POSTER
101 E

Presented at MAD-ID
May 9-12, 2018
Orlando, FL

COMPARISON OF SAFETY PROFILE OF DELAFLOXACIN (DLX) VERSUS VANCOMYCIN/AZTREONAM (VAN/AZ) IN THE TREATMENT OF PATIENTS (PTS) WITH ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI): INTEGRATED SAFETY FINDINGS FROM TWO PHASE III STUDIES

G. R. Corey[1], D. Hooper[2], T. P. Lodise Jr.[3], C. Tseng[4], S. Cammarata[5]

[1]Duke University Medical Center, Durham, NC, [2]Infection Control Unit, Massachusetts General Hospital, Boston, MA, [3]Albany College of Pharmacy & Health Sciences, Albany, NY, [4]Firma Clinical LLC, Hunt Valley, MD, [5]Melinta Therapeutics Parsippany, NJ

1-800-MELINTA
medinfo@melinta.com

ABSTRACT

Background: Delafloxacin (DLX) is a broad-spectrum fluoroquinolone (FQ) antibiotic which has been approved by FDA for the treatment of in adults with ABSSSI caused by designated susceptible bacteria. The objective of this analysis was to compare the incidence of adverse events (AE) between DLX and VAN/AZ across two phase III registrational ABSSSI studies.

Material/methods: Study design and population: two global multi-center, double-blind randomized Phase 3 trials of adults with ABSSSI who received either DLX IV/oral monotherapy q12h or VAN 15mg/kg with AZ q12H for 5 – 14 days. Collected safety data included all reported AEs (baseline to 30 days after the final dose of study drug). Adverse events were reported by the blinded investigator who also assessed whether the reported events were potentially related to the treatment. Pre-specified laboratory tests were also collected from baseline through day 21-28.

Results: Across the 2 studies, 1492 ABSSSI pts received at least one dose of treatment. Mean age was 49 years; 13% >age 65. Among the 1492 pts, 42% were obese, 11% were diabetic, and 16% had renal impairment. Overall, rates of any AE were comparable between treatment groups (table). The most common AEs were gastrointestinal, seen in 17% and 13% of DLX and VAN/AZ pts, respectively. Less than 1% of DLX pts discontinued treatment due to related AEs. For DLX and VAN/AZ, there were 1.1% and 1.7% pts, respectively, with ALT>5X ULN at any time in the study. There was one case of *C. difficile* infection on DLX in a patient with prior Bactrim/clindamycin therapy. There was no increase in events previously associated with FQs compared to VAN/AZ. There were no cases of tendon rupture or reports of pts with symptoms consistent with fluoroquinolone associated disability (FQAD).

% patients with at least one:	DLX N=741	VAN/AZ N=751
Any adverse event (AE) report (%)	45.1	47.7
Diarrhea[#]	7.8	3.2
Nausea	7.6	6.3
Vomiting	2.3	2.4
Headache	3.2	5.5
Abnormal Liver function tests*	3.1	4.0
Treatment Related AE	22.1	26.1
Moderate to severe AE	18.3	20.2
AE leading to drug discontinuation	1.8	3.5
Related AE leading to drug discontinuation	0.8	2.4
Serious AE (SAE)	3.6	3.5
Related SAE	0.3	0.5
Deaths (none considered treatment-related)	0.1	0.4

[#] selected events reported ≥2% DLX pts regardless of causality
*pooled reports

Conclusions: Overall, the safety profile of DLX was comparable to VAN/AZ among patients with ABSSSI.

INTRODUCTION

Delafloxacin was recently approved by the FDA for the treatment of patients with ABSSSI. DLX is an anionic fluoroquinolone antibiotic with a number of unique properties that may make it useful in treatment of ABSSSI. 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] Previous safety reviews of fluoroquinolones have highlighted adverse events of interest that assist in a targeted analyses of the delafloxacin safety profile. 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. Pooled data from these studies allow for analysis of the safety of delafloxacin in patients with ABSSSI.

