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Objective Measures of Clinical Efficacy in a Phase 2b Exploratory Study of Delafloxacin Compared to Vancomycin and Linezolid in Adults with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

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Abstract

Objectives: Understand the performance of Delafloxacin (DLX) vancomycin (VAN) and Zyvox (LNZ) against the new objective endpoints defined by the FDA. Efficacy was measured by manual and digital measurements of erythema.
Methods: Multicenter, randomized, double-blind, US trial of adults with infections ≥75 cm^2 of erythema or induration, lymph node enlargement, and one or more sign of systemic infection. Patients were randomized 1:1:1 to receive BID 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 objective efficacy endpoint analysis of total area of erythema, and length of leading edge of major and minor axes of erythema, performed on the intent to treat (ITT) population 48-72 hours after the first dose of study drug was measured digitally using acetate tracings and manually with a disposable rulers, compared the objective measures response rate of either cessation of lesion spread or reduction of lesion spread and absence or resolution of fever 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. *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).

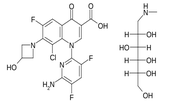
	Success rate at 48-72 Hours (ITT) by Lesion Cessation or Reduction and Absence or Resolution of Fever					
	Digital			Manual		
	DLX	LNZ	VAN	DLX	LNZ	VAN
Cessation of lesion spread	61/78 (78.2)	56/71 (74.7)	69/95 (72.6)	61/81 (75.3)	62/77 (80.5)	74/97 (76.3)
Reduction 10%	60/78 (76.9)	56/75 (74.7)	68/95 (71.6)	60/80 (74.1)	60/77 (77.9)	72/97 (74.2)
Reduction 20%	58/78 (74.4)	55/75 (73.3)	65/95 (68.4)	59/80 (72.8)	57/77 (74.0)	70/97 (72.2)
Reduction 30%	56/78 (71.8)	50/75 (66.7)	57/95 (60.0)	58/80 (71.6)	55/77 (71.4)	63/97 (64.9)

Conclusions: Success rates for DLX dosed at 300 mg BID were numerically greater than LNZ and VAN for digital measurement at all levels. Success rates for DLX were numerically greater than VAN for ≥20% reduction and nearly statistically significant for ≥30% reduction. Standard deviation (STD) for digital measurement was one third of manual measurements STD.

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

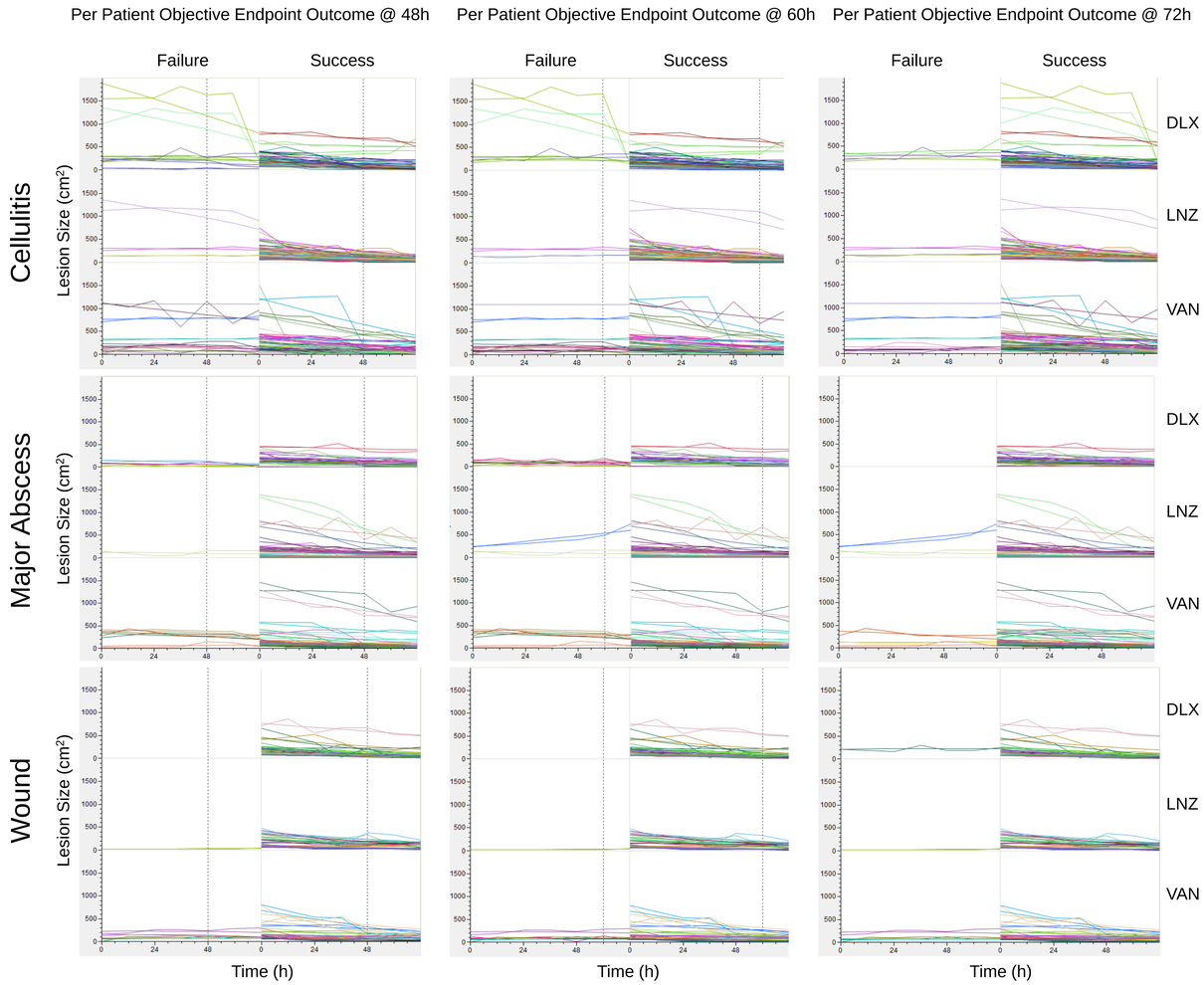
This was a stratified, randomized, double blind, Phase 2, multicenter study of IV DLX compared with IV LNZ and IV VAN for the treatment of ABSSSI. Subjects who met entry criteria were randomly assigned in a 1:1:1 ratio to DLX 300 mg every 12 hours, LNZ 600 mg every 12 hours, or VAN 15 mg/kg (based on 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 cm2; 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.

