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A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections

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SUMMARY

Background: A randomized, double-blind, multicenter trial was done to compare two doses of delafloxacin with tigecycline in patients with various complicated skin and skin-structure infections (wound infections following surgery, trauma, burns, or animal/insect bites, abscesses, and cellulitis).
Methods: Patients were randomized 1:1:1 to receive delafloxacin 300 mg intravenous (IV) every 12 h, delafloxacin 450 mg IV every 12 h, or tigecycline 100 mg IV × 1, followed by 50 mg IV every 12 h; randomization was stratified by infection type. Duration of therapy was 5–14 days. The primary efficacy analysis, performed on the clinically evaluable (CE) population at the test-of-cure (TOC) visit (14–21 days after the final dose of study drug), compared clinical response rates in the delafloxacin and tigecycline arms. Clinical response rates in the two delafloxacin arms were also compared.
Results: Among CE patients, clinical cure rates at TOC visit were similar in the delafloxacin and tigecycline arms (94.3%, 92.5%, and 91.2%, respectively in delafloxacin 300-mg, delafloxacin 450-mg, and tigecycline arms). Overall, the most frequent adverse events were nausea, vomiting, and diarrhea; the 300-mg delafloxacin arm was the best-tolerated regimen.
Conclusions: Delafloxacin was similarly effective as tigecycline for a variety of complicated skin and skin-structure infections and was well tolerated. (Clinicaltrials.gov NCT 0719810)

1. Introduction

Complicated infections of the skin and skin structures (cSSSIs) are common and can affect patients of all ages. Gram-positive bacteria, in particular *Staphylococcus aureus* and *Streptococcus pyogenes*, are the most common causative pathogens. Over the course of the last 15–20 years, after largely being localized to hospitals and other healthcare settings, methicillin-resistant strains of *S. aureus* (MRSA) have made inroads into community-based settings, where they have become an increasingly common cause of skin and skin-structure infections.[1–3] In 2011, the Infectious Diseases Society of America published their first set of guidelines for the treatment of MRSA infections.[4] While several agents, both oral and intravenous (IV), are cited as treatment options for skin and skin-structure infections, a number of them have limitations, including rapid development of resistance, inadequate coverage of beta-hemolytic streptococci, static vs. cidal antibacterial activity, and adverse effects such as nephrotoxicity and gastrointestinal (GI) intolerance,[5] all of which underscore the need for continued development of effective drugs for MRSA.

Delafloxacin (RX-3341, ABT-492, WQ-3034) is a next-generation fluoroquinolone antibiotic active against an array of Gram-positive pathogens (methicillin-susceptible *S. aureus* (MSSA), MRSA, *Streptococcus pyogenes*, and enterococci), Gram-negative pathogens (*Escherichia coli*, *Klebsiella spp*, *Pseudomonas aeruginosa*, and *Neisseria gonorrhoeae*), and anaerobes.[6–8] Like other fluoroquinolones, it exerts its effects via inhibition of bacterial topoisomerases involved in maintaining appropriate DNA supercoiling and

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chromosome segregation. The anionic structure of delafloxacin (1-deoxy-1-(methylamino)-D-glucitol, 1-(6-amino-3,5-difluoro-2- pyridinyl)-8-chloro-6-fluoro-7-(3-hydroxy-1-azetidinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate (salt)) appears to enhance its potency in acidic environments, which are characteristic of sites of infection, and thus could be a benefit when treating infections. For example, *S. aureus* has a high tolerance for low pH and can survive and multiply in mildly acidic surroundings, like the skin.[9] This, coupled with the fact that delafloxacin exhibits a low probability for the selection of resistant MRSA mutants,[10] suggests that it could be an important treatment for skin infections, including abscesses, which are frequently caused by resistant strains of *S. aureus*.

Tigecycline is a glycylcycline antibiotic active against a variety of Gram-positive organisms, including MSSA, MRSA, and *Enterococcus faecalis* (including vancomycin-resistant strains), as well as a broad spectrum of Gram-negative and anaerobic organisms.[11] Tigecycline is US Food and Drug Administration (FDA)-approved for cSSSIs, complicated intra-abdominal infections, and community-acquired pneumonia.

