POSTER #1153

COMPARISON OF DELAFLOXACIN (DLX) AND VANCOMYCIN (VAN) IN THE TREATMENT OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) BY AGE AND GENDER IN TWO PHASE 3 TRIALS

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E. Hansen[1], S. Ungureanu[2], B. Ninov[3], O. Pamo Reyna[4], M. Quintas[5], L. Lawrence[5], S. Cammarata[5]

[1] South Jersey Infectious Disease, USA, [2] Republican Clinical Hospital, Moldova, [3] University Multiprofile Hospital, Bulgaria, [4] Hospital Arzobispo Loayza, Peru, [5]Melinta Therapeutics, USA.

203-624-5606
info@melinta.com

ABSTRACT

Background: Delafloxacin (DLX) is a novel investigational anionic fluoroquinolone being developed for oral or intravenous (IV) administration for infections caused by Gram-positive organisms (including methicillin-resistant *Staphylococcus aureus* [MRSA]), Gram-negative organisms, atypical organisms, and anaerobes.

Methods: Data on age and gender were reviewed from 2 randomized, double-blind trials of adults with ABSSSI. At baseline, patients had a lesion size ≥75 cm^2 with ≥2 signs of systemic infection. Patients received 5-14 days BID DLX 300 mg IV/ 450 mg oral, or vancomycin (VAN) 15 mg/kg (based on actual body weight) with aztreonam (AZ). Both studies included endpoints for objective response at 48-72 hours based on ≥20% reduction of lesion size and investigator-assessed response rates based on complete resolution of signs and symptoms (Cure) at Follow up (FU; Day 14) and Late Follow up (LFU; Day 21-28).

Results: In the combined patient pool, 1510 patients (754 DLX, 756 VAN/AZ) in the Intent to Treat (ITT) had a mean age of 49.0 years for DLX and 48.1 years for VAN/AZ; 1314 were ≤65 and196 were>65, with the majority male (62% DLX, 64% VAN/AZ). Baseline digital mean lesion size was 321.1 cm^2 and 344.7 cm^2 for DLX and VAN/AZ, respectively. Infection types included cellulitis (44.0%), wound infection (30.1%), major cutaneous abscess (25.1%), and burn infection (0.8%). Below is the comparison of DLX and VAN for the objective response at 48-72 hours in the ITT population.

Patient population		DLX	VAN/ AZ	Diff (95% CI)
Overall n/N (%)		613/754 (81.3)	610/756 (80.7)	0.8 (-3.2, 4.7)
Age n/N (%)	≤65	538/653 (82.4)	543/661 (82.1)	0.4 (-3.7, 4.5)
	>65	75/101 (74.3)	67/95 (70.5)	4.3 (-8.1, 16.6)
Gender n/N (%)	Male	381/468 (81.4)	397/485 (81.9)	-0.1 (-5.1, 4.8)
	Female	232/286 (81.1)	213/271 (78.6)	2.6 (-4.2, 9.3)

Investigator-assessed cure rates for all subjects were similar at FU (55.2% DLX, 55.7% VAN/AZ) and LFU (69.0% DLX, 69% VAN/AZ). Overall, treatment-emergent adverse events (TEAE) were similar between treatment groups regardless of age and gender. The most common adverse events (AE) related to treatment were nausea (6.1% DLX, 4.3% VAN/AZ), pruritus (0.4% DLX, 2.3% VAN/AZ), and diarrhea (6.1% DLX, 2.0% VAN/AZ).

Conclusions: In a pooled analysis based on age and gender, DLX had comparable outcomes to VAN/AZ for the objective response at 48-72 hours. DLX was also well tolerated regardless of age or gender.

INTRODUCTION

DLX is an anionic fluoroquinolone antibiotic with several unique properties that may make it useful in the treatment of severe infections, including acute bacterial skin and skin structure infections (ABSSSI). DLX has excellent *in vitro* activity against Gram-positive pathogens, including MRSA and also demonstrates good activity against Gram-negative organisms.[1]

Two phase 3 studies compared the efficacy and safety of IV/oral DLX monotherapy to that of IV VAN/AZ in patients with ABSSSI caused by both Gram-positive and Gram-negative pathogens. The endpoints reflect those mandated by the FDA[2] and EMA,[3] including early assessment of response at 48-72 hours and evidence of a sustained clinical response, based on investigator assessment of outcomes at time points following the end of therapy (EOT).

