Clinical Infectious Diseases
SUPPLEMENT ARTICLE

Profile of a Novel Anionic Fluoroquinolone—Delafloxacin

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Fluoroquinolones have been in clinical use for over 50 years with significant efficacy. However, increasing resistance and emergence of some marked adverse events have limited their usage. The most recently approved class member, delafloxacin, is the only available anionic (non-zwitterionic) fluoroquinolone. Its unique molecular structure provides improved in vitro activity against most Gram-positive pathogens, including quinolone-resistant strains, which is further enhanced at acid pH. Delafloxacin shows favorable pharmacological properties, with about 60% bioavailability after oral administration, only mild inhibition of cytochrome P450 3A, and no evidence of cardiac- or phototoxicity in healthy volunteers (tested against positive controls). Its twice daily dosing, suitability for intravenous, oral, or switch dosing, the lack of many clinically significant drug-drug interactions, and acceptable adverse event profile in registration clinical trials supports its use in the treatment of acute bacterial skin and skin structure infections, and potentially in other infections, where resistance to other agents, safety, and/or the need for early discharge is of concern.

Keywords. fluoroquinolones; delafloxacin; skin infections.

Acute bacterial skin and skin structure infections (ABSSSIs) are associated with significant morbidity and mortality. Several studies have documented increasing patient encounters for treatment of ABSSSIs both in ambulatory and inpatient settings [1–4], but this trend may now be decreasing [5]. A variety of Gram-positive and Gram-negative pathogens have been identified as etiologic agents. However, the predominant causative pathogen across geographic regions is *Staphylococcus aureus*, followed by other Gram-positive pathogens (eg, coagulase-negative staphylococci, *Enterococcus* spp., *Streptococcus agalactiae* [Group B Streptococcus], and *Streptococcus pyogenes*) and Gram-negative pathogens including *Pseudomonas aeruginosa* and *Escherichia coli*, which are more frequently seen in surgical site infections [6, 7]. Morbidity, mortality, and costs associated with hospitalization for treatment of these infections are significant and are appreciably higher in patients with mixed infections compared with those caused by Gram-positive or Gram-negative pathogens alone [8]. Another significant concern is the emergence of pathogens resistant to antimicrobial agents, including methicillin-resistant *S. aureus* (MRSA) [9], which contributes to higher morbidity and mortality as well as high treatment costs [10, 11], resulting primarily from longer hospital stays [12].

Current guidelines on the treatment of ABSSSIs classify them into nonpurulent (necrotizing infections, cellulitis, and erysipelas) and purulent (furuncles, carbuncles, and abscesses) and further on the basis of severity (mild, moderate, and severe) [13]. A variety of antimicrobial agents are recommended depending upon the type and severity of infection, and if caused by *S. aureus*, the methicillin susceptibility of the causative strain. As recently reviewed [14], oxacillin (or another β-lactamase resistant penicillin such as dicloxacillin or nafcillin) or cefazolin (in case of allergy to penicillin) are usually recommended for the treatment of infections caused by methicillin-sensitive *S. aureus* (MSSA), whereas vancomycin, linezolid, daptomycin, or ceftaroline are most often specifically recommended when the infection is caused by MRSA. Older agents such as clindamycin, doxycycline/minocycline, or trimethoprim-sulfamethoxazole are also used to treat infections caused by MSSA or MRSA. However, all of these drugs are associated with limitations that include local high level of resistance (clindamycin or doxycycline), high cost and toxicity (linezolid), decreased susceptibility (vancomycin; often requiring higher dosing that results in renal toxicity), and heightened risk of *Clostridium difficile* infection (eg, clindamycin) [13, 15]. Although these drugs still form the mainstay of current treatment strategies, recent approvals of agents including dalbavancin, tedizolid, oritavancin, and delafloxacin have provided additional options for the treatment of ABSSSIs, including those caused by MRSA [14, 16].

An additional concern is the ability of *S. aureus* to survive in the acidic environment of the skin. Their survival is dependent on expression of an enzyme that confers resistance to polyamines, anti-inflammatory compounds capable of promoting wound healing and tissue regeneration, which are present in the acidic environment of the skin and are toxic to *S. aureus* [17,

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Clinical Infectious Diseases® 2019;68(S3):S213–22

DOI: 10.1093/cid/ciy1079

18]. Moreover, *S. aureus* can adopt specific modes of life (eg, in biofilms or intracellularly after phagocytosis by permissive cells) that play a role in the development of persistent/recurrent infections, including in skin and skin-associated structures [19, 20]. Thus, there is a need for therapeutic agents that are not only effective against resistant pathogens but also retain or even increase their activity at the acid pH prevailing at the surface of the skin [21], deep in biofilms [22], or in phagolysosomes [23].

