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Results of a Phase 2 Study of Delafloxacin (DLX) Compared to Vancomycin (VAN) and Linezolid (LNZ) in Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

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Abstract

Background
DLX is an investigational fluoroquinolone active against Gram-positive and –negative bacteria, including methicillin- and quinolone-resistant strains of *Staphylococcus aureus* (MRSA, QRSA).

Methods
Multicenter, randomized, double-blind, US trial of adults with wound, burn, major abscesses, or cellulitis infections with ≥75 cm2 of erythema or induration, lymph node enlargement, and at least one sign of systemic infection. Patients were randomized 1:1:1 to receive BID either DLX 300 mg IV, LNZ 600 mg IV, or VAN 15 mg/kg adjusted body weight (ABW) or 1000 - 1250 mg IV for 5 – 14 days. The primary efficacy analysis, performed on the intent to treat (ITT) population at the Follow up (FU) visit (14 days after the first dose of study drug), compared the clinical response rates in the treatment arms by the Cochran-Mantel-Hanszel test.

Results
256 patients randomized, 59% male; mean age 43.2 yrs; total average area of erythema of all infections 292 cm^2; 10% of patients fever at baseline; 21% received single dose of short-acting antibiotic prior to enrolment. Forty-five percent had cellulitis, 29% major abscesses, 25% wound infections and 2% burn infections; 175 (68%) patients had pathogens identified at baseline. *S. aureus* (177) was the most frequent isolate; 67% (119/177) were MRSA (MIC_{90} values were: DLX = 0.12, LNZ = 2, VAN = 0.5, levofloxacin = 4, ciprofloxacin= 16 μg/mL). The AE incidence was similar across treatment arms and the most frequent adverse events were nausea, vomiting and diarrhea.

Success rate at FU Visit (ITT) by Investigator			
Baseline Infection	**DLX n/Total (%)**	**LNZ n/Total (%)**	**VAN n/Total (%)**
All	57/81 (70.4)	50/77 (64.9) p = 0.496*	53/98 (54.1) p=0.031#
Abscess	15/21 (71.4)	16/24 (66.7)	15/28 (53.6)
Cellulitis	28/39 (71.8)	24/32 (75.0)	19/44 (43.2)
Wound	12/19 (63.2)	8/19 (42.1)	19/26 (73.1)
Burn	2/2 (100)	2/2 (100)	0/0

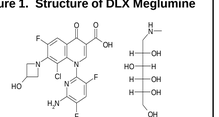
* p value for comparison between DLX and LNZ
# p value for comparison between DLX and VAN

Conclusion
Success rates for DLX dosed at 300 mg BID were numerically greater than LNZ. DLX was statistically significantly more efficacious than VAN (p=0.031) when used to treat adults with a variety of ABSSSI, including those caused by MRSA and QRSA.

Introduction

Delafloxacin (DLX, RX-3341) is an investigational fluoroquinolone active against Gram-positive and –negative bacteria, including methicillin- and quinolone-resistant strains of *Staphylococcus aureus* (MRSA, QRSA). In general, the in vitro antibacterial activity of DLX is more potent than that of levofloxacin (LVX) against most quinolone susceptible pathogens. DLX is more active than LVX against most gram-positive pathogens, including LVX-nonsusceptible isolates ,and notably is 64 fold more active than LVX against MRSA isolates. In addition, DLX has good activity against gram-negative organisms that are susceptible to LVX (1-3). DLX has demonstrated good clinical efficacy in previous Phase 2 trials in complicated skin and skin structure, community-acquired pneumonia, and bronchitis infections. A Phase 2 US study was conducted in 2011 according to new FDA inclusion/exclusion criteria (4) to evaluate the safety and efficacy of DLX compared to linezolid and vancomycin in patients with ABSSSI.