Results from both studies were pooled and the subcategories of age and gender were analyzed for early objective response and traditional investigator-assessed response.

METHODS

STUDY DESIGN

- Two stratified, randomized, double-blind, phase 3, multicenter studies of IV or IV/oral DLX vs IV VAN/AZ for the treatment of ABSSSI, including
- Patients had wounds, burns, major cutaneous abscesses, or cellulitis ≥75 cm^2 in size; at least 2 systemic signs of infections; and met the other entry criteria
- Patients randomly assigned (1:1) to receive either DLX 300 mg IV q12h for 5-14 days (Study 1) or for 3 days with a mandatory blinded switch in all patients to DLX 450 mg oral q12h (Study 2) or VAN/AZ 15 mg/kg IV (actual body weight) for 5-14 days.
- Enrollment stratified by baseline infection type and prior antibiotic use (Study 1) as well as BMI in Study 2
- Patients evaluated at screening, daily on therapy, at FU (Day 14±1) and LFU (Day 21-28)
- Efficacy evaluated through assessments of the signs and symptoms of infection; measurement of lesion size by digital planimetry; and culture and susceptibility testing of bacterial isolates

ENDPOINTS AND ANALYSES

Endpoints

- **Primary endpoint**: proportion of patients who achieved an objective response at 48-72 hours following initiation 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 endpoint for EMA**: investigator-assessed response based on complete resolution of signs and symptoms (Cure) at FU and LFU
- **Secondary endpoint**: proportion of patients achieving investigator-assessed clinical Success (Cure + Improved)
- **Safety**: AEs, vital sign and body temperature measurements, clinical laboratory test abnormalities, physical examination findings, concomitant medications, and ECGs (if clinically indicated

Analysis

- For the 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 using a stratified method proposed by Miettinen and Nurminen (1985); if the lower limit of the CI exceeded −0.10, DLX was considered noninferior to VAN/AZ
- The study was designed with at least 90% power to demonstrate noninferiority of DLX with respect to the objective clinical response rate of VAN/AZ, with a noninferiority margin of 10%
- In the primary analysis investigator assessment of outcome, patients were classified as Cured, Improved, Failure, or missing/indeterminate based on clinical assessment of signs and symptoms
- The primary analysis required that patients were completely cured (ie, no signs or symptoms, not merely improved symptoms) for a positive investigator response
- Improved responses (ie, some symptoms remained, but patient improved to an extent that no additional antibiotic treatment was necessary) were considered failures for a more stringent primary analysis
- The definition of Success (Cure + Improved) has usually been the investigator assessment used in prior antibiotic studies and is typically how treating physicians view antibiotic outcomes, where no further antibiotics are needed

RESULTS

PATIENTS

Patients in Study 1 and 2 (n=1510) represented countries in North America, Asia, Europe, and Latin America. Both groups received a median of 6.0 days of therapy. Overall, 85% completed the study through the LFU visit. There was no upper limit on age for enrollment, with almost 200 patients >65 years of age. Baseline demographics were similar between treatment groups as shown in Table 1.

TABLE 1. SUMMARY OF BASELINE PATIENT DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF POOLED ABSSSI STUDIES (ITT)

