

DELAFLOXACIN (DLX) IS EFFECTIVE AND WELL-TOLERATED IN TREATMENT OF OBESE PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) VERSUS VANCOMYCIN/AZTREONAM (VAN/AZ)

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ABSTRACT

Background: DLX, an investigational anionic fluoroquinolone antibiotic with activity against Gram-positive and Gram-negative pathogens, including MRSA, is in development for treatment of ABSSSI. Two global phase 3 ABSSSI trials (studies 302 and 303) included obese patients (BMI ≥30kg/m²).

Methods: Two multicenter, double-blind, double-dummy trials of adults with ABSSSI randomized patients 1:1 to receive either DLX monotherapy or VAN 15 mg/kg (actual body weight) with AZ for 5 – 14 days. Study 302 used DLX 300 mg BID IV only; study 303 used DLX 300 mg BID IV for 3 days with a mandatory blinded switch to DLX 450 mg oral BID. Key endpoints were objective response at 48-72 hours with ≥20% reduction in lesion size and investigator assessment of outcome based on resolution of signs and symptoms at Follow-up (FU day 14±1) and Late Follow-up (LFU day 21-28).

Results: In the 2 studies, 639 obese patients were randomized in US, Europe, Latin America and Asia. 56% were male with mean age 51 yrs. Average erythema area at baseline was 408 cm². 55% had cellulitis, 22% abscesses, 23% wound and 1% burn infections. 53% of patients had *S. aureus*, with over 1/3 being MRSA. Patients were treated for a median of 6 days. Key endpoints are shown below:

Key Endpoints	DLX n/Total (%)	VAN/AZ n/Total (%)	DLX – VAN/AZ (95% CI) stratified by study
Objective response 48 – 72h (ITT)	266/331 (80.4)	244/308 (79.2)	1.7 (-4.5, 7.9)
Investigator-Assessed Success (FU ITT)	285/331 (86.1)	262/308 (85.1)	1.3 (-4.2, 6.8)
Investigator-Assessed Success (LFU ITT)	278/331 (84.0)	250/308 (81.2)	3.1 (-2.9, 9.0)
Micro Success (FU ME) for <i>S. aureus</i>	99/101 (98.0)	64/69 (92.8)	8.4 (0.6, 16.2)
Micro Success (FU ME) for MRSA	40/40 (100.00)	19/21 (90.5)	15.4 (-1.2, 32.0)

The overall % of patients with at least one treatment-emergent adverse event (TEAE) was comparable for DLX (44.3%) compared to VAN/AZ (42.8%). The most frequent TEAEs were gastrointestinal in nature including diarrhea seen in 6.1% of DLX and nausea seen in 4.6% of VAN/AZ patients, which were primarily mild to moderate in severity. There was one case of *C. difficile* diarrhea. Discontinuations due to treatment-related AEs were lower with DLX (0.6%) compared to VAN/AZ (2%).

Conclusion: Fixed dose DLX monotherapy was comparable to VAN/AZ combination therapy in treatment of ABSSSI in obese patients based on the early objective response as well as investigator-assessed response at FU and LFU. DLX was also comparable to VAN/AZ in treating patients with *S. aureus*. DLX appears effective and well tolerated in obese patients with ABSSSI.

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INTRODUCTION

Delafloxacin (DLX) is an investigational anionic fluoroquinolone antibiotic which is being studied in treatment of acute bacterial skin and skin structure infections (ABSSSIs). DLX has excellent *in vitro* activity against Gram-positive organisms including Methicillin-resistant *Staphylococcus aureus* (MRSA) while retaining good activity against gram-negative organisms.¹

We conducted two multicenter, double-blind, double-dummy trials (302² and 303³) comparing the efficacy and safety of IV/oral DLX monotherapy to that of IV VAN/AZ combination therapy in patients with ABSSSIs caused by both Gram-positive and Gram-negative pathogens. Key endpoints included both those mandated by both the FDA⁴ (objective response at 48-72 hours) and EMA⁵ (investigator assessments of response).

Obesity is an established risk factor for antibiotic treatment failure⁶; however, there are limited data on correct dosing recommendations in obese patients⁷. The correct dosing of vancomycin in obese patients is still not clear⁸. Simpler treatment options are needed for these patients.

