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A profile of delafloxacin in the treatment of adults with community-acquired bacterial pneumonia

Silvia Gómez-Zorrilla [a,b,c,d], Elena Sendra [a,b] and Juan P. Horcajada [a,b,c,d]

[a]Department of Infectious Diseases, Hospital del Mar, Barcelona, Spain; [b]Infectious Pathology and Antimicrobals Research group (IPAR), Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain; [c]Department of Medicine and Life Sciences (MELIS), Universitat Pompeu Fabra, Barcelona, Spain; [d]Center for Biomedical Research in Infectious Diseases Network (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain

ABSTRACT

Introduction: Community-acquired bacterial pneumonia (CABP) is the most common infectious cause of hospital admission in adults, and poses a significant clinical and economic burden. At the same time, antimicrobial resistance is increasing worldwide with only a few new antibiotics developed in recent years. Delafloxacin is an anionic fluoroquinolone available in intravenous and oral formulations and with a broad spectrum of activity targeting Gram-positives, including methicillin-resistant *Staphylococcus aureus* (MRSA), gram-negative organisms, and atypical and anaerobic organisms. It also has a better adverse event profile compared to other fluoroquinolones.

Areas covered: This article reviews the current epidemiology of CABP, etiologic agents and current resistance rates, current treatment guidelines, characteristics of delafloxacin (chemistry, microbiology, PK/PD), clinical efficacy and safety in pneumonia and other indications, and regulatory affairs.

Expert opinion: Delafloxacin's susceptibility profile against respiratory pathogens, bioequivalent intravenous and oral formulations and favorable safety profile, support its use for the treatment of CABP. It could be useful as empirical treatment in countries with high rates of penicillin-resistant *S. pneumoniae* and in patients with suspected or documented pneumonia due to MRSA. In post-influenza staphylococcal bacterial pneumonia, MRSA could be also considered an important pathogen.

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Antimicrobial resistance; community acquired pneumonia; delafloxacin; efficacy; MRSA; safety

1. Introduction

Community-acquired pneumonia (CAP) is considered a global health problem with great morbidity and mortality, particularly among people over 65 years of age [1] and carries a high economic burden [2,3]. It remains the world's deadliest communicable disease, ranking as the fourth leading cause of death [4], and one of the main leading causes of disability-adjusted life-years [5].

On the etiology of CAP in immunocompetent patients, a 2015 US study found that the most common pathogens detected were human rhinovirus (9%), influenza (6%), and *Streptococcus pneumoniae* (5%) [6]. In another multicenter study focused on the bacterial etiology, the most frequent causative pathogens were *S. pneumoniae* (8.2%) followed by *Pseudomonas aeruginosa* (4.1%), *Klebsiella pneumoniae* (3.4%) and methicillin-resistant *Staphylococcus aureus* (MRSA) (3.0%) [7]. Other important pathogens to consider are *Haemophilus influenzae*, *group A Streptococci, Moraxella catarrhalis, Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Legionella pneumophila* [8,9]. Regarding aspiration pneumonia, it is estimated that explains between 5 to 15% of cases of CAP [10]. Risk factors include diseases with impaired swallowing, consciousness, and cough reflex, as well as patients with an increased probability of gastric content reaching the lung (with enteral tubes feedings or gastroesophageal reflux) [11]. Since 2020, SARS-CoV2 has been added as a major cause of CAP worldwide in pandemic form [12].

Current treatment guidelines, both European [13] and American [14], differentiate treatment groups according to severity, hospitalization, comorbidities or risk factors for *P. aeruginosa* or MRSA. In outpatients, they recommend monotherapy with amoxicillin, tetracycline or macrolide (in countries with low pneumococcal resistance). When comorbidities or risk factors for bacterial resistance exist or in hospitalized patients, treatment with a respiratory fluoroquinolone (FQ) or combination therapy with beta-lactam plus macrolide or doxycycline are recommended. In severe CAP guidelines suggest combination treatment with beta-lactam and a macrolide or fluoroquinolone. In patients with risk factors for P.aeruginosa, antipseudomonal empirical therapy should be used. In case of risk factor for MRSA, monotherapy with vancomycin, linezolid, or clindamycin (if susceptible) is recommended. In aspiration pneumonia, only the American guidelines specifies there is no enough evidence to justify additional anaerobic coverage. For duration of antimicrobial therapy, both recommend a minimum of 5 days, according to clinical judgment, emphasizing that shorter courses of treatment are as effective as longer ones (except in cases of complicated pneumonia) **[13,14].**

In recent decades, the increasing emergence of pathogens resistant to first-line antibiotics has become a major global

CONTACT Juan P. Horcajada jhorcajada@psmar.cat Department of Infectious Diseases, Hospital del Mar, Passeig Marìtim 25, Barcelona 08003, Spain

Article highlights

- CABP is the most frequent infectious cause of hospital admission.
- There is increasing antimicrobial resistance worldwide.
- There is an unmet need for new available antimicrobial drugs.
- Delafloxacin is a new fluoroquinolone active against Gram-positive bacteria including MRSA, gram-negatives including *P. aeruginosa*, bacteria causing atypical pneumonia and anaerobes
- Delafloxacin has demonstrated non-inferiority to comparators in CABP.
- Delafloxacin bioequivalence between oral and intravenous regimen is advantageous for sequential therapy and outpatient management.
- The safety profile of delafloxacin is superior to that of other fluoroquinolones, primarily due to the lack of corrected QT interval prolongation, absence of phototoxicity, major central nervous system events, hepatotoxicity, and drug interactions.
- The efficacy and safety profile of delafloxacin supports its use for the treatment of CABP.

threat. Drug-resistant *S. pneumoniae* became a major concern worldwide after several reports of treatment failure related to pneumococcal isolates with decreased susceptibility to penicillin or macrolides [15–21]. MRSA and drug-resistant *Enterales*, which were previously only considered as causes of pneumonia in hospital settings, have been identified in some regions as important causative agents of CAP [20] In the context of MRSA-pneumonia, this generally occurs after influenza infection and shows as severe necrotizing pneumonia associated with the Panton-Valentine gene and other toxin production [21–23]. There is a clear need therefore for the development of new therapeutic options in CAP that can help to reduce the associated clinical and economic burden.

2. Overview of the market

The currently unmet need for therapies to treat community-acquired bacterial pneumonia (CABP) is related to the increase in antimicrobial resistance in Gram-positive cocci causing CABP, such as *S. pneumoniae*. According to EARS-Net data from 2020, whereas penicillin resistance rates in several European countries (Spain, Germany, Belgium, Sweden) were below 5%, in others, such as Greece (66.3%), Romania (48%), Italy (29.5%) and Bulgaria (28.1%), the rates were very high [24]. In the United States, penicillin resistance has decreased in recent years due to the effect of pneumococcal vaccination, although current rates are around 9 cases per 100,000 habitants in adults older than 65 years [25]. In addition, while MRSA-CABP is infrequent in European countries, rates in the US are higher. In a multinational study performed in 2015, investigators found that 4.8% of CAP patients in North America who had at least one diagnostic test for a pathogen had MRSA. The prevalence of MRSA in this cohort (range 6.1–16.4%) was highest in North America (16.4%), followed by South America (15.3%), and Oceania (7.7%) [26].

Both penicillin-resistant *S. pneumoniae* and MRSA-causing pneumonia are a major concern. Regarding MRSA, penicillin and derivatives, including in combination with beta-lactamase inhibitors, first- to fourth- generation cephalosporins, and carbapenems, may be to manage MARSA-causing pneumonia. Ceftaroline [27] and ceftobiprole [28] are new cephalosporins active against MRSA with a lower MIC against *S. pneumoniae*; both are currently good options for CAP, but with the risk of bacterial resistance. FQs such as levofloxacin are good options against penicillin-resistant *S. pneumoniae*, but they are not active against MRSA. Linezolid (oxazolidinone) is indicated for the treatment of MRSA-pneumonia but is usually reserved for hospital acquired pneumonia due to its potential toxicity. Tedizolid is a newer safer oxazolidinone but is only approved for skin and soft tissue infections. Other compounds in development that may be useful for bacterial resistance in CAP are lefamulin and omadacycline. Lefamulin is a pleuromutilin which mechanism of action involves inhibition of protein synthesis by binding to the peptidyl transferase center of the 50s bacterial ribosome, thus preventing the binding of tRNA for peptide transfer [29]. Omadacycline is a tetracycline-derived semisynthetic compound that has demonstrated *in vitro* activity against common etiologies of CAP, such as methicillin-resistant staphylococci, penicillin-resistant streptococci, gram-negative strains, and atypical bacterial pathogens [30] Omadacycline has demonstrated non-inferiority to moxifloxacin in CAP and is a once-daily antimicrobial option for CAP [31].

