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Effect of a Single Prior Dose Short Acting Antibiotic on Clinical Efficacy in a Phase 2 Exploratory Study of Delafloxacin (DLX) Compared to Vancomycin (VAN) and Linezolid (LNZ) in Adults with Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

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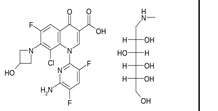
Abstract

Objectives: DLX is an investigational fluoroquinolone active against Gram-positive and –negative bacteria, including methicillin- and quinolone-resistant strains of *Staphylococcus aureus* (MRSA, QRSA). This is analysis of a Phase 2b Study to understand the impact of the use of a single dose of a short acting antibiotic prior to enrolment in the study and the potential impact on overall success rates.
Methods: Multicenter, randomized, double-blind, US trial of adults with ABSSSI ≥75 cm² of erythema or induration, lymph node enlargement, and one 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 primary endpoint of global assessment (GA) of cure was evaluated at test of cure visit (TOC) (day 5-14), follow-up (FU) (day 14-15) and late follow-up (LFU) (day 21-28) in the treatment arms and 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 administered and was measured digitally using acetate tracings and manually with a disposable rulers, compared the objective measures response of cessation of lesion spread and absence or resolution of fever in the treatment arms. Both the primary and the objective endpoints were evaluated using Cochran-Mantel-Hanszel test to compare the treatment arms in each endpoint.
Results: 256 patients randomized, 20.7% of subjects received a single dose of short-acting antibiotic before enrollment. The use of a short-acting antibiotic before enrollment did not impact efficacy rates. Twenty-five of 98 subjects (25.5%) in the VAN arm, 16 of 77 subjects (20.8%) in the LNZ arm, and 12 of 81 subjects (14.8%) in the DLX arm received prior antibacterial therapy. Twelve of 25 subjects (48.0%) in VAN arm receiving prior antibacterial therapy failed, 8 of 16 (50.0%) in LNZ arm and 6 of 12 (50.0%) in DLX.
Conclusion: Neither the primary end point, GA, nor the assessment of the objective end point as measured at 48-72 hours was affected by the use of a single dose of a short-acting prior antibiotic.

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.

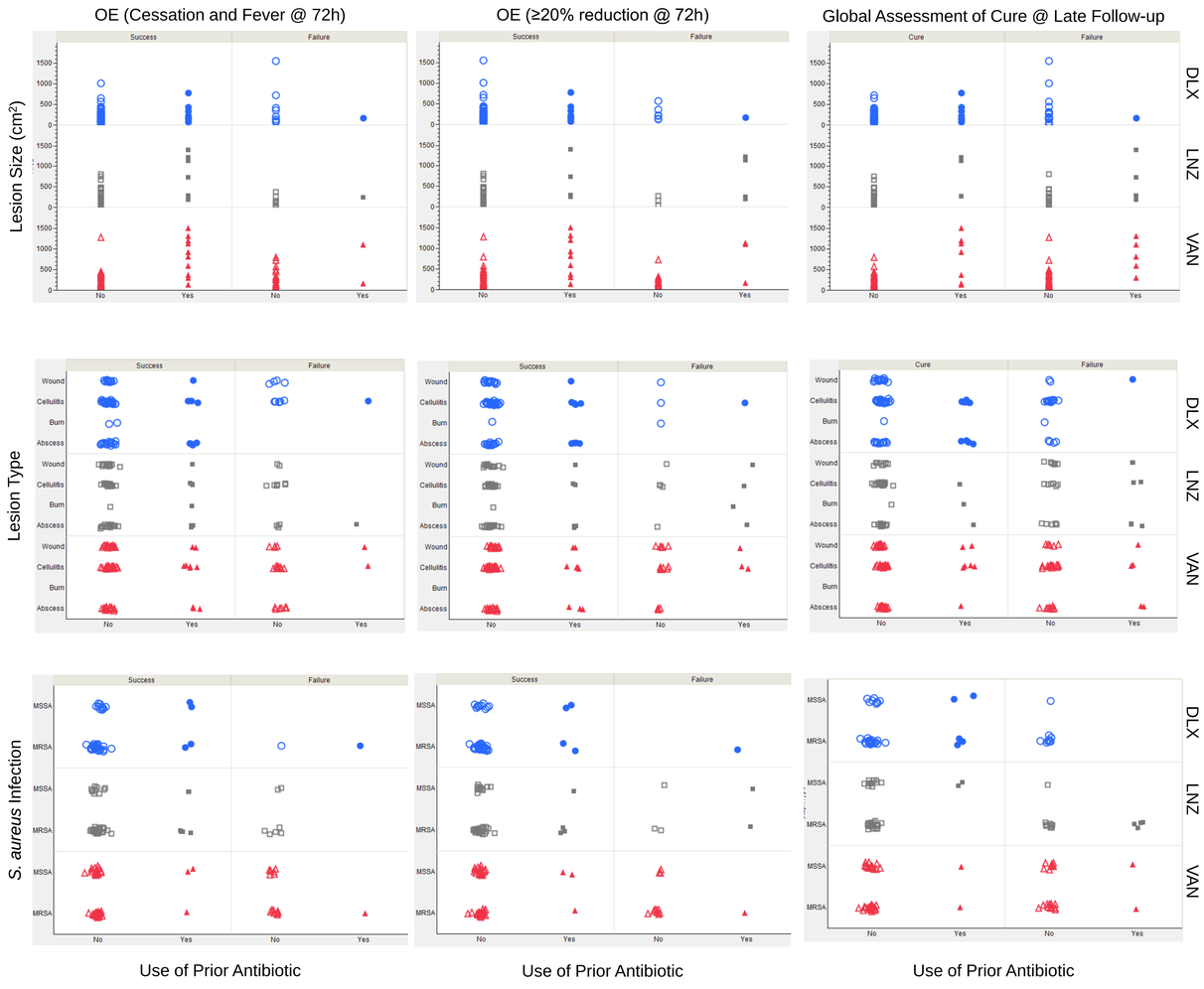
Subjects aged 18 and above, who had a diagnosis of ABSSSI, defined as cellulitis/erysipelas, wound infection, major cutaneous abscess, or burn infection, of a minimum surface area of 75 cm2; had lymph node enlargement caused by the present infection or at least one of the following symptoms of systemic 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. Clinical response was determined at Follow up (FU) and Late Follow up (LFU) by the investigator's assessment of signs and symptoms of the ABSSSI. The secondary endpoint 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. This was defined as the Objective Endpoint (OE) . Additionally, patients were evaluated for reduction of lesion size from baseline and the absence or resolution of fever in the 48-72h timeframe in the ITT population.

