Delafloxacin: A Review in Acute Bacterial Skin and Skin Structure Infections

L. J. Scott[1]

Abstract

The global spread of antibacterial-resistant strains, especially methicillin-resistant *Staphylococcus aureus* (MRSA) for acute bacterial skin and skin structure infections (ABSSSIs), has driven the need for novel antibacterials. Delafloxacin [Quofenix™ (EU); Baxdela® (USA)], a new fluoroquinolone (FQ), has a unique chemical structure that enhances its antibacterial activity in acidic environments such as occurs in ABSSSIs (including *S. aureus* infections). Delafloxacin (intravenous and oral formulations) is approved in several countries for the treatment of adults with ABSSSIs (featured indication). In intent-to-treat analyses in pivotal phase 3 trials in adults with ABSSSIs, including those with comorbid disease, intravenous delafloxacin monotherapy (± oral switch after six doses) twice daily was noninferior to intravenous vancomycin + aztreonam for primary endpoints, as specified by the FDA (objective response rate at 48–78 h after initiation of therapy) and the EMA [investigator-assessed clinical cure rate at the follow-up visit at day 14 (± 1 day)]. Delafloxacin was generally well tolerated, with most treatment-related adverse events mild to moderate in severity and few patients discontinuing treatment because of these events. Relative to vancomycin + aztreonam (a non-FQ regimen), delafloxacin treatment was not associated with an increased risk of FQ-associated AEs of special interest. Given its unique chemical structure that confers novel properties relative to other FQ and its broad spectrum of activity against common clinically relevant Gram-positive pathogens, including against MRSA strains (± FQ-resistance mutations), and Gram-negative pathogens, intravenous delafloxacin (± oral switch) provides a novel emerging option for the treatment of adult patients with ABSSSIs.

✉ L. J. Scott
  demail@springer.com

[1] Springer Nature, Mairangi Bay, Private Bag 65901, Auckland 0754, New Zealand

Delafloxacin: clinical considerations in acute bacterial skin and skin structure infections

Novel anionic FQ, acts via equipotent targeting of the bacterial enzymes topoisomerase IV and DNA gyrase

Potent in vitro activity against a broad spectrum of relevant Gram-positive and Gram-negative bacteria, including those carrying specific resistance mutations such as MRSA (± FQ-resistant mutations)

Noninferior efficacy to vancomycin plus aztreonam and generally well tolerated in pivotal phase 3 trials

Unlike other FQs, not associated with clinically relevant QT prolongation or phototoxicity

1 Introduction

Acute bacterial skin and skin structure infections (ABSS-SIs) are heterogeneous, potentially life-threatening infections involving the skin and underlying subcutaneous tissue, fascia or muscle, and include cellulitis/erysipelas, wound infections and major cutaneous abscesses [1]. ABSSSIs are associated with increased morbidity, mortality and duration of stay in hospital, thereby imposing a significant burden from a societal and healthpayer perspective. The most common causative pathogens are *Staphylococcus aureus* and *Streptococcus* spp. [1, 2]. ABSSSIs may be mono- or polymicrobial (include Gram-positive, Gram-negative and/or obligate anaerobic pathogens) in nature, with polymicrobial infections especially prevalent in patients with comorbidities or those who have failed prior antibacterial treatment. Patients with polymicrobial infections may be at higher risk of inadequate treatment and require broad-spectrum antibacterials [3]. Fluoroquinolones (FQs), given their broad spectrum of activity against clinically relevant Gram-positive and Gram-negative bacteria and availability as intravenous and oral formulations (provides flexibility to transition from intravenous to oral therapy), are amongst the most commonly utilized classes of antibacterials for treating infectious diseases [4]. However, in recent years, the global emergence of methicillin-resistant *S. aureus* (MRSA) strains and other resistant pathogens, including FQ-resistant and multi-drug resistant (MDR) bacteria, has posed a major concern for contemporary healthcare systems [3]. In light of this, there has been a drive to develop novel classes and novel agents within existing classes of antibacterials. Indeed, improved crystallographic techniques and structure–activity studies have played an important role in identifying novel multiple targets within known antibacterial classes (such as FQs) [4–6].

One such chemically unique FQ is delafloxacin [Quofenix™ (EU); Baxdela® (USA)]. Intravenous and oral formulations of delafloxacin are approved in several countries for the treatment of adults with ABSSSIs (featured indication) [7, 8] and/or community-acquired bacterial pneumonia (approved in the USA [7], but not in the EU [8]; discussion of this indication is beyond the scope of this review). This article reviews the clinical use of delafloxacin in adults with ABSSSIs, and summarizes its pharmacological properties and in vitro activity.

2 Pharmacodynamic Properties of Delafloxacin

Delafloxacin is a novel fully synthetic anionic FQ, with modifications of the quinolone structure performed to enhance its spectrum of antibacterial activity, pharmacokinetic profile and toxicity profile. Three unique changes in the chemical structure of quinolone differentiate delafloxacin from other FQs: namely, the presence of a substituted heteroaromatic ring at the N1 position (enhances its antibacterial activity vs other FQs), a weak polarity at the C8 position (postulated to enhance its potency against quinolone-resistant Gram-positive bacteria) and the absence of a basic group at the C7 position (makes it a weakly acidic molecule, thereby enhancing its antibacterial activity in acidic environments such as in ABSSSIs) [4–6, 9–13].

The antibacterial activity of delafloxacin is due to its dual-targeted equipotent inhibition of the essential bacterial enzymes topoisomerase IV and DNA gyrase (topoisomerase II). Conversely, other FQs (e.g. ciprofloxacin, levofloxacin and trovafloxacin) differ in their relative binding affinity for each these enzymes, exhibiting more potent inhibition of either topoisomerase IV or DNA gyrase. As a consequence of dual targeting, delafloxacin exhibits a broad spectrum of activity against clinically relevant microorganisms and a low risk of the emergence of resistance amongst susceptible pathogens [4–6, 9, 10, 14].

