POSTER # 1856

OUTCOMES WITH IV/ORAL DELAFLOXACIN (DLX) COMPARED TO VANCOMYCIN/AZTREONAM (VAN/AZ) IN TREATMENT OF PATIENTS (PTS) WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) AND GRAM-NEGATIVE (GN) PATHOGENS

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IDWEEK
San Diego, California, USA
October 4-8, 2017

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ABSTRACT

Background: Delafloxacin (DLX) is a broad-spectrum fluoroquinolone antibiotic which has been approved by FDA for the treatment in adults with ABSSSI caused by designated susceptible bacteria. Two global phase 3 ABSSSI trials included patients with both Gram-positive and -negative pathogens (studies 302 and 303).

Material/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 300mg q12h IV only; study 303 used DLX 300mg q12h IV for 3 days with a mandatory blinded switch to DLX 450 mg oral q12h. 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) and Late Follow-up (LFU day 21-28). The study was conducted in US, Europe, Latin America and Asia

Results: In the 2 studies, 1042/1510 patients enrolled had a pathogen at baseline (Micro Intent to Treat (MITT). 197 patients (18%) had a GN pathogen isolated at baseline; most (13.6%) were part of a mixed infection. 66% were male with mean age 52 yrs. Median digital erythema area at baseline was ~226 cm^2. 25% had cellulitis, 27% abscesses, and 47% wound infections. The most common location was the lower extremities. *K. pneumoniae* was the most frequent GN isolate. The MIC_{50}, MIC_{90} and MIC range for key pathogens were 0.12, 0.25, 0.03-4 μg/mL for *K. pneumoniae*; 0.12, 2, 0.03-4 μg/mL for *E. cloacae*; 0.03, 1, 0.008-2 μg/mL for *E coli*; and 0.25, 4, 0.12-4 μg/mL for *P. aeruginosa*. Key endpoints are shown below:

Key Endpoints Phase 3 Patients with GN pathogens	DLX n/Total (%)	VAN/AZ n/Total (%)
Objective response 48-72h (ME)	77/90 (85.6)	83/94 (88.3)
Investigator-Assessed Success (FU ME)	74/75 (98.7)	80/82 (97.6)
Investigator-Assessed Success (LFU ME)	73/75 (97.3)	76/78 (97.4)
Micro Success (FU ME) for key GN organisms:		
K. pneumoniae	17/17 (100)	17/17 (100)
E. cloacae	11/12 (91.7)	9/10 (90)
E. coli	11/11 (100)	16/17 (94.1)
P. aeruginosa	11/11 (100)	10/10 (100)

In the overall population, the proportion of patients with at least one treatment-emergent AE (TEAE) was similar for DLX (45.1%) compared to VAN/AZ (47.7%). The most frequent treatment-related adverse events were gastrointestinal in nature including nausea seen in 6.1% and 4.3% and diarrhea seen in 6.1% and 2% of DLX and VAN/AZ patients, respectively. There were 0.8% of DLX patients and 2.4% VAN/AZ patients who discontinued treatment due to treatment related AEs.

Conclusions: GN pathogens are a consideration in ABSSSI antibiotic selection. Fixed dose DLX monotherapy was effective in clinical and microbiologic response in patients with GN pathogens based on the early objective response as well as investigator-assessed response at FU and LFU and microbiologic response. DLX appears effective and well tolerated in patients with GN pathogens in ABSSSI, whether part of a monomicrobial or mixed infection.

INTRODUCTION

DLX is an anionic fluoroquinolone antibiotic, approved for the treatment of ABSSSI, with a number of unique properties that may make it useful in treatment of severe infections. DLX has excellent *in vitro* activity against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), while retaining good activity against Gram-negative organisms.[1] Two Phase 3 studies were conducted to compare the efficacy and safety of IV or IV/oral DLX monotherapy to that of IV vancomycin + aztreonam (VAN/AZ) combination therapy in patients with ABSSSIs. The endpoints reflect those mandated by the FDA[2] and EMA[3], including the early assessment of response at 48-72 hours, the Objective Response, as well as evidence of a sustained clinical response, based on the Investigator assessment of outcome at later time-points after the end of therapy (EOT). Baseline pathogens were also evaluated and analyzed for an endpoint of microbial response and tested for susceptibility.