Figure 1. Structure of DLX Meglumine



Methods

This was a stratified, randomized, double blind, Phase 2, multicenter study of IV DLX compared with IV LNZ and IV VAN for the treatment of ABSSSI. Subjects who met entry criteria were randomly assigned in a 1:1:1 ratio to DLX 300 mg every 12 hours, LNZ 600 mg every 12 hours, or VAN 15 mg/kg (based on actual body weight) or according to local standard of care, up to 1250 mg every 12 hours. Treatment was given for 5 to 14 days based on the investigator's judgment.

Subjects aged 18 and above, who had a diagnosis of ABSSSI, defined as cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection, of a minimum surface area of 75 cm^2; had lymph node enlargement caused by the present infection or at least one of the following symptoms of systemic infection: fever ≥ 38° C, lymphangitis, white blood cell (WBC) count ≥ 15,000 cells/μL, or CRP > 5.0 mg/L; and who required, and was a suitable candidate for IV antibiotic therapy. Subjects could not have any hypersensitivities or allergies to any study medications, or any underlying skin condition at the site of infection. Subjects were required to have adequate artery supply to the limb containing the ABSSSI and could not have severely compromised immune systems. Subjects were inpatient or outpatient during their participation in the study. Subjects were evaluated at Screening, daily on Days 1 (first day of study drug therapy) through 14 (or until the last day study drug was administered), at Follow up (Day 14 ± 1 day), and at Late Follow up (Day 21 to Day 28). In addition, a telephone call 30 days after the last dose of study drug was made to each subject who received more than 5 days of study drug treatment to follow up for AEs and concomitant medications.

The primary endpoint, clinical response in the ITT population, was determined by the success rate at Follow up expressed as (success)/(success + failure) in percentage, in which "cure" was classified as success, and improved, indeterminate, and failure responses were treated as failures and was based on the investigator's assessment at the Follow up visit. Clinical response was determined at Follow up and Late Follow up by the investigator's assessment of signs and symptoms of the ABSSSI. Microbiological response was determined for subjects in the microbiologically evaluable (ME) population at the Follow up and late Follow up assessments at both the subject and pathogen levels.

Specimens from the ABSSSI site were collected at Screening and sent to a local laboratory for microbiological Gram stain, culture, and susceptibility testing. If material was available for culture, samples were collected from the ABSSSI site at the Follow up and Late Follow up visits. Wound care management of the ABSSSI, including any surgical procedures, were performed according to the standard of practice of the investigator or institution, excluding dressings with antibacterial properties, topical antibiotic solutions, hyperbaric oxygen therapy, and unplanned surgical debridement after 48 hours.

Results

Table 1. Subject Disposition (All Randomized Subjects)

	DLX (n=81)	LNZ (n=77)	VAN (n=98)	Overall (n=256)
Total number of subjects, n (%)				
Completed	69 (85.2)	63 (81.8)	78 (79.6)	210 (82.0)
Discontinued	12 (14.8)	14 (18.2)	20 (20.4)	46 (18.0)
Study populations, n (%)				
Intent-to-treat (ITT)[a]	81 (100.0)	77 (100.0)	98 (100.0)	256 (100.0)
Safety[b]	78 (96.3)	75 (97.4)	96 (98.0)	249 (97.3)
Microbiological ITT (MITT)[c]	51 (63.0)	58 (75.3)	66 (67.3)	175 (68.4)
Clinically evaluable (CE)[d]	60 (74.1)	58 (75.3)	73 (74.5)	191 (74.6)
Microbiologically evaluable (ME)[e]	34 (42.0)	39 (50.6)	52 (53.1)	125 (48.8)
Reasons for discontinuation				
Investigator discretion	0	1 (7.1)	2 (10.0)	3 (6.5)
Violation of eligibility criteria	0	0	1 (5.0)	1 (2.2)
Prohibited concomitant medication	0	1 (7.1)	0	1 (2.2)
Lost to follow-up	8 (66.7)	6 (42.9)	8 (40.0)	22 (47.8)
Withdrawal of consent	2 (16.7)	5 (35.7)	2 (10.1)	9 (19.6)
Other	2 (16.7)	1 (7.1)	7 (35.0)	10 (21.7)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CE, clinically evaluable; ITT, intent-to-treat; ME, microbiologically evaluable; MITT, microbiological intent-to-treat.
[a] All subjects who were randomized.
[b]All enrolled subjects who received at least 1 dose of study drug.
[c]All ITT subjects who had a baseline bacterial pathogen known to cause ABSSSI.
[d]All ITT subjects who had no major protocol deviations, received at least 80% of total dose in treatment period with a minimum of 8 infusions, had a follow-up visit in the appropriate window (Day 14 ± 1), and did not receive any concomitant or systemic antibacterial therapy with activity against the causative pathogen.
[e]All MITT who also met the criteria for the CE population.