MATERIALS AND METHODS

Study Design:

- Randomized, double-blind, Phase 3, multicenter studies of IV/oral DLX vs IV VAN/AZ in patients with ABSSSI, including wounds, burns, major abscesses, or cellulitis ≥75 cm² in size and ≥2 systemic signs of infection;
- Patients were randomly assigned (1:1) to receive DLX monotherapy or VAN 15 mg/kg (actual body weight) IV q12h with AZ 1-2 g IV q12h for 5-14 days at the investigators' discretion; aztreonam was discontinued in VAN arm once cultures confirmed no Gram-negative pathogens;
- In study 302, the DLX dose was 300 mg IV BID for the full course; in study 303, subjects received DLX 300 mg IV BID for 3 days followed by a mandatory blinded switch to DLX 450 mg PO BID;
- Patients were evaluated at screening, daily on therapy, FU (Day 14±1), and LFU (Day 21-28);
- Efficacy was evaluated through assessments of signs and symptoms; digital planimetry measurement of lesion size; and culture and susceptibility testing of bacterial isolates;
- Enrollment was stratified by baseline infection type and prior antibiotic use in study 302 and also by BMI in study 303;
- Patients were limited to 140kg in study 302 and 200kg in study 303, due to the limitations of IV blinding and vancomycin volume as well as infusion times.

Endpoints

- Primary endpoint for FDA: proportion of patients achieving an objective response at 48-72 hours after start of treatment, defined as ≥20% decrease in lesion size with no further antibiotics, major procedures, or death in the ITT population;
- Key endpoint for EMA: investigator-assessed response based on complete or near resolution of signs and symptoms (Cure + Improved = Success) at FU (Day 14±1) and LFU (Day 21 to 28);
- Additional efficacy endpoint: Microbiological response (documented or presumed eradication) for patients in the ME and MITT analysis sets were based on results of baseline and post-baseline cultures (FU) and susceptibility testing, together with the clinical response assigned by investigators;
- Safety: adverse events (AE), vital signs and body temperature measurements, clinical laboratory test abnormalities, physical examination findings, concomitant medications, and ECGs (if clinically indicated).

Statistical Analysis

- For the key endpoints, a 2-sided 95% confidence interval (CI) for noninferiority testing was computed based on difference in responder rates for DLX and VAN/AZ at 48-72 hours (±2) after initiation of treatment as well as the investigator response at FU and LFU; DLX was noninferior to VAN/AZ for ABSSSIs if lower limit of 2-sided 95% CI exceeded –0.10.

Analysis Populations

- ITT: all patients randomized; Microbiological ITT: ITT patients with eligible pathogen; Clinically evaluable (CE): patients completing protocol; Microbiologically evaluable (ME): CE patients with eligible pathogen.

RESULTS

As shown in Table 1, in the two pivotal trials overall, DLX was comparable to VAN/AZ in treatment of ABSSSI patients.^{2,3}

TABLE 1: OVERALL OUTCOMES IN STUDIES 302 AND 303.

Overall	STUDY 302			STUDY 303		
	DLX n/Total (%)	VAN/AZ n/Total (%)	Delta (95% CI)	DLX n/Total (%)	VAN/AZ n/Total (%)	Delta (95% CI)
Objective response 48-72h (ITT)	259/331 (78.2)	266/329 (80.9)	-2.6 (-8.8, 3.6)	354/423 (83.7)	344/427 (80.6)	3.1 (-2.0, 8.3)
Investigator-Assessed Success (FU ITT)	270/331 (81.6)	274/329 (83.3)	-1.7 (-7.6, 4.1)	369/423 (87.2)	362/427 (84.8)	2.5 (-2.2, 7.2)
Investigator-Assessed Success (LFU ITT)	265/331 (80.1)	267/329 (81.2)	-1.1 (-7.2, 5.0)	353/423 (83.5)	351/427 (82.2)	1.3 (-3.8, 6.3)
Micro Success (FU ME) for MRSA	58/58 (100)	65/66 (98.5)	1.5 (-4.8, 8.1)	48/50 (96.0)	32/33 (97.0)	-1.0 (-11, 11.8)

Difference = Difference in responder rates (Delafloxacin treatment group minus vancomycin + aztreonam treatment group). Confidence intervals are calculated using Miettinen and Nurminen method.

TABLE 2: SUMMARY OF PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF ABSSSIs. ITT ANALYSIS SET. OBESE PATIENTS, POOLED PHASE 3.