We conducted a study comparing two different doses of delafloxacin with a standard dose of tigecycline. This study was presented in part at the 19th European Congress of Clinical Microbiology and Infectious Diseases.[12]

2. Materials and methods

This was a phase 2, multicenter, randomized, double-blind study comparing the efficacy and tolerability of two doses of delafloxacin vs. tigecycline in patients with cSSSIs (Clinicaltrials.gov identifier NCT 0719810). This study was conducted at 14 sites in the USA between June and September 2008. Written consent for participation in the study was obtained from all patients, and the study was conducted in accordance with the Declaration of Helsinki.

2.1. Study population

Eligible patients were ≥18 years of age and had received a diagnosis of cSSSI. Complicated skin or skin-structure infections were defined as those involving subcutaneous tissues or requiring surgical intervention. Patients could have had one or more of the following three infection types: (1) A wound infection that had developed within 30 days of surgery, trauma, or an animal/insect bite injury; patients were required to have either purulent drainage from the wound or three or more of the following symptoms: fever, swelling, erythema of ≥10 mm, pain, or tenderness. (2) An abscess, without an open wound, that had developed during the 7 days before enrollment, with purulent drainage or a purulent aspirate; patients were required to have evidence of a loculated fluid collection that required intervention within 48 h of enrollment and erythema and/or induration of ≥20 mm in diameter or tenderness. (3) Cellulitis that had developed during the 7 days before enrollment, with advancing edema, erythema, or induration; in addition patients must have had at least one of the following: documented fever or reported fever during the 3 days before enrollment, a white blood cell count of 10×10^9/l or ≥10% band forms, or lymphangitis and adenopathy.

Key exclusion criteria included known hypersensitivity to fluoroquinolones, tetracycline, or tetracycline derivatives, pregnancy or lactation, and the presence of conditions such as diabetic foot ulcers, prosthetic device infections, osteomyelitis, septic arthritis, necrotizing fasciitis, and severely impaired arterial blood supply.

2.2. Study design

Patients were equally randomized to one of three treatment arms: delafloxacin 300 mg IV every 12 h, delafloxacin 450 mg IV every 12 h, or tigecycline 100 mg IV × 1, followed by 50 mg IV every 12 h. To ensure that the types of cSSSI were evenly distributed across treatment arms, randomization was stratified by infection type: abscess, wound infection, or cellulitis. Patients, investigators, and sponsor personnel were blinded to the identification of the study drug and to randomization assignments until the study was formally unblinded. Study drug infusions were prepared by a pharmacist who was unblinded to treatment and who ensured blinding of the delivered treatment. Treatment was given for 5–14 days, based on the investigator's judgment. Wound care management of the cSSSI, including any surgical procedures, was performed according to the standard of practice of the investigator or institution. Topical antibiotics were not permitted at the site of the cSSSI.

2.3. Clinical and microbiological assessments

All patients had an assessment of infection-site signs and symptoms at all visits. Clinical and microbiological outcomes were assessed at the test-of-cure (TOC) visit, which was to occur 14–21 days after the last dose of study drug. For a clinical outcome of 'cure', baseline signs and symptoms of infection had to be either completely resolved or improved to the extent that additional antibiotic treatment was not necessary. A response of 'failure' was assigned if additional, i.e., non-study antibiotics were required either because of lack of efficacy after at least 2 days of treatment (i.e., four doses) or because of treatment-related adverse events (AEs), and/or the need for surgical intervention at >48 h after study entry. For those patients who were categorized as clinical cures at the TOC visit, a late follow-up phone contact was made 28–35 days after the final dose of study drug to determine if the patients had experienced a relapse. Microbiological assessments were performed at screening, at end of treatment, if indicated, and, if material for culture was available, at TOC. Microbiological outcomes were categorized as follows: 'documented eradicated' (baseline pathogen was absent in follow-up cultures of the original site of infection), 'presumed eradicated' (no material available for culture and the patient had a clinical response of 'cure'), 'documented persisted' (baseline pathogen was present in follow-up cultures of the original site of infection), 'presumed persisted' (no material available for culture and the patient had a clinical response of 'failure'), and 'superinfection' (during therapy, a new pathogen was cultured from the original site of infection in the presence of signs and/or symptoms of infection).