Table 2. Summary of Subject Demographics and Baseline Characteristics (ITT)

	DLX (n=81)	LNZ (n=77)	VAN (n=98)	Overall (n=256)
Sex, n (%)				
Male	49 (60.5)	52 (67.5)	51 (52.0)	152 (59.4)
Female	32 (39.5)	25 (32.5)	47 (48.0)	104 (40.6)
Race, n (%)				
American Indian or Alaska Native	3 (3.7)	2 (2.6)	2 (2.0)	7 (2.7)
Asian	0	1 (1.3)	3 (3.1)	4 (1.6)
Black or African American	10 (12.3)	15 (19.5)	15 (15.3)	40 (15.6)
Native Hawaiian or other Pacific Islander	3 (3.7)	0	0	3 (1.2)
Caucasian	63 (77.8)	58 (75.3)	74 (75.5)	195 (76.2)
Other	2 (2.5)	1 (1.3)	4 (4.1)	7 (2.7)
Ethnicity, n (%)				
Not Hispanic or Latino	62 (76.5)	66 (85.7)	71 (72.4)	199 (77.7)
Hispanic or Latino	19 (23.5)	11 (14.3)	27 (27.6)	57 (22.3)
Age (years)				
Mean (SD)	39.7 (14.26)	44.8 (14.91)	44.8 (15.54)	43.2 (15.08)
Median	36.0	47.0	45.0	43.0
Min, max	19, 81	19, 82	18, 91	18, 91
Weight (kg)				
Mean (SD)	87.4 (18.98)	88.4 (18.95)	85.6 (20.36)	87.0 (19.47)
Median	86.3	89.0	83.0	85.1
Min, max	42.0, 132.9	51.0, 135.4	53.0, 138.9	42.0, 138.9

Abbreviations: max, maximum; min, minimum; SD, standard deviation.

Table 3. Success Rate at Follow-up Visit Using Investigator Assessment (ITT)

	Treatment Group		
Baseline Infection Category	**DLX n/Total (%)**	**LNZ n/Total (%)**	**VAN n/Total (%)**
All subjects	57/81 (70.4)	50/77 (64.9)	53/98 (54.1)
Major cutaneous abscess	15/21 (71.4)	16/24 (66.7)	15/28 (53.6)
Cellulitis/erysipelas	28/39 (71.8)	24/32 (75.0)	19/44 (43.2)
Wound infection	12/19 (63.2)	8/19 (42.1)	19/26 (73.1)
Burn infection	2/2 (100.0)	2/2 (100.0)	0/0

Mean Difference for all subjects (95% CI)[a]: VAN vs DLX -16.3% (-30.3, 2.3) *P* value = 0.031[b]; LNZ vs DLX -5.4% (-20.0, 9.1) *P* value = 0.496.

Abbreviations: CI, confidence interval; IWRS, interactive web response system.
Note: Success rate was expressed as (success)/(success + failure) in percentage and was based on the investigator's assessment at the Follow-up visit. Cure was treated as success, and improved, indeterminate, and failure responses were treated as failures.
[a]Treatment effects and their confidence intervals were based on the overall difference in proportions.
[b]This *P* value of non-zero correlation from Cochran-Mantel-Haenszel statistics stratified by baseline infection indicates the significance of association between treatments and clinical responses (success vs. failure).