2.1 Antibacterial Activity

This section focuses on the in vitro antibacterial activity of delafloxacin against clinical isolates of Gram-positive and Gram-negative bacteria associated with ABSSSIs against which delafloxacin has demonstrated efficacy in clinical trials. In the EU summary of product characteristics [8] and/or US prescribing information [7] specified pathogens are *S. aureus* [including MRSA and methicillin-susceptible (MSSA) isolates] [7, 8], *Staphylococcus haemolyticus* [7, 8], *Staphylococcus hominis* [8], *Staphylococcus lugdunensis* [7, 8], *Streptococcus agalactiae* [7, 8], *Streptococcus anginosus* group (including *Streptococcus anginosus*, *Streptococcus intermedius*, *Streptococcus constellatus*) [7, 8], *Streptococcus dysgalactiae* [8], *Streptococcus mitis* group (including *Streptococcus cristatus*, *Streptococcus gordonii*, *Streptococcus oralis*, *Streptococcus mitis*, *Streptococcus sanguinis*) [8], *Streptococcus pyogenes* [7, 8], *Enterococcus faecalis* [7, 8], *Escherichia coli* [7, 8], *Enterobacter cloacae* [7, 8], *Klebsiella oxytoca* [8], *Klebsiella pneumoniae* [7, 8], *Proteus mirabilis* [8] and *Pseudomonas aeruginosa* [7, 8]. EUCAST defined minimum inhibitory concentration (MIC) breakpoints for susceptibility of delafloxacin against specified microorganisms are: *S. aureus* (0.25 μg/mL); *S. pyogenes*, *S. dysgalactiae, S. agalactiae* and *S. anginosus* (all 0.03 μg/mL); *E. coli* (0.125 μg/mL) [8]. Emphasis is given to results from recent in vitro studies involving > 500 clinical isolates collected since 2014 [15, 16] (or year not reported [17, 18]). MICs were determined using CLSI broth microdilution methods [15–17].

Against clinical isolates collected globally or in the EU and/or USA, delafloxacin exhibited potent in vitro activity (based on MIC required to inhibit the growth of 90% of isolates; MIC_{90}) against a broad spectrum of Gram-positive and Gram-negative pathogens commonly associated with ABSSSIs (Table 1) [15–18]. Delafloxacin also exhibited potent in vitro activity against Gram-positive strains exhibiting resistance to one or more clinically relevant antibacterial drugs, including against MRSA and MSSA strains (both ± levofloxacin resistance), MR and MS coagulase-negative staphylococci (CoNS), and *S. pneumoniae* strains resistant to ceftriaxone, levofloxacin, penicillin or multiple drugs (Table 1). In the largest of these study, the vast majority of MSSA (99.5% of isolates from both the EU and USA), MRSA (95.3 and 91.2%), MS CoNS (100 and 97.6%) and MR CoNS (99.5 and 84.5%) isolates were inhibited by delafloxacin at an MIC breakpoint of ≤0.5 µg/mL, with delafloxacin inhibiting 88.3% (484/548 isolates) of FQ-resistant *S.*

Table 1 In vitro activity of delafloxacin against selected clinical isolates

Pathogen	Total no of isolates	MIC_{90} (µg/mL; range across studies) [% susceptible; CLSI/EUCAST]		
		Delafloxacin	Levofloxacin	Vancomycin
Gram-positive isolates				
Enterococcus faecalis [15]	450	1	> 4 [70.7/70.7]	2 [97.8/97.8]
Staphylococcus aureus [15, 17]	2035	0.25	> 4 [64.4/64.4]	1 [100/100]
MRSA [15, 17]	867	0.25–0.5	> 4 [30/30]	1 [100/100]
MRSA LEV-R [17]	195	0.25	NR	NR
MRSA LEV-S [17]	101	0.008	NR	NR
MSSA [15, 17]	1172	0.008–0.03	2 [89.8/89.8]	1 [100/100]
MSSA LEV-R [17]	39	0.25	NR	NR
MSSA LEV-S [17]	358	0.008	NR	NR
S. aureus LEV-R [17]	232	0.25	NR	NR
S. aureus LEV-S [17]	455	0.008	NR	NR
MR CoNS [15]	125	0.5	> 4 [38.4/38.4]	2 [100/100]
MS CoNS [15]	75	0.06	4 [88/88]	2 [100/100]
Streptococcus agalactiae [15, 18]	335	0.015–0.03	1 [97.8/96.9]	0.5 [100/100]
Streptococcus anginosus group [18]	105	0.008	NR	NR
Streptococcus dysgalactiae [15, 18]	232	0.015–0.03	1 [99.2/97.0]	0.25 [100/100]
Streptococcus mitis group [18]	101	0.06	NR	NR
Streptococcus pneumoniae [15, 16, 18]	747	0.015–0.03	1 [98.9/98.9]	NA
S. pneumoniae CEF-R [16]	9	≤ 0.004–0.015	NR	NR
S. pneumoniae LEV-R [16]	30	0.5	NR	NR
S. pneumoniae MDR [16]	82	0.015	NR	NR
S. pneumoniae PR [16]	13	0.015	NR	NR
Streptococcus pyogenes [15, 18]	532	0.015–0.016	1 [99.8/96.5]	0.5 [100/100]
Gram-negative isolates				
Escherichia coli [15]	500	4	> 4 [69.6/69.6]	NA
E. coli ESBL [15]	92	> 4	> 4 [21.7/21.7]	
Enterobacter spp [15]	384	1	0.5 [96.6/95.8]	NA
Klebsiella oxytoca [15]	111	0.12	≤ 0.12 [100/100]	NA
Klebsiella pneumoniae [15]	389	> 4	> 4 [81.5/80.2]	NA
K. pneumoniae ESBL [15]	102	> 4	> 4 [34.3/32.4]	NA
Proteus mirabilis [15]	211	2	> 4 [78.7/71.1]	NA
Pseudomonas aeruginosa [15]	200	> 4	> 4 [72.5/62.5]	NA

Pathogens against which delafloxacin has demonstrated efficacy in clinical trials [7, 8]. Studies involving > 500 clinical isolates collected globally in pivotal phase 3 delafloxacin trials [17], globally in the SENTRY program [18], in the EU and USA [15] or in the USA [16] in 2014 [15, 16] (year not reported [17, 18]); not all studies reported all drugs or susceptibilities. Abstract plus poster presentation [18]