Characteristic	DLX (N=331)	VAN/AZ (N=308)
BMI, mean (SD)	35.7 (5.75)	36.1 (6.26)
Age, years		
Mean (SD)	51.8 (14.80)	51.2 (14.43)
Median (min, max)	52.0 (18, 89)	51.0 (22, 90)
Sex, n (%)		
Male	180 (54.4)	180 (58.4)
Female	151 (45.6)	128 (41.6)
Race, n (%)		
American Indian or Native American	7 (2.1)	5 (1.6)
Asian	3 (0.9)	1 (0.3)
Black	17 (5.1)	14 (4.5)
Native Hawaiian or other Pacific Islander	--	1 (0.3)
White	287 (86.7)	274 (89.0)
Other	17 (5.1)	13 (4.2)
Region		
Europe	148 (44.7)	142 (46.1)
North America	159 (48.0)	142 (46.1)
Asia	1 (0.3)	1 (0.3)
Latin America	23 (6.9)	23 (7.5)
Received antibiotics in the 14 days prior to enrollment	77 (23.3)	79 (25.6)
Baseline infection type, n (%)		
Cellulitis/erysipelas	150 (35.5)	161 (35.9)
Wound infection	149 (35.2)	162 (36.2)
Major cutaneous abscess	120 (28.4)	121 (27.0)
Burn infection	4 (0.9)	4 (0.9)
Patients with diabetes, n (%)	62 (18.7)	59 (19.2)
Bacteremia present, n (%)	8 (2.4)	7 (2.3)
Baseline erythema area (digital), cm ²		
Subjects	328	306
Mean (SD)	393.7 (369.29)	422.4 (445.99)

PATIENTS

Of the 1510 patients randomized in the two studies, 639 were obese (BMI ≥30 kg/m²) (42.3%). The median duration of exposure to study drug was 7 and 6.5 days in the DLX and VAN/AZ treatment arms, respectively. Those in the VAN/AZ received AZ for a mean of 3.2 days. Key demographic and clinical characteristics are shown in Table 2.

Eligible pathogens identified at baseline, from the site of infection and from blood, are presented in Table 3.

TABLE 3: BASELINE ELIGIBLE PATHOGENS. MITT ANALYSIS SET. OBESE PATIENTS, POOLED PHASE 3.

Organism ²	DLX (N = 91)	VAN/AZ (N = 78)
<i>Staphylococcus aureus</i>	120 (56.9%)	93 (48.7%)
MSSA	72 (34.1%)	60 (31.4%)
MRSA	49 (23.2%)	33 (17.3%)
<i>S. epidermidis</i>	17 (8.1%)	25 (13.1%)
<i>S. pyogenes</i>	6 (2.8%)	12 (6.3%)
<i>E. coli</i>	7 (3.3%)	9 (4.7%)
<i>E. faecalis</i>	4 (1.9%)	9 (4.7%)
<i>S. agalactiae</i>	8 (3.8%)	10 (5.2%)
<i>K. pneumoniae</i>	7 (3.3%)	9 (4.7%)
<i>E. cloacae</i>	6 (2.8%)	4 (2.1%)
<i>P. aeruginosa</i>	5 (2.4%)	9 (4.7%)

PRIMARY EFFICACY OUTCOME IN OBESE PATIENTS

In obese patients, DLX IV/oral was comparable to VAN/AZ in the primary endpoint. In addition, DLX IV/oral was comparable to VAN/AZ in the secondary endpoints of investigator-assessed response of success (Cure + Improved) at both FU and LFU (Table 4).

TABLE 4: CLINICAL EFFICACY OBESE PATIENTS, POOLED PHASE 3.

Endpoint	Analysis Set	DLX n/N (%)	VAN/AZ n/N (%)	Difference (95% CI)
Early Objective Response (48-72 hours)	ITT	266/331 (80.4)	244/308 (79.2)	1.7 (-4.5, 7.9)
	CE	259/309 (83.8)	231/281 (82.2)	2.2 (-3.9, 8.3)
Investigator-Assessed Response of Success at FU	ITT	285/331 (86.1)	262/308 (85.1)	1.3 (-4.2, 6.8)
	CE	305/312 (97.8)	330/337 (97.9)	-0.3 (-3.0, 2.5)
Investigator-Assessed Response of Success at LFU	ITT	278/331 (84.0)	250/308 (81.2)	3.1 (-2.9, 9.0)
	CE	308/315 (97.8)	335/341 (98.2)	-0.9 (-3.5, 1.7)

MICROBIOLOGIC EFFICACY OUTCOMES

- DLX was as effective as VAN/AZ against key ABSSSI pathogens like *S. aureus*, including MRSA, and against Gram-negative organisms as well (Table 5).

SAFETY IN OBESE PATIENTS

- The incidence of TEAEs was comparable in the two treatment arms, as was the incidence of drug-related TEAEs (Table 6).
- The incidence of serious adverse events (SAEs) was comparable in the two arms, and the majority of these events were considered unrelated to study therapy.
- GI events were the most common TEAE in both treatment arms (Table 7). There was one case of *C. difficile* diarrhea in the DLX arm, which was considered mild in severity. This occurred in a patient who had entered the trial as a prior treatment failure with prior antibiotics (Bactrim™/clindamycin).
- There were 3 AEs of renal failure in the VAN/AZ group, none in the DLX group.
- There were no significant differences in laboratory values between the two treatment groups during the study including liver or glucose measures.
- There were no reports of cases meeting the Hy's law definition in DLX-treated patients.

