POSTER #1347

A GLOBAL PHASE 3 STUDY OF DELAFLOXACIN (DLX) COMPARED TO VANCOMYCIN/ AZTREONAM (VAN/AZ) IN PATIENTS WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI)

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ABSTRACT

Background: Delafloxacin (DLX) is an IV/oral investigational anionic fluoroquinolone with full spectrum of activity under development for the potential treatment of a variety of infections, including acute bacterial skin and skin structure infections (ABSSSI).

Methods: Multicenter, randomized, double-blind trial of adults with major abscesses, cellulitis, wound or burn infections with ≥75 cm^2 erythema and ≥2 systemic signs. Patients were randomized 1:1 to receive BID DLX 300 mg IV for 3 days with a switch to 450 mg oral DLX, or vancomycin (VAN) 15 mg/kg IV with aztreonam (AZ) for 5-14 days. The primary endpoint was response at 48-72 hours. Secondary endpoints were investigator-assessed response based on complete resolution of signs and symptoms (Cure) at Follow up (FU [Day 14±1]), and Late Follow up (LFU [Day 21–28]). Clinical success was defined as Cure + Improved (no further antibiotics needed per investigator assessment).

Results: 850 patients randomized; 63% were male and mean age was 50.7 years. Average lesion size was 353 cm^2; 48% cellulitis, 25% abscesses, 26% wound and 1% burn infections. 552 patients (65%) had pathogens identified at baseline. Efficacy data for the intent-to-treat (ITT) population are presented here.

Key Outcomes	DLX (n=423) n (%)	VAN/AZ (n=427) n (%)	DLX-VAN/AZ Delta (95% CI)
Objective Response at 48-72 hours	354 (83.7)	344 (80.6)	3.1 (-2.0,8.3)
Investigator-assessed response			
Cure at FU	244 (57.7)	255 (59.7)	-2.0 (-8.6,4.6)
Clinical success at FU	369 (87.2)	362 (84.8)	2.5 (-2.2,7.2)
Cure at LFU	287 (67.8)	303 (71.0)	-3.1 (-9.3,3.1)
Clinical success at LFU	353 (83.5)	351 (82.2)	1.3 (-3.8,6.3)

In the micro-evaluable (ME) population, DLX was comparable to VAN/AZ in eradication of methicillin-resistant *Staphylococcus aureus* (MRSA) at 96.0% (48/50) vs 97.0% (32/33) at FU. 43.6% DLX and 39.3% VAN/AZ patients had ≥1 treatment-emergent adverse events (TEAE). The most common DLX events were diarrhea and nausea, which were mild and did not lead to discontinuation (DC). DC rates were similar at 7.3% for DLX and 8.9% for VAN/AZ in the ITT population, with equal rates of serious adverse events (SAEs) at 3.8% for DLX and 4.0% for VAN/AZ. The only 2 deaths occurred in the VAN/AZ arm.

Conclusion: IV/oral DLX was comparable to IV VAN/AZ for ABSSSIs, and DLX was also comparable to VAN/AZ for MRSA. DLX appears well tolerated with low DC rates.

INTRODUCTION

Delafloxacin is an anionic fluoroquinolone antibiotic with a number of unique properties that may make it useful in the treatment of severe infections, including acute bacterial skin and skin structure infections (ABSSSIs). Delafloxacin has excellent in vitro activity against Gram positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) while retaining good activity against gram-negative organisms.[1] The present Phase 3 study was conducted to compare the efficacy and safety of IV/oral delafloxacin monotherapy to that of IV vancomycin + aztreonam combination therapy in patients with ABSSSIs caused by both Gram-positive and Gram-negative pathogens. The endpoints reflect those mandated by the FDA[2] and EMA[3], including the early assessment of response at 48-72 hours, the objective response, as well as evidence of a sustained clinical response, based on the investigator assessment of outcome at later time-points after the end of therapy (EOT).