MATERIALS AND METHODS

STUDY DESIGN

- Adults with ABSSSI randomized 1:1 received either DLX monotherapy or vancomycin (VAN) 15 mg/kg (actual body weight) with aztreonam (AZ) in two stratified, randomized, double-blind Phase 3 global studies (302 and 303).
- Patients had wounds, burns, major abscesses, or cellulitis of ≥75 cm^2 in size; at least 2 systemic signs of infections; and met other entry criteria.
- Patients received DLX 300 mg IV q12 (302), or DLX 300 mg IV q12h for 3 days with a mandatory blinded switch to DLX 450 mg oral q12h (303), or VAN 15 mg/kg IV (actual body weight) with AZ. Total treatment duration was 5 – 14 days at the investigator's discretion.
- Enrollment was stratified by baseline infection type, prior antibiotic use, and BMI (303 only), and patients were evaluated at screening, daily on therapy, at the Follow-up (FU, Day 14 ± 1) and Late Follow-up Visits (LFU, Day 21 to 28).
- Efficacy was 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.
- Isolates were submitted to the central laboratory (JMI Laboratories, North Liberty, IA) for identification and susceptibility testing per CLSI guidelines.[4]

ENDPOINTS AND ANALYSES

Primary endpoint: Proportion of patients who achieved an objective response at 48-72 hours following initiation of treatment, based on at least a 20% decrease in lesion size with no further antibiotics, major procedures or death, in the intent-to-treat (ITT) population.

Secondary efficacy endpoint for FDA and Primary endpoint for EMA: Investigator-assessed response based on complete resolution of signs and symptoms (cure) at FU and LFU visits.

- In the primary analysis of the investigator response, it was required that patients were completely cured (ie, no signs or symptoms), not merely improved (ie, some symptoms remain, but the patient has improved to an extent that no additional antibiotic treatment is necessary), for the positive investigator response. Improved responses were considered failures for purposes of the primary analysis.
- An additional analysis was completed to assess the proportion of patients who were a clinical success (cure + improved).
- Microbiological response to treatment was an additional efficacy endpoint.
- Safety was assessed through adverse event reporting, vital sign and body temperature measurements, clinical laboratory test abnormalities, physical examination findings, concomitant medications, and ECGs (if clinically indicated).

Key analysis populations included:

- Intent-to-treat (ITT; all patients randomized)
- Microbiological intent-to-treat (MITT; ITT patients with eligible pathogen)
- Clinically evaluable (CE; patients who completed activities as defined in the protocol)
- Microbiologically evaluable (ME; CE patients with eligible pathogen)

RESULTS

DEMOGRAPHICS

Patients (n=1510) were randomized in North America, Asia, Europe, and Latin America (ITT population). 69% (n=1042) of patients had pathogens identified at baseline (MITT). DLX patients received study drug for an average of 6.8 days days. Vancomycin patients received an average of 6.6 days of treatment and aztreonam for a mean of 2.8 days.

TABLE 1. SUMMARY OF SUBJECT DEMOGRAPHICS AND BASELINE CHARACTERISTICS OF ABSSSI IN GRAM-NEGATIVE PATIENTS VS GRAM-POSITIVE (MITT)[a]

Baseline Characteristic	Gram-negative Patients[a] (N=197)	Gram-positive Patients[a] (N=845)
Age, years		
Mean (SD)	52.5 (15.24)	46.7 (14.79)
Median (Min, max)	53.0 (18, 87)	47.0 (18, 94)
Sex, n/N (%)		
Male	130 (66.0)	530 (62.7)
Female	67 (34.0)	315 (37.3)
Race, n/N (%)		
Black or African American	5 (2.5)	52 (6.2)
White	182 (92.4)	745 (88.2)
Other[b]	10 (5.1)	48 (5.7)
Region, n/N (%)[c]		
Europe	73 (37.1)	210 (24.9)
North America	116 (58.9)	601 (71.1)
Asia	1 (0.5)	2 (0.2)
Latin America	7 (3.6)	32 (3.8)
Baseline infection type, n/N (%)		
Cellulitis/erysipelas	49 (24.9)	261 (30.9)
Wound infection	93 (47.2)	310 (36.7)
Major cutaneous abscess	53 (26.9)	267 (31.6)
Burn infection	2 (1.0)	7 (0.8)
BMI (kg/m^2) Mean (SD)	29.8 (7.71)	28.6 (6.51)
Patients with diabetes, n/N (%)	16 (8.1)	88 (10.4)
Anatomical site of infection n/N (%)		
Head/neck/face	4 (2.0)	37 (4.4)
Back	6 (3.0)	28 (3.3)
Thorax	5 (2.5)	19 (2.2)
Upper extremities	48 (24.4)	279 (33.0)
Lower extremities	98 (49.7)	349 (41.3)
Abdomen	14 (7.1)	42 (5.0)
Pubic/perineum/groin	4 (2.0)	17 (2.0)
Buttocks	21 (10.7)	86 (10.2)
Area baseline erythema (digital), cm^2	284.2 (N=195[d])	273.3 (N=845)

