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ADISINSIGHT REPORT

Delafloxacin: First Global Approval

Anthony Markham[1]

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Abstract Delafloxacin (Baxdela™) is a fluoroquinolone antibacterial with activity against both gram-positive and gram-negative pathogens being developed by Melinta Therapeutics. The drug is being investigated or considered as a treatment for various bacterial infections and in June 2017 received approval in the USA for the treatment of acute bacterial skin and skin structure infections. This article summarizes the milestones in the development of delafloxacin leading to this first global approval for the treatment of acute bacterial skin and skin structure infections.

1 Introduction

Melinta Therapeutics (formerly Rib-X Pharmaceuticals) are developing delafloxacin (Baxdela™), a fluoroquinolone antibacterial with activity against both gram-positive and gram-negative pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA). Both oral and intravenous (IV) formulations of delafloxacin have been approved by the US FDA for the treatment of acute bacterial skin and skin structure infections (ABSSSI) [1] and a study is currently underway evaluating the efficacy of the drug as treatment for community-acquired bacterial pneumonia. The recommended dose of delafloxacin in ABSSSI is 300 mg IV or 450 mg orally once every 12 h [1].

1.1 Company Information

In March 2017 Melinta Therapeutics entered into a development and commercialisation agreement with Menarini Group, granting Menarini exclusive rights to commercialise delafloxacin under its own brands in 68 countries including Europe, China, South Korea, Australia, and the Commonwealth of Independent States including Russia. Under the terms of the agreement Melinta will receive an upfront payment and near-term development and regulatory milestone payments, share the clinical costs for Baxdela indication expansion, as well as sales milestone and royalty payments from Menarini Group. Menarini will be responsible for submitting regulatory applications and pursuing pricing approvals for delafloxacin in countries where it has commercialisation rights [2].

In January 2015, Melinta Therapeutics and Eurofarma Laboratórios entered into an agreement for the commercialisation and distribution of delafloxacin in Brazil. Under the terms of the agreement, Eurofarma Laboratórios will acquire the rights to market and distribute the drug, pursuant to obtaining the regulatory approval for delafloxacin for the treatment of ABSSSIs. Melinta received $US15 million as upfront cash and equity payments, and will be eligible to receive milestone payments and royalties on sales [3].

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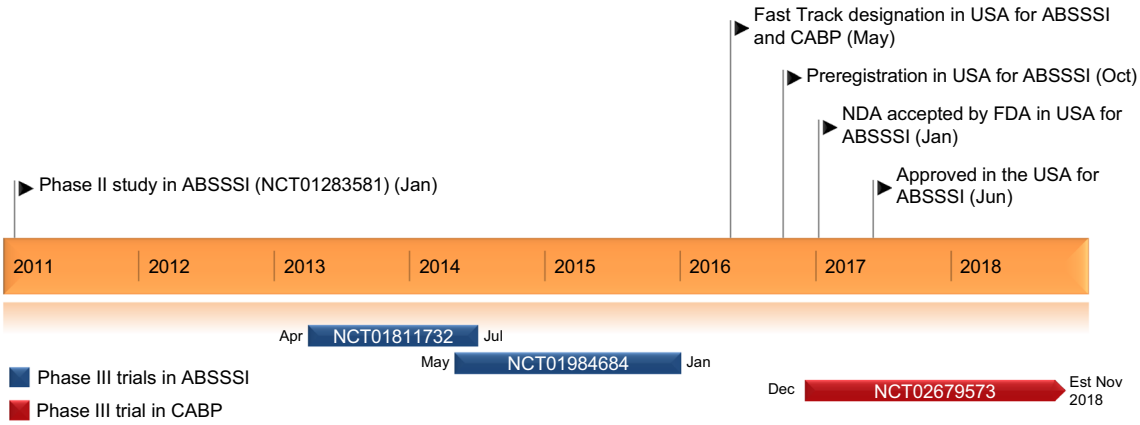
✉ Anthony Markham
dru@adis.com

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



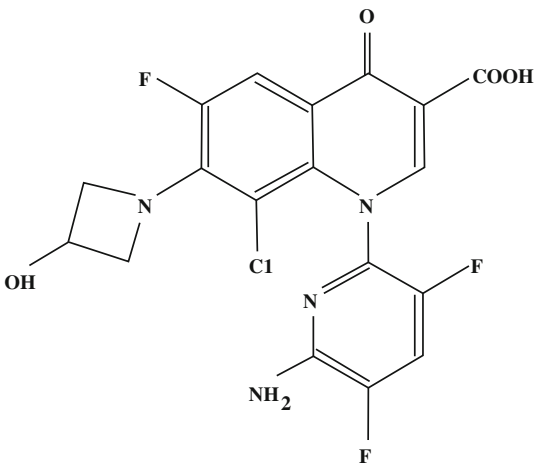
Key milestones in the development of delafloxacin. *ABSSSI*, acute bacterial skin and skin structure infections, *CABP* community-acquired bacterial pneumonia, *Est* estimated completion date

