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DELAFLOXACIN (DLX) IS EFFECTIVE AND WELL-TOLERATED IN TREATMENT OF PATIENTS WITH RENAL IMPAIRMENT 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 patients with renal impairment (CrCl < 90 mL/min).

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, 244 patients with mild, moderate or severe renal impairment were randomized in US, Europe, Latin America and Asia. 42% were male with mean age 65 yrs. Average erythema area at baseline was 435 cm^2. 57% had cellulitis, 15% abscesses, 26% wound and 2% burn infections. 52% of baseline isolates were *S. aureus*, of which ~1/3 were MRSA. 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)	93/122 (76.2)	92/122 (75.4)	0.7 (-10.2, 11.5)
Investigator-Assessed Success (FU ITT)	107/122 (87.7)	108/122 (88.5)	-4.0 (-12.7, 4.8)
Investigator-Assessed Success (LFU ITT)	104/122 (85.2)	108/122 (88.5)	-4.0 (-12.7, 4.8)
Micro Success (FU ME) for *S. aureus*	37/39 (94.9)	32/34 (94.1)	3.1 (-11.5, 17.8)

The overall % of patients with at least one treatment-emergent AE (TEAE) was comparable for DLX (45.5%) compared to VAN/AZ (44.6%). The most frequent TEAEs were gastrointestinal in nature including diarrhea seen in 4.1% and 1.7% of DLX and VAN/AZ patients respectively, which were primarily mild or moderate in severity. There were no cases of *C. difficile* diarrhea. There were 1 and 3 patients who discontinued due to treatment-related AEs in the DLX and VAN/AZ groups respectively.

Conclusion:

Fixed dose monotherapy DLX was comparable to VAN/AZ combination therapy in treatment of ABSSSI in patients with renal impairment based on the 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 patients with renal impairment and ABSSSI and offers a potential treatment option in patients with renal impairment.

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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 (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. Key endpoints included those mandated by both the FDA[4] (objective response at 48-72 hours) and EMA[5] (investigator assessments of response).

Patients with renal disease have an enormous burden of infection including skin infections. The majority of the infections are unrelated to dialysis.[6] Prior studies have reported an increased risk of infection, bacteremia, sepsis and sepsis mortality among patients receiving chronic hemodialysis as well as those patients with predialysis CKD.[7,8] Additional options for antimicrobial therapy are needed for these patients given their complicated comorbidities and concomitant medications.

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 q12h for the full course; in study 303, subjects received DLX 300 mg IV q12h for 3 days followed by a mandatory blinded switch to DLX 450 mg PO q12h;
- 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.

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: 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 Microbiologically evaluable (ME) and Microbiological ITT (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 endpoint, 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; MITT: 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 Key Endpoints	STUDY 302 DLX n/Total (%)	STUDY 302 VAN/AZ n/Total (%)	STUDY 302 Delta (95% CI)	STUDY 303 DLX n/Total (%)	STUDY 303 VAN/AZ n/Total (%)	STUDY 303 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 RENAL IMPAIRMENT, POOLED PHASE 3.

Characteristic	DLX (N=122)	VAN/AZ (N=122)
BMI, mean (SD)	27.4 (7.39)	27.5 (6.46)
Patients with diabetes, n (%)	24 (19.7)	27 (22.1)
Age, years		
Mean (SD)	65.4 (14.61)	65.0 (15.47)
Median (min, max)	66.0 (20, 94)	65.0 (19, 93)
Sex, n (%)		
Male	42 (34.4)	61 (50.0)
Female	80 (65.6)	61 (50.0)
Race, n (%)		
American Indian or Native American	2 (1.6)	--
Asian	3 (2.5)	6 (4.9)
Black	9 (7.4)	8 (6.6)
White	102 (83.6)	101 (82.8)
Other	6 (4.9)	7 (5.7)
Region		
Europe	64 (52.5)	59 (48.4)
North America	47 (38.5)	49 (40.2)
Asia	3 (2.5)	5 (4.1)
Latin America	8 (6.6)	9 (7.4)
Degree of renal impairment . N = 121 each group, n (%)		
Mild (60 to 89 mL/min)	82 (67.8)	84 (69.4)
Moderate (30 to 59 mL/min)	37 (30.6)	35 (28.9)
Severe (<30 mL/min)	2 (1.7)	2 (1.7)
Received antibiotics in the 14 days prior to enrollment	28 (23.0)	33 (27.0)
Baseline infection type, n (%)		
Cellulitis/erysipelas	67 (54.9)	73 (59.8)
Wound infection	35 (28.7)	29 (23.8)
Major cutaneous abscess	19 (15.6)	17 (13.9)
Burn infection	1 (0.8)	3 (2.5)
Bacteremia present, n (%)	6 (4.9)	4 (3.3)
Baseline erythema area (digital), cm^2		
Subjects	122	121
Mean (SD)	440.3 (403.86)	429.3 (458.79)

PATIENTS WITH RENAL IMPAIRMENT

Of the 1510 patients randomized in the two studies, 244 patients had renal impairment (CrCl < 90 mL/min at baseline, as calculated using the Cockcroft-Gault formula). The median duration of exposure to study drug was 7 days in both treatment arms. Those in the VAN/AZ received AZ for a mean of 3.5 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 RENAL IMPAIRMENT, POOLED PHASE 3.

