)	7.93 (20.8)	8.10 (23.0)	8.17 (23.4)	9.19 (13.6)	9.39 (15.1)	9.52 (15.1)	10.1 (25.3)	10.4 (28.6)	10.5 (29.2)
CL _{avg} (L/hr)	12.2 (37.8)	10.5 (46.9)	8.56 (48.0)	11.4 (25.9)	8.66 (30.5)	6.39 (41.1)	11.1 (34.2)	5.70 (73.0)	4.73 (52.2)
V _c (L)	25.6 (22.6)	25.6 (22.6)	25.6 (22.6)	21.6 (18.9)	21.6 (18.9)	21.6 (18.9)	19.6 (27.1)	19.6 (27.1)	19.6 (27.1)
V _{ss} (L)	87.7 (13.3)	87.7 (13.3)	87.7 (13.3)	80.3 (9.36)	80.3 (9.36)	80.3 (9.36)	76.7 (14.0)	76.7 (14.0)	76.7 (14.0)
t _{1/2α} , avg (hr)	0.309 (18.2)	0.313 (18.3)	0.321 (20.3)	0.267 (16.7)	0.275 (17.1)	0.282 (17.5)	0.243 (24.1)	0.255 (22.6)	0.260 (26.6)
t _{1/2β} , avg (hr)	2.80 (12.1)	3.12 (18.3)	3.57 (21.4)	2.51 (17.5)	3.07 (20.9)	3.78 (25.8)	2.33 (16.7)	3.67 (20.6)	4.17 (30.4)
t _{1/2pV} , avg (hr)	23.7 (7.28)	24.4 (5.03)	25.4 (8.86)	23.9 (6.58)	24.9 (6.14)	26.8 (11.3)	23.4 (4.59)	27.4 (11.8)	28.5 (15.3)

To visually assess the impact of covariate relationships retained in the final population PK model on delafloxacin plasma exposures, Day 1 and Day 3 post-hoc estimates of AUC₀₋₂₄ and C_{max} in CAP patients enrolled in Study 306 were compared to simulated Day 1 and Day 4 values at various covariate

strata (such as degrees of renal impairment). Monte Carlo simulations (n=500 per scenario) using the final population PK model and specified delafloxacin IV and PO dosing regimens were conducted to produce distributions of predicted delafloxacin AUC₀₋₂₄ and C_{max} for each stratum (for AUC in Figure 3 and for C_{max} in Figure 4). Day 3 post-hoc exposures were leveraged instead of Day 4 as the design of Study 306 did not specify PK sampling beyond Day 3, which results in a lack of PK information following PO dosing. Reciprocally, Day 4 simulations were favored over Day 3 to afford exposure predictions following IV-to-PO switch. As steady-state delafloxacin exposure is expected to occur prior to Day 3, the MAH stated that this difference is not anticipated to affect interpretation of the comparison.

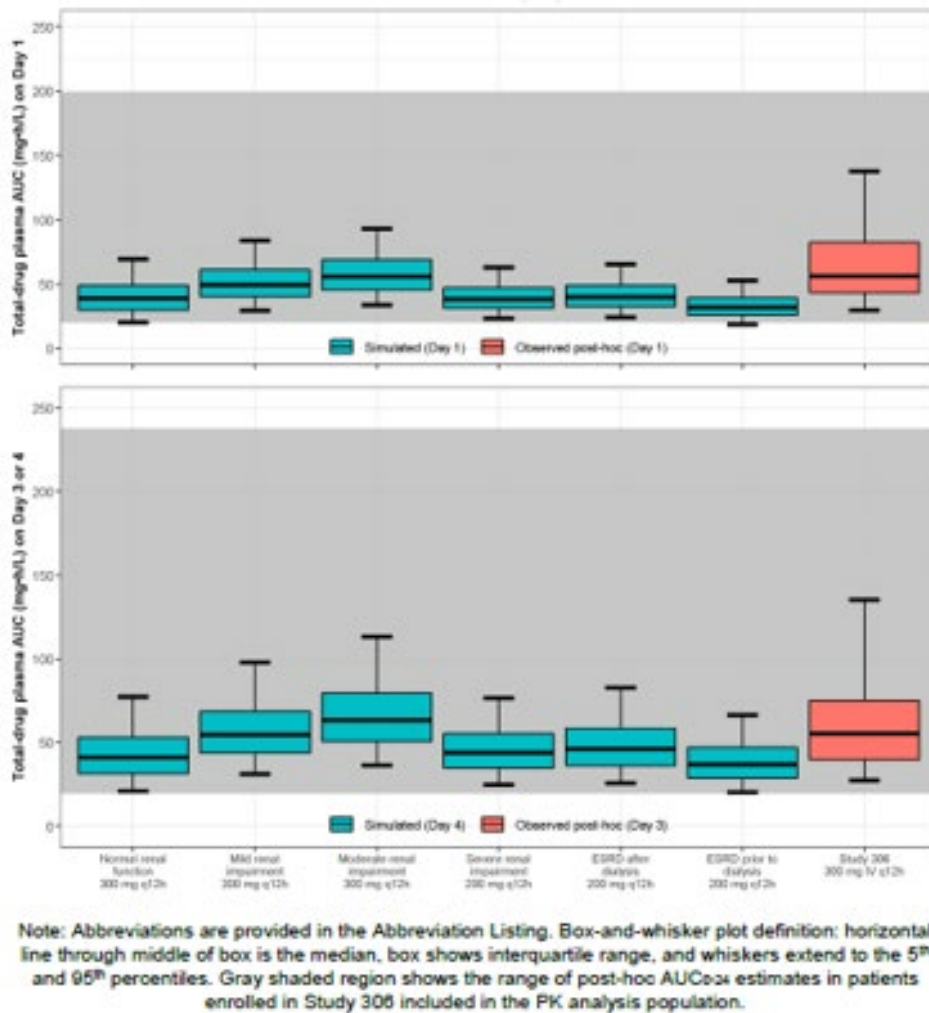


Figure 3: Comparison of predicted delafloxacin exposures (AUC) in patients with varying degrees of renal impairment relative to the range of exposures seen in Study 306 CAP patients (IV only regimens)

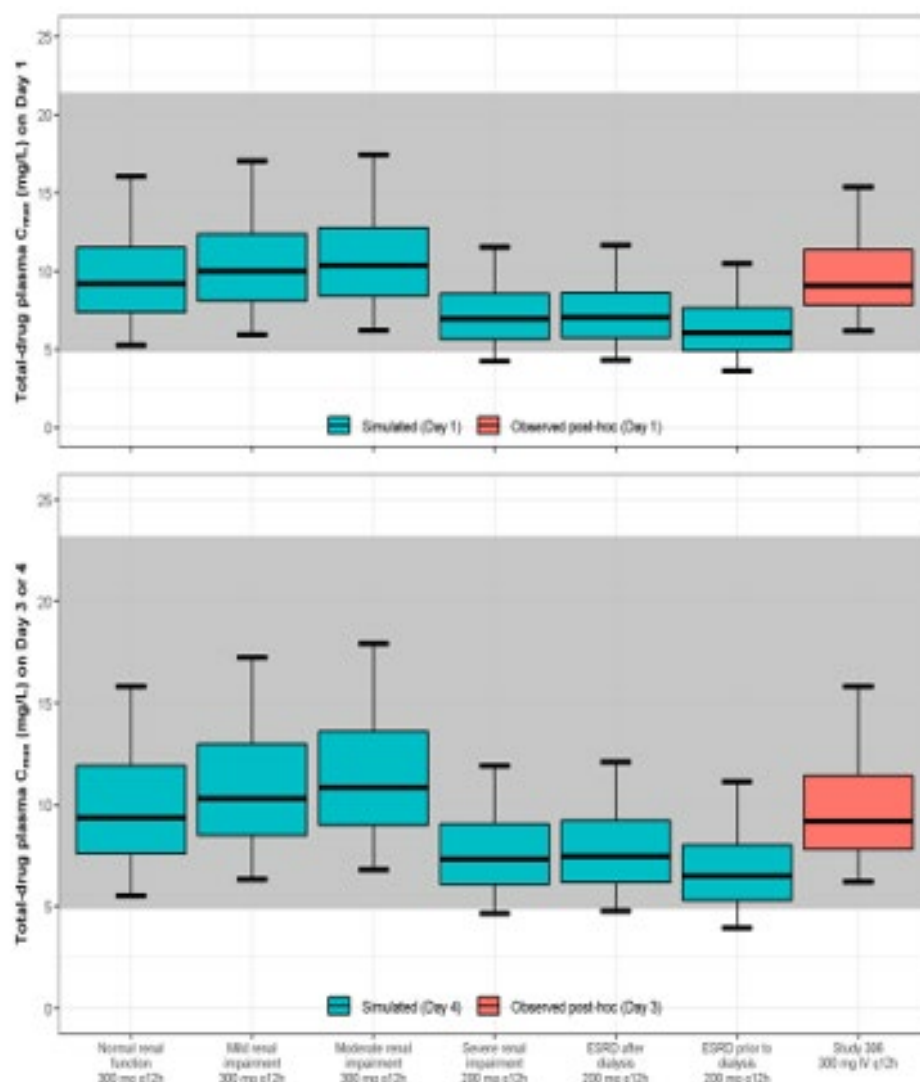


Figure 4. Comparison of predicted delafloxacin Cmax in patients with varying degrees of renal impairment relative to the range of exposures seen in Study 306 CAP patients (IV only regimens)

Pharmacokinetic interaction studies

DDI were described and assessed during procedure EMEA/H/C/004860.

2.3.3. Pharmacodynamics

Mechanism of action

Delafloxacin N-methylglucamine salt hereafter referred to as delafloxacin, is an anionic fluoroquinolone antibiotic with a broad spectrum of antibacterial activity against Gram-positive, Gram-negative, and atypical pathogens. The antibacterial activity of delafloxacin is due to the inhibition of bacterial

topoisomerase IV and DNA gyrase (topoisomerase II), enzymes required for bacterial DNA replication, transcription, repair, and recombination.

Primary pharmacology

Delafloxacin is approved for the treatment of ABSSSI caused by susceptible isolates of *S. aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *S. haemolyticus*, *S. hominis*, *S. lugdunensis*, *S. agalactiae*, *S. anginosus* Group, *S. dysgalactiae*, *S. mitis* group, *S. pyogenes*, *Enterococcus faecalis*, *E. coli*, *Enterobacter cloacae*, *K. oxytoca*, *K. pneumoniae*, *Proteus mirabilis* and *P. aeruginosa*.

The proposed indication is the treatment of adults with CAP caused by susceptible isolates of:

- *S. pneumoniae*
- *S. aureus* (MSSA)
- *E. coli*
- *H influenzae*
- *Chlamydia pneumoniae*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*

Antimicrobial spectrum of activity (*in vitro*)

The *in vitro* activity of delafloxacin against selected clinically prevalent Gram-positive and Gram-negative pathogens including anaerobes has been determined via both a) preclinical profiling studies and b) surveillance studies.

a) Pre-clinical Profiling studies

The *in vitro* spectrum of activity of delafloxacin was analysed against several pathogens from the families of Staphylococci, Enterococci, Streptococci and Enterobacterales and others within the profiling studies that have already been submitted within the original submission for ABSSSI MAA. However, hereinafter the pre-clinical profiling study results for MIC_{50/90} determination of the most relevant pathogens associated with CAP should be summarised and outlined again (see Table 14, Table 15). Data for atypical pathogens associated with CAP (see Table 16) were included in those studies and are presented below since these organisms are not included in the recent surveillance studies.

Table 14: Summary of Delafloxacin and Levofloxacin Activity Against Common Gram-positive CAP Pathogens During Profiling Studies

Organism	Phenotype	Delafloxacin			Levofloxacin			
		N	MIC ₅₀	MIC ₉₀	N	MIC ₅₀	MIC ₉₀	% LVX-R
<i>S. aureus</i>	Overall	2609	0.12	0.5	2609	4	32	64.0
	MSSA	396	≤ 0.004	0.12	396	0.25	8	14.4
	MRSA	2174	0.12	1	2174	8	32	74.1
<i>S. pneumoniae</i>	Overall	100	0.008	0.015	100	0.5	1	3.0
	PSSP ^a	77	0.008	0.015	77	0.5	1	1.3
	PNSP ^a	23	0.008	0.03	23	0.5	2	8.7

MIC = minimum inhibitory concentration; MIC₅₀ = MIC against 50% of the isolates; MIC₉₀ = MIC against 90% of the isolates; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; PNSP = penicillin-non-susceptible *S. pneumoniae*; PSSP = penicillin-susceptible *S. pneumoniae*; % LVX-R = percent levofloxacin-resistant. Source: original submission for ABSSSI MAA pre-clinical profiling App. 1 and 2

Table 15: Summary of Delafloxacin and Levofloxacin Activity Against Common Gram-negative CAP Pathogens During Profiling Studies

Organism	Phenotype	Delafloxacin			Levofloxacin			
		N	MIC ₅₀	MIC ₉₀	N	MIC ₅₀	MIC ₉₀	% LVX-R
<i>E. coli</i>	Overall	239	0.06	8	231	0.12	> 8	45.4
	Non-ESBL	41	0.06	8	40	0.12	> 8	42.5
	ESBL ^a	57	4	> 8	50	> 8	> 8	96.0
<i>K. pneumoniae</i>	Overall	150	0.12	8	150	0.25	> 32	38.0
	Non-ESBL	8	0.06	NA	8	0.12	NA	37.5
	ESBL	34	1	2	34	8	16	67.6
<i>P. aeruginosa</i>	Overall	351	0.5	> 16	351	1	> 32	46.4
	CEPH-S	49	0.5	> 16	49	1	> 32	42.8
	CEPH-R	31	8	> 16	31	32	> 32	83.9
<i>M. catharralis</i>	Overall	102	0.002	0.004	102	0.03	0.06	0.0
<i>H. influenzae</i>	Overall	107	≤ 0.001	0.001	107	0.008	0.015	0.0
<i>H. parainfluenzae</i>	Overall	101	0.004	0.125	101	0.03	0.5	12.8

CEPH-S = susceptible to either ceftazidime or ceftriaxone; ESBL = phenotypically screen-positive for extended-spectrum beta-lactamases; MIC = minimum inhibitory concentration; MIC₅₀ = MIC against 50% of the isolates; MIC₉₀ = MIC against 90% of the isolates; 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 (EUCAST or CLSI M100-S26). Source: original submission for ABSSI MAA pre-clinical Appendix 1 and 2.

Table 16: Delafloxacin and Comparator Fluoroquinolone Activity Against Atypical Bacteria from Profiling studies

Organism	Study	N	Drug	MIC range	MIC ₅₀	MIC ₉₀
<i>Legionella pneumophila</i>	R&D/01/296	14	Delafloxacin	0.12	0.12	0.12
			Levofloxacin	0.5	0.5	0.5
	MB-3341-002	22	Delafloxacin	0.0025 - 0.0005	0.0005	0.0005
			Levofloxacin	0.002 - 0.004	0.004	0.004
	MB-3341-079	48	Delafloxacin	0.00025 - 0.008	0.001	0.001
			Levofloxacin	0.008 - 0.125	0.03	0.015
<i>Legionella spp.</i>	R&D/01/296	5	Moxifloxacin	0.015 - 0.125	0.06	0.03
			Delafloxacin	0.12	0.12	NA
<i>Mycoplasma pneumoniae</i>	R&D/01/296	18	Levofloxacin	0.5	0.5	NA
			Delafloxacin	0.25 - 0.5	0.5	0.5
	MB-3341-002	19	Levofloxacin	1 - 2	1	2
			Delafloxacin	0.12 - 0.5	0.5	0.5
	Waites et al., 2003	101	Levofloxacin	0.25 - 1	0.5	1
			Delafloxacin	0.06 - 0.5	0.25	0.5
	MB-3341-053	30	Levofloxacin	0.5 - 2	0.5	1
			Delafloxacin	0.12 - 1	0.5	0.5
<i>Chlamydia pneumoniae</i>	MB-3341-002	5	Levofloxacin	0.5 - 1	1	1
			Delafloxacin	0.25	NA	NA
	Hammerschlag and Roblin, 2004	13	Levofloxacin	0.5	NA	NA
			Delafloxacin	0.06 - 0.12	0.12	0.12
	MB-3341-068	5	Levofloxacin	0.5 - 1	0.5	0.5
			Delafloxacin	0.5 - 1	NA	NA

Abbreviations: MIC = minimum inhibitory concentration; MIC₅₀ = MIC against 50% of the isolates; MIC₉₀ = MIC against 90% of the isolates; N = Number of isolates; NA = not applicable.

Source: R&D/01/296; MB-3341-002; MB-3341-079; Waites et al., 2003; MB-3341-053; Hammerschlag and Roblin, 2004; MB-3341-068.

b) Surveillance studies

A total amount of 84,440 clinical isolates from 24 European countries plus Israel and the US were tested for delafloxacin and key comparators susceptibility during several surveillance studies conducted between 2014 and 2018. Bacterial susceptibility was assessed using standard broth microdilution susceptibility test methods according to CLSI (CLSI M7-A10, in force), starting from 2018 also with EUCAST method for fastidious organisms (EUCAST Media for MIC Determination by the Broth Microdilution Method and ISO 20776-1, in force). Interpretation of susceptibility to the various

comparator agents reported is based on EUCAST interpretive criteria. For delafloxacin, the breakpoints agreed by EUCAST and EMA are shown in Table 17.

Table 17: Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for delafloxacin MIC breakpoints (mg/L)

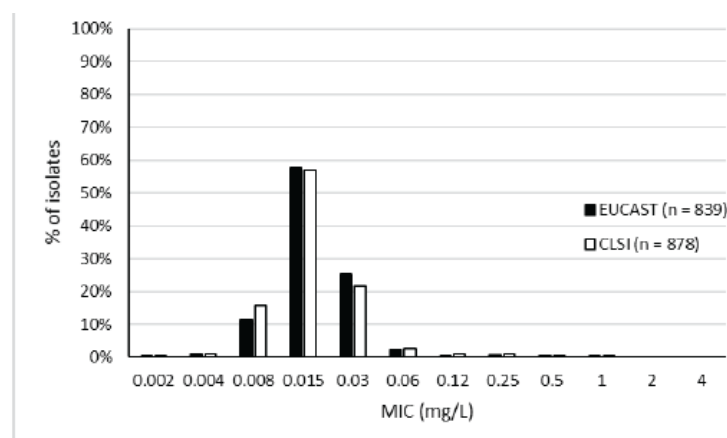
Organism	MIC breakpoints (mg/L)	
	Susceptible (S ≤)	Resistant (R >)
<i>Staphylococcus aureus</i> (Acute bacterial skin and skin structure infections)	0.25	0.25
<i>Staphylococcus aureus</i> (Community-acquired pneumonia)	0.016	0.016
<i>Streptococcus pneumoniae</i>	0.06	0.06
<i>Streptococcus pyogenes</i>	0.03	0.03
<i>Streptococcus dysgalactiae</i>	0.03	0.03
<i>Streptococcus agalactiae</i>	0.03	0.03
<i>Streptococcus anginosus group</i>	0.03	0.03
<i>Escherichia coli</i>	0.125	0.125
<i>Haemophilus influenzae</i>	0.004	0.004

Surveillance results have been discussed during initial submission and it was generally concluded that delafloxacin was shown to have potent *in vitro* activity for several bacterial species such as staphylococci or streptococci. Compared to levofloxacin and other antibiotics delafloxacin had an overall enhanced activity against Gram-positive isolates. Additionally, potent activity was also demonstrated against strains with quinolone resistance like MRSA. Delafloxacin was also shown to be active against Gram-negative isolates, although activity was decreased in isolates with high fluoroquinolone-resistance rates.

A brief summary of the surveillance results for the pathogens most commonly involved in CAP is outlined below.

Streptococcus pneumoniae

Delafloxacin and comparators were tested against 5,095 isolates of *S. pneumoniae* using the CLSI susceptibility testing methods. For fastidious organisms collected during 2018, data in delafloxacin susceptibility were also generated in line with EUCAST's broth microdilution susceptibility testing guidelines recommendations. A comparison of the MIC results obtained in line with either CLSI or EUCAST methodologies revealed that there was no striking difference in MICs between both methods (see Figure 5).



Abbreviations: MIC = minimum inhibitory concentration.
Source: Generated from JMI MVP database.

Figure 5: Delafloxacin MIC Distribution Against *S. pneumoniae* Collected During 2018 Surveillance from Europe / US by EUCAST and CLSI methodologies

For delafloxacin 50/90 % of all of the tested isolates either in the EU or US were inhibited at concentrations of 0.015/ ≤ 0.03 $\mu\text{g/mL}$ (see Table 18). Furthermore, the MIC_{50/90} values remained constant from year to year and by region (see Table 19). Activity of levofloxacin as well as of moxifloxacin against *S. pneumoniae* isolates was shown to be less effective. Tested isolates also included penicillin-susceptible (PSSP), penicillin-intermediate (PISP) as well as penicillin-resistant (PRSP) *S. pneumoniae* strains. The same MIC_{50/90} values as for the total amount of isolates apply to these phenotypes indicating a consistent and potent activity regardless of penicillin-susceptibility phenotype. Delafloxacin however, showed decreased activity against levofloxacin-resistant *S. pneumoniae* (LVX-R) with MIC_{50/90} values of 0.12 $\mu\text{g/mL}$ and 0.5 $\mu\text{g/mL}$, respectively.

Table 18: Delafloxacin, Levofloxacin (2014 - 2018) and Moxifloxacin (2016 - 2018) Activity Against Gram-positive European/US Surveillance Isolates

Organism	Type	N	Delafloxacin			Levofloxacin			N	Moxifloxacin		
			MIC ₅₀	MIC ₉₀	DLX-R % ^a	MIC ₅₀	MIC ₉₀	LVX-R % ^a		MIC ₅₀	MIC ₉₀	MOX-R % ^a
CAP pathogens												
European Surveillance Isolates	Overall	2,599	0.015	0.03	□	1	2	2.2	2,438	≤ 0.12	0.25	1.6
	PSSP ^b	1,905	0.015	0.03	□	1	2	2.0	1,792	≤ 0.12	0.25	1.5
	PISP ^b	558	0.015	0.03	□	1	2	2.3	517	≤ 0.12	0.25	2.1
	PRSP ^b	136	0.03	0.06	□	1	2	3.7	129	≤ 0.12	0.25	1.6
	LVX-R ^a	56	0.12	0.5	□	> 4	> 4	100	54	2	> 4	68.5
US Surveillance Isolates	Overall	2,496	0.015	0.03	□	1	1	0.8	2,168	≤ 0.12	0.25	0.8
	PSSP ^b	1,587	0.015	0.03	□	1	1	0.4	1,381	≤ 0.12	0.25	0.7
	PISP ^b	822	0.015	0.03	□	1	1	1.5	708	≤ 0.12	0.25	1.0
	PRSP ^b	87	0.03	0.03	□	1	1	1.1	79	≤ 0.12	0.25	1.3
	LVX-R ^a	19	0.12	0.25	□	> 4	> 4	100	16	2	4	81.2

Note: MICs were determined according to CLSI susceptibility testing methodology approved at the time of testing.

Abbreviations: DLX-R %: percent delafloxacin-resistant; EUCAST: European Committee on Antimicrobial Susceptibility Testing; LVX-R %: percent levofloxacin-resistant; LVX-S %: percent levofloxacin-susceptible; MIC: minimum inhibitory concentration; MIC₅₀: MIC against 50% of the isolates; MIC₉₀: MIC against 90% of the isolates; MOX-R %: percent moxifloxacin-resistant; MRCoNS: methicillin-resistant coagulase-negative staphylococci; MRSA: methicillin-resistant *S. aureus*; MSCoNS: methicillin-susceptible coagulase-negative staphylococci; MSSA: methicillin-susceptible *S. aureus*; N: Number of isolates; PISP: penicillin-intermediate *S. pneumoniae*; PRSP: penicillin-resistant *S. pneumoniae*; PSSP: penicillin-susceptible *S. pneumoniae*.

^a EUCAST breakpoints applied for delafloxacin, where applicable; EUCAST (2019) breakpoints applied for levofloxacin and moxifloxacin

^b EUCAST non-meningitis (2019) penicillin breakpoints were applied for interpretation of penicillin phenotype.

Table 19: Percentage MIC Distribution, MIC₅₀ and MIC₉₀ of Delafloxacin Against *S. pneumoniae* Collected During 2014 - 2018 by year and by region.

Region	Year	N	MIC (µg/mL)													MIC ₅₀	MIC ₉₀
			0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	> 4		
Europe / US Combined	2014 - 18	5,095	0.0	1.6	17.7	52.8	23.8	3.0	0.6	0.4	0.0	0.1	0.0	0.0	0.0	0.015	0.03
	2014	450	0.0	11.1	57.6	27.6	2.4	0.7	0.4	0.2	0.0	0.0	0.0	0.0	0.0	0.008	0.015
	2015	489	0.0	1.6	25.6	55.8	13.9	2.2	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.015	0.03
	2016	1,303	0.1	0.1	8.0	52.1	34.5	4.5	0.4	0.3	0.0	0.2	0.0	0.0	0.0	0.015	0.03
	2017	1,329	0.0	0.4	11.4	55.2	27.5	4.1	0.8	0.5	0.0	0.0	0.0	0.0	0.1	0.015	0.03
Europe	2018	1,524	0.1	1.0	17.1	57.9	20.8	1.7	0.7	0.5	0.1	0.1	0.0	0.0	0.0	0.015	0.03
	2014 - 18	2,599	0.0	1.2	15.0	50.9	27.4	3.9	0.7	0.7	0.1	0.1	0.0	0.0	0.0	0.015	0.03
	2014	150	0.0	10.7	60.0	26.7	2.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.008	0.015
	2015	161	0.0	0.6	29.2	47.8	19.3	2.5	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.015	0.03
	2016	685	0.1	0.0	6.4	46.6	40.0	5.8	0.3	0.4	0.0	0.3	0.0	0.0	0.0	0.015	0.03
US	2017	725	0.0	0.3	9.7	53.7	29.4	4.8	1.1	1.0	0.0	0.0	0.0	0.0	0.1	0.015	0.03
	2018	878	0.1	1.0	15.7	56.8	21.6	2.5	0.9	0.9	0.2	0.1	0.0	0.0	0.0	0.015	0.03
	2014 - 18	2,496	0.0	2.1	20.5	54.8	20.0	2.0	0.6	0.1	0.0	0.0	0.0	0.0	0.0	0.015	0.03
	2014	300	0.0	11.3	56.3	28.0	2.3	1.0	0.7	0.3	0.0	0.0	0.0	0.0	0.0	0.008	0.015
	2015	328	0.0	2.1	23.8	59.8	11.3	2.1	0.9	0.0	0.0	0.0	0.0	0.0	0.0	0.015	0.03
US	2016	618	0.0	0.2	9.7	58.3	28.3	2.9	0.5	0.2	0.0	0.0	0.0	0.0	0.0	0.015	0.03
	2017	604	0.0	0.5	13.6	57.0	25.3	3.1	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.015	0.03
	2018	646	0.0	1.1	18.9	59.3	19.7	0.6	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.015	0.03

Of the evaluated EU isolates of *S. pneumoniae*, 21.4% were PISP and 5.2% were PRSP based on EUCAST non-meningitis breakpoints. A high degree of resistance to erythromycin was observed.

The same was true for the evaluated US isolates from whom 35.3% were PISP and 3.5% were PRSP based on oral penicillin breakpoints. Again, a high degree of these strains was resistant to erythromycin.

Staphylococcus aureus

The current clinical breakpoints for *S. aureus* established by EUCAST are ≤0.25 µg/mL (S) and >0.25 µg/mL (R). According to current surveillance data (2014-2018) MIC values are generally low with overall MIC_{50/90} values of 0.008 µg/mL and 0.5 µg/mL for *S. aureus*, respectively, and remained constant from year to year and by region. In contrast, overall levofloxacin MIC_{50/90} values were shown to be 0.25 µg/mL and >4 µg/mL, respectively.

MRSA rates were generally lower among European isolates (22.2%) compared to US isolates (43.2%). Delafloxacin showed for both, EU and US isolates, potent activity (see Table 20). MIC_{50/90} values for EU and US MSSA isolates were ≤0.004/0.008 µg/mL and ≤0.004/0.06 µg/mL, respectively. For MRSA the MIC₉₀ values for EU and US isolates were 1 µg/mL. Anyhow, the majority of MRSA (72.1%) had delafloxacin MIC values ≤0.25 µg/mL. Overall, high proportions of tested isolates (between 30% and 100%) were highly resistant to erythromycin, clindamycin, levofloxacin and moxifloxacin according to EUCAST criteria. Levofloxacin-resistance was more pronounced in MRSA isolates. However, delafloxacin remained good activity even in these isolates with MIC₉₀ values of 1 µg/mL and 2 µg/mL for EU and US isolates, respectively.

Table 20: Delafloxacin, Levofloxacin (2014 - 2018) and Moxifloxacin (2016 - 2018) Activity Against Gram-positive EU and US Surveillance Isolates.

Organism	Type	N	Delafloxacin			Levofloxacin			N	Moxifloxacin		
			MIC ₅₀	MIC ₉₀	DLX-R % ^a	MIC ₅₀	MIC ₉₀	LVX-R % ^a		MIC ₅₀	MIC ₉₀	MOX-R % ^a
CAP pathogens												
<i>S. aureus</i>	Overall	7,362	≤ 0.004	0.5	10.4	0.25	> 4	19.2	6,859	≤ 0.06	4	18.9
	MSSA	5,728	≤ 0.004	0.008	1.9	0.25	0.25	4.3	5,348	≤ 0.06	≤ 0.06	4.2
	MRSA	1,634	0.25	1	40.1	> 4	> 4	71.7	1,511	2	> 4	70.9
	LVX-S	5,946	≤ 0.004	0.008	0.0	0.25	0.25	0.0	5,559	≤ 0.06	≤ 0.06	0.1
	LVX-R	1,416	0.5	1	53.9	> 4	> 4	100.0	1,300	4	> 4	99.4
<i>S. aureus</i>	Overall	14,542	0.008	0.5	12.4	0.25	> 4	35.7	12,439	≤ 0.06	4	35.4
	MSSA	8,255	≤ 0.004	0.06	3.1	0.25	4	10.9	7,087	≤ 0.06	1	11.0
	MRSA	6,287	0.12	1	24.7	4	> 4	68.1	5,352	2	> 4	67.8
	LVX-S	9,357	≤ 0.004	0.008	0.0	0.25	0.25	0.0	8,039	≤ 0.06	≤ 0.06	0.2
	LVX-R	5,185	0.25	2	34.8	> 4	> 4	100.0	4,400	2	> 4	99.8

Abbreviations: DLX-R %: percent delafloxacin-resistant; LVX-R %: percent levofloxacin-resistant; LVX-S %: percent levofloxacin-susceptible; MIC: minimum inhibitory concentration; MIC₅₀: MIC against 50% of the isolates; MIC₉₀: MIC against 90% of the isolates; MOX-R %: percent moxifloxacin-resistant; MRSA: methicillin-resistant *S. aureus*; MSSA: methicillin-susceptible *S. aureus*; N: Number of isolates;

Source: JMI MVP database; MB-3341-051; MB-3341-062; 16-MEL-01-EU, 17-MEL-01-EU and 18-MEL-01-EU, MB-3341-050; MB-3341-061; 16-MEL-01-US, 17-MEL-01-US and 18-MEL-01-US.

Haemophilus influenzae

The testing of delafloxacin against *H. influenzae* isolates (N=2,634) revealed potent activity of delafloxacin with overall MIC_{50/90} values of ≤0.001/0.002 µg/mL compared with MIC₉₀ values of 0.03 µg/mL, 0.015 µg/mL, and 0.06 µg/mL for levofloxacin, ciprofloxacin, and moxifloxacin, respectively (see Table 21). There was no significant difference between EU and US isolates and the MIC distribution was similar from year to year and by region (see Figure 6).

Overall, isolates were highly susceptible to all evaluated agents excluding ampicillin and trimethoprim-sulfamethoxazole (TMP/SMX). Analyses revealed that 18.2% (227/1,249) of the European and 30.9% (299/969) US isolates were β-lactamase positive. However, potent activity could still be shown for delafloxacin and other fluoroquinolones regardless of β-lactamase phenotype (see Module 2.7.2, Table 2.7.2-41).

Table 21: Delafloxacin and Comparator Activity Against *H. influenzae* During 2015 - 2018 European and US Surveillance

Antimicrobial agent	No. of isolates	mg/L			EUCAST ^a		
		MIC ₅₀	MIC ₉₀	MIC range	%S	%I	%R
Delafloxacin	2,634	≤ 0.001	0.002	≤ 0.001 to > 0.25			
Levofloxacin	2,634	≤ 0.015	0.03	≤ 0.015 to > 2	98.0		2.0
Ciprofloxacin	2,634	0.015	0.015	≤ 0.008 to > 1	98.1		1.9
Moxifloxacin	2,339	0.03	0.06	≤ 0.008 to > 1	98.5		1.5
Amoxicillin-clavulanic acid	2,634	0.5	2	≤ 0.12 to > 8	93.7 93.7 ^b		6.3 6.3
Ampicillin	2,634	0.5	> 8	≤ 0.12 to > 8	68.7		31.3
Azithromycin	2,634	1	2	≤ 0.12 to > 4	98.6 ^c		
Ceftaroline	2,633	0.008	0.03	≤ 0.004 to > 0.5	95.9		4.1
Ceftazidime	295	0.06	0.12	≤ 0.015 to 1			
Ceftriaxone	2,634	≤ 0.015	≤ 0.015	≤ 0.015 to 0.5	99.7		0.3
Clarithromycin	2,633	8	16	≤ 0.12 to > 16	100.0 ^c		
Meropenem	2,633	0.06	0.25	≤ 0.008 to 1	99.6 ^d 100.0 ^e		0.4 0.0
Tetracycline	2,634	0.5	1	≤ 0.12 to > 8	98.8	0.3	0.9
Tigecycline	295	0.12	0.25	0.06 to 1			
Trimethoprim-sulfamethoxazole	2,634	0.12	> 4	≤ 0.06 to > 4	61.9	1.7	36.4

Abbreviations: MIC = minimum inhibitory concentration; MIC₅₀ = MIC against 50% of the isolates; MIC₉₀ = MIC against 90% of the isolates; N = number of isolates; %I = % intermediate; %R = % resistant; %S = % susceptible; blank = no interpretive criteria available.

^a. Criteria as published by EUCAST (2019).

^b. Using oral breakpoints.

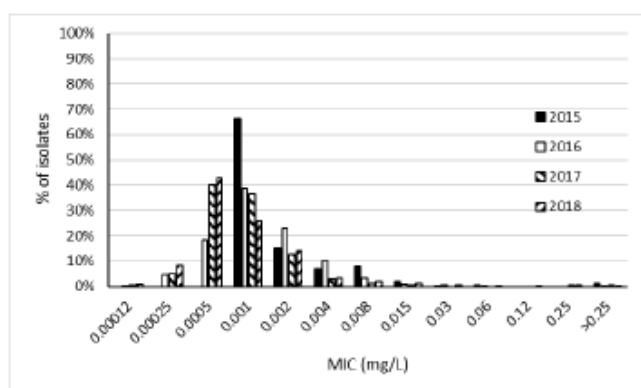
^c. Percentage of wild type based on ECOFF (EUCAST version 8.0 (2018)).

^d. Using meningitis breakpoints.

^e. Using non-meningitis breakpoints.

Source: JMI MVP database; MB-3341-062; 16-MEL-01-EU, 17-MEL-01-EU, 18-MEL-01-EU, MB-3341-061; 16-MEL-01-US; 17-MEL-01-US and 18-MEL-01-US.

A. By Year



B. By Region

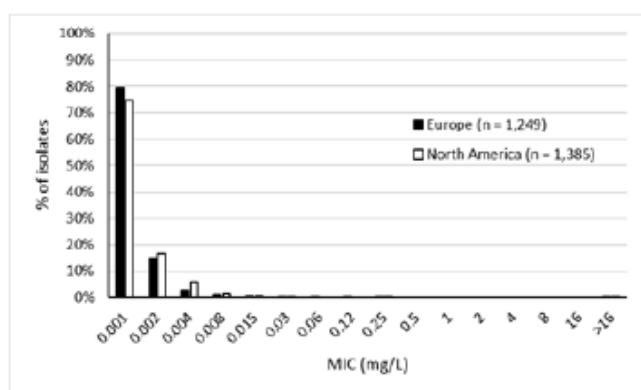


Figure 6: Delafloxacin MIC Distribution Against *H. influenzae* Collected During 2015 – 2018 Surveillance by Year and by Region

Haemophilus parainfluenzae

Delafloxacin as well as comparator antibiotics (see Table 22) was also tested against 136 *H. parainfluenzae* isolates. Overall, MIC₉₀ for delafloxacin was low with 0.015 µg/mL. Interestingly, a difference in MIC values has been determined between EU and US isolates as MIC₉₀ for EU isolates (N=44) was >0.25 µg/mL while it was 0.015 µg/mL for US isolates (see Module 2.7.2, Table 2.7.2-42). Generally, the MIC distribution for delafloxacin was similar from year to year and by region (see Figure 7).

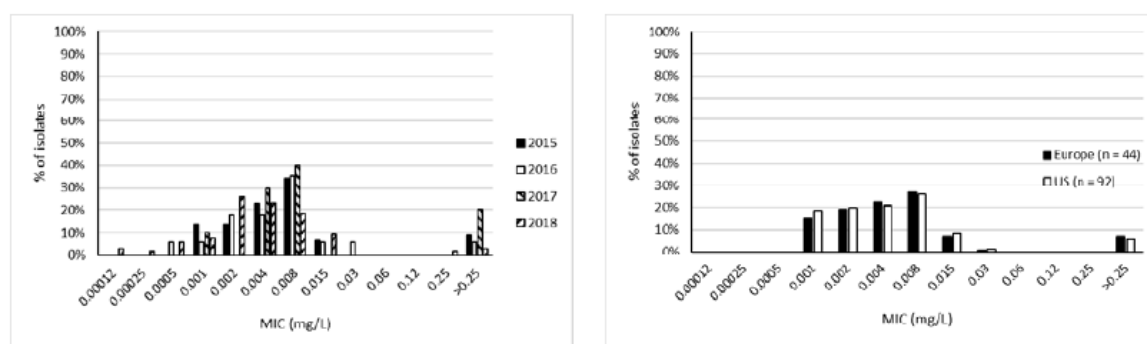


Figure 7: MIC distribution by year and region.

Potent activity was shown for most of the tested antibiotics against *H. parainfluenzae*. Delafloxacin showed potent activity against *H. parainfluenzae* isolates with a MIC₉₀ value of 0.015 mg/L compared with 0.12 mg/L, 0.03 mg/L and 0.25 mg/L for levofloxacin, ciprofloxacin and moxifloxacin, respectively. Susceptibility to ampicillin and TMP/SMX was comparably worse as shown for *H. influenzae* isolates.

Only 4.4% of the total isolates tested were β -lactamase positive and regardless of phenotype delafloxacin was shown to have potent activity (see Module 2.7.2, Table 2.7.2-46).

Table 22: Delafloxacin and Comparator Activity Against *H. parainfluenzae* During 2015 – 2018 European and US Surveillance.

Antimicrobial agent	No. of isolates	mg/L			EUCAST ^a		
		MIC ₅₀	MIC ₉₀	MIC range	%S	%I	%R
Delafloxacin	136	0.004	0.015	≤ 0.001 to > 0.25			
Levofloxacin	136	0.03	0.12	≤ 0.015 to > 2	89.0		11.0
Ciprofloxacin	136	0.015	0.03	≤ 0.008 to > 1	92.6		7.4
Moxifloxacin	92	0.06	0.25	≤ 0.008 to > 1	77.2		22.8
Amox-Clav	136	0.25	1	≤ 0.12 to 8	97.8 97.8 ^b		2.2 2.2
Ampicillin	136	0.25	2	≤ 0.12 to > 8	89.7		10.3
Azithromycin	136	1	2	≤ 0.12 to > 4	95.6 ^c		
Ceftaroline	136	0.015	0.06	≤ 0.004 to > 0.5	87.5		12.5
Ceftazidime	44	0.06	0.25	≤ 0.015 to > 2			
Ceftriaxone	136	≤ 0.015	≤ 0.015	≤ 0.015 to > 2	97.8		2.2
Clarithromycin	136	8	16	0.25 to > 16	100.0 ^c		
Meropenem	136	0.03	0.06	≤ 0.008 to > 1	98.5 ^d 100.0 ^e		1.5 0.0
Tetracycline	136	0.5	4	0.25 to > 8	89.0	0.0	11.0
Tigecycline	44	0.25	1	0.12 to 1			
TMP/SMX	136	≤ 0.06	> 4	≤ 0.06 to > 4	78.7	2.2	19.1

Abbreviations: MIC = minimum inhibitory concentration; MIC₅₀ = MIC against 50% of the isolates; MIC₉₀ = MIC against 90% of the isolates; N = number of isolates; %I = % intermediate; %R = % resistant; %S = % susceptible; blank = no interpretive criteria available.

^a. Criteria as published by EUCAST (2019).

^b. Using oral breakpoints.

^c. Percentage of wild type based on ECOFF (EUCAST version 8.0 (2018)).

^d. Using meningitis breakpoints.

^e. Using non-meningitis breakpoints.

Source: JMI MVP database; MB-3341-062; 16-MEL-01-EU, 17-MEL-01-EU, 18-MEL-01-EU, MB-3341-061; 16-MEL-01-US; 17-MEL-01-US and 18-MEL-01-US.

Moraxella catarrhalis

M. catarrhalis isolates (N=1500) from the EU and US showed overall MIC_{50/90} values for delafloxacin of 0.004/0.008 µg/mL for surveillance between 2015-2018. The MIC distribution was consistent from year to year and by region (see Module 2.7.2, Figure 2.7.2-20).

Isolates were tested against the same comparator antibiotics as shown for *Haemophilus* spp. (see Table 23). Analyses revealed that all of the tested antibiotics had potent activity against *M. catarrhalis* except for penicillin. Analyses for β -lactamases revealed that >96% of the isolates were β -lactamase positive (96.7% (638/660) and 98.0% (630/643) amongst European and US isolates, respectively). However, β -lactamase phenotype had no relevant influence on delafloxacin, levofloxacin or moxifloxacin activity (see Module 2.7.2, Table 2.7.2-51). In comparison to levofloxacin and moxifloxacin, delafloxacin was shown to be 8-fold more active.

Table 23: Delafloxacin and Comparator Activity Against *M. catarrhalis* During 2015 - 2018 European and US Surveillance

Antimicrobial agent	No. of isolates	mg/L			EUCAST ^a		
		MIC ₅₀	MIC ₉₀	MIC range	%S	%I	%R
Delafloxacin	1,500	0.004	0.008	≤ 0.001 to 0.12			
Levofloxacin	1,500	0.03	0.06	≤ 0.015 to 2	99.3		0.7
Moxifloxacin	1,298	0.06	0.06	≤ 0.008 to 1	99.8		0.2
Amoxicillin-clavulanic acid	1,499	≤ 0.25	≤ 0.25	≤ 0.25 to 0.5	100.0		0.0
Azithromycin	1,489	≤ 0.03	≤ 0.03	≤ 0.03 to 1	99.9	0.0	0.1
Ceftaroline	1,498	0.06	0.25	≤ 0.008 to > 0.5			
Ceftazidime	1,499	0.06	0.25	≤ 0.015 to > 2			
Ceftriaxone	1,500	0.25	0.5	≤ 0.015 to 2	99.5	0.5	0.0
Clarithromycin	1,490	≤ 0.12	0.25	≤ 0.12 to 4	99.5	0.4	0.1
Meropenem	1,500	≤ 0.015	≤ 0.015	≤ 0.015 to 0.03	100.0		0.0
Penicillin	1,500	> 4	> 4	≤ 0.03 to > 4			
Tetracycline	1,499	0.25	0.5	≤ 0.06 to > 8	99.8	0.0	0.2
Tigecycline	202	0.03	0.06	0.015 to 0.12			
Trimethoprim-sulfamethoxazole	1,499	0.12	0.25	≤ 0.06 to 4	96.9	1.7	1.3

Abbreviations: MIC = minimum inhibitory concentration; MIC₅₀ = MIC against 50% of the isolates; MIC₉₀ = MIC against 90% of the isolates; N = number of isolates; %I = % intermediate; %R = % resistant; %S = % susceptible; blank = no interpretive criteria available.

^a Criteria as published by EUCAST (2019).

Source: JMI MVP database; MB-3341-062; 16-MEL-01-EU, 17-MEL-01-EU, 18-MEL-01-EU, MB-3341-061; 16-MEL-01-US; 17-MEL-01-US and 18-MEL-01-US.

E. coli

Overall delafloxacin MIC_{50/90} values for *E. coli* during Surveillance from 2014-2018 were 0.06 µg/mL and 4 µg/mL, respectively and distribution was similar from year to year and by region (EU and US).

Similar MIC values were obtained for other fluoroquinolones like levofloxacin, ciprofloxacin or moxifloxacin. About 20.0% of the isolates collected within Europe and the US were ESBL-producers, with slightly more ESBL-producers amongst the European isolates than the US isolates (21.2% (1,459/6,867) vs. 18.4% (1,015/5,501), respectively. Similar to other fluoroquinolones, delafloxacin was more potent against non-ESBL isolates (with MIC_{50/90} of 0.03-0.06/4 µg/mL compared to 4/>4 µg/mL for the ESBL-isolates). The MIC distribution was bimodal (see Module 2.7.2, Figure 2.7.2-23) reflecting decreased delafloxacin activity in ESBL isolates.

K. pneumoniae

For the 6038 *K. pneumoniae* isolates collected between 2014-2018, 33.1 % [1,966/6,038] of them screened ESBL-positive with a higher proportion of ESBL-producers in EU vs. US isolates (47.7% [1,484/3,111] vs. 17.5% [512/2,927]). CRE rates were also higher for EU than US isolates (11.8% [368/3,111] vs. 2.0% [58/2,927]). As with the other fluoroquinolones, delafloxacin was more potent against non-ESBL isolates with an MIC_{50/90} of 0.12 / 0.5 mg/L but against ESBL and CRE isolates, all the fluoroquinolones, including delafloxacin, had MIC_{50/90} values of > 4 / > 4 mg/L (see Table 24).

The MIC distribution for delafloxacin on a geographic and phenotypic level (see Figure 8) indicates that (i) MICs from 2 to >4 µg/mL are more distributed in EU isolates and (ii) that ESBL and CRE isolates have higher MIC values compared to non-ESBL isolates reflecting the MIC_{50/90} data for both phenotypes (see Table 24).

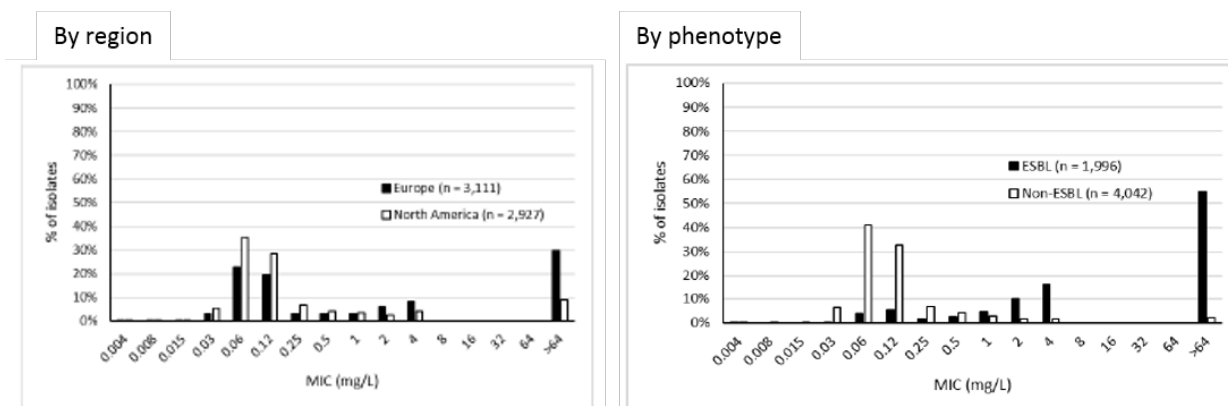


Figure 8: MIC distribution by region and phenotype.

P. aeruginosa

Delafloxacin showed activity against *P. aeruginosa* isolates (N=6,302) comparable to levofloxacin and ciprofloxacin with MIC_{50/90} values of 0.5/>4 µg/mL (see Table 24). About 20.6% of 6,301 tested isolates from the Surveillance studies were tested as ceftazidime resistant (CAZ-R). Furthermore, about 37.2% and 29.8% of tested strains were levofloxacin or ciprofloxacin resistant, respectively. Resistant rates for piperacillin-tazobactam (Pip-Taz) were 24.6% of the tested isolates (see Module 2.7.2, Table 2.7.2-61).

Table 24: Delafloxacin, Levofloxacin and Moxifloxacin Activity Against Gram-negative 2014 - 2018 European Surveillance Isolates

Organism	Type	N	Delafloxacin			Levofloxacin			N	Ciprofloxacin			Moxifloxacin			
			MIC ₅₀	MIC ₉₀	% DLX-R ^a	MIC ₅₀	MIC ₉₀	% LVX-R ^a		MIC ₅₀	MIC ₉₀	% CIP-R ^a	N	MIC ₅₀	MIC ₉₀	% MOX-R ^a
CAP pathogens																
<i>H. influenzae</i> ^b	Overall	1,249	≤ 0.001	0.002	–	≤ 0.015	0.03	1.9	1,249	0.015	0.015	1.8	1,149	0.03	0.06	1.6
<i>H. parainfluenzae</i> ^b	Overall	44	0.004	> 0.06	–	0.03	0.5	11.4	44	0.015	0.25	11.4	38	0.06	> 1	18.4
<i>M. catarrhalis</i> ^b	Overall	760	0.004	0.008	–	0.03	0.06	0.8	–	–	–	–	659	0.06	0.06	0.3
<i>E. coli</i>	Overall	6,868	0.06	4	37.3	≤ 0.12	> 4	28.0	6,835	≤ 0.03	> 4	28.9	6,474	≤ 0.25	> 4	36.1
	Non-ESBL	5,408	0.03	4	24.9	≤ 0.12	> 4	15.9	5,382	≤ 0.03	> 4	16.6	5,102	≤ 0.25	> 4	23.7
	ESBL ^c	1,459	4	> 4	83.3	> 4	> 4	72.9	1,452	> 4	> 4	74.4	1,371	> 4	> 4	82.3
<i>K. pneumoniae</i>	Overall	3,111	0.5	> 4	–	0.5	> 4	36.9	3,094	0.25	> 4	45.0	2,769	0.5	> 4	52.1
	Non-ESBL	1,627	0.12	0.5	–	≤ 0.12	0.5	5.4	1,613	≤ 0.03	0.5	7.6	1,443	≤ 0.25	1	16.1
	ESBL ^c	1,484	> 4	> 4	–	> 4	> 4	71.5	1,481	> 4	> 4	85.8	1,326	> 4	> 4	91.3
	CRE ^d	368	> 4	> 4	–	> 4	> 4	97.8	368	> 4	> 4	98.9	331	> 4	> 4	99.1
<i>P. aeruginosa</i>	Overall	3,300	0.5	> 4	–	0.5	> 4	38.2	3,285	0.25	> 4	31.5	3,145	2	> 4	–

Abbreviations: DLX=delafloxacin; LVX=levofloxacin; CIP=ciprofloxacin; CRE = carbapenem-resistant Enterobacteriaceae; CSE = carbapenem-susceptible Enterobacteriaceae; ESBL = phenotypically screen-positive for extended-spectrum beta lactamases; non-ESBL = phenotypically screen-negative for extended-spectrum beta lactamases; MIC = minimum inhibitory concentration; MIC₅₀ = MIC against 50% of the isolates; MIC₉₀ = MIC against 90% of the isolates; MOX-R = moxifloxacin-resistant; N = number of isolates.