The median (minimum, maximum) baseline erythema size for the three treatment groups were: DLX 187.9 cm^2 (7.5, 1555.3), LNZ 197.4 cm^2 (6.1, 4658.9), and VAN 164.6 cm^2 (0 – 1503.6). Demographics across all treatment arms were similar (Table 2). The primary pathogen isolated at baseline was *S. aureus* (Table 5). The percent of subjects with baseline pathogens (n=175) with at least 1 MRSA pathogen was 61%. The primary endpoint the investigator's assessment of clinical response in the ITT population at the Follow-up visit, as determined by the success rate, was achieved by 57 of 81 subjects (70.4%) in the DLX group compared with 50 of 77 subjects (64.9%) in the LNZ group and 53 of 98 subjects (54.1%) in the VAN group. The difference between DLX and VAN was shown to be statistically significant based on an alpha of 0.05 in a two-tailed test with a *P* value of 0.031. In general the adverse events were similar in frequency across treatment arms, except for skin and subcutaneous tissue disorders (pruritis), in which VAN had higher AE rates compared to DLX or LNZ.

Table 4. Success Rate at Follow-up Visit Using Investigator Assessment for MITT and With Subjects Having MRSA at Baseline

	Treatment Group		
Baseline Infection Category	**DLX n/Total (%)**	**LNZ n/Total (%)**	**VAN n/Total (%)**
MITT population			
All subjects	36/51 (70.6)	37/58 (63.8)	41/66 (62.1)
Major cutaneous abscess	12/17 (70.6)	16/23 (69.6)	14/24 (58.3)
Cellulitis/erysipelas	17/21 (81.0)	14/19 (73.7)	11/22 (50.0)
Wound infection	7/13 (53.8)	6/15 (40.0)	16/20 (80.0)
Burn infection	0/0	1/1 (100.0)	0/0
Mean Difference for all subjects (95% CI)[a]: VAN vs DLX –8.5% (–25.6, 8.7) P value = 0.333[b]; LNZ vs DLX -6.8% (–24.4, 10.8) P value = 0.453.			
MITT population with MRSA at Baseline			
All subjects	19/29 (65.5)	21/34 (61.8)	21/32 (65.6)
Major cutaneous abscess	6/11 (54.5)	10/15 (66.7)	8/13 (61.5)
Cellulitis/erysipelas	10/13 (76.9)	9/12 (75.0)	6/11 (54.5)
Wound infection	3/5 (60.0)	2/7 (28.6)	7/8 (87.5)
Burn infection	0/0	0/0	0/0
Mean Difference for all subjects (95% CI) [a]: VAN vs DLX 0.1% (–23.8, 24.0) P value = 0.970[b]; LNZ vs DLX –3.8% (–27.5, 20.0) P value = 0.887.			

Abbreviations: CI, confidence interval; IWRS, interactive web response system; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*.
Note: Success rate was expressed as (success)/(success + failure) in percentage and was based on the investigator's assessment at the Follow-up visit. Cure was treated as success, and improved, indeterminate, and failure responses were treated as failures.
[a]Treatment effects and their confidence intervals were based on the overall difference in proportions.
[b]This *P* value of non-zero correlation from Cochran-Mantel-Haenszel statistics stratified by baseline infection indicates the significance of association between treatments and clinical responses (success vs. failure).