Among the newly approved agents, the anionic fluoroquinolone delafloxacin uniquely shows improved activity at acidic pH (as opposed to most other antibiotics including currently approved fluoroquinolones) and exhibits broad spectrum activity that includes most Gram-positive bacteria involved in ABSSSI and, to some extent, important Gram-negative bacteria. It was approved by the US Food and Drug Administration (FDA) in 2017 for the treatment of ABSSSI [16]. We review some of the pertinent data about the key features of delafloxacin to provide a concise overview of its basic properties that may be of interest to clinicians. More clinically oriented reviews are available elsewhere in this Special Issue and in other recent publications [24–27].

CHEMICAL STRUCTURE AND MECHANISM OF ACTION

Delafloxacin (CAS registry number 189279-58-1; PubChem CID 487101; formerly known as WQ-3034 and ABT-492) has the molecular formula $C_{18}H_{12}ClF_3N_4O_4$ and the chemical structure 1-(6-amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-hydroxyazetidin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Figure 1) [28–30]. The compound differs from other fluoroquinolones in 3 main respects: (1) lack of a basic group at position C7, which makes it a weak acid and therefore predominantly anionic at neutral pH (and not zwitterionic as for most other fluoroquinolones), (2) addition of a chlorine at position C8, which serves as an electron-withdrawing group on the aromatic ring and confers polarity and enhanced activity, and (3) a voluminous heteroaromatic substitution at position N1 that imparts a larger molecular surface to delafloxacin compared to most other fluoroquinolones [28, 31]. These combined structural features directly impact on the activity of delafloxacin (with very low minimal inhibitory concentrations [MICs] against a large array of Gram-positive organisms) and may explain its enhanced potency at acid pH relative to other fluoroquinolones (eg, ciprofloxacin, levofloxacin, moxifloxacin), for which activities decrease (higher MICs) in acidic environments. This enhanced potency at acid pH likely relates to increased accumulation by *S. aureus*, whereas lower accumulation was seen with moxifloxacin [32]. Delafloxacin may therefore fulfill one of the important requisites for enhanced activity in ABSSSI [33], particularly in infections caused by *S. aureus* [31, 33] and where high local concentrations are considered essential (see [22, 34]).

The structural characteristics of delafloxacin also enable it to target both DNA gyrase and DNA topoisomerase IV from Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) pathogens with equal affinity [35]. The dual targeting of gyrase and topoisomerase IV decreases likelihood of resistance, which requires the accumulation of multiple mutations affecting both enzymes [36]. This feature may contribute to the activity

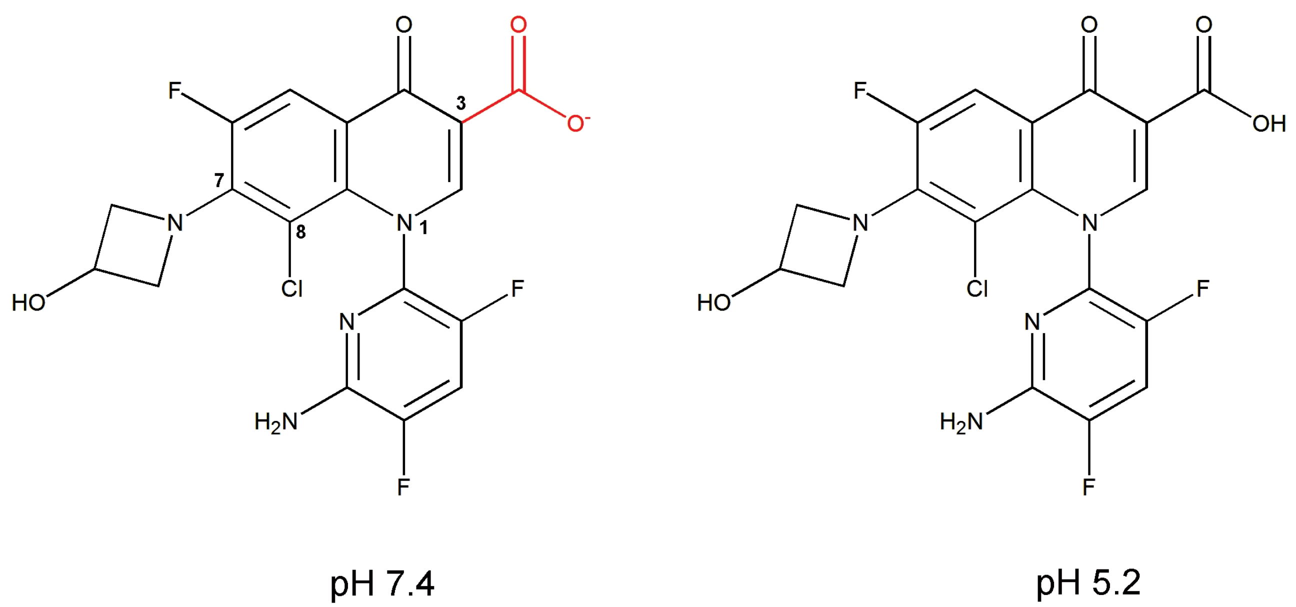

Figure 1. Chemical structure of delafloxacin with atom numbering for the key positions discussed in the text. Due to the lack of basic group in the C7 substituent, the only ionizable group is the carboxylate function attached to position C3 (calculated pKa = 5.43). The figure shows the calculated predominant forms at pH 7.4 (left; anionic [to 98.5%]) and at pH 5.2 (right; neutral [62.7%]). Calculations were made with MarvinSketch version 18.9.0 (academic license) available from http://www.chemaxon.com.

of delafloxacin against MRSA isolates, including those harboring mutations in the quinolone resistance determining region (QRDR) and to the low levels of resistance to delafloxacin among these MRSA isolates [29].