CEF-R ceftriaxone resistant, *CLSI* Clinical and Laboratory Standards Institute, *CoNS* coagulase-negative staphylococci, *ESBL* extended-spectrum β-lactamase, *EUCAST* European Committee on Antimicrobial Susceptibility Testing, *LEV* levofloxacin, *LEV-R* LEV-resistant, *LEV-S* LEV-susceptible, *MDR* multi-drug resistant, *MIC90* minimum inhibitory concentration required to inhibit 90% of isolates, *MR* methicillin-resistant, *MRSA* MR *S. aureus*, *MS* methicillin-susceptible, *MSSA* MS *S. aureus, NA* not applicable, *NR* not reported, *PR* penicillin-resistant

aureus and CoNS isolates at this breakpoint. At a breakpoint of ≤ 0.03 μg/mL, ≈ 99% of *S. pneumoniae* isolates were inhibited by delafloxacin, with delafloxacin several times more potent than ceftaroline (8-fold), moxifloxacin (16-fold) and levofloxacin (64-fold) [15]. In two global phase 3 trials in adults with ABSSSIs (Sect. 4), similar high microbiological response rates (i.e. eradication or presumed eradication) were observed against levofloxacin-nonsusceptible *S. aureus* (80/91 isolates; 98.8%) and MRSA isolates (70/71; 98.6%), as well as against isolates with mutations in the quinolone resistance determining region (QRDR) [17]. Amongst delafloxacin recipients with infections caused by *S. aureus* isolates that had S84L and S90Y mutations in *gyrA* and *parC*, respectively (the most commonly observed QRDR mutations in phase 3 trials), the microbiological response rate was 98.6% [17].

In vitro, delafloxacin exhibited potent activity at clinically achievable concentrations against biofilms of both MSSA and MRSA, reducing biofilm viability by at least 50% and also reducing film thickness [19, 20]. For example, in one of these studies, the biofilm activity of delafloxacin was better than that of daptomycin against MRSA biofilms, with both of these agents more effective than other tested anti-staphylococcal agents, including moxifloxacin, linezolid, rifampin, tigecycline and vancomycin [20]. The more potent activity of delafloxacin, at least in part, reflects its penetration into the acidic microenvironment of the biofilm.

For Gram-negative pathogens, 80.9% of *Enterobacteriaceae* strains ($n = 2250$; delafloxacin MIC$_{90}$ 4 μg/mL) were inhibited by delafloxacin at an MIC breakpoint of ≤ 1 μg/mL, although 90% of FQ-resistant *Enterobacteriaceae* strains (i.e. MIC > 1 μg/mL) exhibited decreased susceptibility to delafloxacin. Delafloxacin demonstrated more potent in vitro activity against non-extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* than against respective ESBL-producing strains (Table 1). Conversely, delafloxacin demonstrated potent in vitro activity against both nonESBL- and ESBL-producing strains of *K. oxytoca* (MIC$_{90}$ 0.12 μg/mL for both) [15].

In vitro, delafloxacin exhibits concentration-dependent bactericidal activity against Gram-positive and Gram-negative bacteria [7]. Delafloxacin demonstrated bactericidal in vitro activity against strains of MRSA collected in 2013 from patients participating in delafloxacin phase 3 trials in ABSSSI, with minimum bactericidal concentrations of 0.008 μg/mL, 0.5 μg/mL and 8 μg/mL against MRSA strain 110 (levofloxacin susceptible), 124 (triple mutant) and 165 (quadruple mutant), respectively (vs 0.5, 8 and > 32 μg/mL for levofloxacin) [21]. Against strain 110, bactericidal activity was observed at 6 h for most concentrations of delafloxacin and levofloxacin; at 16 × MIC, delafloxacin was associated with more rapid killing of MRSA strain 124 than the same concentration of levofloxacin; and at 24 h, delafloxacin was bactericidal at 16 and 32 × MIC against MRSA strain 165 [21].

In vitro drug combination studies showed no synergy or antagonism occurred between delafloxacin and amoxicillin/clavulanate, azithromycin, aztreonam, ceftaroline, ceftazidime, ceftriaxone, colistin, daptomycin, doxycycline, linezolid, meropenem, penicillin, rifampin, tigecycline, trimethoprim/sulfamethoxazole or vancomycin [7].

2.2 Resistance

Resistance to FQs, including delafloxacin, can occur due to mutations in defined regions of the target bacterial enzymes topoisomerase IV and DNA gyrase (i.e. QRDRs) or other resistance mechanisms such as altered efflux [7, 8]. Cross-resistance between delafloxacin and other FQs may be observed, although some isolates resistant to other FQs may retain susceptibility to delafloxacin [7, 8], including *S. aureus* isolates carrying mutations in the QRDR (*gyrA*, *gyrC* and *parE*) (Sect. 2.1) [7]. Although delafloxacin may be affected by targeted mutations, elevations in MIC values potentially have a minimal impact, given the intrinsic antibacterial in vitro activity of delafloxacin is markedly higher than other FQs, including moxifloxacin (considered the most potent FQ against Gram-positive pathogens) [22]. MIC$_{90}$ values for delafloxacin were twofold to fourfold lower than those of moxifloxacin [22]. This difference was more marked at acidic pH (pH 5.5), with MIC values for delafloxacin 5–7 dilutions lower than at neutral pH, whereas those for moxifloxacin increased by 2–3 dilutions at the lower pH [6]

In vitro, resistance to delafloxacin develops in multiple step mutations in the QDRDs of Gram-positive and Gram-negative bacteria [7]. In vitro, delafloxacin was associated with a low probability of selecting resistance against MRSA strains (2×10^{-9} to $< 9.5 \times 10^{-11}$) [23].

2.3 Pharmacodynamic/Pharmacokinetic Considerations

As for other FQs, the pharmacodynamic/pharmacokinetic relationship most closely associated with the efficacy of delafloxacin was the 24-h free-drug area under the plasma concentration–time curve (*f*AUC)/MIC ratio [8]. In a neutropenic murine lung infection model, the median *f*AUC/MIC targets associated with net stasis with delafloxacin were 1.42 for *S. aureus*, 0.56 for *S. pneumoniae* and 40.3 for *K. pneumoniae*, with respective 1-log kill targets of 7.92, 3.36 and 55.2 [24]. In a neutropenic murine pneumonia model, against *P. aeruginosa* isolates, the median *f*AUC/MIC target associated with net stasis with delafloxacin was 5.66, with a 1-log kill value of 14.3 [25].

