

A Comparison of the Efficacy and Safety of Intravenous Followed by Oral Delafloxacin With Vancomycin Plus Aztreonam for the Treatment of Acute Bacterial Skin and Skin Structure Infections: A Phase 3, Multinational, Double-Blind, Randomized Study

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Background. Delafloxacin is an intravenous (IV)/oral anionic fluoroquinolone with activity against gram-positive (including methicillin-resistant *Staphylococcus aureus* [MRSA]), gram-negative, atypical, and anaerobic organisms. It is approved in the United States for acute bacterial skin and skin structure infections (ABSSSIs) caused by designated susceptible gram-positive and gram-negative organisms, and is in development for the treatment of community-acquired bacterial pneumonia.

Methods. A multicenter, randomized, double-blind trial of 850 adults with ABSSSI compared delafloxacin 300 mg IV every 12 hours for 3 days with a switch to 450 mg oral delafloxacin, to vancomycin 15 mg/kg IV with aztreonam for 5–14 days. The primary endpoint was objective response at 48–72 hours. Investigator-assessed response based on resolution of signs and symptoms at follow-up (day 14 ± 1), and late follow-up (day 21–28) were secondary endpoints.

Results. In the intent-to-treat analysis set, the objective response was 83.7% in the delafloxacin arm and 80.6% in the comparator arm. Investigator-assessed success was similar at follow-up (87.2% vs 84.4%) and late follow-up (83.5% vs 82.2%). Delafloxacin was comparable to vancomycin + aztreonam in eradication of MRSA at 96.0% vs 97.0% at follow-up. Frequency of treatment-emergent adverse events between the groups was similar. Treatment-emergent adverse events leading to study drug discontinuation was higher in the vancomycin + aztreonam group (1.2% vs 2.4%).

Conclusions. In ABSSSI patients, IV/oral delafloxacin monotherapy was noninferior to IV vancomycin + aztreonam combination therapy for both the objective response and the investigator-assessed response at follow-up and late follow-up. Delafloxacin was well tolerated as monotherapy in treatment of ABSSSIs.

Clinical Trials Registration. NCT01984684.

Keywords. delafloxacin; ABSSSI; skin; vancomycin; fluoroquinolone.

Skin and soft tissue infections (SSTIs) represent a heterogeneous range of diseases and severity, and are among the most common infections seen in hospital settings [1–5]. While gram-positive pathogens are most common, gram-negative pathogens play a role in both polymicrobial and monomicrobial SSTIs and those with mixed or gram-negative infections have a longer length of

stay, greater mortality, and higher total costs [3, 4, 6]. Though early appropriate therapy is associated with better clinical outcomes and lower healthcare resource utilization, many patients with complicated SSTIs (cSSTIs) do not receive adequate first-line treatment [7, 8]. Inadequate empiric therapy (odds ratio, 9.25) is one of the leading risk factors for cSSTI treatment failure [9].

Delafloxacin is an anionic fluoroquinolone antibiotic with a number of unique properties that may make it useful in the treatment of severe infections, including ABSSSIs. Compared to other quinolones, delafloxacin demonstrates excellent in vitro activity against gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), while retaining good activity against gram-negative organisms [10]. Delafloxacin is more active in vitro than levofloxacin against most gram-positive pathogens, including levofloxacin-nonsusceptible isolates, and is 32-fold more active than levofloxacin against MRSA isolates [11]. This phase 3 study compared the

Received 14 August 2017; editorial decision 28 November 2017; accepted 4 March 2018.

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Presented in part: IDWeek, New Orleans, Louisiana, 2016. Abstract 1347.

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Clinical Infectious Diseases® 2018;XX(00):1–10

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DOI: 10.1093/cid/ciy165

efficacy and safety of intravenous (IV) followed by oral delafloxacin monotherapy to IV vancomycin plus aztreonam combination therapy in adult patients with ABSSSIs caused by either gram-positive or gram-negative pathogens.

METHODS

Trial Design

This multicenter, multinational, stratified, randomized, double-blind trial enrolled patients at 76 study centers in 16 countries between May 2014 and January 2016. Written informed consent was obtained from each patient and the study protocol was approved by an independent ethics committee or institutional review board at each site. The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice.

Setting and Participants

Eligibility criteria included age ≥18 years and a diagnosis of ABSSSI defined as cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection that was characterized by ≥75 cm² of erythema and ≥2 signs of systemic infection. Patients could receive study drug as inpatients or outpatients, provided that all study drug infusions and oral tablets were administered by blinded study site staff. Complete inclusion and exclusion criteria are presented in the [Supplementary Materials](#).

Interventions

Study treatments are summarized in [Table 1](#). Study visits took place at screening, daily until the last day of study drug administration, follow-up (FU [day 14 ± 1]), and late follow-up (LFU [days 21–28]). Telephone follow-up was conducted 30 days following the last dose of study drug to collect 28-day all-cause mortality data, adverse events (AEs), and use of posttreatment medications.