^a EUCAST (2019) breakpoints applied for levofloxacin, ciprofloxacin and moxifloxacin.

^b 2015-2018 surveillance data presented; no data presented for 2014.

^c EUCAST breakpoints (2019) were applied for interpretation of ESBL phenotype.

^d EUCAST breakpoints (2019) were applied for interpretation of CRE phenotype.

Source: JMI MVP database; MB-3341-051; MB-3341-062; 16-MEL-01-EU, 17-MEL-01-EU and 18-MEL-01-EU.

Susceptibility testing methodology

Bacterial susceptibility was assessed using standard broth microdilution susceptibility test methods according to CLSI (*CLSI M7-A10, 2015*) which were compliant with EUCAST methodology for non-fastidious organisms. However, MIC testing for fastidious organisms according to CLSI differed from the EUCAST methodology (which requires the use of MHF medium).

To compare both methods (CLSI and EUCAST) two additional studies have been submitted by the MAH (ECOFF-DELA-01; 17-MEL-07). Both studies aimed to determine the susceptibility of fastidious and non-fastidious organisms to delafloxacin according to EUCAST SOP and finally results were compared

with the surveillance data for European isolates using CLSI methodology. The results are described below:

ECOFF-DELA-01

Study ECOFF-DELA-01 was conducted at 5 Italian centres and collected at least 30 isolates of each of 11 non-fastidious and 9 fastidious species and tested these using EUCAST methodology (EUCAST Media Preparation v 5.0, 2017) in line with ISO 20776-1 standards.

In vitro activity of delafloxacin (MIC distribution and MIC_{50/90}) using EUCAST methodology was comparable to or better than that seen against the European surveillance isolates using CLSI testing methodology (Table 25).

In summary, study ECOFF-DELA-01 confirmed the activity of delafloxacin against both Gram-positive and -negative CAP pathogens against isolates and demonstrated that delafloxacin MICs were comparable to or lower when EUCAST susceptibility methodology is used compared with CLSI susceptibility testing methodology.

17-MEL-07

In addition to the above described ECOFF-DELA-01 study, the 17-MEL_07 study was the first study conducted to compare EUCAST and CLSI Methodology. 17-MEL 07 study was conducted at 2 centres in Italy and at JMI Laboratories.

A total of 899 fastidious organisms were randomly selected from the delafloxacin surveillance isolates collected during 2017 and tested according to the EUCAST and ISO 20776-1 standards.

The MICs obtained were then compared with the MICs originally obtained by JMI Laboratories using CLSI methodology Table 26.

Delafloxacin showed potent activity against the 899 strains of nine fastidious species (*S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, *S. agalactiae*, *S. anginosus* GP, *S. dysgalactiae*, *S. mitis* group, *S. pyogenes*) tested and, overall, delafloxacin MIC values were similar by EUCAST and CLSI methods.

In vitro activity of delafloxacin (MIC distribution and MIC_{50/90}) using EUCAST methodology for the nine fastidious species tested was comparable to or better than that seen against the European surveillance isolates using CLSI testing methodology Table 26.

Table 25: *In Vitro* Activity of Delafloxacin and Comparator Fluoroquinolones against 11 Common Gram-positive and Gram-negative pathogens ECOFF-DELA-01 Study.

Organism	Study	N	MIC (mg/L)													MIC ₅₀	MIC ₉₀
			≤ 0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	> 4		
<i>S. pneumoniae</i>	DELA-01 ^a	150	22.0	24.7	43.3	8.7	0.7	0.0	0.0	0.0	0.7	0.0	0.0	0.0	0.0	0.004	0.015
	2014-18 EU ^b	2,599	0	1.2	15	50.9	27.4	3.9	0.7	0.7	0.1	0.1	0	0	0	0.015	0.03
<i>S. aureus</i>	DELA-01 ^a	150	26.0	40.7	22.0	1.3	2.0	1.3	2.0	2.0	0.7	0.7	1.3	0.0	0.0	0.004	0.015
	2014-18 EU	7362	0	51.8	25.8	3.2	0.3	0.4	2.2	5.8	5	3.6	0.6	0.6	0.6	≤ 0.004	0.5
<i>H. influenzae</i>	DELA-01 ^a	150	100	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	≤ 0.002	≤ 0.002
	2014-18 EU	1298	91.6	3.5	2.3	0.9	0.2	0.3	0	0	1.1 ^c	-	-	-	-	≤ 0.001	0.002
<i>H. parainfluenzae</i>	DELA-01 ^a	150	43.3	28.7	15.3	7.3	1.3	0.0	0.0	0.0	0.7	0.0	0.0	0.0	3.3	≤ 0.002	≤ 0.002
	2014-18 EU	44	27.2	27.3	29.5	4.5	0	0	0	0	11.4 ^c	-	-	-	-	0.004	> 0.25
<i>M. catarrhalis</i>	DELA-01 ^a	149	90.6	7.4	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.3	≤ 0.002	≤ 0.002
	2014-18 EU	760	25.6	48.7	22.6	2.5	0.3	0.1	0.1	0	0 ^c	-	-	-	-	0.004	0.008
<i>E. coli</i>	DELA-01 ^a	150	0.0	1.3	4.7	32.7	36.0	14.7	1.3	0.0	2.0	4.0	1.3	0.7	1.3	0.03	0.12
	2014-18 EU	6868	-	-	1.4 ^d	10.2	31.6	15.5	4	4.8	2.2	1.6	7.3	13.1	8.3	0.06	4
<i>K. pneumoniae</i>	DELA-01 ^a	150	0.0	0.0	0.0	2.7	16.7	42.7	26.7	3.3	0.7	0.7	0.0	0.7	6.0	0.06	0.25
	2014-18 EU	3111	-	-	0.1 ^d	0.16	3.25	22.95	19.45	3.31	3.31	3.15	6.11	8.39	29.8	0.5	> 4
<i>P. aeruginosa</i>	DELA-01 ^a	150	0.0	0.0	0.0	0.0	2.0	2.0	12.7	24.7	34.7	11.3	8.0	1.3	3.3	0.5	2
	2014-18 EU	3300	-	-	0.3 ^d	0.3	0.7	1.5	5	26.2	27.2	7.7	6.5	4.8	19.8	0.5	> 4

Abbreviations: MIC = minimum inhibitory concentration.

a) Data from study ECOFF-DELA-01. Susceptibility testing performed using EUCAST methodology.

b) Isolates collected from Europe during 2014 - 18 surveillance. Susceptibility testing performed using CLSI methodology.

c) ≥ 0.25 mg/L

d) ≤ 0.008 mg/L

Source: Data Set 5 labs Final version 08-09-2018

Table 26: Delafloxacin Activity Against Fastidious Pathogens Tested by EUCAST and CLSI Susceptibility Testing Methodology.

Species	N	mg/L					
		MIC ₉₀		MIC ₅₀		MIC Range	
		EUCAST	CLSI	EUCAST	CLSI	EUCAST	CLSI
<i>S. pneumoniae</i>	97	0.016	0.03	0.004	0.016	≤ 0.002 - 0.5	≤ 0.004 - 0.5
<i>H. influenzae</i>	101	0.001	0.002	0.00025	0.001	0.00025 - 0.002	0.000125 - 0.004
<i>H. parainfluenzae</i>	98	0.125	0.25	0.004	0.008	0.0005 - > 0.25	0.0005 - > 0.25
<i>M. catarrhalis</i>	98	0.004	0.008	0.002	0.004	0.00025 - 0.008	≤ 0.001 - 0.016
<i>S. agalactiae</i>	100	0.03	0.03	0.008	0.016	≤ 0.002 - 0.5	≤ 0.004 - 0.5
<i>S. anginosus</i> Gp. ^a	105	0.008	0.03	0.004	0.008	0.0005 - 0.125	≤ 0.002 - 0.06
<i>S. dysgalactiae</i>	100	0.016	0.03	0.008	0.016	≤ 0.002 - 0.125	≤ 0.004 - 0.25
<i>S. mitis</i> group	101	0.06	0.06	0.016	0.03	0.004 - 1	0.008 - 0.5
<i>S. pyogenes</i>	99	0.016	0.03	0.008	0.008	≤ 0.002 - 0.03	≤ 0.004 - > 0.03

Abbreviations: MIC = minimum inhibitory concentration.

^a *S. anginosus* group.

Source: 17-MEL-07.

Bactericidal activity

Studies of the bactericidal effects were conducted with delafloxacin using MBC and time-kill assessments based on CLSI guidelines (*CLSI M26-A, 1999*). Delafloxacin was bactericidal against several Gram-positive as well as Gram-negative CAP-relevant bacterial species (*S. aureus*, *S. pneumoniae*, *H. influenzae*, *E. coli*, *K. pneumoniae*, *P. aeruginosa* etc.). Delafloxacin demonstrated rapid and concentration-dependent killing in time-kill assays against a diverse array of Gram-positive and Gram-negative CAP-pathogens confirming a bactericidal effect, as well.

Factors affecting *in vitro* susceptibility of delafloxacin

Factors affecting the *in vitro* susceptibility of delafloxacin have already been discussed during MAA for ABSSSI. However, it should be noted in the context of this line extension that no effect of pulmonary surfactants on the activity of delafloxacin against pulmonary pathogens (*S. aureus*, *S. pneumoniae* (PISP/PRSP), *H. influenzae*, *M. catarrhalis*) was detected.

In vitro antibacterial activity - clinical studies

Baseline Microbiology from Phase III CAP – ML-3341-306

Causative pathogens were identified by isolation from a baseline culture specimen (either a respiratory specimen or blood), by urinary antigen, serology, and/or PCR in the Phase III (ML-3341-306). Local or regional laboratories performed routine culture of all sputum and blood specimens. Bacterial isolates were forwarded to the central microbiology laboratory for confirmation of identity, antimicrobial susceptibility testing, and further molecular or phenotypic characterization.

Of 746 subjects 453 subjects (60.7%) had at least 1 pathogen detected at baseline by any method (including culture, serology, PCR, and urinary antigen), comprising the modified Intention-To-Treat (ModITT)-1 population.

Overall, the distribution of all pathogens between the two treatment groups was well balanced at baseline in the ModITT population. The most common baseline pathogens detected (by any method) were *S. pneumoniae* (43.3%), *H. parainfluenzae* (13.2%), *M. pneumoniae* (12.6%), *H. influenzae* (11.9%), *L. pneumophila* (11.7%), *S. aureus* (11.7%), *C. pneumoniae* (7.7%), *K. pneumoniae* (6.6%), *E. coli* (5.5%), *P. aeruginosa* (5.3%). Among 125 baseline *S. pneumoniae* isolates with susceptibility test results available, 26.4% were macrolide-resistant *S. pneumoniae* (MRSP) (33 isolates), 1.6% were penicillin-resistant *S. pneumoniae* (PRSP) (2 isolates), and 1.6% were multiple drug-resistant *S. pneumoniae* (MDRSP) (2 isolates). Overall, 0.4%, 7.0%, and 0.4% of *S. pneumoniae* from delafloxacin-treated subjects, respectively, were penicillin-resistant *Streptococcus pneumoniae* (PRSP), macrolide-resistant *Streptococcus pneumoniae* (MRSP), or multiple drug-resistant *Streptococcus pneumoniae* (MDRSP). The distribution in the moxifloxacin-group was similar. The atypical pathogens (*M. pneumoniae*, *L. pneumophila*, and *C. pneumoniae*) were commonly encountered. Percental distribution was 14.0%, 11.4%, and 9.2%, respectively, for delafloxacin-treated subjects and 11.1%, 12% and 6.2%, respectively, for moxifloxacin-treated subjects. *S. aureus* was encountered frequently in both the delafloxacin and moxifloxacin treated patients. One isolate of MRSA was identified in the delafloxacin group and none in the moxifloxacin-group, whereas 52 isolates were identified for MSSA, which were equally distributed in both groups.

Most of the infections in the delafloxacin and moxifloxacin groups were monomicrobial with Gram-positive infections compared to polymicrobial infections (~60% monomicrobial vs 36% polymicrobial infection) in the ModMITT-1 population.

Summary of Activity of Delafloxacin Against Target Pathogens at Baseline

The MIC summary statistics (MIC range, MIC₅₀, and MIC₉₀) for delafloxacin against key baseline target pathogens in the ModMITT-2 analysis are summarized in

Table 27.

Table 27: Summary of Delafloxacin and Comparator Activity Against Baseline Pathogens (ModMITT-2; Delafloxacin and Moxifloxacin Treatment Groups).

Baseline Target Pathogen	ModMITT-2 Population (Treatment Groups Combined) N = 358						
	Delafloxacin				Moxifloxacin or Ciprofloxacin ^a		
	n	MIC Range (mg/L)	MIC ₅₀ (mg/L) ^b	MIC ₉₀ (mg/L) ^b	MIC Range (mg/L)	MIC ₅₀ (mg/L) ^b	MIC ₉₀ (mg/L) ^b
Gram-positive organisms							
<i>Streptococcus pneumoniae</i> ^c	125	0.004 – 0.03	0.008	0.015	0.06 – 0.25	0.12	0.25
PSSP	91	0.004 – 0.03	0.008	0.015	ND	ND	ND
PISP	35	0.004 – 0.015	0.008	0.015	ND	ND	ND
PRSP	2	0.008 – 0.015	—	—	ND	ND	ND
MDR	2	0.008 – 0.015	—	—	ND	ND	ND
Macrolide-susceptible	92	0.004 – 0.03	0.008	0.015	ND	ND	ND
Macrolide-nonsusceptible	33	0.004 – 0.015	0.008	0.008	ND	ND	ND
<i>Staphylococcus aureus</i>	53	0.001 – 0.12	0.002	0.004	0.03 – 2	0.06	0.12
MSSA	52	0.001 – 0.12	0.002	0.004	0.03 – 2	0.06	0.12
MRSA	1	0.004 – 0.004	—	—	0.06–0.06	—	—
Fluoroquinolone-susceptible	50	0.001 – 0.008	0.002	0.004	ND	ND	ND
Fluoroquinolone-nonsusceptible	3	0.12 – 0.12	—	—	ND	ND	ND
Gram-negative organisms (fastidious)							
<i>Haemophilus parainfluenzae</i>	60	0.001 – 2	0.008	0.5	0.015 – 64	0.12	8
Macrolide-susceptible	0	—	—	—	—	—	—
Macrolide-nonsusceptible	60	0.001 – 2	0.008	0.5	ND	ND	ND
β-lactamase-negative	57	0.001 – 2	0.008	1	ND	ND	ND
β-lactamase-positive	3	0.001 – 0.004	—	—	ND	ND	ND
Fluoroquinolone-susceptible	47	0.001 – 0.03	0.004	0.015	ND	ND	ND
Fluoroquinolone-nonsusceptible	13	0.06 – 2	0.05	1	ND	ND	ND
<i>Haemophilus influenzae</i>	54	0.00025 – 0.004	0.001	0.002	0.008 – 0.12	0.03	0.06
Macrolide-susceptible	1	0.00025 – 0.00025	—	—	ND	ND	ND
Macrolide-nonsusceptible	53	0.00025 – 0.004	0.001	0.002	ND	ND	ND
β-lactamase-negative	53	0.00025 – 0.004	0.001	0.002	ND	ND	ND
β-lactamase-positive	1	0.001 – 0.001	—	—	ND	ND	ND
Fluoroquinolone-susceptible	54	0.00025 – 0.004	0.001	0.002	ND	ND	ND
Fluoroquinolone-nonsusceptible	0	—	—	—	—	—	—
<i>Moraxella catarrhalis</i> ^c	11	0.004 – 0.015	0.004	0.008	0.12 – 0.5	0.12	0.12

Baseline Target Pathogen	ModMITT-2 Population (Treatment Groups Combined) N = 358						
	Delafloxacin				Moxifloxacin or Ciprofloxacin ^a		
	n	MIC Range (mg/L)	MIC ₅₀ (mg/L) ^b	MIC ₉₀ (mg/L) ^b	MIC Range (mg/L)	MIC ₅₀ (mg/L) ^b	MIC ₉₀ (mg/L) ^b
Gram-negative organisms (Enterobacteriales)							
<i>Klebsiella pneumoniae</i>	30	0.03 – > 256	0.12	0.25	0.03 – > 8	0.06	0.25
Fluoroquinolone-susceptible	27	0.03 – 0.25	0.12	0.25	ND	ND	ND
Fluoroquinolone-nonsusceptible	3	2 – > 256	—	—	ND	ND	ND
ESBL-negative	26	0.03 – 2	0.12	0.25	ND	ND	ND
ESBL-positive	4	0.12 – > 256	—	—	ND	ND	ND
<i>Escherichia coli</i>	25	0.015 – 4	0.06	4	0.015 – > 8	0.03	> 8
Fluoroquinolone-susceptible	22	0.015 – 4	0.03	0.06	ND	ND	ND
Fluoroquinolone-nonsusceptible	3	4 – 4	—	—	ND	ND	ND
ESBL-negative	21	0.03 – 4	0.06	0.06	ND	ND	ND
ESBL-positive	4	0.015 – 4	—	—	ND	ND	ND
<i>Enterobacter cloacae</i> complex	14	0.06 – 256	0.12	0.25	0.015 – > 8	0.06	0.12
Fluoroquinolone-susceptible	13	0.06 – 0.25	0.12	0.25	ND	ND	ND
Fluoroquinolone-nonsusceptible	1	256 – 256	—	—	ND	ND	ND
<i>Klebsiella oxytoca</i> ^d	10	0.06 – 4	0.12	2	0.015 – 1	0.03	0.25
Gram-negative organisms (other non-fastidious)							
<i>Pseudomonas aeruginosa</i>	24	0.008 – 16	0.5	4	0.008 – > 8	0.25	> 8
Fluoroquinolone-susceptible	17	0.008 – 0.5	0.25	0.5	ND	ND	ND
Fluoroquinolone-nonsusceptible	7	1 – 16	—	—	ND	ND	ND
Atypical organisms							
<i>Mycoplasma pneumoniae</i>	15	0.125 – 0.5	0.25	0.5	0.125 – 0.5	0.125	0.25
Macrolide-susceptible	14	0.125 – 0.5	0.25	0.5	ND	ND	ND
Macrolide-resistant	1	0.125 – 0.125	—	—	ND	ND	ND
<i>Legionella pneumophila</i>	5	0.00025 – 0.001	—	—	0.03 – 0.03	—	—

Abbreviations: — = not applicable; ESBL = extended-spectrum β-lactamases; MDR = multiple drug-resistant; MIC₅₀ = 50th percentile of MIC values from all pathogens; MIC₉₀ = 90th percentile of MIC values from all pathogens; MRSA = methicillin-resistant *S. aureus*; MRSP = macrolide-resistant *S. pneumoniae*; MSSA = methicillin-susceptible *S. aureus*; n = number of pathogens; ND = not done; PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; PSSP = penicillin-susceptible *S. pneumoniae*.

^a Ciprofloxacin MIC summary statistics are presented for all Enterobacteriales and *P. aeruginosa*; moxifloxacin MIC summary statistics are presented for all other organisms.

^b MIC₅₀ and MIC₉₀ values were calculated only when 10 or more isolates were available.

^c All isolates were fluoroquinolone-susceptible.

^d All isolates were fluoroquinolone-susceptible and ESBL-negative.

Source: ML-3341-306 End-of-Text Tables 14.2.8.3.4.2, 14.2.8.3.6.2, 14.2.8.3.7.2, 14.2.8.3.8.2, 14.2.8.3.9.2, 14.2.8.3.10.2, 14.2.8.3.11.2, 14.2.8.3.12.2, and 14.2.8.3.12.2a.

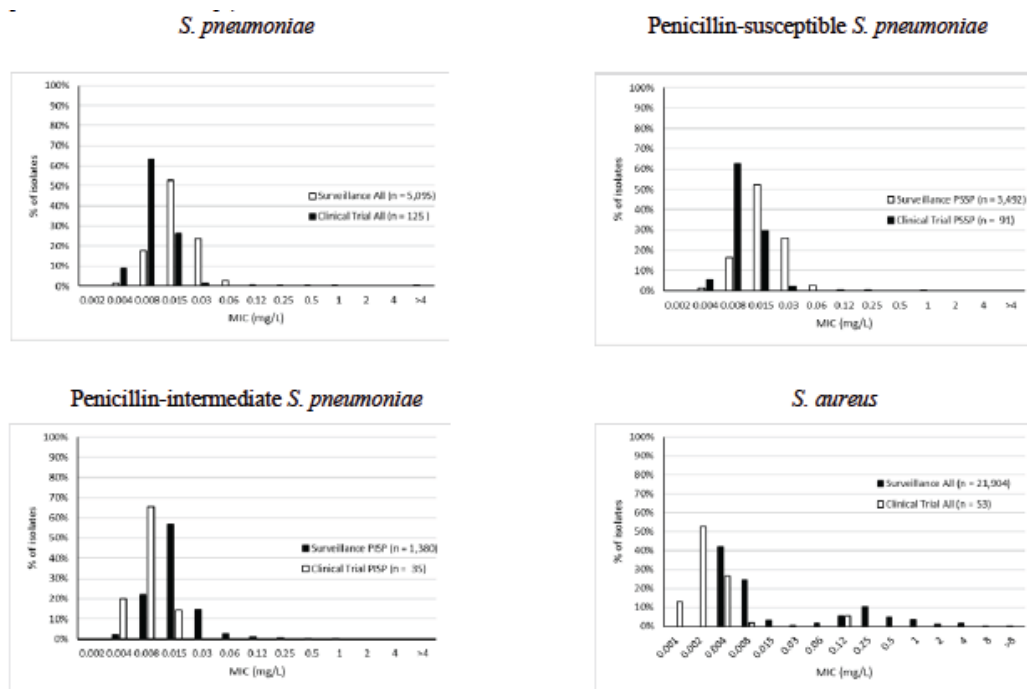
As shown in

Table 27, delafloxacin had potent activity against target Gram-positive pathogens overall by MIC₅₀ and MIC₉₀. Based on MIC₉₀ values at baseline, delafloxacin exhibited at least 16-fold greater activity than moxifloxacin for all Gram-positive and fastidious Gram-negative pathogens in the ModMITT-2 population. The majority of these isolates were FQ-S, macrolide-susceptible, and penicillin-susceptible (PSSP), methicillin-susceptible (MSSA), or β -lactamase-negative (*Haemophilus* spp.). However, delafloxacin retained potent activity against resistant phenotypes found in *S. pneumoniae* (PRSP, PISP, MRSP, MDRSP), *Haemophilus* species (β -lactamase and MR) and *S. aureus* (MRSA, FQ-RSA MSSA). Delafloxacin and moxifloxacin had similar activity against *M. pneumoniae* isolates (including 2 MR isolates), and delafloxacin had greater activity than moxifloxacin against *L. pneumophila* isolates including macrolide-resistant isolates .

Delafloxacin and ciprofloxacin demonstrated comparable activity against Enterobacterales and *P. aeruginosa* isolates. The majority of these isolates were FQ-S. Delafloxacin demonstrated reduced activity to fluoroquinolone-nonsusceptible and ESBL phenotypes.

A comparison of the delafloxacin MIC distribution against clinical study isolates (ModMITT-2; both treatment arms) to that observed in recent surveillance for both Gram-positive and Gram-negative target pathogens is shown by histoGram in Figure 9.

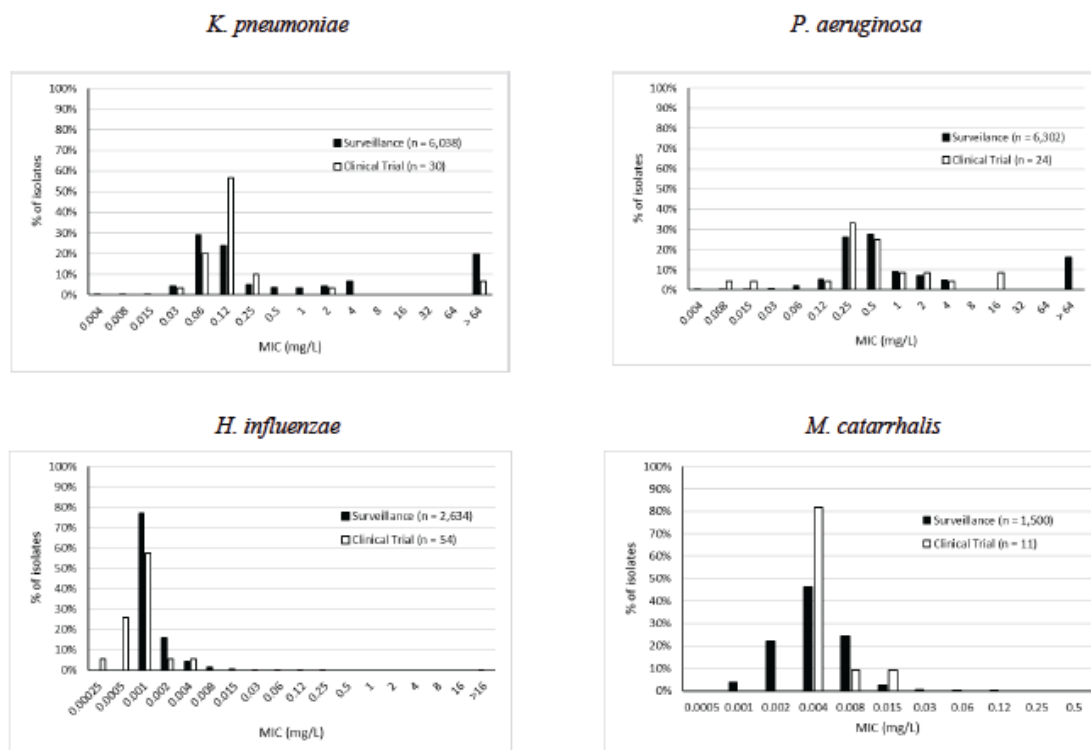
In these histoGrams the MIC distribution of delafloxacin against target pathogens isolated in clinical studies (ModMITT-2 population; both treatment arms) is shown relative to recent global surveillance (US and European isolates from 2014 to 2018). Overall, the delafloxacin MIC distribution observed with clinical study isolates was similar to that observed during recent global surveillance. However, only 2 isolates of PRSP and 1 isolate of MRSA was obtained from patients in the clinical trial.



Abbreviations: MIC = minimum inhibitory concentration; ModMITT = microbiological intent-to-treat; n = number of subjects; PSSP = penicillin-susceptible *S. pneumoniae*; PISP = penicillin-intermediate *S. pneumoniae*.
 NB: Only 2 PRSP isolates (delafloxacin MIC = 0.008 and 0.015 mg/L) and 1 MRSA isolate (delafloxacin MIC = 0.004 mg/L) obtained from study ML-3341-306, therefore, no graphs presented.
 Source: ML-3341-306 End-of-Text Table 14.2.8.3.1.2; JMI MPV Database.

Figure 9: MIC Distribution of Delafloxacin Against Gram-positive Isolates from ML-3341-306 (MITT-2 at Baseline - Delafloxacin and Comparator Treatment Groups) and 2014 - 2018 Global Surveillance studies.

Delafloxacin MIC distributions for *K. pneumoniae*, *P. aeruginosa*, *H. influenzae* and *M. catarrhalis* are shown in Figure 10.



Abbreviations: MIC = minimum inhibitory concentration; ModMITT = microbiological intent-to-treat; n = number of subjects.
Source: ML-3341-306 End-of-Text Table 14.2.8.3.1.2; JMI MPV Database.

Figure 10: MIC Distribution of Delafloxacin Against Gram-negative Isolates from ML-3341-306 (MITT-2 at Baseline - Delafloxacin and Comparator Treatment Groups) and 2014 - 2018 Global Surveillance studies.

Resistance

Like other fluoroquinolone-class antibacterial agents, delafloxacin-resistant mutants were selected *in vitro* at a very low frequency ($< 10^{-9}$) during spontaneous mutation studies at concentrations $4 \times$ the MIC and above.

In both laboratory-derived mutants and clinical isolates, the predominant mutation in *S. aureus* observed was in Ser84-Leu in *gyrA*/Ser80-Tyr or Ser80-Phe in *grlA*. For both laboratory-derived and clinical *S. aureus* isolates with double mutations in *gyrB* and *gyrA*, higher delafloxacin MIC values were observed, but such isolates had decreased fitness *in vitro* relative to the parent strain.

For ABSSSI clinical isolates, delafloxacin demonstrated high rates of microbiological response against levofloxacin nonsusceptible isolates as well as isolates with documented mutations in the quinolone-resistance determining region (QRDR).

For Gram-negative isolates, delafloxacin, like other fluoroquinolones, can be affected by plasmid-mediated resistance mechanisms such as Qnr (target protection), Oqx (efflux pumps), and / or the aminoglycoside acetyltransferase AAC-6'-Ib-CR-like (enzymatic inactivation). This was apparent in fluoroquinolone-resistant Enterobacteriaceae in CAP clinical trials isolates and to a lesser extent in ABSSSI Enterobacteriaceae clinical trial isolates.

Emergence of Resistance During Therapy

Genotypic resistance analyses (molecular QRDR analysis) of clinical isolates was conducted in the Phase 3 study (ML-3341-306) if sequential isolates from the same patient demonstrated > 4-fold increase in a delafloxacin and / or moxifloxacin MIC value.

One subject in the delafloxacin arm and three subjects in the moxifloxacin arm met this criterion.

In summary, one confirmed incidence of emergence of resistance during therapy occurred in a delafloxacin treated subject in study ML-3341-306. While a > 4-fold increase in fluoroquinolone MIC values were observed in 3 *H. parainfluenzae* isolates from moxifloxacin treated patients, all of the paired isolates were found to be unrelated. It is interesting to note, that all of the isolates that had a > 4-fold increase in fluoroquinolone MIC values were *H. parainfluenzae* and 3 out of the 4 isolates were genetically unrelated.

Animal Therapeutic studies

The efficacy of delafloxacin was evaluated in several animal models of infection. Delafloxacin was highly effective in protecting mice from systemic lethal infections caused by *S. aureus* including MRSA, and *S. pneumoniae*, and to a lesser extent effective in protection against *E. coli* and *P. aeruginosa*; in neutropenic thigh infections caused by *S. aureus*, *S. pneumoniae*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa*; in pulmonary infections caused by *S. pneumoniae* and *H. influenzae* and in a murine pyelonephritis model. Delafloxacin was also effective in neutropenic thigh infections caused by *S. pneumoniae* in neutropenic rats. In rats, delafloxacin was further active against Gram-negative and Gram-positive bacteria in a rat granuloma pouch infection.

Secondary pharmacology

Pharmacodynamic interaction with other medicinal products or substances

The antimicrobial interaction of delafloxacin with other agents from different antibiotic classes (cyclic lipopeptides [Daptomycin], oxazolidinones [Linezolid], carbapenems [Meropenem], cephalosporins [Ceftazidime], sulphonamides and trimethoprim, glycopeptides [Vancomycin], tetracyclines [Tigecycline], polymyxins [Colistin] and monobactams [Aztreonam]) was assessed by measuring fractional inhibitory concentrations via checkerboard panels for both Gram-positive and Gram-negative bacteria. Based on the mean fractional inhibitory concentration index (FICI) values the antimicrobial interaction was found to be indifferent for all antibiotic combinations and bacteria evaluated in checkerboard titration studies.

Besides of the above mentioned studies which have already been submitted and discussed during initial MAA for ABSSSI the MAH submitted a new study (12-05-2018-Melinta 9v2) which again analysed the antimicrobial interaction of delafloxacin using antibiotics typically used to treat CAP pathogens.

As shown in Table 28 the mean FICI values for delafloxacin in combination with other agents were >0.5-4. In line with the interpretation criteria (< 0.5 = synergy, >0.5-4 = additive/indifferent, and >4 = antagonism) it can be concluded that there was no signal for synergy or antagonism between delafloxacin and agents commonly used in the treatment of respiratory infections among target respiratory pathogens. Thus, a co-administration of the tested agents is principally possible.

Table 28: Summary of Mean FICI Values for Delafloxacin in Combination with Other Agents During Checkerboard Assays

Organism	Isolate ID	Type	Mean FICI							
			PEN	AMOX/CLAV	CRO	CPT	CLI	AZI	DOX	RIF
<i>S. aureus</i>	ATCC 29213	QC; MSSA, LVX-S	1.19	0.99	1.09	1.04	2.06	1.19	1.19	1.04
	ATCC 43300	MRSA, LVX-S	1.19	1.09	0.91	0.99	1.19	1.19	1.39	1.19
	MMX 3884	MRSA, LVX-R	0.83	1.16	1.03	1.08	2.07	1.16	1.14	1.14
<i>S. epidermidis</i>	MMX 3242	MRSE, LVX-S	NT	NT	NT	NT	NT	NT	NT	1.19
	MMX 1266	MRSE, LVX-R	NT	NT	NT	NT	NT	NT	NT	2.23
<i>S. pneumoniae</i>	ATCC 49619	QC; PISP, LVX-S	0.90	1.16	0.61	0.95	1.09	0.84	1.84	NT
	MMX 7807	PSSP, LVX-S	1.04	1.84	0.94	1.09	0.89	1.15	1.59	NT
	MMX 4873	PSSP, LVX-R	1.24	1.01	1.03	0.91	1.09	1.19	1.09	NT
	MMX 5427	PRSP, MDR, LVX-S	0.80	1.09	1.61	1.08	1.15	NA	0.81	NT
<i>H. influenzae</i>	ATCC 49247	QC; LVX-S	1.29	1.13	1.38	0.88	1.13	0.79	1.29	NT
	MMX 2801	BLNAR, LVX-S	1.13	0.96	1.14	0.88	1.29	1.13	1.29	NT
<i>H. parainfluenzae</i>	MMX 2529	LVX-S	1.59	1.63	1.59	1.09	1.09	1.19	1.09	NT
<i>M. catarrhalis</i>	ATCC 8193	LVX-S	1.19	1.19	1.54	1.19	1.09	1.18	1.41	NT
<i>E. coli</i>	ATCC 25922	QC, LVX-S	1.13	1.53	1.01	0.76	0.96	1.38	1.38	NT
	MMX 9054	ESBL, LVX-R	1.29	1.29	1.47	0.97	1.29	1.23	0.98	NT
<i>K. pneumoniae</i>	MMX 6117	LVX-S	1.29	0.86	1.11	0.99	1.29	1.24	1.24	NT
	MMX 10218	KPC-2, LVX-R	1.23	1.23	1.23	1.23	1.23	1.23	1.11	NT
<i>K. oxytoca</i>	MMX 6107	LVX-S	<u>0.61</u>	0.86	1.62	1.55	1.24	1.32	2.19	NT
<i>E. cloacae</i>	MMX 1332	LVX-S	1.24	1.24	1.55	0.79	1.24	1.24	1.49	NT
	MMX 1457	LVX-R	1.10	1.19	1.19	1.19	1.19	1.19	1.19	NT
<i>P. aeruginosa</i>	ATCC 27853	QC; LVX-S	1.19	1.19	1.29	0.83	1.00	1.19	0.59	NT
	MMX 2562	MDR, LVX-R	1.16	1.16	1.16	1.16	1.16	1.16	1.16	NT

Abbreviations AMOX / CLAV: amoxicillin / clavulanate (2:1 fixed ratio); ATCC: American Type Culture Collection; AZI: azithromycin; BLNAR: beta-lactamase negative ampicillin-resistant; CLI: clindamycin; CLSI: Clinical and Laboratory Standards Institute; CPT: ceftaroline; CRO: ceftriaxone; DOX: doxycycline; ESBL: extended-spectrum beta lactamase; FICI: fractional inhibitory concentrations indices; KPC: *Klebsiella pneumoniae* carbapenemase; LVX-R: levofloxacin-resistant; LVX-S: levofloxacin-susceptible; MDR: multidrug-resistant; MMX: micromyx; MRSA: methicillin-resistant *Staphylococcus aureus*; MRSE: methicillin-resistant *Staphylococcus epidermidis*; MSSA: methicillin-susceptible *Staphylococcus aureus*; NT: not tested; PEN: penicillin; PISP: penicillin-intermediate *Streptococcus pneumoniae*; PRSP: Penicillin-resistant *Streptococcus pneumoniae*; PSSP: penicillin-susceptible *Streptococcus pneumoniae*; QC: quality control; RIF: rifampin.

Both drugs were inactive against the test isolate across the evaluated concentrations.

Italicized and underlined text indicates that at least one row on the test panel had an individual FICI value ≤ 0.5 (indicative of synergy).

Source: 12-05-2018-Melinta 9v2

2.3.4. PK/PD modelling

Relationship between plasma concentration and effect

Non-clinical PK/PD targets – PK/PD index

Delafloxacin's PKPD relationships have been investigated *in vitro* in a one-compartment model for *H. influenzae*, and *in vivo* in both neutropenic thigh and neutropenic lung murine models.

In vitro

H. influenzae

According to Lorian 2005 *H. influenzae* does not exhibit sufficiently growth in the lungs of rodents over a 24 h period as compared to the other pathogens. Thus, the PD target was defined by a one-compartment-infection *in vitro* model (00543).

The free-drug AUC/MIC ratio associated with efficacy against a panel of five clinical *H. influenzae* isolates from surveillance studies (including 2 WT strains and 3 fluoroquinolone non-susceptible strains (MICs from 0.001 to 1 µg/mL; see Module 2.7.2, Table 2.7.2-84)) was determined through a series of dose-ranging susceptibility studies in a one-compartment *in vitro* infection model delivering 24-hour delafloxacin concentration-time profiles representing those observed in humans after IV administration. Density of drug-resistant sub-populations was evaluated, as well.

The strains at initial bacterial burden of 10⁶ CFU/mL were exposed to delafloxacin regimens ranging from 0.09 to 15000 mg q12h and PK profiles were measured (see Table 29).

Table 29: Summary of delafloxacin doses studied and associated free-drug AUC values for each of the delafloxacin dosing regimens evaluated in the one-compartment dose-ranging studies.

Delafloxacin IV dose (mg q12h)	Delafloxacin free-drug AUC value based on observed PK
0.09	0.002
0.19	0.004
0.38	0.008
0.75	0.016
1.5	0.03
3.0	0.06
6.0	0.14
12.0	0.40
24.0	0.66
37.5	0.78
75.0	1.58
150	3.19
300	6.39
450	9.96
600	11.2
750	16.4
1500	35.0

All doses were administered over a 1-hour infusion simulating a 4-hour half-life and free-drug profiles assuming 84% human protein binding. Samples were collected over the study duration for enumeration of total and resistant bacterial burden as well as observation of simulated PK profiles. Data from the dose-ranging studies were pooled and modelled using Hill-type models and non-linear least squares regression. All data was weighted using the inverse of the estimated measurement variance. The relationship between the change in log₁₀ CFU from baseline at 24 hours and the AUC/MIC value was evaluated.

Results revealed that 4/5 strains responded to all of the tested dosing regimens. The median fAUC/MIC ratio associated with net bacterial stasis and 1- and 2-log₁₀ CFU/mL reductions from baseline at 24 hours were 23.5, 28.7, and 36.0, respectively (see Table 30). There was some inter-isolate variability in target values (up to 2-fold):

Table 30: Summary of Free-drug AUC/MIC Ratio Targets and Mean Parameter Estimates for *H. influenzae* Isolates

H. influenzae isolate	Delafloxacin free-drug AUC:MIC ratio targets			Hill-model mean parameter estimates (standard error)				Hill model r ²
	Net bacterial stasis	1-log ₁₀ CFU/mL reduction	2-log ₁₀ CFU/mL reduction	E ₀	E _{max}	EC ₅₀	H	
1065871	21.1	22.7	24.4	1.99 (0.35)	6.25 (0.45)	22.9 (3.07)	9.33 (5.47)	0.953
1067953	17.4	21.7	26.6	2.10 (0.65)	7.72 (1.04)	25.3 (5.92)	2.61 (1.63)	0.823
1026008	26.0	34.7	45.5	2.12 (0.28)	7.00 ^c (3.01)	38.4 (17.3)	2.12 (1.04)	0.923
1001665	35.5	40.7	47.6	2.61 (0.10)	6.10 (0.37)	37.7 (1.43)	4.86 (0.67)	0.989
1021325	N / A	N / A	N / A	N / A	N / A	N / A	N / A	N / A
Pooled with isolate 1021325 ^a	26.6	33.8	42.3	2.26 (0.23)	7.23 (0.51)	36.6 (3.41)	2.41 (0.53)	0.812
Pooled without isolate 1021325 ^b	23.6	30.4	38.6	2.29 (0.28)	7.18 (0.53)	32.6 (3.43)	2.35 (0.54)	0.826
Median	23.5	28.7	36.0					

Abbreviations: AUC:MIC = ratio of area under the mean concentration-time curve to pathogen minimum inhibitory concentration; MIC = minimum inhibitory concentration; CFU = colony forming units; EC₅₀ = The value of the PK - PD index at which there is half-maximal effect; E₀ = baseline effect; E_{max} = maximum effect.

^a. Determined using a Hill model based on pooled data for the five *H. influenzae* isolates.

^b. Determined using a Hill model based on pooled data for the four *H. influenzae* isolates, excluding isolate 1021325.

^c. A cap was placed on E_{max} (to a 7-log reduction from E₀) secondary to the data not providing information on the parameter.

Source: ICPD-00543

The Hill models describing the relationship between change in log₁₀ CFU/mL from baseline at 24 hours and delafloxacin fAUC/MIC ratio for individual *H. influenzae* isolates described the data well (r² values of 0.823 to 0.989; see Table 30). However, dose fractionation was not performed in this study and comparison with other potential PKPD indices is not presented.

With regard to possibly resistant subpopulations it was shown that no resistance could be observed for the tested wild-type (WT)-strains.

In vivo

Murine thigh infection model

Neutropenic mouse thigh infection models (NMTIM) were used to investigate the *in vivo* PK-PD index (PDI) relating to efficacy in ABSSSI which has already been described in the D80 AR for ABSSSI MAA. However, for a better understanding a brief overview of the results is given below:

The PDI in neutropenic murine thigh infection models was evaluated against 5 strains of *S. aureus* (incl. MRSA and MSSA), 3 *P. aeruginosa* isolates as well as 3 *E. coli* strains (incl. 1 ESBL-positive, MDR strain). The PK/PD index (PDI) for delafloxacin that mostly correlated with efficacy was found to be fAUC₂₄/MIC as shown in the linear square regression analysis (see Figure 11).

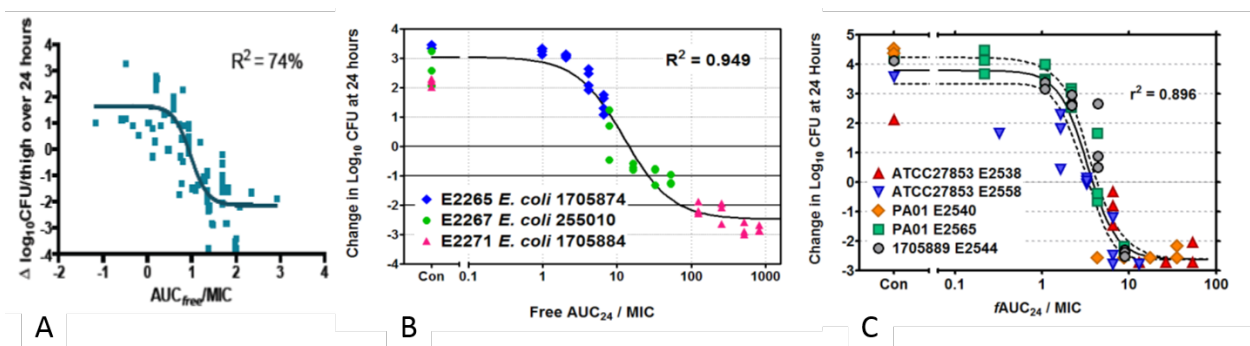


Figure 11: Delafloxacin PK/PD vs. (A) 5 *S. aureus* strains, (B) three *E. coli* Strains, and (C) 3 *P. aeruginosa* isolates in mouse (source: PK-3341-005; PK-3341-011; PK-3341-020).

The mean fAUC/MIC magnitudes (PDTs) required for a net static response and a 1- $\log_{10}$ reduction are outlined in Table 31.

Table 31: fAUC₂₄/MIC Values for Bacterial Stasis, 1 $\log_{10}$ and 2 $\log_{10}$ CFU Reduction

Bacterial species	Free-Drug AUC:MIC Ratios Associated With Efficacy		
	Net Bacterial Stasis	1- $\log_{10}$ CFU↓	2- $\log_{10}$ CFU ↓
<i>S. aureus</i>	9.3	14.3	22.0
<i>P. aeruginosa</i>	3.81	5.02	
<i>E. coli</i>	14.5	26.2	71.3

AUC = area under the concentration-time curve; CFU = colony-forming unit; fAUC₂₄/MIC = ratio of free delafloxacin area under the mean concentration-time curve from time 0 to 24 hours to pathogen minimum inhibitory concentration.

Murine lung infection model

The PDT for delafloxacin in the context of this variation was further determined based on a neutropenic mouse lung infection model (NMLIM) against *S. aureus* including MRSA and MSSA, *S. pneumoniae* (PSSP and PRSP), *K. pneumoniae* (1 WT, 3 ESBL-positive and 8 additional clinical isolates from patients with pneumonia) as well as *P. aeruginosa* in two studies performed in 2016 and 2019 (see Table 32; PK-3341-028; (Lepak and Andes 2016)). Delafloxacin MIC's for the tested strains ranged between 0.004 to 4 $\mu\text{g/mL}$.

Table 32: MIC Values for Isolates Used in Neutropenic Murine Lung Infections Model

Organism and Isolate Number	Study Year	Phenotype	Delafloxacin MIC (mg/L)	Levofloxacin MIC (mg/L)	Ciprofloxacin MIC (mg/L)
<i>S. aureus</i> ATCC 29213	2016	MSSA	0.008	0.25	-
<i>S. aureus</i> ATCC 33591	2016	MRSA (USA 200)	0.008	0.25	-
<i>S. aureus</i> MW2	2016	MRSA (USA 400)	0.004	0.25	-
<i>S. aureus</i> R2527	2016	MRSA (USA 300)	0.004	0.12	-
<i>S. pneumoniae</i> ATCC 10813	2016	Pen-S	0.03	1	-
<i>S. pneumoniae</i> ATCC 49619	2016	Pen-R	0.125	1	-
<i>S. pneumoniae</i> 145	2016	Pen-R	0.016	0.5	-
<i>S. pneumoniae</i> 1329	2016	Pen-R	0.016	0.5	-
<i>K. pneumoniae</i> ATCC 43816	2016	WT	0.06	0.06	-
<i>K. pneumoniae</i> 4105	2016	TEM26, SHV4	1	1	
<i>K. pneumoniae</i> 4110	2016	TEM1, SHV1	0.5	1	
<i>K. pneumoniae</i> 81-1260A	2016	CTX-M, AmpC	0.06	0.06	
<i>K. pneumoniae</i> 2017 JMI 993043	2019	-	0.03	0.03	0.03
<i>K. pneumoniae</i> 2017 JMI 1004234	2019	-	0.06	0.06	0.03
<i>K. pneumoniae</i> 2017 JMI 1008721	2019	-	0.12	0.12	0.12
<i>K. pneumoniae</i> 2017 JMI 1014490	2019	-	0.25	0.12	0.06
<i>K. pneumoniae</i> 2017 JMI 109343	2019	-	0.25	0.12	0.25
<i>K. pneumoniae</i> 2017 JMI 1037570	2019	-	0.5	1	2
<i>K. pneumoniae</i> 2017 JMI 997613	2019	-	1	0.5	0.25
<i>K. pneumoniae</i> 2017 JMI 1002059	2019	-	4	1	0.5
<i>P. aeruginosa</i> CAP isolate 71	2019	WT	1	-	2
<i>P. aeruginosa</i> CAP isolate 62	2019	WT	2	-	4
<i>P. aeruginosa</i> CAP isolate 65	2019	<i>parC</i> S87L <i>gyrA</i> T83I	4	-	> 8
<i>P. aeruginosa</i> CAP isolate 724	2019	WT	0.12	-	≤ 0.06
<i>P. aeruginosa</i> JMI 1004586	2019	-	0.5	0.5	0.12

Abbreviations: ATCC = American Type Culture Collection, HA = hospital-associated, MIC = minimum inhibitory concentration; MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; Pen-R = penicillin resistant; Pen-S = penicillin susceptible; WT = wild-type.
Source: Lepak 2016 and PK-3341-028.

Neutropenic mice were treated with delafloxacin single subcutaneous doses of 2.5, 10, 40, and 160 mg/kg and PK parameters (AUC, C_{max}, t_{1/2}) were measured at different time points for groups of three mice (see Figure 12).