2.4 Other Effects

In healthy adult volunteers, therapeutic and supratherapeutic intravenous doses of delafloxacin had no clinically relevant effects on the QT/QTc interval (i.e. no clinically relevant QT prolongation), atrioventricular conduction or cardiac depolarization (as assessed by the PR and QRS interval durations) in two cardiac safety studies (M01-365 and RX-3341-11; $n = 68$ and 52 enrolled) [26, 27].

In healthy adult volunteers ($n = 47$), delafloxacin exhibited no clinically significant phototoxic potential at all wavelengths tested (295–430 nm) after 6 days of oral delafloxacin 200 mg/day or 400 mg/day [28].

3 Pharmacokinetic Properties of Delafloxacin

Pharmacokinetic parameters of delafloxacin are similar in patients with ABSSSI to those in healthy volunteers [8]. In healthy adult volunteers, after single and multiple doses of intravenous (300 mg) and oral (450 mg) delafloxacin, the pharmacokinetics of the drug were bioequivalent [8, 29], supporting the switching regimen (from intravenous to oral formulations) utilized in phase 3 trials [29].

Oral delafloxacin exhibited linear pharmacokinetics across a dose range of 50 to 1600 mg in healthy volunteers [30]. Delafloxacin was rapidly absorbed after intravenous (300 mg) or oral (450 mg) administration, with respective median times to maximum plasma concentration of 0.75 h and 1 h after single and multiple (once every 12 h) oral doses (vs 1 h after single and multiple intravenous doses) [7]. Steady-state concentrations of the drug occurred within ≈ 3 days [7] (3–5 days [29]), with accumulation of $\approx 10\%$ after intravenous administration [7, 8] and $\approx 36\%$ after oral administration [7]. The absolute bioavailability of delafloxacin after a single oral 450 mg dose was 58.5%. The steady-state volume of distribution of delafloxacin is 30–48 L [7] (40 L [8]; i.e. $\approx$ total body water). Delafloxacin is $\approx 84\%$ bound to plasma protein, primarily to albumin; plasma protein binding is not significantly affected by renal impairment [7, 8]. There was no clinically relevant effect of food on the pharmacokinetics of delafloxacin [7, 8, 30].

Delafloxacin is primarily metabolized via glucuronidation (mainly by UGT1A1, UGT1A3 and UGT2B15), with oxidative metabolism representing $\approx 1\%$ [7] ($< 1\%$ [8]) of an administered dose. Unchanged parent drug is the predominant component in plasma, with no significant circulating metabolites [7, 8]. After a single intravenous dose of radiolabeled delafloxacin, 65% of the radioactivity is excreted in the urine and 28% in the faeces [7, 8, 31]. After a radiolabelled oral dose, 50% is excreted in the urine and 48% in the faeces [7]. Delafloxacin is excreted in the urine as unchanged drug

and glucuronide metabolites; in the faeces, the drug is eliminated as unchanged parent compound [7, 8]. After a single intravenous 300 mg dose, the mean elimination half-life of delafloxacin was 3.7 h and, after multiple oral doses, ranged from 4.2 to 8.5 h. The mean clearance of delafloxacin was 16.3 L/h after a single intravenous 300 mg dose, with renal clearance accounting for 35–45% of the total clearance [7].

In vitro, delafloxacin has a low potential for drug-drug interactions based on in vitro studies. At clinically relevant concentrations, delafloxacin does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 in vitro [7, 8], nor does it inhibit UGT1A1 and UGT2B7 [8]. Delafloxacin does not induce CYP1A2, CYP2B6, CYP2C9, CYP2C8, CYP2C19 and CYP3A4/5 in vitro. At clinically relevant concentrations, delafloxacin does not inhibit the transporters MDR1, BCRP, OAT1, OAT3, OCT1, OCT2, OAT1B1, OAT1B3, MATE1, MATE2K and BSEP [7, 8]. The drug is a probable substrate of BCRP [7, 8] and P-gp [7]; it is not a substrate of OAT1, OAT3, OCT1, OCT2, OAT1B1 or OATP [7]. The clinical relevance of coadministration of delafloxacin and P-gp and/or BCRP inhibitors is unknown [7]. There were no clinically relevant effects on the pharmacokinetics of midazolam (a CYP3A4 substrate) when it was coadministered with delafloxacin after steady state dosing [32]. As with other FQs, the absorption of oral delafloxacin is significantly reduced when it is coadministered with antacids containing aluminium or magnesium, sucralfate, metal irons such as iron, multivitamins containing iron or zinc, formulations containing divalent and trivalent cations or with didanosine buffered tablets for suspension or the paediatric powder for oral solution. Therefore, oral delafloxacin should be taken ≥ 2 h before or 6 h after these agents [7, 8].

There were no clinically meaningful effects of gender [7, 8], age (adults) [7, 8], race [7], bodyweight [7], body mass index (BMI) [7, 8], disease status [7] or hepatic impairment [7, 8, 33] on the pharmacokinetics of delafloxacin.

Given its predominantly renal route of elimination, renal impairment has an impact on the clearance of delafloxacin [34, 35], including the intravenous vehicle (sulfobutylether-β-cyclodextrin; SBECD) [36]. There is no clinically relevant impact of mild or moderate renal impairment [creatinine clearance (CL_{CR}) 30–89 mL/min] on the pharmacokinetics of delafloxacin, with no dosage adjustments required in these patients [7, 8, 35]. In patients with severe renal impairment ($CL_{CR} < 30$ mL/min), the dosage of intravenous delafloxacin should be reduced to 200 mg every 12 h and/or switch to oral delafloxacin 450 mg every 12 h at the investigators discretion [7, 8]. In patients with severe renal impairment receiving intravenous delafloxacin, closely monitor serum creatinine levels and estimated glomerular filtration rate (eGFR); if serum creatinine levels increase, consider switching to oral delafloxacin and discontinue delafloxacin if eGFR decreases

to < 15 mL/min/1.73 m^2 [7]. Accumulation of the intravenous SBECD vehicle occurs in patients with severe renal impairment [7, 8, 36]. Delafloxacin is not recommended in patients with end-stage renal disease (ESRD; due to insufficient information [7]) [7, 8, 34].

