POSTER # 470

TREATMENT OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) IN PATIENTS WITH SIGNIFICANT DRUG ABUSE: OUTCOMES FROM GLOBAL PHASE 3 STUDIES OF DELAFLOXACIN (DLX)

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INTRODUCTION

Delafloxacin is a novel fluoroquinolone that is approved in the US as an IV and oral formulation for the treatment of serious skin infections. Delafloxacin is more active than levofloxacin against most Gram-positive pathogens and has been shown to have an MIC_{90} (minimum inhibitory concentration required to inhibit the growth of 90% of organisms) of at least 8-fold more active than levofloxacin against MRSA isolates[1]. Delafloxacin has good activity against Gram-negative organisms that are susceptible to levofloxacin. Delafloxacin has FQ class labelling but has no QT restrictions or phototoxicity, no food effects and no significant drug-drug interactions, which may be a consideration in antibiotic choice for IVDA patients[2]. Amid the opioid crisis, the incidence of ABSSSI in communities has increased or resulted in outbreaks, and physicians require options which cover predominant organisms which are well tolerated in the population[3]. Two Phase 3 studies were conducted to compare the efficacy and safety of IV and oral delafloxacin monotherapy to that of IV vancomycin + aztreonam (VAN/AZ) combination therapy in patients with ABSSSI and included a significant percentage of Intravenous Drug Abusers (IVDA). This analysis focuses on the patients with significant drug abuse including IVDA.

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.

Endpoints and Analyses

- FDA primary endpoint: 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.
- EMA primary endpoint: investigator-assessed response based on complete resolution or near resolution of signs and symptoms at FU (Day 14) and LFU (Day 21 to 28).
  - Definition of Success: A response of cure (complete resolution of all baseline signs and symptoms of ABSSSI) or improved (some symptoms remained) where the investigator felt that no further antibiotics were needed.
- 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).
- For 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 for the investigator assessed responses at FU and LFU.

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.

IVDA Subjects

- Subjects from 302 and 303 with Medical History Relevant to Substance Abuse Including Intravenous Drug User were identified for analysis.

RESULTS

DEMOGRAPHICS AND EFFICACY

In the 2 studies, 620/1510 patients with substance abuse, excluding alcoholism, but including heroin, cocaine and methamphetamine abuse, were randomized in the US. Median total drug exposure was 5.0 days for either treatment arm (DLX and VAN/AZ). IVDA study demographics are presented in **Table 1**. Primary and secondary endpoint outcomes for the study are presented in **Tables 2-3.**

TABLE 1. PATIENT BASELINE CHARACTERISTICS OF IVDA PATIENTS (ITT POPULATION)

Characteristic	DLX (N=306)	VAN/AZ (N=314)
Age, years		
Mean (SD)	44.7 (10.98)	43.6 (11.4)
Median (min, max)	47 (18, 68)	46 (19, 64)
Sex, n (%)		
Male	218 (71.2)	223 (71.0)
Female	88 (28.8)	91 (29.0)
Race, n (%)		
Black	16 (5.2)	15 (4.8)
White	275 (89.9)	289 (92.0)
Other	15 (4.9)	10 (3.2)
BMI, mean (SD)	26.8 (5.1)	26.6 (5.5)
Patients with diabetes, n (%)	11 (3.6)	12 (3.8)
Baseline infection type, n(%)		
Major cutaneous abscess	93 (30.4)	96 (30.6)
Wound Infection	161 (52.6)	170 (54.1)
Cellulitis/erysipelas	52 (17.0)	48 (15.3)
Cause of Infection, n(%)		
Trauma	229 (74.8)	241 (76.8)
Surgical wound	1 (0.3)	0
Other	76 (24.8)	72 (22.9)
Missing	0	1 (0.3)
Anatomical Site of Infection, n (%)		
Head/neck/face	7 (2.3)	6 (1.9)
Back	8 (2.6)	1 (0.3)
Thorax	0	4 (1.3)
Upper Extremities	143 (46.7)	151 (48.1)
Lower Extremities	91 (29.7)	104 (33.1)
Abdomen	17 (5.6)	12 (3.8)
Public/perineum/groin	1 (0.3)	2 (0.6)
Buttocks	44 (14.4)	38 (12.1)
Erythema size, mean (SD) cm^2	223.3 (145.6)	252.4 (189.7)
Induration size, mean (SD) cm^2	82.5 (112.7)	99.5 (120.8)

Note: (Body mass index) is calculated as (body weight in kilograms)/(height in meters)^2.

