POSTER #1154

EVALUATION OF DIGITAL VERSUS MANUAL MEASURES OF LESION SIZE IN A PHASE 3 TRIAL OF DELAFLOXACIN (DLX) IN PATIENTS WITH ACUTE BACTERIAL SKIN AND SOFT TISSUE INFECTIONS (ABSSSI)

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ABSTRACT

Background: The primary endpoint in the FDA guidance on development of antibiotics for acute bacterial skin and structure infections (ABSSSI) requires ≥20% reduction in lesion size at 48-72h after start of therapy. Either manual measures (MM) or digital measures (DM) may be used, but assessment of the correlation of these methods has been limited. A Phase 3 ABSSSI trial of DLX vs vancomycin (VAN) used MM and DM to document the resolution of infected lesions during the study and these measures were compared to assess the reliability and correlation of these methods.

Methods: Adult patients with ABSSSIs were enrolled in a randomized, double-blind trial of DLX vs VAN with aztreonam (VAN/AZ). Measurements of lesion size were performed at baseline, 48-72h after the start of treatment, and at other defined time points, including end of treatment (EOT). A disposable ruler was used for the MM of the longest length and the perpendicular width of lesions. DM were obtained by digital planimetry of the photographed lesion, which had been contoured by the investigator with a disposable marker. The analysis compared MM to DM.

Results: 660 patients were enrolled, with a baseline mean lesion size according to DM and MM of 306.98 cm^2 and 510.70 cm^2, respectively. Using corresponding DM and MM at all time points, the 2 methods were well correlated, with a correlation coefficient of 0.9334. At 48-72h after initiation of therapy, DM and MM showed similar percentages of subjects for whom treatment stopped the spread of lesion (94.4% vs 94.2%, respectively) and ≥20% reduction in lesion size (85.7% vs 87.8%, respectively). At EOT, DM and MM showed similar percentages of subjects for whom treatment resulted in ≥70% reduction in lesion size (86.4% vs 88.1%, respectively) and ≥90% reduction in lesion size (61.3% vs 64.6%, respectively).

Conclusion: MM consistently exceeded DM as expected, given manual surface areas were calculated as a rectangle. The 2 methods were well correlated, with comparable assessments of percent change from baseline over time. Either MM or DM could serve as the primary source of data on lesion size and response to therapy by showing percent change in lesion size.

INTRODUCTION

- 2013 FDA guidance for the development of antibiotics for the treatment of ABSSSI supports a primary efficacy endpoint that requires ≥20% reduction in lesion size at 48-72 hours.[1]
- Historically, ABSSSI trials have used MM to document changes in lesion size.
- However, published data on digital planimetry demonstrate differences from MM as large as 55.3% compared to DM.[1]
- The Phase 3 RX-3341-302 study performed DM with the Quantificare (QC) 2D DermaVix™ camera as well as MM.
- The 302 study was conducted with DLX, an investigational, anionic fluoroquinolone in development for the treatment of serious skin infections.

METHODS

- The 302 study was a multicenter, randomized double-blind ABSSSI trial, and patients were randomized 1:1 to receive DLX or VAN/AZ for 5-14 days.
- MM and DM of infection sites were obtained at Screening, Day 1, Day 2, twice on Day 3, Day 4, EOT, follow-up (FU), and late follow-up (LFU).

METHODS

- Manual measurements of each lesion were taken with a disposable ruler by assessing the longest length (longest dimension of the infection) and the longest perpendicular width of erythema and induration. Data points were recorded on electronic case report forms (eCRFs) and used to calculate the area.
- Digital measurements were obtained with the 2D DermaViz™ camera that uses a Nikon D5100 camera body and a custom built "Dual Beam" light system that allows users to take high-resolution, focused, reproducible photos at a fixed distance (Figure 1).
- Using the Dual Beam system, investigators photographed infection sites by positioning the camera perpendicular to each lesion (Figure 2). Optimal distance is achieved when the 2 red circles projected by the dual beams are exactly super-imposed.
- Prior to photographing each lesion, investigators drew the contours of the erythema and induration areas on the skin using different colored pens. Calibration stickers with patient identification codes were placed next to the infected area as shown in Figure 2.
- The standardization of the digital photography method allowed investigators to create repeatable quality photos.
- DermaPix® 2.22.2 software was used by qualified QC personnel to obtain planimetry measurements from the digital photographs by calibrating precise pixels with the ruler visible in the image and using 2D splines to electronically retrace the erythema and induration regions drawn in pen by investigators.
- The surface area was computed by measuring the number of pixels or proportion of pixels enclosed by the splines.
- In the case of significant skin surface curvature, investigators were trained to take several overlapping photographs of lesions and surface computation was performed piecewise. This method enabled the management of holes or several unconnected lesions in case an infected area was split into several parts over time.