3. Chemistry

Delafloxacin is the only anionic FQ and differs from the other members of the group in terms of its structure. The lack of a strongly basic group at the C-7 position makes it a weakly acidic molecule, which facilitates transmembrane passage into the bacterial cell where the pH is neutral. Delafloxacin will therefore be in its ionic form and retained in the bacteria where it can accumulate in high concentrations. In its ionic form, it has increased potency in acidic environments prevalent at many infectious sites such as the skin, mouth, urinary tract, or vagina. It also has a heteroaromatic substitution at the N-1 position, which contributes to a larger molecular surface area, and a chlorine atom at position C-8, contributing to an electron-withdrawing effect on the aromatic ring at N-1, stabilizing the molecule [32,33].

The FQs target the bacterial topoisomerase enzymes topoisomerase II (DNA gyrase) and topoisomerase IV. DNA gyrase is more capable of inhibiting gram-negative (GN) bacteria, whereas topoisomerase IV is more prone to inhibition in Gram-positive (GP) bacteria. Unlike other FQs, delafloxacin displays roughly equal affinity for DNA gyrase and topoisomerase IV, conferring a broad spectrum of activity *in vitro* against both GN and GP bacteria, including MRSA [34]. Dual targeting also reduces the probability of resistance, since this requires the accumulation of multiple mutations that affect both enzyme [35].

4. Microbiology

Delafloxacin provides broad-spectrum coverage for GP and GN pathogens, as well as anaerobes (see Table 1). The *in vitro*

Table 1. *In vitro* susceptibility of selected pathogens to delafloxacin.

Organism (number of isolates) [ref.]	MIC50 (μg/ml)	MIC90 (μg/ml)	MIC range (μg/ml)
Gram positive			
S. pneumoniae (450) [37]	0.008	0.015	≤0.004 to 0.25
S.pneumoniae penicillin resistant (>1 μg/ml) [37]	0.008	0.015	0.008 to 0.015
MSSA (777) [37]	≤0.004	0.008	≤0.004 to 4
MRSA (573) [37]	0.06	0.5	≤0.004 to 4
MS- CoNS (75) [37]	≤0.004	0.06	≤0.004 to 1
MR- CoNS (125) [37]	0.06	0.5	≤0.004 to 2
Streptococcus pyogenes (433) [37]	0.008	0.0015	≤0.004 to 0.03
Streptococcus agalactiae (225) [37]	0.008	0.015	≤0.004 to 0.5
Streptococcus dysgalactiae (132) [37]	0.008	0.015	≤0.004 to 0.03
Viridans group streptococci (294) [37]	0.015	0.03	≤0.004 to 2
E. faecalis (450) [37] All	0.06	1	≤0.004 to 2
Vancomycin-susceptible [45]	NA	1	≤0.004 to 2
Vancomycin-resistant [45]	NA	1	≤0.008 to 2
E. faecium (295) [37]	>4	>4	0.008 to >4
Vancomycin-susceptible [45]	NA	>4	0.008 to >4
Vancomycin-resistant [45]	NA	<4	>4
Gram negative			
Enterales (2.250) [37]	0.06	4	≤0.004 to >4
Escherichia coli (500) [37]	0.03	4	≤0.004 to >4
E.coli isolates of the ESBL phenotype (92) [37]	2	>4	0.008 to >4
Klebsiella pneumoniae (389) [37]	0.06	>4	0.015 to >4
K.pneumoniae isolates of the ESBL phenotype (102) [37]	4	>4	0.06 to >4
Klebsiella oxytoca (111) [37]	0.06	0.12	0.03 to 1
Proteus mirabilis (211) [37]	0.06	2	0.015 to >4
Enterobacter spp. (384) [37]	0.06	1	≤0.004 to >4
Citrobacter spp. (178) [37]	0.06	2	0.008 to >4
Indole positive Proteus spp. (249) [37]	0.12	4	0.008 to >4
Serratia spp. (193) [37]	1	2	0.03 to >4
P.aeruginosa (200) [37]	0.25	>4	0.015 to >4
Acinetobacter baumannii-A.calcoaceticus (200) [40]	2	>4	0.015 to >4
Anaerobes			
Clostridioides difficile (50) [46]	0.064	0.125	0.008 to 0.5
Gram-positive anaerobic cocci [43]	0.008	0.032	0.008 to 0.25
Propionibacterium acnés (32) [43]	0.125	0.125	0.032 to 0.125
Clostridium perfringens (50) [43]	0.008	0.008	0.008 to 0.032
Bacteroides fragilis (100) [43]	0.064	0.125	0.032 to 0.125
Porphyromonas and Prevotella spp. (55) [43]	0.032	0.25	0.008 to 0.5
Fusobacterium nucleatum (30) [43]	0.008	0.064	0.008 to 0.125
Respiratory pathogens			
Haemophilus influenzae (200) [38]	≤ 0.001	0.004	≤ 0.001 to 0.25
Moraxella catarrhalis (100) [38]	0.008	0.008	0.004 to 0.015
Chlamydia pneumoniae (13) [39]	N/A	0.125	0.06 to 0.125
Mycoplasma pneumoniae (101) [43]	0.25	0.5	0.063 to 0.5
Legionella pneumophila (14) [39]	0.12	0.12	0.12
Miscellaneous			
Neisseria gonorrhoeae (117) [44]	0.06	0.125	≤0.001 to 0.25

MIC: minimum inhibitory concentration, NA, not available.

activities of delafloxacin and comparator agents were tested against 6,485 bacterial isolates from medical centers in Europe and the United States in 2014 and published by Pfaller *et al*. in 2017 [36]. In that study, delafloxacin exhibited very low MIC values against GP pathogens, including FQ-resistant strains of *S. aureus*, coagulase-negative staphylococci (CoNS) and *S. pneumoniae*.

Against respiratory infections-causing microorganisms, delafloxacin was the most active agent tested against *S. pneumoniae* (MIC_{50} 0.008 and MIC_{90} 0.015 μg/ml), *H. influenzae* (MIC_{50} ≤ 0.001 and MIC_{90} 0.004 μg/ml) and *M. catarrhalis* (MIC_{50} 0.008 and MIC_{90} 0.08) [37]. Regarding S.*pneumoniae*, all strains (5/5) were inhibited by 0.25 μg/ml of delafloxacin, which was 8-fold more active than ceftaroline, 16-fold more active than moxifloxacin and 64-fold more active than levofloxacin [36]. Delafloxacin has also shown good activity against atypical respiratory microorganisms, included *Legionella pneumophila, Mycoplasma pneumoniae* and *Chlamydia pneumoniae* [38–40].

An *in vitro* study against *S. aureus* showed that, among *S. aureus* methicillin-sensitive (MSSA) isolates, delafloxacin was the most potent antimicrobial agent tested ($MIC_{50/90}$ values were 0.004/ 0.008 μg/ml respectively); based on the MIC_{90s}, it was 8-to at least 64-fold more potent than ceftaroline and at least 64-fold more potent than levofloxacin. Among MRSA isolates, $MIC_{50/90}$ values were 0.06/0.5 μg/ml, being at least 64-fold more active than levofloxacin (according to MIC50s) and at least 8-fold more potent than ceftaroline [36]. Nevertheless, in a report conducted in 7 different hospitals in New York, the emergence of delafloxacin resistance was observed in MRSA,

indeed, 22% of isolates were non-susceptible to delafloxacin, despite the fact that the study was conducted in early 2017, prior to FDA approval of the drug [41]

As for other GP bacteria, delafloxacin CoNS MIC_{50} and MIC_{90} values for CoNS were 0.008 and 0.5 µg/ml, respectively. Compared with other agents, delafloxacin was the most active against isolates of beta-hemolytic streptococci (MIC_{50} 0.008 µg/ml and MIC_{90} 0.015 µg/ml, for each group of organisms) and viridans group streptococci (MIC_{50}0.015 µg/ml and MIC_{90} 0.03 µg/ml). Delafloxacin was also one of the most powerful antimicrobials tested against isolates of *Enterococcus faecalis* (MIC_{50} and MIC_{90}, 0.06 and 1 µg/ml, respectively). However, delafloxacin displayed limited activity against *Enterococcus faecium* strains (MIC_{50} and MIC_{90}, >4 and >4 µg/ml, respectively) and only 10.5% of isolates were susceptible at ≤1 µg/ml, in spite of vancomycin susceptibility patterns [36].