All microbiological testing was conducted by a single central laboratory (Eurofins Medinet, Chantilly, VA, USA) and included pathogen identification and susceptibility testing performed according to Clinical and Laboratory Standards Institute standards.[13–15] In addition, all *S. aureus* isolates were evaluated for the presence of Panton–Valentine leukocidin (PVL) and *mec*A using a multiplex PCR method[16] and standard gel electrophoresis techniques.[17]

2.4. Safety and tolerability

All patients who received at least one dose of study medication were evaluated for safety. Safety evaluations included the incidence of AEs, laboratory test results, vital signs, electrocardiographic results, and physical examination findings.

2.5. Analysis populations

The intent-to-treat (ITT) population included all randomized patients who received at least one dose of study drug. The modified

intent-to-treat (mITT) population included all ITT patients who had a clinical diagnosis of cSSSI, as defined in the protocol. The clinically evaluable (CE) population comprised those mITT patients who received at least 80% of the planned course of study drug therapy, had a TOC visit in the appropriate window, did not receive any concomitant, systemic antibacterial therapy with activity against the causative pathogen, and had a culture attempted at the screening visit. The microbiologically evaluable population included all CE patients who had a pathogen isolated at screening that was susceptible to a study drug.

2.6. Statistics

The primary efficacy analysis was the comparison of the clinical response rates in the delafloxacin and tigecycline arms in the CE population at the TOC visit; the clinical response rates in the two delafloxacin arms were also compared. The Fisher's exact test was used for the comparisons.

3. Results

3.1. Patient disposition

One hundred fifty patients were randomized (Figure 1; Table 1). Overall, 90% of patients completed the study. One hundred nine patients were included in the CE population; the most common reason for being unevaluable was lack of a TOC visit (25 patients overall).

3.2. Demographic and baseline characteristics

Patient demographics were similar in the three treatment groups (Table 2). The mean age was 40 years, two-thirds of the patients were male, and over 80% were white. The most frequent diagnosis at entry into the study was cellulitis (36%), followed by major abscess (33%) and wound infection (31%); most of the wound infections followed some form of trauma. The mean lesion size at baseline by digital measurements was 185.9 cm^2 (standard deviation 427.1). Overall, about one-third of enrolled patients had received prior doses of antibiotic(s) within the constraints of the exclusion criteria. The mean duration of therapy in the ITT population was 7.9 days, 7.5 days, and 6.8 days in the delafloxacin 300-mg, delafloxacin 450-mg, and the tigecycline arms, respectively; overall, 92% of patients received therapy for 5–14 days.

One hundred eleven patients (74%) had at least one pathogen isolated at baseline (Table 3). *S. aureus* was by far the most commonly identified – 96 isolates; of these, 68 (71%) were methicillin-resistant. Oxacillin resistance correlated well with the presence of *mec*A, as detected by PCR; only one isolate was oxacillin-susceptible but *mec*A-positive. PVL toxin was detected by