Outcomes

The US Food and Drug Administration (FDA)–defined primary efficacy endpoint [12] was the objective response assessment 48–72 hours after initiation of treatment based on ≥20% decrease in lesion size assessed by digital planimetry of the leading edge in the absence of clinical failure. The definition of clinical failure was (1) <20% reduction of the ABSSSI lesion spread of erythema area; (2) administration of rescue antibacterial drug therapy or administration of nonstudy antibacterial drug therapy for treatment of the ABSSSI before the primary efficacy endpoint assessment; (3) unplanned surgical intervention excluding limited bedside debridement and standard wound care before the primary efficacy endpoint assessment; or (4) death within 72 hours after initiation of study drug. If digital planimetry was not available within the 48- to 72-hour window, patients were classified as missing and clinical failures in the intent-to-treat (ITT) analysis.

Table 1. Study Treatments and Blinding Strategy

Treatment Arm Study Drug	CrCl at Screening	Dose	Method of Administration	Blinding Strategy
Delafloxacin	>29 mL/min	300 mg IV, Q12h	Patients received delafloxacin over a 1-h infusion Q12h for 6 doses with mandatory switch to oral delafloxacin for all remaining doses.	Blinded placebo infusion was given in place of aztreonam, which was discontinued if a gram-negative organism was not identified in baseline culture.
		450 mg orally, Q12h	Administered as a single tablet with 8 oz of water.	IV placebo was continued BID to maintain blinding.
Vancomycin + aztreonam	15–29 mL/min	200 mg IV, Q12h	Patients received IV delafloxacin 200 mg over a 1-h infusion Q12h for all doses.	Blinded placebo infusion was given in place of aztreonam, which was discontinued if a gram-negative organism was not identified in baseline culture.
		Vancomycin 15 mg/kg Q12h	Vancomycin dosing was based on actual body weight with a target trough concentration of >15–20 µg/mL. It was recommended that study sites monitor vancomycin therapeutic drug levels on day 2 and day 6.	All sites had to have an approved vancomycin blinding plan with vancomycin dosing managed by designated unblinded personnel.
	15–29 mL/min	Aztreonam 2 g Q12h	Administered as a 30-min infusion until baseline cultures were confirmed negative for gram-negative pathogens.	After the first 6 doses, patients randomized to vancomycin also received oral placebo BID to maintain blinding.
		Vancomycin	Renal adjustment for vancomycin patients was allowed and was part of an approved vancomycin dosing plan for each site to maintain trough target.	
		Aztreonam 1 g Q12h	Administered as a 30-min infusion until baseline cultures were confirmed negative for gram-negative pathogens.	

Abbreviations: BID, twice daily; CrCl, creatinine clearance; IV, intravenous; Q12h, every 12 hours.

The European Medicines Agency (EMA)-defined primary efficacy measure [13] was the investigator assessment of clinical response at the FU visit in the ITT population, defined as all randomized patients. Clinical response was based on ABSSI signs and symptoms and was categorized as cure (complete resolution); improved (some symptoms but no additional need for antibiotics); failure (additional nonstudy antibiotics required); or indeterminate (incomplete assessment). Patients with missing follow-up data and those with improved outcomes were combined with failures in the primary ITT analysis. An additional secondary endpoint was investigator-assessed success (cure plus improved and no further antibiotic needed) at the FU visit. Other antibiotic studies in skin infections have defined a successful outcome as resolution or near resolution of signs and symptoms that no longer require antibiotic therapy. This definition aligns with the definition of success in this study.

Patients' subjective assessment of pain was recorded on a numerical rating scale ranging from 0 (no pain) to 10 (pain as bad as imaginable) at baseline, during treatment, and at end of therapy (EOT), FU, and LFU.

Microbiological Assessments

Microbiological response was categorized as documented eradicated (baseline pathogen absent in follow-up cultures); presumed eradicated (no follow-up material available for culture, but the patient had a clinical response of success); documented persisted (baseline pathogen present in follow-up cultures); or presumed persisted (no follow-up material available for culture, but the patient had a clinical response of failure).

Safety and Tolerability Assessments

Safety assessments included all AEs, physical examinations, vital sign measurements, 12-lead electrocardiograms at baseline and as clinically indicated thereafter, and clinical laboratory tests. Patients were contacted by telephone 30 days after the final dose of study drug to assess the occurrence of long-term AEs. Treatment-emergent adverse events (TEAEs) were defined as events that occurred or worsened following administration of the first dose of the study drug through the 30-day telephone follow-up.

Randomization and Blinding

Patients were randomized (1:1), with randomization stratified by infection category and baseline body mass index (BMI). Infection categories were limited to $\leq 25\%$ of patients with a major cutaneous abscess and $\leq 30\%$ with wound infections. Patients were characterized by BMI as $<30 \text{ kg/m}^2$ and $\geq 30 \text{ kg/m}^2$ (obese); patients with a BMI $\geq 30 \text{ kg/m}^2$ were limited to no more than 50% of enrolled patients.

Statistical Methods

Separate statistical analysis plans for the FDA and the EMA were prospectively developed prior to database lock and unblinding. Clinical efficacy outcomes were analyzed for the ITT population

while the safety analysis population included all enrolled patients administered at least 1 dose of study drug. Analysis of microbiological outcomes was based on the microbiological intent-to-treat (MITT) population. There were multiple microbiologically evaluable (ME) and clinically evaluable (CE) analysis sets, each based on the type of assessment (investigator-assessed or objective) and timing of the assessment (48–72 hours, EOT, FU, LFU).

Descriptive statistics (mean, median, minimum, and maximum) described continuous variables while counts and percentages were calculated for categorical data. The rate of the primary FDA-defined efficacy endpoint was the sample responder rate defined as (responder / [responder + nonresponder]). The rate of the primary EMA-defined efficacy endpoint was the sample cure rate defined as (cure / [cure + failure]).

