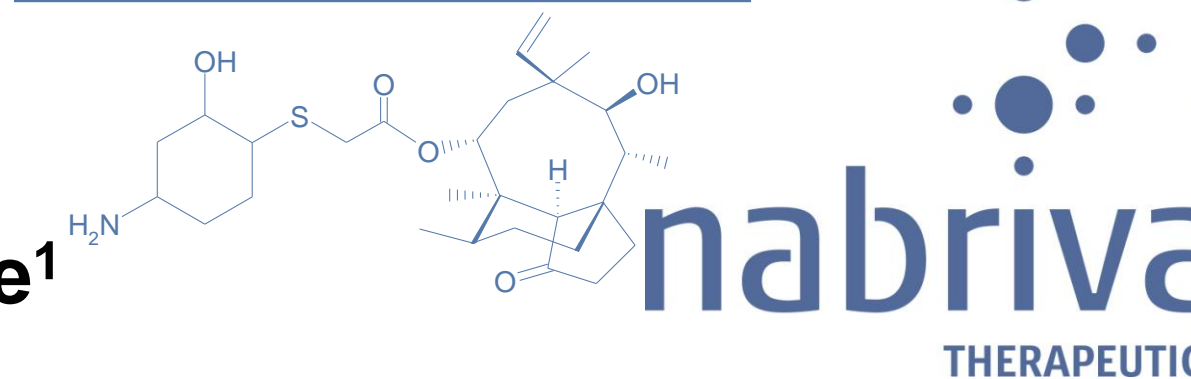


Pharmacokinetic-Pharmacodynamic Analysis for Efficacy of BC-3781 Using New Clinical Trial Endpoints in Patients with Acute Bacterial Skin and Skin Structure Infection

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ABSTRACT

Background: BC-3781, a pleuromutilin antimicrobial agent, is being developed for the treatment of patients with acute bacterial skin and skin structure infection (ABSSSI). The recently updated FDA guidance for industry for developing drugs for ABSSSI advocates collection of continuous measures of drug response (e.g., extent of infection). Using Phase 2 data, pharmacokinetic-pharmacodynamic (PK-PD) relationships for efficacy using new and traditional endpoints were evaluated.

Methods: AUC₀₋₂₄ values were derived using a previously-developed population PK model for microbiologically evaluable patients with PK who received BC-3781 100 or 150 mg q12h. Day 1 total-drug AUC₀₋₂₄:MIC ratio, the PK-PD index associated with efficacy (CAAC 2010, abstract F1-2108), was evaluated. Relationships for clinical and microbiological (micro) response and time to reduction in the extent of erythema and swelling were examined for AUC₀₋₂₄:MIC, and AUC₀₋₂₄:MIC ratio.

Results: Dose-related differences between response and time to erythema and swelling reduction were not observed for the 80 evaluable patients (74 with *S. aureus*). While PK-PD relationships for AUC₀₋₂₄ or MIC alone were weak or not evident, such relationships were apparent for AUC₀₋₂₄:MIC ratio. Micro success was 99% and 71% for patients with AUC₀₋₂₄:MIC ratios \geq and $<$ 35.8 ($p \leq 0.02$), respectively. AUC₀₋₂₄:MIC ratios of 34-38 were associated with shorter time to erythema and swelling reduction (See Table 2).

Conclusions: While differences between the 2 doses for new and traditional endpoints were not identified, PK-PD relationships for these endpoints were identified after indexing AUC₀₋₂₄ to MIC. AUC₀₋₂₄:MIC ratios associated with micro response were similar to those identified for time-to-event endpoints.

INTRODUCTION

BC-3781, a pleuromutilin antimicrobial agent, demonstrates *in vitro* activity against a wide range of bacterial pathogens including those causing acute bacterial skin and skin structure infection (ABSSSI) such as *Staphylococcus aureus*, including methicillin-resistant strains.

BC-3781 is being developed for the treatment of patients with ABSSSI. The recently updated FDA guidance for industry for developing drugs for ABSSSI advocates collection of continuous measures of drug response (e.g., extent of infection).

The objectives of these analyses were to characterize the pharmacokinetic-pharmacodynamic (PK-PD) relationships for efficacy using dichotomous, continuous, and time-to-event endpoints and to evaluate PK-PD target attainment and model-predicted response percent probabilities to support BC-3781 dose selection for future Phase 3 clinical studies.