ANTIBACTERIAL ACTIVITY

As explained above, delafloxacin has structural attributes that confer activity at low pH. This has been demonstrated in a series of studies comparing its activity with other fluoroquinolones in media at different pH levels. Against *S. aureus* ATCC25923, delafloxacin MIC was 5 log_2 dilutions lower at pH 5.5 (0.00003 mg/L) than at pH 7.4 (0.001 mg/L), whereas moxifloxacin MIC was 2 log_2 dilutions higher at pH 5.5 (0.125 mg/L) than at pH 7.4 (0.03 mg/L). Similar observations were made in a series of clinical isolates [32]. Another study examined the in vitro activity of delafloxacin and ciprofloxacin at pH values ranging from 6 to 8 [37]. Variable MICs reported for delafloxacin against MRSA strain W44 at pH values of 6, 7, and 8 were 0.006 mg/L, 0.05 mg/L, and 0.2 mg/L, respectively. Also, time-kill experiments against MRSA W44 that evaluated delafloxacin across the pH range at concentrations of 0.025 mg/L and 0.1 mg/L (ie, half and 2 times the MIC at pH 7) showed bactericidal activity at both pH 6 and 7 but not at pH 8. Accumulation of delafloxacin within MRSA W44 was also pH dependent, being highest at pH 6 and lowest at pH 8.

An early study that evaluated the in vitro activity of delafloxacin against a panel of fluoroquinolones including trovafloxacin, levofloxacin, and ciprofloxacin demonstrated its activity against multiple quinolone-susceptible pathogens [35]. Activity against 7 quinolone-susceptible *Enterobacteriaceae* was comparable with that of other fluoroquinolones. Delafloxacin was more active than the other agents against fastidious Gram-negative pathogens including *Haemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, and *Legionella* spp. and other Gram-negative pathogens such as *P. aeruginosa* and *Helicobacter pylori*. Delafloxacin was more potent than trovafloxacin and levofloxacin against multidrug-resistant Streptococcus *pneumoniae* (including isolates resistant to penicillin and macrolides) and *H. influenzae* (including β-lactam-resistant isolates). A subsequent study that included an expanded panel of comparators including moxifloxacin, gatifloxacin, and gemifloxacin in addition to trovafloxacin, levofloxacin, and ciprofloxacin reported that delafloxacin was more active against quinolone-susceptible and -resistant Gram-positive pathogens but was equipotent against quinolone-susceptible, nonfermentative Gram-negative pathogens [38]. This study also reported that delafloxacin was bactericidal against quinolone-resistant strains of *E. coli* within 6 h, *S. aureus* within 10 h, and *S. pneumoniae* by 24 h.

The in vitro activities of delafloxacin and a comprehensive panel of comparators (levofloxacin, ceftaroline, ciprofloxacin, clindamycin, daptomycin, erythromycin, linezolid, oxacillin, tetracycline, tigecycline, trimethoprim-sulfamethoxazole, and vancomycin) against 6485 isolates collected from multiple sites in Europe and the United States in 2014 have been evaluated (Table 1) [39]. This study applied 2016 interpretation criteria of the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for comparator agents. Although there are neither CLSI nor EUCAST interpretive criteria (breakpoints) for delafloxacin, those set by the FDA for the United States in 2017 (see prescribing information and medication guide [16]) have been listed below Table 1 for comparison. (Since 2006, the FDA has reasserted its rights to define breakpoints for antibiotics, which affects all new drugs registered in the United States since then. EUCAST breakpoints are set up during the registration process of new antibiotics with the European Medicine Agency [EMA], but this has not yet been finalized for delafloxacin at the time of the final writing and revision of this review [December 8, 2018].) Delafloxacin had the lowest MICs among agents tested against MSSA, MRSA, *S. pneumoniae*, and *viridans* group and beta-hemolytic *Streptococci* and MICs comparable to those of ciprofloxacin and levofloxacin against some *Enterobacteriaceae*. Its low MICs against pathogens associated with ABSSSI as well as respiratory and urinary tract infections (UTIs) were confirmed. These findings have been corroborated by a more recent susceptibility analysis of 36 683 Gram-positive and Gram-negative isolates (of which 10 153 were identified as associated with skin and skin structure infections [SSSI]) collected between 2014 and 2016 from sites in the United States and Europe [40]. Application of the CLSI and EUCAST 2017 breakpoints for comparator agents and FDA breakpoints for delafloxacin from the 2017 package insert enabled confirmation of the broad-spectrum in vitro activity of delafloxacin against this contemporary panel of isolates. Delafloxacin demonstrates lower MICs than levofloxacin and moxifloxacin against *S. aureus* (MIC_{50}/MIC_{90} 0.008/0.5 mg/L, 0.25/>4 mg/L, and ≤0.06/4 mg/L for delafloxacin, levofloxacin, and moxifloxacin, respectively), coagulase-negative staphylococci (CoNS) (MIC_{50}/MIC_{90} 0.015/0.5 mg/L, 0.25/>4 mg/L, and 0.12/4 mg/L, respectively), *S. pneumoniae* (MIC_{50}/MIC_{90} 0.015/0.03 mg/L, 1/1 mg/L, and ≤0.12/0.25 mg/L, respectively), and *S. pyogenes* and *S. agalactiae* (MIC_{50}/MIC_{90} 0.015/0.03 mg/L and 0.5/1 mg/L for delafloxacin and levofloxacin, respectively, against both pathogens). Other studies have shown lower MICs for delafloxacin than comparators against clinical isolates of *Neisseria gonorrhoeae* and *Chlamydophila pneumoniae* [41, 42] and against isolates of *S. aureus* resistant to methicillin [29] and other fluoroquinolones (eg, levofloxacin and ciprofloxacin) [43]. The latter study examined the in vitro activity of delafloxacin against *S. aureus* isolates from participants in Phase 3 studies harboring mutations in the QRDR, including isolates with the most frequently encountered mutations in clinical trials—the S84L