A 2-sided 95% confidence interval (CI) for noninferiority testing was computed based on the difference in sample responder rates and investigator-assessed response rates for vancomycin/aztreonam and delafloxacin at 48–72 hours following initiation of treatment using a nonstratified method [14]. Noninferiority was concluded if the lower limit of the 2-sided 95% CI exceeded -10% . Mean differences between treatments were expressed as delafloxacin minus vancomycin/aztreonam.

All analyses were performed with SAS software version 9.2 or higher (SAS Institute, Cary, North Carolina).

RESULTS

Patient Disposition and Analysis Sets

Eight hundred fifty patients were randomized (ITT population), including 423 to delafloxacin and 427 to vancomycin/aztreonam (Figure 1). Overall, 766 (90.1%) enrolled patients completed the study through the FU visit. A total of 842 randomized patients received at least 1 dose of study drug (safety population), and 552 patients had an identified baseline pathogen known to cause ABSSIs (MITT population).

Baseline Characteristics

Baseline characteristics were similar between treatment groups (Table 2). Overall, 46.8% of patients were from North America with an additional 39.8% from Europe; 23.5% received antibacterial therapy in the 14 days prior to enrollment. ABSSI categories were similarly distributed between the treatment groups (Table 3).

Among the 839 patients with an ABSSI culture at baseline, *S. aureus* was the most frequently identified organism in 58.2% of isolates in the delafloxacin group and 57.0% of isolates in vancomycin/aztreonam patients. MRSA was detected in 24.0% and 18.1%, respectively (Table 3). Delafloxacin minimum inhibitory concentration (MIC)_{50/90} was 0.008/0.25 $\mu\text{g/mL}$ (range, 0.002–4 $\mu\text{g/mL}$) for *S. aureus*, 0.12/0.25 $\mu\text{g/mL}$ (range, 0.002–4 $\mu\text{g/mL}$) for MRSA, and 0.008/0.008 $\mu\text{g/mL}$ (range, 0.002–0.12 $\mu\text{g/mL}$) for methicillin-susceptible *S. aureus* (MSSA). Overall, 96% of MRSA isolates were susceptible to delafloxacin (delafloxacin MIC $\leq 0.25 \mu\text{g/mL}$).