TABLE 2. OBJECTIVE RESPONSE OUTCOMES AT 48 – 72 HOURS FOR IVDA PATIENTS

Key Endpoints	DLX	VAN/AZ	Difference (95% CI)
ITT Population	**N=306**	**N=314**	
Objective Responders, n/N (%)	263 (85.9)	265 (84.4)	2.6 (-2.9, 8.1)
CE Population	**N=270**	**N=270**	
Objective Responders, n/N (%)	253 (93.7)	251 (93.0)	0.9 (-3.1, 5.0)

Difference = Difference in responder rates (DLX treatment group minus VAN/AZ treatment group). Confidence intervals are calculated using Miettinen and Nurminen method stratified by the two studies.

TABLE 3. INVESTIGATOR ASSESSED OUTCOMES AT FOLLOW-UP FOR IVDA PATIENTS

Key Endpoints	DLX	VAN/AZ	Difference (95% CI)
ITT Population	**N=306**	**N=314**	
Success, n (%)	251 (82.0)	249 (79.3)	3.2 (-3.0, 9.4)
CE Population	**N=223**	**N=213**	
Success, n (%)	221 (99.1)	211 (99.1)	0.5 (-2.4, 3.3)

Difference = Difference in cure/success rates (DLX treatment group minus VAN/AZ treatment group). Confidence intervals are calculated using Miettinen and Nurminen method stratified by the two studies.

TABLE 4. MOST COMMON BASELINE PATHOGENS IN IVDA PATIENTS (MITT POPULATION) AND PER PATHOGEN MICROBIOLOGICAL RESPONSE (ME POPULATION) AT FOLLOW-UP

Most Common Baseline Pathogens (MITT)				Per Pathogen Micro Response (ME) – Eradicated[1]	
Pathogen	DLX (N=249)	VAN/AZ (N=259)		DLX (N=184)	VAN/AZ (N=177)
Gram-Positive Organisms					
***Staphylococcus aureus,* n (%)**	160 (64.3)	175 (67.6)		115/116 (99.1)	118/118 (100)
MRSA	80 (32.1)	87 (33.6)		56/57 (98.2)	57/57 (100)
MSSA	83 (33.3)	88 (34.0)		61/61 (100)	61/61 (100)
***Streptococcus intermedius,* n (%)**	27 (10.8)	28 (10.8)		21/21 (100)	17/17 (100)
***S. anginosus,* n (%)**	20 (8.0)	20 (7.7)		14/14 (100)	11/12 (91.7)
***S. epidermidis,* n (%)**	17 (6.8)	16 (6.2)		13/13 (100)	10/10 (100)
***S. constellatus,* n (%)**	11 (4.4)	12 (4.6)		8/8 (100)	11/11 (100)
Gram Negative Organisms					
***Klebsiella pneumoniae,* n (%)**	17 (6.8)	19 (7.3)		12/12 (100)	15/15 (100)
***Enterobacter cloacae,* n (%)**	7 (2.8)	3 (1.2)		5/5 (100)	3/3 (100)
***Haemophilus parainfluenzae,* n (%)**	5 (2.0)	7 (2.7)		2/2 (100)	6/6 (100)
***K. oxytoca,* n (%)**	3 (1.2)	1 (0.4)		3/3 (100)	0
***Escherichia coli,* n (%)**	2 (0.8)	4 (1.5)		1/1 (100)	3/3 (100)

Note: Eligible pathogens are organisms identified as baseline pathogens by the investigator and submitted for culture and susceptibility testing at the central laboratory. Success is defined as documented or presumed eradication. MRSA = Methicillin Resistant Staphylococcus aureus, MSSA = Methicillin Susceptible *Staphylococcus aureus*.
[1]Denominator is the number of patients who have the given target pathogen at baseline from the ABSSSI or blood culture, not the total ME population at FU (N).