METHODS

STUDY DESIGN

- Stratified, randomized, double-blind, Phase 3, multicenter study of IV/oral DLX vs IV VAN/AZ for ABSSSI, including wounds, burns, major abscesses, or cellulitis ≥75 cm^2 in size and ≥2 systemic signs of infection
- Patients were randomly assigned (1:1) to receive DLX 300 mg IV q12h for 3 days with a mandatory blinded switch to DLX 450 mg oral q12h, or VAN 15 mg/kg IV (actual body weight) with AZ for 5-14 days at investigators' discretion
- 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 stratified by baseline infection type, BMI, and prior antibiotic us

ENDPOINTS AND ANALYSES

- Primary endpoint: proportion of patients achieving an objective response at 48-72 hours after start of treatment, based on ≥20% decrease in lesion size with no further antibiotics, major procedures, or death in the ITT population
- Secondary efficacy endpoint for FDA, primary for EMA: investigator-assessed response based on complete resolution of signs and symptoms (Cure) at FU and LFU
- Secondary endpoint: investigator-assessed Success (Cure + Improved and no further antibiotic needed)
- Additional efficacy endpoint: Microbiological response 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).

Analysis

- For primary endpoint, a 2-sided 95% 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; DLX was noninferior to VAN/AZ for ABSSSIs if lower limit of 2-sided 95% CI exceeded −0.10.
- The primary analysis of the investigator response required complete cure (ie, no signs or symptoms) rather than improved (ie, some remaining symptoms despite improvement to extent of no need for additional antibiotics) for a positive investigator response.
- Improved responses were considered failures as a more stringent criterion for the primary analysis
- An additional analysis assessed proportion of patients who were a clinical success (Cure + Improved), which is the typical investigator assessment used in antibiotic studies and consistent with views of treating physicians for antibiotic outcomes

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

PATIENTS

Patients (N=850) were randomized in North America, Asia, Europe, and Latin America. Patients in both treatment groups received study drug for an average of 7 days. Those in VAN/AZ arm received AZ for a mean of 3 days. Demographic and clinical characteristics are shown in Table 1.

TABLE 1: SUMMARY OF PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF ABSSSIs (ITT)

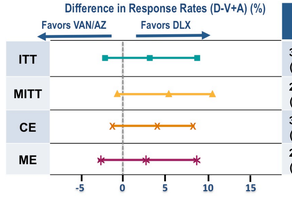
Characteristic	DLX (n=423)	VAN/AZ (n=427)	Total (N=850)
Age, years			
Mean (SD)	51.2 (15.98)	50.2 (16.03)	50.7 (16.00)
Median (min, max)	51.3 (18, 89)	50.3 (19, 93)	50.8 (18, 93)
Sex, n (%)			
Male	262 (61.9)	276 (64.6)	538 (63.3)
Female	161 (38.1)	151 (35.4)	312 (36.7)
Race, n (%)			
Black or African American	13 (3.1)	18 (4.2)	31 (3.6)
White	348 (82.3)	355 (83.1)	703 (82.7)
Other[a]	62 (14.7)	54 (12.6)	116 (13.6)
Region, n (%)[b]			
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)
Baseline infection type, n(%)			
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)
BMI, mean (SD)	30.4 (7.44)	30.7 (7.54)	30.5 (7.49)
Patients with diabetes, n (%)	53 (12.5)	54 (12.6)	107 (12.6)
Patients with renal impairment[c], n (%)	69 (16.3)	67 (15.7%)	136 (16.0)
Patients with vascular disorders, n (%)	146 (34.5)	136 (31.9)	282 (33.2)
Bacteremia present, n (%)	11 (2.6)	8 (1.9)	19 (2.2)
Baseline erythema area (digital), cm^2			
Subjects	421[d]	426	847
Mean (SD)	341.5 (312.89)	364.4 (391.70)	353.0 (354.70)

[a]Includes American Indian or Alaska Native, Asia, Native Hawaiian/other Pacific Islander, or Other. [b]Europe includes Latvia, Hungary, Estonia, Moldova, Romania, Bulgaria, Georgia. North America includes United States. Asia includes Taiwan, Korea. Latin America includes Peru, Argentina, Mexico, Chile, Brazil. [c]Creatinine clearance <90 mL/min. [d]Several patients in treatment arms did not have baseline erythema measurements.