MATERIAL/METHODS

Study Population:

Data for these analyses were obtained from a Phase 2 study conducted to evaluate the clinical response of 2 BC-3781 dosing regimens, 100 or 150 mg IV administered over 2 h q12h for 5 to 14 days, in patients with ABSSSI.

The analysis population consisted of patients who received BC-3781, were microbiologically evaluable, and had PK data. A subset of patients with ABSSSI due to *S. aureus* was evaluated as a separate analysis population.

MATERIALS & METHODS (cont.)

Determination of PK-PD Index:

The PK-PD index of interest was the AUC₀₋₂₄:MIC ratio, which has been demonstrated to be most predictive of BC-3781 efficacy [1]. The determination of Day 1 total-drug AUC₀₋₂₄ was based on a previously-developed population PK model [2].

PK-PD Analyses:

- Univariable relationships for dichotomous, continuous and time-to-event efficacy endpoints were evaluated as described below:
 - Univariable relationships for dichotomous efficacy endpoints, clinical or microbiological response at test-of-cure (TOC), cessation of spread in the area of erythema and swelling on Day 3, and $\geq 20\%$ reduction from baseline in the area of erythema and swelling on Day 3, were examined using chi-square or Fisher's exact tests for categorical independent variables and logistic regression for continuous independent variables.
 - Univariable relationships for continuous efficacy endpoints, percent change from baseline in the area of erythema and swelling on Days 2, 3, 4, and 5 and at end-of-therapy and TOC, were evaluated using linear regression.
 - Univariable relationships for time-to-event efficacy endpoints were examined by using log rank tests for categorical independent variables and Cox proportional hazards regression for continuous independent variables.
 - Continuous independent variables were evaluated in their original form and as 2- and 3-group categorical variables to account for potential nonlinearity and non-monotonicity, respectively.
- Multivariable analyses were considered for each efficacy endpoint if an intuitive and significant univariable relationship between a measure of BC-3781 exposure or MIC value and given efficacy endpoint was identified.

PK-PD Target Attainment and Model-Predicted Response Analyses:

- Using mean parameter estimates and the variance-covariance matrix from the population PK model for BC-3781 [2], structural PK parameter estimates were simulated for 2000 patients and Day 1 total-drug AUC₀₋₂₄ values were calculated for each simulated patient by numerical integration.
- PK-PD target attainment and model-predicted response percent probabilities based on the univariable analyses for Day 1 total-drug AUC₀₋₂₄:MIC ratio and dichotomous efficacy endpoints described above were evaluated for each dosing regimen, by MIC value and over the MIC distribution for BC-3781 for *S. aureus* based on US/EU surveillance data from the SENTRY Antimicrobial Surveillance Program [3].

RESULTS

Summary of Analysis Populations:

- A total of 80 and 78 patients were evaluable for PK-PD analyses of time-to-event efficacy endpoints and clinical and microbiological response at TOC, respectively. Among these patients, 74 had ABSSSI due to *S. aureus* and were evaluable for PK-PD analyses of time-to-event efficacy endpoints, while 72 were evaluable for clinical and microbiological response at TOC.

RESULTS

Univariable PK-PD Analyses:

- Regardless of analysis population, the evaluation of the univariable relationships between dosing regimen, Day 1 total-drug AUC₀₋₂₄:MIC value, and Day 1 total-drug AUC₀₋₂₄:MIC ratio, and each of the dichotomous and time-to-event efficacy endpoints demonstrated consistent and similar findings.
 - While statistically significant univariable relationships were not observed for dosing regimen and Day 1 total-drug AUC₀₋₂₄ or not always significant at the 0.05 level for MIC, such relationships were evident for Day 1 total-drug AUC₀₋₂₄:MIC ratio. Examples of such relationships based on data from patients with *S. aureus* infection are described in Figures 1 and 2.
 - Figure 1 shows a comparison of univariable relationships between dosing regimen (A), Day 1 total-drug AUC₀₋₂₄ (evaluated as a 2 group variable, defined as < 9.6 and ≥ 9.6) (B), and MIC value (evaluated as a 2 group variable, defined as 0.12 and 0.25 or 0.5 mg/L) (C), and time to 20% reduction from baseline in the area of swelling.
 - Figure 2 shows the univariable relationships between Day 1 total-drug AUC₀₋₂₄:MIC ratio, evaluated as a 2 group variable, and time to 20% reduction from baseline in the area of erythema (A) and swelling (B).