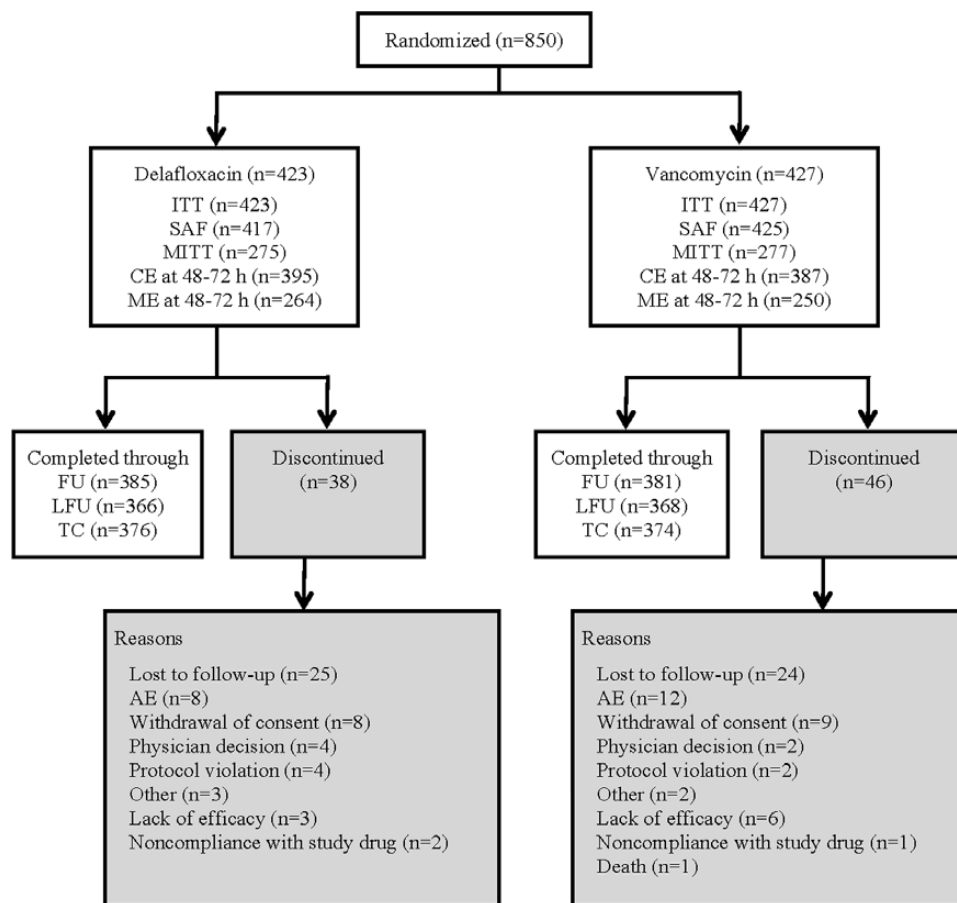


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of patient disposition. Intent-to-treat (ITT) analysis set included all patients who were randomly assigned to treatment. Clinically evaluable (CE) analysis set included all patients in the ITT population who (1) received $\geq 80\%$ of the total expected doses of the assigned study drug or experienced clinical failure and received ≥ 4 doses of study drug; (2) did not receive any concomitant, systemic antibacterial therapy with activity against the identified pathogen; and (3) had no major protocol deviations. Microbiological ITT (MITT) analysis set consisted of all patients in the ITT analysis set who had bacterial pathogens known to cause acute bacterial skin and skin structure infections at baseline. Microbiologically evaluable analysis set included all patients in the MITT population who met the criteria established for the CE analysis set. Abbreviations: AE, adverse event; CE, clinically evaluable; FU, follow-up; ITT, intent-to-treat; LFU, late follow-up; ME, microbiologically evaluable; MITT, microbiological intent-to-treat; SAF, safety; TC, telephone call.

Approximately 26% of *S. aureus* isolates were levofloxacin nonsusceptible (delafloxacin MIC range, 0.012–4 $\mu\text{g/mL}$); of these, 93% of levofloxacin-nonsusceptible *S. aureus* isolates were susceptible to delafloxacin; the majority were also MRSA. Gram-negative pathogens were identified in 20.7% (114/552) of patients with pathogens at baseline. Overall, 19 (2.2%) patients had bacteremia at baseline.

Clinical Outcomes

Objective Response

The percentage of patients classified as responders in the ITT analysis population at 48–72 hours after initiation of study drug was similar between the 2 groups at 83.7% and 80.6% for delafloxacin and vancomycin/aztreonam, respectively. The difference in responder rates was 3.1% (95% CI, –2.0% to 8.3%; (Figure 2), demonstrating noninferiority of delafloxacin compared to vancomycin/aztreonam. Equivalent efficacy for delafloxacin was also demonstrated for the CE, ME, and MITT analyses. The

percentage reduction from baseline in digital measurements of erythema was similar between the 2 groups at each visit (48–72 hours; EOT; FU; LFU) in the ITT analysis group.

Investigator-Assessed Response

The primary efficacy endpoint for the EMA submission and a secondary efficacy endpoint for the FDA submission was the investigator-assessed response of signs and symptoms of infection at FU in the ITT population. The cure rate of 57.7% for the delafloxacin group was noninferior to the rate of 59.7% observed in the vancomycin/aztreonam group with a difference of –2.0% (95% CI, –8.6 to 4.6). Noninferiority of delafloxacin compared to vancomycin/aztreonam was also confirmed for the MITT, CE, and ME analysis sets (Figure 2).

A sensitivity analysis in which success was defined as cure plus improved and failure as indeterminate plus failure revealed similar success rates between the 2 groups in the ITT analysis set (87.2% and 84.8% [difference, 2.5%; 95% CI, –2.2% to 7.2%]

Table 2. Patient Baseline Demographic and Clinical Characteristics: Intent-to-Treat Population

Characteristic	Delafloxacin (n = 423)	Vancomycin + Aztreonam (n = 427)	Overall (N = 850)
Age, y, mean \pm SD (range)	51.2 \pm 15.98 (18–89)	50.2 \pm 16.03 (19–93)	50.7 \pm 16.00 (18–93)
Age category, y, No. (%)			
≤65	344 (81.3)	352 (82.4)	696 (81.9)
65–75	79 (18.7)	75 (17.6)	154 (18.1)
>75	35 (8.3)	31 (7.3)	66 (7.8)
Male sex, No. (%)	262 (61.9)	276 (64.6)	538 (63.3)
Race, No. (%)			
White	348 (82.3)	355 (83.1)	703 (82.7)
Black/African American	13 (3.1)	18 (4.2)	31 (3.6)
American Indian/Alaska Native	12 (2.8)	7 (1.6)	19 (2.2)
Asian	11 (2.6)	15 (3.5)	26 (3.1)
Native Hawaiian/Other Pacific Islander	2 (0.5)	2 (0.5)	4 (0.5)
Other	37 (8.7)	30 (7.0)	67 (7.9)
Ethnicity, No. (%)			
Hispanic or Latino	132 (31.2)	99 (23.2)	231 (27.2)
Region, No. (%)			
Europe	165 (39.0)	173 (40.5)	338 (39.8)
North America	202 (47.8)	196 (45.9)	398 (46.8)
Asia	9 (2.1)	14 (3.3)	23 (2.7)
Latin America	47 (11.1)	44 (10.3)	91 (10.7)
BMI, kg/m ² , mean \pm SD	30.4 \pm 7.44	30.7 \pm 7.54	30.5 \pm 7.49
≥30	211 (49.9)	214 (50.1)	425 (50.0)
Diabetes, No. (%)	53 (12.5)	54 (12.6)	107 (12.6)
Prior antibiotic use, No. (%)	89 (21.0)	111 (26.0)	200 (23.5)
Baseline pain score, mean \pm SD	7.4 \pm 2.30	7.2 \pm 2.40	
Medical history relevant to substance abuse including IVDA, No. (%) ^a	129 (30.5)	125 (29.3)	
Duration of exposure, d			
No.	417	425	
Mean \pm SD	7.3 \pm 2.97	7.0 \pm 2.92	
Median	6.5	6.5	
Min, Max	0.5, 14.0	0.5, 14.5	

Abbreviations: BMI, body mass index; IVDA, intravenous drug abuse; SD, standard deviation.