Organism	DLX (N=91)	VAN/AZ (N=78)
Staphylococcus aureus	45 (49.5%)	44 (56.4%)
MSSA	31 (34.1%)	24 (30.8%)
MRSA	14 (15.4%)	20 (25.6%)
S. epidermidis	12 (13.2%)	7 (9.0%)
S. pyogenes	3 (3.3%)	4 (5.1%)
E. coli	7 (7.7%)	6 (7.7%)
E. faecalis	2 (2.2%)	6 (7.7%)
S. agalactiae	4 (4.4%)	2 (2.6%)
K. pneumoniae	2 (2.2%)	3 (3.8%)
E. cloacae	3 (3.3%)	3 (3.8%)
P. aeruginosa	4 (4.4%)	--

PRIMARY EFFICACY OUTCOMES IN PATIENTS WITH RENAL IMPAIRMENT

In patients with renal impairment as calculated by Cockcroft-Gault, DLX IV/oral was comparable to VAN/AZ in the primary endpoint. In addition, DLX IV/oral was comparable to VAN/AZ in investigator-assessed response of success (Cure or Improved) at both FU and LFU. This was evident in the ITT and CE populations **(Table 4)**.

TABLE 4: CLINICAL EFFICACY. PATIENTS WITH RENAL IMPAIRMENT, POOLED PHASE 3.

Endpoint	Analysis Set	DLX n/N (%)	VAN/AZ n/N (%)	Difference (95% CI)
Early Objective Response (48-72 hours)	ITT	93/122 (76.2)	92/122 (75.4)	0.7 (-10.2, 11.5)
	CE	91/116 (78.4)	89/114 (78.1)	-0.2 (-10.9, 10.5)
Investigator-Assessed Response of Success at FU	ITT	107/122 (87.7)	108/122 (88.5)	-2.0 (-10.3, 6.3)
	CE	95/101 (94.1)	86/90 (95.6)	-0.6 (-8.1, 6.8)
Investigator-Assessed Response of Success at LFU	ITT	104/122 (85.2)	108/122 (88.5)	-4.0 (-12.7, 4.8)
	CE	99/107 (92.5)	90/93 (96.8)	-4.2 (-11.7, 3.3)

MICROBIOLOGIC EFFICACY OUTCOMES IN PATIENTS WITH RENAL IMPAIRMENT

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)**. One DLX-treated patient (baseline CrCl 35 mL/min) had baseline *P. aeruginosa* (MIC 0.5 mg/L) bacteremia and was cured at FU and LFU .

SAFETY IN PATIENTS WITH RENAL IMPAIRMENT

- The incidence of TEAEs was comparable in the two treatment arms, as was the incidence of drug-related TEAEs **(Table 6)**.
- Seven patients in each arm experienced SAEs, all but one of which were considered unrelated to study therapy.
- GI events were 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, such as hepatic or glucose 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 5: PER PATHOGEN MICROBIOLOGICAL RESPONSE[1] RATE. ME AT FU ANALYSIS SET, PATIENTS WITH RENAL IMPAIRMENT, POOLED PHASE 3.

Organism[2]	DLX (N=77)	VAN/AZ (N=58)
Staphylococcus aureus	37/39 (94.9%)	32/34 (94.1%)
MSSA	25/27 (92.6%)	18/20 (90.0%)
MRSA	12/12 (100.0%)	14/14 (100.0%)
S. epidermidis	7/9 (77.8%)	6/6 (100.0%)
S. pyogenes	3/3 (100.0%)	2/2 (100.0%)
E. coli	4/4 (100.0%)	6/6 (100.0%)
E. faecalis	2/2 (100.0%)	5/5 (100.0%)
S. agalactiae	1/1 (100.0%)	1/2 (50.0%)
K. pneumoniae	1/1 (100.0%)	2/2 (100.0%)
E. cloacae	3/3 (100.0%)	2/2 (100.0%)
P. aeruginosa	4/4 (100.0%)	--

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

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

	DLX (N=121)	VAN/AZ (N=121)
Any TEAE	55 (45.5%)	54 (44.6%)
TEAE related to study drug	24 (19.8%)	23 (19.0%)
TEAE with moderate or severe intensity	27 (22.3%)	23 (19.0%)
Any TEAE leading to premature study drug DC	3 (2.5%)	4 (3.3%)
Any related TEAE leading to premature study drug DC	1 (0.8%)	3 (2.5%)
Any SAE	7 (5.8%)	7 (5.8%)
Any SAE related to study drug	--	1 (0.8%)
Death	1 (0.8%)	1 (0.8%)

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

	DLX (N=121)	VAN/AZ (N=121)
Patients with ≥1 TEAE	24 (19.8%)	23 (19.0%)
Diarrhea	5 (4.1%)	2 (1.7%)
Nausea	5 (4.1%)	3 (2.8%)
Renal impairment	2 (1.7%)	--
Pruritus generalized	1 (0.8%)	2 (1.7%)
Blood creatinine increased	--	2 (1.7%)
Headache	--	2 (1.7%)

CONCLUSION

DISCUSSION/CONCLUSIONS

- Patients with renal impairment are high risk for infections; additional treatment options are needed given the complications of dosing, comorbidities and concomitant medications.
- In a population of patients with renal impairment, 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 48-72h and 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.