Table 1. Comparative In Vitro Activities of Delafloxacin and Comparators Against Relevant Gram-positive and Gram-negative Clinical Isolates From the United States and Europe

Organism Group (No. of Isolates Tested)/Antibiotic	% of Isolates Susceptible by Following Criteria:		MIC (mg/L)		
	CLSI	EUCAST	50%	90%	Range
Gram-positive pathogens					
Staphylococcus aureus (1350)					
Delafloxacin[a]			≤0.004	0.25	≤0.004 to 4
Levofloxacin	64.4	64.4	0.25	>4	≤0.12 to 4
Ciprofloxacin	0.0	0.0	64	>128	64 to >128
Ceftaroline	98.0	98.0	0.25	1	0.03 to 2
Clindamycin	87.0	86.8	≤0.25	>2	≤0.25 to >2
Daptomycin	99.8	99.8	0.25	0.5	≤0.06 to 2
Linezolid	100.0	100.0	1	1	0.25 to 2
Oxacillin	57.6	57.6	0.5	>2	≤0.25 to >2
Trimethoprim-sulfamethoxazole	98.5	98.5	≤0.5	≤0.5	≤0.5 to >4
Vancomycin	100.0	100.0	1	1	0.25 to 2
MSSA (777)					
Delafloxacin[a]			≤0.004	0.008	≤0.004 to 4
Levofloxacin	89.8	89.8	0.25	2	≤0.12 to >4
Ciprofloxacin	0.0	0.0	>128	>128	>128 to >128
Ceftaroline	100.0	100.0	0.25	0.25	0.03 to 1
Clindamycin	94.0	93.7	≤0.25	≤0.25	≤0.25 to >2
Daptomycin	100.0	100.0	0.25	0.5	≤0.06 to 1
Linezolid	100.0	100.0	1	1	0.25 to 2
Oxacillin	100.0	100.0	0.5	0.5	≤0.25 to 2
Trimethoprim-sulfamethoxazole	99.0	99.0	≤0.5	≤0.5	≤0.5 to >4
Vancomycin	100.0	100.0	1	1	0.25 to 2
MRSA (573)					
Delafloxacin[a]			0.06	0.5	≤0.004 to 4
Levofloxacin	30.0	30.0	4	>4	≤0.12 to >4
Ciprofloxacin	0.0	0.0	>128	>128	64 to >128
Ceftaroline	95.3	95.3	1	1	0.25 to 2
Clindamycin	77.5	77.5	≤0.25	>2	≤0.25 to >2
Daptomycin	99.5	99.5	0.25	0.5	0.12 to 2
Linezolid	100.0	100.0	1	1	0.25 to 2
Oxacillin	0.0	0.0	>2	>2	>2 to >2
Trimethoprim-sulfamethoxazole	97.9	97.9	≤0.5	≤0.5	≤0.5 to >4
Vancomycin	100.0	100.0	1	1	0.5 to 2
Enterococcus faecalis (450)					
Delafloxacin[b]			0.06	1	≤0.004 to 2
Levofloxacin	70.7	70.7	1	>4	0.25 to >4
Ceftaroline			2	8	0.25 to >32
Clindamycin			>2	>2	≤0.25 to >2
Daptomycin	100.0		1	2	0.12 to 4
Linezolid	99.8	100.0	1	1	≤0.12 to 4
Trimethoprim-sulfamethoxazole			≤0.5	≤0.5	≤0.5 to >4
Vancomycin	97.8	97.8	1	2	0.5 to >16
Streptococcus pyogenes (433)					
Delafloxacin[c]			0.008	0.015	≤0.004 to 0.03
Levofloxacin	99.8	96.5	0.5	1	0.25 to >4
Moxifloxacin		100.0	≤0.12	0.25	≤0.12 to 0.5
Ceftaroline	100.0	100.0	≤0.015	≤0.015	≤0.015 to 0.03
Clindamycin	91.5	91.9	≤0.25	≤0.25	≤0.25 to >2
Vancomycin	100.0	100.0	0.25	0.5	≤0.12 to 0.5
Streptococcus agalactiae (225)					
Delafloxacin[d]			0.008	0.015	≤0.004 to 0.5
Levofloxacin	97.8	96.9	0.5	1	0.25 to >4
Moxifloxacin		97.8	≤0.12	0.25	≤0.12 to >4

