

Analysis of Pooled Phase III Efficacy Data for Delafloxacin in Acute Bacterial Skin and Skin Structure Infections

Philip A. Giordano,¹ Jason M. Pogue,² and Sue Cammarata³

¹Department of Emergency Medicine, Orlando Health, Florida; ²Division of Infectious Diseases, Detroit Medical Center, Wayne State University, Michigan; and ³Melinta Therapeutics, Lincolnshire, Illinois

Background. Delafloxacin is an oral or intravenous (IV) antibiotic indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI), including both gram-positive (including methicillin-resistant *Staphylococcus aureus* [MRSA]) and gram-negative organisms. Chemically distinct from other quinolones, delafloxacin exhibits enhanced potency, particularly against gram-positive pathogens. The integration of efficacy data across the Phase III ABSSSI studies is presented here and allows for additional examination of results across subgroups.

Methods. Results of 2 multicenter, randomized, double-blind trials of 1510 adults with ABSSSI were pooled for this analysis. Subjects in the vancomycin arm received 15 mg/kg, plus 1–2 g of aztreonam every 12 hours. Delafloxacin was dosed at 300 mg IV every 12 hours in Study 302; dosing in Study 303 was 300 mg IV every 12 hours for 3 days, with a mandatory, blinded switch to delafloxacin at 450 mg orally every 12 hours. The primary endpoint was objective response (OR), defined as a $\geq 20\%$ reduction of lesion spread of erythema area at the primary infection site at 48 to 72 hours (± 2 hours), in the absence of clinical failure. Investigator-assessed response, based on the resolution of signs and symptoms at follow-up (FU; Day 14 ± 1) and late follow-up (LFU; Day 21–28), were secondary endpoints.

Results. In the intent-to-treat analysis set, the OR was 81.3% in the delafloxacin arm and 80.7% in the comparator arm (mean treatment difference 0.8%, 95% confidence interval -3.2% to 4.7%). Results for OR in the defined subgroups showed delafloxacin to be comparable to vancomycin/aztreonam. Investigator-assessed success was similar at FU (84.7% versus 84.1%) and LFU (82.0% versus 81.7%). Delafloxacin was comparable to vancomycin/aztreonam in the eradication of MRSA, at 98.1% versus 98.0%, respectively, at FU. The frequencies of treatment-emergent adverse events between the groups were similar.

Conclusions. Overall, IV/oral delafloxacin fixed-dose monotherapy was non-inferior to IV vancomycin/aztreonam combination therapy and was well tolerated in each Phase III study, as well as in the pooled analysis, regardless of endpoint or analysis population.

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

Acute bacterial skin and skin structure infections (ABSSSI) are among the most common bacterial infections and are also common reasons for hospitalization [1–6]. Accounting for 6.3 million physician visits per year, the cost of treating these serious infections is substantial, particularly in patients who are hospitalized [7–10].

The clinical manifestations of skin infections vary considerably and range from uncomplicated, superficial infections to limb- or life-threatening infections. ABSSSIs include infected ulcers or burns, major abscesses, wounds, surgical site infections, and extensive cellulitis [11]. These infections may be further complicated by the presence of diabetes mellitus, chronic

kidney disease, or peripheral arterial disease [11, 12]. While overall mortality rates are relatively low, at 10%, ABSSSIs are the third most frequent cause of severe sepsis or septic shock, after pneumonia (55–60%) and intra-abdominal infections (25%), and impact both clinical and economic outcomes [1, 13].

The etiologies of ABSSSI are diverse and depend on a number of factors, including the epidemiological setting (community, hospital, long-term care setting, etc.), the site of infection, and patient risk factors [14, 15]. While the most frequent causative pathogens are the gram-positive bacteria, gram-negative bacteria can also play an important role. Among patients hospitalized with serious skin infections, monomicrobial gram-negative infections have been reported at a rate of 12.8% and mixed infections (both gram-positive and gram-negative) have been observed in 10.6% to 20.5% [7, 16]. The risk of inappropriate antimicrobial therapy has been shown to increase in skin infections when gram-negative and mixed cultures are present [7, 16]. Further compounding the challenge clinicians face is the fact that risk stratification for the purpose of identifying a likely pathogen and targeting antibiotic therapy to that pathogen is unreliable, as few organism-specific risk factors have been identified [17]. Therefore, most antibiotics

Correspondence: P. Giordano, Department of Emergency Medicine, Orlando Regional Medical Center, Corporate Research Operations Orlando Health, 1401 Lucerne Terrace, MP 131, Orlando, FL 32806 (Philip.Giordano@orlandohealth.com).

Clinical Infectious Diseases® 2019;68(S3):S223–32

© The Author(s) 2019. Published by Oxford University Press for the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
DOI: 10.1093/cid/ciz006

must be given empirically and, in fact, initial empiric treatment without documented microbiology is given in up to 88.8% of patients [18]. The failure to provide appropriate initial antibiotic therapy in cSSTI has been shown to increase not only the cost of treatment, but also the risk of mortality [19–21].

Delafloxacin

Structural changes made over time to the core quinolone molecule have resulted in fluoroquinolones with improved pharmacokinetic/pharmacodynamic properties, broad-spectrum activity, and efficacy against both gram-positive and gram-negative pathogens [22–25]. However, with extensive use and overuse of fluoroquinolones in both human and veterinary medicine, the number of quinolone-resistant bacterial strains has grown, and clinical use has become increasingly limited [23].

The anionic fluoroquinolone delafloxacin has been recently approved by the Food and Drug Administration (FDA) for the oral or intravenous treatment of ABSSSI caused by susceptible bacteria, including gram-positive, methicillin-resistant *Staphylococcus aureus* (MRSA), and gram-negative organisms. Delafloxacin targets both DNA gyrase and topoisomerase through intravenous (IV) administration, but is chemically distinct from other quinolones in size, shape, and its anionic versus zwitterionic charge profile. These differences result in an agent with enhanced potency, particularly against gram-positive pathogens [26]. Delafloxacin has demonstrated greater in vitro potency than levofloxacin against most gram-positive pathogens, including retaining activity in many levofloxacin–non-susceptible isolates (Table 1). Notably, delafloxacin has been shown to be 32-fold more active than levofloxacin against MRSA isolates [27], and is active both in vitro and in clinical infections against most isolates of *E. coli*, *K. pneumoniae*, *E. cloacae*, and *P. aeruginosa*, with activity similar to ciprofloxacin. Its anionic structure enhances its potency in acidic environments, which are typical of sites of infection, including skin and soft tissue infections caused by *S. aureus* [28].