4 Therapeutic Efficacy of Delafloxacin

The efficacy of fixed-dose intravenous delafloxacin monotherapy (vs intravenous vancomycin + aztreonam) for the treatment of adult patients (aged ≥ 18 years) with ABSSSIs was evaluated in two large (*n* > 650/trial), randomized, double-blind, double-dummy, multinational, phase 3 noninferiority trials [37, 38]. Results from two US, randomized, double-blind, multicentre, phase 2 trials [39, 40] support these phase 3 trials; phase 2 trials are not discussed further.

In phase 3 trials, eligible patients had a diagnosis of ABSSSI defined as cellulitis/erysipelas, wound infection, major cutaneous abscess or burn infection that was characterized by ≥ 75 cm^2 of erythema and ≥ 2 specified signs of systemic infection [37, 38]. Within each trial there were no significant between-group differences in the demographics and clinical characteristics at baseline, including for the distribution of types of ABSSSI, lesion size, systemic and local signs present, and pathogens identified at baseline. In the overall population, 39%, 35%, 25% and < 1% of patients had cellulitis, wound infection, major cutaneous abscess and burn infection, respectively, in study 302 [37]; corresponding rates of these types of ABSSSI in study 303 were 48%, 26%, 25% and 1% [38]. The overall mean surface area of the infected lesion at baseline was 307 cm^2 [37] and 353 cm^2 [38], as assessed by digital planimetry. In the overall population of each trial, 32% [37] and 50% [38] of patients had a BMI of ≥ 30 kg/m^2; other comorbidities present included hypertension (21 and 31% of patients in studies 302 and 303), diabetes (9 and 13%) and renal impairment (16% in both trials; of whom, 0.2% had severe renal impairment or ESRD). In addition, 55% [37] and 30% [38] of patients had current or a recent history of drug abuse, including intravenous drug abuse. In terms of baseline cultures, 74.2% (490/660 enrolled patients) of patients had positive ABSSSI cultures in study 302, with *S. aureus* (≈ 66% of patients in both groups) the most commonly isolated pathogen [37]. Of these isolates, MRSA infections were confirmed in ≈ 34.5% of cases; ≈ 40% of *S. aureus* isolates were non-susceptible to levofloxacin, the majority of which were also MRSA. Approximately 17% of patients had Gram-negative isolates identified [37]. In the other study, amongst the ABSSSI cultures collected from 839 of 850 enrolled patients at baseline, the most commonly identified pathogen was *S. aureus* (≈ 57.6% of isolates), of which ≈ 21% were MRSA (96% susceptible to delafloxacin) and ≈ 26% were levofloxacin

non-susceptible (93% susceptible to delafloxacin) [38]. Twenty-one percent of patients had Gram-negative isolates identified in baseline cultures [38]. At baseline, ≈ 2.2% of patients within each trial had bacteraemia [37, 38].

Consistent with current ABSSSI guidance, key exclusion criteria (not all inclusive) included: treatment with a systemic antibacterial in the 14 days prior to enrolment unless specified criteria were met; any underlying chronic conditions at the site of infection that may have complicated the assessment of the response; infections associated with a prosthetic joint or the removal of a prosthetic joint; infections caused by other causes such as human or animal bites, osteomyelitis, diabetic foot ulcer, and necrotizing fasciitis, anaerobic cellulitis or synergistic necrotizing cellulitis; and any infection expected to require other systemic antibacterial agents in addition to study drugs [37, 38].

The specific dosage regimens utilized in phase 3 trials are outlined in Table 2, with treatment administered for 5–14 days. The median duration of treatment in the delafloxacin and vancomycin + aztreonam groups was 5 and 5.5 days in study 302 and, in study 303, was 6.5 days in both groups. Where reported, the median duration of treatment with aztreonam or placebo equivalent was 2 days [37].

Delafloxacin (with a switch to oral delafloxacin in study 303) was noninferior to vancomycin + aztreonam for the treatment of ABSSSIs according to FDA- and EMA-defined primary endpoints in the intent-to-treat (ITT) population (primary efficacy population) [Table 2; see table for detailed definitions of these outcomes] [37, 38]. The objective response rate at 48–72 h did not differ between treatment groups in either trial (FDA specified primary endpoint) and there was no between-group difference for investigator-assessed (IA) clinical cure rate at the follow-up (FU) visit (EMA-defined primary endpoint) [Table 2]. Results in the microbiological ITT (MITT; ITT patients with a baseline pathogen known to cause ABSSSI/eligible pathogen), clinically evaluable (CE; patients who completed activities as per-protocol) and microbiologically evaluable (ME; CE patients with an eligible pathogen) populations were consistent with those in the ITT population, with the noninferiority of delafloxacin to vancomycin + aztreonam demonstrated in all of these populations [37, 38].

Results for other secondary efficacy outcomes were also similar between the delafloxacin and vancomycin + aztreonam treatment groups in each trial in ITT analyses, including IA clinical cure rates and IA success rates (i.e. cure + improvement) at the FU and late FU (LFU) visits (Table 2) [37, 38]. Results in MITT, CE and ME analyses were consistent with these ITT analyses [37, 38]. Additional analyses (as per the EMA statistical analysis plan) also showed no between-group differences for IA clinical cure and success rates at the post-treatment evaluation (PTE) within a window 7–14 days (PTE$_{7-14}$) or 6–15 days

Table 2 Efficacy of delafloxacin for the treatment of adults with acute bacterial skin and skin structure infections in randomized, double-blind, multinational phase III trials

Endpoint	Study 302 [37] (% of pts)			Study 303 [38] (% of pts)		
	DLX[a] (n=331)	VAN+AZ[b] (n=329)	TD (95% CI)	DLX[c] (n=423)	VAN+AZ[d] (n=427)	TD (95% CI)
OR at 48–72 h[e]	78.2	80.9	−2.6 (−8.78 to 3.57) NI	83.7	80.6	3.1 (−2.0 to 8.3) NI
IA clinical cure at FU[f]	52.0	50.5	1.5 (−6.11 to 9.11) NI	57.7	59.7	−2.0 (−8.6 to 4.6) NI
IA success at FU[g]	81.6	83.3	−1.7 (−7.55 to 4.13) NI	87.2	84.4	2.5 (−2.2 to 7.2)
IA clinical cure at LFU	70.4	66.6	3.8 (−3.27 to 10.89) NI	67.8	71.0	−3.1 (−9.3 to 3.1)
IA success at LFU	80.1	81.2	−1.1 (−7.15 to 4.97) NI	83.5	82.2	1.3 (−3.8 to 6.3)