Microbiological endpoints were defined for both all of the endpoints described above. 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



Results

Objective Endpoints @ 72h (cessation and fever)	%Success	%Failure
No Prior Antibiotic	86.21	13.79
Yes Prior Antibiotic	90.70	9.30
Fishers Exact Test (2-tail)	0.6177	
Cochran-Mantel-Haenszel Prob χ^2 (grouped by drug)	0.4323	

New Objective Endpoint (20% Reduction)	%Success	%Failure
No Prior Antibiotic	88.24	11.76
Yes Prior Antibiotic	77.14	22.86
Fishers Exact Test (2-tail)	0.1027	
Cochran-Mantel-Haenszel Prob χ^2 (grouped by drug)	0.0716	

Global Assessment @ LFU	%Cure	%Failure
No Prior Antibiotic	88.55	11.45
Yes Prior Antibiotic	83.95	16.05
Fishers Exact Test (2-tail)	0.3190	
Cochran-Mantel-Haenszel Prob χ^2 (grouped by drug)	0.3070	

Conclusions

- The use of a single, short-acting antibiotic does not appear to influence clinical outcomes and is independent of:
  - Lesion size and
  - Lesion type.

  This holds for both objective outcome measures, including lesion-size reduction, and for global assessment of cure at both follow-up (not shown) and late follow-up visits.
- Analysis of the key pathogen (*S. aureus*) in the study reveals no difference in clinical outcomes for MSSA and MRSA.
- There is weak to no correlation among these variables when considering drug used in the treatment arm (DLX, LNZ and VAN).

References

1. Nilius AM, Shen LL, Hensey-Rudloff D, Almer LS, Beyer JM, Balli DJ, Cai Y, Flamm RK. In vitro antibacterial potency and spectrum of ABT-492, a new fluoroquinolone. Antimicrob Agents Chemother 2003; 47:3260-3269.
2. Almer LS, Hoffrage, JB, Keller EI, Flamm RK, Shortridge V. In vitro and bactericidal activities of ABT-492, a novel fluoroquinolone, against gram-positive and gram-negative organisms. Antimicrob Agents Chemother 2004; 48:2771-2777.
3. Harnett SJ, Fraise AP, Andrews JM, Jevons G, Brenwald NP, Wise R. Comparative study of the in vitro activity of a new fluoroquinolone, ABT-492. J Antimicrob Chemother. 2004; 53:783-792. Epub 2004 Mar 31.
4. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (US). Draft guidance. Acute bacterial skin and skin structure infections: developing drugs for treatment. August 2010.
5. O'Riordan W, Babazadeh S, Manos P, Mascolo M, Mehra P, Surber J, Hopkins S, and Burak E. Results of a Phase 2 Study Comparing Two Doses of Delafloxacin to Tigecycline in Adults with Complicated Skin and Skin Structure Infections;, 19th ECCMID, Helsinki, Finland, May 16-20, 2009.