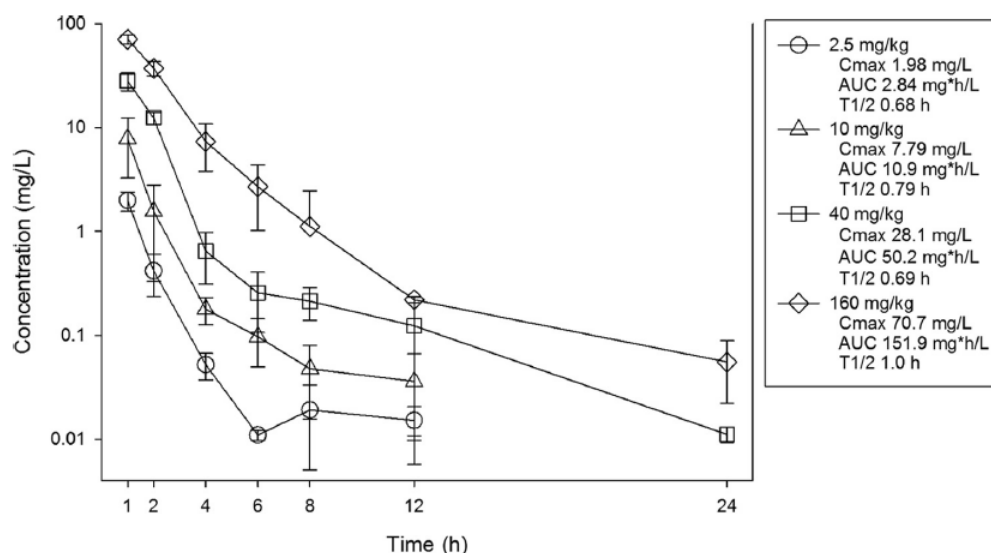


Figure 12: Single-dose plasma pharmacokinetics of delafloxacin in neutropenic mice. Pharmacokinetic parameters listed in the box include maximum drug concentrations (C_{max}), the AUC from 0 h to infinity (AUC), and the elimination half-life (t_{1/2}) for each dose.

For *in vivo* studies, four-fold increasing doses of delafloxacin were administered (q6h) to infected mice and CFUs were counted after 24 hours. The lung infection was produced by administration of 50 μ L of inoculum into the nares of the mice ($\sim 10^{7.3-8.4}$ CFU/mouse). Delafloxacin therapy was initiated 2 h after infection. The correlation between efficacy and PK/PD parameter was determined by non-linear last-square multivariate regression. AUC/MIC was chosen as PDI abased on previous studies. The relationship between 24 h AUC/MIC is graphically shown in Figure 13 A-F. The coefficient of determination (R^2) estimating the variance that might be due to regression was shown to be 0.89 for *S. aureus*, 0.70 for *S. pneumoniae*, and 0.49 for *K. pneumoniae* tested in 2016. *K. pneumoniae* was additionally tested in 2019 and results revealed R^2 of 0.71 or rather 0.66 considering tested isolates in 2016 and 2019. For *P. aeruginosa* a R^2 value of 0.84 was calculated.

The mean fAUC/MIC required for net stasis or a 1-log₁₀ reduction compared to the start of therapy was calculated for each drug-organism combination, along with the associated 24 hours total and free drug AUC/MIC targets. The results are displayed in Table 33 below.

The median fAUC₂₄/MIC 1-log₁₀ kill target was 7.92 for *S. aureus*, 3.36 for *S. pneumoniae*, 64.1 for *K. pneumoniae* considering isolates tested in 2016 and 2019, and 68.2 for *P. aeruginosa*. For *K. pneumoniae* 1-log₁₀ kill was achieved for 6/12 isolates and for *P. aeruginosa* for 4/5 isolates. 1-log₁₀ kill was achieved for all of the other tested strains.

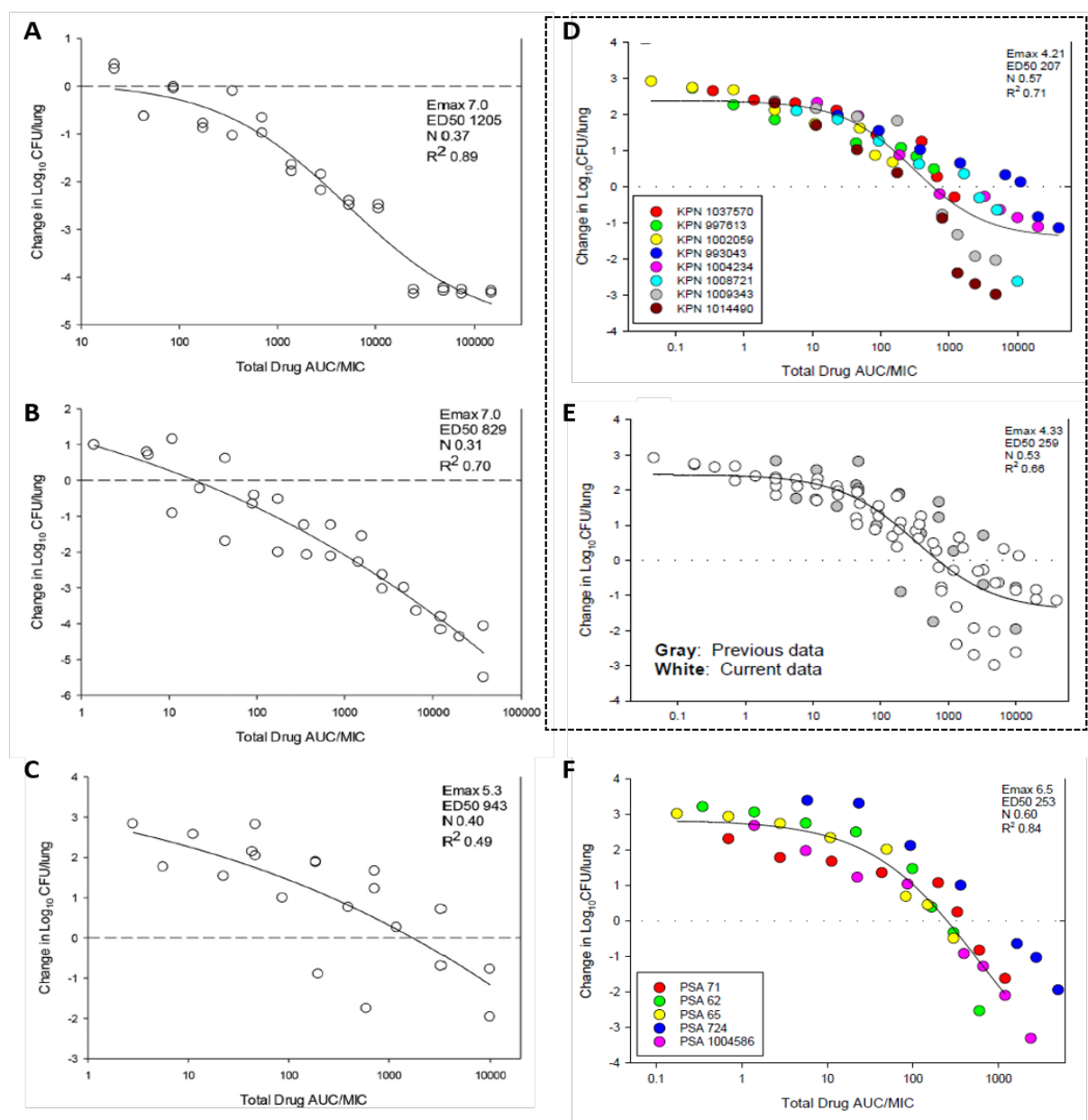


Figure 13: Relationship between PK/PD index total-drug AUC/MIC ratio and treatment efficacy of delafloxacin against (A) four *S. aureus* (2016), (B) four *S. pneumoniae* (2016), (C) four *K. pneumoniae* (2016), (D) eight *K. pneumoniae* (2019), (E) 12 *K. pneumoniae* from 2016 & 2019, and (F) five *P. aeruginosa* strains using a neutropenic murine lung infection model. Each symbol represents the mean from three mice.

Table 33: *In Vivo* Activity and PK / PD Analysis of Delafloxacin Against Study Organisms

Organism	Study Year	DLX MIC mg/L	Burden at Start of Therapy (Log10 CFU/Lung)	24-h Control Growth (Log10 CFU/Lung)	Stasis			1-log kill		
					Dose (mg/kg/24h)	AUC ₂₄ /MIC	fAUC ₂₄ /MIC	Dose (mg/kg/24 h)	AUC ₂₄ /MIC	fAUC ₂₄ /MIC
<i>S. aureus</i> 29213	2016	0.008	6.35	1.99	0.93	130	3.12	3.22	451	10.8
<i>S. aureus</i> 33591	2016	0.008	6.26	2.06	0.53	74.6	1.79	2.25	315	7.57
<i>S. aureus</i> MW2	2016	0.004	6.33	1.53	< 0.16 ^a	< 43.8 ^a	< 1.05 ^a	0.98	276	6.61
<i>S. aureus</i> R2527	2016	0.004	6.29	1.47	< 0.16 ^a	< 43.8 ^a	< 1.05 ^a	1.23	345	8.28
Mean	2016				0.42	65.3	1.57	1.92	347	8.32
Median					0.34	59.2	1.42	1.74	330	7.92
SD					0.40	48.6	1.17	1.03	75	1.79
<i>S. pneumoniae</i> 10813	2016	0.03	6.53	2.23	0.93	34.8	0.84	3.83	143	3.43
<i>S. pneumoniae</i> 49619	2016	0.125	6.48	1.8	1.36	12.2	0.29	15.5	137	3.29
<i>S. pneumoniae</i> 145	2016	0.016	6.27	2.07	< 0.16 ^a	< 10.9 ^a	< 0.26 ^a	0.23	16.5	0.39
<i>S. pneumoniae</i> 1329	2016	0.016	6.22	1.5	1.36	95.1	2.28	6.11	428	10.3
Mean	2016				1.22	38.3	0.92	6.42	181	4.35
Median					1.14	23.5	0.56	4.97	140	3.36
SD					0.25	39.5	0.95	6.52	175	4.21
<i>K. pneumoniae</i> 43816	2016	0.06	6.30	2.86	304	5287	127	NA	NA	NA
<i>K. pneumoniae</i> 4105	2016	1	6.30	3.33	106	128	3.08	196	228	5.47
<i>K. pneumoniae</i> 4110	2016	0.5	6.32	2.82	NA	NA	NA	NA	NA	NA
<i>K. pneumoniae</i> 81-1260A	2016	0.06	6.28	2.83	84.8	1681	40.3	238	4369	105
Median	2016	-	-	-	106	1681	40.3	217	2298	55.2
<i>K. pneumoniae</i> 2017 JMI 993043	2019	0.03	6.71	2.37	157	6467	155	NA	NA	NA
<i>K. pneumoniae</i> 2017 JMI 1004234	2019	0.06	6.64	2.70	50.7	952	22.8	862	13394	321
<i>K. pneumoniae</i> 2017 JMI 1008721	2019	0.12	6.99	2.39	134	1365	32.8	545	4312	103
<i>K. pneumoniae</i> 2017 JMI 1014490	2019	0.25	7.26	2.72	37.2	161	3.87	98.5	474	11.4
<i>K. pneumoniae</i> 2017 JMI 1009343	2019	0.25	6.92	2.76	109	528	12.7	233	1032	24.8
<i>K. pneumoniae</i> 2017 JMI 1037570	2019	0.5	6.64	3.05	639	1192	28.6	NA	NA	NA
<i>K. pneumoniae</i> 2017 JMI 997613	2019	1	6.56	3.04	NA	NA	NA	NA	NA	NA

<i>K. pneumoniae</i> 2017 JMI 1002059	2019	4	6.53	2.95	NA	NA	NA	NA	NA	NA
Mean	2016 / 2019	-	-	-	180	1973	47.4	362	3967	95.2
Median		-	-	-	109	1192	28.6	235	2672	64.1
SD		-	-	-	189	2293	55.0	287	4679	119
<i>P. aeruginosa</i> CAP isolate 71	2019	1	6.23	2.36	294	309	7.41	830	774	18.6
<i>P. aeruginosa</i> CAP isolate 62	2019	2	6.92	3.81	354	179	4.30	903	421	10.1
<i>P. aeruginosa</i> CAP isolate 65	2019	4	6.93	3.64	1057	236	5.66	NA	NA	NA
<i>P. aeruginosa</i> CAP isolate 724	2019	0.12	6.31	3.57	107	1035	24.8	246	2152	51.6
<i>P. aeruginosa</i> JMI 1004586	2019	0.5	6.52	3.11	61.5	142	3.41	169	409	9.82
Mean	2019	-	-	-	374	380	9.12	537	939	22.5
Median		-	-	-	294	236	5.66	538	598	14.3
SD		-	-	-	401	372	8.92	383	826	19.8

Abbreviations: AUC₂₄/MIC = ratio of total delafloxacin area under the mean concentration-time curve from time zero to 24 hours to minimum inhibitory concentration; CAP = community-acquired pneumonia; CFU = colony-forming unit; DLX = delafloxacin; fAUC₂₄/MIC = ratio of free delafloxacin area under the mean concentration-time curve from time 0 to 24 hours to pathogen minimum inhibitory concentration; MOX = moxifloxacin; NA = endpoint not achieved; PK / PD = pharmacokinetic / pharmacodynamic.

^a. Dose and drug exposure (AUC:MIC) were set to the lowest value studied for organisms in which only cidal activity was observed. Source: (Lepak and Andes 2016) and PK-3341-028.

PK/PD modelling

Dose selection

To support the dosing regimens (IV, IV to PO, and PO only) for treatment of patients with CAP in clinical studies (Phase III), PTA analyses were conducted using the results of the NMLIM studies for *S. aureus* and *S. pneumoniae* (PDTs for 1-log₁₀ kill of 3.36 and 7.92, respectively) and a popPK model for IV delafloxacin to support the dose selection for the CAP clinical trial. In this context, free-drug plasma concentration-profiles were generated for 5,000 simulated patients with varying degrees of renal function following 300 mg IV, q12 h for 3 days followed by 450 mg PO, q12 for 2 days. Overall, percent probabilities of PTA were ≥ 93.3%. The MAH concluded that the data supported a dosing regimen in Study ML-3341-306 of 300 mg IV, q12 for 3 days followed by 450 mg PO, q12 for 2 days in CAP patients with normal renal function and mild or moderate renal impairment.

PK/PD relationships for efficacy

Results of the PK/PD relationship analyses for efficacy are based on data from subjects with CAP enrolled in study ML-3341-306. Using data from microbiologically evaluable (ME) populations, PK/PD relationships were evaluated for efficacy endpoints as outlined in Table 34 below:

Table 34: Summary of efficacy endpoints by study visit and analysis populations

Endpoint	Analysis population
ECR ^a	Modified ME-2ECR
Clinical Response at EOT ^b	Modified ME-2EOT
Clinical Response at TOC ^c	Modified ME-2TOC
Microbiological Response at TOC ^{c,d}	Modified ME-2TOC

Note: Abbreviations are provided in the Abbreviation Listing.

a. ECR was assessed at 96 hours (± 24 hours) after the first dose of study drug.

b. Clinical responses at the EOT visit was assessed on the same day or up to 24 hours (+4 hours) after the last dose of study drug.

c. Clinical or microbiological response at the TOC visit was assessed 5 to 10 days after last dose of study drug.

d. Microbiological response was evaluated at the patient level.

Univariable relationships for dichotomous efficacy endpoints were examined to identify relationships between the probability of achieving each efficacy endpoint (including clinical and microbiological endpoints) and delafloxacin fAUC₂₄/MIC ratio, fAUC₂₄, and MIC. A total of 145 delafloxacin-treated patients were included in the ME Populations that had PK data and at least one pathogen with MIC data isolated at baseline. Additionally, these patients were evaluable for ECR at 96 ± 24 hours or clinical response at EOT or TOC. After exclusion of nasopharyngeal (NP) cultures, a total of 132 patients were available with CAP pathogens of interest. Responses for efficacy endpoints are shown in Table 35.

Table 35: Summary of successful responses for efficacy endpoints by visit based on data for all patients and patients with *S. pneumoniae* or *Haemophilus* species at baseline.

Analysis population	Visit	Percentage of successful responses by efficacy endpoint and visit (n/N)		
		ECR	Clinical response	Microbiological response
Patients with all cultures	All patients	96 ± 24 hours	90.3 (131/145)	-
		EOT	94.4 (134/142)	-
		TOC	92.8 (128/138)	91.3 (126/138)
	Patients with <i>S. pneumoniae</i> at baseline	96 ± 24 hours	89.6 (43/48)	-
		EOT	97.9 (47/48)	-
		TOC	95.7 (44/46)	93.5 (43/46)
	Patients with <i>Haemophilus</i> species at baseline	96 ± 24 hours	91.2 (31/34)	-
		EOT	87.9 (29/33)	-
		TOC	87.1 (27/31)	83.9 (26/31)
Patients with all cultures, excluding NP cultures	All patients	96 ± 24 hours	90.2 (119/132)	-
		EOT	93.8 (121/129)	-
		TOC	92.9 (117/126)	91.3 (115/126)
	Patients with <i>S. pneumoniae</i> at baseline	96 ± 24 hours	100 (24/24)	-
		EOT	100 (24/24)	-
		TOC	100 (24/24)	95.8 (23/24)
	Patients with <i>Haemophilus</i> species at baseline	96 ± 24 hours	91.9 (34/37)	-
		EOT	88.9 (32/36)	-
		TOC	88.2 (30/34)	85.3 (29/34)

Note: Abbreviations are provided in the Abbreviation Listing.

Further analyses revealed that >90% of patients with *S. pneumoniae*, *Haemophilus* spp., and *S. aureus* at baseline achieved >90% of non-clinical plasma fAUC/MIC targets associated with 1-log₁₀ and 2-log₁₀ CFU reduction (see Table 36).

Table 36: Summary of the percentage of patients with *S. pneumoniae*, *Haemophilus* species, or *S. aureus* at baseline achieving non-clinical free-drug plasma AUC:MIC ratio targets.

Endpoint for free-drug plasma AUC:MIC ratio targets	% (n/N)					
	Patients with all baseline cultures			Patients with all baseline cultures excluding NP cultures		
	Patients with <i>S. pneumoniae</i> at baseline ^a	Patients with <i>Haemophilus</i> species at baseline ^b	Patients with <i>S. aureus</i> at baseline ^c	Patients with <i>S. pneumoniae</i> at baseline ^a	Patients with <i>Haemophilus</i> species at baseline ^b	Patients with <i>S. aureus</i> at baseline ^c
1-log ₁₀ CFU reduction from baseline	100 (48/48)	91.2 (31/34)	100 (17/17)	100 (24/24)	91.9 (34/37)	100 (19/19)
2-log ₁₀ CFU reduction from baseline	100 (48/48)	91.2 (31/34)	100 (17/17)	100 (24/24)	91.9 (34/37)	100 (19/19)

a. Based on the assessment of median non-clinical free-drug plasma AUC:MIC ratio targets associated with 1- and 2-log₁₀ CFU reductions from baseline of 3.36 and 26.0, respectively, for *S. pneumoniae*.

b. Based on the assessment of median non-clinical free-drug plasma AUC:MIC ratio targets associated with 1- and 2-log₁₀ CFU reductions from baseline of 28.7 and 36.0, respectively, for *H. influenzae*.

c. Based on the assessment of median non-clinical free-drug plasma AUC:MIC ratio targets associated with 1- and 2-log₁₀ CFU reductions from baseline of 7.92 and 50.8, respectively, for *S. aureus*.

For clinical response at EOT or TOC and microbiological response at TOC, univariable PK/PD relationships were identified based on data from patients with *Haemophilus* spp. at baseline (see 00593-2, Table 25). For fAUC:MIC ratio evaluated as a continuous variable, fAUC:MIC ratios of 4,501 to 5,092 were required to achieve percent probabilities of success of 90.0%. For fAUC:MIC ratio evaluated as a two-group variable, the percentage of patients with successful responses were 55.6% to 66.7% and 95.5% to 95.8% for fAUC:MIC ratio < 1,464 and $\geq 1,464$, respectively (see Figure 14).

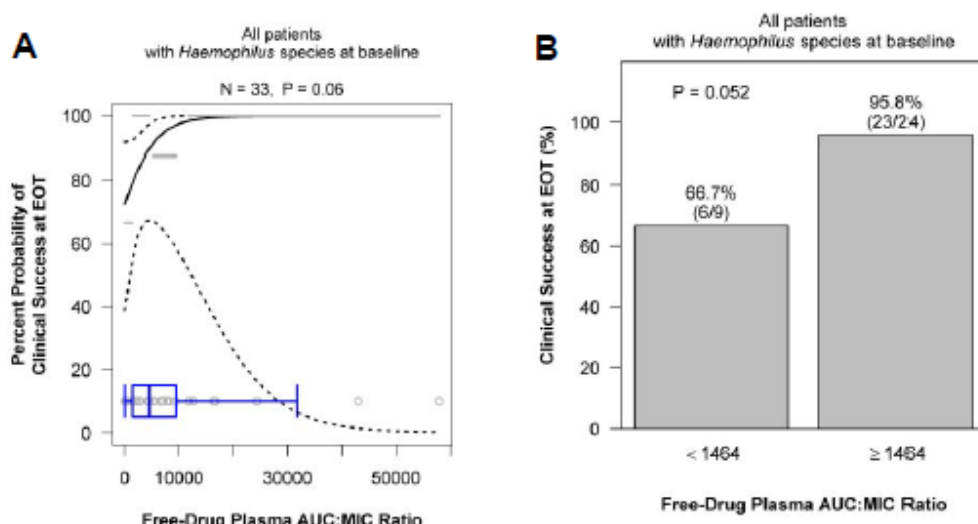


Figure 14: Univariable relationships between the percent probability of clinical success at EOT and free-drug plasma AUC:MIC ratio evaluated as a continuous (A) and twogroup variable (B) based on data from patients with *Haemophilus* species at baseline and all baseline cultures.

PTA based on Phase 3 data from patients with CAP

PopPK modeling and MCS were conducted to determine PTA based on nonclinical PD targets for delafloxacin identified for different CAP relevant species. The overall objective was to evaluate delafloxacin IV, IV-to-PO, and PO dosing regimens for CAP patients and interpretive criteria for the *in vitro* susceptibility testing of delafloxacin against *S. pneumoniae*, *H. influenzae*, *S. aureus*, *P. aeruginosa* and *K. pneumoniae*.

Two sets of simulations were performed including data from 315 CAP patients of Study 306 (ML-3341-306). The dataset was replicated 10 times, yielding a population of 3,150 simulated patients, and further assessed. PK parameters were calculated using the final popPK model (00524-1). The generated PK profiles were then used to assess delafloxacin PTA for plasma, using non-clinical PDTs for 1-log₁₀ and 2-log₁₀ CFU reduction as follows (see Table 37):

Table 37: fAUC:MIC Ratios Associated With Efficacy

		fAUC:MIC Ratios Associated With Efficacy	
Non-clinical model	Bacterial species	1-log ₁₀ CFU↓	2-log ₁₀ CFU↓
NMLIM (<i>in vivo</i>)	<i>S. aureus</i>	7.92	50.8
	<i>S. pneumoniae</i>	3.36	26.0
	<i>K. pneumoniae</i>	14.3	NA
	<i>P. aeruginosa</i>	64.1	NA
One-compartment model (<i>in vitro</i>)	<i>H. influenzae</i>	28.7	36.0

The following dosing regimens have been evaluated for patients with normal renal function ($90 \leq \text{CL}_{\text{cr}} < 200$ mL/min/1.73 m²), mild ($60 \leq \text{CL}_{\text{cr}} < 90$ mL/min/1.73 m²), moderate ($30 \leq \text{CL}_{\text{cr}} < 60$ mL/min/1.73 m²), and severe renal impairment ($15 \leq \text{CL}_{\text{cr}} < 30$ mL/min/1.73 m²) and ESRD patients (w/wo dialysis) ($5 \leq \text{CL}_{\text{cr}} < 15$ mL/min/1.73 m²) as well as for the clinical trial population:

- a. 300 mg IV, q12h (normal renal function, mild or moderate renal impairment)
 - i. 200 mg IV, q12h (severe renal impairment [or ESRD])
- b. 300 mg IV, q12h on Days 1-3 and then switch to 450 mg PO, q12 h on Day 4 (normal renal function, mild or moderate renal impairment)
 - i. 200 mg IV, q12h on Days 1-3 and then switch to 450 mg PO, q12 h on Day 4 (severe renal impairment [or ESRD])
- c. 450 mg PO, q12h (for all patient populations)

The PTA analyses conducted for the different populations and the bacterial species are summarized below. Since in line with the application the use in ESDR patients is not intended, this population will not be considered in the assessment and descriptions below.

The percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 for delafloxacin for the different dosing regimens were analysed among simulated patients by renal function group or those resembling the clinical trial population (see Table 38). The analyses are based on the median plasma fAUC/MIC ratio target for the respective pathogens for 1-log₁₀ and 2-log₁₀ CFU reduction.

S. pneumoniae

IV

The % PTA by MIC on Days 1 and 4 for IV delafloxacin for *S. pneumoniae* associated with 1-log₁₀ kill as well as 2-log₁₀ kill was >90% or close to 90% for MICs of up to 1 mg/L or 0.12 mg/L on Days 1 and 4, respectively (see Table 38). The same PTA analyses based on randomly assigned fAUC/MIC ratio targets among the different patient populations revealed that PTA of close to or over >90 % were only achieved for MICs up to 0.5 µg/mL (for 1-log₁₀ kill) or rather 0.06 µg/mL and 0.12 µg/mL for some populations taking a 2-log₁₀ kill into account (see 00593-2, Table 31).

Sub-analyses for % PTA by MIC on Days 1 and 4 based on data from *S. pneumoniae* isolates collected from centers in Europe and the USA between 2014-2018 revealed that independently from geographical region or resistance phenotype >90 % PTA have been achieved among all patient populations either for 1-log₁₀ kill or 2-log₁₀ kill (see Table 39). The results are congruent using the median or randomly assigned fAUC/MIC ratios (see 00593-2, Table 32).

Table 38: Percent Probabilities of PK - PD Target Attainment by MIC on Days 1 and 4 Based on the Median Free-drug Plasma AUC:MIC Ratio Target for *S. pneumoniae* Among Simulated Patients by Renal Function Group or Those Resembling the Clinical Trial Population after

Dosing regimen	Endpoints for free-drug plasma AUC:MIC ratio targets	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC on Days 1 or 4 by simulated population													
			Normal renal function		Mild renal impairment		Moderate renal impairment		Severe renal impairment		ESRD without dialysis		ESRD with dialysis		Clinical trial population	
			Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
IV	1-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.12	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.25	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.5	99.9	99.9	100	100	100	100	100	100	100	100	100	100	100	100
		1	94.1	95.0	99.7	99.8	99.9	99.9	97.9	98.7	98.2	98.9	89.8	93.8	99.6	99.7
		2	40.8	48.1	71.2	78.2	82.5	88.3	37.9	55.6	43.4	61.1	18.4	36.0	72.1	78.3
		4	1.24	2.92	4.83	11.3	9.78	20.9	0.32	3.30	0.51	4.63	0.10	1.49	6.51	13.8
	2-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	99.9	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.12	96.0	96.7	99.8	99.9	100	100	98.8	99.3	99.1	99.5	93.5	95.8	99.7	99.8
		0.25	44.9	51.8	74.3	81.2	84.9	89.8	42.3	59.6	48.3	64.2	21.4	39.4	75.0	80.9
		0.5	1.62	3.75	6.25	13.2	11.4	23.0	0.51	3.75	0.76	5.78	0.10	1.81	7.90	15.9
		1	0	0	0	0.16	0.03	0.38	0	0.03	0	0.06	0	0	0	0.22
		2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
IV - PO	1-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.12	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.25	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.5	99.9	99.9	100	100	100	100	100	100	100	100	100	99.9	100	100
		1	94.1	89.8	99.7	97.9	99.9	98.5	97.9	98.5	98.2	98.6	89.8	96.5	99.6	97.9
		2	40.8	29.8	71.2	61.2	82.5	73.4	37.9	76.9	43.4	79.1	18.4	61.7	72.1	62.6
		4	1.24	1.02	4.83	4.98	9.78	11.7	0.32	15.0	0.51	19.4	0.10	7.81	6.51	6.83
	2-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	99.9	100	100	100	100	100	100	100	100	100	100	99.9	100	100
		0.12	96.0	92.9	99.8	98.3	100	98.9	98.8	98.8	99.1	98.9	93.5	97.3	99.7	98.4
		0.25	44.9	32.9	74.3	64.3	84.9	76.5	42.3	79.1	48.3	81.1	21.4	64.8	75.0	65.9
		0.5	1.62	1.27	6.25	5.56	11.4	13.6	0.51	17.2	0.76	21.9	0.10	9.17	7.90	8.41
		1	0	0	0	0.03	0.03	0.13	0	0.10	0	0.32	0	0.03	0	0.10
		2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PO	1-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.12	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.25	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.5	99.8	99.9	99.9	100	99.9	100	99.9	100	99.9	100	99.7	99.8	99.9	100
		1	87.1	89.3	96.6	97.4	97.6	98.2	98.1	98.4	98.2	98.5	95.0	96.3	96.6	97.4
		2	21.8	29.3	49.1	60.2	62.3	71.9	69.5	78.5	72.4	80.3	51.1	65.5	52.3	61.3
		4	0.22	1.02	1.46	4.92	3.52	11.9	6.95	20.6	9.49	25.7	2.22	13.0	2.44	7.30
	2-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	99.9	100	100	100	100	100	100	100	100	100	99.8	99.9	100	100
		0.12	90.6	92.4	97.7	98.1	98.3	98.6	98.5	98.8	98.6	98.8	96.3	97.3	97.6	98.1
		0.25	24.8	32.6	52.9	63.3	65.4	74.7	72.4	80.3	75.4	82.2	55.1	67.7	55.7	64.5
		0.5	0.29	1.33	2.03	5.90	4.38	13.8	8.44	22.6	11.4	28.1	2.98	15.0	2.86	8.98
		1	0	0	0	0.03	0	0.13	0	0.48	0.03	1.46	0	0.32	0	0.10
		2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		4	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Note: Abbreviations are provided in the Abbreviation Listing. Shaded cells indicate percent probabilities of PK-PD target attainment by MIC ≥90%.
a. The median free-drug plasma AUC:MIC ratio targets associated with 1- and 2-log₁₀ CFU reductions from baseline for *S. pneumoniae* were 3.36 and 26.0, respectively.

Table 39: Overall percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on the median^a free-drug plasma AUC:MIC ratio targets for *S. pneumoniae* among simulated patients by renal function group or those resembling the clinical trial population after administration of the delafloxacin IV dosing regimen.

Endpoints for free-drug plasma AUC:MIC ratio targets	Isolate group by geographical region	Overall percent probabilities of PK-PD target attainment by MIC on Days 1 or 4 by simulated population ^b													
		Normal renal function		Mild renal impairment		Moderate renal impairment		Severe renal impairment		ESRD without dialysis		ESRD with dialysis		Clinical trial population	
		Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
1- $\log_{10}$ CFU reduction from baseline	Europe + USA														
	All SP	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	PRSP	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8
	Non-PRSP	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	Europe														
2- $\log_{10}$ CFU reduction from baseline	All SP	100	100	100	100	100	100	100	100	100	100	99.9	100	100	100
	Europe + USA														
	All SP	99.6	99.7	99.8	99.8	99.8	99.9	99.6	99.7	99.7	99.7	99.5	99.6	99.8	99.8
	PRSP	99.0	99.1	99.2	99.3	99.3	99.3	99.1	99.2	99.1	99.2	98.9	99.0	99.2	99.3
	Non-PRSP	99.7	99.7	99.9	99.9	99.9	99.9	99.7	99.8	99.7	99.8	99.6	99.7	99.9	99.9
	Europe														
	All SP	99.4	99.4	99.6	99.6	99.7	99.7	99.4	99.5	99.4	99.5	99.2	99.3	99.6	99.6

Note: Abbreviations are provided in the Abbreviation Listing. Shaded cells indicate percent probabilities of PK-PD target attainment by MIC $\geq 90\%$.

a. The median free-drug plasma AUC:MIC ratio targets associated with 1- and 2- $\log_{10}$ CFU reductions from baseline for *S. pneumoniae* were 3.38 and 26.0, respectively.

b. Based on data for *S. pneumoniae* isolates collected from centers in Europe and the USA combined and Europe alone during 2014 to 2018. The MIC distributions for each set of *S. pneumoniae* isolates evaluated are shown in Table 12.

The percent probabilities of PTA by MIC distributions for PRSP and non-PRSP isolates from the EU and US collected in 2014 to 2018 are graphically shown in Figure 15.

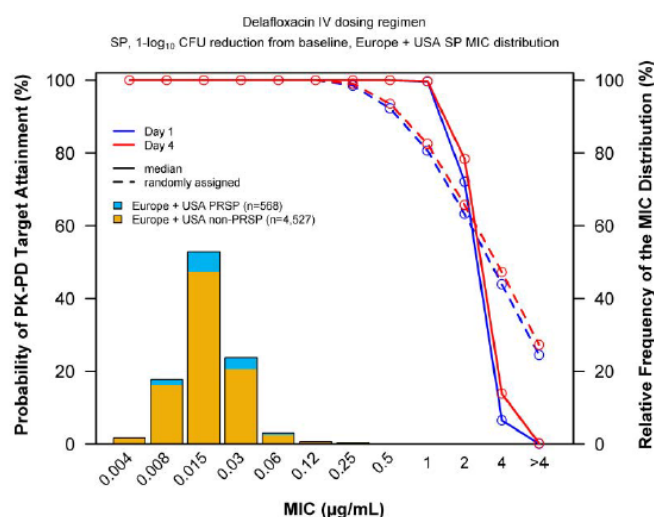


Figure 15: Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on median and randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1- $\log_{10}$ CFU reduction from baseline for *S. pneumoniae* among simulated patients resembling the clinical trial population after administration of the delafloxacin IV dosing regimen, overlaid upon the MIC distribution for *S. pneumoniae* isolates collected during 2014 to 2018 from Europe and the USA combined.

IV- to-PO

The % PTAs by MIC on Days 1 and 4 for the IV-PO dose regimen are similar to those for the IV dosing regimen only. Values of $>90\%$ or close to 90% PTA associated with 1- $\log_{10}$ or 2- $\log_{10}$ kill were described for MICs of up to 1 mg/L or 0.12 mg/L on Days 1 and 4, respectively (see Table 38). The PTA analyses was also performed based on randomly assigned fAUC/MIC ratio targets. According to the results PTAs associated

with 1-log₁₀ kill were >90 % for MIC of 0.25 µg/mL and <90% for MICs of 0.5 µg/mL. For a 2-log₁₀ kill PTAs of >90% were achieved for MICs of up to 0.06 µg/mL and in some populations even for MICs of 0.12 µg/mL (see 00593-2, Table 35).

According to the sub-analyses overall % PTA on Days 1 and 4 based on median or randomly assigned fAUC/MIC ratios for 1-log₁₀ kill and the MIC distribution from *S. pneumoniae* EU and US isolates collected between 2014-2018 PTA ranged between 99.9% and 100%. The % PTA based on MIC distribution for PRSP and non-PRSP ranged between 99.7% and 100% (see 00593-2, Table 34 & 36).

The percent probabilities of PK/PD target attainment by MIC on Day 1 and Day 4 overlaid upon MIC distributions for *S. pneumoniae* surveillance isolates are shown in Figure 16.

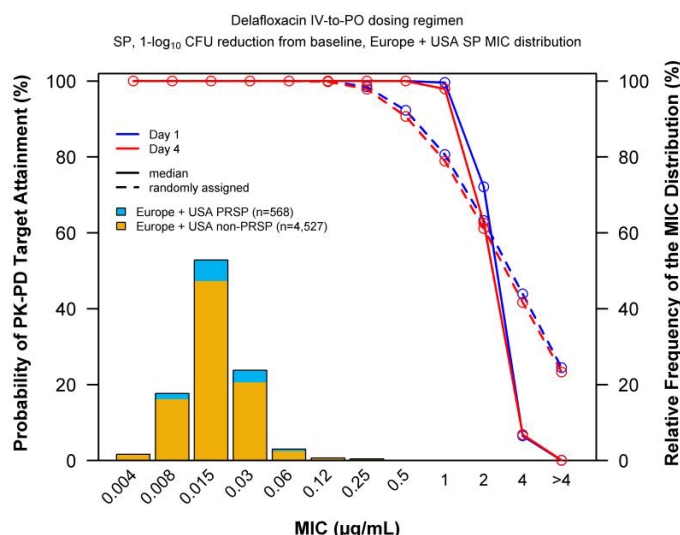


Figure 16: Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on median and randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline for *S. pneumoniae* among simulated patients resembling the clinical trial population after administration of the delafloxacin IV-to-PO dosing regimen, overlaid upon the MIC distribution for *S. pneumoniae* isolates collected during 2014 to 2018 from Europe and the USA combined.

PO

The % PTA by MIC on Days 1 and 4 for oral delafloxacin based on median assigned fAUC/MIC ratio associated with 1-log₁₀ kill as well as 2-log₁₀ kill is outlined in Table 38. Across all of the relevant simulated populations PTAs for 1-log₁₀ kill ranged between 87.1% and 98.2% at a MIC value of 1 µg/mL. For the endpoint of 2-log₁₀ reduction the PTAs were >90% for a MIC value of 0.12 µg/mL. Across simulated patient populations PTAs on Days 1 and 4 based on randomly assigned fAUC/MIC ratio targets associated with 1-log₁₀ kill ranged between 85.0% and 92.9% for a MIC value of 0.5 µg/mL while PTAs >90% were reached for lower MICs. PTAs for 2-log₁₀ kill showed values >90% for a MIC of 0.0.6 µg/mL (see 00593-2, Table 39).

According to the sub-analyses overall % PTA on Days 1 and 4 based on median or randomly assigned fAUC/MIC ratios for 1-log₁₀ kill and 2-log₁₀ kill and the MIC distribution from *S. pneumoniae* EU and US isolates collected between 2014-2018 PTA were >90% independently from geographic region or resistance phenotype (see 00593-2, Table 38 & 40).

The percent probabilities of PK/PD target attainment for the oral dosing regimen associated with 1-log₁₀ kill by MIC on Day 1 and Day 4 overlaid upon MIC distributions for *S. pneumoniae* surveillance isolates are shown in Figure 17.

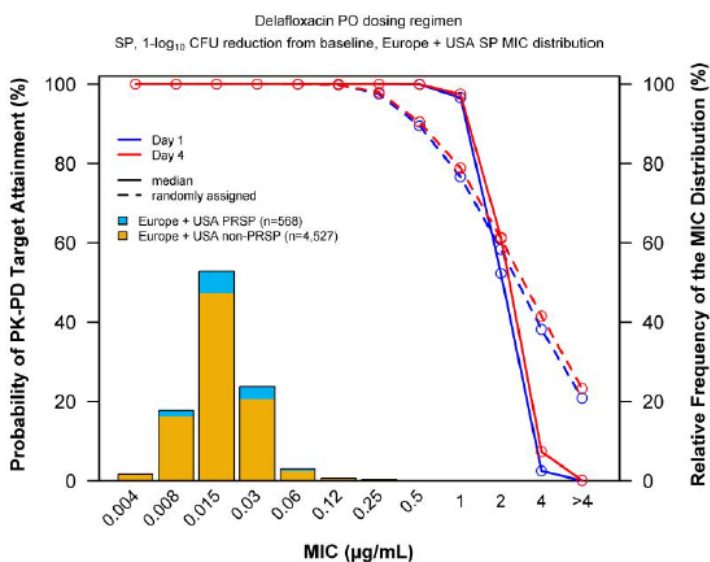


Figure 17: Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on the median and randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline for *S. pneumoniae* among simulated patients resembling the clinical trial population after administration of the delafloxacin PO dosing regimen, overlaid upon the MIC distribution for *S. pneumoniae* isolates collected during 2014 to 2018 from Europe and the USA combined.

The MAH concluded, that based on surveillance data for *S. pneumoniae* isolates (MIC_{50/90} of 0.015/0.03 µg/mL) a susceptible breakpoint of ≤ 1 µg/mL would cover >99 % of all *S. pneumoniae* isolates incl. resistance phenotypes like PRSP or MRSP. Further, clinical study outcome revealed that a clinical success rates of 93.7% was reached taking the ModME-1-TOC population into account (for more details refer to section 2.4.). With regards to the PTA analyses it was concluded that for all of the tested dosing regimens (IV, IV-PO, PO) PTAs on Days 1 and 4 based on median fAUC/MIC ratio targets for 1-log₁₀ kill of >99% were reached for the clinical trial population at a MIC value of 1 µg/mL. Thus, interpretative criteria of ≤ 1/ > 1 are proposed for *S. pneumoniae*.

H. influenzae

IV

The % PTAs by MIC on Days 1 and 4 were analyzed for *H. influenzae* and are outlined in Table 40. The analyses are based on the median plasma fAUC/MIC ratio target for *H. influenzae* for 1-log₁₀ and 2-log₁₀ CFU reduction. PTA results for 1-log₁₀ reduction are >90% for a MIC value of 0.12 µg/mL in the relevant populations on Days 1 and 4. Target attainment of >90% was shown for a 2-log₁₀ kill at a MIC value of 0.06 µg/mL while PTAs ranged between 83.6% and 99.7% for a MIC of 0.12 mg/mL. The same analyses based on randomly assigned fAUC/MIC ratios revealed nearly the same results. PTA results for 1-log₁₀ reduction were >90% for a MIC value of 0.12 µg/mL except for patients with normal renal function on Day 1 (88.6 %). Target attainment of >90% was shown for a 2-log₁₀ kill at a MIC value of 0.06 µg/mL while PTAs ranged between 79.2% and 97.6% in the relevant populations for a MIC of 0.12 mg/mL.

Table 40: Percent Probabilities of PK - PD Target Attainment by MIC on Days 1 and 4 Based on the Median Free-drug Plasma AUC:MIC Ratio Target for *H. influenzae* Among Simulated Patients by Renal Function Group or Those Resembling the Clinical Trial Population after Administration of Delafloxacin IV, IV-to-Oral, and Oral Dosing Regimens.

Dosing regimen	Endpoints for free-drug plasma AUC:MIC ratio targets	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC on Days 1 or 4 by simulated population													
			Normal renal function		Mild renal impairment		Moderate renal impairment		Severe renal impairment		ESRD without dialysis		ESRD with dialysis		Clinical trial population	
			Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
IV	1-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	99.8	99.9	100	100	100	100	100	100	100	100	100	100	100	100
		0.12	93.4	94.5	99.7	99.7	99.8	99.9	97.4	98.3	97.9	98.7	88.5	92.7	99.6	99.7
		0.25	33.4	40.9	63.5	72.8	76.3	84.4	30.5	47.8	35.0	53.6	13.4	29.4	65.6	73.0
		0.5	0.63	2.00	3.02	7.94	6.63	16.5	0.16	2.10	0.25	3.27	0.03	0.89	4.16	10.3
	2-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	99.5	99.6	100	100	100	100	99.9	100	100	100	99.7	99.8	100	100
		0.12	83.6	86.2	97.4	98.3	99.3	99.7	87.6	92.2	89.7	93.6	70.7	79.9	97.3	98.0
		0.25	14.6	20.4	34.2	46.9	49.3	64.0	9.87	23.7	13.0	28.8	3.40	12.8	38.5	50.3
		0.5	0.10	0.32	0.41	2.00	1.02	5.30	0.03	0.25	0.06	0.57	0	0.13	0.63	2.92
IV - PO	1-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	99.8	99.8	100	100	100	100	100	100	100	100	100	99.9	100	100
		0.12	93.4	88.7	99.7	97.7	99.8	98.4	97.4	98.5	97.9	98.5	88.5	96.0	99.6	97.6
		0.25	33.4	23.5	63.5	54.1	76.3	67.9	30.5	71.6	35.0	74.4	13.4	55.5	65.6	55.9
		0.5	0.63	0.63	3.02	3.40	6.63	8.67	0.16	11.1	0.25	15.4	0.03	5.27	4.16	4.95
	2-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	99.5	99.2	100	99.8	100	99.9	99.9	99.8	100	99.9	99.7	99.4	100	99.8
		0.12	83.6	74.4	97.4	92.5	99.3	95.5	87.6	96.0	89.7	96.5	70.7	90.0	97.3	92.4
		0.25	14.6	9.68	34.2	29.4	49.3	45.8	9.87	50.8	13.0	55.8	3.40	34.3	38.5	33.8
		0.5	0.10	0	0.41	0.57	1.02	2.41	0.03	3.27	0.06	4.92	0	1.17	0.63	1.17
PO	1-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	99.7	99.8	99.9	100	99.9	100	99.9	100	99.9	100	99.7	99.8	99.9	99.9
		0.12	85.9	88.1	96.2	97.2	97.3	98.0	97.8	98.4	98.0	98.4	94.5	95.9	96.0	97.1
		0.25	16.8	23.7	41.4	53.1	55.5	66.5	63.9	73.8	67.0	76.3	44.1	59.6	46.2	55.2
		0.5	0.13	0.63	0.70	3.59	2.54	9.05	4.32	16.6	5.94	21.5	1.27	10.3	1.62	4.98
	2-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	98.8	99.0	99.6	99.7	99.7	99.8	99.8	99.8	99.8	99.8	99.0	99.4	99.6	99.7
		0.12	68.8	73.7	89.0	91.7	92.9	95.1	94.6	96.0	95.2	96.3	86.6	90.1	89.2	91.7
		0.25	5.27	9.65	18.1	29.2	29.4	45.2	39.2	55.4	45.0	59.4	22.4	39.5	22.5	33.7
		0.5	0	0	0.03	0.73	0.22	2.86	0.57	6.60	1.17	9.78	0.13	3.52	0.16	1.43

Note: Abbreviations are provided in the Abbreviation Listing. Shaded cells indicate percent probabilities of PK-PD target attainment by MIC ≥90%.
a. The median free-drug plasma AUC:MIC ratio targets associated with 1- and 2-log₁₀ CFU reductions from baseline for *H. influenzae* were 28.7 and 36.0, respectively.

Analyses of overall % PTA by MIC on Days 1 and 4 based on data for *H. influenzae* isolates collected from centers in Europe and the USA between 2014-2018 revealed that % PTA was near to 100% based on the MIC distribution for *Haemophilus influenzae* isolates as well as for *Haemophilus* spp. collected from the EU and US (see Table 41). The results were comparable using median or randomly assigned fAUC/MIC ratio targets.

The percent probabilities of PTA for the IV dosing regimen by MIC distributions for *H. influenzae* isolates from the EU and US collected in 2014 to 2018 are graphically shown in Figure 18 A.

Table 41: Overall percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on median fAUC:MIC ratio targets for *H. influenzae* among simulated patients by renal function group or those resembling the clinical trial population after administration of the delafloxacin PO dosing regimen.

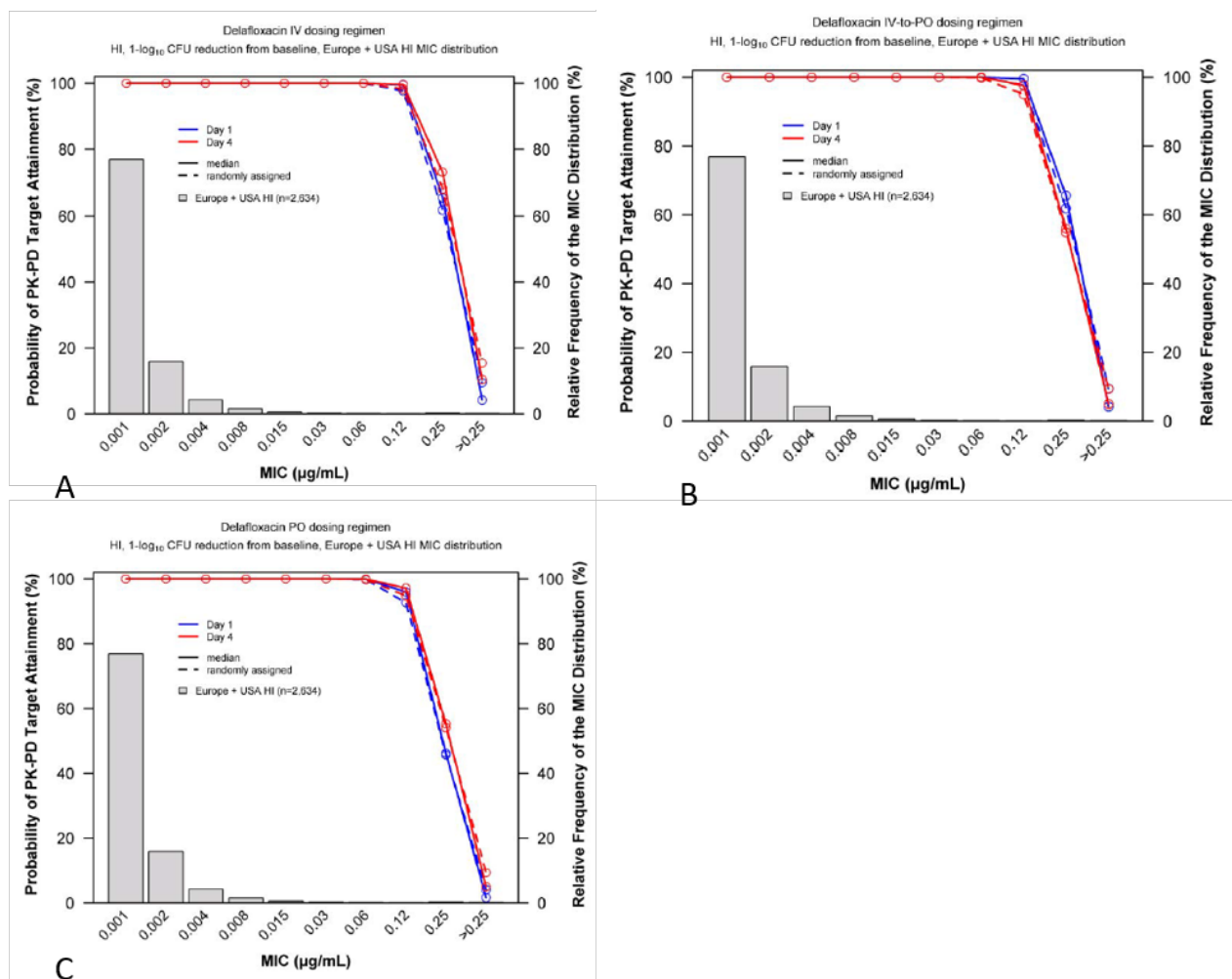
Dosing regimen	Endpoints for free-drug plasma AUC:MIC ratio targets	Isolate group by geographical region	Overall percent probabilities of PK-PD target attainment by MIC on Days 1 or 4 by simulated population ^b													
			Normal renal function		Mild renal impairment		Moderate renal impairment		Severe renal impairment		ESRD without dialysis		ESRD with dialysis		Clinical trial population	
			Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
IV	1-log ₁₀ CFU reduction from baseline	<i>H. influenzae</i>														
		Europe + USA	99.6	99.7	99.7	99.8	99.8	99.8	99.6	99.7	99.6	99.7	99.6	99.6	99.7	99.8
		Europe	99.6	99.6	99.7	99.8	99.8	99.8	99.6	99.7	99.6	99.7	99.5	99.6	99.7	99.8
		<i>Haemophilus</i> spp.														
	2-log ₁₀ CFU reduction from baseline	Europe + USA	99.3	99.3	99.4	99.5	99.5	99.5	99.3	99.4	99.3	99.4	99.2	99.3	99.4	99.5
		<i>H. influenzae</i>														
		Europe + USA	99.6	99.6	99.6	99.7	99.7	99.7	99.6	99.6	99.6	99.6	99.5	99.6	99.7	99.7
		Europe	99.5	99.6	99.6	99.7	99.7	99.7	99.5	99.6	99.5	99.6	99.5	99.5	99.6	99.7
IV - PO	1-log ₁₀ CFU reduction from baseline	<i>H. influenzae</i>														
		Europe + USA	99.6	99.6	99.7	99.7	99.8	99.8	99.6	99.8	99.6	99.8	99.6	99.7	99.7	99.7
		Europe	99.6	99.6	99.7	99.7	99.8	99.7	99.6	99.8	99.6	99.8	99.5	99.7	99.7	99.7
		<i>Haemophilus</i> spp.														
	2-log ₁₀ CFU reduction from baseline	Europe + USA	99.3	99.3	99.4	99.4	99.5	99.4	99.3	99.5	99.3	99.5	99.2	99.4	99.4	99.4
		<i>H. influenzae</i>														
		Europe + USA	99.6	99.5	99.6	99.6	99.7	99.7	99.6	99.7	99.6	99.7	99.5	99.6	99.7	99.6
		Europe	99.5	99.5	99.6	99.6	99.7	99.7	99.5	99.7	99.5	99.7	99.5	99.6	99.6	99.6
PO	1-log ₁₀ CFU reduction from baseline	<i>Haemophilus</i> spp.														
		Europe + USA	99.2	99.3	99.3	99.4	99.4	99.4	99.4	99.5	99.4	99.5	99.3	99.4	99.3	99.4
	2-log ₁₀ CFU reduction from baseline	<i>H. influenzae</i>														
		Europe + USA	99.5	99.5	99.6	99.6	99.6	99.7	99.7	99.7	99.7	99.7	99.6	99.7	99.6	99.6
		Europe	99.5	99.5	99.5	99.6	99.6	99.7	99.6	99.7	99.7	99.7	99.6	99.6	99.6	99.6
		<i>Haemophilus</i> spp.														
	2-log ₁₀ CFU reduction from baseline	Europe + USA	99.2	99.2	99.2	99.3	99.3	99.3	99.3	99.4	99.3	99.4	99.3	99.3	99.3	99.3
		Europe + USA	99.2	99.2	99.2	99.3	99.3	99.3	99.3	99.4	99.3	99.4	99.3	99.3	99.3	99.3

Note: Abbreviations are provided in the Abbreviation Listing. Shaded cells indicate percent probabilities of PK-PD target attainment by MIC $\geq 90\%$.

a. The median free-drug plasma AUC:MIC ratio targets associated with 1- and 2-log₁₀ CFU reductions from baseline for *H. influenzae* were 28.7 and 36.0 respectively.

b. Based on data for *H. influenzae* isolates collected from centers in Europe and the USA combined and Europe alone during 2014 to 2018. The MIC distributions for each set of *H. influenzae* isolates evaluated are shown in Table 13.