In total, 23 Phase I studies enrolled 1071 subjects, with 919 receiving delafloxacin, and, in part, established a recommended

dosing regimen of delafloxacin at 300 mg IV solution every 12 hours and 450 mg oral tablet BID. The 450 mg tablet and 300 mg IV lyophilized formulations are bioequivalent with regard to total exposure, measured by the area under the curve (AUC). The relevant measure for delafloxacin efficacy is AUC/MIC: therefore, switching between these 2 formulations is feasible. The Phase II trial program included 2 randomized, double-blind studies that demonstrated that delafloxacin is well tolerated and clinically efficacious compared with tigecycline, linezolid, and vancomycin [28, 29] (Table 2).

The results from 2 Phase III ABSSSI studies support the efficacy of delafloxacin in this indication (Study 302 and Study 303) [26, 30]. The integration of data across the studies presented here provides evidence for the effectiveness of IV and oral delafloxacin and allows for the examination of efficacy results by subgroups in patients being treated for ABSSSI.

METHODS

The integrated results of the Phase III, multicenter, randomized, double-blind, active-controlled PROCEED (PROve Clinical Efficacy and Effect of Delafloxacin) studies are presented here. Designed in accordance with both the 2013 FDA guidelines for ABSSSI and the current European Medicines Agency guidelines, these trials randomized subjects 1:1 to receive delafloxacin monotherapy or vancomycin plus aztreonam [26, 30] (Table 2). The 2 studies were essentially identical in design. Subjects in the vancomycin arm received 15 mg/kg based upon actual body weight, plus 1–2 g of aztreonam every 12 hours. Delafloxacin was dosed at 300 mg IV every 12 hours in Study 302; dosing in Study 303 was 300 mg IV every 12 hours for 3 days, with a mandatory, blinded switch to delafloxacin at 450 mg orally every 12 hours. The IV and oral formulations are bioequivalent with regard to total exposure (AUC); thus, outcomes were combined. Both studies were stratified by infection type, and Study 303 was also stratified by body mass index (BMI; ≥ 30 kg/m²), based on signals seen in both a Phase II study and Study 302 that showed a potential efficacy benefit in obese patients [29].

The Phase III studies included adult male and female patients (≥ 18 years of age) with a diagnosis of ABSSSI. At baseline, those enrolled in the studies were required to have a minimum ABSSSI lesion of 75 cm² and at least 2 systemic manifestations of infection. Prior antibiotic use was limited to 25% of the enrolled patients, as specified in the 2013 FDA guidelines. Subjects with a weight greater than 140 kg (309 lbs) or with severe renal impairment were excluded from Study 302, while Study 303 allowed subjects who weighed up to 200 kg (441 lbs). Other enrollment criteria were similar between the 2 studies and full inclusion/exclusion criteria have been published elsewhere [26, 30].

The primary study endpoint was objective response (OR), defined as a $\geq 20\%$ reduction of the ABSSSI lesion spread of

Table 1. Delafloxacin In Vitro Activity Against *Staphylococcus aureus* in Isolates From Phase III Trials Stratified by Levofloxacin Susceptibility

Organism	N	MIC Range (μ g/ml)	MIC ₉₀
<i>S. aureus</i>	685	0.002–4	0.25
Levofloxacin–non-susceptible <i>S. aureus</i>	232	0.004–4	0.25
MRSA	294	0.002–4	0.25
Levofloxacin–non-susceptible MRSA	195	0.004–4	0.25
MSSA	395	0.002–0.5	0.03
Levofloxacin–non-susceptible MSSA	39	0.004–0.5	0.25

Pooled data for the delafloxacin and comparator treatment arms for the microbiological intent to treat population. N = number of available MIC values from isolates cultured at baseline from primary infection site or blood. If the same pathogen is identified from both the blood and the culture of the acute bacterial skin and skin structure infections, it is counted only once in the summary. Patients with both MRSA and MSSA at baseline are included once in the overall *Staphylococcus aureus* category.

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

Table 2. Summary of Study Designs for Key Studies in Support of Acute Bacterial Skin and Skin Structure Infections Indication

	RX-3341-201 (Study 201)	RX-3341-202 (Study 202)	RX-3341-302 (Study 302)	RX-3341-303 (Study 303)
Phase, year completed	Phase II; 2008	Phase II; 2011	Phase III; 2014	Phase III; 2016
Population	Adults with cSSSI (pre-2010 definition)	Adults with ABSSSI (required lesion size ≥ 75 cm ²) and at least 1 systemic sign of infection	Adults with ABSSSI (required lesion size ≥ 75 cm ²) and at least 2 systemic signs of infection	Adults with ABSSSI (required lesion size ≥ 75 cm ²) and at least 2 systemic signs of infection
Comparator (N)	Tigecycline (50)	Linezolid (77) and vancomycin (98; optional aztreonam)	Vancomycin and aztreonam (329)	Vancomycin and aztreonam (427)
Delafloxacin dose/route (N)	300 mg IV Q12 h (49), 450 mg IV Q12 h (51)	300 mg IV Q12 h (81)	300 mg IV Q12 h (331)	300 mg IV Q12 h for 6 doses with switch to 450 mg oral Q12 h (423)
Duration of therapy	5–14 d	5–14 d	5–14 d	5–14 d
Time points	NA	48–72 h	48–72 h	48–72 h
EOT	NA	NA	Assessment collected	Assessment collected
FU	NA	Day 14	Day 14	Day 14
LFU	NA	Day 21–28	Day 21–28	Day 21–28
TOC	14–21 days post-last dose	NA	NA	NA
Stratification factors and enrollment limits at randomization	Infection type	Infection type and prior antibiotics enrollment limited to: prior antibiotics – 30%, abscesses – 30%	Infection type enrollment limited to: prior antibiotics – 25%, abscesses – 25%, wounds – 35%	Infection type and BMI (< or ≥ 30 kg/m ²). Enrollment limited to: prior antibiotics – 25%, abscesses – 25%, wounds – 30%, BMI ≥ 30 kg/m ² – $\leq 50\%$
Primary endpoint	Investigator outcome (traditional definition, with complete or near resolution of signs and symptoms as cure)	Investigator assessment of cure only (similar to the Phase III studies, cure was classified as a success and all other responses were classified as failures [ie, improved, failure, and indeterminate]).	Objective response at 48–72 h (at least 20% reduction in lesion size, with no medicines, major procedures, or death)	Objective response at 48–72 h (at least 20% reduction in lesion size, with no non-study medicines, major procedures, or death)
Key clinical efficacy secondary endpoint	NA	Clinical success cessation: cessation of lesion spread at 48–72 h, with resolution or absence of fever. Both must be sustained through 72 h. Clinical success reduction: reduction of lesion size (reported in 10% increments) at other time points, including 48–72 h.	Investigator assessment of response of signs and symptoms of infection at the FU and LFU visits. Cure was the primary analysis.	Investigator assessment of response of signs and symptoms of infection at the FU and LFU visits. Cure was the primary analysis.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; BMI, body mass index; EOT, end of treatment; FU, follow-up; IV, intravenous; LFU, late follow-up; NA, not available; OR, objective response; TOC, test of cure.

