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DELAFLOXACIN (DLX) IS EFFECTIVE AND WELL-TOLERATED IN TREATMENT OF EUROPEAN 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 patients from Europe (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 signs and symptoms at Follow-up (FU day 14±1) and Late Follow-up (LFU day 21-28).

Results: In the 2 studies, 456 patients were randomized in Europe, (Latvia, Hungary, Estonia, Moldova, Ukraine, Romania, Bulgaria, Georgia, Spain, Croatia, Israel). 52% were male with mean age 57 yrs. Average erythema area at baseline was 466 cm^2. 65% had cellulitis, 18% abscesses, 15% wound and 2% burn infections. 283 (62% (had pathogens identified at baseline. *S. aureus* was the most frequent isolate. *E. coli* was the most frequent Gram-negative pathogen. Patients received mean ~8 days of therapy. 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)	178/228 (78.1)	174/228 (76.3)	2.0 (-5.7, 9.8)
Investigator-Assessed Success (FU ITT)	210/228 (92.1)	206/228 (90.4)	1.7 (-3.7, 7.2)
Investigator-Assessed Success (LFU ITT)	205/228 (89.9)	202/228 (88.6)	1.4 (-4.6, 7.3)
Micro Success (FU ME) for *S. aureus*	54/54 (100.0)	48/51 (94.1)	8 (-2.0, 17.9)
Micro Success (FU ME) for *E. coli*	8/8 (100.0)	8/9 (88.9)	10.9 (-25.6, 47.5)

The overall % of patients with at least one treatment-emergent adverse event (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. 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 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 patients with the 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 patients with acute bacterial skin and skin structure infections (ABSSSIs) and Community-Acquired Bacterial Pneumonia. 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 (studies 302[2] and 303[3]) 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 those mandated by the FDA[4] (objective response at 48-72 hours) and EMA[5] (investigator's assessment of response).

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 q12h 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, Follow-up (FU, Day 14±1), and Late Follow-up (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 the FDA: proportion of patients achieving 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 Intent-to-Treat (ITT) population;
- Key outcome for the EMA was the investigator-assessed response based on complete resolution or near resolution of signs and symptoms (Cure or Improved=Success) at FU (Day 14 ±1) and LFU (Day 21 to 28);
- Additional efficacy endpoint: Microbiological response (Documented or presumed eradication) at FU for patients in the Microbiologically evaluable (ME) and Microbiological ITT (MITT) analysis sets were based on results of baseline and post-baseline cultures 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 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 hours (±2) after initiation of treatment as well as the investigator-assessed 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; Clinically evaluable (CE): patients completing protocol activities; MITT: ITT patients with eligible pathogen; ME: CE patients with eligible pathogen

RESULTS

As shown in Table 1, in the two pivotal trials overall in all patients, 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. POOLED PHASE 3 EUROPEAN PATIENTS.

Characteristic	DLX (N=228)	VAN/AZ (N=228)
Age, years		
Mean (SD)	58.2 (16.18)	56.4 (16.42)
Median (min, max)	60.0 (18, 94)	57.5 (20, 93)
Sex, n (%)		
Male	111 (48.7)	128 (56.1)
Female	117 (51.3)	100 (43.9)
Race, n (%)		
Black	--	3 (1.3)
White	228 (100.0)	224 (98.2)
Other	--	1 (0.4)
Received antibiotics in the 14 days prior to enrollment	53 (23.2)	72 (31.6)
Baseline infection type, n (%)		
Cellulitis/erysipelas	153 (67.1)	145 (63.6)
Wound infection	33 (14.5)	34 (14.9)
Major cutaneous abscess	38 (16.7)	46 (20.2)
Burn infection	4 (1.8)	3 (1.3)
BMI, mean (SD)	32.8 (7.9)	32.5 (7.5)
Patients with diabetes, n (%)	43 (18.9)	43 (18.9)
Bacteremia present, n (%)	8 (3.5)	12 (5.3)
Baseline erythema area (digital), cm^2		
Subjects	226	227
Mean (SD)	448.0 (406.15)	483.7 (500.60)

POOLED PHASE 3 EUROPEAN PATIENTS

Of the 1510 patients randomized in the two Phase 3 studies, 456 patients were from Europe (Latvia, Hungary, Estonia Moldova, Ukraine, Romania, Bulgaria, Georgia, Spain, Croatia, and Israel). The median duration of exposure to study drug in both treatment arms was 7 days. Those in the VAN/AZ 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. POOLED PHASE 3 EUROPEAN PATIENTS.