Figure 18: Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on median and randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline for *H. influenzae* among simulated patients resembling the clinical trial population after administration of the delafloxacin (A) IV, (B) IV-to-PO, or (C) PO dosing regimen, overlaid upon the MIC distribution for *H. influenzae* isolates collected during 2014 to 2018 from Europe and the USA combined.



IV-to-PO

The PTAs for 1-log₁₀ CFU reduction from baseline for the IV-to-PO dosing regimen in relevant populations showed PTAs above 90% for a MIC value of 0.12 µg/mL with the exception of patients with normal renal function on Day 4 for whom the PTA was 88.7% at a MIC of 0.12 µg/mL. For a 2-log₁₀ kill PTAs at a MIC of 0.12 µg/mL ranged between 74.4% and 99.3%. Across simulated patient groups % PTAs based on randomly assigned fAUC/MIC ratio targets associated with 1-log₁₀ kill were >90% for a MIC of 0.06 µg/mL in all of the analysed groups as well as for all of the patient groups at a MIC of 0.12 µg/mL with the exception of patients with normal function. For these group PTAs of 88.6% and 83.5% on Days 1 and 4, respectively, were achieved. Results for 2-log₁₀ reduction were less good with PTAs ranging between 71.8% and 96.5% at a MIC of 0.12 µg/mL.

The analyses of overall % PTA by MIC on Days 1 and 4 based on data for *H. influenzae* isolates collected from centers in Europe and the USA between 2014-2018 revealed that % PTA was >99% independently of using median or randomly assigned fAUC/MIC ratio targets (see 00593-2, Table 46 & 48).

The percent probabilities of PTA on Days 1 and 4 for the IV-to-PO dosing regimen by MIC distributions for *H. influenzae* isolates from the EU and US collected in 2014 to 2018 are graphically shown in Figure 18 B.

PO

The PTAs for 1-log₁₀ CFU reduction from baseline for the IV-to-PO dosing regimen in relevant populations showed PTAs above 90% for a MIC value of 0.12 µg/mL with the exception of patients with normal renal function on Days 1 and 4 for whom the PTA was 85.9% and 88.1%, respectively. For a 2-log₁₀ kill PTAs at a MIC of 0.12 µg/mL ranged between 68.8% and 96.0% while PTAs were >90% for all patient populations for a MIC value of 0.06 µg/mL. Results for % PTA for simulated patient groups based on randomly assigned fAUC/MIC ratio targets associated with 1-log₁₀ or 2-log₁₀ kill were similar to those observed based on the median fAUC/ratio target (see 00593-2, Table 51).

The analyses of overall % PTA by MIC on Days 1 and 4 based on data for *H. influenzae* isolates collected from surveillance studies in the EU and US between 2014-2018 revealed that % PTA was >99% independently of using median or randomly assigned fAUC/MIC ratio targets (see 00593-2, Table 49 & 51).

The percent probabilities of PTA on Days 1 and 4 for the PO dosing regimen by MIC distributions for *H. influenzae* isolates from the EU and US collected in 2014 to 2018 are graphically shown in Figure 18 C.

The MAH concluded that based on surveillance data for *H. influenzae* isolates (MIC_{50/90} of ≤0.001/0.002 µg/mL) a susceptible breakpoint of ≤ 0.12 µg/mL would cover 99.5 % of all *H. influenzae* isolates incl. β-lactamase positive strains. Further, clinical study outcome revealed that a clinical success rates of 95.2% was reached taking the ModME-1-TOC population into account (for more details refer to section 2.4.). With regards to the PTA analyses it was concluded that for all of the tested dosing regimens (IV, IV-PO, PO) PTAs on Days 1 and 4 based on median assigned fAUC/MIC ratio targets for 1-log₁₀ kill of > 96% were reached for the clinical trial population at a MIC value of 0.12 µg/mL. Thus, interpretative criteria of ≤ 0.12/ > 0.12 are proposed for *H. influenzae*.

S. aureus

IV

The % PTA by MIC on Days 1 and 4 for IV delafloxacin for *S. aureus* associated with 1-log₁₀ kill was >90% for a MIC value of 0.5 µg/mL except for patients with normal renal function on Day 1 for whom the PTA was 88.3% at this MIC value. The PTAs predict > 99% coverage for MICs up to and including 0.25 mg/L and 100% coverage for MICs of 0.12 mg/L and below regardless of renal status. PTAs for a 2-log₁₀ reduction from baseline were >90% for a MIC value of 0.06 µg/mL and showed a broad range of 52.0% to 93.3% for a MIC of 0.12 µg/mL. Results for the % PTAs based on randomly assigned fAUC/MIC ratio targets were comparable although a little worse for both endpoints (1-log₁₀ and 2-log₁₀ kill) (see 00593-2, Table 55).

The % PTAs on Days 1 and 4 based on data for *S. aureus* isolates from surveillance studies revealed for all of the patient populations that values of >90% (independently of using median or randomly assigned fAUC/MIC ratio targets) were achieved for all isolates combined from EU and US or EU alone (see Table 43 and 00593-2, Table 54 & 56). Focussing on MRSA and MSSA isolates it became clear that % PTAs for Days 1 and 4 were above 90 % for either 1-log₁₀ kill or 2-log₁₀ kill for MSSA isolates. However, the % PTAs for MRSA ranged between 81.0% and 90.3% across simulated patient populations.

Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4, based on median and randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline among simulated patients resembling the clinical trial population, are shown in Figure 19 A.

Table 42: Percent Probabilities of PK - PD Target Attainment by MIC on Days 1 and 4 Based on the Median Free-drug Plasma AUC:MIC Ratio Target for *S. aureus* Among Simulated Patients by

Renal Function Group or Those Resembling the Clinical Trial Population after Administration of Delafloxacin IV, IV-to-Oral, and Oral Dosing Regimens.

Dosing regimen	Endpoints for free-drug plasma AUC:MIC ratio targets	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by MIC on Days 1 or 4 by simulated population													
			Normal renal function		Mild renal impairment		Moderate renal impairment		Severe renal impairment		ESRD without dialysis		ESRD with dialysis		Clinical trial population	
			Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
IV	1-log ₁₀ CFU reduction from baseline	0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.12	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.25	99.7	99.7	100	100	100	100	100	100	100	100	99.9	99.9	100	100
		0.5	88.3	90.3	98.7	99.2	99.7	99.7	92.6	95.5	93.9	96.3	78.3	85.8	98.4	98.8
		1	24.2	30.8	50.6	62.1	66.1	76.7	20.3	35.5	24.1	42.0	8.06	21.1	54.1	63.8
		2	0.25	0.92	1.21	4.76	3.49	10.3	0.10	1.02	0.10	1.78	0.03	0.32	2.00	6.03
	2-log ₁₀ CFU reduction from baseline	4	0	0	0	0	0	0.10	0	0	0	0	0	0	0	0.03
		0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	96.5	96.9	99.8	99.9	100	100	99.0	99.5	99.3	99.6	94.4	96.4	99.7	99.9
		0.12	52.0	58.0	79.6	85.6	89.3	93.3	51.2	66.2	56.7	70.7	28.6	46.4	80.4	85.3
		0.25	1.90	4.29	7.17	14.5	13.4	25.1	0.54	4.19	0.98	6.70	0.13	2.10	9.24	17.3
		0.5	0	0	0.03	0.16	0.06	0.44	0	0.06	0	0.06	0	0	0	0.22
		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
IV - PO	1-log ₁₀ CFU reduction from baseline	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.12	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.25	99.7	99.5	100	99.9	100	99.9	100	99.9	100	99.9	99.9	99.6	100	99.9
		0.5	88.3	81.0	98.7	95.3	99.7	96.9	92.6	97.2	93.9	97.5	78.3	93.0	98.4	94.7
	2-log ₁₀ CFU reduction from baseline	1	24.2	16.8	50.6	42.8	66.1	58.9	20.3	63.4	24.1	67.0	8.06	45.5	54.1	46.7
		2	0.25	0.22	1.21	1.81	3.49	5.21	0.10	6.70	0.10	9.62	0.03	2.92	2.00	2.89
		4	0	0	0	0	0	0.03	0	0.03	0	0.03	0	0	0	0
		0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	99.9	100	100
		0.06	96.5	93.7	99.8	98.6	100	99.0	99.0	99.3	99.0	99.0	94.4	97.5	99.7	98.5
		0.12	52.0	39.5	79.6	70.9	89.3	80.6	51.2	82.8	56.7	85.0	28.6	69.5	80.4	71.9
		0.25	1.90	1.49	7.17	6.57	13.4	15.0	0.54	18.8	0.98	24.0	0.13	10.3	9.24	9.43
PO	1-log ₁₀ CFU reduction from baseline	0.5	0	0	0.03	0.03	0.06	0.16	0	0.22	0	0.38	0	0.03	0	0.13
		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.06	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.12	100	100	100	100	100	100	100	100	100	100	100	100	100	100
	2-log ₁₀ CFU reduction from baseline	0.25	99.3	99.4	99.8	99.9	99.8	99.9	99.9	99.9	99.9	100	99.3	99.6	99.8	99.9
		0.5	76.1	80.3	92.5	94.7	95.3	96.5	96.0	97.0	96.5	97.3	90.3	93.0	92.6	94.2
		1	11.2	16.5	29.9	42.5	44.6	57.5	54.2	66.5	57.9	69.7	34.4	51.0	35.0	46.4
		2	0	0.22	0.32	1.94	0.89	5.30	2.54	11.3	3.56	15.7	0.38	6.67	0.57	3.14
		4	0	0	0	0	0	0.03	0	0.10	0	0.32	0	0.06	0	0
		0.015	100	100	100	100	100	100	100	100	100	100	100	100	100	100
		0.03	99.9	100	100	100	100	100	100	100	100	100	99.9	99.9	100	100
		0.06	91.5	93.4	97.9	98.3	98.5	98.8	98.6	98.9	98.6	98.9	96.7	97.5	97.8	98.3
		0.12	31.0	38.9	59.8	69.2	71.5	79.6	77.7	84.0	80.0	85.8	61.4	71.8	62.1	70.8
	2-log ₁₀ CFU reduction from baseline	0.25	0.35	1.52	2.25	6.63	5.24	15.3	9.65	24.6	12.5	29.8	3.78	16.3	3.37	9.68
		0.5	0	0	0	0.03	0	0.13	0.03	0.67	0.03	1.75	0	0.41	0	0.10
		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		4	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Note: Abbreviations are provided in the Abbreviation Listing. Shaded cells indicate percent probabilities of PK-PD target attainment by MIC ≥90%.

a. The median free-drug plasma AUC:MIC ratio targets associated with a 1- and 2-log₁₀ CFU reduction from baseline for *S. aureus* were 7.92 and 50.8, respectively.

Table 43: Overall percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on the median^a free-drug plasma AUC:MIC ratio targets for *S. aureus* among simulated patients by renal function group or those resembling the clinical trial population after administration of the delafloxacin dosing regimens.

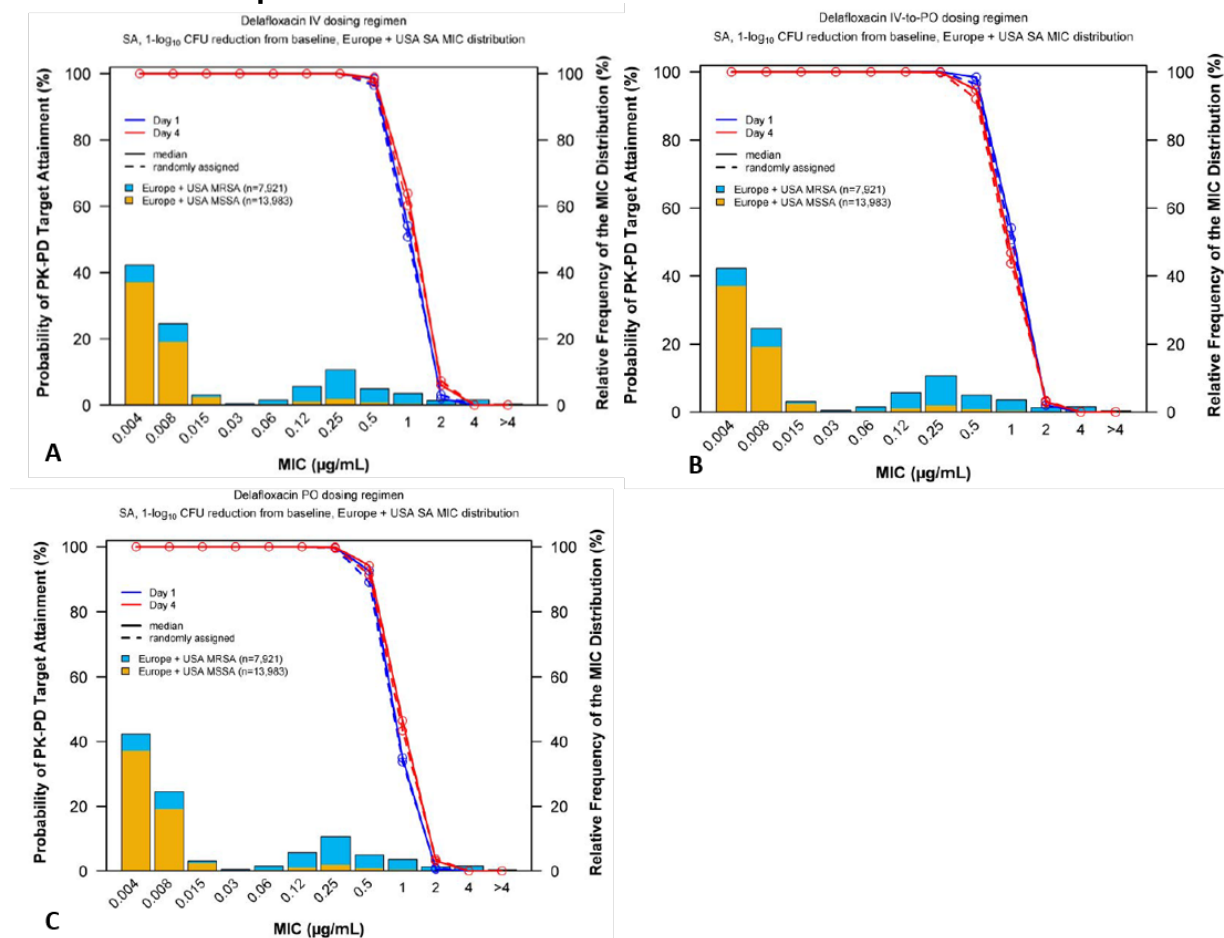
Dosing regimen	Endpoints for free-drug plasma AUC:MIC ratio targets	Isolate group by geographical region	Overall percent probabilities of PK-PD target attainment by MIC on Days 1 or 4 by simulated population ^b													
			Normal renal function		Mild renal impairment		Moderate renal impairment		Severe renal impairment		ESRD without dialysis		ESRD with dialysis		Clinical trial population	
			Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
IV	1-log ₁₀ CFU reduction from baseline	Europe + USA														
		All SA	93.5	93.8	94.9	95.4	95.6	96.0	93.6	94.3	93.8	94.5	92.4	93.3	95.1	95.5
		MRSA	84.1	84.9	87.6	88.8	89.1	90.3	84.3	86.0	84.8	86.6	81.6	83.6	87.9	88.9
		MSSA	98.8	98.8	99.1	99.2	99.2	99.3	98.8	99.0	98.9	99.0	98.5	98.7	99.1	99.2
		Europe														
		All SA	94.9	95.3	96.4	96.9	97.0	97.5	95.0	95.7	95.2	96.0	93.9	94.7	96.5	96.9
	2-log ₁₀ CFU reduction from baseline	Europe + USA														
		All SA	75.0	75.6	77.2	78.3	78.4	79.9	74.9	76.1	75.2	76.7	73.5	74.7	77.5	78.6
		MRSA	42.2	43.6	47.1	49.7	49.9	53.3	41.9	44.7	42.7	45.9	38.7	41.5	47.7	50.3
		MSSA	93.6	93.8	94.3	94.6	94.6	95.0	93.6	94.0	93.7	94.1	93.2	93.5	94.3	94.7
		Europe														
		All SA	82.8	83.1	83.8	84.3	84.4	85.1	82.7	83.3	82.9	83.5	82.2	82.7	83.9	84.5
IV - PO	1-log ₁₀ CFU reduction from baseline	Europe + USA														
		All SA	93.5	92.8	94.9	94.5	95.6	95.2	93.6	95.4	93.8	95.6	92.4	94.5	95.1	94.6
		MRSA	84.1	82.6	87.6	86.6	89.1	88.2	84.3	88.7	84.8	89.1	81.6	86.5	87.9	86.9
		MSSA	98.8	98.6	99.1	99.0	99.2	99.1	98.8	99.2	98.9	99.2	98.5	99.0	99.1	99.0
		Europe														
		All SA	94.9	94.3	96.4	96.0	97.0	96.6	95.0	96.8	95.2	97.0	93.9	95.9	96.5	96.1
	2-log ₁₀ CFU reduction from baseline	Europe + USA														
		All SA	75.0	74.2	77.2	76.6	78.4	78.1	74.9	78.6	75.2	79.3	73.5	76.9	77.5	77.0
		MRSA	42.2	40.4	47.1	45.8	49.9	49.1	41.9	50.3	42.7	51.9	38.7	46.5	47.7	46.7
		MSSA	93.6	93.4	94.3	94.1	94.6	94.5	93.6	94.7	93.7	94.9	93.2	94.2	94.3	94.2
		Europe														
		All SA	82.8	82.5	83.8	83.5	84.4	84.3	82.7	84.5	82.9	84.9	82.2	83.7	83.9	83.7
PO	1-log ₁₀ CFU reduction from baseline	Europe + USA														
		All SA	92.4	92.8	93.9	94.5	94.5	95.1	94.9	95.6	95.1	95.8	93.9	94.7	94.1	94.6
		MRSA	81.5	82.4	85.1	86.5	86.7	88.1	87.6	89.1	88.0	89.6	85.1	87.1	85.5	86.8
		MSSA	98.5	98.6	98.9	99.0	99.0	99.1	99.1	99.2	99.1	99.3	98.9	99.0	98.9	99.0
		Europe														
		All SA	93.8	94.2	95.4	95.9	96.0	96.6	96.4	97.0	96.6	97.1	95.4	96.2	95.5	96.0
	2-log ₁₀ CFU reduction from baseline	Europe + USA														
		All SA	73.6	74.2	75.5	76.5	76.5	78.1	77.4	79.3	77.8	80.1	75.8	77.7	75.8	77.0
		MRSA	39.0	40.3	43.3	45.6	45.6	49.1	47.4	51.9	48.4	53.6	43.9	48.3	43.9	46.6
		MSSA	93.2	93.4	93.8	94.1	94.1	94.5	94.3	94.9	94.4	95.1	93.8	94.4	93.9	94.2
		Europe														
		All SA	82.3	82.5	83.0	83.5	83.5	84.2	83.9	84.9	84.1	85.3	83.2	84.1	83.1	83.7

Note: Abbreviations are provided in the Abbreviation Listing. Shaded cells indicate percent probabilities of PK-PD target attainment by MIC $\geq 90\%$.

a. The median free-drug plasma AUC:MIC ratio targets associated with a 1- and 2-log₁₀ CFU reduction from baseline for *S. aureus* were 7.92 and 50.8, respectively.

b. Based on data for *S. aureus* isolates collected from centers in Europe and the USA combined and Europe alone during 2014 to 2018. The MIC distributions for each set of *S. aureus* isolates evaluated are shown in Table 14.

Figure 19: Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on median and randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline for *S. aureus* among simulated patients resembling the clinical trial population after administration of the delafloxacin (A) IV, (B) IV-to_PO, (C) PO dosing regimen, overlaid upon the MIC distribution for *S. aureus* isolates collected during 2014 to 2018 from Europe and the USA combined.



IV-to-PO

For *S. aureus* with the IV-to-oral dosing regimen, the PTAs predicted a similar coverage to the IV dose regimen with almost complete coverage (> 99%) for MICs up to and including 0.25 mg/L. The % PTA by MIC on Days 1 and 4 for IV-to-PO delafloxacin for *S. aureus* associated with 1-log₁₀ kill was >90% for a MIC value of 0.5 µg/mL except for patients with normal renal function on Day 1 and 4 for whom the PTAs were 88.3% and 81.0%, respectively at this MIC value. PTAs for a 2-log₁₀ reduction from baseline were >90% for a MIC value of 0.06 µg/mL and showed a broad range of 39.5% to 89.3% for a MIC of 0.12 µg/mL. Results for the % PTAs based on randomly assigned fAUC/MIC ratio targets were comparable although a little worse for both endpoints (1-log₁₀ and 2-log₁₀ kill) (see 00593-2, Table 59).

The % PTAs on Days 1 and 4 based on data for *S. aureus* isolates from surveillance studies revealed for all of the patient populations that values of >90% (independently of using median or randomly assigned fAUC/MIC ratio targets) were achieved for all isolates combined from EU and US or EU alone (see Table 43 and 00593-2, Table 58 & 60). PTAs for MSSA isolates were >90%, as well, either for 1-log₁₀ kill or 2-log₁₀ kill. In contrast, % PTAs for Days 1 and 4 for MRSA ranged between 82.0% and 89.1% for relevant populations for 1-log₁₀ kill while PTAs for 2-log₁₀ kill were less good (between 40.4% and 50.7%).

Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4, based on median and randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline among simulated patients resembling the clinical trial population, are shown in Figure 19 B.

PO

The % PTA by MIC on Days 1 and 4 for IV-to-PO delafloxacin for *S. aureus* associated with 1-log₁₀ kill was >90% for a MIC value of 0.5 µg/mL except for patients with normal renal function on Day 1 and 4 for whom the PTAs were 76.1% and 80.3%, respectively at this MIC value. PTAs predict > 99% coverage for MICs up to and including 0.25 mg/L and 100% coverage for MICs of 0.12 mg/L and below regardless of renal status. PTAs for a 2-log₁₀ reduction from baseline were >90% for a MIC value of 0.06 µg/mL. Results for the % PTAs based on randomly assigned fAUC/MIC ratio targets were comparable although a little worse for both endpoints (1-log₁₀ and 2-log₁₀ kill) (see 00593-2, Table 63).

The % PTAs on Days 1 and 4 based on data for *S. aureus* isolates from surveillance studies revealed for all of the patient populations that values of >90% (independently of using median or randomly assigned fAUC/MIC ratio targets) were achieved for all isolates combined from EU and US or EU alone (see Table 43 and 00593-2, Table 62 & 64). PTAs for MSSA isolates were >90%, as well, either for 1-log₁₀ kill or 2-log₁₀ kill. In contrast, % PTAs for Days 1 and 4 for MRSA ranged between 80.8% and 89.1% for relevant populations for 1-log₁₀ kill while PTAs for 2-log₁₀ kill were less good (between 39.0% and 52.2%).

Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4, based on median and randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline among simulated patients resembling the clinical trial population, are shown in Figure 19 C.

The MAH concluded that based on surveillance data for *S. aureus* isolates (MIC_{50/90} of ≤0.004/0.5 µg/mL) a susceptible breakpoint of ≤ 0.25 µg/mL would cover 88.3% of contemporary *S. aureus* isolates as well as 72.1% and 9.2% of contemporary MRSA and MSSA isolates, respectively. Further, clinical study outcome revealed that a clinical success rates of 92.3% was reached taking the ModME-1-TOC population into account (for more details refer to section 2.4.). With regards to the PTA analyses it was concluded that for all of the tested dosing regimens (IV, IV-PO, PO) PTAs on Days 1 and 4 based on median assigned fAUC/MIC ratio targets for 1-log₁₀ kill of > 99% were reached for the clinical trial population at a MIC value of 0.25 µg/mL. Thus, interpretative criteria of ≤ 0.25 / > 0.25 are proposed for *S. aureus*.

K. pneumoniae

For *K. pneumoniae* only endpoints for fAUC/MIC ratio targets associated with 1-log₁₀ kill have been analysed since 2-log₁₀ kill could be observed in the animal *in vivo* models for a few strains only.

IV

The % PTA by MIC on Days 1 and 4 for IV delafloxacin for *K. pneumoniae* associated with 1-log₁₀ kill was >90% for a MIC value of 0.06 µg/mL except for patients with normal renal function for whom on the PTA was 89.7% on Day 1. At MIC 0.03 mg/L, PTAs predict > 99% coverage regardless of renal status. Results based on randomly assigned fAUC/MIC ratio targets showed that the MIC covered with PTAs >90 % was 2-fold lower than for the analyses using median assigned fAUC/MIC ratio targets.

Full coverage (PTA >90%) was thus observed for a MIC value of 0.015 µg/mL while the PTAs for a MIC of 0.03 µg/mL ranged between 86.0% and 92.4% for the relevant populations (see 00593-2, Table 65).

The overall % PTAs by MIC on Days 1 and 4 based on the median and randomly assigned fAUC:MIC ratio targets for *K. pneumoniae* among simulated patients by renal function group or those resembling the clinical trial population after administration of the delafloxacin dosing regimens is shown in Table 44. The PTAs

based on data for *K. pneumoniae* from EU and US surveillance studies range between 29.3% and 52.9% for the relevant populations only.

A graphical illustration of the % PTAs by MIC on Days 1 and 4 based on median and randomly assigned fAUC/MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline among simulated patient populations resembling the clinical trial population after administration of the delafloxacin IV dosing regimen, overlaid upon the MIC distribution for *K. pneumoniae* isolates from surveillance (EU and US) is shown in Figure 20 A.

Table 44: Overall percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on the median and randomly assigned free-drug plasma AUC:MIC ratio targets for *K. pneumoniae* among simulated patients by renal function group or those resembling the clinical trial population after administration of the delafloxacin IV, IV-PO, PO dosing regimen

Dosing regimen	Endpoints for free-drug plasma AUC:MIC ratio targets	Geographical region for <i>K. pneumoniae</i> isolates	Overall percent probabilities of PK-PD target attainment by MIC on Days 1 or 4 by simulated population ^c													
			Normal renal function		Mild renal impairment		Moderate renal impairment		Severe renal impairment		ESRD without dialysis		ESRD with dialysis		Clinical trial population	
			Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
IV	Median ^a	Europe + USA	37.1	39.0	46.4	49.3	50.3	52.9	37.3	42.0	38.6	43.7	30.3	35.5	47.1	49.5
		Europe	29.3	30.9	36.9	39.3	40.0	42.1	29.5	33.3	30.6	34.7	23.9	28.1	37.4	39.4
	Randomly assigned ^b	Europe + USA	41.4	42.5	45.6	47.1	47.3	49.2	41.6	43.6	42.1	44.4	38.4	40.9	45.9	47.4
		Europe	32.9	33.8	36.3	37.6	37.7	39.3	33.0	34.7	33.5	35.4	30.4	32.5	36.6	37.8
IV - PO	Median ^a	Europe + USA	37.1	33.1	46.4	43.3	50.3	47.8	37.3	48.9	38.6	49.9	30.3	43.5	47.1	44.3
		Europe	29.3	26.1	36.9	34.4	40.0	38.0	29.5	38.9	30.6	39.7	23.9	34.5	37.4	35.2
	Randomly assigned ^b	Europe + USA	41.4	39.7	45.6	44.5	47.3	46.6	41.6	47.3	42.1	48.1	38.4	44.5	45.9	44.9
		Europe	32.9	31.5	36.3	35.4	37.7	37.2	33.0	37.8	33.5	38.4	30.4	35.5	36.6	35.7
PO	Median ^a	Europe + USA	30.4	32.8	39.6	43.2	43.9	47.3	46.3	49.8	47.4	50.8	39.9	44.9	40.9	44.0
		Europe	24.0	25.9	31.4	34.3	34.8	37.6	36.8	39.6	37.7	40.4	31.6	35.6	32.4	34.9
	Randomly assigned ^b	Europe + USA	38.4	39.6	42.7	44.3	44.5	46.5	45.7	48.1	46.3	49.0	42.6	45.6	43.1	44.8
		Europe	30.5	31.4	34.0	35.3	35.4	37.1	36.4	38.4	36.9	39.2	33.9	36.3	34.3	35.7

Note: Abbreviations are provided in the Abbreviation Listing. Shaded cells indicate percent probabilities of PK-PD target attainment by MIC $\geq$ 90%.

a. The median free-drug plasma AUC:MIC ratio target associated with a 1-log₁₀ CFU reduction from baseline for *K. pneumoniae* was 64.1.

b. Free-drug plasma AUC:MIC ratio targets were randomly assigned based on an estimated log normal distribution of free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline. The distribution of free-drug plasma AUC:MIC ratio targets was truncated on the log scale such that randomly selected targets were all within 2 standard deviations of the mean value.

c. Based on data for *K. pneumoniae* isolates collected from centers in Europe and the USA combined and Europe alone during 2014 to 2018. The MIC distributions for each set of *K. pneumoniae* isolates evaluated are shown in Table 15.

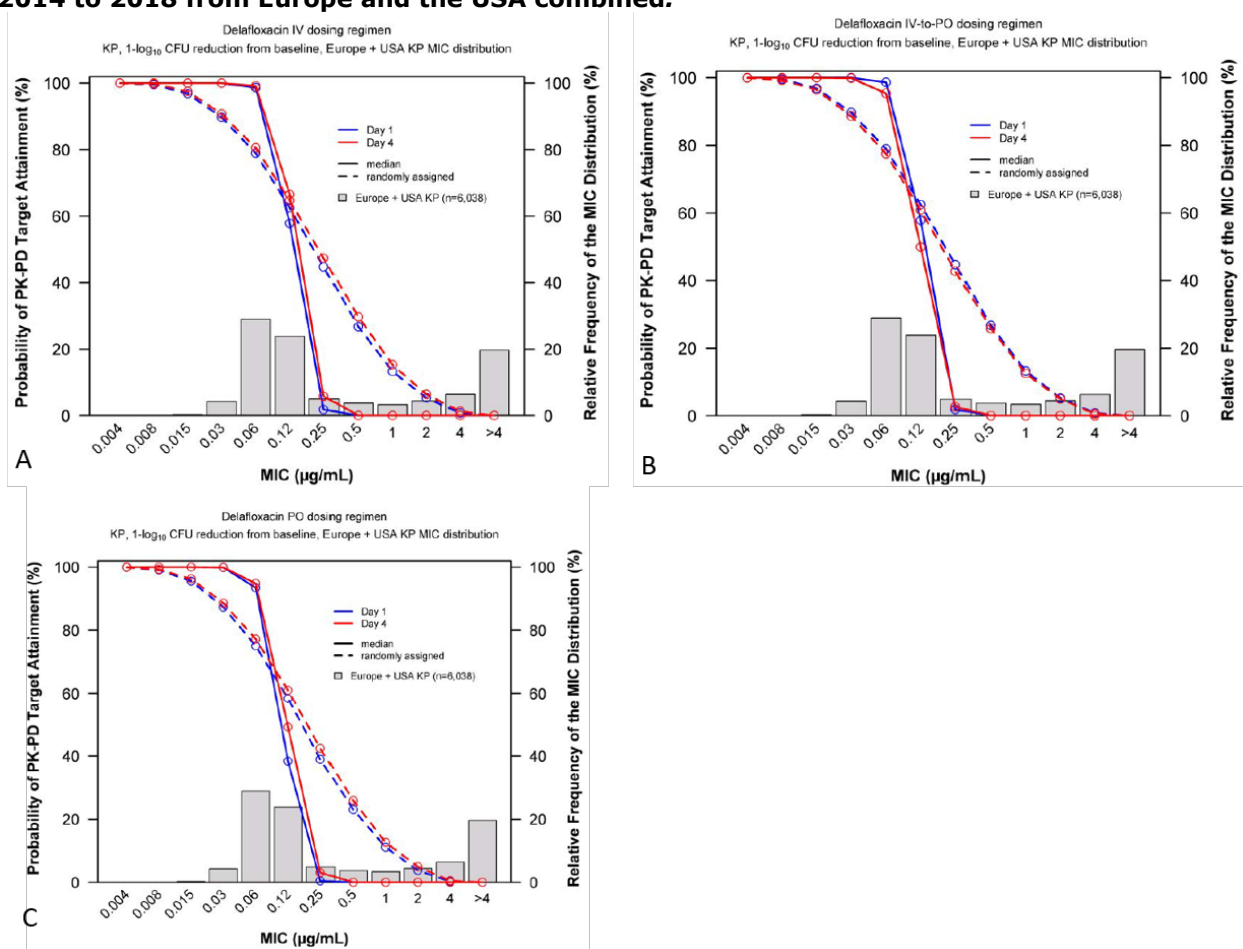
IV-to-PO

The % PTA by MIC on Days 1 and 4 for IV delafloxacin for *K. pneumoniae* associated with 1-log₁₀ kill was >90% for a MIC value of 0.06 µg/mL except for patients with normal renal function for whom on the PTA was 89.7% on Day 1 and 83.0% on Day 4. Results based on randomly assigned fAUC/MIC ratio targets showed that the MIC covered with PTAs >90 % was 2-fold lower than for the analyses using median assigned fAUC/MIC ratio targets. Full coverage (PTA >90%) was thus observed for a MIC value of 0.015 µg/mL while the PTAs for a MIC of 0.03 µg/mL ranged between 83.6% and 91.2% for the relevant populations (see 00593-2, Table 67).

The overall % PTAs by MIC on Days 1 and 4 based on the median and randomly assigned fAUC:MIC ratio targets for *K. pneumoniae* among simulated patients by renal function group or those resembling the clinical trial population after administration of the delafloxacin dosing regimens is shown in Table 44. The PTAs based on data for *K. pneumoniae* from EU and US surveillance studies range between 29.3% and 50.3% for the relevant populations only.

A graphical illustration of the % PTAs by MIC on Days 1 and 4 based on median and randomly assigned fAUC/MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline among simulated patient populations resembling the clinical trial population after administration of the delafloxacin IV dosing regimen, overlaid upon the MIC distribution for *K. pneumoniae* isolates from surveillance (EU and US) is shown in Figure 20 B.

Figure 20: Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on median and randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline for *K. pneumoniae* among simulated patients resembling the clinical trial population after administration of the delafloxacin (A) IV, (B) IV-to-PO, (C) PO dosing regimen, overlaid upon the MIC distribution for *K.pneumoniae* isolates collected during 2014 to 2018 from Europe and the USA combined.



PO

The % PTAs by MIC on Days 1 and 4 analyzed for *K. pneumoniae* and the PO dosing regimen are outlined in 00593-2, Table 69. The analyses are based on median assigned plasma fAUC/MIC ratio target for *K. pneumoniae* associated with 1-log₁₀ CFU reduction. PTA results for 1-log₁₀ reduction are >90% in total for a MIC value of 0.03 µg/mL in the relevant populations on Days 1 and 4. This was also true for a MIC value of 0.06 µg/mL with the exception of patients with normal renal function for whom PTAs of 78.6% and 82.3% were achieved on Day 1 and 4, respectively. The results based on randomly assigned plasma fAUC/MIC ratio target for *K. pneumoniae* associated with 1-log₁₀ CFU reduction show a total coverage (>90% PTA) for a MIC

of 0.015 µg/mL although the PTAs for a MIC of 0.03 µg/mL achieved also PTAs near to 90% ranging between 82.5% and 91.1%.

The overall % PTAs by MIC on Days 1 and 4 based on the median and randomly assigned fAUC:MIC ratio targets for *K. pneumoniae* among simulated patients by renal function group or those resembling the clinical trial population after administration of the delafloxacin dosing regimens is shown in Table 44. The PTAs based on data for *K. pneumoniae* from EU and US surveillance studies range between 24.0% and 49.8% for the relevant populations only.

A graphical illustration of the % PTAs by MIC on Days 1 and 4 based on median and randomly assigned fAUC/MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline among simulated patient populations resembling the clinical trial population after administration of the delafloxacin IV dosing regimen, overlaid upon the MIC distribution for *K. pneumoniae* isolates from surveillance (EU and US) is shown in Figure 20 C.

The MAH concluded that 62.5% of contemporary *K. pneumoniae* isolates would be covered by a susceptible breakpoint of 0.25 µg/mL. Furthermore, it was stated that a clinical success rate of 81.3% (13/16) was seen using the ModME-1TOC population (for more details refer to section 2.4.). However, the MAH conceded that the PTA analyses taking all dosing regimens into account revealed low coverage since PTAs >90% were achieved for a MIC value of 0.06 µg/mL, only. Looking at the analyses based on the randomly assigned fAUC/MIC ratio target % PTAs above the critical cut-off of 90 % were reached for a MIC of 0.015 µg/mL, only. The MAH further stated that proposed interpretative criteria of ≤0.25 / <0.25 µg/mL are supported by the data and that the target attainment data underestimate clinical outcomes since a clinical success rate of 81.3% was observed. Finally, the conclusion was drawn that due to lower percent probabilities of PK/PD target attainment for *K. pneumoniae* at relevant MIC values, supportive data should be considered.

P. aeruginosa

For *P. aeruginosa* only endpoints for fAUC/MIC ratio targets associated with 1-log₁₀ kill have been analysed since 2-log₁₀ kill could be observed in the animal *in vivo* models for a few strains only.

IV, IV-to-PO, and PO

The % PTAs by MIC on Days 1 and 4 analyzed for *P. aeruginosa* and the IV, IV-PO, and PO dosing regimen are outlined in 00593-2, Table 71/73/75. The analyses based on median assigned plasma fAUC/MIC ratio target for *P. aeruginosa* associated with 1-log₁₀ CFU reduction show the same tendency for all of the tested dosing regimens. PTA results for 1-log₁₀ reduction are near to or >90% for a MIC value of 0.25 µg/mL, and >99% was achieved for MICs up to and including 0.12 µg/mL regardless of renal status. However, for the IV-PO and PO dosing regimen PTAs between 83.9% and 92.4% were achieved for patients with normal renal function on Days 1 and 4. The results based on randomly assigned plasma fAUC/MIC ratio target for *K. pneumoniae* associated with 1-log₁₀ CFU reduction were basically the same taking one dilution factor lower (MIC of 0.125 µg/mL associated with PTAs near to or >90%) into account.

The overall % PTAs by MIC on Days 1 and 4 based on the median and randomly assigned fAUC:MIC ratio targets for *K. pneumoniae* among simulated patients by renal function group or those resembling the clinical trial population after administration of the delafloxacin dosing regimens is shown in Table 45. The PTAs based on data for *K. pneumoniae* from EU and US surveillance studies range between 34.3% and 59.7% for the IV dosing regimen, between 31.9% and 56.7% for the IV-PO dosing regimen, and between 29.9% and 55.0% for the PO regimen, only.

The graphical illustrations for the PTAs by MIC on Days 1 and 4 based on median and randomly assigned fAUC/MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline among simulated patient populations resembling the clinical trial population after administration of the delafloxacin IV, IV-PO, and PO

dosing regimen, overlaid upon the MIC distribution for *K. pneumoniae* isolates from surveillance (EU and US) are shown in Figure 20 A-C, respectively.

Table 45: Overall percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on median or randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline for *P. aeruginosa* among simulated patients by renal function group or those resembling the clinical trial population after administration of the delafloxacin dosing regimens.

Dosing regimen	Endpoints for free-drug plasma AUC:MIC ratio targets	Geographical region for <i>P. aeruginosa</i> isolates	Overall percent probabilities of PK-PD target attainment by MIC on Days 1 or 4 by simulated population ^c													
			Normal renal function		Mild renal impairment		Moderate renal impairment		Severe renal impairment		ESRD without dialysis		ESRD with dialysis		Clinical trial population	
			Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4	Day 1	Day 4
IV	Median ^a	Europe + USA	42.4	44.8	52.8	55.8	56.7	59.7	42.5	47.8	43.9	49.7	35.2	41.0	53.3	56.0
		Europe	41.3	43.7	51.6	54.5	55.4	58.4	41.5	46.7	42.9	48.6	34.2	39.9	52.1	54.7
	Randomly assigned ^b	Europe + USA	35.7	37.6	43.3	46.2	46.7	49.7	35.5	39.8	36.7	41.3	30.6	34.8	44.0	46.4
		Europe	34.5	36.4	42.0	44.7	45.3	48.2	34.3	38.6	35.5	40.0	29.5	33.7	42.6	45.0
IV - PO	Median ^a	Europe + USA	42.4	38.3	52.8	49.5	56.7	54.1	42.5	55.3	43.9	56.6	35.2	49.6	53.3	50.1
		Europe	41.3	37.2	51.6	48.4	55.4	52.8	41.5	54.0	42.9	55.2	34.2	48.4	52.1	48.9
	Randomly assigned ^b	Europe + USA	35.7	33.1	43.3	41.0	46.7	44.8	35.5	46.1	36.7	47.5	30.6	41.4	44.0	41.8
		Europe	34.5	31.9	42.0	39.7	45.3	43.4	34.3	44.7	35.5	46.0	29.5	40.1	42.6	40.5
PO	Median ^a	Europe + USA	35.5	38.1	45.4	49.1	49.7	53.6	52.4	56.4	53.4	57.6	45.6	51.2	46.7	49.8
		Europe	34.5	37.1	44.3	48.0	48.6	52.4	51.2	55.0	52.2	56.1	44.6	50.0	45.6	48.6
	Randomly assigned ^b	Europe + USA	31.0	32.9	37.9	40.7	40.8	44.6	43.3	47.5	44.2	48.9	38.2	42.9	38.7	41.6
		Europe	29.9	31.8	36.7	39.4	39.5	43.2	41.9	46.0	42.8	47.3	37.0	41.5	37.4	40.3

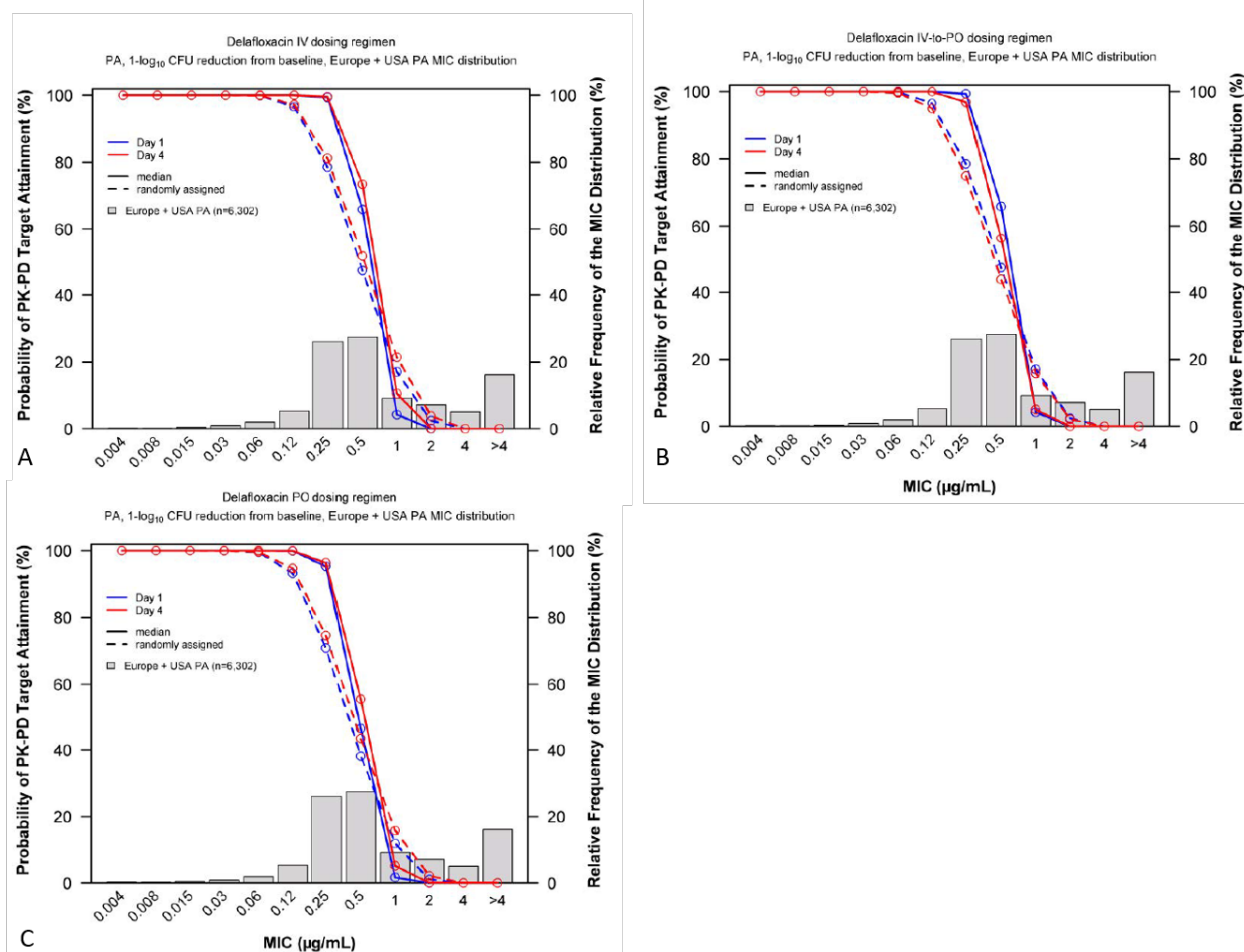
Note: Abbreviations are provided in the Abbreviation Listing. Shaded cells indicate percent probabilities of PK-PD target attainment by MIC $\geq 90\%$.

a. The median free-drug plasma AUC:MIC ratio target associated with a 1-log₁₀ CFU reduction from baseline for *P. aeruginosa* was 14.3.

b. Free-drug plasma AUC:MIC ratio targets were randomly assigned based on an estimated log normal distribution of free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline. The distribution of free-drug plasma AUC:MIC ratio targets was truncated on the log scale such that randomly selected targets were all within 2 standard deviations of the mean value.

c. Based on data for *P. aeruginosa* isolates collected from centers in Europe and the USA combined and Europe alone during 2014 to 2018. The MIC distributions for each set of *P. aeruginosa* isolates evaluated are shown in Table 16.

Figure 21: Percent probabilities of PK-PD target attainment by MIC on Days 1 and 4 based on median and randomly assigned free-drug plasma AUC:MIC ratio targets associated with a 1-log₁₀ CFU reduction from baseline for *P. aeruginosa* among simulated patients resembling the clinical trial population after administration of the delafloxacin IV, IV-PO, PO dosing regimen, overlaid upon the MIC distribution for *P. aeruginosa* isolates collected during 2014 to 2018 from Europe and the USA combined.



The MAH concluded that only 35% of contemporary *P. aeruginosa* isolates would be covered by a susceptible breakpoint of 0.25 µg/mL. Furthermore, it was stated that a clinical success rate of 91.7% (11/12) was seen using the ModME-1TOC population (for more details refer to section 2.4). However, the MAH conceded that the PTA analyses taking all dosing regimens into account revealed low coverage since PTAs >90% were achieved for a MIC value of 0.06 µg/mL, only. Looking at the analyses based on the randomly assigned fAUC/MIC ratio target % PTAs above the critical cut-off of 90 % were reached for a MIC of 0.015 µg/mL, only. The MAH further stated that proposed interpretative criteria of ≤0.25 / <0.25 µg/mL are supported by the data and that the target attainment data underestimate clinical outcomes since a clinical success rate of 81.3% was observed. As breakpoints or posology are no longer being pursued for *P. aeruginosa* and *K. pneumoniae*, no further analyses are considered warranted.

Breakpoints

Proposed clinical breakpoints (see Table 46) are based on delafloxacin MIC distribution in contemporary clinical isolates, available PD modelling data and both clinical and microbiological outcome by delafloxacin MIC.

