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Assessment of Pharmacokinetic-Pharmacodynamic Target Attainment for the Anti-Staphylococcal Antibiotic AFABICIN

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INTRODUCTION

Afabicin (Debio 1450) is a novel antimicrobial in clinical development for the treatment of staphylococcal infections [1]. Its active moiety, afabicin desphosphono (Debio 1452), inhibits the essential enoyl-ACP reductase enzyme, FabI, exerting antimicrobial effects by disrupting fatty acid biosynthesis (Fig. 1). Herein, we describe an assessment of the probability of pharmacokinetic-pharmacodynamic (PK-PD) target attainment to support afabicin dose selection for patients with bone and joint infections (BJI).

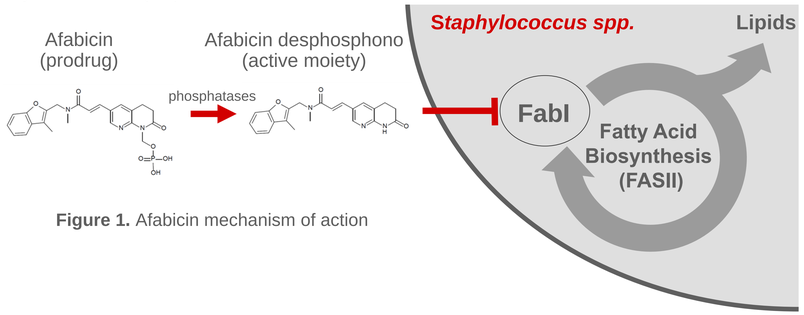

Figure 1. Afabicin mechanism of action

MINIMUM INHIBITORY CONCENTRATIONS

- Minimum inhibitory concentrations (MIC) for afabicin desphosphono and comparator antibiotics were determined for 872 *Staphylococcus aureus* clinical isolates, which included methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) subsets collected from 2017 to 2023, according to Clinical Laboratory Standards Institute (CLSI) guidelines (M07, [2]).

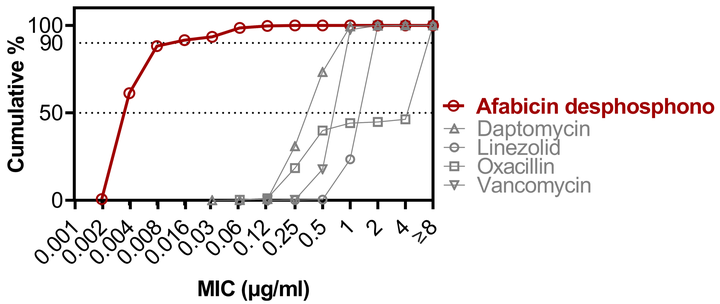

Figure 2. Cumulative MIC distributions for afabicin desphosphono and comparators against *S. aureus.*

- Afabicin desphosphono was the most potent antimicrobial tested against *S. aureus* in vitro (Fig. 2).
- The afabicin desphosphono MIC range, MIC_{50} and MIC_{90} were 0.002–0.25, 0.004 and 0.016 µg/ml, respectively.
- The assessment of percent probabilities of PK-PD target attainment by MIC value was carried out for the complete range of afabicin desphosphono MIC values.

REFERENCES

[1] Wittke F, Vincent C, Chen J et al. *Antimicrob Agents Chemother* 2020; 64(10). **[2]** CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; CLSI standard M07-A10. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2018 **[3]** Drusano GL, Liu W et al. *Antimicrob Agents Chemother* 2011; 55(11). **[4]** Banevicius MA, Kaplan N, Hafkin B et al. *J Chemother* 2013; 25(1). **[5]** Bader JC, Lakota EA, Bravo J, et al. Pharmacokinetic-pharmacodynamic analyses for Debio 1450, a staphylococcal-specific antibiotic, using data from a murine-thigh infection model. ASM-Microbe 2017 Poster Sunday-207.

CLINICAL POPULATION PK MODELING

- A population PK model was developed using data from Phase 1 studies and an ongoing Phase 2 study in BJI (initial Phase 2 data are presented in **IDweek 2024 poster P-65**).
- A 2-compartment model with auto-induction of clearance and dose-dependent oral bioavailability was shown to adequately describe the data (Fig. 3).

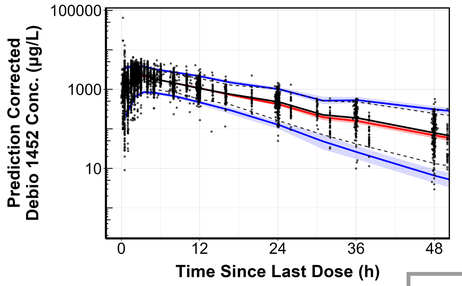

Figure 3. Prediction-corrected visual predictive check plot using Phase 1 and 2 data. Black circles show observed afabicin desphosphono concentrations with the median as the solid black line and 5th and 95th percentiles as dashed lines. Median values from the simulations for the median are represented by the red line and for the 5th and 95th percentiles by the blue lines. Red and blue shaded regions show the 90% prediction intervals for the median and for the 5th and 95th percentiles from the simulations, respectively.