^aMedical history was coded using the Medical Dictionary for Regulatory Activities version 16.1. At each level of summarization, a subject was counted once if the subject reported 1 or more events. Preferred terms used: drug dependence, drug abuse, substance use, drug abuser, substance abuse, and substance abuser.

for the delafloxacin and vancomycin/aztreonam groups) as well as for the CE, MITT, and ME analysis sets (Figure 2).

In patients with bacteremia, 8 of 11 (72.7%) delafloxacin-treated patients and 5 of 8 (62.5%) vancomycin/aztreonam-treated patients had successful outcomes (investigator assessment of success, ITT). This included 1 patient with *Pseudomonas aeruginosa* bacteremia who was a clinical success in the delafloxacin arm.

The mean baseline patient-reported pain score was 7.4 and 7.2 for delafloxacin and vancomycin/aztreonam, respectively. In the ITT analysis set, mean pain scores were similar between the delafloxacin and vancomycin/aztreonam groups at the FU assessment at 0.5 and 0.6, respectively. Mean pain scores were the same for both groups at 1.2 and 0.3 for EOT and LFU, respectively.

Microbiological Efficacy

Overall pathogen eradication rates were similar between the delafloxacin group at 97.8% and 97.6% for the vancomycin/aztreonam group, with a difference of 0.2% (95% CI, –2.9% to 3.5%).

The most common pathogen was *S. aureus*; rates of microbiological success approached 100.0% in both groups at FU. Per-pathogen early objective response at 48–72 hours and microbiological response rates were similar between the 2 treatment groups Tables 4 and 5. The microbiological response was similar for patients with MRSA infections at 96.0% and 97.0% for delafloxacin and vancomycin/aztreonam, respectively. Additionally, there was 97% documented or presumed eradication for the levofloxacin-nonsusceptible *S. aureus* isolates in the delafloxacin group. No isolates were shown to have an increase in delafloxacin MIC values during the course of therapy; emergence of resistance was not seen.

Safety

In the safety analysis set, 43.6% of those administered delafloxacin and 39.3% of the vancomycin/aztreonam group reported 1 or more TEAEs, and the percentage of TEAEs considered related

Table 3. Summary of Acute Bacterial Skin and Skin Structure Infection Characteristics: Intent-to-Treat Population

Characteristic	Delafloxacin (n = 423)	Vancomycin + Aztreonam (n = 427)	Overall (N = 850)
ABSSSI category, No. (%)			
Cellulitis/erysipelas	202 (47.8)	206 (48.2)	408 (48.0)
Wound infection	111 (26.2)	112 (26.2)	223 (26.2)
Major cutaneous abscess	106 (25.1)	106 (24.8)	212 (24.9)
Burn infection	4 (0.9)	3 (0.7)	7 (0.8)
Erythema size (cm ² ; digital), mean ± SD	341.5 ± 312.89	364.4 ± 391.70	353 ± 354.70
25th, 75th percentile	(134.0, 407.0)	(127.5, 437.9)	(132.5, 428.0)
Induration size (cm ² ; digital), mean ± SD	116.1 ± 205.29	159.3 ± 288.69	137.8 ± 251.51
25th, 75th percentile	15.3, 115.2	19.0, 146.9	17.3, 129.3
Systemic signs, No. (%)			
Lymph node enlargement	273 (64.5)	275 (64.4)	548 (64.5)
Elevated WBC ≥10 000 cells/μL	207 (48.9)	204 (47.8)	411 (48.4)
Elevated CRP >10× ULN	185 (43.7)	198 (46.4)	383 (45.1)
Fever ≥38°C	174 (41.1)	177 (41.5)	351 (41.3)
Lymphangitis	97 (22.9)	101 (23.7)	198 (23.3)
Bacteremia, No. (%)	11 (2.6)	8 (1.9)	19 (2.2)
Identified pathogens, No. (%) ^a			
<i>Staphylococcus aureus</i> ^b	160 (58.2)	158 (57.0)	318 (57.6)
MRSA	66 (24.0)	50 (18.1)	116 (21.0)
MSSA	96 (34.9)	108 (39.0)	204 (37.0)
Assessment, No. (%)			
Erythema/extension of redness	422 (99.8)	426 (99.8)	848 (99.8)
Pain/tenderness	422 (99.8)	423 (99.1)	845 (99.4)
Heat/localized warmth	421 (99.5)	423 (99.1)	844 (99.3)
Swelling/induration	398 (94.1)	395 (92.5)	793 (93.3)
Drainage/discharge	270 (63.8)	264 (61.8)	534 (62.8)
Fluctuance	184 (43.5)	206 (48.2)	390 (45.9)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CRP, C-reactive protein; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; SD, standard deviation; ULN, upper limit of normal; WBC, white blood cell count.

^an = 275 for delafloxacin and n = 277 for vancomycin + aztreonam.