2 Scientific Summary

2.1 Pharmacodynamics

Delafloxacin had potent in vitro activity against contemporary (2014–2016) bacterial isolates frequently associated with ABSSSIs from European [4] and US [5, 6] medical centres participating in the SENTRY surveillance program. The drug had potent activity against *Staphylococcus aureus* (n = 903/3163 European/US; MIC_{90} 0.25 μg/mL) and coagulase-negative staphylococci (CoNS [n = 165/228 European/US] MIC_{90} 0.5 μg/mL) including fluoroquinolone (levofloxacin) and methicillin-resistant strains (MIC_{90} ≤1 μg/mL). Delafloxacin had an MIC_{90} of 0.03 μg/mL against β-haemolytic streptococci (n = 254/967 European/US) and viridans group streptococci (n = 27/133 European/US). The drug had an MIC_{90} of 1 μg/mL against *Enterococcus faecalis* (n = 173/235), >4 and 2 μg/mL against European (n = 867) and US (1325) Enterobacteriaceae isolates, respectively, and >4 and 4 μg/mL against European (n = 275) and US (224) *Pseudomonas aeruginosa* isolates, respectively. Delafloxacin had considerably greater in vitro activity than levofloxacin against *E. faecalis*, Enterobacteriaceae and *P. aeruginosa* (levofloxacin MIC_{90} >4 μg/mL) in these studies [4–6]. Delafloxacin had an MIC_{90} of 0.25 μg/mL against *S. aureus* isolates (n = 685, including 294 methicillin-resistant *S. aureus* (MRSA) and 232 levofloxacin-resistant strains) collected from patients with ABSSSIs participating in two phase III trials [7].

Delafloxacin has demonstrated bactericidal activity in vitro against MRSA [7, 8] with minimum bactericidal concentrations (MBC) of 0.008, 0.5 and 8 μg/mL against MRSA strain 110 (levofloxacin susceptible), 124 (triple mutant) and 165 (quadruple mutant), respectively, compared to 0.5, 8 and >32 μg/ml for levofloxacin. Bactericidal activity was observed at 6 h for most concentrations of delafloxacin and levofloxacin against MRSA strain 110; delafloxacin at 16 times MIC killed MRSA strain 124 more quickly than levofloxacin at the same concentration, and was bactericidal at 16 and 32 times MIC against MRSA strain 165 at 24 h [8]. In two global phase III trials, high rates of microbiological response (>98% eradication rates) were seen against levofloxacin nonsusceptible *S. aureus* and MRSA isolates and against isolates with mutations in the Quinolone Resistance Determining Region (QRDR) [7].



Chemical structure of delafloxacin

Delafloxacin had potent activity against *S. aureus* (n = 4 [including 2 MRSA strains]), *Streptococcus pneumoniae* (n = 4 [including 2 penicillin-resistant strains]), and *Klebsiella pneumoniae* (n = 4 [including 3 extended-spectrum β-lactamase-producing (ESBL) strains]) in vivo in a neutropenic murine lung infection model. Increasing 0.03 to 160 mg/kg doses of delafloxacin were administered once every 6 h to infected mice with treatment outcome measured according to the organism burden in the lung (colony forming units) after 24 h. The median free drug area under the time–concentration curve (AUC)/MIC targets associated with net stasis were 1.42 for *S. aureus*, 0.56 for *S. pneumoniae* and 40.3 for *K. pneumoniae*; 1-log kill targets were 7.92, 3.36 and 55.2, respectively [9].

Delafloxacin had no clinically relevant effect on the QT/QTc interval after administration of therapeutic (300 mg) and supratherapeutic (900 mg) IV doses in thorough QT studies in volunteers (n = 52 and 51, respectively) [10].

Delafloxacin showed no clinically significant phototoxic potential at all wavelengths tested after 6 days' administration of 200 or 400 mg/day oral doses in volunteers (n = 12 and 11, respectively) [11].