MATERIALS AND METHODS

STUDY DESIGNS OF 2 PHASE 3 TRIALS

- Adults with ABSSSI randomized 1:1 received either DLX monotherapy or VAN 15 mg/kg (actual body weight) with 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 the other entry criteria.
- Patients received between 5 – 14 days of DLX 300 mg IV q12 (study 302), or DLX 300 mg IV q12h for 3 days with a mandatory blinded switch to DLX 450 mg orally q12h (study 303), or VAN 15 mg/kg IV (actual body weight) with AZ every 12 hours.
- 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).
- Data from two Phase 3 pivotal trials were pooled since the studies were of similar design and used identical comparators. The Safety Analysis Set (all enrolled patients who received at least 1 dose of study drug was used for analysis).
- Safety was assessed by the collection of adverse event (AE) reports, scheduled laboratory testing and physical examination.
  - The investigator assessed the "relatedness" of the event to the treatments, severity and seriousness.
  - Events were coded using Medical Dictionary for Regulatory Activities (MedDRA) 16.1 which allows standardization in classification and coding into organ classes.
  - In study 302, blood samples for intensive blood glucose analysis were obtained on Day 3 (± 1 day) within 2 hours before the first study drug administration, and at 1, 2, 3, 5, and 12 hours after the start of the first infusion (± 10-minute window after a minimum of 3 consecutive doses of study drug).
- Adverse event reports potentially related to the adverse events of special interest (AESIs) were identified by medical review and use of Standardized MedDRA queries (SMQ) where possible. SMQs are validated, standard sets of MedDRA terms, which have undergone extensive review, testing, analysis and expert discussion by a working group of MedDRA and product safety experts. The SMQs cast a wide net over multiple adverse event terms that could potentially be associated with a medical event of interest. For example, the SMQ for potential QT prolongation includes events as specific as Torsade de pointes as well as events as general as syncope.

RESULTS

TABLE 1. DEMOGRAPHICS IN THE POOLED PHASE 3 SKIN STUDIES

Baseline Characteristic	DLX N=741	VAN/AZ N=751	Total N=1492
Age, years			
Mean (SD)	49.2 (15.32)	48.2 (15.54)	48.7 (15.43)
Median (Min, max)	49.0 (18, 94)	48.0 (19, 93)	49 (18, 94)
Sex, n (%)			
Male	459 (61.9)	483 (64.3)	942 (63.1)
Female	282 (38.1)	268 (35.7)	550 (36.9)
Race, n (%)			
Black or African American	38 (5.1)	36 (4.8)	74 (5.0)
White	636 (85.8)	656 (87.4)	1292 (86.6)
Other[a]	67 (9.0)	59 (7.9)	126 (8.4)
Region, n (%)[b]			
Europe	225 (30.4)	228 (30.4)	453 (30.4)
North America	461 (62.2)	466 (62.1)	927 (62.1)
Asia	9 (1.2)	14 (1.9)	23 (1.5)
Latin America	46 (6.2)	43 (5.7)	89 (6.0)
BMI (kg/m^2), n (%)			
BMI <30	414 (55.9)	445 (59.3)	859 (57.6)
BMI ≥30	327 (44.1)	306 (40.7)	633 (42.4)
Baseline Renal Impairment[c], n (%)			
Yes	121 (16.3)	121 (16.1)	242 (16.2)
Patients with Diabetes, n (%)			
Yes	84 (11.3)	83 (11.1)	167 (11.2)
Patients with History of Infectious Hepatitis[d], n (%)			
Yes	216 (29.1)	217 (28.9)	433 (29.0)

a. Other = American Indian or Alaskan native, Asian, Native Hawaiian or Other, Pacific Islander, or Other
b. Europe = Latvia, Hungary, Estonia, Moldova, Romania, Bulgaria, Georgia, Spain, Croatia, Israel, Ukraine. North America = United States. Asia = Taiwan, Korea. Latin America = Peru, Argentina, Mexico, Chile, Brazil.
c. Baseline Renal Impairment is defined as CrCl < 90 mL/min.
d. Infectious hepatitis is defined as hepatitis A, B or C noted in medical history.

TABLE 3. SELECTED ADVERSE REACTIONS OCCURRING IN ≥ 2% OF PATIENTS RECEIVING DLX IN THE POOLED ADULT PHASE 3 ABSSSI CLINICAL TRIALS

	DLX N = 741	VAN/AZ N = 751
Any adverse event report (%)	45.1	47.7
Diarrhea[#]	7.8	3.2
Nausea	7.6	6.3
Vomiting	2.3	2.4
Headache	3.2	5.5
Abnormal Liver function tests*	3.1	4.0

[#] The data are not an adequate basis for comparison of rates between the study drug and the active control.
* Pooled reports include hypertransaminasaemia, increased transaminases, and increased ALT and AST.