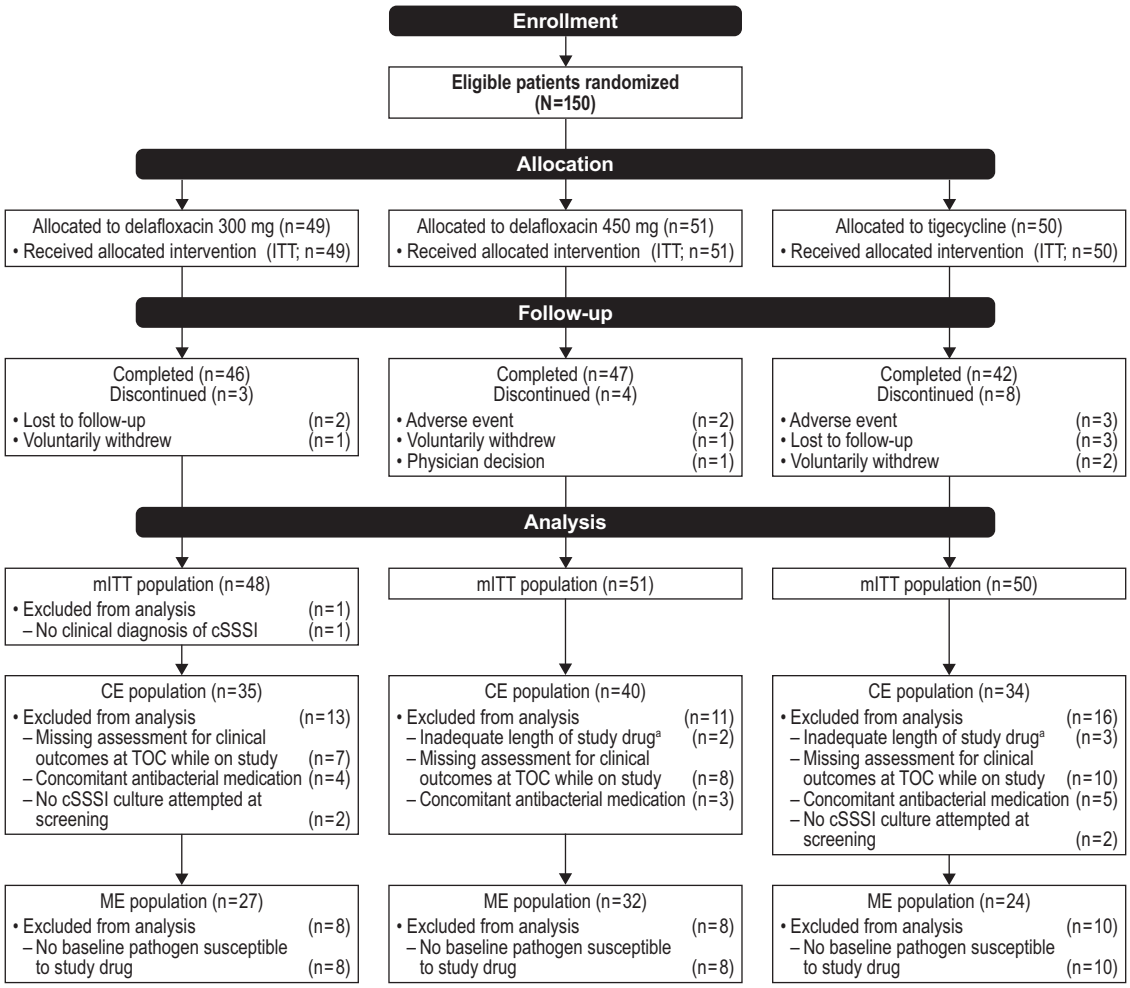

Figure 1. Flow diagram of the 150 study patients.
CE, clinically evaluable; cSSSI, complicated skin and skin structure infection; ITT, intent-to-treat; ME, microbiologically evaluable; mITT, modified intent-to-treat; TOC, test-of-cure.
[a]The required adequate length was at least eight infusions of study drug or at least four infusions of study drug for patients deemed to be failing.

Table 1
Patient disposition and analysis populations

n (%)	Delafloxacin 300 mg IV	Delafloxacin 450 mg IV	Tigecycline 50 mg IV
Intent-to-treat	49 (100.0)	51 (100.0)	50 (100.0)
Modified intent-to-treat	48 (98.0)	51 (100.0)	50 (100.0)
Clinically evaluable	35 (71.4)	40 (78.4)	34 (68.0)
Microbiologically evaluable	27 (55.1)	32 (62.7)	24 (48.0)
Hospitalized for infection under study	2	-	2

IV, intravenous.