2.2 Pharmacokinetics

Administration of single 300–1200 mg IV doses of delafloxacin to volunteers (n = 52) was associated with proportionally increasing maximum plasma concentrations (C_{max}) and more than proportional increases in AUC. The mean terminal half-life was ≈12 h and steady-state volume of distribution (V_d) was ≈35 litres. C_{max} and AUC_{12} were 9.29 μg/mL and 23.4 μg·h/mL, respectively, after administration of IV delafloxacin 300 mg twice daily for 14 days to volunteers (n = 7). Minimal accumulation was observed (accumulation ratio 1.09) [12].

The equivalence of IV and orally administered delafloxacin has been evaluated in an open two period, two sequence crossover study in volunteers (n = 56). Participants were randomised to receive a single 450 mg oral dose and a single 300 mg IV infusion of the drug. Geometric least squares mean AUC_∞ was considered equivalent between the 2 dosage forms (22.97 and 26.2 μg·h/mL, respectively [percent ratio 87.68]), however C_{max} (5.8 and 10.51 μg/mL, respectively [percent ratio 55.16]) was not. These data support the use of both formulations in IV to oral switch settings in phase III clinical trials [12].

Oral administration of single 50–1600 mg doses of delafloxacin to male volunteers (n = 56) was associated with a dose-normalised decrease in C_{max} with increasing dose; AUC_∞ increased proportionally with doses ≥200 mg. Mean half-life was ≤2.5 h after administration of 50 and 100 mg doses and 5.9–7.7 h with doses ≥200 mg. The proportion of drug excreted unchanged in urine decreased with increasing dose (from 35.6% at 50 mg to 12.8% at 1600 mg) [13].

Dose-normalised C_{max} and AUC decreased with increasing dose after administration of multiple oral delafloxacin 100–1200 mg once daily for 5 days to volunteers (n = 37). AUC values on day 5 were higher than on day 1 but accumulation was minimal (mean accumulation ratio ≤1.24). Steady state was achieved after ≈3 days. Mean half-life was 4.2 h in the 100 mg/day group and 7.4–8.5 h in the ≥200 mg/day groups at day 5 [13].

Delafloxacin C_{max} and AUC_∞ were significantly ($p \leq 0.001$) higher in elderly (n = 12) than in young volunteers (n = 28) after administration of a single 250 mg dose which appeared to be related to decreased creatinine clearance in the elderly cohort. The pharmacokinetic profile of the drug was similar in men and women in both the elderly and young cohorts [13].

Administration of delafloxacin 900 mg in a formulated tablet with a high fat meal was associated with a reduction in C_{max} compared with fasting conditions but this did not affect total exposure [13].

The pharmacokinetic properties of delafloxacin were similar in subjects with mild, moderate, and severe hepatic impairment (Child–Pugh class A, B, and C, respectively) compared with matched volunteers with normal hepatic function after administration of a single 300 mg IV dose, indicating that dose adjustment of delafloxacin is not necessary in patients with hepatic impairment [14].

The mean total exposure (AUC_t) of delafloxacin after a single oral 400 mg dose was ≈1.5-fold higher in patients with moderate (estimated glomerular filtration rate [eGFR] 31–50 mL/min/1.73 m^2) and severe (eGFR 15–29 mL/min/1.73 m^2) renal impairment compared to volunteers. However, total systemic exposures of delafloxacin in subjects with mild renal impairment (eGFR 51–80 mL/min/1.73 m^2) was similar to that in volunteers.

The IV vehicle sulfobutylether-β-cyclodextrin (SBECD) accumulates in patients with moderate or severe renal impairment, or end stage renal disease (ESRD) on haemodialysis, with AUC increasing 2-, 5-, 7.5- and 27-fold, respectively, after administration of IV delafloxacin between 1 h before and 1 h after haemodialysis compared to volunteers. In patients with ESRD undergoing haemodialysis, SBECD is dialyzed with a clearance of 4.74 L/h. When haemodialysis occurred 1 hour after infusion of delafloxacin in patients with ESRD, the mean fraction of SBECD recovered in the dialysate was 56.1% over ≈4 h [1]. It is recommended that the dosage of IV delafloxacin be reduced to 200 mg every 12 h or 200 mg every 12 h with a switch to 450 mg orally at the discretion of the physician. Administration to patients with ESRD is not recommended as there are insufficient data to recommend a dose regimen for this patient population [1].