erythema area, as determined by digital planimetry at the primary infection site at 48 to 72 hours (± 2 hours) in the absence of clinical failure. Investigator-assessed response, based on the resolution of signs and symptoms at follow-up (FU; Day 14 \pm 1) and late follow-up (LFU; Day 21– 28) were secondary endpoints. The investigator response was categorized as cure (complete resolution) or success (cure plus improved and no further antibiotic needed). A 2-sided 95% confidence interval [CI] for non-inferiority testing was computed based on the difference in sample responder rates for vancomycin + aztreonam and delafloxacin using Miettinen and Nurminen methodology stratified by studies.

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

Subgroup analyses were performed for OR and summarized across both studies. Subgroups assessed included age, sex, race, geographic region, ethnicity, presence of diabetes, baseline infection type, prior antibiotic use, bacteremia at baseline, quartiles of baseline erythema area, surgical procedure up to 72 hours from the first dose, and target pathogen. These subgroup analyses were performed in the intent-to-treat (ITT; all patients randomized) and clinically evaluable (CE; patients who completed activities as defined in the protocol) analysis sets, except the subgroup by target pathogens, which were performed in the microbiological ITT (MITT; all patients in the ITT analysis set that had bacterial pathogens known to cause ABSSSI at baseline) and microbiologically evaluable (ME; MITT population who met the criteria established for the CE analysis set) analysis sets. Analyses of investigator-assessed outcomes at FU and LFU in the ITT and CE analysis sets in subgroups, based on the BMI, presence of diabetes, or presence of renal impairment, were also included.

RESULTS

There were 1510 patients randomized (ITT population) and integrated into the pooled data, including 754 patients in the delafloxacin group and 756 in the vancomycin/aztreonam group. A total of 1042 patients had an identified baseline pathogen known to cause ABSSSIs (MITT population). Overall, no differences in patient demographics, baseline characteristics, infection type, symptoms, or baseline lesion surface areas were observed between the treatment groups (Table 3).

Objective Response

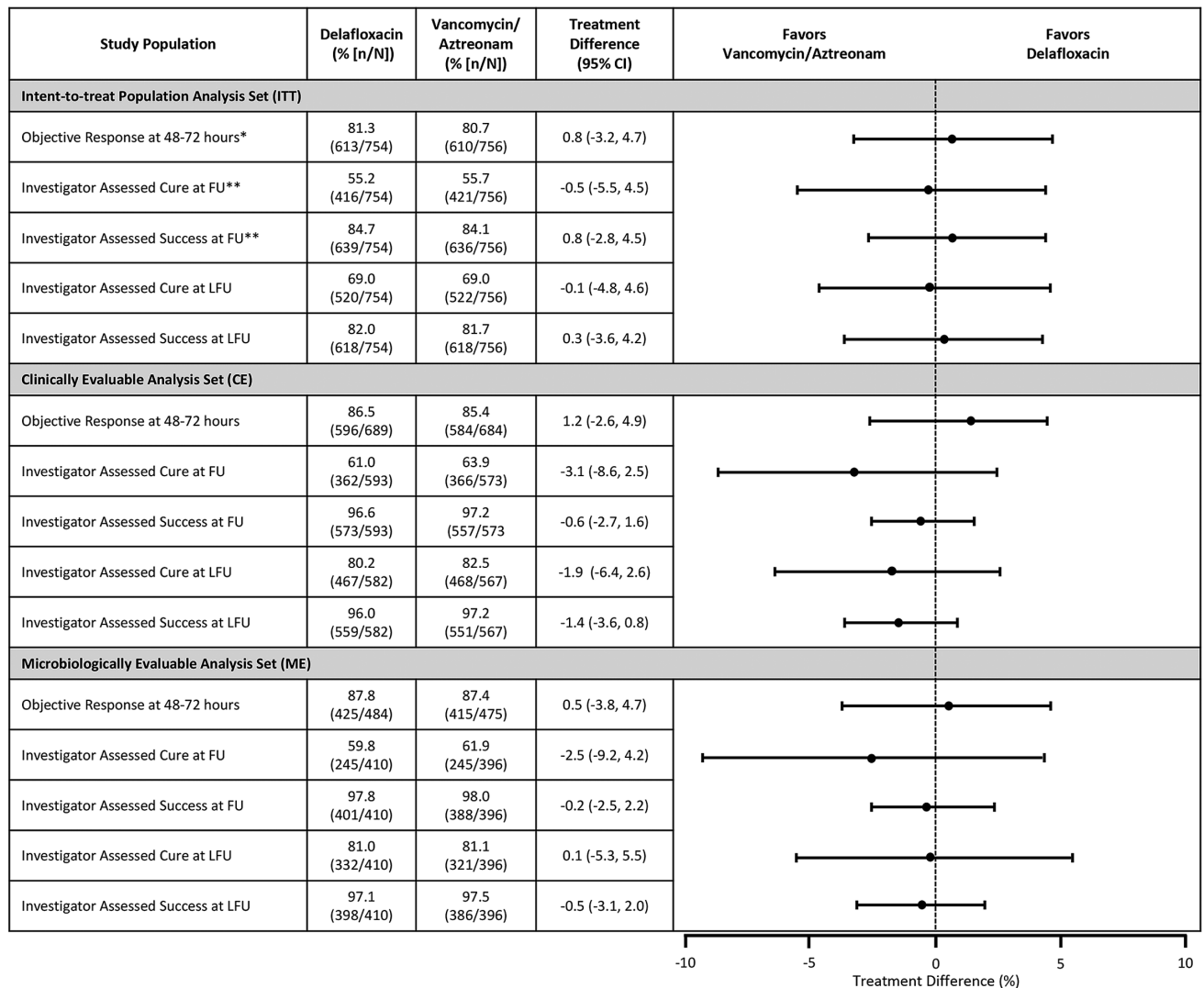
An analysis of the primary endpoint of OR at 48–72 hours after initiation of therapy showed delafloxacin to be noninferior to vancomycin/aztreonam in both pivotal studies, as well

Table 3. Demographics and Baseline Characteristics: Pooled Phase III Analysis Set