Table 2
Demographic and baseline characteristics (intent-to-treat population)

Characteristics	Delafloxacin 300 mg IV (*n* = 49)	Delafloxacin 450 mg IV (*n* = 51)	Tigecycline 50 mg IV (*n* = 50)	Total (*N* = 150)
Age, years				
Mean (SD)	42.7 (15.10)	37.2 (14.35)	40.4 (13.83)	40.1 (14.51)
Median	42.0	33.0	40.0	40.0
Range	20–83	19–87	18–77	18–87
Gender, *n* (%)				
Male	31 (63.3)	36 (70.6)	35 (70.0)	102 (68.0)
Female	18 (36.7)	15 (29.4)	15 (30.0)	48 (32.0)
Race, *n* (%)				
Caucasian	39 (79.6)	44 (86.3)	40 (80.0)	123 (82.0)
Black	7 (14.3)	4 (7.8)	9 (18.0)	20 (13.3)
Asian	0	1 (2.0)	0	1 (0.7)
Other	3 (6.1)	2 (3.9)	1 (2.0)	6 (4.0)
Diagnosis, *n* (%)				
Cellulitis	19 (38.8)	17 (33.3)	18 (36.0)	54 (36.0)
Major abscess	16 (32.7)	18 (35.3)	16 (32.0)	50 (33.3)
Wound infection	14 (28.6)	16 (31.4)	16 (32.0)	46 (30.7)
Trauma	7	8	10	25
Bite	5	8	6	19
Surgical	2	0	0	0
Received at least 1 prior antibiotic, *n* (%)	13 (26.5)	18 (35.3)	18 (36.0)	49 (32.7)

IV, intravenous; SD, standard deviation.

Table 3
Gram-positive and Gram-negative pathogens (intent-to-treat population)

n	Delafloxacin 300 mg IV (*n* = 49)	Delafloxacin 450 mg IV (*n* = 51)	Tigecycline 50 mg IV (*n* = 50)
Patients with at least 1 pathogen at baseline	35	41	35
Patients with multiple pathogens at baseline	6	2	3
Gram-positive pathogens	34	42	34
Staphylococcus aureus	31	36	29
MRSA	21	27	20
MSSA	10	9	9
Streptococcus pyogenes	2	1	1
Enterococcus faecalis	0	1	2
Streptococcus agalactiae	0	2	1
Streptococcus group F	0	1	1
Peptostreptococcus asaccharolyticus	0	1	0
Streptococcus group G	1	0	0
Gram-negative pathogens	7	2	4
Acinetobacter baumannii	3	1	0
Acinetobacter junii	0	0	1
Acinetobacter radioresistens	0	0	1
Enterobacter cloacae	1	0	0
Enterobacter intermedius	0	0	1
Klebsiella pneumoniae	1	0	0
Prevotella bivia	0	1	0
Proteus mirabilis	1	0	0
Pseudomonas aeruginosa	0	0	1
Stenotrophomonas maltophilia	1	0	0

IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

PCR in 82.8% of MRSA isolates and in 35% of MSSA isolates. Only three patients, one in the delafloxacin 450-mg arm (Streptococcus group F) and two in the tigecycline arm (Streptococcus group F; MRSA), had positive blood cultures at baseline. The minimum inhibitory concentration (MIC) range, MIC_{50} and MIC_{90}, of delafloxacin and other comparator drugs against baseline *S. aureus* isolates is presented in Table 4.

3.3. Clinical outcomes

The clinical cure rates at the TOC visit in the CE population were 94.3% for delafloxacin 300 mg, 92.5% for delafloxacin 450 mg, and 91.2% for tigecycline (Table 5); there were no statistical differences in outcome between the three arms. All three categories of infection were effectively treated. All three patients with positive baseline blood cultures were considered clinical cures.