TABLE 6: OVERALL SUMMARY OF ADVERSE EVENTS. SAFETY ANALYSIS SET. OBESE PATIENTS, POOLED PHASE 3.

	DLX (N=327)	VAN/AZ (N=306)
Any TEAE	145 (44.3%)	131 (42.8%)
TEAE related to study drug	74 (22.6%)	73 (23.9%)
TEAE with moderate or severe intensity	64 (19.6%)	60 (19.6%)
Any TEAE leading to premature study drug DC	6 (1.8%)	9 (2.9%)
Any related TEAE leading to premature study drug DC	2 (0.6%)	6 (2.0%)
Any SAE related to study drug	2 (0.6%)	3 (1.0%)
Death	--	2 (0.7%)

CONCLUSION

DISCUSSION/CONCLUSIONS

- Obese patients are at risk for serious skin infections. However, the correct antibiotic dosing in these patients is often not clear. Patients are often inadequately dosed.
- In a population of obese patients, IV/oral monotherapy with DLX was as effective as the combination of IV VAN/AZ when used to treat ABSSSIs caused by both Gram-positive and Gram-negative organisms. DLX does not require weight-based dosing or therapeutic monitoring.
- IV/oral DLX monotherapy was comparable to IV VAN/AZ combination therapy for both the objective response (decrease in lesion size ≥20%) at 48-72 hours after initiation of study drug, and the investigator-assessed response rates of success (Cure + Improved) at FU and LFU.
- DLX patients had comparable per-pathogen microbiological response rates vs VAN/AZ patients against important pathogens that cause ABSSSIs, including *S. aureus* (both MSSA and MRSA) and Gram-negative bacteria.
- DLX was well tolerated in this study; the most common TEAEs among DLX-treated patients were mild-to-moderate gastrointestinal events.
- There was no signal for significant abnormalities in laboratory values, with no significant difference between treatment groups.

TABLE 5: PER PATHOGEN MICROBIOLOGICAL RESPONSE¹ RATE. ME AT FU ANALYSIS SET. OBESE PATIENTS, POOLED PHASE 3.

Organism ²	DLX (N=180)	VAN/AZ (N=145)
<i>Staphylococcus aureus</i>	99/101 (98.0%)	64/69 (92.8%)
MSSA	60/62 (96.8%)	45/48 (93.8%)
MRSA	40/40 (100.0%)	19/21 (90.5%)
<i>S. epidermidis</i>	12/14 (85.7%)	20/20 (100.0%)
<i>S. pyogenes</i>	6/6 (100.0%)	10/10 (100.0%)
<i>E. coli</i>	6/6 (100.0%)	7/8 (87.5%)
<i>E. faecalis</i>	4/4 (100.0%)	6/7 (85.7%)
<i>S. agalactiae</i>	7/7 (100.0%)	9/10 (90.0%)
<i>K. pneumoniae</i>	6/6 (100.0%)	5/5 (100.0%)
<i>E. cloacae</i>	4/5 (80.0%)	3/4 (75.0%)
<i>P. Aeruginosa</i>	5/5 (100.0%)	8/8 (100.0%)

¹ Documented or presumed eradicated; ² Baseline pathogens isolated from skin or blood

TABLE 7: ALL RELATED TREATMENT-EMERGENT ADVERSE EVENTS, OCCURRING IN ≥ 1% OF PATIENTS. SAFETY ANALYSIS SET. OBESE PATIENTS, POOLED PHASE 3.

	DLX (N=327)	VAN/AZ (N=306)
Patients with ≥1 TEAE	74 (22.6%)	73 (23.9%)
Diarrhea	20 (6.1%)	7 (2.3%)
Nausea	16 (4.9%)	14 (4.6%)
Headache	5 (1.5%)	6 (2.0%)
Vaginal yeast infection	5 (1.5%)	2 (0.7%)
Increased ALT	5 (1.5%)	4 (1.3%)
Infusion site phlebitis	4 (1.2%)	1 (0.3%)
Increased AST	3 (0.9%)	4 (1.3%)
Pruritus	2 (0.6%)	5 (1.6%)
Pruritus generalized	2 (0.6%)	5 (1.6%)
Urticaria	2 (0.6%)	3 (1.0%)
Vomiting	--	5 (1.6%)
Chills	--	4 (1.3%)
Rash	--	3 (1.0%)
Renal failure	--	3 (1.0%)
Upper abdominal pain	--	3 (1.0%)