a. Gram-negative includes polymicrobial gram-negative, monomicrobial gram-negative or polymicrobial gram mixed. Gram-positive includes monomicrobial gram-positive or polymicrobial gram-positive.
b. American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, Other
c. Europe includes Latvia, Hungary, Estonia, Moldova, Romania, Bulgaria, Georgia, Spain, Croatia, Israel, Ukraine. North America includes United States. Asia includes Taiwan, Korea. Latin America includes Peru, Argentina, Mexico, Chile, Brazil.
d. Two patients in this group did not have baseline erythema measurements

TABLE 2. INCIDENCE OF MONOMICROBIAL VS. POLYMICROBIAL BASELINE INFECTIONS IN POOLED PHASE 3 PATIENTS (MITT)

Infection Type[a]	DLX PATIENTS (N = 518)	VAN/AZ PATIENTS (N = 524)
Monomicrobial, n/N (%)		
Gram-positive	339 (65.4)	356 (67.9)
Gram-negative	17 (3.3)	29 (5.5)
Aerobe	349 (67.4)	375 (71.6)
Anaerobe	7 (1.4)	10 (1.9)
Polymicrobial, n/N (%)		
Gram-positive	82 (15.8)	68 (13.0)
Gram-negative	7 (1.4)	2 (0.4)
Gram-positive/negative	73 (14.1)	69 (13.2)
Aerobe	134 (25.9)	106 (20.2)
Anaerobe	0	3 (0.6)
Aerobe/Anaerobe	28 (5.4)	30 (5.7)

a. Gram-negative includes polymicrobial Gram-negative, monomicrobial Gram-negative or polymicrobial gram mixed. Gram-positive includes monomicrobial Gram-positive or polymicrobial Gram-positive.

Note: Patients were counted only once within each subgroup.

TABLE 3. GRAM-NEGATIVE BASELINE PATHOGENS (≥1%) IN POOLED PHASE 3 PATIENTS (MITT) AND DLX SUSCEPTIBILITY RESULTS

Organism	DLX PATIENTS (N = 518)	DLX + VAN PATIENTS (ALL) (N = 1042)	DLX $MIC_{50}/_{90}$ (Range) ALL PATIENTS
Gram-negative organisms[a]			
Klebsiella pneumoniae	22	45	0.12/0.25 (0.03 – 4)
Enterobacter cloacae	14	26	0.12/2 (0.03 - >8)
Escherichia coli	14	35	0.06/4 (0.008 – 4)
Pseudomonas aeruginosa	11	24	0.25/4 (0.12 - >8)

a. Eligible pathogens are organisms identified as potential pathogens from blood or skin specimens by the investigator and were submitted for culture and susceptibility testing at the central laboratory. The n in the table is the number of all available MIC values in the specified pathogen within each treatment group and each region.

TABLE 4. RESULTS OF KEY ENDPOINTS IN POOLED PHASE 3 PATIENTS WITH GRAM-NEGATIVE PATHOGENS

Endpoint	DLX n/Total (%)	VAN/AZ n/Total (%)
Objective response 48-72h (ME)	77/90 (85.6)	83/94 (88.3)
Investigator-Assessed Success (FU ME)	74/75 (98.7)	80/82 (97.6)
Investigator-Assessed Success (LFU ME)	73/75 (97.3)	76/78 (97.4)