Table 1. Continued

Organism Group (No. of Isolates Tested)/Antibiotic	% of Isolates Susceptible by Following Criteria:		MIC (mg/L)		
	CLSI	EUCAST	50%	90%	Range
Ceftaroline	100.0	100.0	≤0.015	0.03	≤0.015 to 0.03
Clindamycin	70.7	72.4	≤0.25	>2	≤0.25 to >2
Vancomycin	100.0	100.0	0.5	0.5	0.25 to 1
Gram-negative pathogens					
Enterobacteriaceae (2250)					
Delafloxacin[e]			0.06	4	≤0.004 to ≥4
Ceftazidime	86.3	82.8	0.25	16	0.03 to >32
Ceftriaxone	80.3	80.3	0.12	>8	≤0.06 to >8
Ciprofloxacin	81.6	79.3	≤0.03	>4	≤0.03 to >4
Piperacillin-tazobactam	89.3	85.7	2	32	≤0.5 to >64
Escherichia coli (500)					
Delafloxacin[e]			0.03	4	≤0.004 to >4
Ceftazidime	89.2	83.4	0.12	8	0.03 to >32
Ceftriaxone	84.0	84.0	≤0.06	>8	≤0.06 to >8
Ciprofloxacin	69.4	68.8	≤0.03	>4	≤0.03 to >4
Piperacillin-tazobactam	94.2	90.0	2	8	≤0.05 to >64
Klebsiella pneumoniae (389)					
Delafloxacin[e]			0.06	>4	0.015 to >4
Ceftazidime	76.9	74.8	0.12	>32	0.03 to >32
Ceftriaxone	75.3	75.3	≤0.06	>8	≤0.06 to >8
Ciprofloxacin	77.4	75.6	≤0.03	>4	≤0.03 to >4
Piperacillin-tazobactam	81.2	75.8	4	>64	≤0.5 to >64
Pseudomonas aeruginosa (200)					
Delafloxacin[f]			0.25	>4	0.015 to >4
Ceftazidime	78.5	78.5	2	>32	0.25 to >32
Ceftriaxone			>8	>8	1 to >8
Ciprofloxacin	75.0	70.0	0.25	>4	≤0.03 to >4
Piperacillin-tazobactam	78.0	78.0	8	>64	≤0.5 to >64

Adapted from Pfaller et al [39]. Only data for pathogens for the treatment of which delafloxacin is approved (only in the United States so far [16]) and data on antimicrobial agents recommended for the treatment of skin and soft tissue infections in the 2014 Infectious Diseases Society of America guidelines [13] are presented.

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

US Food and Drug Administration–designated breakpoints (for use in the United States [16]) against the following pathogens are listed below.

[a]*Staphylococcus aureus* (MRSA and MSSA isolates): Susceptible, ≤0.25 mg/L; intermediate, 0.5 mg/L; resistant, ≥1 mg/L.

[b]*Enterococcus faecalis*: Susceptible, ≤0.12 mg/L; intermediate, 0.25 mg/L; resistant, ≥0.5 mg/L.

[c]*Streptococcus pyogenes*: Susceptible, ≤0.06 mg/L; intermediate, –; resistant, –. Isolates yielding results other than "susceptible" should be submitted to a reference laboratory for testing.

[d]*Streptococcus agalactiae*: Susceptible, ≤0.06 mg/L; intermediate, 0.12 mg/L; resistant, ≥0.25 mg/L.

[e]Enterobacteriaceae (including *Escherichia coli* and *Klebsiella pneumoniae*): Susceptible, ≤0.25 mg/L; intermediate, 0.5 mg/L; resistant, ≥1 mg/L.

[f]*Pseudomonas aeruginosa*: Susceptible, ≤0.5 mg/L; intermediate, 1 mg/L; resistant, ≥2 mg/L.

mutation at the *gyrA* locus and the S80Y mutation at the *parC* locus—and documented high rates of microbiological response against such isolates. Notably, the MIC values for isolates with single mutations were considerably larger than for susceptible isolates but did not exceed 0.5 mg/L (a value considered as "intermediate" by the FDA; see definition in [16]). A sole isolate harboring both mutations showed an MIC of 4 mg/L (thus reported as resistant) but was presumed eradicated by delafloxacin treatment.