- Mean days of exposure for DLX was 6.8 and for VAN/AZ was 6.6 days.
- The majority of patients in both groups (~60%) received 11-23 doses of drug over 4 - < 6 days.
- For the VAN/AZ group, aztreonam mean dosing was 2.8 days for the 739 patients that were affected.

TABLE 4. ALL AEs AND POTENTIALLY RELATED TEAES BY SYSTEM ORGAN CLASS FOR PHASE 3 PATIENTS (AT LEAST REPORTED AS 1% BY SYSTEM ORGAN CLASS IN EITHER TREATMENT GROUP)

System Organ Class	ALL TEAEs, regardless of causality		RELATED* TEAEs	
	DLX N=741	VAN/AZ N=751	DLX N=741	VAN/AZ N=751
Total Number of TEAEs	775	879	268	331
Subjects with at least one TEAE	334 (45.1)	358 (47.7)	164 (22.1)	196 (26.1)
Gastrointestinal Disorders	125 (16.9)	95 (12.6)	90 (12.1)	59 (7.9)
Infections and Infestations	98 (13.2)	94 (12.5)	17 (2.3)	11 (1.5)
General Disorders and Administration Site Conditions	99 (13.4)	116 (15.4)	28 (3.8)	35 (4.7)
Skin and Subcutaneous Tissue Disorders	43 (5.8)	74 (9.9)	16 (2.2)	55 (7.3)
Nervous System Disorders	44 (5.9)	50 (6.7)	15 (2.0)	22 (2.9)
Investigations	37 (5.0)	55 (7.3)	19 (2.6)	33 (4.4)
Musculoskeletal and Connective Tissue Disorders	19 (2.6)	20 (2.7)	3 (0.4)	6 (0.8)
Psychiatric Disorders	18 (2.4)	15 (2.0)	1 (0.1)	1 (0.1)
Metabolism and Nutrition Disorders	19 (2.6)	33 (4.4)	5 (0.7)	9 (1.2)
Respiratory, Thoracic and Mediastinal Disorders	16 (2.2)	9 (1.2)	2 (0.3)	1 (0.1)
Vascular Disorders	12 (1.6)	25 (3.3)	4 (0.5)	10 (1.3)
Injury, Poisoning and Procedural Complications	7 (0.9)	15 (2.0)	1 (0.1)	0
Blood and Lymphatic System Disorders	9 (1.2)	12 (1.6)	1 (0.1)	4 (0.5)
Renal and Urinary Disorders	5 (0.7)	15 (2.0)	4 (0.5)	7 (0.9)

Notes: A 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.

Percentages are calculated as 100 x (n/N).The total number of TEAEs counts all TEAEs for subjects.

At each level of subject summarization, a subject with 1 or more reported events was counted only once, and the most severe reported event was used for the maximum severity.

*Potentially related to treatment as per investigator assessment and includes 'Possibly Related', 'Probably Related' and 'Definitely Related'

TABLE 5. RELATED TEAES BY PREFERRED TERM WITH INCIDENCE OF EITHER TREATMENT ARM OF ≥2% (POOLED PHASE 3)

System Organ Class	DLX N=741	VAN/AZ N=751
Total number of related TEAEs with incidence of preferred term ≥2%	103	85
Subjects with at least one related TEAE with incidence of preferred term ≥2%	88 (11.9)	74 (9.9)
Gastrointestinal Disorders		
Nausea	45 (6.1)	32 (4.3)
Diarrhea	45 (6.1)	15 (2.0)
Skin and Subcutaneous Tissue Disorders		
Pruritus	3 (0.4)	17 (2.3)
Pruritus Generalized	4 (0.5)	19 (2.5)

Note: The total number of TEAEs counts all TEAEs for subjects. Related includes 'Possibly Related', 'Probably Related' and 'Definitely Related'. If relationship is missing, the TEAE is summarized as related. At each level of subject summarization, a subject was counted once if the subject reported one or more events.