Table 46: Proposed Susceptibility Interpretive Criteria for Delafloxacin

Organism	Minimum Inhibitory Concentrations (µg/mL)	
	Susceptible	Resistant
Gram-positives		
<i>Streptococcus pneumoniae</i>	≤ 1	> 1
<i>Staphylococcus aureus</i>	≤ 0.25	> 0.25
<i>Haemophilus influenzae</i>	≤ 0.12	> 0.12
<i>Moraxella catarrhalis</i>	≤ 0.12	> 0.12
<i>Klebsiella pneumoniae</i>	≤ 0.25	> 0.25
<i>Pseudomonas aeruginosa</i>	≤ 0.25	> 0.25

According to the minutes on Delafloxacin from April 21-22 2020 EUCAST Steering Committee the current breakpoint proposal for delafloxacin against pneumonia pathogens is as follows (Table 47):

Table 47 EUCAST Steering Committee the current breakpoint proposal for delafloxacin against pneumonia pathogens

Species	Proposed BP (mg/L)
<i>Streptococcus pneumoniae</i>	0.06
<i>Staphylococcus aureus</i>	0.016
<i>Haemophilus influenzae</i> *	0.004
<i>Moraxella catarrhalis</i>	IE
<i>Klebsiella pneumoniae</i>	–
<i>Pseudomonas aeruginosa</i>	–

* EUCAST does not consider *H. parainfluenzae* a community-acquired pneumonia pathogen

2.3.5. Discussion on clinical pharmacology

The penetration of delafloxacin in ELF and AM was investigated in study ML-3341-119. Following IV administration of 300 mg delafloxacin in healthy subjects at steady state, the achieved delafloxacin concentrations in ELF and AM were lower than in plasma. Relative to unbound plasma exposure, the exposure in ELF and AM as measured by AUC₀₋₁₂ were 64% and 51%, respectively, based on the median concentrations at each sample time.

PK plasma samples were collected from CAP patients in study ML-3341-306 at 3 time points on Day 3 of treatment (within 30 minutes before study drug administration and at 1.5 and 3 hours after start of the infusion). Delafloxacin exposure (AUC and C_{max}) was generally higher in CAP patients than in ABSSSI patients. These differences could be explained by differences in age, weight and renal function between these two patient groups. An updated population pharmacokinetic analysis was reported including data from CAP patients of study ML-3341-306. With the updated combined dataset, the model was slightly refined. Parameters of the final model were in a similar range compared to the previous analysis. A wider distribution of exposure is seen in CAP patients compared to ABSSSI patients. This is at least in part expected due to the higher number of older patients and more patients with impaired renal function included in study 306 compared to the previous studies. Overall, model performance appeared acceptable.

With regard to pharmacodynamics adequate data for delafloxacin have been submitted to evaluate PD in the context of this line extension although ELF data have not been taken into account for any PK/PD analysis. Given the lack of reliable pre-clinical ELF data for delafloxacin and uncertainties regarding the clinical relevance of ELF data, results of the Phase 3 study are considered sufficient to support the indication. PTA analyses based on plasma PK/PD targets are considered adequate and the chosen PDI for efficacy has been justified. The results of the PK/PD analyses might suggest that the initially proposed dosing regimens are far too low for CAP caused by *K. pneumoniae* or *P. aeruginosa*. However, the MAH has agreed that a posology or clinical breakpoints for *K. pneumoniae* or *P. aeruginosa* are no longer being pursued. Given that *K.*

pneumoniae and *P. aeruginosa* are considered less relevant in the indication CAP but are rather more associated with nosocomial pneumonia (HAP/VAP), no further investigations or analyses regarding these pathogens are warranted within this extension of indication variation for the second line indication CAP. Overall, it is agreed that PK/PD analyses support the proposed dosing regimens for CAP caused by *S. pneumoniae*, *S. aureus* and *H. influenzae*. The breakpoints set by EUCAST have been adopted for the SmPC.

2.3.6. Conclusions on clinical pharmacology

All issues raised have been adequately addressed.

2.4. Clinical efficacy

The indication applied for is:

Treatment of community acquired pneumoniae (CAP) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections.

Dosage recommendations are given for IV delafloxacin with the option to switch to oral delafloxacin and for sole oral treatment of CAP.

The clinical support for this indication mainly includes one pivotal Phase 3 study (ML-3341-306). In addition, results of a phase 2b study were provided as supportive data (M01-344).

2.4.1. Dose response study

Study **M01-344** was a double-blind, randomized, parallel-group, Phase II study to determine the safety and efficacy of a 7-day course of oral delafloxacin in subjects with CAP. Subjects were randomized to 1 of 3 dosing groups: 100, 200, or 400 mg of delafloxacin once daily for 7 days.

Study M01-344 was investigated between 18 March 2002 and 29 November 2002 in 58 sites.

The summary of study design is shown in the Table 48 below.

Table 48 Study design M01-344

Characteristic		M01-344
Phase		IIb
ITT Population		299 adults with CAP
Comparator Doses (N) and Duration of Therapy		NA
Delafloxacin Dose(s) (N) and Duration of Therapy		Oral, 100 mg QD (N = 104), 200 mg QD (N = 91), or 400 mg QD (N = 104) for 7 days
Time points	1st Assessment	Day 3
	EOT	Days 9 - 10 (48 - 72 hours after last dose)
	TOC	Days 16 - 21 (9 - 14 days after last dose)
Stratification Factors		N/A
Enrollment Limits at Randomization		N/A
Primary Endpoint		Clinical cure rate at TOC
Key Clinical Efficacy Secondary Endpoint		Clinical cure rate, radiographic resolution / improvement rate, bacteriological cure rate, pathogen eradication rate

The primary efficacy variable for statistical analysis was the clinical cure rate at TOC. The clinical cure rate was defined as the percent of subjects who had a clinical response of cure.

Seven to 21 days post-treatment was used as the TOC window for clinically evaluable and clinically and bacteriologically evaluable analyses. Seven days post-treatment and greater were used as the TOC window in the ITT analyses.

This study was not powered to test dose-response trends.

The numbers of subjects randomized into the 100-, 200-, and 400-mg groups were 110, 93, and 106 subjects. A total of 92, 83, and 97 subjects, respectively, were included in the per-protocol clinical analyses of efficacy; 68, 56, and 60 subjects, respectively, were included in the ITT bacteriological analyses; and 60, 50, and 50 subjects, respectively, were included in the clinical and bacteriological analyses.

Overall, there were a similar percentage of male (51%) and female subjects (49%), and the mean age of subjects was 45.3 years (range, 18 - 82 years). The mean weight of subjects was 75.4 kg (range, 40 - 165 kg).

As required by the protocol, all subjects had cough and produced sputum at pretreatment (59%, mucopurulent; 39%, purulent; and 3%, mucoid). Other frequently reported signs and symptoms at pretreatment for the 3 groups combined included rales / crackling (88%), dyspnea (72%), pleuritic chest pain (59%), and rhonchi / wheezing (57%).

Efficacy results

Table 49 Clinical and Bacteriological Cure Rates in Study M01-344

Efficacy Endpoints at TOC	Delafloxacin 100 mg QD	Delafloxacin 200 mg QD	Delafloxacin 400 mg QD	P value
Clinical cure rates (% [n/N])				
CE	90 (83/92)	95 (79/83)	93 (90/97)	0.509
ITT	80 (83/104)	87 (79/91)	87 (90/104)	0.182
Clin & bact evaluable	90 (54/60)	96 (48/50)	94 (47/50)	0.382
Bacteriological cure rates (% [n/N])				
Clin & bact evaluable	88 (53/60)	96 (48/50)	96 (48/50)	0.103
ITT	79 (54/68)	88 (49/56)	88 (53/60)	0.154

Abbreviations: CE = clinically evaluable; clin = clinically; bact = bacteriologically; ITT = intent-to-treat; QD = once daily; TOC = Test of Cure.

^a Cochran-Armitage trend test. Source: 2.7.6 Section 3.

The overall pathogen eradication rate was defined as the percentage of all evaluable pretreatment pathogens eradicated (regardless of number of subjects). Among subjects who were clinically and bacteriologically evaluable, no statistically significant dose-response trend was observed in overall pathogen eradication rates ($p = 0.150$). At TOC, 91% of pathogens in the 100-mg group, 95% of pathogens in the 200-mg group, and 97% of pathogens in the 400-mg group were eradicated.

Among clinically and bacteriologically evaluable subjects, no statistically significant dose-response trend was observed in overall pathogen eradication rates in subjects with 1 target pathogen ($p = 0.063$) or subjects with multiple target pathogens ($p = 0.758$). Among subjects with 1 target pathogen, 84% of pathogens in the 100-mg group, 97% of pathogens in the 200-mg group, and 95% of pathogens in the 400-mg group were eradicated at TOC. Among subjects with multiple target pathogens, 100% of pathogens

in the 100-mg group, 92% of pathogens in the 200-mg group, and 100% of pathogens in the 400-mg group were eradicated at TOC. No statistically significant pairwise differences were observed in overall pathogen eradication rates or eradication rates for any individual target pathogen among subjects with 1 or multiple target pathogens.

Table 50 Target Pathogen Eradication Rates at Test of Cure for Subjects with One Pathogen and Subjects with Multiple Pathogens (Clinically and Bacteriologically Evaluable Population) – M01-344

Target Pathogen ^a	Subjects With 1 Target Pathogen			Subjects With Multiple Target Pathogens		
	Delafloxacin 100 mg	Delafloxacin 200 mg	Delafloxacin 400 mg	Delafloxacin 100 mg	Delafloxacin 200 mg	Delafloxacin 400 mg
Overall rate	38/45 (84)	38/39 (97)	39/41 (95)	32/32 (100)	22/24 (92)	19/19 (100)
<i>Streptococcus pneumoniae</i>	7/9 (78)	8/9 (89)	10/10 (100)	7/7 (100)	4/5 (80)	6/6 (100)
<i>Moraxella catarrhalis</i>	3/3 (100)	3/3 (100)	0/0	3/3 (100)	1/1 (100)	0/0
<i>Haemophilus influenzae</i>	8/9 (89)	9/9 (100)	10/11 (91)	6/6 (100)	4/4 (100)	5/5 (100)
<i>Haemophilus parainfluenzae</i>	10/12 (83)	8/8 (100)	9/9 (100)	8/8 (100)	6/7 (86)	6/6 (100)
<i>Staphylococcus aureus</i>	4/4 (100)	4/4 (100)	0/0	4/4 (100)	3/3 (100)	2/2 (100)
<i>Legionella pneumophila</i>	0/0	0/0	1/1 (100)	0/0	1/1 (100)	0/0
<i>Mycoplasma pneumoniae</i>	5/6 (83)	5/5 (100)	8/8 (100)	2/2 (100)	1/1 (100)	0/0
<i>Chlamydia pneumoniae</i>	1/2 (50)	1/1 (100)	1/2 (50)	2/2 (100)	2/2 (100)	0/0

^aBacteriological assessment was made at Test of Cure (TOC) (7 to 21 days posttreatment) unless the subject was a persistent before TOC.

Source: M01-344 End-of-Text Table 14.2_5.3

2.4.2. Main study

Title of Study

Study **ML-3341-306** was a phase 3, multicenter, randomized, double-blind, comparator-controlled study to evaluate the safety and efficacy of intravenous to oral delafloxacin in adult subjects with community-acquired bacterial pneumonia.

Study ML-3341-306 was investigated between 14 December 2016 and 07 August 2018 in 88 sites (sites in Europe were located in Bulgaria (4), Georgia (5), Germany (2), Hungary (3), Latvia (4), Poland (3), Romania (6), Serbia (9), Slovenia (2), Spain (5) and Ukraine (11)).

The summary of study design is shown in Table 51 below.

Table 51 Study design ML-3341-306

Characteristic		ML-3341-306
Phase		III
ITT Population		859 adults with CAP
Comparator Doses (N) and Duration of Therapy		Moxifloxacin; IV, 400 mg QD (N = 428) with option to switch to oral 400 mg for 5 - 10 days ^a
Delafloxacin Dose(s) (N) and Duration of Therapy		IV, 300 mg BID (N = 431), with option to switch to oral, 450 mg BID, for 5 - 10 days
Time points	1st Assessment	ECR, 96 hours ($\pm$ 24 hours) after first dose of study drug
	EOT	Last dose + 1 calendar day
	TOC	5 - 10 days after last dose
Stratification Factors		– PORT Risk Class – Medical history of COPD or asthma – Prior single dose / regimen systemic antimicrobial use

Enrollment Limits at Randomization	NMT 25% of subjects: – PORT Risk Class II – Received 1 dose of a single, potentially effective, short-acting antimicrobial drug or drug regimen for treatment of the CAP under study within 24 hours of enrollment
Primary Endpoint	Clinical outcome at TOC (primary EP EMA)
Key Clinical Efficacy Secondary Endpoint	Clinical outcome at EOT; microbiological response, ECR with improvement in vital signs

Abbreviations: BID = twice daily (every 12 hours); CAP = community-acquired pneumonia; COPD = chronic obstructive pulmonary disease; ECR = Early Clinical Response; EOT = End of Treatment; ITT = intent-to-treat; NMT = not more than; PORT = Pneumonia Patient Outcomes Research Team; QD = once daily; TOC = Test of Cure.

^a At local Investigator discretion, subjects in the moxifloxacin arm with confirmed MRSA, in place of remaining moxifloxacin doses, could receive 600 mg of linezolid administered as a 1-hour IV infusion every 12 ($\pm$ 2) hours for the remaining doses.

Methods

Subjects who consented to the study had screening procedures performed. Subjects were evaluated for baseline characteristics that included chest radiography within 48 hours before the first dose of study drug, and medical history, physical examination, clinical laboratory tests, and blood cultures within 24 hours before the first dose of study drug. A pre-treatment respiratory specimen was collected for Gram stain and culture and, if positive for a respiratory pathogen, susceptibility testing. The following were obtained at Day 1: blood samples for procalcitonin and serology, nasopharyngeal and oropharyngeal swabs for culture and polymerase chain reaction (PCR) testing, and urine samples for antigen testing. Subjects could enrol and start study drug before any results of the baseline pathogen identification were known.

Respiratory and blood specimens were sent to local, regional, or specialty laboratories for culture, microorganism identification, and antibiotic sensitivity testing and were processed according to standard recognized methods. Two Gram stain slides of each sputum specimen were prepared by the local or regional laboratories. One slide was stained and read locally. Both slides, read and unread, were sent to the central laboratory to confirm results. An additional Gram stain slide could be retained by the local microbiology laboratory, if required by local regulations.

Study participants

Eligible patients in pivotal study ML-3341-306 were male or female $\geq$ 18 years of age with clinical and radiographic evidence of CABP and a PORT Risk Class of II, III, IV and V (pneumonia severity index score [PSI] $>$ 50).

Main inclusion criteria were as follows:

To be enrolled into the study, subjects met all the following criteria at Screening:

- Male and female subjects 18 years of age or older.
- Evidence of acute onset of CABP:

Subjects had to have at least 2 of the following clinical signs and symptoms (new or worsening):

- Cough
- Production of purulent sputum consistent with a bacterial infection
- Difficulty breathing (dyspnea)

- Chest pain due to pneumonia

AND

- Subjects had to also have at least 2 of the following findings:
 - Fever (oral temperature > 38°C or equivalent) within 24 hours before randomization
 - Hypothermia (oral temperature < 35°C or equivalent) within 24 hours before randomization
 - Tachycardia (> 100 beats per minute)
 - Tachypnea (elevated respiratory rate > 18 breaths per minute)

AND

- Subjects had to also have at least 1 of the following findings:
 - Hypoxemia (oxygen saturation < 90% or partial pressure of oxygen in arterial blood [PaO₂] < 60 mmHg) on room air or with subject's baseline (pre-CABP under study) supplemental oxygen flow rate
 - Clinical evidence of pulmonary consolidation and/or presence of pulmonary rales
 - An elevated white blood cell (WBC) count > 10,000/mm³ or 15% immature neutrophils (bands), regardless of total peripheral WBC count or leukopenia with WBC count < 4500/mm³
- Presence of lobar, multilobar, or patchy parenchymal infiltrate(s) consistent with acute bacterial pneumonia on a pulmonary imaging study (e.g., chest radiograph [CXR] [posteroanterior and lateral preferred; single view acceptable if conclusive] or computed tomography [CT] of thorax), as per local standard of care, within 48 hours before the first dose of study drug.
- PORT Risk Class II, III, IV, or V (PSI score > 50).⁹ Subjects could be initially prescreened if they had a CURB-65 score of 2 to 4. PORT Risk Class II was limited to no more than 25% of randomized subjects.
- Females of childbearing potential (including females < 2 years postmenopausal) had to have a negative pregnancy test before enrolment. Sexually active women and men with partners of childbearing potential had to agree to use an acceptable form of contraception, as determined by the Investigator (e.g., abstinence, oral contraceptives, double-barrier methods, hormonal injectable, transdermal, or implanted contraceptives, tubal ligation, or vasectomy) during participation in the study through FU (Day 28). During the study and through FU (Day 28), female partners of male subjects were also to use an additional reliable method of contraception, such as spermicide with male or female condoms; cervical sponge; intrauterine device; cervical cap or diaphragm; or oral, implantable, transdermal, or injectable contraceptives.

Main exclusion criteria were as follows:

- Medical history of significant hypersensitivity or allergic reaction to antibiotics of the quinolone or oxazolidinone class or study drug excipients in the judgment of the Investigator.
- Women who were pregnant or lactating.
- Any infection expected to require other systemic antibacterial agents in addition to study drug.
- Receipt of systemic antibiotic therapy in the 7 days before enrolment unless one or more of the following were documented:

- The subject received at least 48 hours of antibiotic therapy for CABP and the clinic notes documented treatment failure (i.e., not by subject history or pulmonary imaging alone) with new or worsening symptoms while on prestudy therapy, or identification of a respiratory pathogen that was resistant to a prestudy antibiotic that would be susceptible to study drug (delafloxacin or moxifloxacin) in subjects with new or worsening signs and symptoms of CABP.
- The subject received 1 dose of a single, potentially effective, short-acting antimicrobial drug or a short-acting antimicrobial drug regimen for treatment of the CABP under study within 24 hours of enrolment. (Note: 1 dose of a regimen was defined as the standard therapy for CABP at the study site.) Subjects who received prior antimicrobial drug under this criterion were limited to no more than 25% of total randomized subjects.
- Respiratory infection confirmed or suspected to be secondary to hospital-acquired or ventilator-associated pneumonia or that required treatment in an intensive-care setting (because they were hemodynamically unstable, and/or likely to need mechanical ventilation) at the time of informed consent.
- Intubated at the time of informed consent or clinical presentation with pneumonia that required invasive mechanical ventilation.
- Current or suspected diagnosis of:
 - Viral pneumonia or fungal pneumonia, including *Pneumocystis jirovecii* pneumonia
 - Aspiration pneumonia
 - Other noninfectious causes of pulmonary infiltrates (e.g., pulmonary embolism, hypersensitivity pneumonia, or congestive heart failure)
 - Primary or metastatic lung cancer
 - Cystic fibrosis
 - Active or suspected tuberculosis
 - Empyema (not including sterile parapneumonic effusions)
- Known anatomical or pathological bronchial obstruction, a history of bronchiectasis, or documented Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage 4 COPD, or a history of postobstructive pneumonia.
- Severely compromised immune system, for example:
 - Known absolute neutropenia (absolute neutrophil count < 500 cells/μL)
 - Known human immunodeficiency virus infection (HIV) with a CD4 count < 350 cells/μL within the last 4 months
 - Cancer chemotherapy or radiation in the last 3 months
 - Hematological malignancy
 - Bone marrow transplantation
 - Chronic steroid use (> 20 mg/day of prednisone or equivalent) before enrollment
- Known history of Child-Pugh Class B or C liver disease and/or presence or possible signs of significant hepatic disease or alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN).

- Severe renal disease, creatinine clearance (CrCl) ≤ 29 mL/min using Cockcroft- Gault formula, or need for hemodialysis or peritoneal dialysis.
- Uncorrected hypokalemia or known uncorrected hypomagnesemia at the time of enrollment. If treatment normalized the serum potassium or magnesium, confirmed by retest during the screening period, the subject could then be enrolled.
- Ongoing treatment for seizures or untreated history of seizures.
- History of peripheral neuropathy.
- History of tendon damage or disorders due to quinolone therapy.
- Known history of myasthenia gravis.
- History of prolonged QT syndrome or mean QT interval corrected with the Fridericia formula (QTcF) greater than 450 ms for males and 470 ms for females on screening summary electrocardioGram (ECG).
- Concomitant use of drugs known to prolong the QT interval, including class IA (e.g., quinidine, procainamide, disopyramide) or Class III (e.g., amiodarone, sotalol, bretylium, ibutilide) antiarrhythmics.

Subjects who met the entry criteria were randomly assigned in a 1:1 ratio to receive delafloxacin or moxifloxacin. Randomization was stratified by PORT Risk Class, medical history of chronic obstructive pulmonary disease (COPD) or asthma, and prior single dose/regimen systemic antimicrobial use. Enrolment was limited to no more than 25% of subjects who were PORT Risk Class II, and no more than 25% of subjects who received 1 dose of a single, potentially effective, short-acting antimicrobial drug or drug regimen for treatment of the CABP under study within 24 hours of enrolment.

Treatments

Subjects were randomized to receive either delafloxacin or moxifloxacin as follows:

- Delafloxacin 300 mg was administered as a 1-hour IV infusion BID (± 2 hours) for a minimum of 6 doses, with an option to switch to delafloxacin, 450 mg tablet, administered orally BID (± 2 hours) for the remaining doses.
- Moxifloxacin 400 mg was administered as a 1-hour IV infusion every 24 (± 2) hours for a minimum of 3 active doses, with an option to switch to moxifloxacin 400 mg (over-encapsulated tablet) administered orally every 24 (± 2) hours for the remaining doses.
- At local Investigator discretion, subjects in the moxifloxacin arm with confirmed MRSA, in place of remaining moxifloxacin doses, could receive 600 mg of linezolid administered as a 1-hour IV infusion every 12 (± 2) hours for the remaining doses.

The total duration of treatment (IV and oral) was from 5 days up to 10 days, as clinically indicated.

Allowed concomitant treatment

As with other quinolones, concurrent administration of oral delafloxacin and moxifloxacin with magnesium, aluminum, or calcium antacids, with metal cations such as iron or multivitamin preparations containing zinc, or with didanosine chewable or buffered tablets was to be avoided. The study drug was to be taken 4 hours before or 8 hours after taking these food supplements or medicinal products.

Systemic steroid use during the treatment period was allowed for a short duration (e.g., steroid burst). Inhaled steroids were allowed without any restriction.

Any concomitant medication deemed necessary for the welfare of the subject during the study could be given at the discretion of the Investigator. However, it was the responsibility of the Principal Investigator to ensure that details regarding the medication were recorded completely in the source records and in the eCRF.

Prohibited medications and restrictions

Concurrent systemic antimicrobial treatments were prohibited. Any subject who required additional (i.e., nonstudy) antibiotics for any of the following reasons was considered a treatment failure: lack of efficacy after at least 4 doses of study drug by the end of Day 3, antibiotic therapy required for more than 20 delafloxacin/delafloxacin placebo doses. Study drug was stopped for all treatment failures, and the subject completed EOT procedures.

Subjects could not take other investigational products during the study.

Refer to the moxifloxacin and/or linezolid SmPC or prescribing information for additional prohibited medications and restrictions, including but not limited to, contraindications for the concomitant use of MAO A or B inhibitor agents and adrenergic and serotonergic agents with linezolid.

Objectives

This study was designed with primary objectives intended to satisfy both FDA and EMA guidance recommendations. The primary and secondary objectives for submission to the EMA are as follows:

Primary objective

- To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at 5 to 10 days after the last dose of study drug (Test of Cure [TOC]) compared to IV to oral comparator study drug arm in the modified intent-to-treat (ModITT) and modified clinically evaluable (ModCE) populations.

Secondary objectives

- To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on ECR, defined as improvement at 96 hours ($\pm$ 24 hours) after the first dose of study drug compared to IV to oral moxifloxacin in the ModITT and ModCE populations.
- To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at TOC compared with IV to oral moxifloxacin in the modified microbiological intent to treat (ModMITT) and modified microbiologically evaluable (ModME) populations.
- To assess the microbiological response to delafloxacin in respiratory pathogens in the ModMITT and ModME populations.
- To assess the safety and tolerability of IV to oral delafloxacin in adult subjects with CABP in Safety population.
- To assess the all-cause mortality in adult subjects with CABP on Day 28 in ModITT.
- To assess delafloxacin PK in adult subjects with CABP in PK population.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint for the EMA was Clinical Outcome at Test of Cure (TOC) in the modified intent-to-treat (ModITT) and modified clinically evaluable (ModCE) population evaluated 5 to 10 days after last dose.

The Investigator defined the clinical outcome based on the assessment of the subject's signs and symptoms of infection at End of Treatment (EOT) and TOC. The Investigator's assessment of clinical response was categorized as success, failure, or indeterminate / missing, as follows:

Success: Resolution or near resolution of the symptoms of CAP present at study entry, and no use of additional antimicrobial therapy for the current infection, and no new symptoms associated with the current CAP infection.

Failure: Symptoms of CAP present at study entry had not resolved, new symptoms of CAP had developed, the subject died from pneumonia, or use of additional nonstudy antimicrobial therapy for treatment of the current CAP infection due to lack of efficacy. Failure outcome due to lack of efficacy was carried forward to later time points if the subject discontinued the trial for lack of efficacy. Subjects had to receive at least 4 doses of study drug by the end of Day 3 to be called a failure.

Indeterminate/Missing: A response could not be determined because an efficacy assessment was not completed at the visit or subject did not complete the planned course of study therapy for reasons other than lack of efficacy. Indeterminate/missing responses were considered failures for purposes of the analyses in the ModITT population and were excluded from analyses in the ModCE and modified microbiologically evaluable (ME) populations.

The primary endpoint was also analysed in several subgroups, including:

- Age categories (age < 65 years, ≥ 65 years, ≥ 75 years);
- Sex;
- Body mass index (BMI) categories (BMI < 30 kg/m² and ≥ 30 kg/m²);
- Baseline PORT Risk Class (III, IV, or V);
- Baseline CURB-65 score (0 - 5);
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, or not applicable);
- Region (Europe, Latin America, North America, and South Africa);
- Race (American Indian or Alaska Native, Asian, black or African American, native Hawaiian or other Pacific Islander, white, not applicable, or other);
- Prior systemic antibiotic use and the further subcategories of subjects with documented failure before randomization and subjects with a single dose / regimen of a prior antibiotic;
- Presence or absence of baseline bacteremia, multilobar pneumonia, diabetes, history of chronic obstructive pulmonary disease (COPD) or asthma, history of infectious hepatitis, renal impairment / disease based on creatinine clearance (CrCl), baseline nursing home status / hospitalization in last 90 days, and baseline Gram stain adequacy (yes or no) ;
- Baseline procalcitonin level (≥ 0.15 µg/L, ≥ 0.25 µg/L, ≥ 1 µg/L);
- Baseline pathogen;
- Monomicrobial versus polymicrobial infection;
- System Organ Class (SOC) of Cardiac Disease;

- SOC of Vascular Disease;
- SOC of Cardiac or Vascular Disease

These subgroup analyses were performed using the ModITT population. Analyses of clinical outcome at TOC by pathogen and monomicrobial / polymicrobial infections were performed for the ModMITT-1 and ModME-1TOC populations.

Secondary efficacy analysis

Secondary efficacy analyses for the EMA included ECR (the primary efficacy endpoint for the FDA), ECR with improvement of vital signs, clinical outcome at EOT, per subject microbiological response at TOC, per pathogen microbiological response at TOC, superinfections, new infections, postbaseline colonization, and Day 28 mortality.

Microbiological Efficacy Response Definitions

The following by-pathogen microbiological responses were defined for baseline pathogens:

Eradication: The respiratory and / or blood specimen at TOC showed the pathogen(s) present at enrollment was eradicated and there was no use of additional antimicrobial therapy for the current infection. Investigator-assessed clinical outcome was not considered a determining factor for this microbiological response definition.

Presumed Eradication: No respiratory and / or blood specimen was available at TOC with a clinical assessment of success.

Persistence: The respiratory and / or blood specimen collected at TOC was positive for the causative pathogen(s) present at enrollment. Persistence of the baseline pathogen at EOT was carried forward to TOC. Investigator-assessed clinical outcome was not considered a determining factor for this microbiological response definition.

Presumed Persistence: No respiratory or blood specimen was available for a case classified as clinical failure (including failures carried forward to TOC).

Indeterminate / Missing: No respiratory or blood specimen was available at TOC with a clinical assessment of indeterminate / missing, unless there was evidence of persistence of the baseline pathogen at EOT (carried forward to TOC).

Analysis Set Description

Modified Intent-to-Treat (ModITT) Population

The ModITT population comprised all randomized subjects who signed informed consent form (ICF), received at least 1 dose of study drug and were classified as PORT Risk Class III through V. Subjects were analyzed according to the treatment arm to which they were randomized.

Modified Microbiological Intent-to-Treat (ModMITT) Population

The ModMITT population comprised all subjects in the ModITT population who had a baseline bacterial pathogen identified, either by culture of a respiratory or blood specimen(s) or a nonculture method of detection (i.e., urinary antigen test, polymerase chain reaction (PCR), or serologic testing) that was known to cause CAP and against which the study drug had antibacterial activity.

The ModMITT was divided into the following 2 subgroups:

- ModMITT-1: baseline pathogens detected by all methods (i.e., including culture, serology, PCR, and urinary antigen). All microbiological analyses based on ModMITT-1 were displayed for all pathogens, as well as definite and probable pathogens (see ML-3341-306, Table 11).
- ModMITT-2: baseline pathogens isolated by culture only (blood or any respiratory source, including organisms cultured from nasopharyngeal and oropharyngeal swabs (*S. pneumoniae* or *M. pneumoniae*)). For *S. pneumoniae* from nasopharyngeal swabs, there had to be a concomitant *lytA* PCR value of ≥ 1000 gene copies per mL.

Modified Clinically Evaluable (ModCE) Populations

There were 3 ModCE populations, each based on the type of assessment (clinical response based on the clinical signs and symptoms of CAP and the Investigator-assessed clinical outcome) and timing of the assessment, including ECR (96 (± 24) hours), EOT (same day or up to 28 hours after the last dose of study drug), and TOC (5 - 10 days after the last dose of the study drug).

Subjects in the ModCE populations were analyzed according to the treatment they were assigned at randomization. Subjects had to receive at least 4 doses of study drug by the end of Day 3 to be classified as a clinical failure / nonresponder. Subjects who received both study therapies or received less than 4 doses were excluded from the ModCE populations. Subjects with indeterminate / missing values (including out of window assessments) were excluded from the ModCE populations.

Modified Microbiologically Evaluable (ModME) Populations

The ModME populations each consisted of all subjects in the ModMITT populations who also met the criteria for the corresponding ModCE (ModCE-ECR, ModCE-EOT, ModCE-TOC) population as follows:

- ModME-ECR: microbiologically evaluable at 96 (± 24) hours for ECR
- ModME-EOT: microbiologically evaluable at EOT for clinical outcome
- ModME-TOC: microbiologically evaluable at TOC for clinical outcome

Sample size

At least 860 adult male and female subjects (430 subjects per treatment group) were to be randomized. Used on a normal approximation approach (Miettinen and Nurminen's Likelihood Score Test), and assuming approximately 12% of patients would be in Pneumonia Patient Outcomes Research Team (PORT) Class II, and 80% of patients would be clinically evaluable, 755 subjects in the modified intent-to-treat (ModITT) population and 604 subjects in the modified clinically evaluable (ModCE) population would provide, respectively, a power of 91% and 83% to assess noninferiority of delafloxacin vs. moxifloxacin based on the following assumptions: (1) a rate of Clinical Outcome at the TOC visit for moxifloxacin and delafloxacin of 88% and 86%, respectively; (2) 1-sided type I error (α) of 0.025; (3) a noninferiority margin of 10%.

Randomisation

Patients who met all of the inclusion criteria and none of the exclusion criteria were randomly assigned to 1 of 2 treatment groups in a 1:1 ratio to receive either delafloxacin or moxifloxacin.

Randomization was stratified by PORT Risk Class, medical history of chronic obstructive pulmonary disease (COPD) or asthma, and prior single dose/regimen systemic antimicrobial use. Enrolment was limited to no more than 25% of subjects who were PORT Risk Class II, and no more than 25% of subjects who received

1 dose of a single, potentially effective, short-acting antimicrobial drug or drug regimen for treatment of the CABP under study within 24 hours of enrolment.

Blinding (masking)

Most involved parties in this study (subjects, Investigators, laboratories, contract research organizations (CROs), and Sponsor personnel) were blinded to the identity of study drug and randomization assignments until the study was formally unblinded. Unblinding occurred after all subjects had completed the study and after resolution of all data queries. Each site documented a blinding plan before the study started.

The pharmacist was not blinded; the pharmacist covered all IV infusion bags and tubing so that the identification of the study drug solution was not seen by the blinded study staff or study subjects. Certain clinical research staff were not blinded so that they could monitor the pharmacy, administer study drug (if applicable), and monitor study administration records; they did not reveal a subject's treatment assignment to study staff. The statistician who created the randomization code was not otherwise involved in the conduct of the study.

Statistical methods

Analysis sets

Analysis sets are described in Outcomes/Endpoints section above. The primary efficacy endpoint for the EMA, clinical outcome at TOC, was analyzed in the ModITT and ModCE-TOC populations. In these analyses, subjects with indeterminate/missing assessments were treated as failures (ModITT) or excluded (ModCE-TOC).

Primary analysis

The primary efficacy endpoint for the EMA was investigator-assessed Clinical Outcome at Test of Cure (TOC, 5 to 10 days after last dose), based on the assessment of the subject's signs and symptoms of infection at End of Treatment (EOT) and TOC. Levels of the endpoint were classified as success, failure, or indeterminate/missing.

Clinical outcome rate was defined as $\text{success} = \text{success} / (\text{success} + \text{failure})$. The null (H_0) and alternative (H_a) hypotheses to be tested in order to establish the non-inferiority of delafloxacin were:

$H_0: P_d - P_m \leq -0.10$

$H_a: P_d - P_m > -0.10$

The difference (delafloxacin – moxifloxacin) in response rate and the treatment comparison using the 2-sided 95% CI on the difference in response rate stratified by baseline PORT Risk Class, medical history of COPD or asthma, and prior receipt of systemic antimicrobials using the Miettinen-Nurminen test were presented. This analysis was performed using the ModITT and ModCE-TOC populations.

Secondary analyses

Secondary analyses for the EMA comprised the primary efficacy FDA endpoint ECR, ECR with improvement of vital signs, clinical outcome at EOT, per subject microbiological response at TOC, per pathogen microbiological response at TOC, superinfections, new infections, postbaseline colonization, and Day 28 mortality.

Sensitivity analysis

Sensitivity analyses of primary EMA endpoints were performed to investigate the robustness of the primary efficacy results (overall and for each region):

- The primary analysis without stratification using the Miettinen-Nurminen test.
- The primary analysis, without stratification, performed on the ModMITT and modified microbiologically evaluable at TOC for clinical outcome (ModME-TOC) analysis populations.
- to assess influence of age, the primary endpoint with stratification, age categories <65 years and ≥65 years were used as additional factor.

Multiplicity

If non-inferiority of delafloxacin was declared in the primary analysis, the secondary endpoints were to be tested for non-inferiority, with the possibility of establishing a switch to superiority in the ModITT, ModCE, ModMITT, and ModME analysis populations.

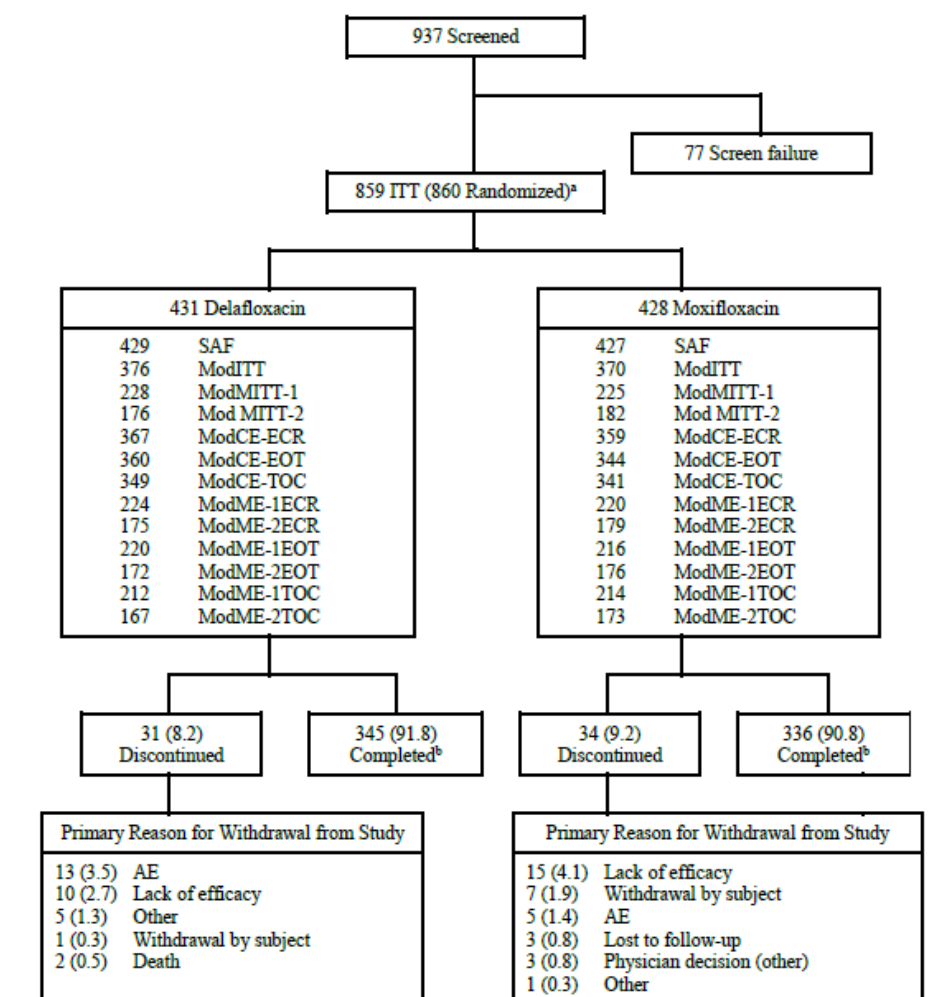
Subgroups analysis

Assessment homogeneity of efficacy across subgroups was undertaken by constructing two-sided 95% CIs for the treatment groups' differences in rates of the primary efficacy endpoint, similar to the primary efficacy analysis using the nonstratified Miettinen and Nurminen method. If there were large imbalances between treatment groups in these subgroups, further exploration was to be performed as an adjusted analysis of the primary outcome. Subgroup factors are detailed in the Outcomes/Endpoints section above.

Results

Participant flow

Disposition of subjects



Abbreviations: AE, adverse event; ModCE-EOT, modified clinically evaluable at EOT for clinical outcome; ModCE-TOC, modified clinically evaluable at TOC for clinical outcome; ECR, Early Clinical Response; EOT, End of Treatment; ITT, intent-to-treat; IXRS, interactive voice and web response system; ModME, modified microbiologically evaluable; ModMITT, modified microbiological intent-to-treat; SAF, safety; TOC, Test of Cure.

^a One subject mistakenly was randomized into the IXRS but did not provide informed consent; therefore, this subject was not included in the ITT population (refer to Section 10.1.2).

^b Completed the study through TOC.

Sources: End-of-Text Tables 14.1.1.1 and 14.1.2.1.3.

In the following table (Table 52) the subject disposition for the modified intent-to-treat (ModITT) population is displayed which is the relevant population for the primary analysis.

Table 52 Subject Disposition - ModITT Population

Disposition Category	Delafloxacin (N = 376)	Moxifloxacin (N = 370)	Total (N = 746)
Total number of subjects (n [%]) who:			
Completed study through TOC	345 (91.8)	336 (90.8)	681 (91.3)
Prematurely discontinued from study	31 (8.2)	34 (9.2)	65 (8.7)
Primary reasons for withdrawal from study, n (%)			
Lack of efficacy	10 (2.7)	15 (4.1)	25 (3.4)
AE	13 (3.5)	5 (1.4)	18 (2.4)
Withdrawal by subject	1 (0.3)	7 (1.9)	8 (1.1)
Other	5 (1.3)	1 (0.3)	6 (0.8)
Physician decision	0	3 (0.8)	3 (0.4)
Noncompliance with study drug	0	0	0
Randomized but never dosed	0	0	0
Other	0	3 (0.8)	3 (0.4)
Lost to follow-up	0	3 (0.8)	3 (0.4)
Death	2 (0.5)	0	2 (0.3)
Total number of subjects (n [%]) who:			
Completed study drug	351 (93.4)	345 (93.2)	696 (93.3)
Completed at least 10 doses of study drug/placebo	367 (97.6)	357 (96.5)	724 (97.1)
Prematurely discontinued from study drug	25 (6.6)	25 (6.8)	50 (6.7)
Primary reasons for withdrawal from study drug, n (%)			
Lack of efficacy	10 (2.7)	13 (3.5)	23 (3.1)
Lost to follow-up	0	1 (0.3)	1 (0.1)
Physician decision	0	3 (0.8)	3 (0.4)
Noncompliance with study drug	0	0	0
Randomized but never dosed	0	0	0
Other	0	3 (0.8)	3 (0.4)
Withdrawal by subject	1 (0.3)	3 (0.8)	4 (0.5)
AE	12 (3.2)	5 (1.4)	17 (2.3)
Death	1 (0.3)	0	1 (0.1)
Other	1 (0.3)	0	1 (0.1)

Abbreviations: AE, adverse event; ModITT, modified intent-to-treat; TOC, Test of Cure.

Source: [End-of-Text Table 14.1.2.1.3.](#)

Recruitment

A total of 88 sites were opened for enrolment, of which 86 randomized at least 1 subject. The majority of subjects was recruited from 54 sites in Europe. In addition, sites were located in Russia, North-America, South-America and Africa. The study was performed between 14 December 2016 and 07 August 2018. A total of 860 subjects were randomized (see also above).

Conduct of the study

Protocol amendments

There were 3 amendments to the original study protocol (dated 03 September 2015): Amendment 1 was dated 15 December 2015, Amendment 2 was dated 29 March 2016, and Amendment 3 was dated 04 December 2017. The amendments went into effect at each clinical site after approval by the IEC or IRB. The protocol and amendments were provided by the MAH.

Significant protocol deviations

In the following table (Table 53) the number of patients with significant protocol deviations in the ModITT population are outlined.

Table 53 Subjects With Significant Protocol Deviations (ModITT Population)

Deviation	n (%) of Subjects With Significant Protocol Deviations ^a		
	Delafloxacin (N = 376)	Moxifloxacin (N = 370)	Total (N = 746)
Subjects (%) with 1 or more significant protocol deviation	19 (5.1)	25 (6.8)	44 (5.9)
Inclusion/exclusion criteria deviation	17 (4.5)	19 (5.1)	36 (4.8)
Dosing error	0	2 (0.5)	2 (0.3)
Randomization (including stratification) error	0	0	0
Procedural error	2 (0.5)	5 (1.4)	7 (0.9)
Administration of prohibited concomitant medication	0	1 (0.3)	1 (0.1)

Abbreviation: ModITT, modified intent-to-treat.

^a A significant protocol deviation was defined as nonadherence to the protocol that resulted in a significant additional risk to the subject when the subject, Principal Investigator, or subinvestigator failed to adhere to significant protocol requirements.

Source: [End-of-Text Table 14.1.3.2](#).

The primary inclusion or exclusion deviation applied to Exclusion Criterion 12; per this criterion, subjects were not to have uncorrected hypokalemia, which was strictly defined as any result outside of the normal laboratory reference range based on local laboratory testing, whether or not deemed clinically significant by the Investigator. However, 13 of 17 subjects in the delafloxacin group and 14 of 19 subjects in the moxifloxacin group had either low levels of potassium, as determined by the local laboratory, or the test was not performed by the local laboratory or results not received, prior to randomization.

Of the 13 subjects with a hypokalemia (Exclusion Criterion 12) deviation in the delafloxacin group, 5 had potassium levels that were not available prior to randomization, but once obtained (locally or centrally), levels were within the reference range; and for the remaining subjects where local levels were reported, 4 had screening potassium result from the central laboratory that was within the reference range, 1 was missing a screening potassium result from the central laboratory, and 3 had central laboratory screening potassium levels ranging from 2.8 to 3.3 (reference range, 3.4-5.4 mmol/L).

Of the 14 subjects with an Exclusion Criterion 12 deviation in the moxifloxacin group, 3 had potassium levels that were not available prior to randomization, but once obtained (locally or centrally), levels were within the reference range; and for the remaining subjects where local levels were reported, 4 had a screening potassium result from the central laboratory that was within the reference range, 1 was missing a screening

potassium result from the central laboratory, and 6 had central laboratory screening potassium levels ranging from 2.6 to 3.3 (reference range, 3.4-5.4 mmol/L).

Days between time points

For most subjects in the ModITT population, the number of days between EOT and TOC ranged from 5 to 8 (see Table 54). In the delafloxacin and moxifloxacin groups, 2 and 5 subjects, respectively, had > 10 days between visits.

Table 54 Days Between Time Points (ModITT Population)

Time Between Time Points (days)	Delafloxacin (N = 376)	Moxifloxacin (N = 370)	Total (N = 746)
EOT and TOC			
n ^a	348	337	685
0 to 4	32	45	77
5 to 8	282	260	542
9 or 10	32	27	59
> 10	2	5	7

Abbreviations: EOT, End of Treatment; ModITT, modified intent-to-treat; TOC, Test of Cure.

^a Subjects with both EOT and TOC.

Source: End-of-Text Table 14.1.2.2.2.

Baseline data

Table 55 provides information about demographics and other baseline characteristics.

Table 55 Subject Demographics and Baseline Characteristics (ModITT Population)
—ML-3341-306

Characteristic	Delafloxacin (N = 376)	Moxifloxacin (N = 370)	Total (N = 746)
Age, years			
Mean (SD)	62.3 (15.44)	60.7 (16.41)	61.5 (15.94)
Median	65.0	62.0	64.0
Min, max	18, 89	18, 93	18, 93
Age category, n (%)			
< 65 years	184 (48.9)	202 (54.6)	386 (51.7)
≥ 65 years	192 (51.1)	168 (45.4)	360 (48.3)
≥ 75 years	83 (22.1)	95 (25.7)	178 (23.9)
Sex, n (%)			
Male	226 (60.1)	225 (60.8)	451 (60.5)
Female	150 (39.9)	145 (39.2)	295 (39.5)
Race, n (%)			
White	347 (92.3)	336 (90.8)	683 (91.6)
Black or African American	19 (5.1)	28 (7.6)	47 (6.3)
Asian	4 (1.1)	5 (1.4)	9 (1.2)
American Indian or Alaska Native	4 (1.1)	0	4 (0.5)
Other	2 (0.5)	1 (0.3)	3 (0.4)
Ethnicity, n (%)			
Hispanic or Latino	31 (8.2)	19 (5.1)	50 (6.7)
Not Hispanic or Latino	345 (91.8)	351 (94.9)	696 (93.3)
Region, n (%) ^d			
Europe	321 (85.4)	316 (85.4)	637 (85.4)
South Africa	26 (6.9)	35 (9.5)	61 (8.2)

Latin America	28 (7.4)	14 (3.8)	42 (5.6)
North America	1 (0.3)	5 (1.4)	6 (0.8)
Weight, kg			
Mean (SD)	76.48 (17.468)	77.39 (16.770)	76.93 (17.120)
Median	74.55	76.55	75.00
Min, max	39.2, 160.0	33.5, 136.0	33.5, 160.0
BMI, kg/m ²			
Mean (SD)	26.88 (5.629)	27.05 (5.589)	26.96 (5.606)
Median	26.21	25.97	26.05
Min, max	14.4, 50.8	12.6, 48.2	12.6, 50.8
BMI category, n (%)			
< 30 kg/m ²	282 (75.0)	271 (73.2)	553 (74.1)
≥ 30 kg/m ²	94 (25.0)	99 (26.8)	193 (25.9)
NIH BMI category, kg/m ²			
≤ 18.4 (underweight)	10 (2.7)	7 (1.9)	17 (2.3)
18.5 to 24.9 (normal weight)	140 (37.2)	139 (37.6)	279 (37.4)
25 to 29.9 (overweight)	132 (35.1)	124 (33.5)	256 (34.3)
≥ 30 (obese)	94 (25.0)	100 (27.0)	194 (26.0)
Diabetes, n (%)			
Yes	63 (16.8)	57 (15.4)	120 (16.1)
No	313 (83.2)	313 (84.6)	626 (83.9)
Renal impairment category, n (%) ^U			
Severe (CrCl < 30 mL/min)	5 (1.3)	7 (1.9)	12 (1.6)
Moderate (CrCl 30 to < 60 mL/min)	80 (21.3)	75 (20.3)	155 (20.8)
Mild (CrCl 60 to < 90 mL/min)	122 (32.4)	121 (32.7)	243 (32.6)
Normal (CrCl ≥ 90 mL/min)	161 (42.8)	158 (42.7)	319 (42.8)
Missing	8 (2.1)	9 (2.4)	17 (2.3)
CURB-65 score, n (%)			
0	38 (10.1)	44 (11.9)	82 (11.0)
1	167 (44.4)	167 (45.1)	334 (44.8)
2	135 (35.9)	125 (33.8)	260 (34.9)
3	25 (6.6)	25 (6.8)	50 (6.7)
4	3 (0.8)	3 (0.8)	6 (0.8)
5	0	0	0
Missing	8 (2.1)	6 (1.6)	14 (1.9)
CURB-65 score category, n (%)			
0 - 1	205 (54.5)	211 (57.0)	416 (55.8)
2	135 (35.9)	125 (33.8)	260 (34.9)
3 - 5	28 (7.4)	28 (7.6)	56 (7.5)
Missing	8 (2.1)	6 (1.6)	14 (1.9)
PORT Risk class, n (%)			
III	258 (68.6)	259 (70.0)	517 (69.3)
IV	114 (30.3)	103 (27.8)	217 (29.1)
V	4 (1.1)	8 (2.2)	12 (1.6)
PORT Risk score			
Mean (SD)	87.9 (13.61)	88.3	88.1 (14.73)
Median	84.5	84.0	84.0
Min, max	71, 146	71, 161	71, 161
Baseline Bacteremia, n (%)			
Yes	5 (1.3)	8 (2.2)	13 (1.7)
No	371 (98.7)	362 (97.8)	733 (98.3)
Baseline Procalcitonin, n (%)			
≥ 0.15 µg/L	167 (44.4)	152 (41.1)	319 (42.8)
≥ 0.25 µg/L	125 (33.2)	120 (32.4)	245 (32.8)
≥ 1 µg/L	72 (19.1)	73 (19.7)	145 (19.4)
Baseline Adequate Gram stain, n (%) ^d			
Yes	244 (64.9)	263 (71.1)	507 (68.0)
No	132 (35.1)	107 (28.9)	239 (32.0)
History of Hepatitis B or C, n (%) ^e			
Yes	21 (5.6)	18 (4.9)	39 (5.2)
No	355 (94.4)	352 (95.1)	707 (94.8)

Abbreviations: BMI = body mass index; BSA = body surface area; CrCl = creatinine clearance; CRF = case report form; CURB-

65 = scoring system based on confusion, urea, respiratory rate, blood pressure, age 65 or older; ITT = intent-to-treat; Max = maximum; Min = minimum; NIH = National Institutes of Health; PORT = Patient Outcomes Research Team; SD = standard deviation.