	Delafloxacin (n = 754)	Vancomycin + Aztreonam (n = 756)
Age categories (year), n (%)		
≤65	653 (86.6)	661 (87.4)
>65	101 (13.4)	95 (12.6)
Sex, n (%)		
Male	468 (62.1)	485 (64.2)
Female	286 (37.9)	271 (35.8)
Race, n (%)		
American Indian or Alaska Native	17 (2.3)	9 (1.2)
Asian	12 (1.6)	16 (2.1)
Black or African American	40 (5.3)	37 (4.9)
Native Hawaiian or Other Pacific Islander	3 (0.4)	4 (0.5)
White	645 (85.5)	659 (87.2)
Other	37 (4.9)	31 (4.1)
Ethnicity, n (%)		
Hispanic or Latino	233 (30.9)	202 (26.7)
Not Hispanic or Latino	521 (69.1)	554 (73.3)
Region, n (%)		
Asia	9 (1.2)	14 (1.9)
Europe	225 (30.4)	228 (30.4)
Latin America	46 (6.2)	43 (5.7)
North America	461 (62.2)	466 (62.1)
Weight (kg)		
Mean (SD)	85.4 (21.6)	85.8 (22.1)
Median	82.5	82.9
Min, Max	30.8, 198.5	43.8, 185.0
BMI ranges (kg/m²), n (%)		
BMI <30	414 (55.9)	445 (59.3)
BMI ≥30	327 (44.1)	306 (40.7)
Diabetes, n (%)		
Diabetes, n (%)	84 (11.3)	83 (11.1)
Baseline renal impairment, n (%)		
Baseline renal impairment, n (%)	121 (16.3)	121 (16.1)
Patients with history of hepatitis B or C, n (%)		
Patients with history of hepatitis B or C, n (%)	216 (29.1)	217 (28.9)

Abbreviations: BMI, body mass index; SD, standard deviation.

as in the combined dataset. In Study 302, the percentages of responders were 78.2% and 80.9% for delafloxacin and vancomycin/aztreonam, respectively (mean treatment difference -2.6, 95% CI -8.78 to 3.57). In Study 303, the response rates were 83.7% and 80.6% for delafloxacin and vancomycin/aztreonam, respectively (mean treatment difference 3.1%, 95% CI -2.0 to 8.3). In the combined dataset, response rates were 81.3% in the delafloxacin arm and 80.7% in the vancomycin/aztreonam arm (mean treatment difference 0.8, 95% CI -3.2 to 4.7; Figure 1). Results for objective response in the defined subgroups showed delafloxacin to be comparable to vancomycin/aztreonam across all subgroups, including those compared by age, gender, race, geographic region, ethnicity, presence of diabetes, baseline infection type, prior antibiotic use, bacteremia at baseline, baseline erythema area, target pathogen, geographic region, and surgical procedure up to 72 hours from first dose (Table 4).



* Primary endpoint. ** The primary efficacy endpoint for the EMA submission, and a secondary efficacy endpoint for the FDA submission
Cure = no remaining signs and symptoms; Improved = some remaining signs and symptoms but no further antibiotics required; Success = Cure + Improved
Intent-to-treat (ITT; all patients randomized) ; Clinically evaluable (CE; patients who completed activities as defined in the protocol) ; Microbiologically evaluable (ME; CE patients with eligible pathogen)
MRSA, Methicillin Resistant *Staphylococcus aureus*.
Confidence intervals are calculated using Miettinen and Nurminen method without stratification for individual studies and stratified by studies for Pool 1 analysis.

Figure 1. Objective response and investigator-assessed response at follow-up and late follow-up. Pooled Phase III data set. Abbreviations: CI, confidence interval; EMA, European Medicines Agency; FDA, Food and Drug Administration; FU, follow-up; LFU, late follow-up.

Investigator-assessed Response

Secondary outcomes included the investigator-assessed response of signs and symptoms of infection at FU in the ITT population. Results for each of the 2 pivotal Phase III studies were similar, where Study 302 used delafloxacin IV only and Study 303 required a switch from IV to oral dosing. Combined, for the ITT analysis set in the pooled data, the proportion of patients who were cured at the FU visit was similar between the 2 treatment groups. In the delafloxacin treatment group, 416 of 754 patients (55.2%) were classified as cured at the FU visit. In the vancomycin/aztreonam treatment group, 421 of 756 patients (55.7%) were classified as cured. Clinical success (cure + improved) occurred in 84.7% of the delafloxacin group

and 84.1% in the vancomycin/aztreonam group at the FU visit. Similar results were observed at the LFU visit. Delafloxacin was comparable to vancomycin/aztreonam for these outcomes in the MITT, CE, and ME analysis sets (Figure 1).

Analyses of investigator-assessed outcomes at FU and LFU were completed in the ITT and CE analysis sets, in subgroups based on the BMI, presence of diabetes, or presence of renal impairment. Results were similar to those observed in the larger populations and were similar between treatment groups (Figure 2).

Microbiological Response

In the pooled ME analysis set, 401 of 410 patients (97.8%) in the delafloxacin treatment group had a microbiological response of

Table 4. Objective Responder at 48–72 Hours by Subgroup: Pooled Phase III Intent to Treat Analysis Set

Subpopulation	Delafloxacin	Vancomycin/Aztreonam
	(n = 754)	(n = 756)
	[n/N1 (%)] ^a	[n/N1 (%)] ^a
Age		
≤65	538/653 (82.4)	543/661 (82.1)
>65	75/101 (74.3)	67/95 (70.5)
Gender		
Male	381/468 (81.4)	397/485 (81.9)
Female	232/286 (81.1)	213/271 (78.6)
Ethnicity, N1		
Hispanic or Latino, n/N1 (%)	201/233 (86.3)	170/202 (84.2)
Not Hispanic or Latino	412/521 (79.1)	440/554 (79.4)
Race		
American Indian or Alaska Native	13/17 (76.5)	9/9 (100.0)
Asian	6/12 (50.0)	11/16 (68.8)
Black or African American	32/40 (80.0)	33/37 (89.2)
Native Hawaiian or Other Pacific Islander	3/3 (100.0)	2/4 (50.0)
White	530/645 (82.2)	537/659 (81.5)
Other	29/37 (78.4)	18/31 (58.1)
Region, n (%)		
Asia	4/9 (44.4)	9/14 (64.3)
Europe	178/228 (78.1)	174/228 (76.3)
Latin America	38/47 (80.9)	31/44 (70.5)
North America	393/473 (83.6)	396/470 (84.3)
Diabetes		
Yes	63/83 (75.9)	63/81 (77.8)
No	550/671 (82.0)	547/675 (81.0)
Baseline infection type		
Abscess	166/190 (87.4)	165/189 (87.3)
Cellulitis/Erysipelas	244/330 (73.9)	246/334 (73.7)
Wound	198/227 (87.2)	196/228 (86.0)
Burn	5/7 (71.4)	3/5 (60.0)
Prior antibiotic use		
Yes	104/141 (73.8)	142/182 (78.0)
No	509/613 (83.0)	468/574 (81.5)
Bacteremia at baseline		
Yes	12/17 (70.6)	10/17 (58.8)
No	601/737 (81.5)	600/739 (81.2)
Baseline erythema area^b		
Quartile 1	164/188 (87.2)	164/186 (88.2)
Quartile 2	152/184 (82.6)	157/190 (82.6)
Quartile 3	164/196 (83.7)	142/178 (79.8)
Quartile 4	133/175 (76.0)	147/199 (73.9)
Surgical procedure ≤72 hours from start of study drug		
With surgical procedure	35/45 (77.8)	37/48 (77.1)
Without surgical procedure	578/709 (81.5)	573/708 (80.9)