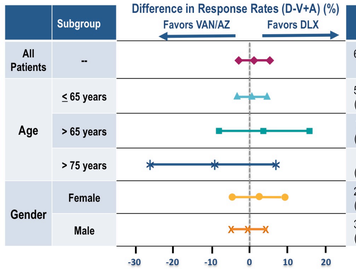
Characteristic	DLX (n=754)	VAN/AZ (n=756)
Age, years		
Mean (SD)	49.0 (15.29)	48.1 (15.54)
Median (min, max)	49.0 (18, 94)	48.0 (19, 93)
Age category, n (%)		
≤65 years	653 (86.6)	661 (87.4)
>65 years	101 (13.4)	95 (12.6)
>75 years	42 (5.6)	41 (5.4)
Sex, n (%)		
Male	468 (62.1)	485 (64.2)
Female	286 (37.9)	271 (35.8)
Race, n (%)		
Black or African American	40 (5.3)	37 (4.9)
White	645 (85.5)	659 (87.2)
Other[a]	69 (9.2)	59 (7.8)
Region, n (%)[b]		
Europe	228 (30.2)	228 (30.2)
North America	470 (62.3)	470 (62.2)
Asia	9 (1.2)	14 (1.9)
Latin America	47 (6.2)	44 (5.8)
Infection type, n(%)		
Cellulitis/erysipelas	330 (43.8)	334 (44.2)
Wound infection	227 (30.1)	228 (30.2)
Major cutaneous abscess	190 (25.2)	189 (25.0)
Burn infection	7 (0.9)	5 (0.7)
BMI, mean (SD)	29.5 (7.1)	29.5 (7.2)
Patients with diabetes, n (%)	83 (11.0)	81 (10.7)
Patients with renal impairment[c], n(%)	122 (16.2)	122 (16.1)
Patients with vascular disorders, n (%)	234 (31.0)	204 (27.0)
Bacteremia present,n (%)	17 (2.3)	17 (2.2)
Mean (SD) erythema area (digital), cm^2	321.1 (311.6)	344.7 (360.5)

[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, Spain, Croatia, Israel, and Ukraine. North America includes United States. Asia includes Taiwan and Korea. Latin America includes Peru, Argentina, Mexico, Chile, and Brazil. [c]Creatinine clearance <90 mL/min

PRIMARY EFFICACY OUTCOME

- The pooled analysis for the primary endpoint of early objective response demonstrated that DLX IV/ oral was noninferior to VAN/AZ (Figure 1).
- When analyzed by age subgroups and by gender, DLX had similar outcomes to VAN/AZ (Figure 1).

FIGURE 1. EARLY OBJECTIVE RESPONSE (48-72 HOURS) at FU: OVERALL, AGE SUBGROUP, AND GENDER



	Subgroup	DLX	VAN/AZ	Difference [95% CI]
All Patients	--	613/754 (81.3)	610/756 (80.7)	0.8 (-3.2, 4.7)
Age	≤ 65 years	538/653 (82.4%)	543/661 (82.1%)	0.4 (-3.7, 4.5)
	> 65 years	75/101 (74.3%)	67/95 (70.5%)	4.3 (-8.1, 16.6)
	> 75 years	30/42 (71.4%)	33/41 (80.5%)	-9.9 (-27.6, 7.8)
Gender	Female	232/286 (81.1%)	213/271 (78.6%)	2.6 (-4.2, 9.3)
	Male	381/468 (81.4%)	397/485 (81.9%)	-0.1 (-5.1, 4.8)

SECONDARY EFFICACY OUTCOME

- Investigator response was analyzed by age subgroups (Table 2) and gender groups (Table 3 at FU.
- In general, DLX was comparable to VAN/AZ across age subgroups and gender groups for investigator response in the ITT analysis set.

TABLE 2. INVESTIGATOR-ASSESSED RESPONSE BY AGE AT FU

Investigator-assessed Response by Age (ITT)	Subgroup	DLX	VAN/AZ
At FU			
Cure*, n/N (%)	≤65 years	349/653 (53.4)	360/661 (54.5)
Success*, n/N (%)		550/653 (84.2)	551/661 (83.4)
At FU			
Cure, n/N (%)	>65 years	67/101 (66.3)	61/95 (64.2)
Success, n/N (%)		89/101 (88.1)	85/95 (89.5)
At FU			
Cure, n/N (%)	>75 years	32/42 (76.2)	24/41 (58.5)
Success, n/N (%)		37/42 (88.1)	37/41 (90.2)

Cure: Complete resolution of all baseline signs and symptoms of ABSSSI
Improved: Some symptoms remain, but the patient improved to an extent that no additional antibiotic treatment was necessary.
Success: Cure + Improved