With respect to GN bacteria, delafloxacin showed good antimicrobial activity against *Enterobacterales*, with 80.9% of isolates being inhibited at ≤1 µg/ml. Against *P. aeruginosa*, delafloxacin inhibited 74.0% of *P. aeruginosa* isolates at ≤1 µg/ml. Ciprofloxacin susceptibility rates using CLSI (Clinical and Laboratory Standards Institute) and EUCAST (European Committee on Antimicrobial Susceptibility Testing, 2016) criteria were 75.0 and 70.0%, respectively (MIC_{50} 0.25 and MIC_{90} > 4 g/ml), and the rates of susceptibility to levofloxacin, again according to CLSI and EUCAST, were 72.5 and 62.5% (MIC_{50} 0.5 and MIC_{90} > 4 g/ml). Delafloxacin was most active against *Klebsiella oxytoca* (MIC_{50} and MIC_{90}, 0.06 and 0.12 g/ml, respectively), *Enterobacter aerogenes* (MIC_{50} and MIC_{90}, 0.12 and 0.25 g/ml), *Citrobacter koseri* (MIC_{50} and MIC_{90}, 0.015 and 0.06 g/ml), and other *Enterobacterales* (MIC_{50} and MIC_{90}, 0.06 and 0.25 g/ml, respectively) and was less active against *Klebsiella pneumoniae, Providencia spp., P. aeruginosa* (74.0% of isolates were inhibited by delafloxacin at ≤1 µg/ml) and *Acinetobacter baumannii-Acinetobacter calcoaceticus* (MIC90s 4 g/ml; only 44.0% of isolates were inhibited at ≤1 µg/ml [36]. In strains of *Enterobacterales* with the ESBL phenotype, only 28.3% of ESBL-producing *E. coli* and 18.6% of ESBL-producing *K. pneumoniae* isolates were inhibited by delafloxacin at 1 g/ml (MIC_{50} 2 g/ml and 4 g/ml, respectively). On the other hand, delafloxacin showed comparable activity to that of other fluoroquinolones tested against AmpC-producing strains of *Enterobacterales* [36]. Regarding anaerobic bacteria, the *in vitro* activity of delafloxacin was significantly superior to other FQs. It had good activity against *Clostridioides difficile* (MIC_{50} 0.064 and MIC_{90} 0.125 µg/ml) and was also very active against Gram-positive anaerobic cocci, *Propionibacterium acnes, Clostridium perfringens, Bacteroides fragilis, Porphyromonas, Prevotella spp*. and *Fusobacterium nucleatum* [42]. Finally, in another *in vitro* study with 117 *Neisseria gonorrhoeae* isolates, delafloxacin exhibited potent activity against *N. gonorrhoeae* strains, with MIC_{50} and MIC_{90} values of 0.06 µg/ml and 0.125 µg/ml, respectively. It also proved to have low potential for selecting spontaneous resistance mutants (107 to 109) in ciprofloxacin-susceptible and ciprofloxacin-resistant *N. gonorrhoeae* [43].

5. Pharmacodynamics

Delafloxacin is a concentration-dependent bactericidal agent. The pharmacokinetic/pharmacodynamic (PK/PD) parameter most closely associated with its activity is the ratio of the area under the free drug concentration-time curve to the minimum inhibitory concentration of the infecting organism (fAUC24/MIC), as in other FQs [44,45]. The pharmacodynamics of delafloxacin have been studied in a series of experiments using the murine lung and thigh infection models [46–48]. As discussed below in the section on 'Animal models,' these studies demonstrated high penetration into the lung compartment, since concentrations in the epithelial lining fluid were significantly higher than those of free drug in plasma (mean penetration ratio 13:1) [46,47].

Delafloxacin has also shown good activity against bacterial biofilm production, which is explained by its potency under acidic conditions and its increased penetration into the biofilm matrix. In an *in vitro* PD model, *Bauer et al*. [49] compared the activity of delafloxacin versus eight other anti-staphylococcal drugs against *S. aureus* biofilm. Delafloxacin was shown to reduce both MSSA and MRSA biofilm viability by at least 50% at clinically achievable concentrations, as well as biofilm thickness. Delafloxacin, oxacillin and daptomycin were the most effective drugs against MSSA, and delafloxacin appeared to be more active than moxifloxacin and daptomycin against MRSA strains in biofilm [49]. In another biofilm study, *Lemaire et al*. showed that pH strongly enhances the uptake of delafloxacin as compared with moxifloxacin and other anti-staphylococcal drugs [50]. In a murine model of systemic infection, *Ding et al*. showed that delafloxacin was more active than moxifloxacin against renal abscesses formed by a community-associated MRSA strain (MWS) [51]. This supports the potential of delafloxacin for use in the treatment of staphylococcal infections with biofilm production, as well as for abscess-forming infections, where antibiotics are generally ineffective because of the presence of a large proportion of bacteria in the stationary phase of growth, the acidic environment and overproduction of efflux pumps.

6. Pharmacokinetics and metabolism

6.1. Absorption

The PK properties of delafloxacin have been evaluated in phase I and phase II studies. Further information is provided in Table 2. Delafloxacin was found to be rapidly absorbed due to the relatively short time to peak concentrations (Tmax), which range from 1.0 to 2.5 h. At steady state, 300 mg delafloxacin every 12 hours administered as a 1-hour infusion achieves a maximum serum concentration (Cmax) of 9.29 mg/L and total exposure (AUC from 0 to 12

Table 2. Pharmacokinetic and pharmacodynamic differences of delafloxacin with levofloxacin and moxifloxacin.

	Delafloxacin IV 300 mg every 12 h	Levofloxacin PO 500 mg every 24 h	Moxifloxacin PO 400 mg every 12 h
Protein Binding (%)	84	24–38	50
Urinary fraction (%)	64.5	87	20
Bioavailability (%)	58.8	99	90
T_{max} (h)	1.00	6–7	1.49
C_{max} (mg/L)	9.29	6.2	4.5
$T_{1/2}$ (h)	3.7	6–7	12
MIC_{90}	0.015	1	0.25
$AUC_{0\text{-}24}$ (mg/h/L)	61.6	47.5	48
24-h fAUC/MIC (mg/h/L)	9.86	34	29
References	[37,52,54,56]	[44,55]	[44,55]

Tmax: time to Cmax; Cmax: peak serum concentration; T1/2: half-life; MIC_{90}: Minimum inhibitory concentration of 90% of the *S.pneumoniae* strains evaluated; $AUC_{0\text{-}24}$: 24-h area under plasma concentration curve over 24 h; *fAUC/MIC*: ratio of the area under the free drug concentration–time curve to the minimum inhibitory concentration of the infecting organism.

h, AUCs) of 23.4 mg h/l. The average terminal half-life of delafloxacin is approximately 12 hours (ranging from 8 to 17 hours) [52–54]. Oral bioavailability (58.8%) is lower than that of other FQs such as levofloxacin and moxifloxacin (99% and 92% respectively), although the AUC of 450 mg of orally administered delafloxacin (20.6 mg h/l) is comparable to that achieved with a labeled IV dose of 300 mg. The decrease in total exposure (AUC) is minimal when delafloxacin is administered with food and not considered clinically relevant [53].

6.2. Distribution

The volume of distribution of delafloxacin at steady state (Vss) is large (around 40 l), which is similar to that of total body water. In plasma, it binds primarily to albumin (84%) [52,56]. No significant differences in PK profile were observed between the sexes [53] In terms of age, systemic exposure to delafloxacin was higher in elderly participants, which was attributed to lower creatinine clearance in elderly subjects [53].

6.3. Metabolism and elimination

IV Delafloxacin is primarily excreted by the kidneys (65%) as unchanged delafloxacin and glucuronide metabolites and 28% was excreted in feces as unchanged delafloxacin [54,57] Secondarily, almost 30% of the drug showed biliary excretion or intestinal elimination [57]. More information is provided in Table 3 and in the section on phase I clinical trials. Delafloxacin is not an inhibitor of cytochrome P450 (CYP) enzymes at clinically relevant concentrations but does appear to be a mild inducer of CYP3A4 *in vitro*. Nevertheless, in a phase 1 study no clinically relevant inhibition of cytochrome P450 enzymes occurred during administration of delafloxacin with the CYP3A4 substrate, midazolam [58].