Features and properties of delafloxacin

Alternative names	ABT-492, Baxdela, RX-3341, RX-3341-83, WQ-3034
Class	Antibacterials, azetidines, fluoroquinolones, pyridines, small molecules
Mechanism of Action	DNA gyrase inhibitors; DNA topoisomerase IV inhibitors
Route of Administration	Oral, IV
Pharmacodynamics	MIC_{90} 0.25 μg/mL against *Staphylococcus aureus*, 0.5 μg/mL against coagulase-negative staphylococci, 0.03 μg/ml against β-haemolytic and viridans group streptococci, 1 μg/mL against *Enterococcus faecalis*, and >2 μg/mL against Enterobacteriaceae and *Pseudomonas aeruginosa*
Pharmacokinetics	C_{max} 7.45/9.29 μg/mL, AUC 30.8/23.4 μg·h/mL, CL/F/CL 16.8/13.8 L/h at steady state (oral/IV)
Adverse events	
Most frequent	Nausea, diarrhoea
Occasional	Headache, vomiting
Rare	
ATC codes	
WHO ATC code	J01M-A (fluoroquinolones)
EphMRA ATC code	J1G (fluoroquinolones)
Chemical name	1-(6-amino-3,5-difluoropyridin-2-yl)-8-chloro-6-fluoro-7-(3-hydroxyazetidin-1-yl)-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid

2.2.1 Drug Interactions

Coadministration of midazolam and delafloxacin in volunteers was not associated with clinically relevant changes in the pharmacokinetic profile of midazolam indicating delafloxacin can be co-administered with cytochrome P4503A substrates without regard for drug–drug interactions [15].

Oral delafloxacin should be given at least 2 h before or 6 h after antacids containing aluminium or magnesium, sucralfate, metal cations such as iron, multivitamins containing iron or zinc, or with formulations containing divalent and trivalent cations as these may interfere with the absorption of delafloxacin, resulting in sub-optimal systemic concentrations [1].

2.3 Therapeutic Trials

2.3.1 Phase III

Delafloxacin had similar efficacy to vancomycin plus aztreonam as treatment for ABSSSIs in two phase III multicentre double-blind trials. In study 302 (NCT01811732) patients were randomised to IV delafloxacin 300 mg twice daily (n = 331) or IV vancomycin 15 mg/kg twice daily plus twice daily aztreonam (n = 329) for 5–14 days; 19% of patients received a single dose of short-acting antibiotic prior to enrolment. Pathogens were identified at baseline in 490 patients, most frequently *S. aureus* [1, 16]. An objective clinical response (≥20% reduction in lesion size with no further antibiotics, major procedures or death) was seen in 78.2 and 80.9% of delafloxacin and vancomycin plus aztreonam recipients, respectively, 48–72 h after completing treatment. Complete resolution of signs and symptoms (investigator-assessed cure) was seen in 81.6 and 83.3% of patients in the respective treatment groups (ITT analysis; 96.7 and 97.5% of patients in the clinically evaluable population) at follow up (day 13–15). Similar success rates were seen at late follow-up (day 21–28) [1]. Documented or presumed bacterial eradication (microbiological response) was observed in 97.8 and 98.4% of delafloxacin and vancomycin plus aztreonam recipients, respectively, including 100 and 98.5% of patients with MRSA [16].

In study 303 (NCT01984684) patients were randomised to IV delafloxacin 300 mg twice daily for 3 days then oral delafloxacin 450 mg (n = 423), or vancomycin 15 mg/kg IV plus aztreonam (n = 427) for 5–14 days. Pathogens were identified at baseline in 552 patients, most frequently *S. aureus* [1, 17]. An objective clinical response (as per study 302 above) was seen in 83.7 and 80.6% of delafloxacin and vancomycin plus aztreonam recipients, respectively, 48–72 h after commencing treatment. Complete resolution of signs and symptoms (investigator-assessed cure) was seen in 87.2 and 84.8% of patients in the respective treatment groups (ITT analysis; 96.0 and 97.0% of patients in the clinically evaluable population) at follow up (day 13–15). Similar success rates were seen at late follow-up (day 21–28) [1]. Documented or presumed eradication of MRSA was observed 96 and 97% of

delafloxacin and vancomycin plus aztreonam recipients, respectively [17].

2.3.2 Phase II

Delafloxacin had similar efficacy to tigecycline (study 201 [NCT0719810]) [18] as treatment for a variety of complicated skin and skin-structure infections and was similar to linezolid and superior to vancomycin as treatment for ABSSSI (study 202 [NCT01283581]) [19] in randomised double-blind phase II trials.

