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DELAFLOXACIN (DLX) IS EFFECTIVE AND WELL-TOLERATED IN TREATMENT OF DIABETIC (DM) 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 included DM patients (studies 302 and 303).

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, 164 DM patients were randomized in US, Europe, Latin America and Asia. 59% were male with mean age 59 yrs. Average erythema area at baseline was 424 cm^2. 60% had cellulitis, 24% abscesses, 15% wound and 1% burn infections. 52% of patients had *S. aureus*, and over 1/3 were MRSA. ~ 12% of patients had baseline Gram-negative pathogens. 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)	**63/83 (75.9)**	**63/81 (77.8)**	**-1.4 (-14.4, 11.6)**
Investigator-Assessed Success (FU ITT)	**71/83 (85.5)**	**68/81 (84.0)**	**2.2 (-9.2, 13.6)**
Investigator-Assessed Success (LFU ITT)	**71/83 (85.5)**	**69/81 (85.2)**	**1.7 (-9.5, 12.9)**
Micro Success (FU ME) for *S. aureus*	**20/23 (87.0)**	**22/25 (88.0)**	**-1.6 (-23.4, 20.3)**

The overall % of DM patients with at least one treatment-emergent AE (TEAE) was lower for DLX (41.7%) compared to VAN/AZ (50.6%). The most frequent TEAEs were gastrointestinal in nature including diarrhea seen in 7.1% and 4.8% of DLX and VAN/AZ patients respectively, and was generally mild to moderate in nature. There were no cases of *C. difficile* diarrhea. There were no discontinuations on DLX due to AEs, but 6% of VAN/AZ-treated DM patients discontinued due to AEs.

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

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INTRODUCTION

Delafloxacin (DLX) is an investigational 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). 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 (302[2] and 303[3]) comparing the efficacy and safety of IV/oral DLX monotherapy to that of IV vancomycin + aztreonam (VAN/AZ) combination therapy in patients with ABSSSIs caused by both Gram-positive and Gram-negative pathogens. Evaluated endpoints included those mandated by both the FDA[4] (objective response at 48-72 hours) and EMA[5] (investigator assessments of response).

Diabetic patients have special considerations in ABSSSI. In a review by Ray et al, having diabetes was one of the biggest risk factors for being diagnosed with skin and soft–tissue infections. Patients with DM had nearly double the rate of SSTI compared to persons without DM and In all patients, Gram-negative bacteria accounted for 14% of the pathogens identified.[6]

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 cm^2 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, BMI, and prior antibiotic use.

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 outcome for EMA was the investigator-assessed response based on complete resolution 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% CI for noninferiority testing was computed based on difference in responder rates for DLX and VAN/AZ at 48-72 (±2) hours after initiation of treatment as well as for the investigator assessed responses 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		
Key Endpoints	**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. PATIENTS WITH DIABETES MELLITUS, POOLED PHASE 3.

Characteristic	DLX (N=83)	VAN/AZ (N=81)
Age, years		
Mean (SD)	58.5 (12.97)	58.8 (12.78)
Median (min, max)	59.0 (20, 89)	58.0 (28, 90)
Sex, n (%)		
Male	50 (60.2)	46 (56.8)
Female	33 (39.8)	35 (43.2)
Race, n (%)		
American Indian or Alaska Native	2 (2.4)	--
Asian	1 (1.2)	2 (2.5)
Black or African American	5 (6.0)	7 (8.6)
Native Hawaiian/other Pacific Islander	1 (1.2)	1 (1.2)
White	71 (85.5)	68 (84.0)
Other	3 (3.6)	3 (3.7)
Region		
Europe	43 (51.8)	43 (53.1)
North America	33 (39.8)	31 (38.3)
Asia	1 (1.2)	2 (2.5)
Latin American	6 (7.2)	5 (6.2)
Received antibiotics in the 14 days prior to enrollment	27 (32.5)	30 (37.0)
Baseline infection type, n (%)		
Cellulitis/erysipelas	55 (66.3)	44 (54.3)
Wound infection	11 (13.3)	13 (16.0)
Major cutaneous abscess	16 (19.3)	23 (28.4)
Burn infection	1 (1.2)	1 (1.2)
BMI, mean (SD)	34.3 (7.47)	35.1 (9.03)
Bacteremia present, n (%)	3 (3.6)	4 (4.9)
Baseline erythema area (digital), cm^2		
Subjects	82	80
Mean (SD)	396.8 (347.42)	451.7 (493.94)

PATIENTS WITH DIABETES

Of the 1510 patients randomized in the two studies, 164 patients had diabetes mellitus (10.9%). The median duration of exposure to study drug was 7.0 and 7.5 days in the DLX and VAN/AZ arms, respectively. Those in the VAN/AZ arm received AZ for a mean of 3.6 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. PATIENTS WITH DIABETES MELLITUS, POOLED PHASE 3.