Results for intent-to-treat analyses (primary efficacy population). All study drugs given IV unless stated otherwise; treatment for 5–14 days

BL baseline, *CF* clinical failure, CL_{CR} creatinine clearance, *DLX* delafloxacin, *FU* follow-up (day 14±1), *IA* investigator-assessed, *IV* intravenous, *LFU* late FU (day 21–28), *NI* noninferior to VAN+AZ (based on prespecified criteria), *OR* objective response, *q12h* every 12 h, *TD* treatment difference, *VAN+AZ* vancomycin+aztreonam, −*ve* negative

[a]DLX 300 mg q12h plus a blinded PL infusion in place of AZ infusion

[b]VAN 15 mg/kg q12h with a target trough level of 15–20 µg/mL (monitor on day 2 and 6)+AZ 2 g q12h until BL cultures proven −ve for Gram −ve pathogens

[c]In pts with $CL_{CR} > 29$ mL/min: DLX 300 mg q12h IV for 6 doses then mandatory switch to oral DLX 450 mg q12h for all remaining doses; in pts with CL_{CR} 15–29 mL/min: DLX 200 mg q12h IV for all doses

[d]Pts with $CL_{CR} > 29$ mL/min, VAN 15 mg/kg q12h with a target trough level of 15–20 µg/mL (monitor on day 2 and 6)+AZ 2 g q12h until BL cultures proven −ve for Gram −ve pathogens; in pts with CL_{CR} 15–29 mL/min, renal adjustment of VAN was allowed according to the VAN dosing plan for each site to maintain trough levels+AZ 1 g q12h until BL cultures proven −ve for Gram −ve pathogens

[e]FDA defined primary endpoint; defined as ≥20% reduction in the size of the ABSSSI lesion determined by digital planimetry of the leading edge without evidence of CF (based on specified CF criteria, including if planimetry data at this timepoint were not available)

[f]EMA defined primary endpoint; IA of clinical cure (no remaining/complete resolution of signs or symptoms) at the FU visit

[g]Success defined as cure or improved and no further antibacterial therapy needed

$(PTE_{6–15})$ of the end of treatment visits [26]. For example, in the pooled ITT efficacy analysis population, respective IA clinical cure and success rates at the $PTE_{7–14}$ visit in the delafloxacin group (n=754) were 51.2% (vs 54.0% in the vancomycin+aztreonam group; n=756) and 74.8% (vs 73.7%); at the $PTE_{6–15}$ visit, respective IA cure and success rates in delafloxacin recipients were 55.6% (vs 56.7%) and 80.8% (vs 79.9%). Results in CE analyses were consistent with these ITT analyses [26].

Overall pathogen eradication rates were also generally similar between the delafloxacin and vancomycin+aztreonam groups (n=179 and 184 [37]; n=275 and 277 [38]) in each trial (97.8 vs 98.4% [37]; 97.8 vs 97.6% [38]). Amongst those with a baseline MRSA isolate, virtually all patients in the delafloxacin and vancomycin+aztreonam groups had documented or presumed eradication of the pathogen (100 vs 98.5% [37]; 96.0 vs 97.0% [38]). All (100%) [37] and 97% [38] of delafloxacin recipients who had a levofloxacin non-susceptible *S. aureus* isolate identified at baseline had documented or presumed eradication. There were also similar per pathogen early objective response rates at 48–72 h and per pathogen microbiological

response rates (documented or presumed eradication) at the FU visit in both groups, including for *S. aureus*, MRSA, MSSA, *S. anginosus* group, *K. pneumoniae*, *E. coli*, *S. pyogenes*, *S. lugdunensis* and *S. haemolyticus* [37, 38]. These response rates were similar in the delafloxacin and vancomycin+aztreonam groups regardless of whether patients had Gram-positive or Gram-negative infections [37, 38]. Microbiological response rates at the FU visit were also similar in both groups irrespective of whether patients had mono- or polymicrobial Gram-positive or Gram-negative infections, or had mixed Gram-positive and Gram-negative infections [38].

In prespecified subgroup analyses of obese (baseline BMI ≥ 30 kg/m^2) and non-obese (< 30 kg/m^2) patients, there were generally no statistically significant between-group differences in objective response rate at 48–72 h or IA cure and success rates at the FU or LFU visits in either obese or non-obese patients. However, in obese patients, a statically significant difference in favour of delafloxacin over vancomycin+aztreonam treatment was observed for the IA cure rate at the LFU (71.7 vs 57.4%; between-group difference 14.2; 95% CI 1.34–26.90; n=120 and 94) [37].

Pooled analyses in the overall population ($n = 1510$) for primary and secondary outcomes were consistent with those in individual trials for all populations (ITT, MITT, CE, ME) [41]. In prespecified subgroups of patients, there were no significant differences between the delafloxacin and vancomycin + aztreonam for primary and secondary outcomes assessed at 48–72 h, FU or LFU in subgroups of patients with diabetes, a BMI of ≥ 30 kg/m^2 or renal impairment (CL$_{CR}$ < 90 mL/min) [41]. There was also no between-group difference in patients with significant drug abuse (abstract) [42] or in those with a history of cardiac or vascular disease (abstract) [43].

In pooled data, there was no effect on the efficacy of delafloxacin based on the presence of baseline risk factors related to the host, pathogen and disease, including aged > 65 years, BMI ≥ 30 kg/m^2, diabetes, prior antibacterial treatment, MRSA infection, bacteraemia, polymicrobial infection, ≥ 3 signs of systemic infection, type of infection (wound infection and erythema $\geq$ 4th percentile) [abstract] [44]. Treatment success rates in higher-risk (≥ 3 risk factors; $n = 625$) and lower-risk (< 3 risk factors; $n = 881$) groups were high in both groups at the end-of-treatment visit (90.3 vs 90.8%) and FU visit (82.9 vs 86.0%).