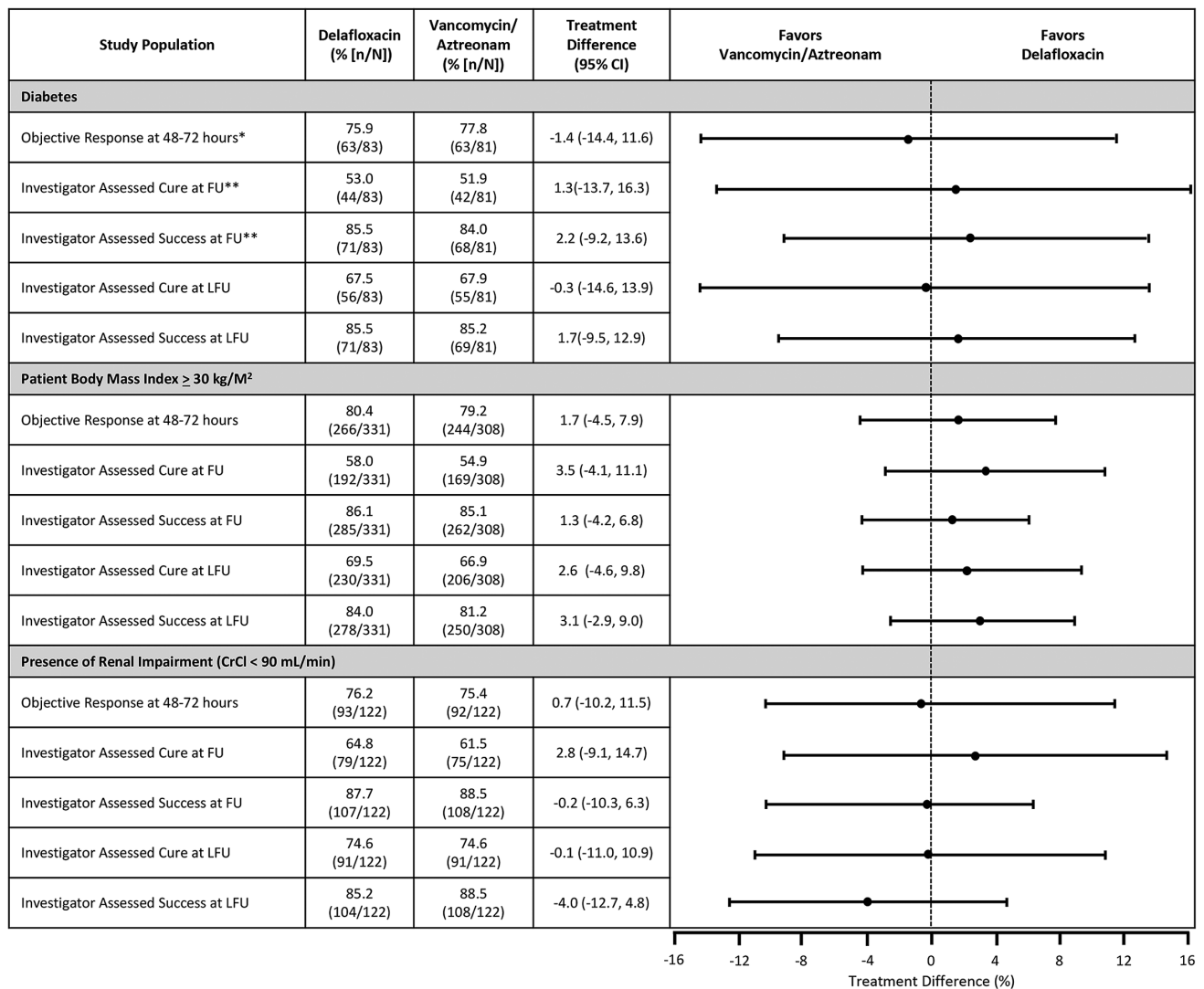
Results are based on data closest to and through 72 hours within a window of 48–72 hours (+/- 2 hour window for each visit).

^aN1 = number of intent-to-treat patients in each subgroup.

^bOnly subjects with baseline erythema area information were included. Baseline erythema size is defined as area of erythema from the digital planimetry prior/closest to first dose. The total baseline erythema size is divided into quartiles, with quartile 1 0–25%, quartile 2 > 25–50%, quartile 3 > 50–75%, and quartile 4 > 75–100%. Quartiles were calculated for individual studies and pool analysis respectively.

eradicated at the FU visit, whereas in the vancomycin/aztreonam treatment group, 388 of 396 patients (98.0%) had a microbiological response of eradicated at the FU visit. At the LFU visit, 397 of 410 patients (96.8%) in the delafloxacin treatment

group had a microbiological response of eradicated, versus 386 of 396 patients (97.5%) in the vancomycin/aztreonam group. Microbiological success rates by baseline pathogen were similar between patients in the delafloxacin and vancomycin/



Cure = no remaining signs and symptoms; Improved = some remaining signs and symptoms but no further antibiotics required; Success = Cure + Improved
 Intent-to-treat (ITT; all patients randomized)
 MRSA, Methicillin Resistant *Staphylococcus aureus*.
 Confidence intervals are calculated using Miettinen and Nurminen method without stratification for individual studies and stratified by studies for Pool 1 analysis.