^bPatients with both MRSA and MSSA were counted only once.

to study drug was comparable between the 2 groups (Table 6). The percentages of TEAEs resulting in early discontinuation of study drug and serious AEs were similar between treatment groups. Most TEAEs were considered to be mild in severity in both treatment groups, with 30 patients experiencing ≥1 severe TEAE, including 16 (3.8%) patients in the delafloxacin group and 14 (3.3%) patients in the vancomycin/aztreonam group. Two deaths occurred in the vancomycin/aztreonam group and none in the delafloxacin arm; both deaths were considered not related to treatment. One (0.2%) patient treated with delafloxacin developed *Clostridium difficile* diarrhea (prior treatment failure on trimethoprim/sulfamethoxazole and clindamycin), with no cases reported in the vancomycin/aztreonam arm. There were no cases of tendinitis, tendon rupture, or myopathy and 1 case of paresthesia in each treatment group that was thought to be potentially related to treatment. There were no reports of treatment-related hypo- or hyperglycemia during trial in either group.

There were no significant differences between the 2 treatments in changes from baseline in hematology and/or chemistry parameters. There were no increases in hepatic AEs in the delafloxacin treatment group when compared to vancomycin/

aztreonam. A lower percentage of patients in the delafloxacin group compared with the vancomycin/aztreonam group had an alanine aminotransferase value at least once postbaseline that was >5 times the upper limit of normal (ULN) (1.2% [5/417] delafloxacin vs 1.9% [8/425] vancomycin/aztreonam). Only 4 and 2 patients in delafloxacin and vancomycin/aztreonam groups, respectively, had aspartate aminotransferase >5 times the ULN at any time during the trial. No patient in either treatment group met potential Hy's law criteria. Serum creatinine >2 times the ULN was seen in 7 vancomycin-treated patients at any time during the trial, compared to no reports in delafloxacin patients.

DISCUSSION

This phase 3 trial of IV followed by oral delafloxacin showed that in patients with ABSSSI, IV/oral delafloxacin monotherapy was noninferior to IV vancomycin/aztreonam combination therapy. The addition of oral delafloxacin appears to maintain the initial clinical response seen with IV delafloxacin providing an option of switching from IV to oral therapy as soon as patients are clinically stable.