All three treatments were effective in treating patients with infections caused by *S. aureus* (Table 6). Among patients with infections caused by MRSA, efficacy rates in the delafloxacin arms were higher than in the tigecycline arm, but differences were not statistically significant. For all three arms, microbiological eradication rates mirrored the clinical response by pathogen rates. There was no documented persistence of any baseline pathogens in any of the treatment arms.

3.4. Safety and tolerability

Delafloxacin was well tolerated at a dose of 300 mg IV every 12 h. AEs, particularly those of a GI nature, were higher in the other two treatment arms (Table 7). Infusion-site pain, while noted in seven

Table 4
MIC range, MIC_{50}, and MIC_{90} of drugs against baseline *Staphylococcus aureus* (modified intent-to-treat population)

Drug	Group	*n*	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Delafloxacin	All	95	≤0.004–0.12	0.03	0.06
	MRSA	67	≤0.004–0.12	0.03	0.06
	MSSA	28	≤0.004–0.12	≤0.004	0.06
Tigecycline	All	95	0.03–0.5	0.12	0.12
	MRSA	67	0.06–0.5	0.12	0.12
	MSSA	28	0.03–0.25	0.12	0.12
Ciprofloxacin	All	95	0.12–>32	8	8
	MRSA	67	0.12–16	8	16
	MSSA	28	0.12–>32	0.25	8
Clindamycin	All	95	0.06–>16	0.12	0.12
	MRSA	67	0.12–>16	0.12	0.12
	MSSA	28	0.06–0.12	0.12	0.12
Daptomycin	All	95	≤0.5–1	≤0.5	≤0.5
	MRSA	67	≤0.5–1	≤0.5	≤0.5
	MSSA	28	≤0.5–≤0.5	≤0.5	≤0.5
Erythromycin	All	95	0.5–>8	>8	>8
	MRSA	67	0.5–>8	>8	>8
	MSSA	28	0.5–>8	0.5	>8
Gentamicin	All	95	0.25–>16	0.5	1
	MRSA	67	0.25–>16	0.5	1
	MSSA	28	0.25–2	0.5	1
Gentamicin (high-level testing)	All	95	≤500–≤500	≤500	≤500
	MRSA	67	≤500–≤500	≤500	≤500
	MSSA	28	≤500–≤500	≤500	≤500
Levofloxacin	All	95	0.12–32	4	4
	MRSA	67	0.12–4	4	4
	MSSA	28	0.12–32	0.12	4
Linezolid	All	95	0.5–2	1	2
	MRSA	67	0.5–2	1	1
	MSSA	28	0.5–2	1	2
Oxacillin	All	95	0.12–>4	>4	>4
	MRSA	67	4–>4	>4	>4
	MSSA	28	0.12–0.5	0.25	0.5
Vancomycin	All	95	0.5–1	0.5	0.5
	MRSA	67	0.5–1	0.5	0.5
	MSSA	28	0.5–0.5	0.5	0.5

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

Table 6
Clinical cure rates for *Staphylococcus aureus* at test-of-cure by baseline pathogen in the clinically evaluable population

	Delafloxacin 300 mg IV	Delafloxacin 450 mg IV	Tigecycline 50 mg IV
Staphylococcus aureus	*n* = 22	*n* = 27	*n* = 20
Cure, *n* (%)	21 (95.5)	25 (92.6)	18 (90.0)
Failure, *n* (%)	1 (4.5)	2 (7.4)	2 (10.0)
MRSA	*n* = 14	*n* = 20	*n* = 14
Cure, *n* (%)	13 (92.9)[a,b]	19 (95.0)[c]	12 (85.7)
Failure, *n* (%)	1 (7.1)	1 (5.0)	2 (14.3)
MSSA	*n* = 8	*n* = 7	*n* = 6
Cure, *n* (%)	8 (100.0)	6 (85.7)	6 (100.0)
Failure, *n* (%)	-	1 (14.3)	-

IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.
[a] $p = 1.0000$ vs. tigecycline 50 mg IV by Fisher's exact test.
[b] $p = 1.0000$ vs. delafloxacin 450 mg IV by Fisher's exact test.
[c] $p = 0.5555$ vs. tigecycline 50 mg IV by Fisher's exact test.