Figure 2. Pooled Phase III data sub-populations: diabetes, body mass index, and renal impairment. Objective response and investigator-assessed response at follow-up and late follow-up in intent-to-treat population. Abbreviations: CI, confidence interval; FU, follow-up; LFU, late follow-up.

aztreonam treatment groups at the FU and LFU visits for the ME analysis set (Table 5).

Monomicrobial and Polymicrobial Infections

When the microbiologic responses at FU for target pathogens by monomicrobial status were examined, response rates for delafloxacin and vancomycin/aztreonam, respectively, were 97.4% and 98.1% (mean treatment difference -0.8, 95% CI -3.9 to 2.3) for gram-positive and 93.8% and 96.2% (mean treatment difference -5.1, 95% CI -26.3 to 16.1) for gram-negative pathogens. When the microbiologic response at FU for target pathogens by mixed gram-positive and gram-negative polymicrobial status were examined, response rates for delafloxacin

and vancomycin/aztreonam were 100% and 98.1% (mean treatment difference 2.4, 95% CI -7.0 to 11.8), respectively, for all target pathogens.

Safety

Delafloxacin was well tolerated at the 300 mg IV and 450 mg oral doses in adult patients with ABSSSI. The most commonly reported adverse events for delafloxacin in clinical studies have been diarrhea, nausea, vomiting, and headaches. The rate of adverse events commonly associated with fluoroquinolones does not appear to be increased with delafloxacin and, generally, occurred less frequently among delafloxacin-treated patients than in comparator groups. The safety of delafloxacin

Table 5. Per-pathogen Microbiological Response Rate at Follow-up: Microbiologically Evaluable Population

n/N1 ^b	Per-pathogen Microbiological Response (Documented or Presumed Eradication) ^a ME at FU Analysis Set	
	Delafloxacin (n = 410)	Vancomycin + Aztreonam (n = 396)
<i>S. aureus</i>	244/248 (98.4%)	233/239 (97.5%)
MRSA	106/108 (98.1%)	97/99 (98.0%)
MSSA	140/142 (98.6%)	136/140 (97.1%)
<i>S. anginosus</i> ^c	47/47 (100.0%)	34/35 (97.1%)
<i>S. pyogenes</i>	18/19 (94.7%)	15/15 (100.0%)
<i>K. pneumoniae</i>	17/17 (100.0%)	17/17 (100.0%)
<i>P. aeruginosa</i>	11/11 (100.0%)	10/10 (100.0%)
<i>E. coli</i>	11/11 (100.0%)	16/17 (94.1%)
<i>S. haemolyticus</i>	12/12 (100%)	7/7 (100%)
<i>E. cloacae</i>	11/12 (91.7%)	9/10 (90.0%)
<i>S. agalactiae</i>	11/11 (100%)	11/12 (91.7%)
<i>E. faecalis</i>	9/10 (90.0%)	12/13 (92.3%)
<i>S. lugdunensis</i>	10/10 (100%)	7/7 (100%)

If the same pathogen is identified from both the blood and the culture of the ABSSSI, it is counted only once in the summary. Patients with both MRSA and MSSA at baseline are included once in the overall *Staphylococcus aureus* category. The overall count of patients with *Staphylococcus aureus* includes patients whose isolates were not tested for susceptibility and, therefore, do not contribute to either the MRSA or MSSA counts.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; FU, follow-up; ME, microbiologically evaluable; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

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

^bN1 = number of patients who have the given target pathogen at baseline from the ABSSSI or blood culture; n = success, which is defined as documented or presumed eradication.

^cThe *Staphylococcus anginosus* group includes *S. anginosus*, *S. intermedius*, and *S. constellatus*.

is addressed more completely in a separate safety paper in this supplement.

DISCUSSION

Delafloxacin is both structurally and clinically different from other fluoroquinolones. Chemically distinct in its size, shape, and charge profile, its anionic structure has been shown to improve potency, particularly against gram-positive pathogens, in acidic environments typical of ABSSSI [31, 32]. Clinically, it is indicated for the treatment of adult patients with ABSSSI from both gram-positive and gram-negative infections, is the only fluoroquinolone to have an indication for MRSA, and is available in both IV and oral formulations.

The delafloxacin ABSSSI Phase III program consisted of 2 randomized, double-blind, controlled, Phase III studies using delafloxacin at 300 mg IV/450 mg orally Q12 h fixed-dose monotherapy, compared to the IV combination of vancomycin/aztreonam. These studies had near identical designs and methodologies and were well balanced between the treatment groups, based on baseline stratification factors and enrollment criteria, regardless of type of infection, age, gender, race, BMI, lesion size, and severity of illness. Overall, IV/oral delafloxacin

fixed-dose monotherapy was comparable to IV vancomycin/aztreonam combination therapy in each Phase III study, as well as in the pooled analysis, regardless of endpoint or analysis population.

The types of patients enrolled in the delafloxacin clinical program mirror the challenging ABSSSI patient types that clinicians treat today. Even as overall hospitalizations for SSSI have increased over the years, admission for patients with no comorbidities decreased 37% between 2005 and 2011 [33]. At the same time, lengths of stay have decreased [34]. Patients are released from the hospital to receive IV antibiotics at home or in an outpatient infusion center, or are transitioned to oral therapy. Overall, in the ITT analysis set, 10.9% of patients had diabetes, 29.0% had vascular disease, and 9.7% had cardiac disease. Further, 196 patients were >65 years of age, including 83 patients who were >75 years. A total of 244 patients had renal impairment (creatinine clearance <90 ml/min, calculated by Cockcroft-Gault formula). These types of patients may benefit from the IV to oral formulation that delafloxacin offers.

Approximately 40% of those enrolled were obese patients, which make up a population that acts as natural aggregators of comorbidities. The association between obesity and infectious disease risk factors, such as wound complications, surgical-site infections, and recurrence of skin infections due to MRSA, have been noted. Obesity is also a predictor of poor outcomes, including increased treatment costs, and obese patients have higher rates of ABSSSI-related 30-day readmission than non-obese patients [33–42]. The analysis of outcome data by BMI is particularly important, as the management and treatment of infections in obese patients pose additional challenges to physicians and pharmacists [41]. Delafloxacin, administered at the standard dose of 300 mg every 12 hours IV and oral delafloxacin 450 mg every 12 hours, was found to be non-inferior to vancomycin/aztreonam, with vancomycin dosed to 15 mg/kg based upon actual body weight, and to provide good outcomes in obese patients (BMI ≥ 30 kg/m²), potentially simplifying dosing in this patient population. In contrast to vancomycin, delafloxacin does not require weight-based dosing or drug monitoring.