Delafloxacin showed two- to five-fold lower broth MICs than ciprofloxacin against Enterobacteriaceae (*E. coli* and *K. pneumoniae*) isolated from the urine of patients with suspected urinary tract infections (UTIs) [44]. In addition, delafloxacin proved more active than moxifloxacin against *S. aureus* intracellularly [32] as well as in biofilms, both in vitro and in vivo [22, 45]. In this case, its activity was enhanced by agents capable of disrupting the biofilm, such as the antifungal agent caspofungin, which inhibits the synthesis of polysaccharide constituents of the biofilm matrix [46]. Taken together, these studies highlight the utility of delafloxacin in the treatment of a variety of infections caused by most Gram-positive pathogens. The situation is more difficult for *E. faecalis* and for Gram-negative pathogens (Enterobacteriaceae [current name: Enterobacterales] or *P. aeruginosa*), for which the MIC90 may exceed the FDA breakpoints (see [39]), requiring documentation of the susceptibility and making empiric treatments more risky.

Table 2. Mean (Standard Deviation) Pharmacokinetic Parameters and Statistical Analysis of Pharmacokinetic Parameters Following Administration of a Single 1-Hour Intravenous Infusion or a Single Oral Dose of Delafloxacin in Healthy Volunteers

Parameter	Oral Delafloxacin (450 mg) (n = 55)	Intravenous Delafloxacin (300 mg) (n = 55)
T_{max}, h[a]	0.817 (0.50–4.00)	1.00 (0.75–1.13)
C_{max}, mg/L	6.12 (1.96)	10.7 (2.29)
AUC_{0-t}, mg.h/L	23.3 (7.00)	26.9 (5.78)
$AUC_{0-\infty}$, mg.h/L[b]	24.2 (6.45)	26.7 (6.03)
F[c]	58.8 (10.5)[d]	

Statistical Analysis

Parameter	Geometric Least Squares Mean (90% CI)	Ratio of Geometric Least Squares Mean (Oral/IV), % (90% CI)
C_{max}, mg/L		
Oral (N = 55)	5.80 (5.44–6.17)	55.16 (51.50–59.08)
IV (N = 55)	10.51 (9.87–11.19)	
$AUC_{0-\infty}$, mg.h/L		
Oral (N = 42)	22.97 (21.61–24.41)	87.68 (83.56– 92.00)
IV (N = 49)	26.20 (24.71–27.78)	
AUC_{0-t}, mg.h/L		
Oral (N = 55)	22.24 (20.99–23.57)	84.45 (80.90– 88.15)
IV (N = 55)	26.34 (24.85–27.91)	

Adapted from Hoover et al [49].

Abbreviations: AUC, area under the curve; CI, confidence interval; IV, intravenous.

[a]Median (range).

[b]n = 42 for the oral dose and n = 49 for the IV infusion.

[c]F was calculated for each participant as ($AUC_{0-\infty}$ after oral) (IV dose)/($AUC_{0-\infty}$ after IV) (oral dose).

[d]n = 37.

PHARMACOKINETICS

Evaluation of the pharmacokinetics (PK) and disposition of delafloxacin following a single intravenous dose administered to healthy male volunteers showed the mean C_{max}, area under the curve ($AUC_{0-\infty}$), T_{max}, and $T_{½}$ to be 8.98 mg/L, 21.31 mg.h/L, 1 h, and 2.35 h, respectively [47]. Excretion was predominantly (66%) via the kidney, with a lower proportion (29%) of the dose excreted in the feces. The predominant circulating components were determined to be delafloxacin and its direct glucuronide conjugate. Delafloxacin exhibits linear PK that reach steady-state following 3 days of daily oral dosing, with minimal accumulation [48]. Delafloxacin oral bioavailability is 58.8%, which is lower than for levofloxacin or moxifloxacin, but total systemic exposure (AUC_{0-t} and $AUC_{0-\infty}$) following a single intravenous (300 mg) and a single oral dose (450 mg) of delafloxacin was equivalent (Table 2) [49]. Thus, a transition between dosing routes with daily dose adjustment is possible and has been approved in the United States [16]. The mean absolute bioavailability of delafloxacin was not affected by food. The steady state volume of distribution of delafloxacin is 30–48 L, which approximates total body water. The plasma protein binding of delafloxacin is approximately 84% (involving primarily albumin). Plasma protein binding of delafloxacin is not significantly affected by renal impairment. In a mass balance study, the mean half-life for delafloxacin was 3.7 h (standard deviation [SD] 0.7 h) after a single dose intravenous administration. The mean half-life values for delafloxacin ranged from 4.2 to 8.5 h following multiple oral administrations.