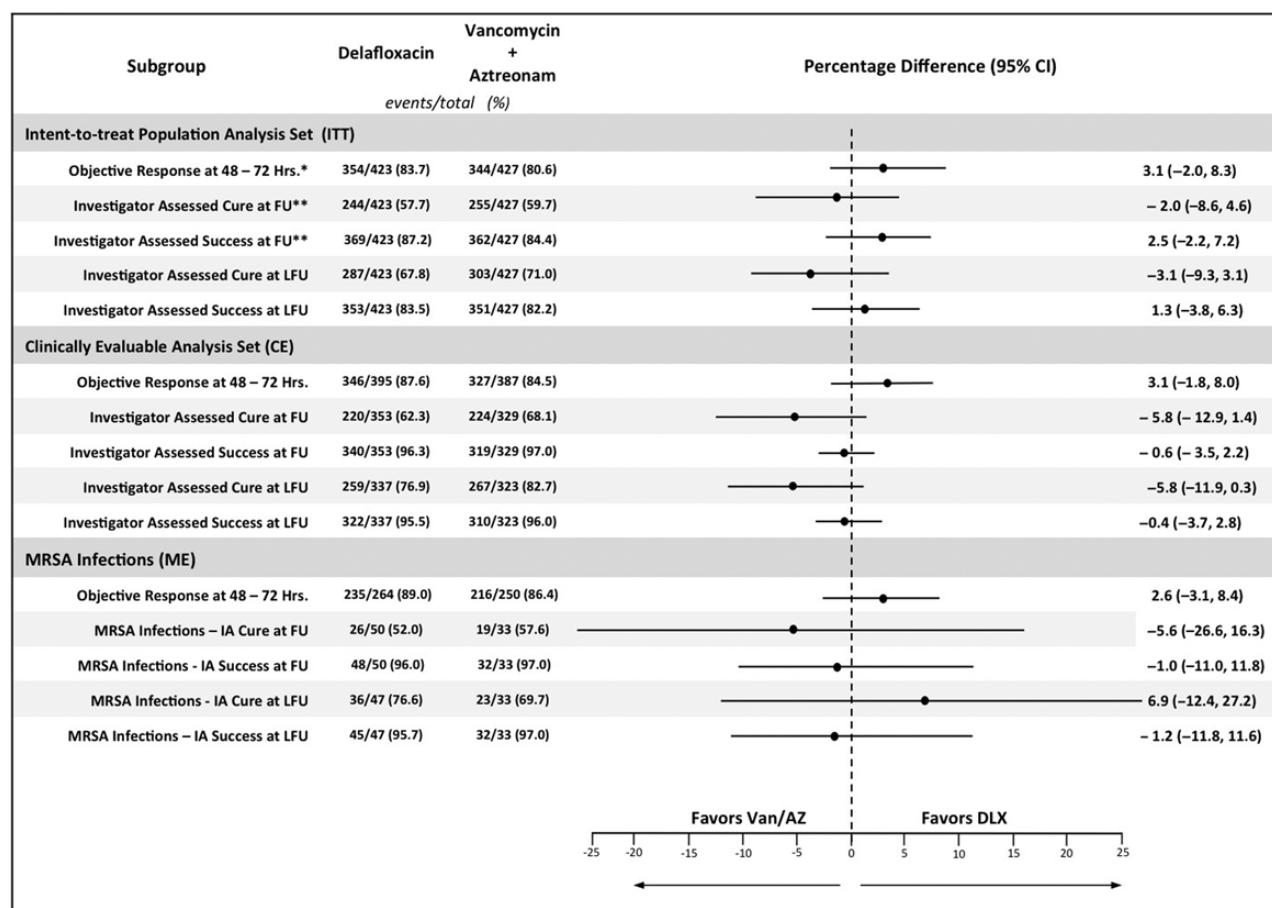


Figure 2. Objective response and investigator-assessed response at follow-up and late follow-up by analysis set, methicillin-resistant *Staphylococcus aureus* (MRSA) infection at baseline. *Primary endpoint. **The primary efficacy endpoint for the European Medicines Agency submission, and a secondary efficacy endpoint for the US Food and Drug Administration submission. Cure = no remaining signs and symptoms; Improved = some remaining signs and symptoms but no further antibiotics required; Success = Cure + Improved. Abbreviations: CE, clinically evaluable (patients who completed activities as defined in the protocol); CI, confidence interval; DLX, delafloxacin; FU, follow-up; IA, investigator assessed; ITT, intent-to-treat (all patients randomized); LFU, late follow-up; ME, microbiologically evaluable (clinically evaluable patients with eligible pathogen); MRSA, methicillin-resistant *Staphylococcus aureus*; Van/AZ, vancomycin/aztreonam.

Delafloxacin patients had comparable per-pathogen microbiological response rates vs vancomycin/aztreonam patients against important pathogens that cause ABSSSIs, including MRSA and gram-negative bacteria. The eradication rate in patients with MSSA was higher in the delafloxacin group compared with the vancomycin/aztreonam group. Although the numbers were small, IV/oral delafloxacin monotherapy had eradication rates of 100% for gram-negative pathogens such as *Escherichia coli*, *P. aeruginosa*, and *Klebsiella pneumoniae*, which included isolates from monomicrobial infections.

Emergence of resistance was not seen in the study. In a resistance selection study, delafloxacin demonstrated a low probability for the selection of resistant mutants in MRSA [15, 16]. In addition, analysis of phase 3 data shows high eradication of fluoroquinolone-nonsusceptible isolates.

Delafloxacin appeared to be well tolerated in this study with a lower rate of discontinuation due to related TEAEs than vancomycin/aztreonam: 5 of 417 (1.2%) and 10 of 425 (2.4%),

respectively. Previous studies have documented that delafloxacin was not associated with QT prolongation [17] or phototoxicity [18], and has minimal potential for drug interactions [19].

Similar results were seen in a recently published phase 3 study of 660 patients that compared delafloxacin 300 mg or vancomycin 15 mg/kg plus aztreonam 2 g each administered twice daily intravenously for 5–14 days in the treatment of ABSSSIs. Delafloxacin was found to have comparable clinical activity to vancomycin and was well tolerated [20].

While gram-positive pathogens are the most common bacteria identified in ABSSSI, gram-negative pathogens are increasing in prevalence and must be considered when selecting initial empiric therapy [3]. A large prospective observational study found that nearly 25% of patients hospitalized for cSSTIs received initial inappropriate therapy, a finding similar to those in other studies [8, 21–25]. The most common independent risk factors of initial inappropriate therapy was shown to be infection that included gram-negative pathogens. Clinicians must

Table 4. Per-Pathogen Microbiological Response Rate at Follow-up: Microbiologically Evaluable Population

Pathogen	Per-Pathogen Objective Responders at 48–72 h, ME at 48–72 h Analysis Set		Per-Pathogen Microbiological Response (Documented or Presumed Eradication) ^a , ME at Follow-up Analysis Set	
	Delafloxacin (n = 264)	Vancomycin + Aztreonam (n = 250)	Delafloxacin (n = 231)	Vancomycin + Aztreonam (n = 212)
<i>Staphylococcus aureus</i>	139/152 (91.4)	122/142 (85.9)	129/131 (98.5)	114/118 (96.6)
MRSA	61/64 (95.3)	43/46 (93.5)	48/50 (96.0)	32/33 (97.0)
MSSA	80/89 (89.9)	79/96 (82.3)	83/83 (100.0)	82/85 (97.0)
<i>Streptococcus anginosus</i> ^b	28/28 (100)	20/20 (100)	24/24 (100.00)	16/16 (100.0)
<i>Streptococcus pyogenes</i>	12/16 (75)	7/12 (58.3)	13/14 (92.9)	11/11 (100.0)
<i>Klebsiella pneumoniae</i>	8/9 (88.9)	9/10 (90)	8/8 (100.0)	8/8 (100.0)
<i>Pseudomonas aeruginosa</i>	7/9 (77.8)	7/7 (100)	9/9 (100.0)	6/6 (100.0)
<i>Escherichia coli</i>	9/9 (100)	6/10 (60)	7/7 (100.0)	9/10 (90.0)
<i>Staphylococcus haemolyticus</i>	6/9 (66.7)	5/6 (83.3)	7.7 (100)	5.5 (100)
<i>Enterobacter cloacae</i>	6/8 (75)	5/8 (62.5)	8/8 (100.0)	7/8 (87.5)
<i>Streptococcus agalactiae</i>	6/8 (75)	8/10 (80)	6/6 (100)	9/10 (90.0)
<i>Enterococcus faecalis</i>	8/8 (100)	8/12 (66.7)	7/8 (87.5)	11/12 (91.7)
<i>Staphylococcus lugdunensis</i>	2/3 (66.7)	3/6 (50)	3/3 (100)	6/6 (100)

Data are presented as No. (%). Susceptibility test interpretive criteria can be found in the [Supplementary Data](#).