TABLE 5. OVERALL SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS (TEAE) FOR IVDA PATIENTS

Category	DLX (N=300)	VAN/AZ (N=312)
Subjects with any TEAE, n (%)	147 (49.0)	175 (56.1)
TEAE related to study drug, n (%)	77 (25.7)	91 (29.2)
TEAE with severe intensity, n (%)	9 (3.0)	5 (1.6)
Any TEAE leading to premature study drug DC, n (%)	5 (1.7)	12 (3.8)
Any related TEAE leading to premature study drug DC, n (%)	1 (0.3)	7 (2.2)
Any serious TEAE, n (%)	12 (4.0)	6 (1.9)
Any serious TEAE related to study drug, n (%)	1 (0.3)	0

Note: A treatment-emergent adverse event (TEAE) is defined as an AE with 1) start date/time on or after the date/time of first study drug administration and prior to or on the date/time of last study medication administration + 28 days or 2) start date/time prior to the date/time of first study drug administration and worsening on or after the date/time of first study drug administration and prior to or on the date/time of last study medication administration + 28 days. Related includes possibly, probably, and definitely related. At each level of subject summarization, a subject with 1 or more reported TEAEs was counted only once. DC = Discontinuation

TABLE 6. ALL TEAES IN >2% OF SUBJECTS, REGARDLESS OF CAUSALITY, IN IVDA PATIENTS

Category	DLX (N=300)	VAN/AZ (N=312)
Patients with at least 1 TEAE, n (%)	147 (49.0)	175 (56.1)
Nausea, n (%)	34 (11.3)	24 (7.7)
Diarrhea, n (%)	27 (9.0)	9 (2.9)
Vomiting, n (%)	10 (3.3)	11 (3.5)
Infusion site extravasation, n (%)	34 (11.3)	41 (13.1)
Pyrexia, n (%)	7 (2.3)	6 (1.9)
Infusion site pain, n (%)	6 (2.0)	9 (2.9)
Infection, n (%)	28 (9.3)	32 (10.3)
Alanine aminotransferase increased, n (%)	7 (2.3)	9 (2.9)
Aspartate aminotransferase increased, n (%)	6 (2.0)	11 (3.5)
Blood creatine phosphokinase, n (%)	6 (2.0)	9 (2.9)
Headache, n (%)	10 (3.3)	16 (5.1)
Pruritus, n (%)	2 (0.7)	8 (2.6)

SAFETY

- TEAE rates (drug related or not) were generally comparable between DLX and VAN/AZ or slightly favored DLX in IVDA subjects (**Table 5**).
- IVDA patients with TEAEs leading to study drug or study discontinuation were higher for the VAN/AZ treatment group.
- Serious TEAEs were slightly more common in the DLX treatment group for IVDA subjects.
- Most common AEs were GI events including nausea, diarrhea, and vomiting, and IV site extravasation and infection (secondary) (**Table 6**).
- Abnormal lab TEAEs were low and similar between DLX and VAN/AZ treatment groups.

CONCLUSIONS

- In IVDA patients, DLX was non-inferior to VAN/AZ for objective response: 85.9% DLX vs 84.4% VANAZ [Δ2.6 (95% CI -2.9, 8.1)] as well as the assessment of outcome at FU: 82.0% DLX vs 79.3% VANAZ [Δ3.2 95% (CI -3, 9.4)] in the ITT.
- DLX was also non-inferior to VAN/AZ for both objective response and investigator outcome in the CE population of IVDA patients.
- Micro success in evaluable patients with SA was seen in 99.1% DLX vs 100% VAN/AZ as well as 98.2% DLX vs 100% VAN/AZ in IVDA patients with MRSA.
- DLX was well tolerated in this study; the most common TEAE among DLX-treated patients were gastrointestinal events, IV site extravasation, and secondary infection.

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