Following a single intravenous (300 mg) administration to subjects with mild (estimated Glomerular Filtration Rate [eGFR] = 51–80 mL/min/1.73 m^2), moderate (eGFR = 31–50 mL/min/1.73 m^2), severe (eGFR = 15–29 mL/min/1.73 m^2) renal impairment, and end-stage renal disease with hemodialysis receiving intravenous delafloxacin within 1 h before and 1 h after hemodialysis, mean total delafloxacin exposure (AUC_t) was 1.3, 1.6, 1.8, 2.1, and 2.6-fold higher, respectively, than that for matched normal control subjects [49, 50]. Mild, moderate, or severe hepatic impairment does not adversely affect either exposure or clearance of delafloxacin, indicating that dose adjustments are not required in this population [51]. Also, delafloxacin does not significantly affect the PK of midazolam, a cytochrome P450 [CYP] 3A substrate [52]. A small change in the C_{max} of 1-hydroxymidazolam was documented in this study but was not considered clinically relevant. Neither sex nor age had any significant effect on the pharmacology of delafloxacin.

PHARMACODYNAMICS

Monte Carlo simulation analyses using clinical PK and non-clinical PK/pharmacodynamic (PD) data were used to determine target attainment (TA) probabilities, which were used to support dose selection decisions [53]. Probabilities were determined for delafloxacin doses of 200–450 mg given intravenously every 12 hours, revealing high percent probabilities of TA for MIC values ≤0.5 mg/L with intravenous and oral doses of 300 mg and 450 mg respectively, which were chosen for the Phase 3 studies [53].

Several studies have evaluated the comparative PD of delafloxacin versus other fluoroquinolones, mainly levofloxacin and ciprofloxacin, against multiple clinically relevant pathogens including *S. aureus*, *E. coli*, *S. pneumoniae*, and *K. pneumoniae* in both in vitro and in vivo model systems [54–58]. Exposure of ciprofloxacin-susceptible and ciprofloxacin-resistant clinical isolates of *S. aureus* to clinically achievable ratios of AUC to MIC of delafloxacin and levofloxacin in a model simulating the PK of single and multiple doses of the 2 fluoroquinolones showed that delafloxacin was capable of producing greater anti-staphylococcal effects than levofloxacin at clinically achievable AUC/MICs [54]. Moreover, delafloxacin was more effective in the prevention of the selection of resistant mutants in *S. aureus*, as shown by appreciable differences in the clinically achievable AUC_{24}/MIC ratios (for the same organism, delafloxacin was capable of reaching an AUC_{24h}/MIC ratio of 870 h, which significantly exceeded the protective value of 240 h, whereas levofloxacin achieved a value of only 70 h, which was considerably lower than its protective value of 200 h) [54]. Examination of the killing kinetics of *E. coli* and *P. aeruginosa* exposed to single and multiple doses of delafloxacin and ciprofloxacin at clinically achievable AUC/MIC ratios showed that the killing effect of delafloxacin on *E. coli* at its clinically achievable AUC/MIC ratio (1740 h) was significantly higher than that seen with ciprofloxacin at its clinically achievable AUC/MIC ratio (2200 h) [55]. In the case of *P. aeruginosa*, two 12 h doses of delafloxacin (AUC/MIC 2 × 140 h) were more efficient at killing than ciprofloxacin (AUC/MIC 120 h). This study showed that clinically achievable AUC/MICs of delafloxacin and ciprofloxacin were comparable with regard to efficacy against *E. coli* (quaque die [QD] vs bis in die [BID] dosing) and against *P. aeruginosa* (at BID dosing but not QD dosing of delafloxacin). A subsequent animal study predicted significantly greater efficacy of clinically achievable AUC/MIC ratios of delafloxacin versus levofloxacin against ciprofloxacin-resistant *S. pneumoniae* and similar efficacy against ciprofloxacin-susceptible isolates [56]. Evaluation of the PK/PD targets of delafloxacin for *S. aureus*, *S. pneumoniae*, and *K. pneumoniae* in a murine lung infection model showed its activity against these pathogens, including isolates exhibiting resistance to other classes of antimicrobial agents [57] (in this study, the authors measured the free AUC_{24h}/MIC ratio and observed that at least 1 log_{10} kill was achieved for *S. aureus* when exposing the animals to values similar to those observed in humans during conventional therapy). A more recent study evaluated the PD of delafloxacin against a panel of pathogens causing community-acquired pneumonia including *S. pneumoniae*, MSSA, MRSA, and *K. pneumoniae* in a neutropenic murine lung infection model and documented in vitro and in vivo activity (as measured by the change in log_{10} colony forming unit (CFU) at 24 h compared to 0 h controls) as well as its high degree of penetration into the lung compartment, as evidenced by significantly higher concentrations in epithelial lining fluid compared with free drug in plasma [58].