Table 7
Treatment-related adverse events occurring in ≥5% of patients in any arm[a]

n (%)	Delafloxacin 300 mg IV (*n* = 49)	Delafloxacin 450 mg IV (*n* = 51)	Tigecycline 50 mg IV (*n* = 50)
Any treatment-related AE	22 (44.9)	32 (62.7)	36 (72.0)
Nausea	6 (12.2)	13 (25.5)	23 (46.0)
Diarrhea	5 (10.2)	12 (23.5)	5 (10.0)
ALT increased	3 (6.1)	0	0
Headache	2 (4.1)	4 (7.8)	6 (12.0)
Insomnia	2 (4.1)	1 (2.0)	2 (4.0)
Constipation	1 (2.0)	0	4 (8.0)
Fatigue	1 (2.0)	4 (7.8)	0
Vomiting	0	6 (11.8)	14 (28.0)
Infusion-site pain	0	7 (13.7)	0
Dizziness	0	1 (2.0)	4 (8.0)
Rash	0	2 (3.9)	3 (6.0)

AE, adverse event; ALT, alanine aminotransferase; IV, intravenous.
[a] Events are presented in decreasing order of frequency for the delafloxacin 300-mg arm.

patients receiving delafloxacin 450 mg, did not occur in the 300-mg arm. Five patients, two in the delafloxacin 450-mg arm and three in the tigecycline arm, discontinued the study because of AEs. Seven patients experienced a total of eight serious adverse events (SAEs) during the study (one in the delafloxacin 300-mg arm, three in the delafloxacin 450-mg arm, and four in the tigecycline arm); of these, only one—a generalized seizure in a 53-year-old male in the delafloxacin 450-mg arm—was judged to be possibly related to study therapy. There were no deaths in the study.

In a review of routine chemistry evaluations, 11 delafloxacin-treated patients (two in the 300-mg arm and nine in the 450-mg arm) and one tigecycline-treated patient had below-normal glucose values after having had normal values at baseline. With one exception, all of the low values among delafloxacin-treated patients occurred during the dosing period; one patient's low value was noted at the TOC visit. Only one patient, in the 450-mg arm, had a reported AE of hypoglycemia; the remaining patients were asymptomatic. None of the patients had an ongoing history of diabetes.

Table 5
Clinical cure rates at test-of-cure in the clinically evaluable population

	Delafloxacin 300 mg IV	Delafloxacin 450 mg IV	Tigecycline 50 mg IV
Total, *n*/*N* (%)	33/35 (94.3)[a,b]	37/40 (92.5)[c]	31/34 (91.2)
Cellulitis, *n*/*N* (%)	12/13 (92.3)	14/14 (100)	11/11 (100)
Abscess, *n*/*N* (%)	12/12 (100)	11/13 (84.6)	11/13 (84.6)
Wound infection, *n*/*N* (%)	9/10 (90.0)	12/13 (92.3)	9/10 (90.0)

IV, intravenous.
[a] $p = 0.6733$ vs. tigecycline 50 mg IV by Fisher's exact test.
[b] $p = 1.0000$ vs. delafloxacin 450 mg IV by Fisher's exact test.
[c] $p = 1.0000$ vs. tigecycline 50 mg IV by Fisher's exact test.

4. Discussion

This is the first study exploring the safety and efficacy of IV delafloxacin in patients with cSSSIs. MRSA was the most frequently identified pathogen, accounting for over half of all baseline bacterial isolates collected (68/123, 55.3%), consistent with the epidemiology of Gram-positive bacteria and complicated skin and soft-tissue infections.[18,19] Delafloxacin demonstrated potent in vitro activity against these strains (MIC_{90} of 0.06 μg/ml). Both doses of delafloxacin met the primary endpoints in the treatment of cSSSIs, including the three types of skin infections enrolled in this study, and both were comparable with tigecycline. All three regimens were effective against *S. aureus*, including methicillin-resistant strains, and in no instance were staphylococcal isolates found to have persisted following treatment. The smaller numbers of infections caused by various streptococcal species and Gram-negative pathogens were also treated successfully.