TABLE 6. INCIDENCE OF ELEVATED TRANSAMINASES AND CREATININE FOR POOLED PHASE 3 STUDIES

Lab Parameter	DLX N=741	VAN/AZ N=751
ALT (U/L) > 5x ULN		
Day 3	0	1 (0.1)
Day 7	0	2 (0.3)
EOT	3 (0.4)	6 (0.8)
FU	3 (0.4)	4 (0.5)
LFU	5 (0.7)	1 (0.1)
Overall Worse Post-Baseline	8 (1.1)	13 (1.7)
AST (U/L) > 5x ULN		
Day 3	0	1 (0.1)
Day 7	0	0
EOT	3 (0.4)	2 (0.3)
FU	4 (0.5)	2 (0.3)
LFU	2 (0.3)	1 (0.1)
Overall Worse Post-Baseline	6 (0.8)	4 (0.5)
Serum Creatinine (µmol/L) > 2x ULN		
Day 3	0	1 (0.1)
Day 7	0	2 (0.3)
EOT	0	3 (0.4)
FU	0	3 (0.4)
LFU	0	4 (0.5)
Overall Worse Post-Baseline	0	10 (1.3)

Note: ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, ALP = Alkaline Phosphatase, ULN = Upper limit of normal range. For Overall Worst Post-Baseline, all laboratory assessments including those obtained from unscheduled visits are included, and the patient is included in the numerator if he/she met the criterion at least once post-baseline.

FIGURE 1. BOX-PLOT OF GLUCOSE CONCENTRATIONS (MMOL/L) POST DOSE IN STUDY 302

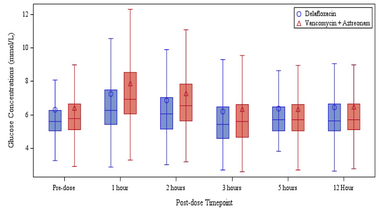
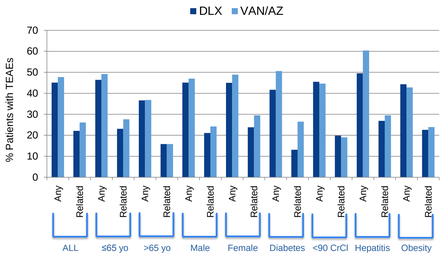


FIGURE 2. SUMMARY OF TREATMENT EMERGENT ADVERSE EVENTS (TEAES) BY SUBGROUPS



- There was one case of *C. difficile* infection on DLX in a patient with prior Bactrim/clindamycin therapy.
- There was no increase in adverse events of special interest previously associated with FQs compared to VAN/AZ.
- There were no cases of tendon rupture or reports of pts with symptoms consistent with FQAD.

CONCLUSION

- Study drug exposures, baseline demographics, and medical history were similar between DLX and VAN/AZ treatment groups in two pooled Phase 3 studies.
- Overall, patients in the DLX treatment group had slightly lower incidence of TEAEs (related or not). The incidence of serious TEAEs was identical between groups, but there were fewer DLX patients with related serious TEAEs and related TEAEs leading to discontinuations.
- The most common treatment-related TEAEs in both treatment groups were gastrointestinal events and headache. In the pooled data, transaminase elevations were reported in 3% and 4% of DLX and VAN/AZ patients, respectively.
- AE incidence between treatment groups was similar regardless of age, gender, renal impairment, diabetic status or hepatitis medical history.
- Overall there was no signal for an increase in hepatic or glucose events for delafloxacin by laboratory testing or in AE reports.
- There was no increase in events previously associated with FQs compared to VAN/AZ including QT prolongation. There were no cases of tendon rupture or reports of patients with symptoms consistent with FQAD.
- Prior dedicated studies have shown that delafloxacin does not have QT-prolongation liability or risk of phototoxicity.[2,3]
- The Pooled phase 3 data from ABSSSI patients demonstrates that delafloxacin was well-tolerated in these patients.

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. Litwin, Jeffrey S. et. al, A Thorough QT Study to Evaluate the Effects of Therapeutic and Supratherapeutic Doses of Delafloxacin on Cardiac Repolarization. 2015, 59 (6): 3469 – 3473.
3. Dawe, RS *et al.*, Lack of Phototoxicity Potential with Delafloxacin in Healthy Male and Female Subjects: Comparison to Lomefloxacin, 2017, submitted.

Refer to full prescribing information at www.baxdela.com