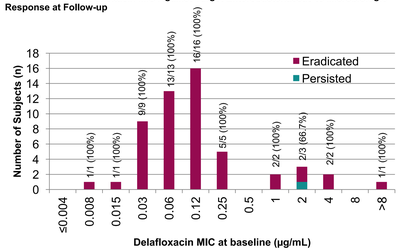
TABLE 5. BY PATHOGEN MICROBIOLOGICAL RESPONSE AT FOLLOW-UP

Per-Pathogen Microbiological Response (ME Analysis Set[a,b])	Follow Up Visit	
	DLX N=410	VAN/AZ N=396
E. coli (%)	11/11 (100)	16/17 (94.1)
E. cloacae (%)	11/12 (91.7)	9/10 (90.0)
K. pneumoniae (%)	17/17 (100)	17/17 (100)
P. aeruginosa (%)	11/11 (100)	10/10 (100)

a. Documented or Presumed eradicated
b. Baseline pathogens from blood or skin

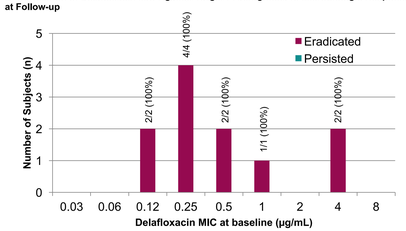
FIGURE 1. MICROBIOLOGICAL RESPONSE BY MIC DISTRIBUTION OF DLX AGAINST PHASE 3 GRAM-NEGATIVE BACTERIA (EVALUABLE POPULATION POOLED PHASE 3)[a]

A. Correlation of Delafloxacin MIC Against Target Enterobacteriaceae to Microbiologic Response at Follow-up



Note: Enterobacteriaceae includes *E. coli*, *Klebsiella spp*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*, and *E. cloacae*

B. Correlation of Delafloxacin MIC Against Target *P. aeruginosa* to Microbiologic Response at Follow-up



a. Documented or presumed eradicated/persisted

SAFETY FOR ALL POOLED PHASE 3 PATIENTS

TABLE 5. TREATMENT EMERGENT ADVERSE EVENTS (TEAE)

TEAEs, Regardless of Causality, ≥2% (Safety Analysis Set)	DLX N=741 (%)	VAN/AZ N=751 (%)
Patients with any TEAE, n/N (%)	334 (45.1)	358 (47.7)
Patients with any related TEAE, n/N (%)	164 (22.1)	196 (26.1)
Patients with any TEAE leading to premature study drug discontinuation, n/N (%)	13 (1.8)	26 (3.5)
Patients with any related TEAE leading to premature study drug discontinuation, n/N (%)	6 (0.8)	18 (2.4)
Patients with any serious adverse event (SAE), n/N (%)	27 (3.6)	26 (3.5)
Patients with any related SAE, n/N (%)	2 (0.3)	4 (0.5)
Patient Deaths*, n/N (%)	1 (0.1)	3 (0.4)
Subjects with any TEAE presented by maximum severity, n/N (%)		
Mild	198 (26.7)	206 (27.4)
Moderate	110 (14.8)	131 (17.4)
Severe	26 (3.5)	21 (2.8)

* All deaths were considered unrelated to treatment

CONCLUSION

- IV and oral monotherapy DLX had outcomes comparable to IV VAN/AZ combination therapy for ABSSI patients with Gram-negative infections with both objective response (decrease in lesion size ≥ 20%) at 48 to 72 hours after initiation of study drug, and investigator-assessed response rates of cure at the Follow-up Visit by Gram-negative pathogens (MITT and ME populations).
- DLX patients had comparable per-pathogen microbiological response rates vs. VAN/AZ patients against important Gram-negative pathogens that cause ABSSSI
- DLX is comparable to VAN/AZ in terms of incidence of AEs, and 96% of TEAEs were mild or moderate for both groups combined.
- The most common TEAEs in DLX-treated patients were mild to moderate gastrointestinal events, but these did not lead to treatment discontinuation.

REFERENCES

1. Van Bambeke F. Delafloxacin, a non-zwitterionic fluoroquinolone in Phase III of clinical development: evaluation of its pharmacology, pharmacokinetics, pharmacodynamics, and clinical efficacy. *Future Microbiol.* 2015;10:1111–1123.
2. Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research (US). Guidance for Industry. Acute bacterial skin and skin structure infections: developing drugs for treatment. October 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf.
3. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP). Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. London, 15 Dec 2011. CPMP/EWP/558/95 rev 2. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003417.pdf.
4. Clinical and Laboratory Standards Institute. 2015, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically: approved standard, 10th ed. CLSI document M07-A10. Clinical and Laboratory Standards Institute, Wayne, PA.

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