7. Clinical efficacy

7.1. Animal models

The *in vivo* efficacy and PK/PD profiles of delafloxacin were evaluated in two different respiratory models [46,47]. The first one by Thabit *et al*. was a model of murine lung infection using *S. pneumoniae* (2 strains), *S. aureus* (2 MSSA and 2 MRSA strains) and 2 *K. pneumoniae* isolates [46], in which delafloxacin showed potent *in vivo* activity and high penetration into the lung compartment, with epithelial lining fluid concentrations higher than the free plasma concentrations. Delafloxacin, like other FQs, exhibited concentration-dependent antibacterial effects and the best PK/PD parameter predictive of therapeutic efficacy was the ƒAUC24/MIC ratio [34,46]. In that study, the fAUC24/MIC ratio of delafloxacin needed to achieve bacterial stasis was considerably lower than that of older FQs [34,44]. In the second model, Lepak et al. described a model of neutropenic mice with lung infection produced by inoculation of S. *aureus, Streptococcus pneumoniae, and Klebsiella pneumonia*e, including penicillin-resistant *S. pneumoniae*, MRSA and ESBL-producing *K. pneumoniae* isolates. Delafloxacin demonstrated potent *in vitro* and *in vivo* efficacy against three pathogen groups, superior to that of other FQs [47].

7.2. Phase I clinical trials

Phase I clinical trials conducted to evaluate delafloxacin are summarized in Table 3. The first was a phase I, open-label, mass balance trial conducted in six healthy volunteers to investigate the PK profile and determine the drug elimination rates and routes of a single IV dose of 300 mg of delafloxacin [57]. The study demonstrated that the drug was primarily eliminated through the kidneys, with 66% of the dose recovered in the urine, mostly unchanged. In addition, around 30% of the drug was recovered in the feces due to biliary and/or intestinal elimination. The major circulating components in plasma identified in the study were mostly unchanged delafloxacin followed by a direct glucuronide conjugate metabolite (delafloxacin glucuronide).

Hoover et al [52] reported the results of three phase I clinical trials conducted to determine the PKs, safety and tolerability of IV delafloxacin after single and multiple dosing. In total, 93 healthy participants were enrolled in the 3 trials. In the first study, a randomized, double-blind, single ascending-dose trial, 62 healthy participants were assigned to receive a single IV 1-hour infusion dose of 300 mg of delafloxacin (12 participants). The remaining 50 received either a single IV 1-hour infusion of a dose of 450 mg, 500, 750, 900 or 1200 mg (8 participants per dose group) or placebo (2 participants per dose group). IV delafloxacin was well tolerated, with the most commonly reported adverse event (AE) being gastrointestinal and dose-related. The mean terminal half-life was approximately 12 hours at most dose levels and renal elimination of unchanged delafloxacin was 30–40% of total clearance. In the second trial, a double-blind, placebo-controlled study, 12 healthy subjects were randomized to receive a single 300-mg IV infusion of delafloxacin or placebo (n ¼ 4) on day 1, followed by 300 mg 1-hour infusion twice

Table 3. Phase I delafloxacin trials: pharmacokinetics, safety and tolerability profile.

PHASE I

Phase	Study type	Sample Size (n) *	Dose and administration route	Outcomes	Main Clinical Results.	Safety and Tolerability
I Mc Ewan 2015 [57]	Open-label, mass balance phase I trial	6	300 mg IV (single dose)	-Determine the rates and routes of excretion. -Investigate the PK profile. -Identify the major circulating drug-related components.	-Elimination: predominant renal excretion. Biliary/intestinal less relevant - 70% circulation and excretion unchanged - Main metabolite: delafloxacin glucuronide	AEs non mentioned
I Litwin 2015 [62]	A Randomized, double-blind, placebo-controlled, 4-period crossover study	52	300 mg IV DLX 900 mg IV DLX 450 mg PO moxifloxacin	-Evaluate effect of DLX in cardiac repolarization	Not evaluated	No prolongation of QTc were observed in DLX arms.
I Hoover 2016 [52]	Double-blind, randomized, single-ascending-dose trial	62	300 mg IV (single dose) 450 mg IV (single dose) 600 mg IV (single dose) 750 mg IV (single dose) 900 mg IV (single dose) 1200 mg IV (single dose)	-Determine the PK, safety and tolerability of a single dose IV DLX.	-Mean terminal half-life 12 hours - Cmax and AUC values increased with the increasing of the IV dose.	Gastrointestinal disorders most common AE (32%): mild intensity and dose-related events.
	Double-blind, randomized, placebo-controlled study	12	300 mg IV bid 14 days	-Evaluate the PK, safety and tolerability of multiple IV DLX doses	- No accumulation of DLX after 14 days.	Well tolerated after multiple doses
	Open-label, randomized, 2-period, 2-sequence crossover study	56	450 mg PO 300 mg IV	Compare PK, safety and tolerability of oral and IV delafloxacin	-No relevant differences in PK profile between oral and IV administration.	Well tolerated (AEs in 20%: mainly headache and diarrhea. Mild intensity)

(*Continued*)

Table 3. (Continued).

PHASE I

Phase	Study type	Sample Size (n) *	Dose and administration route	Outcomes	Main Clinical Results.	Safety and Tolerability
I Hoover 2016 [53]	Randomized, double-blind, placebo-controlled, single ascending-dose study	56	50 mg PO (single dose) 100 mg PO (single dose) 200 mg PO (single dose) 400 mg PO (single dose) 800 mg PO (single dose) 1200 mg PO (single dose) 1600 mg PO (single dose) *(Unformulated drug)*	-Determine PK parameters, safety and tolerability profile of a single ascending oral dose of DLX	- Cmax and AUC increased with increasing oral dose. - Peak concentration about 1 h after oral administration - Half-life 6–8 h	Gastrointestinal AEs the most common -More frequent with higher doses -Mild or moderate intensity -No evidence of QTc interval prolongation nor alteration in laboratory findings. -Food, sex and age did not significantly affect the safety profile. - Well tolerated after multiple doses.
	Randomized, double-blind, single dose, 2-period crossover study	20	250 mg PO (single dose *(Unformulated drug)*	Food-effect study with unformulated drug in a gelatin capsule	Reduction of Cmax and AUC with high-fat meal compared with fasting conditions.	
	Randomized, double-blind, single dose, parallel-group, placebo-control study	32	*(Unformulated drug)*	-Evaluate PK, safety and tolerability in women and healthy elderly people	- Sex: No PK differences between sex - Age: AUC was higher in elderly subjects (attributed to a lower creatinine clearance).	
	Randomized, double-blind, placebo-controlled, multiple ascending-dose study	60	100 mg PO od 5 days 200 mg PO od 5 days 400 mg PO od 5 days 800 mg PO od 5 days 1200 mg PO od 5 days *(Unformulated drug)*	Evaluate PK, safety and tolerability profile after multiple oral dose of DLX	Half-life longer after multiple doses compared with single administration.	
	Single-dose randomized, open-label, 3-period,6-sequence cross- over study	30	900 mg (450 mg PO BID) *(Tablet formulation)*	Food-effect study with formulated tablets	The Cmax of DLX was decreased only slightly in the presence of food, but AUC was not significantly affected.	
I Hoover 2016 [59]	Open-label study (healthy subjects and liver disease patients stratified according to Child-Pugh score)	36	300 mg IV (single dose)	-Evaluate the PK and safety of DLX in hepatic impairment subjects (including Child-Pugh A, B and C).	-No differences in DLX exposure and clearance comparing with healthy subjects). -No need of initial dose adjustment in hepatic impairment subjects.	Well tolerated (mild-moderate AEs).
I Hoover, 2018 [60]	open-label, parallel-group crossover trial (healthy subjects and renal impairment subjects)	34	300 mg IV 400 mg PO	-Evaluate the PK and safety in renal impairment subjects	-DLX clearance decreased as renal function worsened (AUC about 2-fod higher than normal renal group if GFR < 30 mL/min) -Dose adjustment recommendable if GFR < 30 mL/min	Well tolerated (gastrointestinal events most common AE, 17.6%)

(*Continued*)

Table 3. (Continued).