Organism[2]	DLX (N-50)	VAN/AZ (N-54)
Staphylococcus aureus	27 (54.0%)	27 (50.0%)
MSSA	16 (32.0%)	18 (33.3%)
MRSA	11 (22.0%)	9 (16.7%)
S. epidermidis	5 (10.0%)	8 (14.8%)
S. agalactiae	5 (10.0%)	8 (14.8%)
E. coli	4 (8.0%)	2 (3.7%)
E. faecalis	3 (6.0%)	1 (1.9%)
K. pneumoniae	3 (6.7%)	--
P. mirabilis	3 (6.7%)	1 (1.9%)
S. pyogenes	1 (2.0%)	2 (3.7%)

PRIMARY EFFICACY OUTCOMES IN PATIENTS WITH DIABETES

In diabetic patients, DLX IV/oral was comparable to VAN/AZ in the early objective response. DLX IV/oral was also 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. PATIENTS WITH DIABETES MELLITUS, POOLED PHASE 3.

Endpoint	Analysis Set	DLX n/N (%)	VAN/AZ n/N (%)	Difference (95% CI)
Early Objective Response (48-72 hours)	**ITT**	63/83 (75.9)	63/81 (77.8)	-1.4 (-14.4, 11.6)
	CE	63/80 (78.8)	59/73 (80.8)	-1.6 (-14.6, 11.4)
Investigator-Assessed Response of Success at FU	**ITT**	71/83 (85.5)	68/81 (84.0)	2.2 (-9.2, 13.6)
	CE	67/75 (89.3)	57/63 (90.5)	-0.5 (-11.5, 10.5)
Investigator-Assessed Response of Success at LFU	**ITT**	71/83 (85.5)	69/81 (85.2)	1.7 (-9.5, 12.9)
	CE	66/74 (89.2)	55/60 (91.7)	-1.3 (-12.4, 9.8)

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 DIABETIC PATIENTS

- The incidence of treatment-emergent adverse events was somewhat higher in the VAN/AZ arm as was the incidence of drug-related TEAEs **(Table 6)**.
- TEAEs occurring in the VAN/AZ arm were more likely to lead to premature discontinuation of study drug.
- The incidence of SAEs was similar in the two groups and the majority of these were considered unrelated to study therapy.
- Diarrhea was the most common TEAE in both treatment arms **(Table 7)**. There were no cases of *C. difficile* diarrhea.
- There were no significant differences in laboratory values between the two treatment groups during the study.
- 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. PATIENTS WITH DIABETES MELLITUS, POOLED PHASE 3.

	DLX (N=84)	VAN/AZ (N=83)
Any TEAE	35 (41.7%)	42 (50.6%)
TEAE related to study drug	11 (13.1%)	22 (26.5%)
TEAE with moderate or severe intensity	17 (20.3%)	22 (26.5%)
Any TEAE leading to premature study drug DC	--	5 (6.0%)
Any related TEAE leading to premature study drug DC	--	5 (6.0%)
Any SAE	4 (4.8%)	5 (6.0%)
Any SAE related to study drug	--	1 (1.2%)
Death	1 (1.2%)	--

TABLE 5: PER PATHOGEN MICROBIOLOGICAL RESPONSE[1] RATE. ME AT FU ANALYSIS SET. PATIENTS WITH DIABETES MELLITUS, POOLED PHASE 3.

Organism[2]	DLX (N=44)	VAN/AZ (N =44)
Staphylococcus aureus	20/23 (87.0%)	22/25 (88.0%)
MSSA	12/14 (85.7%)	15/17 (88.2%)
MRSA	8/9 (88.9%)	7/8 (87.5%)
Staphylococcus epidermidis	3/4 (75.0%)	6/6 (100.0%)
S. agalactiae	5/5 (100.0%)	7/8 (87.5%)
E. coli	4/4 (100.0%)	2/2 (100.0%)
E. faecalis	2/3 (66.7%)	--
Klebsiella pneumoniae	3/3 (100.0%)	--
P. mirabilis	3/3 (100.0%)	1/1 (100.0%)
S. pyogenes	1/1 (100.0%)	1/1 (100.0%)

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

TABLE 7: RELATED TREATMENT-EMERGENT ADVERSE EVENTS, OCCURRING IN ≥ 2% OF PATIENTS. SAFETY ANALYSIS SET. PATIENTS WITH DIABETES MELLITUS, POOLED PHASE 3.

	DLX (N=84)	VAN/AZ (N=83)
Patients with ≥1 Treatment-Related TEAE	11 (13.1%)	22 (26.5%)
Diarrhea	6 (7.1%)	4 (4.8%)
Nausea	2 (2.4%)	3 (3.6%)
Upper abdominal pain	--	2 (2.4%)
Rash	--	2 (2.4%)
Hypertension	--	2 (2.4%)
Leukopenia	--	2 (2.4%)
Neutropenia	--	2 (2.4%)
Acute renal failure	--	2 (2.4%)

CONCLUSION

DISCUSSION/CONCLUSIONS

- Patients with diabetes are at significant risk for ABSSSI including infections due to Gram-negative pathogens.
- In a population of patients with diabetes mellitus, 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.
- 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.
- 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 gastrointestinal events like diarrhea and nausea.
- There was no signal for significant abnormalities in laboratory values with no difference in lab values vs. comparator.