Abbreviations: ME, microbiologically evaluable; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

^aInvestigator-assessed response in ME at follow-up analysis set was the same as per-pathogen microbiological response.

^b*Streptococcus anginosus* group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*.

be attuned to specific patient risk factors which lead to consideration of gram-negative coverage [3, 9, 25]. The current FDA definition of ABSSSI used in this study excludes patients with infection types including diabetic foot infection, osteomyelitis, and decubitus ulcer from ABSSSI studies and limits the ability to investigate patients with gram-negative infections. Even given this study limitation, 20.7% of patients in this study had a gram-negative pathogen identified. Though further study in patients most likely to have a gram-negative infection would be important, delafloxacin may offer a monotherapy option for the treatment of ABSSSI in these patient types.

Because in previous studies a signal was seen indicating that delafloxacin may provide benefit in obese patients, this study randomized and was stratified for obesity [20, 26]. Rates of cure and success in obese patients were similar between the delafloxacin and vancomycin/aztreonam groups. Delafloxacin administered at the standard dose of 300 mg every 12 hours IV and oral delafloxacin 450 mg every 12 hours was found to provide good

outcomes in obese patients (BMI ≥ 30 kg/m²), potentially simplifying dosing in this patient population. Due to limitations on vancomycin dosing and infusion time and thus blinding, patient weight was limited to a maximum of 200 kg

Additional limitations to this study include a low number of burn and surgical wounds, and relative to the general population, the number of older adults and nonwhites was lower.

Patients in this study were enrolled based upon the most recent FDA guidance for industry for the study of drugs for the treatment of ABSSSI. This guidance was developed to support an indication for the treatment of ABSSSI and exclude less serious skin infections such as impetigo and minor cutaneous abscess [27]. Use of this guidance has made results of more recent trials more consistent by defining infection types and size of lesions that should be included as well as exclusion criteria.

Extensive use of fluoroquinolones has led to recognition of a variety of rare AEs and acknowledgement that the class should be used more appropriately as noted in FDA guidance [28]. Delafloxacin product labeling includes these risks associated with the fluoroquinolones. Based on currently available data, delafloxacin does not appear to be associated with an increased risk of AEs associated with other fluoroquinolones [29]. Future observation as the drug is more widely used in the clinic will be prudent.

In this study, in ABSSSI patients, IV/oral delafloxacin monotherapy was noninferior to IV vancomycin/aztreonam combination therapy for both the objective and the investigator-assessed response rates and was well tolerated. With both an IV and oral formulation, delafloxacin offers a potential treatment option for ABSSSI due to gram-positive (including MRSA) and gram-negative bacteria.

Table 5. Per-Patient Microbiological Response^a for Gram-Positive, Gram-Negative, and Mixed Infections: Microbiologically Evaluable at Follow-up Analysis Set

Infection	Delafloxacin (n = 231)	Vancomycin + Aztreonam (n = 212)
Mono- or polymicrobial gram positive	180/185 (97.3)	163/166 (98.2)
Mono- or polymicrobial gram negative	15/15 (100)	16/17 (94.1)
Mixed (gram positive and gram negative)	31/31 (100)	28/29 (96.6)

Data are presented as No. (%).

^aDocumented or presumed eradication.

Table 6. Overall Summary of Adverse Events and Treatment-Emergent Adverse Events: Safety Population

Adverse Event	Delafloxacin (n = 417)	Vancomycin + Aztreonam (n = 425)
Any TEAE regardless of causality affecting $\geq 2\%$ of patients	182 (43.6)	167 (39.3)
Nausea	32 (7.7)	19 (4.5)
Diarrhea	32 (7.7)	14 (3.3)
Infection	16 (3.8)	15 (3.5)
Headache	14 (3.4)	16 (3.8)
Infusion site extravasation	13 (3.1)	10 (2.4)
Pyrexia	11 (2.6)	9 (2.1)
Vomiting	10 (2.4)	8 (1.9)
Increase in creatinine phosphokinase	5 (1.2)	10 (2.4)
Pruritus	4 (1.0)	9 (2.1)
TEAE related to study drug	87 (20.9)	89 (20.9)
TEAE of moderate or severe intensity	75 (18.0)	86 (20.2)
Any TEAE resulting in premature study drug discontinuation	10 (2.4)	12 (2.8)
Any related TEAE resulting in premature study drug discontinuation	5 (1.2)	10 (2.4)
Any SAE	16 (3.8)	17 (4.0)
Deaths	0 (0.0)	2 (0.5)

Data are presented as No. (%).

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. All authors participated in the execution and completion of the study and drafting and review of this manuscript. E. S., L. L., and S. C. were responsible for development of the protocol. S. L. provided statistical and analytic support. We thank the members of the PROCEED Study Group who enrolled patients in the study.

Financial support. This study was funded by Melinta Therapeutics. Editorial assistance for this manuscript was provided by Strategic Healthcare Communications, Hillsborough, New Jersey, funded by Melinta Therapeutics.

Potential conflicts of interest. W. O., A. M., J. T., I. P., and M. C.-S. were provided research support by Melinta Therapeutics. M. Q., L. L., and S. C. are employed by Melinta Therapeutics. S. L. is employed by H2O Clinical, which was paid to provide statistical and analytic support. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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APPENDIX

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