Figure 1. Univariable Relationships Between BC-3781 Dosing Regimen, Day 1 Total-drug AUC₀₋₂₄:MIC Ratio and MIC value and Time to 20% Reduction From Baseline in the Area of Swelling Using Data from Patients with *S. aureus* Infection

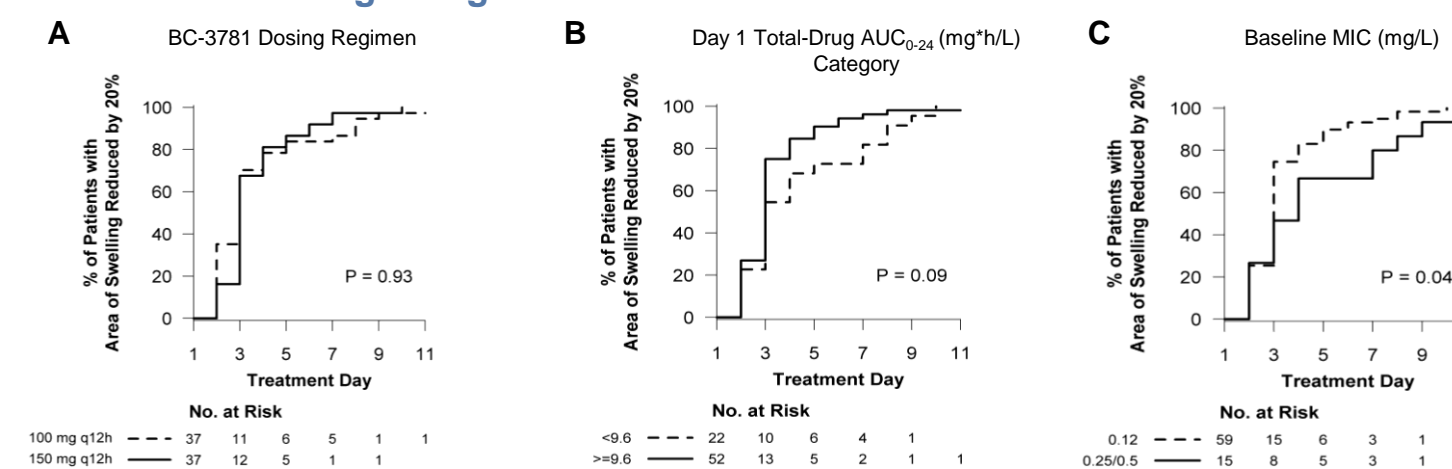
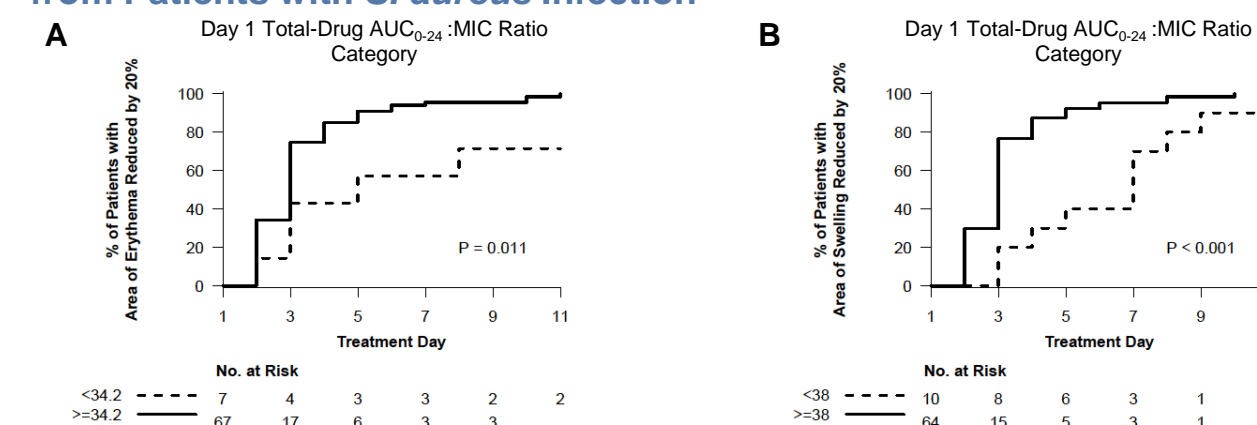