PRIMARY EFFICACY OUTCOME

Objective response was defined as ≥20% reduction in erythema area of the lesion within 48-72 hours (±2) excluding the need for rescue antibacterial therapy, unplanned surgical intervention, death, or missing evaluations. DLX IV/oral was noninferior to VAN/AZ in the primary endpoint (Figure 1).

FIGURE 1: PRIMARY ENDPOINT OF EARLY OBJECTIVE RESPONSE BY ANALYSIS POPULATION AT FU (48-72 HOURS)



	DLX	VAN/AZ	Difference [95% CI]
ITT	354/423 (83.7%)	344/427 (80.6%)	3.1 (-2.0, 8.3)
MITT	241/275 (87.6%)	228/277 (82.3%)	5.3 (-0.7, 11.4)
CE	346/395 (87.6%)	327/387 (84.5%)	3.1 (-1.8, 8.0)
ME	235/264 (89.0%)	216/250 (86.4%)	2.6 (-3.1, 8.4)

TABLE 2: PER PATHOGEN MICROBIOLOGICAL RESPONSE RATE

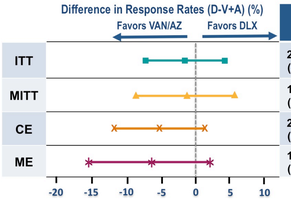
Per-pathogen Microbiological Response ME at FU Analysis Set[a,b]	DLX n=231 (%)	VAN/AZ n=212 (%)	Difference (95% CI)
S. aureus	129/131 (98.5)	114/118 (96.6)	1.9 (-2.5, 7.1)
MRSA	48/50 (96.0)	32/33 (97.0)	-1.0 (-11.0, 11.8)
MSSA	83/83 (100)	82/85 (96.5)	3.5 (-1.0, 9.9)
S. epidermidis	22/24 (91.7)	27/27 (100)	-8.3 (-26.1, 4.9)
S. pyogenes	13/14 (92.9)	11/11 (100)	-7.1 (-32.1, 20.5)
S. intermedius	12/12 (100)	7/7 (100)	NE
E. coli	7/7 (100)	9/10 (90)	10.0 (-28.7, 41.5)
E. cloacae	8/8 (100)	7/8 (87.5)	12.5 (-23.8, 48.3)
K. pneumoniae	8/8 (100)	8/8 (100)	NE
P. aeruginosa	9/9 (100)	6/6 (100)	NE

[a]Documented or presumed eradicated; [b]Baseline pathogens from blood or skin. NE = not estimable

SECONDARY EFFICACY OUTCOMES

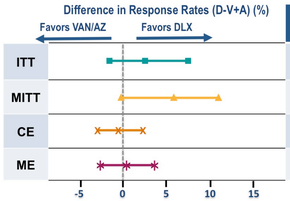
DLX IV/oral was comparable to VAN/AZ in the secondary endpoints of investigator-assessed response at FU and LFU (Figures 2 and 3). DLX had comparable activity in microbiological response to VAN/AZ against *S. aureus*, including MRSA, and several Gram negative pathogens (Table 2).

FIGURE 2: SECONDARY ENDPOINT OF INVESTIGATOR-ASSESSED RESPONSE OF CURE BY ANALYSIS POPULATION AT FU



	DLX	VAN/AZ	Difference [95% CI]
ITT	244/423 (57.7%)	255/427 (59.7%)	-2.0 (-8.6, 4.6)
MITT	158/275 (57.5%)	163/277 (58.8%)	-1.4 (-9.6, 6.8)
CE	220/353 (62.3%)	224/329 (68.1%)	-5.8 (-12.9, 1.4)
ME	141/231 (61.0%)	144/212 (67.9%)	-6.9 (-15.7, 2.1)