FIGURE 1: QUANTIFICARE'S 2D DERMAVIZ CAMERA USING DUAL BEAM POINTERS FOR STANDARDIZATION

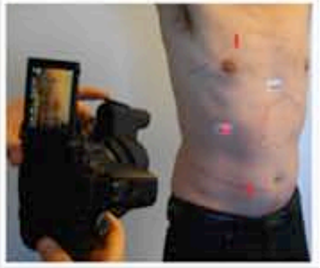
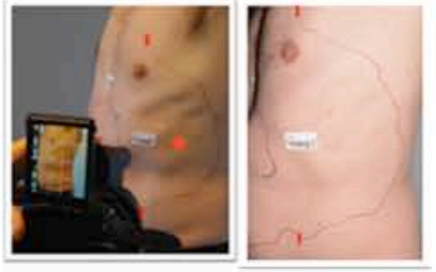


FIGURE 2: QUANTIFICARE'S 2D DERMAVIZ CAMERA PHOTOGRAPHING LARGE ABSSSI AREAS FROM THE SIDES AND THE RESULTING IMAGE TAKEN



RESULTS

Table 1. All ITT Patients

	Baseline Lesion Size		
	n	Mean (SD)	Median (Min, Max)
Area Measured Digitally	654	306.98 (311.21)	199.55 (32.60, 2665.96)
Area Measured Manually	658	510.70 (575.42)	314.48 (76.50, 4200.00)

Patients [n (%)] with Change from Baseline to 48-72 hours				
	Cessation of Spread	≥20% Decrease from Baseline	≥30% Decrease from Baseline	≥40% Decrease from Baseline
Area Measured Digitally	578 (94.4%)	525 (85.8%)	492 (80.4%)	451 (73.7%)
Area Measured Manually	580 (94.2%)	541 (87.8%)	517 (83.9%)	473 (76.8%)

Patients [n (%)] with Change from Baseline to EOT				
	Cessation of Spread	≥50% Decrease from Baseline	≥70% Decrease from Baseline	≥90% Decrease from Baseline
Area Measured Digitally	604 (98.7%)	574 (93.8%)	529 (86.4%)	375 (61.3%)
Area Measured Manually	608 (98.9%)	588 (95.6%)	542 (88.1%)	397 (64.6%)

FIGURE 5: BOX AND WHISKER PLOT OF PERCENT CHANGE FROM BASELINE IN PLANIMETRY OF ERYTHEMA AT EACH VISIT (ITT)

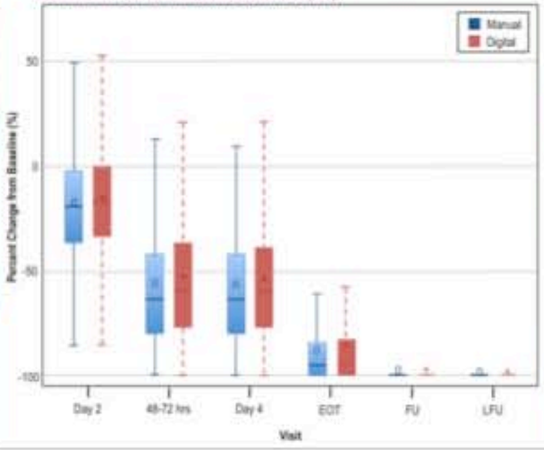


FIGURE 6: PHOTOS FROM SCREENING, EOT, AND LFU FROM THE DLX PHASE 3 302 STUDY

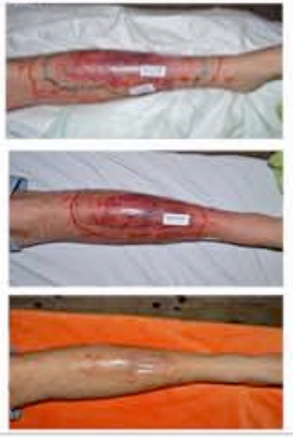
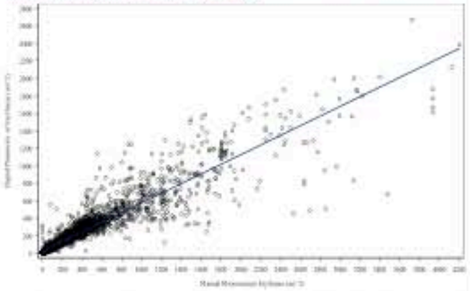


FIGURE 3: SCATTERPLOT OF DIGITAL PLANIMETRY OF ERYTHEMA AND MANUAL MEASUREMENT OF ERYTHEMA



- MM were approximately 1.5 times greater than the DM, which is expected since MM (length x width) generates the area of a rectangle that overestimates the actual lesion size (Table 1).
- The correlation of the DM and MM was high with a correlation coefficient of 0.9334; (Figure 3).
- MM and DM produced comparable results for percent change in lesion size over all time points (Figures 5 and 6).

CONCLUSION

- There is a high correlation between MM and DM using the Dermaviz system. The difference between the percent of patients within each classification of lesion size reduction from baseline by MM and DM was small, with a maximum of 5.4% point separation.
  - This digital measurement method was highly consistent. The maximal difference from MM in this study was substantially smaller than previously reported for digital planimetry, which demonstrated differences from manual measures as large as 55.3%.[2]
- The high correlation between the measurement values indicates that the DermaViz system is appropriate for use in ABSSSI trials as a primary method of data recording.
- The digital planimetry offers the advantage of documenting and preserving evidence of changes over time on the severity of pathology. It also allows for assessment by a central expert, if needed.

REFERENCES

1. US Food and Drug Administration (FDA). Guidance for Industry: Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. October 2013.
2. Bien P, Arata CD, Prokocimer P. Comparison of Digital Planimetry and Ruler Technique To Measure ABSSSI Lesion Sizes in the ESTABLISH-1 Study. *Surgical Infections*. 2014;15(2):105-110. doi: 10.1089/sur.2013.070.