Especially in complicated patient populations, clinicians must be attuned to those specific patient risk factors that lead to the consideration of gram-negative coverage. These risk factors include comorbidities, such as diabetes, surgical site infections, compromised vascular perfusion, and anal and perianal region infections, and severity of illness, as well as the local antibiogram [16, 19, 38]. Compared with patients infected with gram-positive pathogens, those with mixed or gram-negative infections have longer lengths of stay, greater mortality, and higher total costs.^{34,21} Currently, there is no reliable method for determining the causative pathogen at the time antibiotics are initiated and therapy must be empiric until cultures determine the species and its resistance profile [17]. In these situations, antibiotics whose spectrum of activity is limited to gram-positive

pathogens must be used in combination with compounds that provide coverage for gram-negative pathogens [43]. The overall response rates for delafloxacin for subjects with pathogens in monomicrobial gram-positive, monomicrobial gram-negative, polymicrobial gram-positive, and polymicrobial gram-negative infections in the pooled data were high. These findings are consistent with the broad spectrum of activity for delafloxacin, allowing for a monotherapy option for the treatment of ABSSSI in these patient types.

The rise of resistance to fluoroquinolones has recently limited their use. Delafloxacin has been shown to be 32-fold more active than levofloxacin against MRSA isolates, including levofloxacin-resistant strains. This increased potency is thought to be due to its structure-activity relationship, with a large N-1 substitution and weakly polar C-8 group that impacts the potency against quinolone-resistant gram-positive bacteria. Further, the basicity at C-7 increases potency at acidic environments typical of ABSSSIs. Delafloxacin has also demonstrated a low propensity for the development of resistance in MRSA strains, with frequency rates ranging from 10^{-9} to 10^{-11} . In the ME at FU for the 2 global Phase III studies, *S. aureus* isolates were eradicated or presumed eradicated in 98.4% (245/249) of delafloxacin-treated patients. Similar eradication rates were observed with levofloxacin–non-susceptible *S. aureus* isolates (80/81; 98.8%) and MRSA isolates (70/71; 98.6%).²⁷ Regardless, basic stewardship principles should be applied to the use of any antibiotic.

Limitations to the studies that were pooled for this analysis include a low number of burn and surgical wounds, as well as a low number of gram-negative infections, limited by use of the current ABSSSI definition. By excluding some infections that are more likely to be caused by gram-negative pathogens, such as those following animal or human bites, diabetic foot infections, and decubitus ulcers, the definition favors the enrollment of gram-positive infections in studies. Another limitation is that the rate of patients with diabetes enrolled in the study was lower than that of the general population. Due to limitations on vancomycin dosing and infusion time and, thus, blinding, patient weight was limited to a maximum of 140 kg in Study 302 and 200 kg in Study 303. Finally, relative to the general population, the number of older adults and non-Whites were lower.

CONCLUSION

Ultimately, new culture techniques and point-of-care diagnostics may be able to better target antibiotic therapy but, at this point, initial empiric therapy remains the standard of care for ABSSSI [17]. Particularly in sicker patients, where a delay in broad-spectrum coverage could lead to poor outcomes, clinicians must use an individualized approach to each patient, based upon comorbidities and risk factors, in establishing the optimal antimicrobial treatment regimen. Culture and susceptibility testing should be used to attempt to identify the

pathogens, thus allowing for appropriate de-escalation of antibiotic therapy based on antibiotic stewardship standards.

Delafloxacin possesses gram-positive/MRSA and gram-negative activity, thus providing coverage for the most important ABSSSI pathogens. It offers the flexibility of fixed-dose IV and oral treatment of ABSSSI, and does not require therapeutic drug monitoring. These features, in concert with its favorable safety profile, support delafloxacin as an option in the ABSSSI armamentarium.

Notes

Supplement sponsorship. This supplement is sponsored by Melinta Therapeutics, Inc.

Potential conflicts of interest. P. G. has received consulting fees from Melinta, Nabriva, Cemptra, and Paratek. S. C. is an employee of Melinta Therapeutics. J. M. P. reports potential conflicts. 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.

References

1. Eckmann C, Dryden M. Treatment of complicated skin and soft-tissue infections caused by resistant bacteria: value of linezolid, tigecycline, daptomycin and vancomycin. *Eur J Med Res* **2010**; 15:554–63.
2. Esposito S, Bassetti M, Concia E, et al; Italian Society of Infectious and Tropical Diseases. Diagnosis and management of skin and soft-tissue infections (SSTI). A literature review and consensus statement: an update. *J Chemother* **2017**; 29:197–214.
3. Pulido-Cejudo A, Guzmán-Gutierrez M, Jalife-Montaña A, et al. Management of acute bacterial skin and skin structure infections with a focus on patients at high risk of treatment failure. *Ther Adv Infect Dis* **2017**; 4:143–61.
4. Zervos MJ, Freeman K, Vo L, et al. Epidemiology and outcomes of complicated skin and soft tissue infections in hospitalized patients. *J Clin Microbiol* **2012**; 50:238–45.
5. Edelsberg J, Taneja C, Zervos M, et al. Trends in US hospital admissions for skin and soft tissue infections. *Emerg Infect Dis* **2009**; 15:1516–8.
6. Levit K, Wier L, Stranges L, Ryan K, Elixhauser A. HCUP facts and figures: statistics on hospital-based care in the United States. Rockville, MD: Agency for Healthcare Research and Quality, **2007**. Available at: http://www.hcup-us.ahrq.gov/reports/factsandfigures/2007pdfs/FF_report_2007.pdf.
7. Lipsky BA, Napolitano LM, Moran GJ, et al. Economic outcomes of inappropriate initial antibiotic treatment for complicated skin and soft tissue infections: a multicenter prospective observational study. *Diagn Microbiol Infect Dis* **2014**; 79:273–9.
8. Pollack CV Jr, Amin A, Ford WT Jr, et al. Acute bacterial skin and skin structure infections (ABSSSI): practice guidelines for management and care transitions in the emergency department and hospital. *J Emerg Med* **2015**; 48:508–19.
9. Sulham K, LaPensee KT, Fan W, et al. Severity and costs of acute bacterial skin and skin structure infections by treatment setting: an application of the Eron classification to a real-world database. In: Program and abstracts of the International Society for Pharmacoeconomics and Outcomes Research 19th Annual International Meeting (Montreal, Canada). **2014**.
10. Ektare V, Khachatryan A, Xue M, Dunne M, Johnson K, Stephens J. Assessing the economic value of avoiding hospital admissions by shifting the management of gram+ acute bacterial skin and skin-structure infections to an outpatient care setting. *J Med Econ* **2015**; 18:1092–101.
11. Barie PS, Wilson SE. Impact of evolving epidemiology on treatments for complicated skin and skin structure infections: the surgical perspective. *J Am Coll Surg* **2015**; 220:105–116.e6.
12. US Food and Drug Administration. Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, **2013**.
13. Engel C, Brunkhorst FM, Bone HG, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. *Intensive Care Med* **2007**; 33:606–18.
14. Stevens DL, Bisno AL, Chambers HF, et al; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis* **2005**; 41:1373–406.