5 Tolerability of Delafloxacin

Intravenous and/or oral delafloxacin was generally well tolerated in clinical trials in patients with ABSSSIs discussed in Sect. 4. Discussion focuses on pooled safety data from the pivotal phase 3 trials ($n = 741$ and 751 in the delafloxacin and vancomycin + aztreonam groups) [45, 46], including a pooled analysis of adverse events of special interest (AESI) [46]. Baseline characteristics in the overall population were: 11% had diabetes, 16% had renal impairment, $\approx 42\%$ had a BMI of ≥ 30 mg/kg^2 and $\approx 29\%$ had history of hepatitis B or C [45]. The mean exposure to delafloxacin was 6.8 days (range 0.5–14.0 days; vs mean of 6.6 days in vancomycin + aztreonam group), with 39.5% of patients receiving ≤ 10 doses (vs 39.0%) [45].

In the pooled analysis, 45.1% and 47.7% of patients in the delafloxacin and vancomycin + aztreonam groups experienced a treatment-emergent adverse event (TEAE), most of which were of mild to moderate severity (< 4% of patients experienced a severe TEAE) and few patients (1.8 vs 3.5%) discontinued treatment because of these adverse events. Of the TEAEs, 22.1% in the delafloxacin group and 26.1% in the vancomycin + aztreonam group were considered to be treatment related (TRAEs), with 0.8% and 2.4% of patients discontinuing treatment because of these events. The most common (i.e. frequency $\geq 2\%$ in either group) TRAEs occurring in delafloxacin and vancomycin + aztreonam recipients were nausea (6.1 vs 4.3%), diarrhoea (6.1 vs 2.0%) and

skin and subcutaneous tissue disorders (0.9 vs 4.7%; pruritus, urticaria, dermatitis, rash). Relatively few patients in the delafloxacin and vancomycin + aztreonam groups experienced a serious TRAE (0.3 vs 0.5%). The tolerability profiles with delafloxacin and vancomycin + aztreonam treatment were consistent, irrespective of baseline patient characteristics (age, gender, race/ethnicity, degree of renal impairment, diabetes status, BMI or history of infectious hepatitis B or C) [45].

5.1 Adverse Events of Special Interest Associated with Fluoroquinolones

AESI associated with the FQ class occurred in 7.0% and 9.2% of delafloxacin and vancomycin + aztreonam recipients, with most of these events of mild to moderate severity and no apparent increase in the risk of such events between the delafloxacin and vancomycin groups [46]. Of note, comparison of delafloxacin with a non-FQ comparator group (i.e. AESI were not associated FQ use) permits comparison of AESI rates with delafloxacin to that in the general population, especially in patients with a high burden of underlying comorbidities such as the population enrolled in pivotal trials discussed in Sect. 4.

In the pooled phase 3 trial analysis, the rates of AESI were relatively low (typically < 1%) in both treatment groups, with most of these events of mild to moderate severity [46]. In the delafloxacin and vancomycin + aztreonam groups, very few patients experienced treatment-related hepatic-related events (2.2 vs 2.7%), potential myopathy (0.9 vs 2.7%), hyperglycaemia (0.3 vs 0.1%), hypoglycaemia (0.1 vs 0.3%), potential peripheral neuropathy (0.1 vs 0.3%), potential QT prolongation (0 vs 0.1%), potential tendon disorder (no cases in either group), *Clostridium difficile*-associated diarrhoea (0.1 vs 0%), convulsions (0 vs 0.1%) or potential phototoxicity (0 vs 0%). Overall, the rate of hepatic TRAEs (hypertransaminasaemia, increased transaminases or liver function test abnormalities) [2.2 vs 2.7%], was similar in the delafloxacin and vancomycin + aztreonam groups, with no patients meeting Hy's Law criteria. No patients receiving ongoing treatment for seizures or with an untreated history of seizures were included in the pivotal phase 3 trials [46].

FQ use has been associated with disabling and potentially irreversible serious AEs, including tendonitis and tendon rupture (bilateral in some instances), peripheral neuropathy (e.g. paraesthesia, hypoesthesia, dysesthesia and weakness), CNS adverse reactions (e.g. anxiety, agitation, convulsions, depression, hallucinations, increased intracranial pressure, insomnia, nervousness and tremors) and exacerbation of myasthenia gravis [7, 8]. Discontinue delafloxacin treatment immediately and avoid the use of FQs in patients who experience any of these serious adverse reactions [7, 8]. The use of delafloxacin should be avoided in patients with a

known history of tendon disorders [7] (contraindicated [8]) or who have experienced tendinitis or tendon rupture [7], a known history of myasthenia gravis [7] (not recommended [8]) or a history of peripheral neuropathy [7]. As with all FQs, in patients with known or suspected CNS disorders or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold, delafloxacin should only be used when the benefits exceed the risks [7, 8]. FQs have been associated with disturbances in blood glucose, including hypoglycaemia and hyperglycaemia, usually in patients with diabetes receiving concomitant treatment with oral antihyperglycaemic agents (e.g. sulfonylureas) or with insulin. Severe cases of hypoglycaemia resulting in coma or death have been reported (with other FQs [7]). In diabetic patients, careful monitoring of blood glucose levels is recommended. There are no data available on severe cases of hypoglycaemia resulting in coma or death after delafloxacin use [7, 8]. If a hypoglycaemic reaction occurs during delafloxacin treatment, discontinue delafloxacin therapy and initiate appropriate treatment immediately [7].

6 Dosage and Administration of Delafloxacin

Delafloxacin is approved in several countries for the treatment of ABSSSI; specific indications may vary between countries. In the EU, delafloxacin is indicated for the treatment of ABSSSI in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections [8]. In the USA, delafloxacin is indicated for the treatment of adults with ABSSSI or community-acquired bacterial pneumonia caused by designated susceptible bacteria [7]. The recommended dosage of delafloxacin is 300 mg every 12 h administered as a 60-min intravenous infusion. A switch to oral delafloxacin 450 mg every 12 h is possible at the discretion of the physician. The total treatment duration is 5–14 days [7, 8]. Consult local prescribing information for detailed information, including specific indications, contraindications, precautions and warnings, potential drug interactions and use in special patient populations.