Figure 2. Univariable Relationships Between Day 1 Total-drug AUC₀₋₂₄:MIC Ratio and Time to 20% Reduction From Baseline in the Area of Erythema (A) and Swelling (B) Using Data from Patients with *S. aureus* Infection



- As shown in Table 1, results of univariable PK-PD analyses for dichotomous, continuous, and time-to-event efficacy endpoints demonstrated that Day 1 total-drug AUC₀₋₂₄:MIC ratios ranging from 34.2 to 38.8 were significantly associated with improved outcomes.
- Table 2 summarizes univariable relationships between Day 1 total-drug AUC₀₋₂₄:MIC ratio and for time to ≥ 10 to 70% reduction from baseline in the area of erythema and swelling endpoints. Kaplan Meier estimates (%) for the likelihood of achieving a given endpoint on or before Day 5 are shown for patients $<$ and \geq the exposure threshold.
- As shown by Figure 3, the study days on which near maximal or maximal differences between Kaplan Meier estimates for percent reduction from baseline in area of erythema and swelling endpoints occurred were similar (i.e., occurring between Days 3 to 6) but such differences were more dramatic for swelling endpoints.

Table 1. Summary of Results of Univariable Relationships Between Day 1 AUC₀₋₂₄:MIC Ratio and Dichotomous, Continuous, and Time-to-Event Efficacy Endpoints

Efficacy endpoint category	Efficacy endpoint	Day 1 total-drug AUC ₀₋₂₄ :MIC ratio threshold ^b	P-value ^b
Dichotomous	Microbiological response	35.8	0.02/0.02
	Cessation of spread in the area of erythema on Day 3	38.8	0.01/0.01
	$\geq 20\%$ reduction from baseline in the area of erythema on Day 3	34.2	0.06/0.07
	Cessation of spread in the area of swelling on Day 3	34.2	0.008/0.008
Continuous	$\geq 20\%$ reduction from baseline in the area of swelling on Day 3	34.2	0.007/0.008
	Percent change from baseline in the area of swelling on Days 2 to 5	38.0	$\leq 0.047/\leq 0.039$
Time-to-event	Time to $\geq 10, 20, 30, 50,$ and 70% reduction from baseline in the area of erythema	34.2	$\leq 0.097/\leq 0.094$
	Time to $\geq 10, 20, 30, 50,$ and 70% ^a reduction from baseline in the area of swelling	38.0	$\leq 0.019/\leq 0.04$

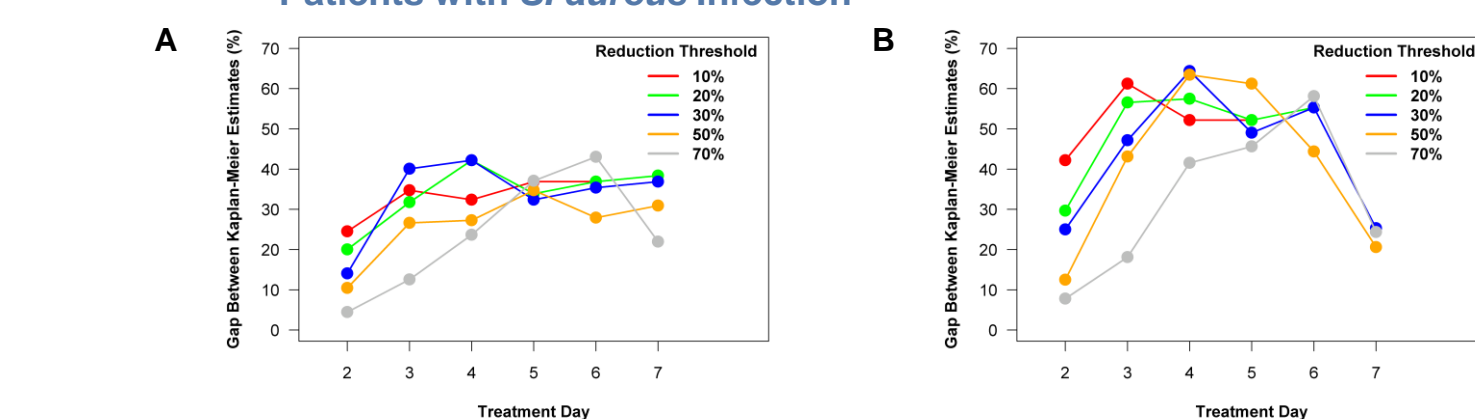
a. Intuitive univariable PK-PD relationship not identified for this efficacy endpoint; b. Based on univariable PK-PD analyses using data from all patients/patients with *S. aureus* infection.