Organism	DLX (N=139)	VAN/AZ (N=144)
Staphylococcus aureus	60 (43.2%)	61 (42.4%)
MSSA	54 (38.8%)	60 (41.7%)
MRSA	6 (4.3%)	1 (0.7%)
S. epidermidis	22 (15.8%)	25 (17.4%)
S. pyogenes	12 (8.6%)	10 (6.9%)
E. coli	10 (7.2%)	11 (7.6%)
S. agalactiae	7 (5.0%)	6 (4.2%)
K. pneumoniae	4 (2.9%)	3 (2.1%)
E. cloacae	4 (2.9%)	8 (5.6%)
P. aeruginosa	4 (2.9%)	8 (5.6%)

KEY EFFICACY OUTCOMES

In European patients, as in the overall population, DLX IV/oral was comparable to VAN/AZ in the early Objective Response. 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. POOLED PHASE 3 EUROPEAN PATIENTS.

Endpoint	Analysis Set	DLX n/N (%)	VAN/AZ n/N (%)	Difference (95% CI)
Early Objective Response (48-72 hours)	ITT	178/228 (78.1)	174/228 (76.3)	2.0 (-5.7, 9.8)
	CE	177/222 (79.7)	169/218 (77.5)	2.5 (-5.2, 10.2)
Investigator-Assessed Response of Success at FU	ITT	210/228 (92.1)	206/228 (90.4)	1.7 (-3.7, 7.2)
	CE	195/199 (98.0)	182/190 (95.8)	2.6 (-1.6, 6.8)
Investigator-Assessed Response of Success at LFU	ITT	205/228 (89.9)	202/228 (88.6)	1.4 (-4.6, 7.3)
	CE	188/193 (97.4)	185/193 (95.9)	1.4 (-3.0, 5.7)

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

- The incidence of treatment-emergent adverse events (TEAEs) was comparable in the two treatment arms, as was the incidence of drug-related TEAEs **(Table 6)**.
- There were twice as many serious adverse events (SAEs) (10 vs. 5) in the VAN/AZ treatment group; the majority of SAEs in both treatment groups 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, such as hepatic enzymes or glucose, 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. POOLED PHASE 3 EUROPEAN PATIENTS.

	DLX (N=225)	VAN/AZ (N=228)
Any TEAE	62 (27.6%)	61 (26.8%)
TEAE related to study drug	25 (11.1%)	28 (12.3%)
TEAE with moderate or severe intensity	24 (10.7%)	35 (15.3%)
Any TEAE leading to premature study drug DC	4 (1.8%)	5 (2.2%)
Any related TEAE leading to premature study drug DC	3 (1.3%)	4 (1.8%)
Any SAE	5 (2.2%)	10 (4.4%)
Any SAE related to study drug	1 (0.4%)	2 (0.9%)
Death	1 (0.4%)	2 (0.9%)

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

Organism[2]	DLX (N=123)	VAN/AZ (N=122)
Staphylococcus aureus	54/54 (100.0%)	48/51 (94.1%)
MSSA	50/50 (100.0%)	48/50 (96.0%)
MRSA	4/4 (100.0%)	0/1 (0.0%)
Staphylococcus epidermidis	16/18 (88.9%)	23/23 (100.0%)
S. pyogenes	12/12 (100.0%)	8/8 (100.0%)
E. coli	8/8 (100.0%)	8/9 (88.9%)
E. faecalis	6/6 (100.0%)	10/11 (90.9%)
S. agalactiae	6/6 (100.0%)	5/6 (83.3%)
K. pneumoniae	4/4 (100.0%)	1/1 (100.0%)
E. cloacae	4/4 (100.0%)	6/7 (85.7%)
P. Aeruginosa	4 (2.9%)	8 (5.6%)

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

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

	DLX (N=225)	VAN/AZ (N=228)
Patients with ≥1 TEAE	62 (27.6%)	61 (26.8%)
Diarrhea	6 (2.7%)	7 (3.1%)
Abscess	3 (1.3%)	--
Headache	3 (1.3%)	5 (2.2%)
Pyrexia	3 (1.3%)	1 (0.4%)
Urticaria	3 (1.3%)	2 (0.9%)
Pruritis	1 (0.4%)	4 (1.8%)
Chills	--	3 (1.3%)
Constipation	--	3 (1.3%)
Hypokalemia	--	3 (1.3%)

CONCLUSION

DISCUSSION/CONCLUSIONS

- In a population of patients enrolled in the EU, 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 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 mild-to-moderate gastrointestinal events.
- There was no signal for significant abnormalities in laboratory values.
- Delafloxacin appears to be a potential therapy in treatment of ABSSSI patients