^a Europe comprises Bulgaria, Georgia, Germany, Hungary, Latvia, Poland, Romania, Russia, Serbia, Spain, Slovenia, and Ukraine. North America comprises the United States. Latin America comprises Argentina, Columbia, Peru, and Dominican Republic.

^b Creatinine clearance was based on the Cockcroft-Gault formula.

^c Creatinine clearance was calculated using the Cockcroft-Gault formula corrected for body surface area.

^d Adequate Gram stain was defined as < 10 squamous epithelial cells and/or > 25 polymorphonuclear neutrophils.

^e Hepatitis history was based upon subject data collected from the medical history page of the CRF.

Source: ML-3341-306 End-of-Text Table 14.1.4.1.3.

Antibiotic status at baseline

Table 56 provides information about antibiotic status at baseline.

Table 56 Antibiotic Status at Baseline (ModITT Analysis Set)

	Delafloxacin (N = 376) n (%)	Moxifloxacin (N = 370) n (%)	Total (N = 746) n (%)
Systemic antibiotic therapy in the 7 days prior to enrolment			
Yes	89 (23.7)	88 (23.8)	177 (23.7)
No	287 (76.3)	282 (76.2)	569 (76.3)
Reasons for receiving systemic antibiotic therapy			
Antibiotic therapy with documented treatment failure ^a new or worsening symptoms while on prestudy therapy	16 (4.3)	16 (4.3)	32 (4.3)
Identification of a respiratory pathogen that is resistant to prestudy antibiotic and susceptible to study drug with new or worsening signs or symptoms	0	0	0
Only one dose of a single, potentially effective short acting antimicrobial drug or a short acting antimicrobial drug regimen for treatment of CAP under study within 24 hours of enrollment	73 (19.4)	72 (19.5)	145 (19.4)

^a Subject received at least 48 hours of antibiotic therapy for CAP and the clinic notes document treatment failure. Source: ML-3341-306 End-of-Text Table 14.1.4.2.2.

Concomitant antibacterial medications

A number of subjects in the ModITT population received at least 1 concomitant antibacterial medication from start of study drug through EOT (3.9% (29 subjects)) or from EOT through follow-up (FU) (7.9% (59 subjects)). The treatment groups were similar with regard to the percentage of subjects who received concomitant antibacterial medications at both time points.

Reasons for receipt of concomitant antibiotics included treatment of the primary study condition (CAP) due to lack of therapeutic efficacy, prophylactic/nontherapeutic use, adverse event, and other. A similar number of subjects in each treatment group received a systemic antibiotic that potentially confounded the assessment of clinical response and therefore were excluded from the ModCE-TOC population (2 in the delafloxacin group and 2 in the moxifloxacin group).

Study drug exposure

In Study ML-3341-306, the mean duration of exposure for the delafloxacin and moxifloxacin groups was similar (8.4 days and 8.5 days, respectively). For both treatment groups, the median total exposure was 9.0 days, with 6.0 days for IV exposure and 2.0 days for oral exposure. For most subjects (59.2% in the delafloxacin group and 62.3% in the moxifloxacin group), exposure was > 8 to 10 days. The median number of IV doses was 12.0 in both treatment groups.

Table 57 provides information about study drug exposure:

Table 57 Study Drug Exposure (Safety Population) – ML-3341-306

Variable	Delafloxacin (N = 429)	Moxifloxacin (N = 427)
Duration of exposure, days		
mean (SD)	8.4 (1.85)	8.5 (1.93)
Median	9.0	9.0
Min, Max	1, 10	0.5, 10
Duration of oral exposure, days		
mean (SD)	2.1 (2.12)	2.2 (2.22)
Median	2.0	2.0
Min, Max	0, 7	0, 7
Duration of IV exposure, days		
mean (SD)	6.3 (2.33)	6.3 (2.32)
Median	6.0	6.0
Min, Max	1, 10	0.5, 10
No. of IV doses		
mean (SD)	12.6 (4.67)	12.6 (4.64)
Median	12.0	12.0
Min, Max	2, 20	1, 20
Duration of exposure, n (%)		
0 days	0	0
0.5 to 4 days	12 (2.8)	15 (3.5)
> 4 to 8 days	163 (38.0)	146 (34.2)
> 8 to 10 days	254 (59.2)	266 (62.3)

Abbreviations: IV = intravenous; Max = maximum; Min = minimum; SD = standard deviation.

Note: One subject in the moxifloxacin group received both delafloxacin (instead of delafloxacin placebo) and moxifloxacin on a single occasion (a significant protocol deviation). This subject is summarized in the moxifloxacin group. No AEs were reported for the subject.

Source: ML-3341-306 End-of-Text Table 14.1.8.1.3.

Baseline pathogens

Of 746 subjects in the ModITT population, 453 subjects (60.7%) had at least 1 pathogen detected at baseline by any method (including culture, serology, PCR, and urinary antigen), comprising the ModMITT-1 population. For the 453 subjects, blood cultures identified *S. pneumoniae* in 10 subjects (2.2%) and *S. aureus*, *K. pneumoniae*, and *E. coli* in 1 subject (0.2%) each.

In Table 58, pathogens identified at baseline in >1% of subjects are provided.

Table 58 Pathogens Identified at Baseline in > 1% of Subjects (ModMITT-1 Population) – ML-3341-306

Baseline Pathogens	No. (%) of Subjects		
	Delafloxacin (N = 228)	Moxifloxacin (N = 225)	Total (N = 453)
<i>Streptococcus pneumoniae</i>	105 (46.1)	91 (40.4)	196 (43.3)
PSSP	44 (19.3)	47 (20.9)	91 (20.1)
PISP	18 (7.9)	17 (7.6)	35 (7.7)
PRSP	1 (0.4)	1 (0.4)	2 (0.4)
MDRSP	1 (0.4)	1 (0.4)	2 (0.4)
MRSP	16 (7.0)	17 (7.6)	33 (7.3)
<i>Haemophilus parainfluenzae</i>	28 (12.3)	32 (14.2)	60 (13.2)
<i>Mycoplasma pneumoniae</i>	32 (14.0)	25 (11.1)	57 (12.6)
<i>Legionella pneumophila</i>	26 (11.4)	27 (12.0)	53 (11.7)
<i>Haemophilus influenzae</i>	24 (10.5)	30 (13.3)	54 (11.9)
<i>Staphylococcus aureus</i>	26 (11.4)	27 (12.0)	53 (11.7)

MRSA	1 (0.4)	0	1 (0.2)
MSSA	25 (11.0)	27 (12.0)	52 (11.5)
<i>Chlamydia pneumoniae</i>	21 (9.2)	14 (6.2)	35 (7.7)
<i>Klebsiella pneumoniae</i>	16 (7.0)	14 (6.2)	30 (6.6)
<i>Escherichia coli</i>	14 (6.1)	11 (4.9)	25 (5.5)
<i>Pseudomonas aeruginosa</i>	13 (5.7)	11 (4.9)	24 (5.3)
<i>Klebsiella oxytoca</i>	6 (2.6)	4 (1.8)	10 (2.2)
<i>Moraxella catarrhalis</i>	6 (2.6)	5 (2.2)	11 (2.4)
<i>Acinetobacter calcoaceticus-baumannii</i> complex	3 (1.3)	4 (1.8)	7 (1.5)
<i>Enterobacter cloacae</i> complex	4 (1.8)	10 (4.4)	14 (3.1)

Abbreviations: MDRSP = multiple drug-resistant *Streptococcus pneumoniae*; ModMITT = modified microbiological intent-to-treat; MRSA = methicillin-resistant *Staphylococcus aureus*; MRSP = macrolide-resistant *Streptococcus pneumoniae*; MSSA = methicillin-susceptible *Staphylococcus aureus*; PISP = penicillin-intermediate *Streptococcus pneumoniae*; PRSP = penicillin-resistant *Streptococcus pneumoniae*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*.
Notes: Pathogens were identified by culture and/or nonculture methods. Organisms isolated by culture were reviewed on a case-by-case basis by the Sponsor to determine eligibility as a causative CAP pathogen. Pathogens identified by nonculture methods were determined proGrammatically. For each subject, if a pathogen was identified by more than 1 method, the subject was counted only once. Subjects with both MRSA and MSSA, or any combination of PSSP, PISP, or PRSP were counted once in the overall category for that organism.
Source: ML-3341-306 End-of-Text Table 14.1.5.4.3.

Numbers analysed

The analysis sets in the pivotal trial for EMA and FDA EPs are presented in Table 59.

Table 59 Analysis Sets – Phase III study ML-3341-306

	Delafloxacin (N=431)	Moxifloxacin (N=428)	Total (N=859)
Analysis Sets, n/N (%)			
ITT	431 (100.0)	428 (100.0)	859 (100.0)
Safety	429 (99.5)	427 (99.8)	856 (99.7)
FK	313 (72.6)	-	313 (36.4)
MITT-1	257 (59.6)	263 (61.4)	520 (60.5)
MITT-2	199 (46.2)	205 (47.9)	404 (47.0)
CE at 96 Hours (± 24 hours) (ECR)	418 (97.0)	414 (96.7)	832 (96.9)
CE at End of Treatment(EOT)	411 (95.4)	398 (93.0)	809 (94.2)
CE at Test of Cure(TOC)	397 (92.1)	394 (92.1)	791 (92.1)
ME-1 at ECR	253 (58.7)	256 (59.8)	509 (59.3)
ME-2 at ECR	198 (45.9)	200 (46.7)	398 (46.3)
ME-1 at EOT	249 (57.8)	251 (58.6)	500 (58.2)
ME-2 at EOT	195 (45.2)	196 (45.8)	391 (45.5)
ME-1 at TOC	240 (55.7)	248 (57.9)	488 (56.8)
ME-2 at TOC	190 (44.1)	193 (45.1)	383 (44.6)
Modified Analysis Sets			
ModITT, N1/N (%)	376 (87.2)	370 (86.4)	746 (86.8)
ModMITT-1, n/N1 (%)	228 (60.6)	225 (60.8)	453 (60.7)
ModMITT-2, n/N1 (%)	176 (46.8)	182 (49.2)	358 (48.0)
ModCE ECR, n/N1 (%)	367 (97.6)	359 (97.0)	726 (97.3)
ModCE at EOT, n/N1 (%)	360 (95.7)	344 (93.0)	704 (94.4)
ModCE at TOC, n/N1 (%)	349 (92.8)	341 (92.2)	690 (92.5)
ModME-1 ECR, n/N1 (%)	224 (59.6)	220 (59.5)	444 (59.5)
ModME-2 ECR, n/N1 (%)	175 (46.5)	179 (48.4)	354 (47.5)
ModME-1 at EOT, n/N1 (%)	220 (58.5)	216 (58.4)	436 (58.4)
ModME-2 at EOT, n/N1 (%)	172 (45.7)	176 (47.6)	348 (46.6)
ModME-1 at TOC, n/N1 (%)	212 (56.4)	214 (57.8)	426 (57.1)
ModME-2 at TOC, n/N1 (%)	167 (44.4)	173 (46.8)	340 (45.6)

Source: Listing 16.2.1.4 Source code: ...Tables\Production\180_t_ana.sas (16JAN2019 14:09)

Outcomes and estimation

The EMA primary EP was to assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CAP at TOC compared to IV to oral moxifloxacin in the ModITT and ModCE populations.

Clinical outcome at TOC (EMA primary efficacy EP)

In the ModITT population the success rate at TOC was 91.0% in the delafloxacin group and 89.2% in the moxifloxacin group. The lower limit of the two-sided 95% confidence interval was above the pre-specified margin -10% (95% CI -3.2, 5.5).

Table 60 Clinical Outcome at Test of Cure (ModITT Population) – ML-3341-306

Clinical Outcome^a	Delafloxacin (N = 376)	Moxifloxacin (N = 370)
Success, n/N (%)	342 (91.0)	330 (89.2)
Failure category, n/N (%)	34 (9.0)	40 (10.8)
Failure, n/N (%)	18 (4.8)	21 (5.7)
Indeterminate/missing, n/N (%)	16 (4.3)	19 (5.1)
Difference^a (95% CI)	1.1 (-3.2, 5.5)	
Reasons for failure, n/N (%)		
Symptoms of CAP present at study entry have not resolved	3 (0.8)	2 (0.5)
New symptoms of CAP have developed	1 (0.3)	1 (0.3)
Death from pneumonia	0	1 (0.3)
Use of additional nonstudy antimicrobial therapy for treatment of the current CAP infection due to lack of efficacy	4 (1.1)	5 (1.4)
Failure carried forward from EOT	13 (3.5)	15 (4.1)
Reasons for indeterminate / missing, n/N (%)		
Efficacy assessment was not completed (including lost to follow-up)	3 (0.8)	2 (0.5)
Planned course of therapy was not completed for reasons other than lack of efficacy	0	0
Other	0	0
Missing	13 (3.5)	17 (4.6)

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; EOT = End of Treatment; ModITT = modified intent-to-treat.

^a Difference = difference in cure/success rates (delafloxacin treatment group minus moxifloxacin treatment group). Confidence intervals were calculated using the Miettinen-Nurminen method stratified by PORT Risk Class, History of COPD/asthma, and Prior Systemic Antimicrobial Use.

Source: ML-3341-306 End-of-Text Table 14.2.3.2.2.

Clinical outcome in ModCE and additional populations

In the ModCE-TOC population the success rate at TOC was 94.8% in the delafloxacin group and 93.8% in the moxifloxacin group. The lower limit of the two-sided 95% confidence interval was above the pre-specified margin -10% (95% CI -2.5, 4.6).

Table 61 Summary of Clinical Outcome at Test of Cure in Additional Populations – ML-3341-306

Clinical Outcome by Population	Delafloxacin	Moxifloxacin	Difference (95% CI)^a
ModMITT-1 population, N	228	225	0.1 (-5.5, 5.7)
Success, n/N (%)	206 (90.4)	203 (90.2)	
Failure, n/N (%)	14 (6.1)	13 (5.8)	
Indeterminate/missing	8 (3.5)	9 (4.0)	
ModMITT-2 population, N	176	182	1.9 (-4.3, 8.2)
Success, n/N (%)	161 (91.5)	163 (89.6)	
Failure, n/N (%)	15 (8.5)	19 (10.4)	
Indeterminate / missing	3 (1.7)	7 (3.8)	
ModCE-TOC population, N	349	341	1.0 (-2.5, 4.6)
Success, n/N (%)	331 (94.8)	320 (93.8)	
Failure, n/N (%)	18 (5.2)	21 (6.2)	
ModME-1TOC population, N	212	214	-0.5 (-5.4, 4.3)
Success, n/N (%)	198 (93.4)	201 (93.9)	

Failure, n/N (%)	14 (6.6)	13 (6.1)	-0.2 (-6.0, 5.5)
ModME-2TOC population, N	167	173	
Success, n/N (%)	155 (92.8)	161 (93.1)	
Failure, n/N (%)	12 (7.2)	12 (6.9)	

Abbreviations: ModCE-TOC = modified clinically evaluable at Test of Cure; CI = confidence interval; ModME = modified microbiologically evaluable; ModMITT = modified microbiological intent-to-treat.

^b Difference = difference in cure/success rates (delafloxacin treatment group minus moxifloxacin treatment group). Confidence intervals were calculated using the Miettinen-Nurminen method without stratification.

Sources: ML-3341-306 End-of-Text Tables 14.2.3.1.5, 14.2.3.1.6, 14.2.3.1.8, 14.2.3.1.11, and 14.2.3.1.12.

Based on these data non-inferiority of delafloxacin to moxifloxacin has been demonstrated.

The reasons for clinical failure at TOC visit were generally well balanced between treatment groups in the study.

Results from additional populations at TOC are in accordance with the primary analysis. Regardless of the analysis population, success rates were comparable between treatment groups. Sensitivity analysis support that treatment of CAP with delafloxacin is non-inferior to treatment with moxifloxacin.

Ancillary analyses

Clinical outcome at TOC by baseline pathogens

Clinical success rates at TOC by baseline pathogens were not statistically different between the treatment groups.

Table 62 Clinical Outcome at Test of Cure by Baseline Pathogens (in > 5 Subjects) in the ModMITT-1 and ModME-1TOC Populations — ML-3341-306

All Pathogens by Any Diagnostic Method	Success, n/N (%)					
	ModMITT-1			ModME-1TOC		
	Delafloxacin (N = 228)	Moxifloxacin (N = 225)	Difference (95% CI) ^a	Delafloxacin (N = 212)	Moxifloxacin (N = 214)	Difference (95% CI) ^a
<i>Streptococcus pneumoniae</i> ^b	94/105 (89.5)	81/91 (89.0)	0.5 (-8.4, 9.9)	89/95 (93.7)	81/86 (94.2)	-0.5 (-8.2, 7.4)
PSSP	42/44 (95.5)	40/47 (85.1)	10.3 (-2.4, 24.0)	40/42 (95.2)	40/43 (93.0)	2.2 (-9.9, 14.7)
PISP	16/18 (88.9)	16/17 (94.1)	-5.2 (-28.5, 18.2)	16/18 (88.9)	16/17 (94.1)	-5.2 (-28.5, 18.2)
PRSP	1/1 (100)	1/1 (100)	NE	1/1 (100)	1/1 (100)	NE
MDRSP	1/1 (100)	1/1 (100)	NE	1/1 (100)	1/1 (100)	NE
MRSP	15/16 (93.8)	16/17 (94.1)	-0.4 (-23.9, 22.3)	15/16 (93.8)	16/17 (94.1)	-0.4 (-23.9, 22.3)
<i>Haemophilus parainfluenzae</i>	25/28 (89.3)	27/32 (84.4)	4.9 (-14.2, 23.2)	25/28 (89.3)	27/30 (90.0)	-0.7 (-19.0, 17.0)
<i>Mycoplasma pneumoniae</i>	31/32 (96.9)	25/25 (100.0)	-3.1 (-15.9, 10.6)	27/28 (96.4)	24/24 (100.0)	-3.6 (-17.9, 10.7)
<i>Legionella pneumophila</i>	25/26 (96.2)	26/27 (96.3)	-0.1 (-15.9, 15.2)	25/26 (96.2)	26/26 (100.0)	-3.8 (-19.1, 9.5)
<i>Haemophilus influenzae</i>	22/24 (91.7)	26/30 (86.7)	5.0 (-14.7, 23.2)	20/21 (95.2)	26/30 (86.7)	8.6 (-11.3, 26.1)
<i>Staphylococcus aureus</i> ^b	24/26 (92.3)	25/27 (92.6)	-0.3 (-18.1, 17.2)	24/26 (92.3)	25/27 (92.6)	-0.3 (-18.1, 17.2)
MSSA	23/25 (92.0)	25/27 (92.6)	-0.6 (-19.0, 16.9)	23/25 (92.0)	25/27 (92.6)	-0.6 (-19.0, 16.9)
MRSA	1/1 (100.0)	0	NE	1/1 (100.0)	0	NE
<i>Chlamydia pneumoniae</i>	21/21 (100.0)	14/14 (100.0)	NE	20/20 (100.0)	13/13 (100.0)	NE
<i>Klebsiella pneumoniae</i>	13/16 (81.3)	14/14 (100.0)	-18.8 (-43.5, 5.4)	13/16 (81.3)	14/14 (100.0)	-18.8 (-43.5, 5.4)
<i>Escherichia coli</i>	13/14 (92.9)	10/11 (90.9)	1.9 (-25.0, 32.7)	11/11 (100.0)	9/9 (100.0)	NE
<i>Pseudomonas aeruginosa</i>	11/13 (84.6)	11/11 (100.0)	-15.4 (-42.9, 13.4)	11/12 (91.7)	11/11 (100.0)	-8.3 (-36.1, 19.6)
<i>Klebsiella oxytoca</i>	6/6 (100.0)	3/4 (75.0)	25.0 (-23.5, 71.6)	6/6 (100.0)	3/4 (75.0)	25.0 (-23.5, 71.6)
<i>Moraxella catarrhalis</i>	6/6 (100.0)	5/5 (100.0)	NE	6/6 (100.0)	5/5 (100.0)	NE
<i>Enterobacter cloacae</i> complex	3/4 (75.0)	9/10 (90.0)	-15.0 (-64.0, 25.2)	3/4 (75.0)	8/8 (100.0)	-25.0 (-71.3, 15.4)

Footnotes on next page.

Abbreviations: CI = confidence interval; MDRSP = multiple drug-resistant *Streptococcus pneumoniae*; ModME = modified microbiologically evaluable; ModMITT = modified microbiological intent-to-treat; MRSA = methicillin-resistant *Staphylococcus aureus*; MRSP = macrolide-resistant *Streptococcus pneumoniae*; MSSA = methicillin-susceptible *Staphylococcus aureus*; NE = not estimable; PISP = penicillin-intermediate *Streptococcus pneumoniae*; PRSP = penicillin-resistant *Streptococcus pneumoniae*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*; TOC = Test of Cure.

^a Difference = difference in cure / success rates (delafloxacin treatment group minus moxifloxacin treatment group). Confidence intervals were calculated using the Miettinen-Nurminen method without stratification.

^b Patients with both MRSA and MSSA, or any combination of PSSP, PISP, or PRSP were counted once in the overall category for that organism.

Sources: ML-3341-306 End-of-Text Tables 14.2.3.4.19.2 and 14.2.3.4.19.4.

Clinical outcome at TOC by baseline monomicrobial versus polymicrobial infections

The clinical outcome at TOC by baseline monomicrobial versus polymicrobial infections was comparable between treatment groups.

Table 63 Clinical Outcome at Test of Cure by Baseline Monomicrobial Versus Polymicrobial Infections - ML-3341-306

Infection Category	Success, n/N (%)					
	ModMITT-1 Population			ModME-1TOC Population		
	Delafloxacin (N = 228)	Moxifloxacin (N = 225)	Difference (95% CI) ^a	Delafloxacin (N = 212)	Moxifloxacin (N = 214)	Difference (95% CI) ^a
Monomicrobial						
Gram-positive	60/69 (87.0)	56/65 (86.2)	0.8 (-11.2, 13.0)	59/63 (93.7)	56/61 (91.8)	1.8 (-8.3, 12.4)
Gram-negative	43/50 (86.0)	49/57 (86.0)	0.0 (-14.2, 13.6)	42/46 (91.3)	49/55 (89.1)	2.2 (-11.0, 14.7)
Atypical	26/27 (96.3)	25/26 (96.2)	0.1 (-15.2, 15.9)	26/27 (96.3)	24/24 (100.0)	-3.7 (-18.5, 10.6)
Polymicrobial	77/82 (93.9)	73/77 (94.8)	-0.9 (-9.1, 7.3)	71/76 (93.4)	72/74 (97.3)	-3.9 (-12.2, 3.6)

Per-subject microbiological response at test of cure

No differences of the per-subject microbiological response at TOC between treatment groups were identified.

Table 64 Per-Subject Microbiological Response at Test of Cure (ModMITT-1 and ModME-1TOC Populations) – ML-3341-306

Microbiologic Response	No. (n/N [%]) of			
	ModMITT-1		ModME-1TOC	
	Delafloxacin n	Moxifloxacin n	Delafloxacin n	Moxifloxacin n
Eradicated	204 (89.5)	201 (89.3)	196 (92.5)	199 (93.0)
Documented eradicated	12 (5.3)	6 (2.7)	12 (5.7)	6 (2.8)
Presumed eradicated	192 (84.2)	195 (86.7)	184 (86.8)	193 (90.2)
Persisted	24 (10.5)	24 (10.7)	16 (7.5)	15 (7.0)
Documented persisted	2 (0.9)	3 (1.3)	2 (0.9)	3 (1.4)
Presumed persisted	14 (6.1)	12 (5.3)	14 (6.6)	12 (5.6)
Indeterminate/Missing	8 (3.5)	9 (4.0)	—	—
Difference (95% CI) ^a	0.1 (-5.7,		-0.5 (-5.7,	

Abbreviations: CI = confidence interval; ModME = modified microbiologically evaluable; ModMITT = modified microbiological intent-to-treat; TOC = Test of Cure.

^a Difference = difference in eradication rates (delafloxacin treatment group minus moxifloxacin treatment group, documented + presumed). Confidence intervals were calculated using the Miettinen-Nurminen method without stratification. If a postbaseline culture was not performed, then the microbiological response was a presumed response based on the clinical response.

Sources: ML-3341-306 End-of-Text Tables 14.2.8.1.1.3 and 14.2.8.1.1.7.

Per-pathogen microbiological response at test of cure by most common baseline pathogens (in > 5 subjects)

The rates of microbiological success by pathogen at TOC were similar between the delafloxacin group and moxifloxacin group for the most common pathogens.

Two patients in the delafloxacin group and three patients in the moxifloxacin group had documented persistence. In the delafloxacin group persistent pathogens included *S. pneumoniae* (1 patient) and *H. parainfluenzae* (1 patient). Each of these pathogens was confirmed as being genetically related to the baseline isolate by multilocus sequence typing or pulsed-field gel electrophoresis (PFGE). Nonetheless, each of these 2 subjects had a clinical outcome of success at EOT and TOC as assessed by the investigator.

For discussion regards to PK/PD, please see PK/PD assessment.

Table 65 Per-Pathogen Microbiological Response at Test of Cure by Most Common Baseline Pathogens (in > 5 Subjects) (ModME-1TOC Population) – ML-3341-306

All Pathogens	Microbiological Success, n/N (%) ^a		
	Delafloxacin n	Moxifloxacin n	Difference (95% CI) ^b
<i>Streptococcus pneumoniae</i> ^c	88/95 (92.6)	80/86 (93.0)	-0.4 (-8.5, 8.0)
PSSP	39/42 (92.9)	40/43 (93.0)	-0.2 (-13.2, 12.6)

PISP	16/18 (88.9)	16/17 (94.1)	-5.2 (-28.5, 18.2)
PRSP	1/1 (100.0)	1/1 (100.0)	NE
MDRSP	1/1 (100.0)	1/1 (100.0)	NE
MRSP	14/16 (87.5)	16/17 (94.1)	-6.6 (-31.8, 17.2)
<i>Haemophilus parainfluenzae</i>	24/28 (85.7)	26/30 (86.7)	-1.0 (-20.6, 18.1)
<i>Mycoplasma pneumoniae</i>	27/28 (96.4)	24/24 (100.0)	-3.6 (-17.9, 10.7)
<i>Legionella pneumophila</i>	25/26 (96.2)	26/26 (100.0)	-3.8 (-19.1, 9.5)
<i>Staphylococcus aureus</i>	24/26 (92.3)	25/27 (92.6)	-0.3 (-18.1, 17.2)
MSSA	23/25 (92.0)	25/27 (92.6)	-0.6 (-19.0, 16.9)
MRSA	1/1 (100.0)	0	NE
<i>Chlamydia pneumoniae</i>	20/20 (100.0)	13/13 (100.0)	NE
<i>Haemophilus influenzae</i>	20/21 (95.2)	26/30 (86.7)	8.6 (-11.3, 26.1)
<i>Klebsiella pneumoniae</i>	13/16 (81.3)	14/14 (100.0)	-18.8 (-43.5, 5.4)
<i>Escherichia coli</i>	11/11 (100.0)	9/9 (100.0)	NE
<i>Pseudomonas aeruginosa</i>	11/12 (91.7)	11/11 (100.0)	-8.3 (-36.1, 19.6)
<i>Klebsiella oxytoca</i>	6/6 (100.0)	3/4 (75.0)	25.0 (-23.5, 71.6)
<i>Moraxella catarrhalis</i>	6/6 (100.0)	5/5 (100.0)	NE
<i>Enterobacter cloacae</i> complex	3/4 (75.0)	8/8 (100.0)	-25.0 (-71.3, 15.4)

Abbreviations: CI = confidence interval; MDRSP = multiple drug-resistant *Streptococcus pneumoniae*; MedME = modified microbiologically evaluable; MRSP = macrolide-resistant *Streptococcus pneumoniae*; MSSA = methicillin-susceptible *Staphylococcus aureus*; NE = not estimable. PISP = penicillin-intermediate *Streptococcus pneumoniae*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*; PRSP = penicillin-resistant *Streptococcus pneumoniae*; TOC = Test of Cure.

^a Microbiological success was defined as documented or presumed eradication.

^b Difference = difference in microbiological success rates (delafloxacin treatment group minus moxifloxacin treatment group).

Confidence intervals were calculated using the Miettinen-Nurminen method without stratification.

^c Subjects with both MRSA and MSSA, or any combination of PSSP, PISP, or PRSP were counted once in the overall category for that organism.

Source: ML-3341-306 End-of-Text Table 14.2.8.2.1.7.

Superinfections and new infections

In the ModITT population, 4 subjects (3 subjects in the delafloxacin group and 1 subject in the moxifloxacin group) had a superinfection (i.e., a new pathogen, cultured during treatment, that caused respiratory infection and was associated with clinical failure). Causative pathogens were *E. coli*, *H. parainfluenzae*, and *Serratia liquefaciens* complex in the delafloxacin group; and *E. cloacae* complex in the moxifloxacin group.

No subject in either treatment group had a new infection (i.e., a new pathogen, cultured after treatment that caused respiratory infection and was associated with clinical failure).

Day 28 mortality

A similar percentage of ModITT subjects in the delafloxacin (2.1% (8 of 376)) and moxifloxacin groups (1.6% (6 of 370)) died during the study (up to Day 28). Using a Cox proportional hazards regression model that adjusted for stratification factors (baseline PORT Risk Class, history of COPD or asthma, and prior systemic antimicrobial use), the hazard ratio for all-cause mortality between delafloxacin and moxifloxacin was 1.516 (95% CI, 0.514 to 4.470).

Comparison of Results in Subpopulations

No significant differences between treatment groups were identified in subgroup analysis.

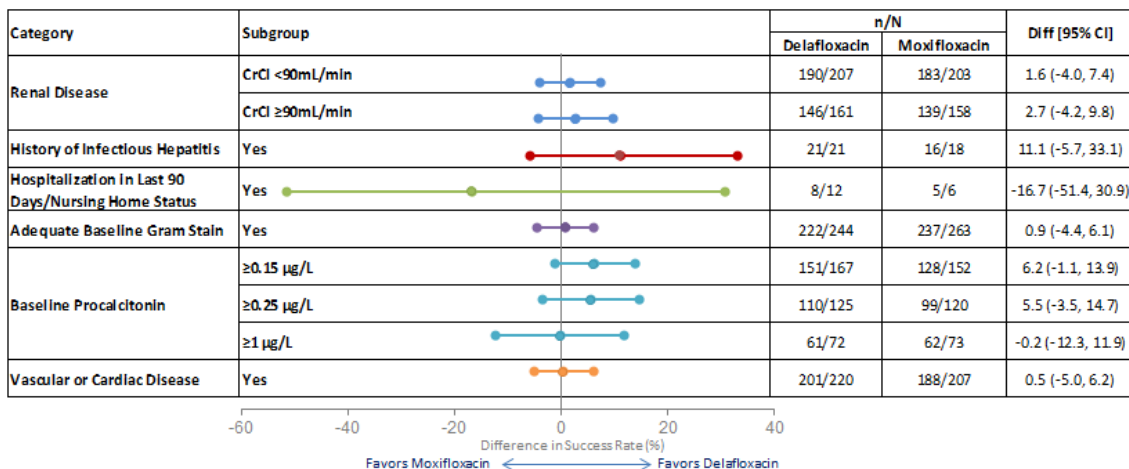
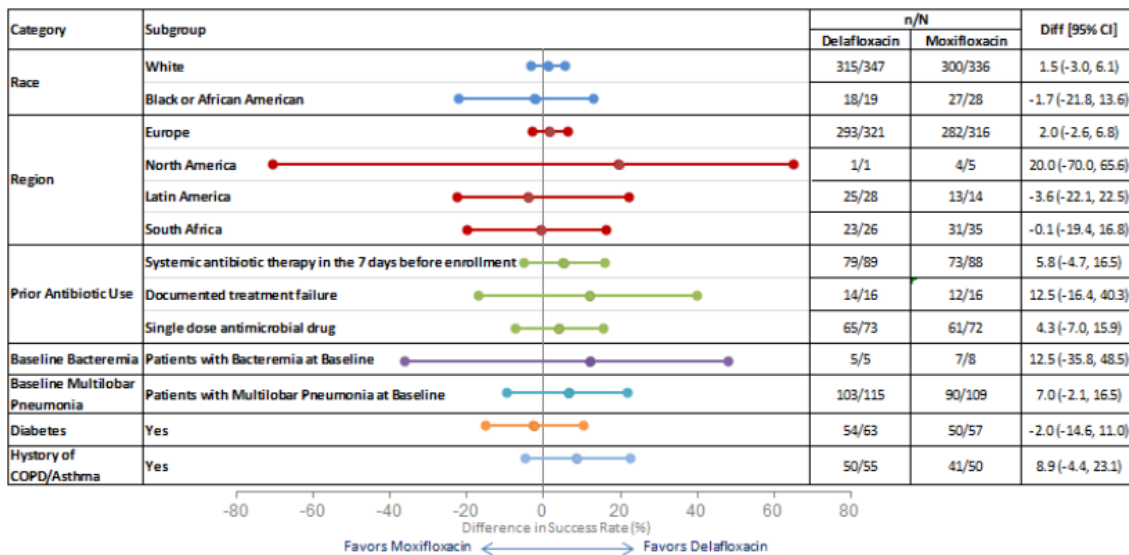
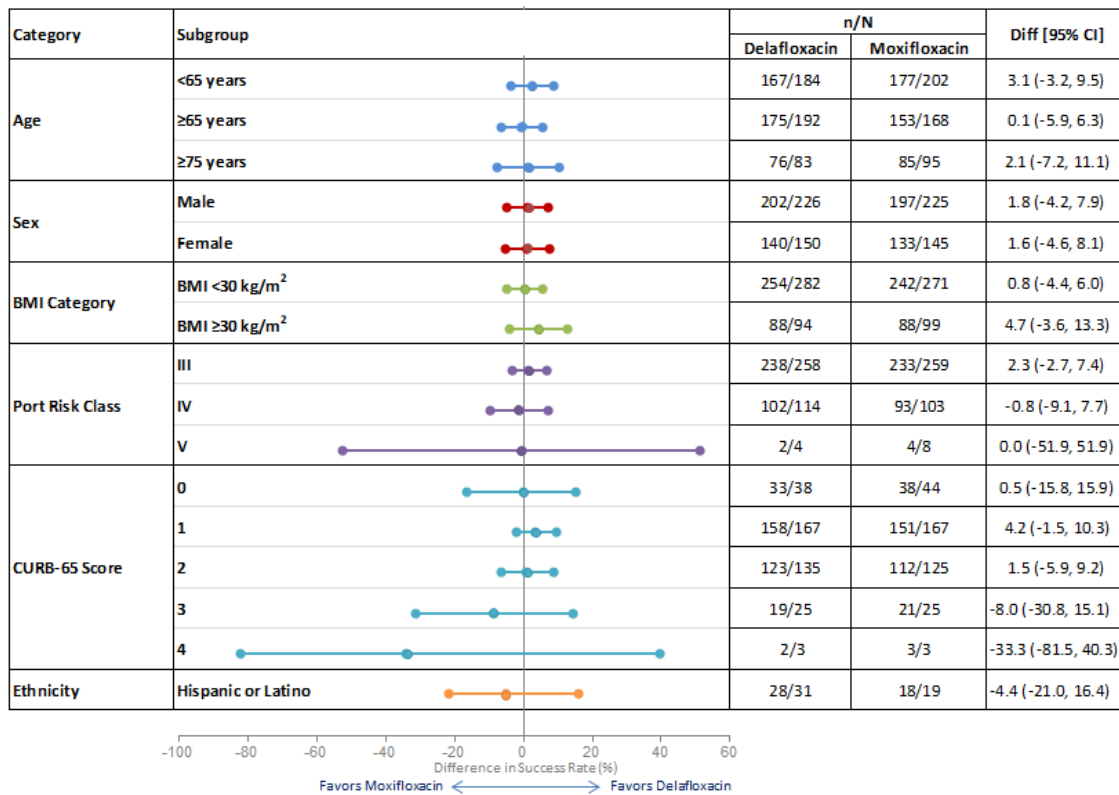


Figure 22 Forest Plot of Clinical Outcome at Test of Cure by Subgroups (ModITT Population)

Abbreviations: CI = confidence interval; CrCl = creatinine clearance; ModITT = modified intent-to-treat.

Notes: Difference was the difference in success rates (delafloxacin group minus moxifloxacin group). The CIs were calculated using the Miettinen-Nurminen method without stratification.

Source: ML-3341-306 End-of-Text Figure 14.2.2.3a.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 66 Summary of Efficacy for trial ML-3341-306

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Comparator-Controlled Study to Evaluate the Safety and Efficacy of Intravenous to Oral Delafloxacin in Adult Subjects with Community-Acquired Bacterial Pneumonia			
Study identifier		NCT02679573	
Design	Phase 3, randomized, double-blind, multi-center, comparative efficacy and safety study to evaluate delafloxacin (IV followed by oral) compared to moxifloxacin (IV followed by oral) in the treatment of adult patients with Community-Acquired Bacterial Pneumonia.		
	Duration of main phase:		28 days
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis		Non-inferiority in the ModITT population, Non-inferiority margin -10%	
Treatments groups	Delafloxacin		Delafloxacin IV, 300 mg every 12 hours (BID), with an option to switch to oral delafloxacin, 450 mg BID, treatment duration 5-10 days
	Moxifloxacin		Moxifloxacin, 400 mg every 24 hours (QD), with an option to switch to oral moxifloxacin, 400 mg QD, treatment duration 5-10 days; switch from moxifloxacin to linezolid (600 mg IV BID) if <i>methicillin-resistant Staphylococcus aureus</i> (MRSA) was confirmed
Endpoints and definitions	Primary endpoint	Non-inferiority	To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at 5 to 10 days after the last dose of study drug (TOC) compared to IV to oral comparator study drug arm in the modified intent-to-treat (ModITT) and modified clinically evaluable (ModCE) populations.

	Secondary endpoints	descriptive	To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP based on ECR, defined as improvement at 96 hours ($\pm$ 24 hours) after the first dose of study drug compared to IV to oral moxifloxacin in the ModITT and ModCE populations. To assess the clinical efficacy of IV to oral delafloxacin in adult subjects with CABP at TOC compared with IV to oral moxifloxacin in the modified microbiological intent to treat (ModMITT) and modified microbiologically evaluable (ModME) populations. To assess the microbiological response to delafloxacin in respiratory pathogens in the ModMITT and ModME populations. To assess the safety and tolerability of IV to oral delafloxacin in adult subjects with CABP in Safety population. To assess the all-cause mortality in adult subjects with CABP on Day 28 in ModITT. To assess delafloxacin PK in adult subjects with CABP in PK population.
Study period	14 December 2016 – 07 August 2018		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	<u>ModITT population:</u> All randomized subjects who signed informed consent form (ICF), received at least 1 dose of study drug and were classified as PORT Risk Class III through V. <u>ModCE-TOC population:</u> Subjects had to receive at least 4 doses of study drug by the end of Day 3 to be classified as a clinical failure / nonresponder. Subjects who received both study therapies or received less than 4 doses were excluded from the ModCE populations. Subjects with indeterminate / missing values (including out of window assessments) were excluded from the ModCE populations. <u>TOC</u> was defined at 5 to 10 days after the last dose of study drug.		
Effect estimate per comparison	Treatment group	Delafloxacin	Moxifloxacin
	Number of subject	ModITT: 376 ModCE-TOC: 349	ModITT: 370 ModCE-TOC: 341
	Success at TOC in ModITT n/N (%)	342 (91.0)	330 (89.2)
	Difference (95% CI)	1.1 (–3.2, 5.5)	
	Success at TOC in ModCE-TOC n/N (%)	331 (94.8)	320 (93.8)
	Difference (95% CI)	1.0 (–2.5, 4.6)	
Analysis description	Secondary analysis		

Analysis population and time point description	In addition to ModITT and ModCE-TOC populations: <u>ModMITT population:</u> All subjects in the ModITT population who had a baseline bacterial pathogen identified, either by culture of a respiratory or blood specimen(s) or a nonculture method of detection (i.e., urinary antigen test, polymerase chain reaction (PCR), or serologic testing) that was known to cause CAP and against which the study drug had antibacterial activity.<u>ME:</u> There are several ME analysis sets, which include all patients in the MITT analysis set who also met the criteria for the corresponding CE analysis set for either objective or investigator-assessed response. <u>ModME-TOC population:</u> All subjects in the ModMITT population who were microbiologically evaluable at TOC for clinical outcome.
Descriptive Statistics and Estimate Variability	For results of relevant secondary endpoints see section outcomes and estimation.

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive studies

Studies performed for ABSSSI indication were regarded as supportive studies. See EPAR for further information.

2.4.3. Discussion on clinical efficacy

In this EoI variation the MAH applied for the indication treatment of community-acquired pneumonia (CAP) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections.

The clinical support for this indication mainly include one pivotal Phase 3 study (ML-3341-306). In addition, results of a phase 2b study were provided as supportive data (M01-344).

For justification of dosage for the indication CAP PK/PD analysis were submitted (please see PK/PD Assessment).

Design and conduct of pivotal clinical study ML-3341-306

Study ML-3341-306 was a phase 3, multicenter, randomized, double-blind, comparator-controlled study to evaluate the safety and efficacy of intravenous to oral delafloxacin in adult subjects with community-acquired bacterial pneumonia.

Inclusion/exclusion criteria

Inclusion and exclusion criteria are in general in accordance with the recommendations for studies in CAP as outlined in the Draft AB GL (EMA/844951/2018 Rev. 3) and therefore acceptable. Patients included on the basis of these criteria meet the requirements for CAP.

Randomization was stratified by PORT Risk Class, medical history of chronic obstructive pulmonary disease (COPD) or asthma, and prior single dose/regimen systemic antimicrobial use. Enrolment was limited to no more than 25% of subjects who were PORT Risk Class II, and no more than 25% of subjects who received one dose of a single, potentially effective, short-acting antimicrobial drug or drug regimen for treatment of the CAP under study within 24 hours of enrolment.

According to the Draft AB GL when treatment is to be initiated by the intravenous route patients should have a minimum PORT score of III and at least 25% should have a score >III. Even if patients were included with PORT score II, this recommendation was considered for primary analysis.

Patients with severe renal impairment (CrCl of <30 mL/min) were excluded from pivotal study. The applied dosage for patients with severe renal impairment and the indication CAP is 200 mg intravenously/450 mg oral delafloxacin every 12 hours which is in line with the approved dosage in ABSSSI.

Treatments

Study ML-3341-306 investigated 300 mg delafloxacin administered as an 1-hour IV infusion BID ($\pm$ 2 hours) for a minimum of 6 doses, with an option to switch to delafloxacin, 450 mg tablet, administered orally BID ($\pm$ 2 hours) for the remaining doses. The minimum duration of treatment (IV and oral) was 5 days and the maximum 10 days.

Moxifloxacin was chosen as comparator. Moxifloxacin is approved in the EU for the indication CAP as second line indication due to safety risk (when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections). Dosage used for IV and oral treatment is in line with the approved dosage. Moxifloxacin is recommended as empiric treatment option for patients with CAP in respective treatment guidelines; therefore, it is acceptable as comparator. It should be considered that the MAH applied for the same second line indication as approved for moxifloxacin.

According to the SmPC of moxifloxacin the recommended treatment duration of intravenous and oral moxifloxacin is 7 - 14 days for CAP. Nevertheless, current treatment guidelines recommend an antibiotic treatment duration of 5-7(10) days in case of CAP. Therefore, the treatment duration as used in study ML-3341-306 can be accepted. This is also supported by the fact that high cure rates were reported for both treatment groups.

It was determined in the study protocol that subjects in the moxifloxacin arm with confirmed MRSA, in place of remaining moxifloxacin doses, could receive 600 mg of linezolid administered as a 1-hour IV infusion every 12 ($\pm$ 2) hours for the remaining doses. Moxifloxacin is not recommended for the treatment of MRSA infections and using linezolid for targeted treatment in patients with confirmed MRSA is supported. Overall, MRSA was confirmed only in one patient in the delafloxacin group. Therefore, no patient received linezolid during study.

Primary endpoint

The study was designed with a primary objective specific to the submission to the FDA and a primary objective specific to the submission to the EMA and separate statistical analysis plans were employed for submission to the FDA and for submission to the EMA, which is supported.

The primary EMA efficacy endpoint was Clinical Outcome at Test of Cure (TOC) evaluated 5 to 10 days after last dose. The analysis was performed considering the outcome of cure in the ModITT population and ModCE population. The ModITT population comprised all randomized subjects who signed informed consent form, received at least 1 dose of study drug and were classified as PORT Risk Class III through V. ModCE-TOC

population included subjects who received at least 4 doses of study drug by the end of Day 3 to be classified as a clinical failure/nonresponder. Subjects with indeterminate / missing values (including out of window assessments) were excluded from the ModCE-TOC population.

The primary EP as defined is in line with the recommendations in the Draft AB GL. The selected non-inferiority margin (-10%) is also in line with this guideline. Since according to the Draft AB GL for a treatment initiation by the intravenous route patients should have a minimum PORT score of III the definition of primary analysis set ModITT is accepted.

The definition of success "Resolution or near resolution of the symptoms of CAP present at study entry, and no use of additional antimicrobial therapy for the current infection, and no new symptoms associated with the current CAP infection." is agreed.

Statistical methods

The design and description of methods of the pivotal study -306 is overall considered acceptable. Analyses were clearly specified and appropriately described. Statistical methods used for the primary analysis are considered adequate. Two sets of primary and secondary analyses were used with different primary endpoints for MAA submission at FDA and EMA, which is acceptable considering different guideline requirements. Non-inferiority was assessed using the Miettinen and Nurminen method and properties of the method are appropriate and favourable compared to other confidence interval based approaches. The non-inferiority margin used was chosen according to the EMA Guideline Addendum. The approach to address multiplicity, switching to superiority analyses for secondary endpoints after the primary analysis was successful, is acceptable. There was no multiplicity due to interim analysis. Missing data is not a major problem with a balanced distribution of missing assessments and drop-outs in both treatment arms and no concerns with regard to intercurrent events and reasons for missingness. Handling of missing data as failures or excluding observations in the main analysis populations is acceptable. Methods used for analysis of secondary endpoints and subgroups analysis are acceptable.

Baseline data

Subjects in the ModITT population were predominantly male (60.5%), white (91.6%), and European (85.4%); 6.7% were Hispanic or Latino. The mean age of subjects was 61.5 years (range, 18 - 93 years), with 48.3% of subjects ≥ 65 years and 23.9% of subjects ≥ 75 years. A slightly higher percentage of subjects in the delafloxacin group were ≥ 65 years (51.1%) compared with the moxifloxacin group (45.4%), while 22.1% and 25.7%, respectively, were ≥ 75 years. A lower percentage of subjects in the delafloxacin group (64.9%) than subjects in the moxifloxacin group (71.1%) had an adequate Gram stain at baseline.

Overall, 30.7% of patients had a PORT score $>III$ which is in line with the recommendation in the Draft AB GL for studies in CAP initiated by intravenous route. Nevertheless, most recruited patients, despite being hospitalised, had CAP of rather moderate severity – 90.7% had CURB-65 score ≤ 2 and 69.3% were categorised to PORT class III. The outcome of such patients is expected to be positive in vast majority of cases. However, about 50% were aged >65 years and 60.3% were overweight; both being risk factors for more severe CAP.

Baseline data including severity scores of the disease are in general comparable between treatment arms.

The majority of the patients in the delafloxacin group (91.8%) and comparator group (90.8%) completed the study through TOC.

The most common reason for withdrawing from study was lack of efficacy (delafloxacin 10 patients [2.7%], moxifloxacin 15 patients [4.1%]), AEs (delafloxacin 13 patients [3.5%], moxifloxacin 5 patients [1.4%]) and withdrawal by subject (delafloxacin 1 patient [0.3%], moxifloxacin 7 patients [1.9%]).

Some more patients discontinued study drug due to AEs in the delafloxacin group (12 patients [3.2%]) compared to the moxifloxacin group (moxifloxacin 5 patients [1.4%]).

Overall, the number of subjects completing the study and reason for discontinuation was comparable between the two treatment arms.

The median total exposure in the safety population in both treatment groups was 9.0 days, with 6.0 days for IV exposure and 2.0 days for oral exposure. Most subjects received study drug for > 8 to 10 days (delafloxacin group 59.2%, moxifloxacin group 62.3%).

Efficacy data and additional analyses of pivotal clinical study ML-3341-306

Primary EP

Clinical response rates were high across both treatment arms. In the ModITT population the success rate at TOC was 91.0% in the delafloxacin group and 89.2% in the moxifloxacin group. The lower limit of the two-sided 95% confidence interval was above the pre-specified margin -10% (95% CI -3.2, 5.5).

In the ModCE-TOC population the success rate at TOC was 94.8% in the delafloxacin group and 93.8% in the moxifloxacin group. The lower limit of the two-sided 95% confidence interval was above the pre-specified margin -10% (95% CI -2.5, 4.6).

Based on these data non-inferiority of delafloxacin to moxifloxacin has been demonstrated (IV followed by oral treatment).

The reasons for clinical failure at TOC visit were generally well balanced between treatment groups in the study.

Results from additional populations at TOC are in accordance with the primary analysis. Regardless of the analysis population, success rates were comparable between treatment groups. Sensitivity analysis supported that treatment of CAP with delafloxacin is non-inferior to treatment with moxifloxacin.

Additional analysis

The rates of microbiological success by pathogen at TOC were similar between the delafloxacin group and moxifloxacin group for the most common pathogens.