Table 5. Summary of Microbiological Culture Pathogens Isolated at Baseline (ITT)

At Baseline	DLX (n=81)	LNZ (n=77)	VAN (n=98)	Overall (n=256)
Number of Subjects				
With at least 1 pathogen, n (%)	51 (63.0)	57 (74.0)	67 (68.4)	175 (68.4)
With multiple pathogens, n (%)	6 (7.4)	15 (19.5)	8 (8.2)	29 (11.3)
With positive blood cultures, n (%)	0	6 (7.8)	1 (1.0)	7 (2.7)
Without pathogens[a], n (%)	30 (37.0)	20 (26.0)	31 (31.6)	81 (31.6)
With at least 1 *S. aureus*, n (%)	45 (55.6)	53 (68.8)	61 (62.2)	159 (62.1)
With at least 1 MRSA, n (%)	34 (42.0)	37 (48.1)	35 (35.7)	106 (41.4)
With at least 1 MSSA, n (%)	11 (13.6)	16 (20.8)	26 (26.5)	53 (20.7)
Number of Pathogens[b]				
Gram-positive pathogens	58	73	74	205
Staphylococcus aureus	48	65	64	177
MRSA	36	45	38	119
MSSA	12	20	26	58
Streptococcus spp.	5	11	6	17
Staphylococcus lugdunensis	4	0	0	4
Enterococcus faecalis	1	1	1	3
Finegoldia magna	0	0	1	1
Peptostreptococcus asaccharolyticus	1	0	0	1
Gram-negative pathogens	4	0	2	6
Acinetobacter baumannii	1	0	0	1
Citrobacter amalonaticus	1	0	0	1
Enterobacter cloacae	1	0	0	1
Klebsiella pneumoniae	0	0	1	1
Proteus mirabilis	0	0	1	1
Pseudomonas aeruginosa	1	0	0	1
Anaerobe	2	1	0	3
Eikenella corrodens	2	1	0	3

Abbreviations: MRSA, methicillin-resistant *S aureus*; MSSA, methicillin-susceptible *S aureus*.
Note: MRSA was defined by Clinical and Laboratory Standards Institute (CLSI) breakpoint for *S aureus* with oxacillin MIC ≤ 4 μg/mL.
Note: MSSA was defined by CLSI breakpoint for *S aureus* with oxacillin MIC ≤ 2 μg/mL.
[a] Subjects without pathogens included subjects without a baseline culture, subjects with negative baseline cultures, and subjects with growth of non-pathogens at Baseline.
[b] Number of pathogens isolated at Baseline included pathogens of subjects that were not treated but had pathogens at Screening.

Table 6. Treatment-Emergent Adverse Events Occurring With at Least 5% Frequency in Any Treatment Group by System Organ Class and Preferred Term (Safety Population)