Study 201 compared IV treatment with delafloxacin 300 or 450 mg once every 12 h, or IV tigecycline (100 mg initial dose then 50 mg once every 12 h) for 12–14 days in patients with various complicated skin and skin-structure infections (wound infections following surgery, trauma, burns, or animal/insect bites, abscesses, and cellulitis). Clinical cure (completely resolved or improved to the extent that additional treatment was not necessary) was achieved in 33 of 35 (94.3%), 37 of 40 (92.5%) and 31 of 34 (91.2%) evaluable patients, in the delafloxacin 300 and 450 mg twice daily groups and the tigecycline group, respectively, at the test-of-cure visit 14–21 days after the final dose of study drug. Infections caused by *S. aureus* (including MRSA) were effectively treated in all three groups and microbiological eradication rates were similar to clinical response by pathogen rates [18].

Study 202 compared delafloxacin 300 mg, linezolid 600 mg and vancomycin 15 mg/kg, all administered IV twice daily for 5–14 days, in patients with ABSSSIs. Investigator-assessed intention-to-treat clinical cure (complete resolution of ABSSSI signs and symptoms) at follow-up (day 13–15) was achieved in 57 of 81 (70.4%) delafloxacin recipients compared to 53 of 98 (54.1) vancomycin ($p < 0.05$) and 50 of 77 (64.9%) linezolid recipients. The microbiological response was presumed eradicated in 88.2, 80.8 and 82.1% of microbiologically evaluable delafloxacin, vancomycin and linezolid recipients, respectively. Apart from one linezolid recipient in whom response was documented persistent, all other responses were presumed persistent [19].

2.4 Adverse Events

Adverse events occurring in at least 2% of delafloxacin recipients participating in the 2 phase III ABSSSI trials included nausea (8 and 6% of delafloxacin [n = 741] and vancomycin plus aztreonam [n = 751] recipients, respectively), diarrhoea (8 and 3%), headache (3 and 6%), transaminase elevations (3 and 4%; pooled reports; includes hypertransaminasaemia, increased transaminases, and increased ALT and AST) and vomiting (2 and 2%) [1]. No cases meeting the Hy's law definition have been reported with delafloxacin in clinical trials [17]. Adverse events occurring at a rate of <2% in delafloxacin recipients included sinus tachycardia, palpitations, bradycardia, tinnitus, vertigo, blurred vision, infusion site extravasation, infusion site reactions (including bruising, discomfort, oedema, erythema, irritation, pain, phlebitis, swelling and thrombosis), abdominal pain, dyspepsia, hypersensitivity, *Clostridium difficile* infection, fungal infection, oral candidiasis, vulvovaginal candidiasis, hyperglycaemia, hypoglycaemia, myalgia, dizziness, hypoesthesia, paraesthesia, dysgeusia, presyncope, syncope, anxiety, insomnia, abnormal dreams, renal impairment or failure, pruritus, urticaria, dermatitis, rash, flushing, hypotension, hypertension and phlebitis [1].

Prescribing information for delafloxacin includes a boxed warning that fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions including tendinitis and tendon rupture, peripheral and central nervous system effects, and states that delafloxacin should be discontinued in patients who experience any of these. Use of delafloxacin should also be avoided in patients with myasthenia gravis [1].

Key clinical trials of delafloxacin (Melinta Therapeutics)

Drugs(s)	Indication	Phase	Status	Location(s)	Identifier
Delafloxacin, tigecycline	Complicated skin infections	II	Completed	US, Puerto Rico	NCT00719810
Delafloxacin, linezolid, vancomycin	Bacterial skin infections	II	Completed	US	NCT01283581
Delafloxacin, ceftriaxone	Uncomplicated gonorrhoea	III	Terminated	US	NCT02015637
Delafloxacin, vancomycin, aztreonam	Skin and skin structure infections	III	Completed	Multinational	NCT01984684
Delafloxacin, vancomycin, aztreonam, placebo	Skin and skin structure infections	III	Completed	Multinational	NCT01811732
Delafloxacin, moxifloxacin, linezolid	Community-acquired bacterial pneumonia	III	Recruiting	Multinational	NCT02679573

2.5 Ongoing Clinical Trials

A phase III study (DEFINE-CABP; NCT02679573) comparing delafloxacin and moxifloxacin as treatment for community-acquired bacterial pneumonia is currently recruiting patients.

3 Current Status

Delafloxacin received its first global approval on the 19 June 2017 in the USA for the treatment of acute bacterial skin and skin structure infections caused by susceptible bacteria.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding

Conflicts of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the author on the basis of scientific completeness and accuracy. A. Markham is a contracted employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest. Additional information about this Adis Drug Review can be found at http://www.medengine.com/Redeem/44E8F06046B3A200.

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