Table 2. Univariable Relationships Between Day 1 Total-drug AUC₀₋₂₄:MIC Ratio and Time to ≥ 10 -70% Reduction From Baseline in the Area of Erythema and Swelling^a

Continuous endpoint	Percent reduction from baseline	Day 1 total-drug AUC ₀₋₂₄ :MIC ratio threshold	Kaplan Meier estimate (%) for likelihood of achieving percent reduction from baseline for a given endpoint on or before Day 5		Log rank p-value
			Below threshold	At or above threshold	
Area of erythema	10	34.2	57.1	94.0	0.011
	20	34.2	57.1	91.0	0.011
	30	34.2	57.1	89.6	0.011
	50	34.2	42.9	77.6	0.048
	70	34.2	28.6	65.7	0.094
Area of swelling	10	38.0	40.0	92.2	0.0004
	20	38.0	40.0	92.2	0.0007
	30	38.0	40.0	89.0	0.002
	50	38.0	20.0	81.3	0.011
	70	38.0	20.0	65.6	0.040

a. Based on time-to-event analyses conducted using data from patients with *S. aureus* (n=74), the results for which were similar to those based on data for all patients (n=80).

Figure 3. Differences Between Kaplan-Meier Estimates for Percent Reduction from Baseline in the Area of Erythema (A) and Swelling (B) for Day 1 Total-drug AUC₀₋₂₄:MIC Ratio Groups by Study Day Using Data from Patients with *S. aureus* Infection^a



a. Based on data from patients with *S. aureus* infection (n=74). Similar such results were evident based on data for all patients (n=80).

Multivariable PK-PD Analyses:

- For multivariable models for time to 20% reduction from baseline in the area of erythema and swelling, Day 1 total-drug AUC₀₋₂₄:MIC ratios ≥ 34.2 were highly associated with faster times to event.
 - Additional independent variables associated with the above-described endpoints included baseline area of swelling, body mass index, ethnic group, and prior antimicrobial therapy.
- ### PK-PD Target Attainment and Model-Predicted Response Analyses:
- Overall percent probabilities of PK-PD target attainment and model-predicted response associated with BC-3781 dosing regimens of 100 and 150 mg q12h, over the US/EU MIC distribution for *S. aureus* (minimum, MIC₅₀, MIC₉₀, maximum: $\leq 0.015, 0.06, 0.12,$ and 8 mg/L), were as follows:
 - For the microbiological response, percent probabilities of target attainment and response were 96.0 and 97.5 for 100 mg q12h and 99.0 and 98.3 for 150 mg q12h, respectively.
 - For the cessation of spread in the area of erythema on Day 3, percent probabilities of target attainment and response were 94.4 and 91.0 for 100 mg q12h and 98.6 and 92.4 for 150 mg q12h, respectively.
 - For the cessation of spread in the area of swelling on Day 3, percent probabilities of target attainment and response were 96.6 and 84.5 for 100 mg q12h and 99.2 and 85.9 for 150 mg q12h, respectively.

CONCLUSIONS

- Results of the univariable PK-PD analyses based on the evaluation of dichotomous, continuous, and time-to-event efficacy endpoints demonstrated consistent and similar findings.
 - Day 1 total-drug AUC₀₋₂₄:MIC ratios ranging from 34.2 to 38.8 were significantly associated with improved outcomes.
- Univariable time-to-event analyses for $\geq 10, 20, 30, 50,$ and 70% reduction from baseline in the area of erythema and swelling revealed that the largest differences in Kaplan-Meier estimates between lower and higher Day 1 total-drug AUC₀₋₂₄:MIC ratio groups occurred during the interval of Days 3 to 6.
- Multivariable models for time to 20% reduction from baseline in the extent of erythema and swelling demonstrated that Day 1 total-drug AUC₀₋₂₄:MIC ratios ≥ 34.2 were highly associated with faster times to event, even when evaluated in the context of other significant independent variables.
- Overall percent probabilities of PK-PD target attainment and model-predicted response were high for both the 100 and 150 mg q12h dosing regimens.
- The results of these analyses provide support for selecting the 150 mg q12h dosing regimen for future Phase 3 clinical trials in patients with ABSSSI.

REFERENCES

- Craig WA et al. ICAAC 2010, abstract F1-2108.
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- Data on file, Nabriva Therapeutics.