7 Place of Delafloxacin in the Management of ABSSSIs

Current 2014 Infectious Diseases Society of America [47] and 2018 World Society of Emergency Surgery/Surgical Infection Society Europe [1] guidelines for managing severe ABSSSIs recommend several first-line empirical treatment options, including ceftaroline, clindamycin, linezolid, telavancin and vancomycin (considered the first-line

parenteral treatment for serious MRSA infections in hospitalized patients [3, 47]). The approval of delafloxacin is too recent for the drug to have been included in these guidelines. Other newer antibacterials that have recently been approved for the treatment of ABSSSIs include dalbavancin, tedizolid, oritavancin and daptomycin. Notably, it is critical that, as is the case with all antibacterials, newer antibacterials such as delafloxacin should be used in a judicious manner to minimize the risk of the emergence of drug resistance, as has occurred with older antibacterials. Antibacterial therapy for ABSSSIs is primarily empirical until a pathogen(s) is identified. The choice of antibacterial is dependent on several factors, including the site of infection (specific pathogens are typically associated with certain wound sites; e.g. MRSA and MSSA are the predominant pathogens involved in wound infections following cardiothoracic surgery), drug characteristics (e.g. drug–drug interactions, ability to transition from intravenous to oral therapy, efficacy and safety profile), patient characteristics (e.g. presence of comorbidities, age), causative pathogen(s) and local antimicrobial resistance patterns [48–50].

Delafloxacin is a novel anionic FQ, with its unique chemical structure resulting in enhanced activity in acidic environments characteristic of skin abscesses and dual equipotent inhibition of topoisomerase IV and DNA gyrase (Sect. 2). Delafloxacin exhibits excellent in vitro activity against a broad spectrum of clinically relevant Gram-positive, including MRSA strains ($\pm$ levofloxacin-resistant strains and those with mutations in the QRDR), and Gram-negative bacteria (Sect. 2.1), and is associated with a low risk for the emergence of resistance (Sects. 2.1, 2.2). Older FQs (e.g. ciprofloxacin, levofloxacin and moxifloxacin) are not commonly used for treating ABSSSIs caused by MRSA, primarily reflecting the requirement for additional antibacterials to cover skin infections caused by FQ-resistant organisms and also because of their safety profile, especially in patients with comorbidities and the elderly [3–5, 10]. Delafloxacin treatment was associated with high rates of microbiological cure against MRSA isolates ($\pm$ levofloxacin-resistant strains and those with mutations in the QRDR) in pivotal phase 3 trials (Sect. 2.1); this suggests that delafloxacin is a good option for treating ABSSSIs caused by *S. aureus* isolates, including MRSA strains in which high rates of ciprofloxacin and levofloxacin nonsusceptibility are observed [17].

Several other drug characteristics are also important in determining the choice of empirical therapy such as the potential for drug-drug interactions and availability of intravenous and oral formulations for ease of transition from the in-patient to the out-patient setting. Delafloxacin is available as an intravenous and oral formulation (Sect. 6), does not alter the QTc interval to a clinically relevant extent (Sect. 2.4) and has a favourable pharmacokinetic profile (good oral bioavailability, low potential for drug-drug

interactions and a convenient twice-daily regimen) [Sect. 3]. Dosage adjustment is required in patients with severe renal impairment with intravenous, but not oral, delafloxacin (Sect. 3).

In primary ITT analyses in the pivotal global phase 3 trials in adults with ABSSSIs, intravenous delafloxacin (with switch to oral delafloxacin after six doses in one study) was noninferior to intravenous vancomycin + aztreonam in terms of the primary FDA- and EMA-defined endpoints (Sect. 4). Results in other study populations (MITT, CE and ME populations), prespecified subgroups (based on age, gender, race/ethnicity, degree of renal impairment, diabetes status, BMI or history of infectious hepatitis B or C) and in pooled analyses were consistent with those in the ITT population. There was no between-group difference in overall pathogen eradication rates ($\approx 89\%$ in both groups in both trials), with similar per pathogen early objective response rates at 48–72 h and per pathogen microbiological response rates at the FU visit in both groups, including for *S. aureus*, MRSA, MSSA, *S. anginosus* group, *K. pneumoniae*, *E. coli*, *S. pyogenes*, *S. lugdunensis* and *S. haemolyticus* isolates. Amongst the limitations of these trials were the low number of burn infections and surgical wounds, and the number of Gram-negative pathogens was limited by the use of the current ABSSSI definition that favours Gram-positive infections.

Delafloxacin was generally well tolerated in clinical trials in adults with ABSSSIs, with relatively few patients discontinuing treatment because of TRAEs and most TRAEs of mild to moderate severity (Sect. 5). The tolerability profile of delafloxacin was similar regardless of baseline patient characteristic, including age, gender, race/ethnicity, degree of renal impairment, diabetes status, BMI or history of infectious hepatitis B or C. The most common TRAEs (incidence $> 1\%$) occurring during delafloxacin treatment were nausea (6.1%) and diarrhoea (6.1%). Moreover, the rates of AESI in delafloxacin recipients were generally low ($\leq 2\%$), including rates of treatment-related hepatic AEs, potential myopathy, dysglycaemic episodes, potential peripheral neuropathy, potential QT prolongation, potential tendon disorder and potential phototoxicity (Sect. 5.1). There was no apparent increase in the risk of AESI between the delafloxacin and vancomycin groups. To date, unlike some other FQs, delafloxacin has not been associated with cases of QT prolongation or phototoxicity and, given its low brain penetration, delafloxacin potentially may be associated with less neurotoxicity than other FQs [2].

In conclusion, ongoing clinical experience with delafloxacin treatment in patients with ABSSSIs will help to define its relative role with respect to other antibacterials in this clinical setting. In pivotal phase 3 trials in adult patients with ABSSSIs, including in those with comorbid diseases, intravenous delafloxacin monotherapy ($\pm$ oral switch) was noninferior to intravenous vancomycin + aztreonam

in terms of clinical efficacy and was generally well tolerated. Given its unique chemical structure that confers novel properties relative to other FQ and its broad spectrum of activity against common clinically relevant Gram-positive pathogens, including against MRSA strains ($\pm$ FQ-resistance mutations), and Gram-negative pathogens, intravenous delafloxacin ($\pm$ oral switch) provides a novel emerging option for the treatment of adult patients with ABSSSIs.

Data Selection Delafloxacin: 534 records identified	
Duplicates removed	249
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	158
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	77
Cited efficacy/tolerability articles	**10**
Cited articles not efficacy/tolerability	**40**
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were delafloxacin, Quifenix, Baxdela, ABSSSI, acute bacterial skin and skin structure infections. Records were limited to those in English language. Searches last updated 29 June 2020	

Compliance with ethical standard

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