FIGURE 3: SECONDARY ENDPOINT OF INVESTIGATOR-ASSESSED RESPONSE OF SUCCESS (CURE + IMPROVED) BY ANALYSIS POPULATION AT FU



	DLX	VAN/AZ	Difference [95% CI]
ITT	369/423 (87.2%)	362/427 (84.8%)	2.5 (-2.2, 7.2)
MITT	247/275 (89.8%)	233/277 (84.1%)	5.7 (0.1, 11.4)
CE	340/353 (96.3%)	319/329 (97.0%)	-0.6 (-3.5, 2.2)
ME	226/231 (97.8%)	207/212 (97.6%)	0.2 (-2.9, 3.5)

SAFETY

- While the number of TEAEs, regardless of causality, was higher for DLX than VAN/AZ, the percent of TEAEs thought to be related to treatment was similar between the 2 arms.
- The number of SAEs was similar between DLX and VAN/AZ, while VAN/AZ arm had the only 2 deaths reported for the study due to myocardial infarction and intestinal ischemia.
- The most common AEs were gastrointestinal that were generally of mild-to-moderate severity and did not lead to treatment DC. There was one case of *C difficile* diarrhea during the study.
- There were no significant differences in laboratory values between the 2 treatment groups during the study.
- Notable abnormal laboratory values included ALT >5 times the upper limit of normal (ULN) at any time in the study in 4/417 (1.0%) for DLX and 7/425 (1.7%) for VAN/AZ, and creatinine >2 times ULN at any time in the study was 0/417 (0%) for DLX and 7/425 (1.7%) for VAN/AZ.
- No reports of cases meeting the Hy's law definition in DLX-treated patients during this or any other previous trial.

SAFETY

TABLE 3: OVERALL ADVERSE EVENTS

Summary of AEs Safety Analysis Set, n (%)	DLX n=417	VAN/AZ n=425
Any TEAE	182 (43.6)	167 (39.3)
TEAE related to study drug	87 (20.9)	89 (20.9)
TEAE with moderate or severe intensity	75 (18.0)	86 (20.2)
Any TEAE leading to premature study discontinuation	10 (2.4)	12 (2.8)
Any related TEAE leading to premature study discontinuation	5 (1.2)	10 (2.4)
Any SAE	16 (3.8)	17 (4.0)
Deaths	0	2 (0.5)

A TEAE was defined as any AE that started after the first dose of study drug or worsened in intensity after the first dose of study drug through telephone call follow-up. AEs were coded using MedDRA Version 16.1

TABLE 4: TREATMENT-EMERGENT ADVERSE EVENTS

TEAEs, Regardless of Causality, ≥2% Safety Analysis Set, n (%)	DLX n=417	VAN/AZ n=425
Patients with ≥1 TEAE	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)
Creatinine phosphokinase increase	5 (1.2)	10 (2.4)
Pruritis	4 (1.0)	9 (2.1)

DISCUSSION/CONCLUSION

- IV/oral monotherapy DLX appears to offer outcomes comparable to IV VAN/AZ therapy for patients with ABSSSIs, including those with MRSA and Gram-negative infections.
- In ABSSSI patients, IV/oral DLX monotherapy was noninferior 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 cure and success (Cure + Improved) at FU.
- The addition of oral DLX appears to maintain the initial clinical response seen with IV DLX.
- DLX patients had comparable per-pathogen microbiological response rates vs VAN/AZ patients against important pathogens that cause ABSSSIs, including MRSA and Gram-negative bacteria.
- DLX appeared to be well tolerated in this study and prior clinical trials. Previous studies documented that DLX was not associated with QT prolongation or phototoxicity, which has been seen in some fluoroquinolones in the past.
- The most common TEAEs in DLX-treated patients were mild-to-moderate gastrointestinal events, but these did not lead to treatment DC. The incidence of treatment-related SAEs was low and similar between DLX (0.5%) and VAN/AZ (0.7%).
- There was no signal for significant abnormalities in laboratory values.

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