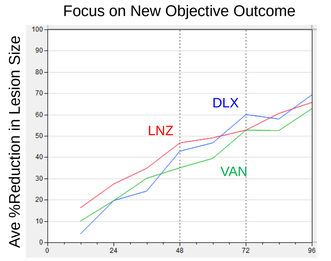
Erythema and induration of the lesion were measured twice daily (every 12 hours), both manually and digitally, for the first five days as well as at end of therapy, Follow up and Late Follow up. Manual measurement was achieved using disposable rulers, capturing length by width to afford the area. Digital measurement was achieved through the use of duplicate acetate tracings that were subsequently scanned; the total area of the tracing was captured digitally. Different colored pens were used to trace erythema (red) and induration (green). If a visible lesion existed, it was traced in black, and that area was subtracted from the total area. Body temperature was measured four times daily (every 6 hours) as well as end of therapy, Follow up and Late Follow up. Surrogate markers of inflammation or infection, including WBC, CRP and IL-6 levels, were captured twice daily (every 12 hours) for the first five days as well as at end of therapy, Follow up and Late Follow up.

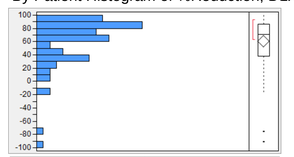
The primary endpoint, clinical response in the ITT population, was determined by the success rate at Follow up expressed as (success)/(success + failure) in percentage, in which "cure" was classified as success, and improved, indeterminate, and failure responses were treated as failures and was based on the investigator's assessment at the Follow up visit. The secondary endpoint, which is the focus of this poster, was defined as both the cessation of lesion spread and the absence or resolution of fever in the 48-72h timeframe in the ITT population. Clinical response was determined at Follow up and Late Follow up by the investigator's assessment of signs and symptoms of the ABSSSI.

Results

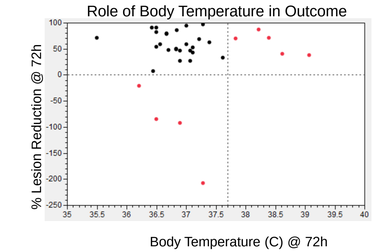


Results





Descriptive Statistic	Value
Mean	60.19
Std Dev	37.21
Std Err Mean	4.32
Upper 95% Mean	68.81
Lower 95% Mean	51.57



N=35 subjects presenting with or experiencing fever within the first 24h.

Conclusions

- DLX was equally efficacious in the treatment of ABSSSI as LNZ and VAN when compared using the objective endpoint of cessation of lesion spread and absence or resolution of fever in the 48-72 hour timeframe.
- The time point for maximal benefit for all three compounds is 72 hours.
- DLX was numerically better than LNZ and VAN in treating ABSSSI when compared using the objective end point of >20% or >30% reduction in lesion size in 48-72 hours.
- DLX was shown to produce a larger percent reduction in the lesion size at 72 hours as compared to either LNZ or VAN with a mode at nearly 80%.
- The objective measure of body temperature did not correlate with resolution or worsening of the infection.

References

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