PHASE I						
Phase	Study type	Sample Size (n) *	Dose and administration route	Outcomes	Main Clinical Results.	Safety and Tolerability
I Hoover 2018, [61]	open-label, parallel-group, crossover trial (ESRD subjects and healthy subjects)	19	300 mg IV (single dose)	Evaluate the PK and safety of in hemodialysis subjects.	- Although dialyzable, a significant DLX accumulation was observed in patients with ESRD (AUC about 2-fod higher in ESRD group than healthy subjects).	Well tolerated (GI AEs most common reported: 50% in ESRD)
I Dave 2018 [63]	Randomized, investigator-blind, placebo/active-controlled, parallel-group study	52	DLX 200 mg PO QD 6 days DLX 400 mg PO QD 6 days LMX 400 mg PO QD 6 days	Evaluate the potential phototoxicity of DLX	Not evaluated	Not clinically significant phototoxic potential demonstrated.

*Phase I trials were conducted in healthy participants. In Phase I trials conducted to evaluate delafloxacin in hepatic and renal impairment subjects [63–65], participants were otherwise healthy. Abbreviations: DLX, delafloxacin; LMX, lomefloxacin; IV, intravenous; PO, oral administration; bid, twice a day; PK, pharmacokinetic; AUC, area under curve, AE, adverse event; ESRD, end-stage renal disease.

daily from day 2 to 12 and no appreciable accumulation of the drug after 14 days twice daily dosing was observed and the drug was well tolerated. Finally, a third trial was conducted in 56 healthy subjects and compared oral delafloxacin (450 mg tablet) with IV delafloxacin (300 mg in 1 h intravenous infusion). The PK parameters of IV and oral delafloxacin administration were comparable. The mean absolute bioavailability of delafloxacin was 58.8%. These data support the possibility of switching between the two formulations.

The PK, tolerability, and safety profile of oral delafloxacin were evaluated in two phase I trials [53]. The first was a single and multiple ascending-dose study to evaluate the effects of age, sex, and food on delafloxacin administration and consisted of 3 parts. Part 1 was a randomized, parallel-group, placebo-controlled study of 56 healthy men to evaluate single ascending oral dose of delafloxacin (50 mg to 1600 mg). Part 2 was a single-dose crossover study in which 20 men received 250 mg delafloxacin with or without food. Part 2 also included a parallel group, double-blind, placebo-controlled study in 16 women and 16 elderly men and women who were randomized (3:1) to receive 250 mg delafloxacin or placebo. Part 3 was a randomized, double-blind, placebo-controlled, multiple (100, 200, 400, 800, 1200 mg once daily for 5 days) ascending-dose study of oral delafloxacin in healthy men. Delafloxacin was rapidly absorbed, with peak concentration occurring approximately 1 hour after administration and a half-life of approximately 6 to 8 hours. The half-life was longer after multiple doses. Delafloxacin was well tolerated, and gastrointestinal events (mainly diarrhea) were the most commonly reported AEs. No pharmacokinetic differences were observed between the sexes. In terms of age, exposure to delafloxacin was higher in elderly participants, which was attributed to lower creatinine clearance in elderly subjects. The second study was a study of the effect of food in 30 healthy subjects. The delafloxacin Cmax was slightly reduced when administered when given with a high-fat meal (20.5% compared with fasting conditions). However, total exposure (AUC) was not significantly affected by administration with food.

As discussed above, while the principal route of delafloxacin elimination is through the kidneys, the liver is also involved in drug elimination. Consequently, studies were conducted to evaluate the PK and safety profile in subgroups of patients with hepatic or renal disease [59–61]. A phase I, open-label study was conducted in 36 patients, stratified into 4 groups according to hepatic function (mild, moderate and severe-A, B, C groups. Group D was the healthy comparator subjects matched) [59]. A single IV dose of 300 mg delafloxacin was administered, and no significant differences in the main PK parameters were observed when patients with hepatic impairment (including the Child-Pugh C group) were compared with healthy subjects. Overall, delafloxacin was well tolerated and, based on these results, no adjustment of the initial dose of delafloxacin is necessary in the presence of hepatic impairment [59].

With respect to renal impairment, 2 phase I trials were conducted to evaluate delafloxacin in patients with renal disease [60,61]. In the first, a phase I open-label, parallel group, crossover trial in 34 healthy subjects with normal renal function (eGFR > 80 mL/min/1.73 m^2) or mild (eGFR >50-80 mL/min/1.73 m^2), moderate (eGFR >30-50 mL/min/1.73 m^2) or severe renal impairment (eGFR < 30 mL/min) received a single dose of IV or oral delafloxacin. Overall, total delafloxacin clearance decreased as renal function deteriorated, with a corresponding increase in AUC as the degree of renal impairment worsened, with an $AUC_{0-\infty}$ for the GFR ≤ 30 mL/min group approximately 2-fold higher than in the normal renal function group [60]. These data are consistent with the earlier report on oral delafloxacin pharmacokinetics in elderly participants, which suggested that decreased delafloxacin clearance correlated with decreased creatinine clearance [53]. Both IV and oral delafloxacin were well tolerated in patients with renal impairment. The authors recommended a dose adjustment in patients with severe impairment (GFR < 30 mL/min). A different phase I trial was conducted to evaluate delafloxacin in subjects with end-stage renal disease (ESRD) undergoing hemodialysis, administering a single 300 mg dose intravenously 1 hour before and 1 hour after hemodialysis sessions, then comparing with healthy participants. A total of 19 subjects participated in the study (10 with ESRD and 9 healthy subjects). The AUC of delafloxacin was approximately 2.1- and 2.6-fold higher in subjects with ESRD than in healthy subjects when dosed 1 hour before and 1 hour after hemodialysis, respectively. Consequently, although delafloxacin can be dialyzed, significant drug accumulation is shown in patients with ESRD [61].

With respect to AEs of concern associated with FQ agents, the risk of QT prolongation and phototoxicity was evaluated in two different phase I trials. First, a randomized, phase I, double-blind, placebo-controlled, 4-period, crossover study was conducted in 52 healthy adults to evaluate the effect of delafloxacin on cardiac repolarization [62]. The corrected QT interval (QTc) was determined after a single therapeutic (300 mg) and supratherapeutic (900 mg) dose of delafloxacin. No clinically significant effect on RR, PR, QT and QRS intervals was found in the delafloxacin arms. Moreover, there was no positive relationship between delafloxacin plasma concentrations and QTc. As a limitation of the study, we highlight that the study was conducted in a population of healthy young adults (below 45 years of age) with no comorbidities or concomitant medication. The results therefore may differ in other populations. Finally, a randomized, investigator-blinded study was conducted to evaluate the photosensitizing potential of delafloxacin and no phototoxic effect was observed [63].

7.3. Phase II clinical trials

Table 4 summarizes phase II clinical trials conducted with delafloxacin.

7.3.1. Phase II clinical trials in respiratory tract infections

Two phase II clinical trials were conducted to evaluate the efficacy and safety of delafloxacin for the treatment of lower respiratory tract infections in both acute bacterial exacerbation

Table 4. Summary table of Phase II and III delafloxacin trials: efficacy.