Primary System Organ Class Preferred Term, n (%)[a]	Delafloxacin (n=78)	Linezolid (n=75)	Vancomycin (n=96)	Overall (n=249)
Number of subjects with at least 1 treatment-emergent adverse event, n (%)	58 (74.4)	54 (72.0)	62 (64.6)	174 (69.9)
Blood and lymphatic system disorders	2 (2.6)	2 (2.7)	5 (5.2)	9 (3.6)
Anaemia	2 (2.6)	0	3 (3.1)	5 (2.0)
Thrombocytopenia	0	2 (2.7)	0	2 (0.8)
Cardiac disorders	2 (2.6)	2 (2.7)	2 (2.1)	6 (2.4)
Gastrointestinal disorders	31 (39.7)	26 (34.7)	22 (22.9)	79 (31.7)
Abdominal pain	3 (3.8)	2 (2.7)	1 (1.0)	6 (2.4)
Constipation	1 (1.3)	5 (6.7)	4 (4.2)	10 (4.0)
Diarrhoea	12 (15.4)	5 (6.7)	4 (4.2)	21 (8.4)
Nausea	17 (21.8)	16 (21.3)	13 (13.5)	46 (18.5)
Vomiting	10 (12.8)	6 (8.0)	8 (8.3)	24 (9.6)
General disorders and administrative site conditions	17 (21.8)	17 (22.7)	22 (22.9)	56 (22.5)
Fatigue	5 (6.4)	3 (4.0)	6 (6.3)	14 (5.6)
Infusion site pain	4 (5.1)	7 (9.3)	5 (5.2)	16 (6.4)
Infusion site swelling	1 (1.3)	0	4 (4.2)	5 (2.0)
Pyrexia	2 (2.6)	3 (4.0)	1 (1.0)	6 (2.4)
Infections and infestations	21 (26.9)	22 (29.3)	18 (18.8)	61 (24.5)
Abscess limb	2 (2.6)	4 (5.3)	2 (2.1)	8 (3.2)
Cellulitis	3 (3.8)	3 (4.0)	5 (5.2)	11 (4.4)
Fungal infection	1 (1.3)	0	4 (4.2)	5 (2.0)
Skin infection	2 (2.6)	4 (5.3)	2 (2.1)	8 (3.2)
Urinary tract infection	2 (2.6)	2 (2.7)	2 (2.1)	6 (2.4)
Injury, poisoning and procedural complications	1 (1.3)	2 (2.7)	3 (3.1)	6 (2.4)
Investigations	4 (5.1)	2 (2.7)	6 (6.3)	12 (4.8)
Metabolism and nutrition disorders	3 (3.8)	7 (9.3)	8 (8.3)	18 (7.2)
Hyperglycaemia	2 (2.6)	1 (1.3)	2 (2.1)	5 (2.0)
Pain in extremity	2 (2.6)	1 (1.3)	4 (4.2)	7 (2.8)
Nervous system disorders	16 (20.5)	9 (12.0)	10 (10.4)	35 (14.1)
Dizziness	5 (6.4)	1 (1.3)	1 (1.0)	7 (2.8)
Headache	5 (6.4)	5 (6.7)	5 (5.2)	15 (6.0)
Psychiatric disorders	3 (3.8)	3 (4.0)	5 (5.2)	11 (4.4)
Insomnia	2 (2.6)	1 (1.3)	3 (3.1)	6 (2.4)
Respiratory, thoracic and mediastinal disorders	2 (2.6)	3 (4.0)	5 (5.2)	10 (4.0)
Skin and subcutaneous tissue disorders	14 (17.9)	12 (16.0)	27 (28.1)	53 (21.3)
Erythema	1 (1.3)	3 (4.0)	2 (2.1)	6 (2.4)
Pruritus	6 (7.7)	6 (8.0)	20 (20.8)	32 (12.9)
Rash	2 (2.6)	5 (6.7)	2 (2.1)	9 (3.6)
Vascular disorders	4 (5.1)	3 (4.0)	7 (7.3)	14 (5.6)

Note: A treatment-emergent adverse event was defined as any event not present before exposure to study drug or any event already present that worsened in either intensity or frequency after exposure to study drug. Adverse events were coded using MedDRA version 13.1.
[a]Within a system organ class, subjects might have reported more than 1 type of adverse event.

Conclusions

- Investigator assessment of clinical response at Follow-up based on subject signs and symptoms determined a success rate of 70.4% in the DLX group compared with 64.9% in the LNZ group and 54.1% in the VAN group. For the primary endpoint, the difference between DLX and VAN was shown to be statistically significant based on an alpha of 0.05 in a two-tailed test with a *P* value of 0.031.
- DLX and LNZ were clinically effective in the treatment of subjects with ABSSSI, including those caused by MRSA.
- The incidence of TEAEs was similar among treatment groups. The TEAEs most frequently considered possibly, probably, or definitely related to study drug included nausea, pruritus, vomiting, diarrhea, and infusion site pain.
- A total of 13 subjects (5.2%) experienced SAEs, 5 of 78 subjects (6.4%) in the delafloxacin group, 2 of 75 subjects (2.7%) in the linezolid group, and 6 of 96 subjects (6.3%) in the vancomycin group. None of the SAEs were considered related to study drug.
- This is the second Phase 2 clinical study involving skin and skin structure infections demonstrating that DLX is effective and well tolerated (5).
- DLX appears to be a potentially promising new antibiotic for the treatment of complicated ABSSSI, including those infections caused by MRSA.

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