Two patients in the delafloxacin group and three patients in the moxifloxacin group had documented persistence. In the delafloxacin group persistent pathogens included *S. pneumoniae* (1 patient) and *H. parainfluenzae* (1 patient). Each of these pathogens was confirmed as being genetically related to the baseline isolate by multilocus sequence typing or pulsed-field gel electrophoresis (PFGE). Nonetheless, each of these 2 subjects had a clinical outcome of success at EOT and TOC as assessed by the investigator.

Regards to mortality a comparable percentage of ModITT patients died during study up to day 28. For further discussion of death cases please see safety assessment.

Subgroup analysis

In subgroup analysis no significant differences between treatment groups were identified, although small absolute numbers in some of these groups precludes any robust conclusions.

Phase 2b study M01-344

This double-blind, randomized, parallel-group, Phase 2b study investigated the safety and efficacy of a 7-day course of oral delafloxacin (3 dosing groups: 100, 200, or 400 mg once daily) in subjects with CAP.

The aim of this study performed in 2002 was to help to identify the optimal dose regimen for future studies. The oral dosages used in this study are not in line with the oral dosage applied for the indication CAP (450 mg oral twice daily). Furthermore, an older capsule formulation was used in this study.

Overall, no statistically significant dose-response trends in clinical response, and no statistically significant pairwise differences were observed between treatment groups among clinically evaluable, ITT, or clinically and bacteriologically evaluable subjects. All 3 doses were effective in resolving or improving clinical signs and symptoms of CAP, eradicating the target pathogens, and resolving or improving radiographic evidence of pneumonia. The 200-mg dose appeared to be similar to the 400-mg dose in clinical cure rates, bacteriological cure rates, and overall pathogen-eradication rates. However, lower clinical cure rates, bacteriological cure rates, and overall pathogen eradication rates were observed in the 100-mg group.

Regards to the application for extension of indication this Phase 2b study is of only some relevance since the study was not powered to test dose-response trends, the dosage applied for was not investigated, the used oral formulation is not in line with the approved one and the study was investigated in 2002, which question the validity of results.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

N/A

2.4.1. Conclusions on the clinical efficacy

The clinical support for this indication mainly includes one pivotal Phase 3 study (ML-3341-306). In addition, results of a phase 2b study were provided as supportive data (M01-344). Furthermore, in phase 1 study ML-3341-119 intrapulmonary disposition of delafloxacin was investigated and dosage was justified by respective PK/PD analysis.

In general, the patient population included in pivotal study ML-3341-306 is considered to be representative for the applied indication. Non-inferiority of delafloxacin to moxifloxacin has been clearly demonstrated in these patients for the primary endpoints.

Pivotal study ML-3341-306 investigated IV followed by oral delafloxacin. Regards to sole oral delafloxacin treatment of CAP it should be considered that in the frame of the initial MAA a BE study was submitted which revealed that 300 mg IV delafloxacin and 450 mg oral delafloxacin can be regarded as bioequivalent. Therefore, results of pivotal study ML-3341-306 can be extrapolated to sole oral treatment with delafloxacin.

It can be concluded that the extension of indication meets the prerequisites for one pivotal study application, as detailed in EMA Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99, 31 May 2001). The pharmacological principle and mechanism of action is established. A robust clinical data package has been provided. Data from Study ML-3341-306 can be regarded as valid in relation to the indication applied for. According to the EMA Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99, 31 May 2001), when the aim is to demonstrate non-inferiority, one study is more likely to be accepted if the lower 95% confidence bound is well away from the non-inferiority margin. In Study ML-3341-306 the lower bound of 95% confidence interval was -3,2% and therefore well away from the non-inferiority margin of -10%. Furthermore, the results of Study

ML-3341-306 support internal consistency of the data set. In addition, patients in Study ML-3341-306 were enrolled across a large number of clinical centres, without dominance of any given centre.

Overall, pivotal study ML-3341-306 provides robust efficacy results and one pivotal study application is agreed. Furthermore, efficacy data are supported by PK/PD analysis of pathogens most relevant for CAP (*S. pneumoniae*, *S. aureus* and *H. influenzae*).

2.5. Clinical safety

Introduction

The Summary of Clinical Safety (SCS) includes safety data from Phase III ML-3341-306 in subjects with CAP. Two additional studies in support of the CAP indication (1 Phase I study (ML-3341-119) and 1 Phase II study (M01-344)) as well as safety data from the initial ABSSSI MAA are described. Post-marketing data are provided.

Adverse events of special interest (AESIs) were selected based on medical issues of interest for the fluoroquinolone class of antibiotics: potential myopathy, *Clostridioides difficile* diarrhoea, convulsions, potential peripheral neuropathy, potential tendon disorder, potential QT prolongation, potential phototoxicity, potential allergic reactions, potential dysglycaemias (hyperglycaemia, hypoglycaemia), hepatic-related events, and aortic aneurysm dissection / rupture. It also included other potential neurological and psychiatric AEs, reflecting the EMA review (EMA/175398/2019, November 2018).

Initial ABSSSI Safety Population

Multiple-Dose ABSSSI safety population

The Multiple-Dose ABSSSI population included 1840 subjects from 4 completed Phase II (RX-3341-201 and RX-3341-202) and Phase III studies (RX-3341-302 and RX-3341-303) (Section 4 - Multiple-Dose ABSSSI Safety Population in Module 2.7.4). Subject demographics were generally similar between the delafloxacin and comparator (vancomycin-aztreonam, linezolid, tigecycline) groups. Subjects ranged from 18 to 94 years of age with a mean of 48.0 years in the delafloxacin group and 47.2 years in the comparator group. In both treatment groups, most subjects were male (> 60%) and white (> 84%) and had a mean BMI of approximately 30 kg/m². In both treatment groups, approximately 11% of subjects had diabetes and 16% had baseline renal impairment (CrCl based on Cockcroft-Gault formula). In the delafloxacin group, 26.8% of subjects had a history of hepatitis B or C compared with 23.8% in the comparator group. Approximately 70% of subjects were from North America.

Overall, 12.9% of subjects treated with delafloxacin withdrew from the studies compared with 15.4% of subjects treated with comparators. The most common reason for withdrawal from study was subjects lost to follow-up (6.6% in the delafloxacin group and 7.2% in the comparator group). Overall, 1.3% of subjects treated with delafloxacin withdrew from the study drug because of an AE compared with 3.2% of subjects treated with comparators. Refer to ABSSSI MAA Section 2.7.4.1.3.2.

Delafloxacin was also safe and well-tolerated in the Phase II and Phase III ABSSSI studies. Fewer subjects had TEAEs in the delafloxacin group versus the comparator group (47.7% and 52.4%, respectively). Similarly, fewer subjects had treatment-related TEAEs in the delafloxacin group versus the comparator group (25.6% and 31.0%, respectively). Most TEAEs were mild or moderate in severity, with < 4% of subjects in either group experiencing severe TEAEs.

Fewer subjects had TEAEs leading to premature study drug discontinuation in the delafloxacin group versus the comparator group (1.6% and 3.8%, respectively). Likewise, fewer subjects had treatment-related TEAEs leading to premature study drug discontinuation in the delafloxacin group versus the comparator group (0.7% and 2.4%, respectively).

Fewer subjects had AESI in the delafloxacin group versus the comparator group (11.1% and 14.2%, respectively). The AESI terms included events associated with fluoroquinolones, including liver events, phototoxicity, and QT prolongation. The comparator group, which did not include a fluoroquinolone, provided an active control reference to assess delafloxacin's safety profile and provided context for potential safety signal detection.

The incidence of SAEs was similar between treatment groups (3.7% with delafloxacin compared to 3.8% with comparators). There was a total of 4 TEAEs leading to death, 1 in the delafloxacin group and 3 in the comparator group, all of which were assessed as unrelated to the study treatment by the Investigator.

The most common TEAEs in the delafloxacin group were nausea (9.1%), diarrhoea (8.6%), infection (5.2%), infusion-site extravasation (4.7%), and headache (3.5%). The incidences of specific TEAEs were generally comparable between delafloxacin and comparators, with the exception of a higher incidence of diarrhoea with delafloxacin versus the comparators (8.6% vs. 3.9%), which was driven by higher rates in the delafloxacin-treated subjects in Phase II studies. The incidence of gastrointestinal events with delafloxacin was lower in the Phase III studies compared with delafloxacin in the Phase II studies (16.9% vs. 33.9%). Gastrointestinal events were reported at comparable rates when delafloxacin was given by IV (17.3%, RX-3341-302) or by IV followed by oral doses (16.8%, RX-3341-303). The oral delafloxacin doses were not associated with an increase in gastrointestinal events in the comparison of these 2 trials.

Initial Phase I Safety Population

The previously submitted pooled Phase I safety experience comprises data from 814 subjects who received at least 1 dose of oral or IV delafloxacin in 20 completed Phase I studies (Section 4 - Phase I Safety Population in Module 2.7.4).

Delafloxacin was safe and well tolerated. There were no deaths or SAEs; 1 subject had a severe TEAE (dysphagia, assessed as unrelated to the study treatment by the Investigator). Few (1.5%) subjects experienced TEAEs leading to premature study drug discontinuation.

The most common TEAEs were diarrhoea (13.3%), nausea (10.2%), and headache (9.3%). Vomiting (4.4%) and infusion-site pain (3.7%) were also noted. The integrated data suggest a greater frequency of gastrointestinal and infusion-related TEAEs (with IV dosing) at higher doses.

The incidence of AESIs regardless of causality in the Phase I studies was low (7.4%). Few subjects (2.7%) had AESI that were considered to be treatment-related by the Investigator.

2.5.1. Safety in healthy volunteers

Study ML-3341-119 (Phase I)

Title: Bronchopulmonary Disposition of Intravenous Delafloxacin

Patient exposure

Healthy adults received 300 mg of delafloxacin intravenously (IV) every 12 hours for a total of 7 doses over 4 days. With one exception, none of the subjects experienced an interruption in any of their infusions. Subject 001007 (Group D [8 hour]) experienced an interruption and resumption of infusion during the Day 3 afternoon dose due to a burning feeling at the IV site. None of the subjects required discontinuation of any of their infusions.

Adverse events

An overall summary of AEs is shown in Table 67. Of the 30 healthy subjects enrolled, 13 subjects (43.3%) reported a total of 23 TEAEs, 17 of which were mild in severity and 6 of which were moderate in severity. The most frequently reported TEAEs overall were infusion-site phlebitis (9 subjects (30.0%)) and diarrhoea (4 subjects (13.3%)). Discoloured faeces were reported by 2 subjects (6.7%). All other TEAEs were reported by 1 subject each (Table 68).

Table 67: Overall Summary of Adverse Events (Safety Population) - ML-3341-119

	Overall (N=30) n (%)
Any subject with a TEAE	13 (43.3)
Any subject with a treatment-related TEAE	11 (36.7)
Any subject with a severe TEAE	0
Any subject with an SAE	0
Any subject with a treatment-related SAE	0
Any subject with a TEAE leading to early discontinuation	0
Any death	0

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Note: Percentages were based on the number of subjects in the safety population. A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in intensity or frequency after exposure. A treatment-related TEAE was defined as a TEAE that was considered by the investigator to be possibly, probably, or definitely related to the study treatment. Any TEAEs with missing relationships were considered definitely related in the summary.

Source: End-of-Text [Table 14.3.1.1](#).

Eleven subjects (36.7%) reported at least 1 delafloxacin-related TEAE (Table 69). The most commonly reported related TEAEs overall (by SOC) were General Disorders and Administrative Site Conditions (9 subjects (30.0%)) and Gastrointestinal Disorders (6 subjects (20.0%)). The most common related TEAEs overall (by Preferred Term) were infusion-site phlebitis (9 subjects (30.0%)) and diarrhoea (4 subjects (13.3%)). The TEAE of discolored feces was reported by 2 subjects (6.7%). All other related TEAEs were reported by 1 subject each.

One subject experienced a mild TEAE of paraesthesia, which began on Day 3 and resolved on Day 4. Concomitant medication was not given, and delafloxacin infusions continued uninterrupted. Paraesthesia was considered as possibly related by the Investigator.

The TEAEs were mild (10 subjects (33.3%)) or moderate (3 subjects (10.0%)) in severity. Moderate TEAEs included infusion-site phlebitis, diarrhoea, nausea, and dehydration. No severe TEAEs were reported. There were no deaths, SAEs, or TEAEs leading to early discontinuation. All TEAEs resolved by the end of the study. There were no clinically significant findings noted or TEAEs reported from clinical laboratory assessments, vital sign measurements, or 12-lead ECG results. Aside from abnormalities of the skin associated with the

TEAEs of infusion site phlebitis, infusion site swelling, and peripheral edema, no other abnormal physical examination finding was associated with a TEAE.

Table 68 Summary of Treatment-Emergent Adverse Events (Safety Population) – ML-3341-119

MedDRA System Organ Class (SOC) and Adverse Event (Preferred Term [PT])	No. (%) of Subjects
	Overall (N = 30)
Total number of TEAEs	23
Number of subjects with at least 1 TEAE	13 (43.3)
General Disorders and Administration Site Conditions	10 (33.3)
Infusion site phlebitis	9 (30.0)
Infusion site dermatitis	1 (3.3)
Infusion site swelling	1 (3.3)
Edema peripheral	1 (3.3)
Gastrointestinal Disorders	6 (20.0)
Diarrhea	4 (13.3)
Faces discolored	2 (6.7)
Hemorrhoids	1 (3.3)
Nausea	1 (3.3)
Nervous System Disorders	2 (6.7)
Headache	1 (3.3)
Paresthesia	1 (3.3)
Metabolism and Nutrition Disorders	1 (3.3)
Dehydration	1 (3.3)

Abbreviation: TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as any event not present before exposure to study drug or any event already present that worsened in severity or frequency after exposure. At each level of subject summarization, a subject was counted once if the subject reported 1 or more events. Percentages were based on the number of subjects in the safety population.

Adverse events were coded by SOC and PT using MedDRA, version 19.1.

Source: ML-3341-119 End-of-Text Table 14.3.1.2.

Table 69 Summary of Treatment-Related Treatment-Emergent Adverse Events (Safety Population) – ML-3341-119

System Organ Class Preferred Term	Overall (N=30) n (%)
Total Number of Treatment-Related TEAEs	19
Number of Subjects with at Least One Treatment-Related TEAE	11 (36.7%)
General disorders and administration site conditions	9 (30.0%)
Infusion site phlebitis	9 (30.0%)
Infusion site swelling	1 (3.3%)
Oedema peripheral	1 (3.3%)
Gastrointestinal disorders	6 (20.0%)
Diarrhoea	4 (13.3%)
Faeces discoloured	2 (6.7%)
Nausea	1 (3.3%)
Nervous system disorders	1 (3.3%)
Paraesthesia	1 (3.3%)

Note: Treatment-emergent adverse events (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. A treatment-related TEAE is defined as a TEAE that is considered by the investigator to be possible, probable or definitely related to the study treatment. At each level of subject summarization, a subject is counted once for the most related event if the subject reported one or more events. TEAEs with a missing relationship are considered definitely related in the summary. Percentages are based on the number of subjects in the safety population. Adverse events were coded by system organ class and preferred term using MedDRA version 19.1.

Source Data: Listing 16.2.7.1

2.5.2. Safety in CAP population

Study M01-344 (Phase IIb)

Title: A Phase 2b Comparative Study of the Safety and Efficacy of Three Oral Doses of ABT-492 for the Treatment of Subjects with Community Acquired Pneumonia

This was a Phase 2b, double-blinded, randomized, parallel-group, multi-centre study with subjects (in the fed state) who had a diagnosis of community-acquired pneumonia (CAP) supported by appropriate signs and symptoms. At enrolment (Screening/Evaluation 1), subjects were evaluated for etiologic pathogens [Gram stain, culture of respiratory (sputum) specimen] and signs and symptoms of CAP. Subjects were seen for Evaluation 2 on Study Day 3, for Evaluation 3 on Study Days 9-10, and for Evaluation 4 (Test-of-Cure) on Study Days 16-21, or within 48 hours after early termination. Evaluation 5 (Study Days 37-39) consisted of a telephone contact for a follow-up evaluation.

Patient exposure

Subjects were randomly assigned in a 1:1:1 ratio to receive:

- ABT-492 1 X 100 mg capsules plus 3 placebo for ABT-492 for 7 days, OR
- ABT -492 2 X 100 mg capsules plus 2 placebo for ABT -492 for 7 days, OR
- ABT-492 4 X 100 mg capsules QD for 7 days.

Adverse events

Of 309 subjects with CAP, diarrhoea was the most commonly reported TEAE in all dosing groups (Table 70). Statistically significant dose-response trends were observed in nausea and diarrhoea for all TEAEs. Liver function abnormalities showed an inverse dose dependence (less effect at increasing doses). No subjects died during the study. A total of 10 subjects from all dose groups had SAEs during the study, none of which were considered by the Investigator to be related to study drug. Of the 9 subjects who withdrew because of AEs, 3 subjects' AEs were considered possibly or probably related to study drug; all were in the 100-mg group (1 with nausea and tendon disorder confirmed as patellar tendonitis, 1 with tendon disorder confirmed as Achilles tendonitis, and 1 with abdominal pain). Although the 2 subjects who withdrew because of a tendon disorder had pre-existing joint complaints, the Investigators considered these events possibly related to delafloxacin.

No clinically meaningful changes in laboratory tests or vital signs were observed during the study.

Table 70 Common Adverse Events (≥ 3%) – Study M01-344

MedDRA Adverse Event (Preferred Term [PT]) (≥ 3%)	No. (%) of Subjects		
	Delafloxacin 100 mg (N = 110)	Delafloxacin 200 mg (N = 93)	Delafloxacin 400 mg (N = 106)
Diarrhoea	8 (7%)	21 (23%)	24 (23%)
Headache	8 (7%)	6 (6%)	4 (4%)
Nausea	6 (5%)	2 (2%)	1 (1%)
Liver function test abnormal	5 (5%)	1 (1%)	0

Source: Table 2.7.4-17.

Study ML-3341-306 (Phase III)

Title: A phase 3, multi-centre, randomised, double-blind, comparator-controlled study to evaluate the safety and efficacy of intravenous to oral delafloxacin in adult subjects with community-acquired bacterial pneumonia

Patient exposure

In ML-3341-306, in total 856 subjects (429 delafloxacin subjects and 427 moxifloxacin subjects) received at least one dose of study medication (Safety population). The mean duration of exposure for the delafloxacin and moxifloxacin groups was similar (8.4 days and 8.5 days, respectively). For both treatment groups, the median total exposure was 9.0 days, with 6.0 days for IV exposure and 2.0 days for oral exposure. For most subjects (59.2% in the delafloxacin group and 62.3% in the moxifloxacin group), exposure was >8 to 10 days. A tabular overview of exposure is shown in Table 71. The median number of IV doses was 12.0 in both treatment groups. Subject disposition (safety population) is shown in Table 72.

Table 71 Study Drug Exposure (Safety Population) – ML-3341-306

Variable	Delafloxacin (N = 429)	Moxifloxacin (N = 427)
Duration of exposure, days		
mean (SD)	8.4 (1.85)	8.5 (1.93)
Median	9.0	9.0
Min, Max	1, 10	0.5, 10
Duration of oral exposure, days		
mean (SD)	2.1 (2.12)	2.2 (2.22)
Median	2.0	2.0
Min, Max	0, 7	0, 7
Duration of IV exposure, days		
mean (SD)	6.3 (2.33)	6.3 (2.32)
Median	6.0	6.0
Min, Max	1, 10	0.5, 10
No. of IV doses		
mean (SD)	12.6 (4.67)	12.6 (4.64)
Median	12.0	12.0
Min, Max	2, 20	1, 20
Duration of exposure, n (%)		
0 days	0	0
0.5 to 4 days	12 (2.8)	15 (3.5)
> 4 to 8 days	163 (38.0)	146 (34.2)
> 8 to 10 days	254 (59.2)	266 (62.3)

Table 72 Subject Disposition (Safety Population) – ML-3341-306

Disposition Category	Delafloxacin (N = 429)	Moxifloxacin (N = 427)	Total (N = 856)
Total number of subjects (n [%]) who:			
Completed study through TOC	394 (91.8)	389 (91.1)	783 (91.5)
Prematurely discontinued from study	35 (8.2)	38 (8.9)	73 (8.5)
Primary reasons for withdrawal from study, n (%)			
Lack of efficacy	12 (2.8)	15 (3.5)	27 (3.2)
AE	13 (3.0)	6 (1.4)	19 (2.2)
Withdrawal by subject	2 (0.5)	9 (2.1)	11 (1.3)
Other	6 (1.4)	2 (0.5)	8 (0.9)
Physician decision	0	3 (0.7)	3 (0.4)
Other	0	3 (0.7)	3 (0.4)
Lost to follow-up	0	3 (0.7)	3 (0.4)

Death	2 (0.5)	0	2 (0.2)
Total number of subjects (n [%]) who:			
Completed study drug	399 (93.0)	399 (93.4)	798 (93.2)
Completed at least 10 doses of study drug / placebo	417 (97.2)	412 (96.5)	829 (96.8)
Prematurely discontinued from study drug	30 (7.0)	28 (6.6)	58 (6.8)
Primary reasons for withdrawal from study drug, n (%)			
Lack of efficacy	13 (3.0)	13 (3.0)	26 (3.0)
Lost to follow-up	0	1 (0.2)	1 (0.1)
Physician decision	0	3 (0.7)	3 (0.4)
Other	0	3 (0.7)	3 (0.4)
Withdrawal by subject	1 (0.2)	4 (0.9)	5 (0.6)
AE	14 (3.3)	7 (1.6)	21 (2.5)
Death	1 (0.2)	0	1 (0.1)
Other	1 (0.2)	0	1 (0.1)

Abbreviations: AE = adverse event; TOC = Test of Cure. Source ML-3341-306 End-of-Text Table 14.1.2.1.7.

Adverse events

Overall, 131 subjects (30.5%) in the delafloxacin group and 112 subjects (26.2%) in the moxifloxacin group experienced a total of 215 and 204 treatment-emergent adverse events (TEAEs), respectively (

Table 73). Of these subjects, 65 (15.2%) in the delafloxacin group and 54 (12.6%) in the moxifloxacin group experienced TEAEs that were considered at least possibly related to study drug. In both treatment groups, most TEAEs were assessed as mild in severity; 19 subjects (4.4%) in the delafloxacin group and 14 subjects (3.3%) in the moxifloxacin group had TEAEs assessed as severe.

Table 73 Overall Summary of Treatment-Emergent Adverse Events (Safety Population)—ML-3341-306

TEAE Category	Delafloxacin (N = 429)	Moxifloxacin (N = 427)
Total no. of TEAEs	215	204
No. (%) of subjects with any ^a		
TEAE	131 (30.5)	112 (26.2)
TEAE at least possibly related to study treatment ^b	65 (15.2)	54 (12.6)
TEAE by maximum severity ^a		
Mild	67 (15.6)	56 (13.1)
Moderate	45 (10.5)	42 (9.8)
Severe	19 (4.4)	14 (3.3)
Serious TEAE	23 (5.4)	20 (4.7)
Related serious TEAE ^b	3 (0.7) ^c	0
TEAE leading to study drug discontinuation	15 (3.5)	7 (1.6)
Related TEAE leading to study drug discontinuation ^b	9 (2.1)	4 (0.9)
TEAE leading to death	9 (2.1)	7 (1.6)
TEAE of special interest	34 (7.9)	32 (7.5)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: TEAEs were coded using MedDRA, version 19.1.

^a At each level of subject summarization, a subject with 1 or more reported TEAEs was counted only once, and the most severe reported TEAE was used for the maximum severity.

^b Related includes possibly, probably, and definitely related.

^c One TEAE was updated by the Investigator to unrelated after clinical study database lock (ML-3341-306 Section 12.3.3.1). The updated subject count is 2 (0.5).

Source: ML-3341-306 End-of-Text Table 14.3.1.1, Section 2.7.4.2.1 Table 2.7.4-5

Common Adverse Events

No TEAE was reported in $\geq 5\%$ of subjects in either treatment group. Total TEAEs and related TEAEs (ADRs) reported in $\geq 1\%$ of subjects in one or both treatment groups are shown in (Table 74).

Pulmonary embolism was reported in 1 subject (0.2%) in the delafloxacin group and 6 subjects (1.4%) in the moxifloxacin group; in 1 and 4 subjects in the delafloxacin and moxifloxacin groups, respectively, the event was considered an SAE. Only 1 of the events was considered related to study drug (moxifloxacin) by the Investigator.

In both treatment groups, about half of the TEAEs were considered related to study drug. The most common related TEAEs were diarrhoea (3.7% [16 subjects]) and transaminases increased (2.6% [11 subjects]) in the delafloxacin group and diarrhoea (3.0% [13 subjects]) and headache (2.3% [10 subjects]) in the moxifloxacin group (CSR End-of-Text Table 14.3.1.7).

Table 74 Summary of Treatment-Emergent Adverse Events (total and related) in $> 1\%$ of Subjects in Any Treatment Group (Safety Population) – ML-3341-306

MedDRA System Organ Class (SOC) and Adverse Event (Preferred Term [PT])	No. (%) of Subjects With TEAE ^a			
	Delafloxacin (N = 429)		Moxifloxacin (N = 427)	
	Total	Related ^a	Total	Related ^a
No. of TEAEs	215	83 ^b	204	73
Subjects with any TEAE, n (%) ^c	131 (30.5)	65 (15.2)	112 (26.2)	54 (12.6)
Gastrointestinal Disorders				
Diarrhea	20 (4.7)	16 (3.7)	14 (3.3)	13 (3.0)
Nausea	5 (1.2)	3 (0.7)	5 (1.2)	4 (0.9)
Investigations				
Hepatic enzyme increased	20 (4.7)	16 (3.7)	11 (2.6)	8 (1.9)
Nervous System Disorders				
Headache	8 (1.9)	2 (0.5)	11 (2.6)	10 (2.3)
Metabolism and Nutrition Disorders				
Hypokalemia ^e	9 (2.1)	1 (0.2)	2 (0.5)	0
Hyperglycemia ^f	2 (0.5)	0	7 (1.6)	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders				
Pulmonary embolism	1 (0.2)	0	6 (1.4)	1 (0.2)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: TEAEs were coded using MedDRA, version 19.1. Related includes possibly, probably, and definitely related.

^b One TEAE was updated by the Investigator to unrelated after clinical study database lock (ML-3341-306 Section 12.3.3.1). The updated TEAE count is 82.

^c At each level of subject summarization, a subject with 1 or more reported TEAEs was counted only once.

^e Refer to Section 12.3.3.3.1.

^f Refer to Section 12.3.3.3.3.4.

^g Refer to Section 12.2.3.

Sources: ML-3341-306 End-of-Text Tables 14.3.1.3 and 14.3.1.7

TEAEs by Severity

In both treatment groups, most TEAEs were assessed as either mild or moderate in severity. Severe TEAEs are shown in Table 75 below.

A total of 33 subjects had 1 or more severe TEAE: 19 subjects (4.4%) in the delafloxacin group and 14 subjects (3.3%) in the moxifloxacin group. The severe TEAEs were single events, except for septic shock and pneumonia (3 subjects [0.7%] each) in the delafloxacin group and cardiac failure and pulmonary embolism (2 subjects [0.5%] each) in the moxifloxacin group (Table 75). One subject in the moxifloxacin group had staphylococcal bacteremia (reported as metastatic *S. aureus* infection), beginning on Day 24, that was considered unrelated to the study drug by the Investigator.

Sudden death was reported in a subject in the moxifloxacin group, but was considered unrelated to study drug upon autopsy by the investigator.

Table 75 Summary of Severe Treatment-Emergent Adverse Events (Safety Population)—ML-3341-306

MedDRA System Organ Class (SOC) and Adverse Event (Preferred Term [PT])	No. (%) of Subjects	
	Delafloxacin (N = 429)	Moxifloxacin (N = 427)
Total no. of severe TEAEs ^a	24	19
Subjects with any severe TEAE, n (%) ^a	19 (4.4)	14 (3.3)
Gastrointestinal Disorders	2 (0.5)	1 (0.2)
Gastrointestinal hemorrhage	1 (0.2)	0
Thrombosis mesenteric vessel	1 (0.2)	0
Duodenal ulcer	0	1 (0.2)
Investigations	0	1 (0.2)
Transaminases increased	0	1 (0.2)
Infections and Infestations	8 (1.9)	3 (0.7)
Septic shock	3 (0.7)	1 (0.2)
<i>Clostridium difficile</i> colitis	1 (0.2)	0
Herpes zoster	1 (0.2)	0
meningomyelitis Pneumonia	3 (0.7)	1 (0.2)
Sepsis	1 (0.2)	0
Staphylococcal bacteremia	0	1 (0.2)
Subcutaneous abscess	0	1 (0.2)
Nervous System Disorders	0	2 (0.5)
Cerebrovascular accident	0	1 (0.2)
Ischemic stroke	0	1 (0.2)
Vascular Disorders	1 (0.2)	0
Hypertensive crisis	1 (0.2)	0
General Disorders and Administration Site Conditions	1 (0.2)	1 (0.2)
Infusion site pain	1 (0.2)	0
Sudden death	0	1 (0.2)
Psychiatric Disorders	0	1 (0.2)
Delirium	0	1 (0.2)
Cardiac Disorders	3 (0.7)	4 (0.9)
Cardiac failure	1 (0.2)	2 (0.5)
Cardiomyopathy	1 (0.2)	0
Myocardial infarction	1 (0.2)	0
Acute myocardial infarction	0	1 (0.2)
Atrial thrombosis	0	1 (0.2)
Respiratory, Thoracic and Mediastinal Disorders	1 (0.2)	3 (0.7)
Acute respiratory failure	1 (0.2)	0
Pulmonary embolism	0	2 (0.5)
Pulmonary edema	0	1 (0.2)

Blood and Lymphatic System Disorders	2 (0.5)	0
Agranulocytosis	1 (0.2)	0
Pancytopenia	1 (0.2)	0
Splenic vein thrombosis	1 (0.2)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.2)	0
Bursitis	1 (0.2)	0
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	1 (0.2)	0
Lung cancer metastatic	1 (0.2)	0
Renal and Urinary Disorders	0	1 (0.2)
Acute kidney injury	0	1 (0.2)
Immune System Disorders	1 (0.2)	0
Hypersensitivity	1 (0.2)	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: TEAEs were coded using MedDRA, version 19.1.

The total number of TEAEs counts all TEAEs for subjects. At each level of subject summarization, a subject was counted once if the subject reported 1 or more TEAEs.

Source: ML-3341-306 End-of-Text Table 14.3.1.5.

Serious adverse event/deaths/other significant events

Deaths

A summary of TEAEs leading to death is provided in Table 76. Nine subjects (2.1%) in the delafloxacin group and 7 subjects (1.6%) in the moxifloxacin group had TEAEs leading to death. Two deaths, one in each treatment groups, occurred after Day 28. All events were considered unrelated to study drug.

Of the 6 subjects in the delafloxacin treatment group who had causes of death grouped under the Infections and Infestations System Organ Class (SOC) (Table 76), 4 died of sepsis / septic shock. Two of the subjects, both diabetic, were critically ill at study entry; one, in PORT Risk Class IV, had underlying pulmonary fibrosis with no baseline pathogen identified, and the other, in PORT Risk Class V, was infected with both MSSA and *S. pneumoniae*. Two subjects appeared to have an intra-abdominal source for sepsis. The 2 remaining subjects had their deaths attributed to pneumonia. One subject in PORT Risk Class III with *P. aeruginosa* identified in his baseline sputum culture developed marked mental status changes and died of cardiopulmonary arrest within the first ~24 hours of the study. The other subject, also in PORT Risk Class III, had *S. pneumoniae* at baseline; he was considered a clinical success at EOT, but he developed recurrent symptoms by the time of the TOC Visit. The subject died the following day at another facility after being referred for further assessment. The cause of death entered on the death certificate was "ARDS secondary to COPD."

One patient in the delafloxacin treatment group died for unknown cause. The patient had a history of anemia, bicytopenia and agranulocytosis. During the study, non-serious leukopenia and neutropenia were recorded on Day 5. The patient was discharged from hospital on Day 7 and considered a clinical cure at the EOT visit on Day 12, with improvement in neutropenia compared with screening. The patient was re-hospitalized on Day 15 for agranulocytosis and died on Day 27 of unknown cause. Further details were not available. The Investigator considered the event as being not related to study drug, and the Sponsor agreed with this assessment.

Table 76 Summary of Treatment-Emergent Adverse Events Leading to Death (Safety Population) — ML-3341-306

MedDRA System Organ Class (SOC) and Adverse Event (Preferred Term [PT])	No. (%) of Subjects	
	Delafloxacin (N = 429)	Moxifloxacin (N = 427)

Total number of TEAEs leading to death ^a	9	7
Subjects with at least one TEAE leading to death ^a	9 (2.1)	7 (1.6)
Infections and Infestations	6 (1.4)	2 (0.5)
Septic shock	3 (0.7)	1 (0.2)
Pneumonia	2 (0.5)	1 (0.2)
Sepsis	1 (0.2)	0
Blood and Lymphatic System Disorders	1 (0.2)	0
Agranulocytosis	1 (0.2)	0
Cardiac Disorders	1 (0.2)	0
Myocardial infarction	1 (0.2)	0
Respiratory, Thoracic, and Mediastinal Disorders	1 (0.2)	3 (0.7)
Acute respiratory failure	1 (0.2)	0
Pulmonary embolism	0	2 (0.5)
Pulmonary edema	0	1 (0.2)
General Disorders and Administration Site Conditions	0	1 (0.2)
Sudden death	0	1 (0.2)
Nervous System Disorders	0	1 (0.2)
Cerebrovascular accident	0	1 (0.2)

Abbreviations: AE = adverse event; FU = Follow-up; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an AE that began (or a preexisting event that worsened in severity) after receiving the first dose of the study drug through FU. TEAEs were coded using MedDRA, version 19.1.

The total number of TEAEs counts all TEAEs for subjects. Within an SOC, a subject was counted once if the subject reported more than 1 type of TEAE.

Source: ML-3341-306 End-of-Text Table 14.3.1.14.3.

Other Serious Adverse Events

A total of 43 subjects reported 51 SAEs during the study: 23 subjects (5.4%) in the delafloxacin group experienced a total of 26 SAEs, and 20 subjects (4.7%) in the moxifloxacin group experienced a total of 25 SAEs (Table 77). All 51 SAEs were treatment-emergent.

Table 77 Summary of Treatment-Emergent Serious Adverse Events (Safety Population)—ML-3341-306

MedDRA System Organ Class (SOC) and Adverse Event (Preferred Term [PT])	No. (%) of Subjects	
	Delafloxacin (N = 429)	Moxifloxacin (N = 427)
Total no. of serious TEAEs ^a	26	25
Subjects with any serious TEAE, n (%) ^a	23 (5.4)	20 (4.7)
Infections and Infestations	10 (2.3)	6 (1.4)
Pneumonia	3 (0.7)	1 (0.2)
Septic shock	3 (0.7)	1 (0.2)
<i>Clostridium difficile</i> colitis	1 (0.2)	1 (0.2)
Herpes zoster meningomyelitis	1 (0.2)	0
Infectious pleural effusion	1 (0.2)	0
Lung abscess	1 (0.2)	0
Sepsis	1 (0.2)	0
Measles	0	1 (0.2)
Oral herpes	0	1 (0.2)
Staphylococcal bacteremia	0	1 (0.2)
Respiratory, Thoracic, and Mediastinal Disorders	4 (0.9)	6 (1.4)
Chronic obstructive pulmonary disease	2 (0.5)	0
Acute respiratory failure	1 (0.2)	0
Pulmonary embolism	1 (0.2)	4 (0.9)
Pleurisy	0	1 (0.2)
Pulmonary edema	0	1 (0.2)

Cardiac Disorders	2 (0.5)	4 (0.9)
Cardiomyopathy	1 (0.2)	0
Myocardial infarction	1 (0.2)	0
Acute myocardial infarction	0	1 (0.2)
Atrial fibrillation	0	1 (0.2)
Cardiac failure	0	2 (0.5)
Cardiac failure acute	0	2 (0.5)
Immune System Disorders	2 (0.5)	0
Hypersensitivity	1 (0.2)	0
Sarcoidosis	1 (0.2)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	2 (0.5)	0
Lung cancer metastatic	1 (0.2)	0
Metastatic malignant melanoma	1 (0.2)	0
Blood and Lymphatic System Disorders	1 (0.2)	0
Agranulocytosis	1 (0.2)	0
Gastrointestinal Disorders	1 (0.2)	1 (0.2)
Gastrointestinal hemorrhage	1 (0.2)	0
Duodenal ulcer	0	1 (0.2)
Musculoskeletal and Connective Tissue Disorders	1 (0.2)	0
Bursitis	1 (0.2)	0
Vascular Disorders	1 (0.2)	0
Hypertensive crisis	1 (0.2)	0
General Disorders and Administration Site Conditions	0	1 (0.2)
Sudden death	0	1 (0.2)
Nervous System Disorders	0	3 (0.7)
Cerebrovascular accident	0	1 (0.2)
Ischemic stroke	0	1 (0.2)
Vertebrobasilar insufficiency	0	1 (0.2)
Psychiatric Disorders	0	1 (0.2)
Delirium	0	1 (0.2)
Renal and Urinary Disorders	0	1 (0.2)
Acute kidney injury	0	1 (0.2)

Abbreviations: AE = adverse event; FU = Follow-up; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an AE that began (or a preexisting event that worsened in severity) after receiving the first dose of the study drug through FU. TEAEs were coded using MedDRA, version 19.1.

The total number of TEAEs counts all TEAEs for subjects. Within an SOC, a subject was counted once if the subject reported more than 1 type of AE.

Source: ML-3341-306 End-of-Text Table 14.3.1.15.1.

Three subjects in the delafloxacin treatment group had SAEs of pneumonia: 2 of the 3 subjects died. The third subject, who had MSSA identified at baseline, responded favourably to delafloxacin therapy but developed recurrent fever and poor O₂ saturation around Day 7; this was considered a new hospital-acquired infection and the patient was treated with other antibiotics. The moxifloxacin-treated subject with an SAE of pneumonia with baseline MSSA was discontinued after 6 doses because of disease progression. Follow-up cultures were not done for these 4 subjects. Narratives for these subjects can be found in Section 2.7.4, Appendix 2.

Most SAEs were single events; SAEs that occurred in more than 1 subject were septic shock and pneumonia (3 subjects (0.7%) each) and COPD (2 subjects (0.5%)) in the delafloxacin group and pulmonary embolism (4 subjects (0.9%)) and cardiac failure and acute cardiac failure (2 subjects [0.5%] each) in the moxifloxacin group.

Two subjects in the delafloxacin group had SAEs that were considered related to study drug by the Investigator. Both related SAEs resulted in discontinuation of study drug.

Clinical Laboratory Adverse Events

In both treatment groups, most clinical laboratory TEAEs were reported in a single subject (Table 78). In the delafloxacin group, clinical laboratory TEAEs reported in more than 1 subject were transaminases increased

(13 subjects (3.0%)), hypokalaemia (8 subjects (1.9%)), alanine aminotransferase (ALT) increased (4 subjects (0.9%)), hepatic enzyme increased, anaemia, and leukopenia (3 subjects (0.7%) each), and hyperglycaemia (2 subjects (0.5%)).

In the moxifloxacin group, clinical laboratory TEAEs reported in more than 1 subject were transaminases increased and hyperglycaemia (6 subjects (1.4%) each), hepatic enzyme increased and hypoglycaemia (3 subjects (0.7%) each), and ALT increased, blood creatine phosphokinase increased, anaemia, hypokalaemia, and leukocytosis (2 subjects (0.5%) each).

Hypokalemia was reported in 8 subjects (1.9%) in the delafloxacin group and 2 subjects (0.5%) in the moxifloxacin group. Hypokalemia was assessed as mild in 8 of 10 subjects overall, and as moderate in 2 of 8 subjects in the delafloxacin group. In all but 1 subject, hypokalemia was considered unrelated to the study drug by the Investigator: in 1 subject in the delafloxacin group, hypokalemia was assessed as mild and possibly related to study drug. Hypokalemia resolved in all subjects on or before Day 12. Five of 8 subjects in the delafloxacin group were receiving concomitant medications that could have played a role in their hypokalemia: 4 were receiving loop diuretics (furosemide, indapamide, or torasemide) and 1 subject received high-dose IV hydrocortisone 3 days before the hypokalemia. In all 10 subjects, hypokalemia resolved with drug treatment, and no subject discontinued delafloxacin because of the hypokalemia.

In addition, 1 subject in the delafloxacin group had an AE of decreased blood potassium on Day 5 which was assessed as mild and unrelated by the Investigator and resolved on the same day following treatment with potassium chloride.

Of the clinical laboratory TEAEs, the events that were reported as related to the study drug by the Investigator in more than 1 subject were transaminases increased (11 subjects (2.6%)), hepatic enzyme increased (3 subjects (0.7%)), and ALT increased and anemia (2 subjects (0.5%) each) in the delafloxacin group; and transaminases increased (4 subjects (0.9%)), hepatic enzyme increased (3 subjects (0.7%)), and hyperglycemia (2 subjects (0.5%)) in the moxifloxacin group.

Table 78 Summary of Subjects With Laboratory Treatment-Emergent Adverse Events (Safety Population)

MedDRA System Organ Class (SOC) and Adverse Event (Preferred Term [PT]) ^a	No. (%) of Subjects			
	Delafloxacin (N =429)		Moxifloxacin (N = 427)	
	Total	Related ^b	Total	Related ^b
Investigations				
Transaminases increased	13 (3.0)	11 (2.6)	6 (1.4)	4 (0.9)
ALT increased	4 (0.9)	2 (0.5)	2 (0.5)	1 (0.2)
Hepatic enzyme increased	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)
Blood potassium decreased	1 (0.2)	0	0	0
Blood potassium increased	1 (0.2)	1 (0.2)	0	0
GGT increased	1 (0.2)	1 (0.2)	0	0
Hemoglobin decreased	1 (0.2)	1 (0.2)	0	0
INR increased	1 (0.2)	1 (0.2)	1 (0.2)	0
Blood creatine phosphokinase increased	0	0	2 (0.5)	1 (0.2)
Blood creatinine increased	0	0	1 (0.2)	1 (0.2)
Blood glucose increased	0	0	1 (0.2)	0
Blood urea increased	0	0	1 (0.2)	1 (0.2)
Prothrombin level decreased	0	0	1 (0.2)	0

Metabolism and Nutrition Disorders				
Hypokalemia	8 (1.9)	1 (0.2)	2 (0.5)	0
Hyperglycemia	2 (0.5)	0	6 (1.4)	2 (0.5)
Hypercholesterolemia	1 (0.2)	0	0	0
Hyperuricemia	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Hypoalbuminemia	1 (0.2)	0	1 (0.2)	0
Hypomagnesemia	1 (0.2)	0	0	0
Dyslipidemia	0	0	1 (0.2)	0
Hypoglycemia	0	0	3 (0.7)	1 (0.2)
Blood and Lymphatic System Disorders				
Anemia	3 (0.7)	2 (0.5)	2 (0.5)	1 (0.2)
Leukopenia	3 (0.7)	1 (0.2)	0	0
Agranulocytosis	1 (0.2)	1 (0.2) ^c	0	0
Neutropenia	1 (0.2)	1 (0.2)	0	0
Pancytopenia	1 (0.2)	0	0	0
Coagulopathy	0	0	1 (0.2)	0
Leukocytosis	0	0	2 (0.5)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FU, Follow-up;

GGT, γ -glutamyltransferase; INR, international normalized ratio; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.

Note: TEAEs were coded using MedDRA, version 19.1.

^a A subject could have more than 1 AE in each SOC.

^b Assessments of possibly or probably related.

^c One TEAE was updated by the investigator to unrelated after clinical study database lock (See ML-3341-306 CSR Section 12.3.3.1). The updated subject count is 0.

Source: ML-3341-306 End-of-Text Tables 14.3.1.3 and 14.3.1.7.

Individual Subject Changes

In general, mean values and changes from baseline in hematology and serum chemistry levels were similar across the treatment groups at all time points. There were no unexpected changes in either treatment group.

Individual Clinically Significant Abnormalities

With 1 exception, the treatment groups were generally similar with regard to the number of subjects who had normal hematology or chemistry values at baseline, but who later had values at ECR, EOT, or TOC that were below or above normal; there were more subjects in the delafloxacin group who had elevated ALT and AST values at EOT and TOC.

Individual Clinically Significant Abnormalities

A higher percentage of subjects in the delafloxacin group compared with the moxifloxacin group had a worst postbaseline ALT value that was $> 2 \times \text{ULN}$ (14.5% vs. 10.0%) or $> 3 \times \text{ULN}$ (5.8% vs. 3.8%), while a similar percentage of subjects in both treatment groups had an ALT value $> 5 \times \text{ULN}$ (1.4% vs. 1.6%). Likewise, a higher percentage of subjects in the delafloxacin group had a worst postbaseline AST value that was $> 2 \times \text{ULN}$ (8.2% vs. 5.4%) or $> 3 \times \text{ULN}$ (3.3% vs. 2.6%), while a similar percentage of subjects in both treatment groups had an AST value $> 5 \times \text{ULN}$ (0.9% vs. 0.5%).

One subject in the delafloxacin group and no subjects in the moxifloxacin group had a total bilirubin value that was $> 2 \times \text{ULN}$. Serum creatinine values that were $> 2 \times \text{ULN}$ or $> 3 \times \text{ULN}$ were observed in 2 and 1 subjects, respectively, in the delafloxacin group and 1 subject each in the moxifloxacin group.

No subject in either treatment group met Hy's Law criteria (i.e., ALT and / or AST $> 3 \times \text{ULN}$, total bilirubin $> 2 \times \text{ULN}$ with alkaline phosphatase $< 2 \times \text{ULN}$).

No subject had an abnormal glucose level ($< 2.22 \text{ mmol/L}$).

Vital signs, physical findings, and other observations related to safety

Vital Signs

In both treatment groups, there were minimal mean changes from baseline for any vital sign measurement (body temperature, diastolic and systolic blood pressure, heart rate, respiratory rate, oxygen saturation). At all time points, the mean values for measurements of vital signs were similar between the treatment groups. Overall, vital sign measurements improved, as expected.

Physical Examination Findings

Findings from the physical examination at Screening and at every postbaseline time point (ECR, EOT, and TOC) were similar between the treatment groups. As expected, the respiratory system exhibited the largest improvements from Screening (i.e., reduction in abnormal findings). At Screening, in the delafloxacin and moxifloxacin groups, 100.0% and 99.8% of subjects had an abnormal finding. The percentage of subjects with abnormal respiratory findings decreased at each subsequent time point and was similar between the delafloxacin and moxifloxacin groups: ECR, 36.1% and 38.2%; EOT, 17.0% and 17.3%; and TOC, 2.6% and 4.4%, respectively.

ElectrocardioGram Results

One subject (0.2%) in the moxifloxacin group had a TEAE of electrocardioGram QT prolongation. This subject was 82 years old with a history of asthma, abdominal aortic aneurysm, arterial hypertension, left bundle branch block, dyslipidemia, and type 2 diabetes mellitus. At baseline, the subject's ECG was assessed as abnormal due to a known left bundle branch block, but it was considered not clinically significant. The subject developed TEAEs of heart failure (an SAE) on Day 3 and mitral insufficiency due to the left bundle branch block and prolonged QTcF(501 ms) due to heart failure on Day 4. The TEAEs were considered unrelated to the study drug, and no action was taken with regard to study treatment because of these events. The QT prolongation resolved on Day 10.

Safety in special populations

Intrinsic Factors ML-3341-306

The incidence of TEAEs (total and related to study drug) according to intrinsic ethnic factors (age, sex, race, ethnicity, and BMI) and by medical history subgroup is presented in (Table 79). The incidence of related TEAEs by subgroup was similar between the treatment groups, with the exception of the National Institutes of Health BMI category ≤ 18.4 kg/m² (underweight), in which 3 of 12 subjects in the delafloxacin group had related AEs compared with 0 of 7 subjects in the moxifloxacin group.

Although there were some numerical differences between the treatment groups in some demographic subgroups, these subgroups had a small number of subjects; no major differences were observed in related events. Medical history subgroups (History of diabetes, Renal disease, PORT risk class, History of COPD or asthma, History of cardiac disease, History of vascular disease, etc.) were compared and no major differences were noted (Table 79).

Table 79 Incidences of Treatment-Emergent Adverse Events by Demographic Factors (Safety Population)

Subgroup	No. (%) of Subjects With Any TEAE			
	Delafloxacin (N = 429)		Moxifloxacin (N = 427)	
	Total	Related ^a	Total	Related ^a
All subjects ^b	131 (30.5)	65 (15.2)	112 (26.2)	54 (12.6)
Age category				
< 65 years, n	227		248	
	66 (29.1)	38 (16.7)	59 (23.8)	33 (13.3)
≥ 65 years, n	202		179	
	65 (32.2)	27 (13.4)	53 (29.6)	21 (11.7)
≥ 75 years, n	84		97	
	25 (29.8)	10 (11.9)	29 (29.9)	8 (8.2)
Sex				
Male, n	250		253	
	75 (30.0)	40 (16.0)	66 (26.1)	28 (11.1)
Female, n	179		174	
	56 (31.3)	25 (14.0)	46 (26.4)	26 (14.9)
Race				
White, n	396		387	
	120 (30.3)	61 (15.4)	102 (26.4)	48 (12.4)
Black or African American, n	22		33	
	8 (36.4)	3 (13.6)	6 (18.2)	3 (9.1)
Asian, n	5		5	
	2 (40.0)	1 (20.0)	3 (60.0)	3 (60.0)
American Indian or Alaska native, n	4		0	
	1 (25.0)	0	0	0
Other, n	2		2	
	0	0	1 (50.0)	0
Ethnicity				
Hispanic or Latino, n	31		23	
	8 (25.8)	1 (3.2)	7 (30.4)	0
Not Hispanic or Latino, n	398		404	
	123 (30.9)	64 (16.1)	105 (26.0)	54 (13.4)

Table continued on next page.

Subgroup	No. (%) of Subjects With Any TEAE			
	Delafloxacin (N = 429)		Moxifloxacin (N = 427)	
	Total	Related ^a	Total	Related ^a
BMI				
< 30 kg/m ² , n	326		316	
	99 (30.4)	49 (15.0)	83 (26.3)	41 (13.0)
≥ 30 kg/m ² , n	103		111	
	32 (31.1)	16 (15.5)	29 (26.1)	13 (11.7)
NIH BMI category, kg/m²				
≤ 18.4 (underweight), n	12		7	
	4 (33.3)	3 (25.0)	0	0
18.5 to 24.9 (normal weight), n	164		165	
	49 (29.9)	27 (16.5)	43 (26.1)	24 (14.5)
25 to 29.9 (overweight), n	150		143	
	46 (30.7)	19 (12.7)	40 (28.0)	17 (11.9)
≥ 30 (obese), n	103		112	
	32 (31.1)	16 (15.5)	29 (25.9)	13 (11.6)

Abbreviations: BMI, body mass index; NIH, National Institutes of Health; TEAE, treatment-emergent adverse event.