PHASE II STUDIES

Indication	Study type	Population (sample size)	Primary Outcome	Delafloxacin (dose, route)	Comparator (dose, route)	Duration of treatment	Main results	Safety
SSSI	O'Riordan 2015: Phase II, randomized (1:1:1), double-blind multicenter trial in SSSI [67]	150	Clinical cure at TOC visit (14–21 days)	DLX 300 mg IV BID DLX 450 mg IV BID	Tigecycline (100 mg IV one dose, followed 50 mg IV BID)	5–14 days	**Similar result in primary outcome**: Clinical cure rates at TOC visit: DLX 300 mg 94.3% (33/35), DLX 450 mg 92.5% (n = 37/40), TIG 91.2% (n = 31/34)	300 mg DLX group was the best-tolerated regimen
	Kingsley 2016: Phase II, randomized (1:1:1), double-blind, multicenter trial in SSSI [68]	256	Clinical cure at follow-up visit	DLX 300 mg IV BID	-Linezolid 600 mg IV BID - Vancomycin 15 mg/kg IV BID	5–14 days	**- Similar result in primary outcome between DLX and LZD, and better results than VAN**: Clinical cure at follow-up visit: DLX 300 mg 70.4% (57/81), LZD 64.9% (50/77), VAN 54.1% (53/98) **- Better clinical cure with DLX than VAN in obese population**. **-No differences in bacterial eradication**	Well tolerated (Gastrointestinal events most common AEs)
Lower Respiratory Tract Infections	Longcor 2012: Phase II, randomized (1:1:1:1), double-blind study in patients with acute bacterial exacerbation of COPD [64]	280	Clinical cure and bacteriological eradication	DLX 100 mg PO QD DLX 200 mg PO QD DLX 400 mg PO QD	LVX 500 mg PO QD	7 days	-**Clinical cure was similar in the four groups**: DLX 100 mg 72% (49/68), 200 mg 69% (47/68). 400 mg 79% (54/68) and LVX 75% (52/69) - **Microbiological eradication: a significant dose-response trend was observed with DLX groups**: DLX 100 mg 81% (21/26), 200 mg 96% (24/25), 400 mg 97% (32/33), LVX 94% (33/35)	Most common AE: diarrhea, nausea and headache (diarrhea was dose-related event)
	Longcor 2012: Phase II, randomized (1:1:1), double-blind study in patients with community-acquired bacterial pneumonia (CABP) [66]	309	Clinical cure and bacteriological eradication	DLX 100 mg PO DLX 200 mg PO DLX 400 mg PO	–	7 days	**-Clinical cure**: DLX 100 mg 80% (83/104), 200 mg 87% (79/91) and 400 mg 87% (90/104) **-Microbiological eradication**: DLX 100 mg 88% (53/60), 96% (48/50), 96% (48/50)	Incidence of drug-related AEs: 23%, 37%, and 28% in the 100, 200, and 400 mg groups (mainly diarrhea, nausea and headache)

PHASE III STUDIES

Indication	**Study type**	**Population (sample size)**	**Primary Outcome**	**Delafloxacin (dose, route)**	**Comparator (dose, route)**	**Duration of treatment**	**Main results**	**Safety**
SSSI	Pullman 2017: A Phase 3, randomized, stratified, double-blind, multicenter trial in SSSI. [72]	660	Objective response at 48–72 h	DLX 300 mg IV BID	VAN 15 mg/kg IV BID + AZT 1 g IV BID	5–14 days	**Non inferiority of DLX for the primary outcome**: DLX and VAN-AZT 78.2% (259/331) and 80.9% (266/329)	Delafloxacin presented a lower overall discontinuation rate compared with vancomycin/aztreonam.
	O'Riordan 2018: Phase III, randomized (1:1) double-blind, multicenter trial in SSSI [73]	850	Clinical response 48–72 h	DLX 300 mg IV BID DLX 450 mg IV BID	VAN 15 mg/kg IV BID + AZT 1 g IV BID	5–14 days	**Non inferiority of DLX**: Objective response 48–72 h: DLX 83.7% (354/423)and VAN-AZT 80.6% (344/427)	Similar incidence of drug-related AEs in both groups (20.9%)

(*Continued*)

Table 4. (Continued).

PHASE II STUDIES

Indication	Study type	Population (sample size)	Primary Outcome	Delafloxacin (dose, route)	Comparator (dose, route)	Duration of treatment	Main results	Safety
CABP	Horcajada 2019: Phase III, randomized, double-blind, comparator-controlled, multicenter study in CABP [69]	860	Early clinical response	DLX 300 mg BID IV DLX 450 mg BID PO	MVX 450 mg QD IV/PO	5–10 days	**Non-inferiority of DLX compared with MVX was demonstrated.** Early clinical response rates: DLX 88.9% (383/431), MVX 89.0% (381/428).	Incidence of drug-related AEs: DLX 15.6%, MVX 12.6%.
Uncomplicated urogenital *Ghonorrhea*	Hook E. 2019: Phase III, randomized (2:1), open-label, single-dose, multicenter study in uncomplicated urogenital ghonorrhea [74]	460	Urogenital microbiological cure in the urogenital samples	DLX 900 mg PO	CFX 250 mg IM	Single-dose	**A single 900 mg dose of DLX did not demonstrated non-inferiority when compared with IM CFX** Urogenital microbiological cure rates: DLX 85.1% (194/228) and CFX 91.0% (91/100)	Most common AEs were gastrointestinal events (mainly diarrhea).

Abbreviations: SSSI, skin and skin structure infections; COPD, chronic obstructive pulmonary disease; CABP, Community-acquired bacterial pneumonia; DLX, delafloxacin; TIG, tigecycline; LZD, linezolid; VAN, vancomycin; AZT, aztreonam; LVX, levofloxacin; MVX, moxifloxacin; CFX, ceftriaxone; IV, intravenous; PO, oral administration; IM, intramuscular; QD, once a day; BID, twice a day; TOC, test of cure.

of chronic bronchitis (ABECB) and CABP. A randomized, double-blind, phase II trial compared delafloxacin (100, 200 or 400 mg PO daily for 5 days) and levofloxacin (500 mg PO for 7 days) in ABECB. 280 patients were included and the clinical response in the four groups was similar (69–79%), with no dose-response trends. However, a significant dose-response trend with delafloxacin was observed for bacteriologic cure rates. The authors concluded that the effectiveness of both the 200 mg and 400 mg delafloxacin doses was equivalent to the 500 mg dose of levofloxacin in the treatment of ABECB [64]. Consistent with these results, an *in vitro* study supported the use of delafloxacin in patients with chronic lung disease, more specifically, patients with cystic fibrosis. The *in vitro* activity of delafloxacin was evaluated against 52 strains of non-mucoid *P. aeruginosa* isolated from adult patients with cystic fibrosis. Delafloxacin demonstrated greater antipseudomonal activity than ciprofloxacin, with potential efficacy for the treatment of ciprofloxacin-resistant *P. aeruginosa* [65]. Another randomized, double-blind phase II trial was conducted to determine the optimal oral dose of delafloxacin for the treatment of CAP. A total of 309 patients were enrolled and randomized to receive 100, 200, or 400 mg of DLX once daily for 7 days. Clinical and bacteriological cure rates were similar in the 200 and 400 mg groups and, although not statistically significant, were higher than those in the 100 mg group [66].

7.3.2. Other Phase II clinical trials with delafloxacin

Prior to the respiratory tract infection studies, the efficacy and safety of delafloxacin was evaluated for the treatment of skin and skin structure infections (SSSIs) in two phase II, randomized, multicenter double-blind clinical trials involving a total of 406 patients (see Table 4). Intravenous delafloxacin was compared with tigecycline [67], vancomycin and linezolid [68]. Overall, the clinical cure rates of delafloxacin, tigecycline and linezolid were comparable. Delafloxacin had significantly better outcomes than vancomycin, with the differences being more marked in obese patients (delafloxacin 78.8% vs. vancomycin 48.8%) [68]. Delafloxacin was well tolerated in both trials.

7.4. Phase III clinical trials

Information related to phase III clinical trials of delafloxacin is summarized in Table 4.

7.4.1. Phase III clinical trial in respiratory tract infections

A phase III, randomized, double-blind, multicenter clinical trial was conducted to evaluate the efficacy and safety of delafloxacin versus moxifloxacin in community-acquired bacterial pneumonia (CABP), PORT risk class II to V [69]. The delafloxacin arm consisted of IV delafloxacin (300 mg BID as 1-h infusion) with the possibility of switching to oral delafloxacin (450 mg BID) when clinical stability was achieved and after completion of at least 6 IV doses. In the comparator arm, it was possible to change from IV moxifloxacin (400 mg OD as 1-h infusion) to IV linezolid (600 mg IV BID) if MRSA was found in respiratory isolates, and switch to oral moxifloxacin (400 mg OD) when stability was achieved. The primary endpoint of the study was early clinical response, defined as improvement at 96 (± 24) h; as a secondary outcome, clinical response at the test-of-cure visit (TOC) was also evaluated. A total of 859 patients were included (431 delafloxacin and 428 moxifloxacin, respectively). In the intention-to-treat (ITT) population analysis, early clinical response rates in the delafloxacin arm were 88.9% (383/431) versus 89% (381/428) in the moxifloxacin arm and the success rate at TOC was 91.0% in the delafloxacin group and 89.2% in the moxifloxacin group. In the subgroup of COPD or asthma patients, clinical response rates were significantly better in the delafloxacin group than the moxifloxacin group (93.4% vs. 76.8%, respectively). Delafloxacin was well tolerated, with AEs generally being of mild severity. The AEs most frequently reported (≥2%) were diarrhea, headaches and increased transaminases. The transaminase increase was more frequent in the delafloxacin (2.6%) than the moxifloxacin group (0.9%). No effect on QTc interval prolongation was observed in the delafloxacin group. No cases of phototoxicity, tendon disorder, myopathy, peripheral neuropathy, or aortic rupture/dissection were observed [69].