TABLE 3. INVESTIGATOR-ASSESSED RESPONSE BY GENDER AT FU

Investigator-assessed Response by Gender (ITT)	Subgroup	DLX	VAN/AZ
At FU			
Cure, n/N (%)	Female	174/286 (60.8)	150/271 (55.4)
Success, n/N (%)		246/286 (86.0)	220/271 (81.2)
At FU			
Cure, n/N (%)	Male	242/468 (51.7)	271/485 (55.9)
Success, n/N (%)		393/468 (84.0)	416/485 (85.8)

SAFETY

- The percent of patients with TEAEs (regardless of causality) was comparable between treatment arms overall and in both age and gender subgroups (Table 4).
- VAN/AZ had numerically slightly higher rates of TEAEs leading to discontinuation, overall, by age subgroup, and gender group.
- The number of patients with serious adverse events was similar for DLX and VAN/AZ
- The most common AEs were gastrointestinal in nature and were similar between treatment arms.
- In general, TEAE rates were slightly lower in patients >65 years compared to those ≤65 years for both DLX and VAN/AZ.
- Nausea, vomiting, and headache TEAEs were slightly higher in both treatment groups for females compared to males.
- The most common adverse events (AE) related to treatment were nausea (6.1% DLX, 4.3% VAN/AZ), pruritus (0.4% DLX, 2.3% VAN/AZ), and diarrhea (6.1% DLX, 2.0% VAN/AZ).

TABLE 4. OVERALL ADVERSE EVENTS

Summary of TEAEs by Age and Gender (Multiple Dose ABSSSI Analysis Set)	DLX n=741 (%)	VAN/AZ n=751 (%)	DLX n=640 (%)	VAN/AZ n=656 (%)	DLX n=101 (%)	VAN/AZ n=95 (%)	DLX n=282 (%)	VAN/AZ n=268 (%)	DLX n=459 (%)	VAN/AZ n=483 (%)
	All subjects		≤65 years old		>65 years old		Female		Male	
Patients with any TEAE	334 (45.1)	358 (47.7)	297 (46.4)	323 (49.2)	37 (36.6)	35 (36.8)	127 (48.9)	131 (48.9)	207 (45.1)	227 (47.0)
Patients with any related TEAE	164 (22.1)	196 (26.1)	148 (23.1)	181 (27.6)	16 (15.8)	15 (15.8)	67 (23.8)	79 (29.5)	97 (21.1)	117 (24.2)
Patients with any TEAE of moderate or severe intensity	136 (18.4)	152 (20.2)	119 (18.5)	132 (20.1)	17 (16.8)	20 (21.1)	57 (20.2)	63 (23.5)	79 (17.2)	89 (18.4)
Patients with TEAE leading to premature study drug DC	13 (1.8)	26 (3.5)	11 (1.7)	22 (3.4)	2 (2.0)	4 (4.2)	5 (1.8)	14 (5.2)	8 (1.7)	12 (2.5)
Patients with related TEAE leading to premature study drug DC	6 (0.8)	18 (2.4)	4 (0.6)	14 (2.1)	2 (2.0)	4 (4.2)	3 (1.1)	9 (3.4)	3 (0.7)	9 (1.9)
Patients with SAE	27 (3.6)	26 (3.5)	24 (3.8)	23 (3.5)	3 (3.0)	3 (3.2)	9 (3.2)	9 (3.4)	18 (3.9)	17 (3.5)
Patients with any TEAE leading to death	1 (0.1)	3 (0.4)	0	2 (0.3)	1 (1.0)	1 (1.1)	0	1 (0.4)	1 (0.2)	2 (0.4)

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.
DC: discontinuation; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

CONCLUSION

- Baseline characteristics were similar between age subgroups and gender groups of patients with ABSSI.
- DLX was comparable to VAN/AZ for the primary endpoint of objective response at 48-72 hours overall, by age subgroup, and by gender group.
- DLX was comparable to VAN/AZ across age subgroups and gender groups for investigator response in the ITT analysis at FU regardless of definition of cure or success.
- Safety results indicated that DLX was comparable to VAN/AZ for any TEAE overall, TEAEs in patients ≤ 65 years and those >65 years, and TEAEs in males and females.
- Nausea, vomiting, and headache TEAEs were slightly higher in both treatment groups for females compared to males.
- VAN/AZ had slightly higher rates of discontinuation due to AEs compared to DLX overall and for each age subgroup, and gender group.

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