PROBABILITY OF PK-PD TARGET ATTAINMENT

- Simulations were performed to generate *f*AUC (considering protein binding of 98%) for 3,000 simulated patients after administration of afabicin 55 mg intravenous (IV) every 12 hours (BID) on day 1 followed by 80 mg oral (PO) BID starting on day 2, emulating dosing in the Phase 2 BJI study.
- Percent probabilities for PK-PD target attainment by MIC were assessed on days 1 and 2 (Fig. 5).

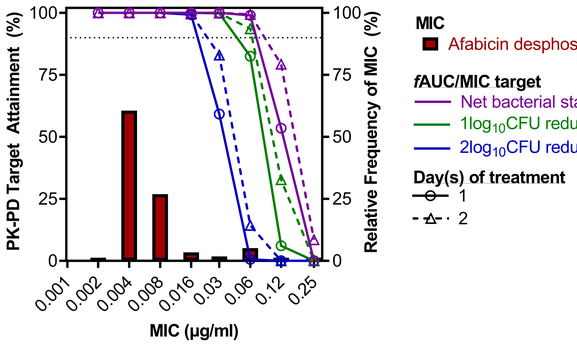

Figure 5. Percent probability of PK-PD target attainment by MIC based on afabicin desphosphono *f*AUC/MIC targets for efficacy generated using immunocompetent mice, overlaid on the MIC distribution for 872 *S. aureus* isolates.

- At the afabicin desphosphono MIC_{90} for *S. aureus* (0.016 µg/ml), percent probabilities of PK-PD target attainment were >99% based on *f*AUC/MIC targets associated with net bacterial stasis, and $1log_{10}$CFU and $2log_{10}$CFU reductions on days 1 and 2.
- Weighted percent probabilities of PK-PD target attainment across the MIC distribution assessed for the *f*AUC/MIC target associated with a $2log_{10}$CFU reduction from baseline were 92.7% and 93.9% on days 1 and 2, respectively.

PK-PD TARGETS FROM NON-CLINICAL MODELS

- Afabicin efficacy was evaluated in dose-ranging studies conducted in both neutropenic and immunocompetent murine thigh infection models as described previously [3] using *S. aureus* strain ATCC 33591 (afabicin desphosphono MIC 0.016 µg/ml).
- Afabicin was administered intraperitoneally four times daily and colony forming units (CFU) from thigh tissue were determined at 24 (data not shown), 48 (data not shown) and 72 hours (Fig. 4).
- The relationship between change in log_{10}CFU from baseline to 72 hours and afabicin desphosphono free-drug plasma area under the concentration-time curve (*f*AUC)/MIC ratio, which is the PK-PD index most correlated with efficacy [4], was evaluated by fitting Hill-type models to the data.

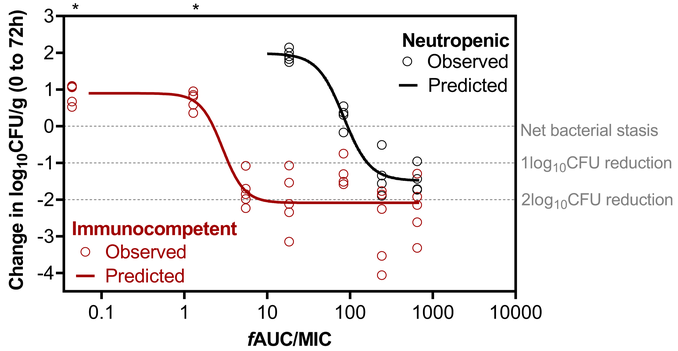

Figure 4. Relationship between afabicin desphosphono exposures ($fAUC_{48\text{-}72h}$/MIC) and change in CFU from baseline for *S. aureus* ATCC 33591 in immunocompetent and neutropenic murine thigh infection models. Asterisks indicate neutropenic groups that were sacrificed prior to the 72-hour timepoint due to clinical condition.

- Following 72 hours of treatment, *f*AUC/MIC targets using data from neutropenic animals for net bacterial stasis and $1log_{10}$CFU reduction from baseline were 93 and 163, respectively, which were similar to previous studies at 24 hours using the same model [5]. In the current study, a $2log_{10}$CFU reduction from baseline was not achieved.
- *f*AUC/MIC targets for net bacterial stasis, and $1log_{10}$CFU and $2log_{10}$CFU reductions from baseline were lower using data from immunocompetent animals (2.2, 3.4 and 8.4, respectively).
- Percent probabilities of PK-PD target attainment by MIC based on *f*AUC/MIC targets from immunocompetent animals were assessed (Fig. 5).

CONCLUSIONS

- Afabicin desphosphono showed potent in vitro activity against *S. aureus* clinical isolates.
- Afabicin *f*AUC/MIC targets associated with net bacterial stasis, and $1log_{10}$CFU and $2log_{10}$CFU reductions from baseline derived from a murine thigh infection model using immunocompetent mice were 2.2, 3.4 and 8.4, respectively.
- Using these *f*AUC/MIC targets, percent probabilities for PK-PD target attainment exceeded 99% for all endpoints at the *S. aureus* MIC_{90}.
- Taken together, these data provide support for the adequacy of the afabicin 55 mg IV BID / 80 mg PO BID dosing regimen for the treatment of patients with *S. aureus* infections, which is further substantiated with clinical observations from an ongoing Phase 2 study in BJI (**ID week 2024, poster P-65**).
- These data support future in vivo studies to characterize PK-PD variability among *S. aureus* isolates.