15. Stevens DL, Bisno AL, Chambers HF, et al; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* **2014**; 59:e10–52.
16. Zilberberg MD, Shorr AF, Micek ST, et al. Epidemiology and outcomes of hospitalizations with complicated skin and skin-structure infections: implications of healthcare-associated infection risk factors. *Infect Control Hosp Epidemiol* **2009**; 30:1203–10.
17. Guillaumet CV, Kollef MH. How to stratify patients at risk for resistant bugs in skin and soft tissue infections? *Curr Opin Infect Dis* **2016**; 29:116–23.
18. Lipsky BA, Moran GJ, Napolitano LM, Vo L, Nicholson S, Kim M. A prospective, multicenter, observational study of complicated skin and soft tissue infections in hospitalized patients: clinical characteristics, medical treatment, and outcomes. *BMC Infect Dis* **2012**; 12:227.
19. Lipsky BA, Napolitano LM, Moran GJ, Vo L, Nicholson S, Kim M. Inappropriate initial antibiotic treatment for complicated skin and soft tissue infections in hospitalized patients: incidence and associated factors. *Diagn Microbiol Infect Dis* **2014**; 79:273–9.
20. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillaumet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in gram-negative severe sepsis and septic shock: a retrospective cohort study. *Crit Care* **2014**; 18:596.
21. Edelsberg J, Berger A, Weber DJ, Mallick R, Kuznik A, Oster G. Clinical and economic consequences of failure of initial antibiotic therapy for hospitalized patients with complicated skin and skin-structure infections. *Infect Control Hosp Epidemiol* **2008**; 29:160–9.
22. Bisacchi GS. Origins of the quinolone class of antibacterials: an expanded “discovery story.” *J Med Chem* **2015**; 58:4874–82.
23. Aldred KJ, Kerns RJ, Osheroff N. Mechanism of quinolone action and resistance. *Biochemistry* **2014**; 53:1565–74.
24. Hooper DC, Jacoby GA. Mechanisms of drug resistance: quinolone resistance. *Ann NY Acad Sci* **2015**; 1354:12–31.
25. Giordano P, Weber K, Gesin G, Kubert J. Skin and skin structure infections: treatment with newer generation fluoroquinolones. *Ther Clin Risk Manag* **2007**; 3:309–17.
26. Pullman j, Gardovskis J, Farley B, et al. Efficacy and safety of delafloxacin compared with vancomycin plus aztreonam for acute bacterial skin and skin structure infections: a Phase 3, double-blind, randomized study. *J Antimicrob Chemother* **2017**; 72:3471–80.
27. McCurdy S, Lawrence L, Quintas M, et al. In vitro activity of delafloxacin and microbiological response against fluoroquinolone-susceptible and nonsusceptible *Staphylococcus aureus* isolates from two Phase 3 studies of acute bacterial skin and skin structure infections. *Antimicrobial Agents Chemother* **2017**; 61:e00772–17.
28. O’Riordan W, Mehra P, Manos P, Kingsley J, Lawrence L, Cammarata S. A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. *Int J Infect Dis* **2015**; 30:67–73.
29. Kingsley J, Mehra P, Lawrence LE, et al. A randomized, double-blind, Phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin. *J Antimicrob Chemother* **2016**; 71:821–9.
30. O’Riordan W, McManus A, Teras J, et al. 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. *Clin Infect Dis* **2018**; 67:657–66.
31. Lemaire S, Tulkens PM, Van Bambeke F. Contrasting effects of acidic pH on the extracellular and intracellular activities of the anti-gram-positive fluoroquinolones moxifloxacin and delafloxacin against *Staphylococcus aureus*. *Antimicrob Agents Chemother* **2011**; 55:649–58.
32. Van Bambeke F. Delafloxacin, a non-zwitterionic fluoroquinolone in Phase III of clinical development: evaluation of its pharmacology, pharmacokinetics, pharmacodynamics and clinical efficacy. *Future Microbiol* **2015**; 10:1111–23.
33. Mehrabi A, Fonouni H, Wente M, et al. Wound complications following kidney and liver transplantation. *Clin Transplant* **2006**; 20(Suppl 17):97–110.
34. Kaye KS, Patel DA, Stephens JM, Khachatryan A, Patel A, Johnson K. Rising United States hospital admissions for acute bacterial skin and skin structure infections: recent trends and economic impact. *PLOS One* **2015**; 10:e0143276.
35. Wiseman JT, Fernandes-Taylor S, Barnes ML, et al. Predictors of surgical site infection after hospital discharge in patients undergoing major vascular surgery. *J Vasc Surg* **2015**; 62:1023–31.e5.
36. Huttunen R, Karppelin M, Syrjänen J. Obesity and nosocomial infections. *J Hosp Infect* **2013**; 85:8–16.
37. Sreeramou P, Porbandarwalla NS, Arango J, et al. Recurrent skin and soft tissue infections due to methicillin-resistant *Staphylococcus aureus* requiring operative debridement. *Am J Surg* **2011**; 201:216–20.
38. Carratalà J, Rosón B, Fernández-Sabé N, et al. Factors associated with complications and mortality in adult patients hospitalized for infectious cellulitis. *Eur J Clin Microbiol Infect Dis* **2003**; 22:151–7.
39. Halilovic J, Heintz BH, Brown J. Risk factors for clinical failure in patients hospitalized with cellulitis and cutaneous abscess. *J Infect* **2012**; 65:128–34.
40. Huttunen R, Syrjänen J. Obesity and the risk and outcome of infection. *Int J Obes* **2013**; 37:333–40.
41. Ayyagari R, Revol C, Tang W, Faust E, Tuttle EG. Association of obesity with 30-day readmission rates among patients hospitalized with acute bacterial skin and skin-structure infections (ABSSSI). In: Program and abstracts of the International Society for Pharmacoeconomics 20th Annual International Meeting (Philadelphia, PA). **2015**.
42. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. *Pharmacotherapy* **2007**; 27:1081–91.
43. Zilberberg MD, Shorr AF, Micek ST, et al. Hospitalizations with healthcare-associated complicated skin and skin structure infections: impact of inappropriate empiric therapy on outcomes. *J Hosp Med* **2010**; 5:535–40.