The microbiological intention-to-treat (MITT) analysis dataset included all patients in ITT analysis dataset who had a baseline bacterial pathogen identified that was known to cause CABP and against which the study drug had antibacterial activity. The MITT included 520 patients; a bacterial pathogen was identified in 60.5% of these. Based on MIC_{90} values, delafloxacin exhibited at least 16-fold greater activity than moxifloxacin for both GP and GN pathogens. The rates of microbiological success between the delafloxacin and moxifloxacin groups were similar for most of the pathogens. For delafloxacin, the cure rates were: 92.7% for *S. pneumoniae* (87.5% for penicillin-resistant *S. pneumoniae*), 92.6% for *S. aureus* (100% in the 2 strains of MRSA included), 100% for *E. coli*, 82.4% for *K. pneumoniae*, 100% for *K. oxytoca*, 100% for *Moraxella catarrhalis*, 91.7% for *P. aeruginosa*, 91.7% for *H. influenzae*, 88.6% for *H. parainfluenzae*, 96.7% for *M. pneumoniae*, 93.1% for *L. pneumophila*, and 100% for *C. pneumoniae* [70]. Delafloxacin had greater activity against *L. pneumophila* than moxifloxacin [71]. Given these results, delafloxacin was considered a good option for the treatment of CBAP [70,71].

7.4.2. Other phase III clinical trials with delafloxacin

Prior to the development of the clinical trial in CABP, the efficacy and safety of delafloxacin was demonstrated in two different phase III, randomized, double-blind, multicenter trials in adults with SSSI [72,73]. More than 1500 patients in all were included (Table 4). IV/oral delafloxacin fixed-dose monotherapy was non-inferior to IV vancomycin/aztreonam combination therapy and was well tolerated in each Phase III study. MRSA eradication rates were also similar between groups in both studies [72,73]. The frequency of drug-related AEs was similar in both groups, although the occurrence of AEs leading to discontinuation of treatment was higher in the vancomycin-aztreonam arm [73].

Finally, a phase III, open-label, randomized, multicenter clinical trial was conducted to evaluate the efficacy of

delafloxacin in uncomplicated urogenital gonorrhea (Table 4). Although *in vitro* data demonstrated potent delafloxacin activity against *Neisseria gonorrhoeae* and a low tendency for spontaneous mutant selection in the laboratory setting [43], a single dose of oral delafloxacin (900 mg) did not demonstrate non-inferiority to single-dose IM ceftriaxone (250 mg) in the phase III clinical trial [74].

8. Safety and tolerability

While FQs had traditionally been considered a safe family of antimicrobials, there has been growing concern about their safety profile in recent decades [45,75]. Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have updated their warnings to include stronger labels regarding the potential risk of serious AEs. These include warnings about the potential risk of tendon, joint and muscle pathologies, peripheral neuropathy, central nervous system (CNS) disturbances, exacerbation of myasthenia gravis or psychiatric disorders. Some of these, such as peripheral neuropathy, may be permanent and severe [75]. More recently, in 2018, two warnings alerted to the possible risk of FQ-related hypo/hyperglycemia and aortic rupture or dissection [76–78]. As a result, the FDA recommends against the use of FQs in uncomplicated infections. Similarly, the EMA recommends against the use of FQs in mild or moderate bacterial infection unless other antimicrobials recommended for such infections cannot be used. The EMA also suggests that FQs be used with caution in patients who are elderly or have kidney disease [79]. Despite the above, delafloxacin has a unique structure that distinguishes it from other FQs and current evidence supports that FQ-related AEs can be minimized with delafloxacin [45,62,63,75]. Overall, delafloxacin has demonstrated an adequate safety profile in several clinical trials to date. The most common AEs were gastrointestinal disorders, followed by headaches [52,53,59–64,66–69,72–74]. In addition, the safety profile of delafloxacin was favorable in patients with kidney or liver disease [59–61]. However, accumulation of the intravenous vehicle (sulfobutylether-β-cyclodextrin, SBECD) may occur with the IV formulation in patients with severe renal impairment and is considered a potential risk of renal damage, thus requiring dose adjustment [60]. The main potential AEs related to FQs and evaluated in delafloxacin [80] are summarized in Table 5 and are described below.

8.1. Gastrointestinal disorders

As in the rest of the FQ family, gastrointestinal disorders (mainly diarrhea, nausea, and vomiting) were the most common drug-related AEs reported in all clinical trials. They were generally mild to moderate in severity, with diarrhea being the most common AE reported [52,53,59–64,66–69,72–74]. Gastrointestinal AEs are dose-related [45,52,53,67]. There were no differences in the occurrence of gastrointestinal events when IV and oral administration were compared [52,53,75].

8.2. CNS effects

Mild CNS events are the second most common AE associated with delafloxacin, as in other FQ drugs [45]. Headaches are the most frequent delafloxacin-related CNS event. One patient with a prior history of seizures presented with a seizure but this was not considered to be related to the study drug [75]. No treatment-related seizures or other severe CNS events related to delafloxacin were reported in other phase III trials [67,68,72,74].

8.3. Tendon disorders and myopathy

Although FQ are associated with an increased risk of tendinitis and tendon ruptures [78], no tendon ruptures have been observed in clinical trials with delafloxacin. A pooled analysis of the two phase III trials in patients with SSSI showed tendinitis in 0.4 (3/741) patients in the delafloxacin arm, but none in the control arm [78]. No tendon ruptures were observed [69,74,75]. No drug-related cases of myopathy have been reported in clinical trials [69,72–74].

8.4. Peripheral neuropathy

One case of possible treatment-related paresthesia was reported in each arm of the phase III SSSI trial [73]. In a pooled analysis of phase III SSSI studies, rates of potential delafloxacin-related peripheral neuropathy were estimated at 0.1% (1/741) [75]. No potential peripheral neuropathy has been observed in other phase III clinical trials [69,74].

Table 5. Safety of delafloxacin in Phase III clinical trials: Overall global data of phase III published trials.

Drug-related adverse events	Delafloxacin (N = 1474)	Comparator group (N = 1332)
Gastrointestinal disorders		
Diarrhea	158 (10.7%)	24 (1.8%)
Nausea and vomits	80 (5.4%)	7 (0.5%)
Flatulence	7 (0.5%)	0 (0%)
CNS disorders		
Headache	17 (1.2%)	17 (1.3%)
Dizziness	7 (0.5%)	1 (0%)
Convulsions	0 (0%)	1 (0%)
Tendon disorders	3 (0.2%)	0 (0%)
Myopathy	7 (0.5%)	25 (1.9%)
Peripheral neuropathy	1 (0%)	2 (0.15%)
Skin disorders	8 (0.5%)	35 (2.6%)
Hyperglicemia	2 (0.1%)	3 (0.2%)
Hypoglicemia	1 (0%)	2 (0.15%)
C. difficile	3 (0.2%)	1 (0%)
QT prolongation	0 (0%)	3 (0.2%)
Transaminases increased	27 (1.83%)	12 (0.9%)
Potential phototoxicity	0 (0%)	0 (0%)

*__Delafloxacin arm__ included: 429 patients with community-acquired bacterial pneumonia (CABP) receiving IV/OR delafloxacin (300 mg BID IV /450 mg BID PO); 304 patients with uncomplicated urogenital gonorrhea treated with a single oral-dose of 900 mg delafloxacin; 741 patients with Skin and Skin Structure Infections (SSSI) treated with delafloxacin 300 mg IV/450 mg oral BID. **Comparator arm included: 427 patients with CABP receiving IV/OR moxifloxacin (400 mg once day); 154 patients with uncomplicated urogenital gonorrhea treated with a single dose of IM ceftriaxone (250 mg); 751 patients with SSSI treated with vancomycin (15 mg/kg) IV and aztreonam 1–2 g IV BID)

8.5. Potential aortic rupture/aneurysm dissection

No aortic rupture or aneurysm disruption has been observed in delafloxacin clinical trials [69,72–74].