^a Related includes possibly, probably, and definitely related.

^b At each level of subject summarization, a subject with 1 or more reported TEAEs was counted only once.

Sources: End-of-Text Tables 14.3.1.3, 14.3.1.4.1, 14.3.1.4.2, 14.3.1.4.3, 14.3.1.4.4, 14.3.1.4.5, 14.3.1.4.12, 14.3.1.7, 14.3.1.8.1, 14.3.1.8.2, 14.3.1.8.3, 14.3.1.8.4, 14.3.1.8.5, and 14.3.1.8.12.

Incidences of TEAEs by subgroup

Renally impaired patients with mild and moderate renal impairment were included in the Phase III study. Patients with severe renal impairment and ESRD patients were not included. However, according to Table 80, 17 patients with severe renal impairment are reported in the delafloxacin arm and 15 patients in the moxifloxacin arm.

Numerical differences in the incidence of TEAEs are observed. However, these differences appear less pronounced when looking at ADRs. The small sample size for some subgroups is acknowledged.

Table 80 Incidences of Treatment-Emergent Adverse Events by Subgroup (Safety Population)

Subgroup	No. (%) of Subjects With Any TEAE			
	Delafloxacin (N = 429)		Moxifloxacin (N = 427)	
	Total	Related ^a	Total	Related ^a
All subjects ^b	131 (30.5)	65 (15.2)	112 (26.2)	54 (12.6)
History of diabetes				
Yes	70		60	
	34 (48.6)	13 (18.6)	20 (33.3)	7 (11.7)
No	359		367	
	97 (27.0)	52 (14.5)	92 (25.1)	47 (12.8)
Renal disease ^c				
Yes (CrCl < 90 mL/min)	227		219	
	74 (32.6)	38 (16.7)	65 (29.7)	30 (13.7)
No (CrCl ≥ 90 mL/min)	193		199	
	54 (28.0)	25 (13.0)	45 (22.6)	23 (11.6)
Renal impairment category (BSA) ^d				
Severe (CrCl ≤ 29 mL/min)	17		15	
	5 (29.4)	1 (5.9)	6 (40.0)	2 (13.3)
Moderate (CrCl 30 to 59 mL/min)	156		154	
	50 (32.1)	28 (17.9)	49 (31.8)	20 (13.0)
Mild (CrCl 60 to 89 mL/min)	147		155	
	43 (29.3)	16 (10.9)	34 (21.9)	23 (14.8)
Normal (CrCl ≥ 90 mL/min)	100		94	
	30 (30.0)	18 (18.0)	21 (22.3)	8 (8.5)
PORT Risk Class				
II	53		57	
	15 (28.3)	11 (20.8)	13 (22.8)	8 (14.0)
III	258		259	
	74 (28.7)	35 (13.6)	66 (25.5)	33 (12.7)
IV	114		103	
	39 (34.2)	19 (16.7)	31 (30.1)	12 (11.7)
V	4		8	
	3 (75.0)	0	2 (25.0)	1 (12.5)
History of COPD or asthma				
Yes	61		55	
	22 (36.1)	14 (23.0)	11 (20.0)	3 (5.5)
No	368		372	
	109 (29.6)	51 (13.9)	101 (27.2)	51 (13.7)

Table continued on next page.

Subgroup	No. (%) of Subjects With Any TEAE			
	Delafloxacin (N = 429)		Moxifloxacin (N = 427)	
	Total	Related ^a	Total	Related ^a
CURB-65 score				
0 to 1	250		259	
	75 (30.0)	37 (14.8)	67 (25.9)	36 (13.9)
2	143		133	
	46 (32.2)	22 (15.4)	34 (25.6)	14 (10.5)
3 to 5	28		29	
	7 (25.0)	5 (17.9)	10 (34.5)	3 (10.3)
Baseline hospitalization in last 90 days/nursing home status				
Yes	15		6	
	7 (46.7)	2 (13.3)	1 (16.7)	1 (16.7)
No	414		421	
	124 (30.0)	63 (15.2)	111 (26.4)	53 (12.6)
History of cardiac disease				
Yes	104		99	
	34 (32.7)	14 (13.5)	37 (37.4)	13 (13.1)
No	325		328	
	97 (29.8)	51 (15.7)	75 (22.9)	41 (12.5)
History of vascular disease				
Yes	218		198	
	73 (33.5)	32 (14.7)	53 (26.8)	25 (12.6)
No	211		229	
	58 (27.5)	33 (15.6)	59 (25.8)	29 (12.7)
History of vascular or cardiac disease				
Yes	241		225	
	80 (33.2)	37 (15.4)	63 (28.0)	27 (12.0)
No	188		202	
	51 (27.1)	28 (14.9)	49 (24.3)	27 (13.4)

Abbreviations: BSA, body surface area; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; CURB-65, confusion, urea, respiratory rate, blood pressure, age 65 or older; PORT, Patient Outcomes Research Team; TEAE, treatment-emergent adverse event.

a Related includes possibly, probably, and definitely related.

b At each level of subject summarization, a subject with 1 or more reported TEAEs was counted only once.

c CrCl was based on the Cockcroft-Gault formula without correction for BSA.

d CrCl was based on the Cockcroft-Gault formula corrected for BSA (i.e., corrected for each subject using the subject's weight and height).

Sources: End-of-Text Tables 14.3.1.3, 14.3.1.4.6, 14.3.1.4.7, 14.3.1.4.8, 14.3.1.4.9, 14.3.1.4.10, 14.3.1.4.11, 14.3.1.4.13, 14.3.1.4.14, 14.3.1.4.15, 14.3.1.4.16, 14.3.1.4.17, 14.3.1.7, 14.3.1.8.1, 14.3.1.8.2, 14.3.1.8.3, 14.3.1.8.4, 14.3.1.8.5, 14.3.1.8.6, 14.3.1.8.7, 14.3.1.8.8, 14.3.1.8.9, 14.3.1.8.10, 14.3.1.8.11, 14.3.1.8.12, 14.3.1.8.13, 14.3.1.8.14, 14.3.1.8.15, 14.3.1.8.16, and 14.3.1.8.17.

Safety related to drug-drug interactions and other interactions

No known drug-drug interactions have been observed in the clinical studies to date.

Regarding the evaluation of the safety of delafloxacin related to interaction with midazolam (ABSSSI MAA, study ML-3341-118) and in vitro interaction data, please refer to initial ABSSSI MAA.

Discontinuation due to adverse events

A total of 22 subjects had treatment withdrawn because of a TEAE: 15 subjects (3.5%) in the delafloxacin group and 7 subjects (1.6%) in the moxifloxacin group (Table 81). In the delafloxacin group, 9 subjects (2.1%) had treatment withdrawn because of related TEAEs; while in the moxifloxacin group, 4 subjects (0.9%) had treatment withdrawn because of related TEAEs. A subject listing of these TEAEs is provided in module 2.7.4, Table 2.7.4-13.

In the delafloxacin group, 15 subjects had single events leading to study drug discontinuation. In 7 subjects, the event was an SAE; in 2 of these subjects, the event was fatal (SAEs of pneumonia and myocardial infarction). The TEAEs were assessed as moderate in 11 subjects and severe in 4 subjects. In the 9 subjects with related TEAEs leading to discontinuation, 6 of the TEAEs were assessed as possibly related; 2, as definitely related (TEAEs of hypersensitivity and hepatic enzyme increased); and 1, as probably related.

In the moxifloxacin group, 6 of 7 subjects had single events leading to study drug discontinuation; 1 subject had 2 TEAEs (infusion-site erythema and infusion-site swelling). In 3 subjects, the event was an SAE, and in 1 of these subjects, the event was fatal (SAE of pulmonary edema). The TEAEs were assessed as mild in 1 subject, moderate in 5 subjects, and severe in 1 subject. Of the related TEAEs leading to discontinuation, 3 were assessed as probably related; 1, as possibly related; and 1, as definitely related (pruritic rash).

Table 81 Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (Safety Population)—ML-3341-306

MedDRA System Organ Class (SOC) and Adverse Event (Preferred Term [PT])	No. (%) of Subjects			
	Delafloxacin (N = 429)		Moxifloxacin (N = 427)	
	Total	Related	Total	Related
Total no. of TEAEs leading to study drug discontinuation ^a	15	9	8	5
Subjects with any TEAE leading to study drug discontinuation, n (%) ^a	15 (3.5)	9 (2.1)	7 (1.6)	4 (0.9)
Infections and Infestations	4 (0.9)	1 (0.2)	1 (0.2)	0
Pneumonia	2 (0.5)	0	0	0
<i>Clostridium difficile</i> colitis	1 (0.2)	1 (0.2)	1 (0.2)	0
Lung abscess	1 (0.2)	0	0	0
Investigations	2 (0.5)	2 (0.5)	1 (0.2)	1 (0.2)
Hepatic enzyme increased	1 (0.2)	1 (0.2)	0	0
Transaminases increased	1 (0.2)	1 (0.2)	0	0
ALT increased	0	0	1 (0.2)	1 (0.2)
Skin and Subcutaneous Tissue Disorders	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Dermatitis allergic	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Urticaria	1 (0.2)	1 (0.2)	0	0
Rash pruritic	0	0	1 (0.2)	1 (0.2)
Vascular Disorders	2 (0.5)	1 (0.2)	0	0
Deep vein thrombosis	1 (0.2)	1 (0.2)	0	0
Hypertensive crisis	1 (0.2)	0	0	0
Cardiac Disorders	1 (0.2)	0	0	0
Myocardial infarction	1 (0.2)	0	0	0
Ear and Labyrinth Disorders	1 (0.2)	1 (0.2)	0	0
Vestibular disorder	1 (0.2)	1 (0.2)	0	0
Gastrointestinal Disorders	1 (0.2)	1 (0.2)	0	0
Abdominal pain upper	1 (0.2)	1 (0.2)	0	0
Immune System Disorders	1 (0.2)	1 (0.2)	0	0
Hypersensitivity	1 (0.2)	1 (0.2)	0	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.2)	0	2 (0.5)	0
Pulmonary embolism	1 (0.2)	0	1 (0.2)	0
Pulmonary edema	0	0	1 (0.2)	0
General Disorders and Administration Site Conditions	0	0	1 (0.2)	1 (0.2)
Infusion site erythema	0	0	1 (0.2)	1 (0.2)
Infusion site swelling	0	0	1 (0.2)	1 (0.2)

Abbreviations: ALT = alanine aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: TEAEs were coded using MedDRA, version 19.1.

The total number of TEAEs counts all TEAEs for subjects. Within an SOC, a subject was counted once if the subject reported more than 1 type of TEAE.

Sources: ML-3341-306 End-of-Text Tables 14.3.1.13.1 and 14.3.1.13.

Adverse Events of Special Interest

AESIs were chosen based on medical issues of interest for the fluoroquinolone class of antibiotics and taking into account the EMA review of serious, disabling and potentially permanent side effects with quinolone and fluoroquinolone antibiotics (EMA/175398/2019, November 2018). The 9 selected topics were *C. difficile* diarrhoea, dysglycaemia, hepatic-related events, potential seizures, potential myopathy, potential peripheral neuropathy, potential tendon disorder, potential QT prolongation, and potential allergic reaction. The search criteria (and Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ), where applicable) used for each medical topic are presented in the statistical analysis plan (SAP). In addition, because of recent fluoroquinolone class product labeling updates, a search for events related to potential aortic dissection / rupture was included. Finally, reflecting the EMA review, other potential neurological and psychiatric AEs were considered.

A similar percentage of subjects in the delafloxacin (7.9% (34 of 429)) and moxifloxacin groups (7.5% (32 of 427)) had AESIs (Table 82). Seven subjects in the delafloxacin group and 9 subjects in the moxifloxacin group had AESIs that lasted longer than 30 days; all but one of these (acute kidney injury in the moxifloxacin group) were hepatic-related events.

Hepatic-related events: a higher percentage of subjects in the delafloxacin group (5.1%) compared with the moxifloxacin group (2.8%) had hepatic-related TEAEs, with transaminases increased reported most frequently (3.0% and 1.4%, respectively). Most of these events were considered related to the study drug (3.7% in the delafloxacin group and 1.9% in the moxifloxacin group). There were 2 and 1 treatment discontinuations, respectively, for delafloxacin and moxifloxacin due to liver enzyme elevations. All the hepatic-related TEAEs were mild or moderate in severity in the delafloxacin group; in 1 subject in the moxifloxacin group, a TEAE of transaminases increased was considered severe. There were no SAEs due to liver abnormalities. Seven subjects in the delafloxacin group and 9 subjects in the moxifloxacin group had hepatic-related events that lasted longer than 30 days. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values $> 5 \times$ upper limit of normal (ULN) at any time during the trial were observed in a similar percentage of subjects in the delafloxacin (1.4% and 0.9%) and moxifloxacin groups (1.6% and 0.5%).

Potential allergic reactions: Eight subjects (1.9%) in the delafloxacin group and 4 subjects (0.9%) subjects in the moxifloxacin group had a potential allergic reaction. There were 3 and 2 subjects, respectively, in delafloxacin and moxifloxacin treatment groups who discontinued treatment due to potential allergic reactions: 1 subject each with allergic dermatitis, urticaria, and hypersensitivity with delafloxacin and 1 subject each with allergic dermatitis and rash pruritic on moxifloxacin. All but 1 TEAE were assessed as mild or moderate. The severe TEAE was an SAE of hypersensitivity that occurred on Day 2 in a delafloxacin-treated subject; treatment with delafloxacin was discontinued. The SAE resolved the same day with appropriate treatment.

***C. difficile* diarrhoea:** Two subjects (0.5%) in the delafloxacin group and 1 subject (0.2%) in the moxifloxacin group had a TEAE of *C. difficile* colitis. One subject in each treatment group discontinued treatment because of the AE. Two of the 3 TEAEs were SAEs (one in each treatment group). The SAE in the delafloxacin-treated subject was assessed as severe and possibly related to study drug. In 1 subject in each treatment group, onset of the TEAE was during treatment with the study drug (Days 3 and 4); in the other subject in the delafloxacin group with the severe SAE, onset of the event was on Day 17, after treatment was

completed on Day 11 and was considered a success at EOT and TOC (Day 19). In all 3 subjects, the TEAE resolved (within 10 to 17 days).

Dysglycemias: No subject withdrew from the study for dysglycemia-related TEAEs; none of these TEAEs was an SAE.

Hyperglycemia: A lower percentage of subjects in the delafloxacin group had a hyperglycemia-related TEAE compared with the moxifloxacin group (0.5% (2 of 429) vs (1.6% (7 of 427))). In the delafloxacin and moxifloxacin groups, subjects had the following hyperglycemia-related TEAEs: hyperglycemia (2 (0.5%) and 6 (1.4%) subjects, respectively) and blood glucose increased (0 and 1 (0.2%), respectively). Seven of 9 TEAEs were considered unrelated to the study drug by the Investigator. Six of the 9 subjects were reported to have diabetes or hyperglycemia at screening, of which 4 were receiving insulin and / or metformin. Four of 9 subjects received treatment (either metformin or insulin) for the hyperglycemia.

Hypoglycemia: No subject in the delafloxacin group and 3 subjects (0.7%) in the moxifloxacin group had a TEAE of hypoglycemia. In these moxifloxacin subjects, 1 of the 3 TEAEs was considered mild, and the other 2 TEAEs were considered moderate. Onsets of the TEAEs were Days 6, 10, and 14; in 2 subjects, the subject recovered the same day. Two of the TEAEs were assessed as unrelated, and one was assessed as related to the study drug. Two of the 3 subjects were reported to have diabetes or hyperglycemia at screening.

Potential myopathy: No subjects in the delafloxacin group and 5 subjects (1.2%) in the moxifloxacin group had a potential myopathy-related TEAE. These TEAEs were blood creatine phosphokinase increased (2 (0.5%) subjects) and acute kidney injury, blood creatinine increased, and myalgia (1 (0.2%) subject each). None of these events led to treatment discontinuation. No subject had documented myopathy.

Potential QT prolongation: There were no potential QT-prolongation events with delafloxacin. Two subjects (0.5%) in the moxifloxacin group had a TEAE in the SMQ of potential QT prolongation. The TEAEs were sudden death and ECG QT prolonged. Sudden death occurred in a subject on Day 20, after the subject had completed 9 IV doses of moxifloxacin. The Investigator considered the event unrelated to study drug. Cause of death was heart failure. Another subject had a prolonged QT interval corrected with the Fridericia formula (QTcF) on Day 4 that was considered mild (QTcF measurements at screening and Day 4 were 345 and 501 ms, respectively) and unrelated to the study drug. At screening, the subject was noted to have a left bundle branch block.

Potential tendon disorder: No subject in either treatment group experienced a potential tendon disorder TEAE.

Potential phototoxicity: No subject in either treatment group experienced a potential phototoxicity TEAE.

Potential aortic rupture / dissection: There were no events of aortic rupture / dissection in subjects treated with delafloxacin. There was 1 case of sudden death in a moxifloxacin subject, with no further information regarding cause of death.

Potential peripheral neuropathy: No subject in either treatment group experienced a potential peripheral neuropathy TEAE.

Table 82 Treatment-Emergent Adverse Events of Special Interest by Type and Preferred Term (Safety Population) — ML-3341-306

MedDRA System Organ Class (SOC) and Adverse Event (Preferred Term [PT])	No. (%) of Subjects			
	Delafloxacin (N = 429)		Moxifloxacin (N = 427)	
	Total	Related ^a	Total	Related ^a

Total no. of AESIs ^b	35	25	34	16
Subjects with any AESI, n (%) ^b	34 (7.9)	24 (5.6)	32 (7.5)	16 (3.7)
Hepatic-related events	22 (5.1)	16 (3.7)	12 (2.8)	8 (1.9)
Transaminases increased	13 (3.0)	11 (2.6)	6 (1.4)	4 (0.9)
ALT increased	4 (0.9)	2 (0.5)	2 (0.5)	1 (0.2)
Hepatic enzyme increased	3 (0.7)	3 (0.7)	3 (0.7)	3 (0.7)
Hepatic steatosis	2 (0.5)	0	0	0
GGT increased	1 (0.2)	1 (0.2)	0	0
Hepatic lesion	0	0	1 (0.2)	0
Potential allergic reactions	8 (1.9)	6 (1.4)	4 (0.9)	3 (0.7)
Rash	2 (0.5)	2 (0.5)	0	0
Urticaria	2 (0.5)	2 (0.5)	0	0
Bronchospasm	1 (0.2)	0	1 (0.2)	0
Dermatitis allergic	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)
Gingival swelling	1 (0.2)	0	0	0
Hypersensitivity	1 (0.2)	1 (0.2)	0	0
Rash pruritic	0	0	1 (0.2)	1 (0.2)
C difficile diarrhoea	2 (0.5)	2 (0.5)	1 (0.2)	0
<i>Clostridium difficile</i> colitis	2 (0.5)	2 (0.5)	1 (0.2)	0
Hyperglycemia	2 (0.5)	0	7 (1.6)	2 (0.5)
Hyperglycemia	2 (0.5)	0	6 (1.4)	2 (0.5)
Blood glucose increased	0	0	1 (0.2)	0
Hypoglycemia	0	0	3 (0.7)	1 (0.2)
Hypoglycemia	0	0	3 (0.7)	1 (0.2)
Potential myopathy	0	0	5 (1.2)	2 (0.5)
Acute kidney injury	0	0	1 (0.2)	0
Blood creatinine phosphokinase increased	0	0	2 (0.5)	1 (0.2)
Blood creatinine increased	0	0	1 (0.2)	1 (0.2)
Myalgia	0	0	1 (0.2)	0
Potential QT prolongation	0	0	2 (0.5)	0
ECG QT prolonged	0	0	1 (0.2)	0
Sudden death	0	0	1 (0.2)	0

Abbreviations: AESI = adverse event of special interest; ALT = alanine aminotransferase; ECG = electrocardiogram; GGT = γ -glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities.

Notes: AESIs were coded using MedDRA, version 19.1. If an AESI did not occur, it was not presented in the table.

^d Assessments of possibly or probably related.

^e The total number of AESIs counts all AESIs for subjects. Within an SOC, a subject was counted once if the subject reported more than 1 type of AESI.

Sources: Table 2.7.4-14.

Potential neurologic and psychiatric AEs

In addition to the above AESIs predefined in the Statistical Analysis Plan, other potential neurological and psychiatric AEs were also considered. Dizziness was reported by 3 patients (0.7%) in the delafloxacin group and 2 patients (0.5%) in the moxifloxacin group; in one patient (0.2%) in each group the AE was considered to be possibly or probably related to study drug. Somnolence was reported by two patients (0.5%) in the delafloxacin group and 1 patient (0.2%) in the moxifloxacin group reported; in one patient (0.2%) in each group the AE was considered to be possibly or probably study drug related. Fatigue was reported by 1 patient (0.2%) in the delafloxacin group, not considered to be drug-related, and by 2 patients (0.5%) in the moxifloxacin group, in one of whom (0.2%) it was possibly or probably study drug related. No patient in either treatment group discontinued study drug due to dizziness, somnolence or fatigue.

Few patients in either treatment group reported possible psychiatric adverse events. In the delafloxacin-treated group, anxiety and insomnia were each reported in 3 (0.7%) patients, confusional state in 2 (0.5%) patients and agitation in 1 (0.2%) patient. In the moxifloxacin-treated group, insomnia was reported in 4 (0.9%) patients, and anxiety, confusional state, delirium and sleep disorder each in 1 (0.2%) patient. No event in either treatment group was considered to be possibly or probably study drug related, and none led to study drug discontinuation. No patient in either group reported depression or problems with memory, vision or hearing, or altered taste or smell.

Post marketing experience

Worldwide Marketing Experience

Quofenix (delafloxacin) is marketed in the US under the tradename Baxdela. Baxdela® (delafloxacin) 450 mg Tablets USP, NDA 208610 and Baxdela (delafloxacin) 300 mg Injection USP, NDA 208611 were approved in US on 19 June 2017 for the treatment of ABSSSI and on 24 October 2019 for the treatment of CABP. The products were launched in US on 29 January 2018. On 11 October 2018, Eurofarma S.A, received authorization to market delafloxacin in the following countries: Argentina, under the trade name Delabax on 11 October 2018, Peru under the trade name Delabaxi on 26 December 2018 (tablets only), and Uruguay under the trade name Delabaxi on 27 December 2018 (IV only). The products have not yet been launched in Europe at time of the data lock point of this Type II variation, therefore the post-marketing data collected up to 30 September 2019, are the only one referred to above-mentioned countries.

Patient Exposure From Marketing Experience

The estimation of cumulative patient exposure from marketing experience was 10,705 patients until data lock point of this Type II variation (30 September 2019). Patient exposure was calculated by assuming each patient received 11.2 days of therapy, where 1 day of therapy is equivalent to two 350 mg vials or two 450 mg tablets. Based on the above assumption, a total of 239,752 units (vials or tablets) were dispensed as retail prescriptions or sold to non-retail medical facilities since the first launch of delafloxacin in January 2018, which corresponds to 119,894 days of therapy and an estimated exposure of 10,705 patients. This estimate of patient exposure for the cumulative reporting period was based on weekly product distribution and dispensing figures and was calculated up to 27 September 2019.

Safety Data From Post-marketing Experience

A total of 162 case reports (291 ADR) were reported by spontaneous sources during the post-marketing period (up to 30 September 2019). The oral formulation of Baxdela (delafloxacin) was identified as the suspect drug in the majority of cases (n= 143 ICSRs). Three cases were specifically reported with the use of Baxdela (delafloxacin) injection. Seventy-six cases occurred in adults or elderly and in eighty-five cases the age was unknown. One non-serious case of diarrhoea was reported in an 8-year-old female patient prescribed oral Baxdela (delafloxacin). No cases of drug exposure during pregnancy or lactation were reported. Of the 162 case reports, 18 were serious (27 Serious ADR). No deaths were reported.

Since the launch of delafloxacin, 6 quarterly Periodic Adverse Event Reports (PADERs) have been submitted to the FDA during the postmarketing period (19 June 2017 - 30 September 2019). No safety concern was raised for Baxdela following review of the respective aggregate reports.

Literature

A literature review of any publication relevant to delafloxacin / meglumine or the fluoroquinolone class from June 2018 to 11 January 2019 was conducted in Embase in the context of this application. The search criteria included synonym terms for delafloxacin and meglumine, as well as Chemical Abstracts Service numbers from the time of Baxdela (delafloxacin) approval (19 June 2017) through 11 January 2019. The literature search identified 1199 clinical and nonclinical articles, of which 4 articles identified new safety information for ciprofloxacin or meglumine. A further literature search from 01 January 2019 through 27 October 2019 was conducted, and no safety issues, not already known with fluoroquinolones, were identified.

2.5.3. Discussion on clinical safety

The Phase I and Phase IIb studies submitted in support of CAP were not integrated in the summary of clinical safety due to differences in study design including posology.

The Phase 1 study (ML-3341-119) showed that delafloxacin was generally well tolerated in healthy adults who received 300 mg of delafloxacin intravenously (IV) every 12 hours for a total of 7 doses over 4 days. No new safety signals were identified.

The Phase IIb study (M01-344) employed a different capsule formulation and posology than the currently approved formulation and dose in ABSSSI that was also used in the pivotal Phase III study in patients with CAP. Although the proportional dose-response relationship of delafloxacin (more ADRs at higher doses) that was previously characterised in the ABSSSI MAA appears not to apply entirely in this study, this is not further pursued since both the formulation used and the dose employed differed from that in the pivotal Phase III study (ML-3341-306) in CAP. As such, the Phase 2b study is considered not relevant to the extension of indication proposed in this MAA.

In the pivotal Phase III study ML-3341-306, the total numbers of subjects who completed the study through TOC or prematurely discontinued the study were comparable in the delafloxacin and moxifloxacin treatment arms, as such patient exposure appears comparable.

The most common TEAEs in the delafloxacin group in the Phase III study were diarrhoea (4.7%), transaminases increased (3.0%), and headache (1.9%). In most subjects, these events were mild or moderate in severity. The most common delafloxacin-related ADRs were diarrhoea (3.7%), and transaminases increased (2.6%). Subjects with any severe TEAE accounted for 19 (4.4%) in the delafloxacin arm vs. 14 (3.3%) in the moxifloxacin arm. Overall, TEAEs and ADRs were numerically higher in the delafloxacin arm than in the moxifloxacin arm. Regarding the higher number of related TEAEs in delafloxacin group (15.2%) than in moxifloxacin group (12.6%). However, overall numbers are small and do not allow identification of a specific pattern. At the Preferred Term (PT) level, some AE splitting is seen among reported PT (e.g. "hypertension" and "blood pressure increased"). In the Product Information, preferred PTs that were split across different terms describing the same entity/concept have been grouped under one PT and frequency categories were changed as a result. This is considered acceptable based on the requirements set out in the SmPC guideline EU (rev 2 dated September 2009). In addition, clarification was provided regarding the inclusion of ADRs based on singular events. The MAH has provided the details of the AE of marrow hyperplasia including the causality assessment. The rationale for causality assessment is based on very limited information. Therefore, it is proposed not to include the PT "marrow hyperplasia" in the product information of Quofenix at this time

Delafloxacin had a rate of discontinuations of 3.5% due to TEAEs and 2.1% due to ADRs compared to Moxifloxacin with 1.6% due to TEAEs and 0.9% due to ADRs. In the delafloxacin group, more subjects discontinued due to an SAE and more had severe TEAEs. Most ADRs leading to study drug discontinuation related to delafloxacin were categorised in the "infections and infestations" SOC and likely reflect the severity of the condition and disease progression, and can be expected considering the target population. Additional TEAEs leading to study drug withdrawal were listed in the "investigations" SOC and were mainly related to transaminase elevations, which are common ADRs labelled for delafloxacin already. Similarly, TEAEs in the "skin and subcutaneous tissue disorders" SOC include known PTs labelled for delafloxacin and related to hypersensitivity reactions (also mapped to AESIs). Narratives for the subjects were provided. The primary reasons for withdrawal from study reported for delafloxacin more often included AEs or Death. Most TEAEs that led to premature treatment discontinuation were of moderate intensity: 65% (11/17) in the delafloxacin arm vs. 50% (4/11) in the moxifloxacin arm. The percentage of severe TEAEs was similar between treatment arms (35% vs 38% for delafloxacin and moxifloxacin, resp.). While the fraction of moderate TEAEs appears 15% higher in the delafloxacin arm, the subject numbers are overall low and the percentages of severe TEAEs leading to premature discontinuation were similar.

No deaths in study ML-3341-306 were considered related to study drug. Based on the patient narratives provided, all patients were characterised as PORT risk class III-V, suffered from co-morbidities and received multiple concomitant medications. The conclusion that the reported deaths were not related to study drug

appears plausible. Delafloxacin-related SAEs included *C. difficile*-colitis and hypersensitivity. In terms of SAE, the safety profile of delafloxacin appears overall similar to that of moxifloxacin. Causality assessment and additional information on the SAEs agranulocytosis and bursitis was provided. Bursitis is not considered related to delafloxacin and close monitoring will be continued for agranulocytosis.

Considering intrinsic factors, there were some numerical differences between the treatment groups in some demographic subgroups. However, these subgroups consisted of small numbers of subjects; no major differences were observed in ADRs. Patients with mild, moderate and severe renal impairment were included in the Phase III study. It remains unclear why patients with severe renal impairment were included in the study despite this being an exclusion criterion. Patients might have been assessed as moderately renally impaired at study entry and progressed after enrolment. The majority of subjects with severe renal impairment completed the study: 88.3% (15/17) vs. 93.3% (14/15) in the delafloxacin vs. moxifloxacin arm. Overall numbers of TEAEs from the renal disorder/investigations SOC were low in these patients and 3 out of the 4 subjects who did not complete the study did so due to lack of efficacy, not due to safety reasons.

The list of AESIs is considered comprehensive. Not all known (fluoro)quinolone class effects were observed with delafloxacin use which is to be expected given that some occur with very rare or unknown frequencies. Overall, relatively low numbers of AESIs per SOC were reported. The majority of AESIs in the delafloxacin arm was reported for hepatic-related events (delafloxacin arm 5.1% vs moxifloxacin arm 2.8%, mostly due to transaminase elevations (3.0% and 1.4%, respectively)) and for potential allergic reactions (8 subjects (1.9%) in the delafloxacin arm and 4 subjects (0.9%) in the moxifloxacin group, 1 SAE of hypersensitivity in the delafloxacin arm. Based on current labelling information for delafloxacin and moxifloxacin, this is to be expected and in line with the known safety profile for both substances.

Potential myopathy and potential QT prolongation AESIs were more frequently reported in the moxifloxacin arm than in the delafloxacin arm. This is in line with a slightly more favourable safety profile of delafloxacin in these terms that was already described in the initial ABSSSI MAA.

Regarding potential neurologic and psychiatric TEAEs, none of which were considered related to study drug by the MAH. Anxiety and insomnia can reasonably be expected in the target population and may be associated with hospitalization. However, anxiety and insomnia are known ADRs of delafloxacin and included in the Product Information already. Moreover, anxiety as well as confusional state and sleep disorders (in particular insomnia) are uncommon/common ADRs of other fluoroquinolones (e.g. moxifloxacin, levofloxacin). Overall, the numbers are relatively low and differences between delafloxacin and moxifloxacin appear minor. Since the comparator is a member of the fluoroquinolone class, the conclusion that these PT are mainly associated with the patient population and/or hospitalization is difficult to judge and a possible class effect cannot be excluded. Therefore, confusional state should be included in the Product Information. Close monitoring is recommended for the PTs "sleep disorder", "agitation" and "delirium"

Overall numbers of AESIs were similar between delafloxacin and moxifloxacin treated patients and in line with known safety profiles of both substances. Updating of section 4.8 to reflect the overall delafloxacin safety database (ABSSSI and CAP patients) is endorsed as there appear to be no major differences in TEAEs and ADRs in both target populations. For additional changes to the product information, please refer to annotated SmPC/PIL.

Overall, some new delafloxacin ADRs are reported, although most of them occurred in single subjects only. No new, major safety signal is identified that would indicate a major difference in overall safety profiles between delafloxacin and moxifloxacin though.

2.5.4. Conclusions on clinical safety

Taken together, safety data from the subjects in the CAP population (ML-3341-306) and the healthy volunteer population (ML-3341-119) support the continued favourable safety profile of delafloxacin. The CAP population was older than the ABSSSI population (60 vs. 48 years on average), with associated increased comorbidities and severity of illness; thus, the overall AE profile for the CAP population is quantitatively different from the ABSSSI population but qualitatively similar. The AE profiles (including incidences of AEs, SAEs, discontinuations due to AEs, and AESIs) of delafloxacin and moxifloxacin were mostly comparable in each respective CAP and ABSSSI patient population, although some issues remain to be clarified. Conclusions are the following:

- Delafloxacin IV / oral treatment was safe and well tolerated at the 300-mg IV and 450-mg oral doses in subjects with CAP.
- There is no evidence of any new, major, disabling or potentially significant side effect(s), although further information on agranulocytosis and bursitis should be provided before this can be regarded as definite. It should be kept in mind that long-lasting, late-onset, or very rare ADRs and those for which no frequency can be estimated cannot yet be excluded based on the available safety database.
- There are some quantitative differences in the overall AE profiles of the 2 different indications, ABSSSI and CAP (reflected by numerically increased numbers of AEs/ADRs in the CAP population), but no new major safety signal.
- New ADRs are added to section 4.8 of the proposed SmPC.
- Compared with the ABSSSI trials, there were more deaths / SAEs in the CAP trial for both delafloxacin and comparator. This is expected, given the older population suffering from a more serious condition.

The safety findings in the submitted studies appear to be mostly consistent with the known safety profile of delafloxacin, indicating no major safety advantage or disadvantage between delafloxacin and moxifloxacin.

2.5.5. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 acceptable.

Safety concerns

Table S VIII–1: Summary of safety concerns

Summary of Safety Concerns	
Important Identified Risks	• Tendinopathy • Peripheral Neuropathy
Important Potential Risks	• Long-lasting and / or potentially irreversible severe adverse reactions • Aortic aneurysm and dissection • Renal damage secondary to sulfobutylether-β-cyclodextrin (SBECD) accumulation in patients with severe renal impairment [IV formulation]
Missing Information	• None

Pharmacovigilance plan

Table Part III–1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None			t	

Risk minimisation measures

Table Part V–3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Tendinopathy	Routine risk minimisation measures: - SmPC section 4.2 Posology and method of administration - SmPC section 4.3 Contraindications - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects - PL section 2 What you need to know before you are given/take delafloxacin You must not be given/Do not take delafloxacin Warning and precautions - PL section 4 Possible side effects Legal status: prescription only medicine Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Peripheral Neuropathy	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions Legal status: prescription only medicine Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important potential risk: Long-lasting and / or potentially irreversible severe adverse reactions	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.8 Undesirable effects - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions - PL section 4 Possible side effects Legal status: prescription only medicine Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction Additional pharmacovigilance activities: None
Important potential risk: Aortic aneurysm and dissection	Routine risk minimisation measures: - SmPC section 4.4 Special warnings and precautions for use - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions Legal status: prescription only medicine Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Important potential risk: Renal damage secondary to sulfobutylether-β-cyclodextrin (SBECD) accumulation in patients with severe renal impairment [IV formulation]	Routine risk minimisation measures: - SmPC section 4.2 Posology and method of administration - SmPC section 4.4 Special warnings and precautions for use - PL section 2 What you need to know before you are given/take delafloxacin Warning and precautions - PL section 3 How to use delafloxacin Legal status: prescription only medicine Additional risk minimisation measures: No additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative to mention United Kingdom (Northern Ireland) in line with the current QRD template (10.2)

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

A RUT of the PLs (IV and oral) has been conducted in December 2018 within the first registration procedure of Quofenix. The differences between the PLs tested so far and the PL proposed with the present application are due only to the addition of the new indication and they are listed below.

- Section 1 What Quofenix is and what it is used for: the wording has been amended to include the new proposed therapeutic indication. The proposed wording is in line with the one already approved for other antibiotic of the same class;
- Section 3 How to take Quofenix: the wording has been amended to include the days of treatment for the new proposed therapeutic indication;
- Section 4 Possible side effects: this section has been updated following the new number of patients exposed to delafloxacin, the relevant new side effects arised and their reclassification based on the frequencies.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication applied for is treatment of CAP in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections for IV delafloxacin with the option to switch to oral delafloxacin and for sole oral treatment.

Community-acquired pneumonia is caused most frequently by *S. pneumoniae* and *Haemophilus influenzae* and some atypical pathogens such as *Legionella pneumophila*, but can also involve rarer atypical and Gram negative organisms. CAP is classified separately from Hospital-acquired pneumonia (HAP) (developing ≥ 48 hours after hospital admission), Ventilator-acquired pneumonia (VAP) or Health-care associated pneumonia (HCAP), which are caused by a different range of pathogens. Management includes systemic antibiotic therapy and supportive care.

3.1.2. Available therapies and unmet medical need

The most commonly used classes of antibiotics for CAP include beta-lactams, oxazolidinones, glycopeptides, macrolides and fluoroquinolones. Delafloxacin does not address an unmet need, but would provide a further antibiotic option.

3.1.3. Main clinical studies

The clinical support for this indication mainly include one pivotal Phase 3 study (ML-3341-306).

Study ML-3341-306 was a phase 3, multicenter, randomized, double-blind, comparator-controlled study to evaluate the safety and efficacy of intravenous to oral delafloxacin in adult subjects with community-acquired bacterial pneumonia.

Eligible patients received either delafloxacin (IV 300 mg a 1-hour IV infusion BID for a minimum of 6 doses, with an option to switch to delafloxacin, 450 mg tablet, administered orally BID) or moxifloxacin (IV 400 mg as a 1-hour IV infusion every 24 hours for a minimum of 3 active doses, with an option to switch to oral moxifloxacin 400 mg administered every 24 hours) for an overall treatment duration of 5 to 10 days.

3.2. Favourable effects

Pivotal study ML-3341-306 demonstrated high rates of overall clinical response at TOC (the EU primary efficacy endpoint) in both treatment arms in both the ModITT population (91.0% delafloxacin, 89.2% moxifloxacin) and ModCE-TOC population (94.8% delafloxacin, 93.8% moxifloxacin). The difference between treatment arms was 1.1 (95% CI -3.2, 5.5) in the ModITT population and 1.0 (95% CI -2.5, 4.6) in the ModCE-TOC population. Given that the lower limit of the 95% CI for the treatment difference between arms in the ModITT and ModCE-TOC populations was above the pre-specified margin of -10%, iv/po delafloxacin was demonstrated non-inferior to iv/po moxifloxacin. Sensitivity analysis supported results from primary analysis. In subgroup analysis no significant differences between treatment groups were identified.

Pivotal study ML-3341-306 investigated IV followed by oral delafloxacin. Regards to sole oral delafloxacin treatment it should be considered that in the frame of the initial MAA a BE study was submitted which revealed that 300 mg IV delafloxacin and 450 mg oral delafloxacin can be regarded as bioequivalent. Therefore, results of pivotal study ML-3341-306 can be extrapolated to sole oral treatment with delafloxacin.

Overall, pivotal study ML-3341-306 provides robust efficacy results. The aspects of the Points to consider on application with one pivotal study (CPMP/EWP/2330/99) are fulfilled. Furthermore, efficacy data are supported by PK/PD analysis of pathogens relevant for the indication CAP (*S. pneumoniae*, *S. aureus*, *H. influenzae*).

3.3. Uncertainties and limitations about favourable effects

Concerning pharmacodynamics, uncertainty remains with regard to the primary pharmacology, in particular related to delafloxacin susceptibility in surveillance studies for selected pathogens. In context of secondary pharmacology, the most important issue is the lack of ELF PK data, which have not been taken into consideration for any PK/PD analyses. Neither PK/PD relationships have been investigated for ELF in animal models nor was ELF PK considered for PK/PD modelling. Pre-clinical ELF data for delafloxacin are deficient and, as the correlation between penetration into human and murine ELF cannot be established, they could not be used in PK/PD analyses or PTA analyses and it remains difficult to interpret the adequacy of delafloxacin exposure at the effect site.

In general, it can be concluded that the PTA analyses based on plasma PK/PD targets are adequate. It is agreed that PK/PD analyses are robust and support the proposed dosing regimens for CAP caused by *S. pneumoniae*, *S. aureus* and *H. influenzae*. In contrast, the proposed dosing regimens are far too low for CAP caused by *K. pneumoniae* or *P. aeruginosa*. However, the MAH has agreed that a posology or breakpoints for these pathogens are no longer being pursued within the current procedure. Given that *K. pneumoniae* and *P. aeruginosa* are considered less relevant in the indication CAP but are rather more associated with

nosocomial pneumonia (HAP/VAP), no further investigations or analyses regarding these pathogens are warranted within this extension of indication variation in CAP.

Regards to pivotal study ML-3341-306 the other concerns raised during first round were adequately addressed.

Overall, most patients in this application had CAP of relatively mild to moderate severity; 90.7% had CURB-65 score of ≤ 2 and 69.3% were categorised to PORT class III. However, 30.7% of patients had a PORT score $>III$ which is in line with the recommendation in the Draft AB GL for studies in CAP initiated by intravenous route. Furthermore, about 50% were aged >65 years and 60.3% were overweight; both being risk factors for more severe CAP. Taking also into account that only second line indication CAP is applied for, patient population studied is regarded as appropriate. Nevertheless, information about the severity of disease that was investigated during the pivotal study was added into section 4.4 of the SmPC.

3.4. Unfavourable effects

The most common TEAEs in the delafloxacin group in the Phase III study were diarrhoea (4.7%), transaminases increased (3.0%), and headache (1.9%). In most subjects, these events were mild or moderate in severity. The most common delafloxacin-related ADRs were diarrhoea (3.7%), and transaminases increased (2.6%).

Subjects with any severe TEAE accounted for 19 (4.4%) in the delafloxacin arm vs. 14 (3.3%) in the moxifloxacin arm.

Delafloxacin had a rate of discontinuations of 3.5% due to TEAEs and 2.1% due to ADRs compared to Moxifloxacin with 1.6% due to TEAEs and 0.9% due to ADRs.

In the delafloxacin group compared with the moxifloxacin group, the incidence of SAEs (5.4% and 4.7%) were similar, and most of these events were considered unrelated to study drug. No deaths were considered related to study drug. In the delafloxacin arm, most TEAEs leading to death were singular events, except for septic shock (3 deaths) and pneumonia (2 deaths), possibly reflecting the relatively old patient population and underlying condition of CAP. These events may reasonably be expected in the disease and target population.

Although low, the incidence of discontinuations, SAEs, and deaths in the CAP population were higher than that reported for the ABSSSI population, reflecting the older and sicker CAP population. An examination of TEAEs by demographic and medical history subgroups similar to those seen in hospitalized CAP patients showed no clinically meaningful differences in the AE profile between delafloxacin and moxifloxacin.

Adverse Events of Special Interest

The 9 selected topics were C. difficile diarrhoea, dysglycemia, hepatic-related events, potential seizures, potential myopathy, potential peripheral neuropathy, potential tendon disorder, potential QT prolongation, and potential allergic reaction. The incidence of AESIs was similar between the delafloxacin and moxifloxacin groups (7.9% and 7.5%). Of the AESIs that lasted longer than 30 days, all but 1 were hepatic-related events.

Regarding potential neurologic and psychiatric TEAEs, none of which were considered related to study drug, the MAH has discussed the causality assessment in more detail. In particular since class effects of (fluoro)quinolones include psychotic reactions and prolonged, disabling, potentially permanent side effects that may include psychiatric effects. While anxiety and insomnia are known ADRs of delafloxacin and labelled as such, the ADR confusional state may at least be possibly related to use of delafloxacin as part of a class effect. Other TEAEs such as sleep disorder, agitation and delirium are recommended for close monitoring at this point. This is also applicable to the TEAE marrow hyperplasia.

There were no cases of laboratory abnormalities meeting the definition of Hy's law. Laboratory changes with delafloxacin were typically unlikely to be related to treatment, were associated with other medical history, events, or social circumstances, did not require treatment, and were reversible.

3.5. Uncertainties and limitations about unfavourable effects

The most common delafloxacin-related ADRs were diarrhoea (3.7%), and transaminases increased (2.6%). Subjects with any severe TEAE accounted for 19 (4.4%) in the delafloxacin arm vs. 14 (3.3%) in the moxifloxacin arm. Most SAEs were considered unrelated to study drug. New ADRs to be labelled for delafloxacin include agranulocytosis and confusional state.

Delafloxacin had a rate of discontinuations of 3.5% due to TEAEs and 2.1% due to ADRs compared to Moxifloxacin with 1.6% due to TEAEs and 0.9% due to ADRs. The primary reasons for withdrawal from study reported for delafloxacin more often included AEs or Death. However, the patient numbers are limited and the percentages of severe TEAEs leading to study drug discontinuation are similar between delafloxacin and moxifloxacin.

3.6. Effects Table

Table 83 Effects Table for delafloxacin/Quofenix in CAP

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Non-inferiority	ML-3341-306 CAP Phase 3 study of IV delafloxacin (300 mg Q12h) with the option to switch to oral delafloxacin (450 mg Q12h) vs. moxifloxacin (400 mg Q24h) with the option to switch to oral moxifloxacin (400 mg Q24h), treatment duration 5-10 days	%	ModITT clinical success at TOC:		Non-inferiority margin (-10%) was met in ModITT and ModCE-TOC populations	CSR study – ML-3341-306
			91.0	89.2	(-3.2, 5.5)	
			ModCE-TOC clinical success at TOC:			
			94.8	93.8	(-2.5, 4.6)	
Unfavourable Effects						
Diarrhoea	ADR	%	3.7	3.0		CSR study – ML-3341-306
Transaminases increased	ADR	%	2.6	0.9		CSR study – ML-3341-306
discontinuation	Due to ADR	%	2.1	0.9		CSR study – ML-3341-306
AESIs	FQ class effects	%	7.9	7.5		CSR study – ML-3341-306
AESI	C. difficile colitis	%	0.5		0.2	CSR study – ML-3341-306

Abbreviations: ADR – adverse drug reaction; FQ – fluoroquinolone; SAE – serious adverse event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The MAH applied for the extension of indication to include treatment of Community Acquired Pneumonia (CAP) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections (second line indication). This is in line with the approved indication for moxifloxacin as well as for levofloxacin. For these fluoroquinolones indication CAP was limited to second line indication mainly due to safety risks.

Pivotal study ML-3341-306 demonstrated high rates of overall clinical response at TOC. The difference between treatment arms was 1.1 (95% CI -3.2, 5.5) in the ModITT population and 1.0 (95% CI -2.5, 4.6) in the ModCE-TOC population. Given that the lower limit of the 95% CI for the treatment difference between arms in the ModITT and ModCE-TOC populations was above the pre-specified margin of -10%, delafloxacin was demonstrated non-inferior to moxifloxacin. Sensitivity analysis supported results from primary analysis.

The PK/PD target attainment analyses based on plasma PDTs performed for *S. pneumoniae*, *S. aureus* and *H. influenzae* are considered acceptable and provide robust support for the proposed dosing regimens in the respective patient populations for the treatment of CAP. However, this conclusion cannot be drawn for *K. pneumoniae* as well as for *P. aeruginosa* where PTAs above 90 % were achieved for low MIC values only, which could not be correlated with MICs observed in surveillance studies. Therefore, concerns were raised whether the proposed dosing regimens might be sufficient to cover these two pathogens, although success rates at TOC in the pivotal Phase III study were high in patients with CAP caused by *K. pneumoniae* and *P. aeruginosa*. Notably, the number of patients with these pathogens and MIC at baseline was low. However, the MAH has agreed to not pursue a posology or breakpoints for *K. pneumoniae* and *P. aeruginosa* due to PK/PD limitations regarding a robust PDI and PTA analyses as well as the limited relevance of these pathogens to the indication CAP.

The limitation remains that no PK/PD target attainment analyses have been performed in ELF. Neither PK/PD relationships have been investigated for ELF in animal models nor was ELF PK considered for PK/PD modelling. Pre-clinical ELF data for delafloxacin are deficient and, as the correlation between penetration into human and murine ELF cannot be established, they could not be used in PK/PD analyses or PTA analyses and it remains difficult to interpret the adequacy of delafloxacin exposure at the effect site.

Regards to safety, data from the subjects in the CAP population (ML-3341-306) and the healthy volunteer population (ML-3341-119) support the continued favourable safety profile of delafloxacin. The safety findings in the submitted studies are mostly consistent with the known safety profile of delafloxacin, indicating no major safety advantage or disadvantage between delafloxacin and moxifloxacin.

Furthermore, it can be concluded that the MAA meets the prerequisites for one pivotal study application, as detailed in EMA Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99, 31 May 2001). The pharmacological principle and mechanism of action is established. A robust clinical data package has been provided. Data from Study ML-3341-306 can be regarded as valid in relation to the indication applied for. According to the EMA Points to consider on application with 1. Meta-analyses; 2. One pivotal study (CPMP/EWP/2330/99, 31 May 2001), when the aim is to demonstrate non-inferiority, one study is more likely to be accepted if the lower 95% confidence bound is well away from the non-inferiority margin. In Study ML-3341-306 the lower bound of 95% confidence interval was -3.2% and therefore well away from the non-inferiority margin of -10%. Furthermore, the results of Study ML-3341-306 support internal consistency of the data set. In addition, patients in Study ML-3341-306 were enrolled across a large number of clinical centres, without dominance of any given centre.

Overall, pivotal study ML-3341-306 provides robust efficacy results and one pivotal study application is agreed. Furthermore, efficacy data are supported by PK/PD analysis of pathogens most relevant for CAP (*S. pneumoniae*, *S. aureus* and *H. influenzae*).

3.7.2. Balance of benefits and risks

Pivotal study ML-3341-306 provides robust efficacy results and one pivotal study application is agreed. Furthermore, efficacy data are supported by PK/PD analysis of pathogens most relevant for CAP (*S. pneumoniae*, *S. aureus* and *H. influenzae*).

The B/R balance of delafloxacin for the second line indication CAP (treatment of CAP in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections) is regarded as positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Quofenix in the second line indication for the treatment of community-acquired pneumonia is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of community-acquired pneumonia (CAP) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections, for Quofenix 450 mg tablets and 300 mg powder for concentrate for solution for infusion; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been approved.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative to mention United Kingdom (Northern Ireland) in line with the current QRD template (10.2).

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Quofenix-H-C-004860-II-0003'

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 25 February 2021.