GI disturbances—nausea, vomiting, and diarrhea—were among the most frequently reported AEs in the study. Both delafloxacin groups had a lower incidence of GI side effects than the tigecycline

group; and in the delafloxacin groups, the incidence of GI AEs appeared to be dose-related. Infusion-site reactions, e.g., pain or phlebitis, were noted in the high-dose delafloxacin group only.

Of the eight SAEs reported in the study, only one—a generalized seizure in a patient in the high-dose delafloxacin group—was considered possibly related to delafloxacin. The patient was a 53-year-old white male with a past medical history notable for hepatitis C and an addiction to pain medications. He was enrolled in the study with a left chest wall abscess and had a witnessed seizure following a dose of delafloxacin on day 3 of the study. During the subsequent evaluation, he disclosed for the first time that he had had seizures in the past, but had never had a medical workup of any kind. A computed tomography scan performed the day after the event was unremarkable, as were an electroencephalogram and magnetic resonance imaging approximately 3 weeks later. No definitive cause for the seizure was identified and the investigator considered the event possibly related to the study drug.

Fluoroquinolones have been associated with dysglycemia in both diabetic and non-diabetic patients, and the risk of a clinically relevant dysglycemic event appears to differ among fluoroquinolones.[20,21] As part of the routine chemistry review, low serum glucose values were observed in 11 delafloxacin-treated patients (nine patients in the 450-mg group and three patients in the 300-mg group) and in one tigecycline-treated patient. Only one patient in the 450-mg delafloxacin group reported an AE of hypoglycemia. The mechanism for the hypoglycemia is believed to be stimulation of insulin release via interference with the K^+/ATPase pump in pancreatic beta cells, although this was not observed in preclinical studies of delafloxacin. However, continued monitoring of serum glucose is warranted in future studies of delafloxacin.

This study was designed in accordance with FDA guidance issued in 1998.[22] In 2013, the FDA issued a new draft guidance document[23] proposing new terminology for the infections in question, acute bacterial skin and skin-structure infections (ABSSSI), as well as a new primary efficacy endpoint where treatment can be assessed by evaluating if there is an at least 20% reduction in lesion size documented at 48–72 h after starting therapy. Resolution of the infection after completion of therapy is now a suggested secondary endpoint. The new endpoint has been assessed in a more recently completed phase 2b study of delafloxacin in ABSSSI[24,25] and has been incorporated into the design of ongoing phase 3 studies of delafloxacin 300 mg as well.

A limitation of this study was the ability to enroll infections under fewer severity constraints that exist today: only four patients required hospitalization for management of their infections. A key feature of the definitions of ABSSSI in the latest FDA guidance is the requirement that the infections under study have a minimum surface area of 75 cm^2. Such a requirement was not in place in the current study; however, many of the lesions within this study met that requirement.

The 300-mg dose of delafloxacin, given its clinical and microbiological effect and its tolerability profile, is currently being evaluated in larger phase 3 studies that not only incorporate the latest definitions of infection type and clinical response, but also evaluate both the IV and oral formulations.

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Ethical approval: Written consent for participation in the study was obtained from all patients, and the study was conducted in accordance with the Declaration of Helsinki.

Conflict of interest: Dr O'Riordan reports fees paid to eStudySite by Melinta Therapeutics, Inc., during the conduct of the study; Dr Mehra has nothing to disclose; Dr Manos has nothing to disclose; Dr Kingsley reports grants from Rib-X Pharmaceuticals during the conduct of the study, and grants from Durata Pharmaceuticals, Affinium, Trius, Tetraphase, Achaogen, and Cempra outside the submitted work; Ms Lawrence and Dr Cammarata are employees of Melinta Therapeutics, Inc.

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