8.6. Dysglycemia

FQs have been associated with dysglycemia in both diabetic and non-diabetic patients. In a phase II study comparing delafloxacin with tigecycline for SSSIs, hypoglycemia was observed in 11 of the 100 delafloxacin-treated patients [67]. Therefore, intensive glucose monitoring was conducted in a phase III trial on SSSIs with no differences between delafloxacin and comparator group [72]. In line with these results, in a pooled analysis, the incidence of dysglycemia in the two phase III trials in SSSIs was similar in the delafloxacin and comparator groups (<1% in both arms) and no treatment discontinuations or serious AEs were attributed to hyper or hypoglycemia in the delafloxacin group [78]. There were no reports of treatment-related hypo or hyperglycemia during treatment in the rest of the phase III trials with delafloxacin [69,73,74].

8.7. Hepatic events

Treatment-related hepatic AEs were estimated at around 2% and were mild or moderate in severity [67,73,75]. In three clinical trials a mild increase in transaminase levels was observed [53,68,69], but **n**o significant changes in laboratory values were observed in the other clinical trials conducted [52,64,66,74]. Moreover, in a phase I clinical trial conducted in subjects with hepatic impairment, a single dose of IV delafloxacin was well tolerated and the authors suggested that initial dose adjustment was not necessary [59].

8.8. QT interval prolongation

Delafloxacin has no effect on QT interval prolongation. In a phase I trial conducted to evaluate the effects of delafloxacin on QT interval, no ECG abnormalities were observed [62]. No significant QT prolongation-related events were observed in phase I, II and III trials conducted with delafloxacin [52,53,63,66–69,74]. Episodes of torsade de pointes have not been reported with delafloxacin [72].

8.9. Photosensitivity

No cases of phototoxicity associated with delafloxacin administration have been reported in clinical trials conducted to date. These data are consistent with the results of a phase I clinical trial conducted to evaluate potential photosensitivity with delafloxacin [63].

8.10. *Clostridioides difficile* infection

In a phase III SSSI trial, one of the 423 patient treated with delafloxacin developed *C. difficile* diarrhea. The patient entered the study as a prior treatment failure with sulfamethoxazole/trimethoprim and clindamycin. The *C. difficile* diarrhea was judged to be related to delafloxacin, was mild in severity, and resolved with treatment with oral metronidazole. No episodes were observed in the comparator arm [73]. In the phase III CAP trial, two subjects (0.5%) in the delafloxacin group and one (0.2%) in the moxifloxacin group presented *C. difficile* colitis. One subject in each arm had to discontinue treatment due to AEs. In the rest of the phase III trials, no cases of *C. difficile* infection have been observed [72,74].

9. Regulatory affairs

In June 2017, the US FDA approved delafloxacin for the management of acute SSSIs, as non-inferiority to vancomycin plus aztreonam was demonstrated in two phase III clinical trials [72,73] including more than 1000 patients. Both oral and parenteral forms (450 mg dose in tablet form and 300 mg injections, respectively) were approved. More recently, on 24 October 2019, the US FDA also approved the use of delafloxacin for the treatment of CABP in adults [81] following the results of a phase III clinical trial including 859 patients with CABP [69].

In Europe, delafloxacin was approved by the EMA in October 2019 for the treatment of acute SSSIs in adults when other antibacterial agents commonly recommended for the initial treatment of those infections are considered inappropriate [82]. In February 2021, the EMA also approved delafloxacin for the treatment of CABP [83]. Delafloxacin may have a potential role also in other indications, such as urinary tract infections, sexually transmitted transmission infections and intra-abdominal infections. More clinical trials are needed to evaluate potential use in other indications.

10. Conclusion

CAP is considered a global health problem with significant clinical and economic impact. In recent decades, the increasing emergence of pathogens resistant to first-line antibiotics has become a major concern worldwide. Delafloxacin is an anionic fluoroquinolone with a broad spectrum of activity targeting GP-bacteria including MRSA, GNs, bacteria causing atypical pneumonia and anaerobes. This broad coverage can be attributed to its structural differences relative to other FQs, resulting in a weakly acidic molecule that facilitates transmembrane passage into the bacterial cell and has greater potency in acidic environments and good activity against bacterial biofilm production. In addition, unlike most other FQs, delafloxacin inhibits DNA gyrase and topoisomerase IV almost to the same extent in both Gram-positive and gram-negative bacteria. This reduces the probability of resistance development which requires the accumulation of multiple mutations that affect both enzymes. Delafloxacin has bactericidal activity and in vivo models have shown high penetration into the pulmonary tissue, making it a good choice for the treatment of respiratory infections. Delafloxacin is primarily eliminated via the kidneys, with more than 60% of the drug eliminated unchanged in urine. Phase I and Phase II trials have demonstrated that delafloxacin is well tolerated both orally and intravenously. The most frequent AEs were gastrointestinal

events of mild or moderate severity. Indeed, the safety profile of delafloxacin is also favorable in patients with kidney or liver disease. Phase II clinical trials have evaluated the efficacy of delafloxacin in respiratory tract infections, including exacerbation of COPD and patients with CABP. Delafloxacin showed similar clinical and microbiologic cure rates to the comparator group. Finally, in a phase III, randomized, multicenter clinical trial involving more than 800 patients, delafloxacin was compared with moxifloxacin/linezolid in CABP, and non-inferiority in both clinical and microbiological cure was demonstrated. Clinical response rates were superior in the delafloxacin arm when patients with prior COPD or asthma comorbidity were analyzed.

11. Expert opinion

Delafloxacin is a novel FQ active against penicillin-resistant *S. pneumoniae*, MRSA, gram-negatives including *P. aeruginosa* and atypical bacteria causing CABP. It has demonstrated efficacy in CABP and a better safety profile than other FQs. Bearing in mind the increasing prevalence in several countries of penicillin-resistant *S. pneumoniae* and of MRSA as a cause of pneumonia, delafloxacin is an attractive option for the treatment of CABP in the context of antimicrobial resistance. Delafloxacin displays a similar affinity for DNA gyrase and topoisomerase IV, conferring a broad spectrum of *in vitro* activity against both GN and GP bacteria, including MRSA [36]. Its dual targeting also reduces the probability of resistance which requires the accumulation of a multitude of mutations that affect both enzymes. The ability of delafloxacin to select for spontaneous mutations in *S. aureus* strains was similar to moxifloxacin and substantially lower than that of levofloxacin [35]. However, a report from New York in 2017 showed that 22% of MRSA isolates from 7 hospitals were non-susceptible to delafloxacin and the possibility of resistance emergence should therefore be considered [41]. There are more advantages of delafloxacin that make it a good option for CABP. The unique anionic chemical structure of delafloxacin facilitates retention of the molecule in the bacteria and accumulation in high concentrations. Moreover, its ionic form increases potency in acidic environments frequent in many infectious foci such as pneumonia, the skin, mouth, urinary tract, or vagina, and allows high penetration into biofilms. Delafloxacin has high penetration into the lung, with epithelial lining fluid concentrations being significantly higher than free drug in plasma (13:1 mean penetration ratio) [46,47]. Because of delafloxacin's high penetration into pulmonary tissue and its bactericidal activity, it is a good choice for CABP. The possibility of using delafloxacin intravenously or orally is a clear advantage for managing hospitalized patients, since sequential therapy can easily be performed. At the same time, its good oral PK/PD properties facilitate outpatient management of non-severe CABP. The unique chemical structure of delafloxacin distinguishes it from other FQs, and current evidence supports that FQ-related AEs are minimal with this drug. The lack of corrected QT interval prolongation, the absence of phototoxicity, and the absence of major central nervous system events are the main differences from other FQs. Hepatotoxicity and drug interactions are absent from the warnings and precautions labels for delafloxaci [56]. However, most of the current available data are from clinical trials in which patients have been selected and frequently lack major comorbidities. Data from real world studies and pharma surveillance systems are needed to conclusively guarantee its safety. In summary, delafloxacin's susceptibility profile against respiratory pathogens, bioequivalent IV and oral formulations, and favorable safety profile support its use for the treatment of CABP. It could be useful as empirical treatment in countries with high rates of penicillin-resistant *S. pneumoniae* and/or those with some incidence of MRSA CABP, or in patients with risk factors for MRSA CABP. In post-influenza staphylococcal bacterial pneumonia, MRSA could be a significant pathogen to consider [84]. Penicillin-allergic patients with CABP could also benefit from this drug. Surveillance for selection of resistant mutants and possible adverse events should be performed when used in the real world.

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ORCID

Silvia Gómez-Zorrilla http://orcid.org/0000-0002-5987-068X
Elena Sendra http://orcid.org/0000-0002-4374-2173
Juan P. Horcajada http://orcid.org/0000-0001-9873-5459

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