SAFETY AND PHARMACOLOGY

Fluoroquinolones have a long history of adverse effects with several of them being considered as class-related such as tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbation of myasthenia gravis. As a result, all fluoroquinolones approved in the United States (including delafloxacin [16]) carry a general boxed warning about these effects (significant decreases in blood sugar and certain mental health side effects have been added recently or will be soon [59]). Both the US FDA and the European Medicines Agency (EMA) are also concerned with rare but severe and permanent or long-lasting serious side effects (see [59, 60], which led to the FDA statement that risks of fluoroquinolones may outweigh benefits for patients with mild infections such as acute sinusitis, acute bronchitis, and uncomplicated UTIs [61]. Likewise, the EMA may reduce the indications of fluoroquinolones to "severe infections when other antibiotics cannot be used" [62]. Most of these class-related adverse effects and/or permanent effects were uncommon in the safety data bases of registration and post-marketing studies undertaken by or under the control of Industry (see, for example, the safety profile of moxifloxacin as compiled from such studies involving about 15 000 patients [63]). The observation period in these studies is limited and they usually exclude patients with known risk factors. In this context, although the FDA label mentions that peripheral neuropathy and central nervous system effects have been observed with delafloxacin (also hypersensitivity, and *Clostridium difficile*-associated diarrhea), these were not specifically observed or reported more frequently in the delafloxacin arm than in the comparator arm in the clinical trials published to date [50, 64, 65, 66]. The current developer of delafloxacin undertook a series of studies aimed at examining specific fluoroquinolone-related side effects. In this context, cardiac safety was examined in clinical models that showed that neither a therapeutic (300 mg administered by IV) nor a supratherapeutic (900 mg IV) dose of delafloxacin was associated with clinically meaningful disturbances in cardiac repolarization (as measured by the corrected QT [QTc] interval) under conditions in which moxifloxacin, used as comparator, gave an unambiguous signal demonstrwating that the study was adequately sensitive to assess QTc prolongation [67]. Also, no relationship was reported between plasma concentrations and the placebo-corrected change from pre-dose baseline in the QTc (ΔΔQTcF) [49]. Because of concern about photosensitivity, commonly associated with a halogen substituent in position C8 (see [68] for review), a study of the photosensitizing potential of delafloxacin to ultraviolet (UVA and

UVB) and visible radiation was conducted in 52 healthy volunteers. Neither delafloxacin given for 7 days at 200 mg/day and 400 mg/day (0.22 and 0.44 times the approved recommended daily oral dosage, respectively, nor placebo demonstrated clinically significant phototoxic potential at any wavelengths tested (295 to 430 nm), including solar simulation. The active comparator (lomefloxacin, which possesses a fluorine substituent in C8) demonstrated a moderate degree of phototoxicity at UVA 335 nm and 365 nm and solar simulation wavelengths [69]. Finally, significant drug-drug interactions are unlikely [16, 49], which is a consideration when choosing non-fluoroquinolone alternatives such as macrolides.

KEY MESSAGES AND CONCLUSION

Delafloxacin is the only anionic member of the fluoroquinolone class approved (in the United States only at the date of writing) for clinical use by intravenous and/or oral routes. This unique biochemical characteristic results in several features, most notably an increased antibacterial activity (lower MICs) in acidic conditions that might occur in many infected sites such as abscesses, biofilms, and/or intracellularly in phagolysosomes. Like other fluoroquinolones, delafloxacin shows highly bactericidal activity. Based on breakpoints currently defined for the United States by the FDA, delafloxacin shows useful activity against most Gram-positive pathogens including strains that are resistant to other currently approved fluoroquinolones. Its activity against Gram-negative species, if confirmed by appropriate susceptibility testing, would support its utility in ABSSSIs caused by these organisms. Additional indications, such as respiratory tract infections for which the in vitro spectrum of activity of delafloxacin seems promising, need to be confirmed in comprehensive clinical trials. Although convincing safety features can only be demonstrated through large-scale clinical use, delafloxacin's safety record in the clinical registration trials was favorable. Moreover, specific studies examining cardiac- and phototoxicities were negative. The pharmacology of delafloxacin supports twice daily dosing and easy transition (with dose adaptation) from intravenous to oral routes, whereas the lack of clinically significant drug-drug interactions provides some assurance of safe use in the out-patient setting. In summary, as a result of its chemical, microbiological, and pharmacological properties, and its adverse event profile to date, delafloxacin may complement our current antibacterial armamentarium for effective treatment of skin/skin structure infections in the face of increasing antimicrobial resistance to other agents.

Notes

Author contributions. All authors were involved in the drafting, review, and approval of the manuscript for submission.

Acknowledgments. The authors thank Glenn Tillotson of GST Micro LLC for his expert feedback during the development of this manuscript. Assistance with the preparation of this manuscript was provided by Rich Friel and Alexandra Rayser of the Health Care Alliance Group, Voorhees, New Jersey.

Financial support. This study was funded by Melinta Therapeutics, New Haven, Connecticut.

Supplement sponsorship. This supplement is sponsored by Melinta Therapeutics, Inc.

Potential conflicts of interest. F. V. B. is Research Director from the Belgian *Fonds de la Recherche Scientifique* (FRS-FNRS). F. V. B. and P. M. T. received research grants for laboratory work about delafloxacin from Melinta Therapeutics, and P. M. T. was a speaker for Menarini S.r.L. about delafloxacin. S. H. Z. reports no conflicts of interest relative to this manuscript. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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