In vivo Pharmacokinetics and Pharmacodynamics of the Lantibiotic, NAI-107, in the Neutropenic Murine Thigh Infection Model

Alexander J. Lepak\textsuperscript{a}, Karen Marchillo\textsuperscript{c}, William A. Craig\textsuperscript{a}, David R. Andes\textsuperscript{a,b,c} #

Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA\textsuperscript{a}

Department of Medical Microbiology and Immunology, University of Wisconsin, Madison, WI, USA\textsuperscript{b}

William S. Middleton Memorial VA Hospital, Madison, WI, USA\textsuperscript{c}

Running Title:
PK/PD of a Lantibiotic in the Murine Thigh Model

#Address correspondence to David R. Andes, dra@medicine.wisc.edu
Abstract

Background: NAI-107 is novel lantibiotic compound with potent in vitro activity against gram positive bacteria, including MRSA. The purpose of this study was to examine the activity of NAI-107 against *S. aureus*, including MRSA in the neutropenic murine thigh infection model. Methods: Serum pharmacokinetics and time kill studies were performed following administration of single subcutaneous doses of 5, 20, and 80 mg/kg. Dose fractionation included total doses ranging from 1.56-400 mg/kg/72h administered broken into 1, 2, 3, or 6 doses. Treatment studies were also performed against 9 *S. aureus* (4 MSSA and 5 MRSA) using a 12h dosing interval and total dose range of 1.56-400 mg/kg/72h. An Emax model was used to determine the PK/PD index that best described the dose response data and to estimate doses required to achieve a net bacteriostatic dose (SD) and a 1 log reduction in CFU/thigh. Results: Pharmacokinetic studies demonstrated an AUC range of 26.8-276 mg*h/l and half-lives of 4.2-8.2h. MICs ranged from 0.125-0.5 µg/ml. The 2 highest single doses produced more than a 2-log kill and prolonged PAEs ranging from 36 to >72h. Dose fractionation response curves were similar and AUC/MIC was the most predictive PD index (AUC/MIC $R^2$ 0.89, Cmax/MIC $R^2$ 0.79, T>MIC $R^2$ 0.63). A 2 log or greater kill was observed against all 9 SA strains. The total drug 24h AUC/MIC associated with stasis and 1 log kill for the 9 SA were 371 ± 130 and 510 ± 227, respectively. Conclusion: NAI-107 demonstrated concentration dependent killing and prolonged PAEs. AUC/MIC was the predictive PD index. Extensive killing was observed for *S. aureus* independent of MRSA status. The AUC/MIC target should be useful for design of clinical dosing regimens.
Introduction

Bacterial resistance to antimicrobial agents is a pervasive problem world-wide. Of chief concern for hospitalized patients is the emergence of a group of organisms termed the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Enterobacter* species), which escape the activity of most available antibacterials (1). It is hoped that the discovery and development of novel antibiotic classes with unique mechanisms of action will stem this epidemic. However, very few new drug classes have been developed in the past decade (1-5).

Lantibiotics are natural product peptide antibiotics with broad Gram-positive spectrum of activity that includes multi-drug resistant *S. aureus* (6, 7). The mechanism of action, as deduced in studies of the prototype lantibiotic, nisin, is inhibition of growth of gram-positive bacteria by interfering with peptidoglycan synthesis by binding to lipid II (8-12). This novel mechanistic site is distinct from that of other antibiotics and cross-resistance has not been described (13, 14).

The following studies were designed to characterize the in-vivo pharmacokinetic-pharmacodynamic characteristics of NAI-107. Specifically, the impact of the dose and dosing regimen on the in vivo efficacy of this drug in experimental thigh infection in neutropenic mice was assessed. Studies included those designed to: [1] investigate the pharmacodynamic characteristics of NAI-107 via time kill and postantibiotic effect studies, [2] determine which pharmacokinetic index (peak serum level, area under the concentration-versus-time curve (AUC), or the duration of time serum levels exceed the MIC) is most closely linked to efficacy of NAI-107 via dose fractionation and
pharmacodynamic modeling and [3] identify the magnitude of the PK/PD index required
for efficacy among multiple *S. aureus* isolates, including beta-lactam resistant strains.

**MATERIALS AND METHODS**

**Organisms, media, and antibiotic**

Nine isolates of *Staphylococcus aureus* were used for these studies, including 4 that are
methicillin-susceptible and 5 that are methicillin-resistant (*Table 1*). The methicillin-resistant strains included hospital- and community-acquired isolates and three USA
genotypes. Organisms were grown, subcultured, and quantified using Mueller-Hinton
broth (MHB) and agar (Difco Laboratories, Detroit, MI). NAI-107 was supplied by the
sponsor, Sentinella.

**In vitro susceptibility testing**

MICs were determined in MHB using a modification of the CLSI microdilution technique
(15). Specifically, the polystyrene microtiter wells were coated with 0.02% bovine serum
albumin to reduce drug binding to the plate. All MICs were performed in triplicate on at
least three occasions. The geometric mean MIC is presented (*Table 1*).

**Murine thigh infection model**

Animals were maintained in accordance with the American Association for Accreditation
of Laboratory Animal Care (AAALAC) criteria (16). All animal studies were approved by
the Animal Research Committees of the William S. Middleton Memorial VA Hospital and
the University of Wisconsin. Six week-old, specific pathogen-free, female ICR/Swiss
mice weighing 24 to 27 g were used for all studies (Harlan Sprague-Dawley, Indianapolis, IN). Mice were rendered neutropenic (neutrophils < 100/mm³) by injecting cyclophosphamide (Mead Johnson Pharmaceuticals, Evansville, IN) intraperitoneally 4 days (150 mg/kg) and 1 day (100 mg/kg) before thigh infection. Previous studies have shown that this regimen produces neutropenia in this model for 5 days (17). Broth cultures of freshly plated bacteria were grown to logarithmic phase overnight to an absorbance of 0.3 at 580 nm (Spectronic 88; Bausch and Lomb, Rochester, N.Y.). After a 1:10 dilution into fresh MHB, bacterial counts of the inoculum ranged from $10^{6.3-6.9}$ CFU/ml. Thigh infections with each of the isolates were produced by injection of 0.1 ml of inoculum into the thighs of isoflurane-anesthetized mice 2 h before therapy with NAI-107.

**Drug pharmacokinetics**

Single dose serum pharmacokinetics of NAI-107 were performed in thigh infected mice. Animals were administered a single subcutaneous doses (0.2 ml/dose) of NAI-107 at dose levels of 5, 20 and 80 mg/kg. Groups of three mice were sampled at each time point (6 or 7 time points) and dose level. Sampling times ranged from 3 to 72h over a 72h period. Serum concentrations were determined by the sponsor using LC-MS/MS techniques. The lower and upper limits of quantification were 8.93 and 6660 ng/mL, respectively. Pharmacokinetic constants (± standard deviation), including elimination half-life ($t_{1/2}$), AUC, and $C_{max}$, were calculated using a noncompartmental model. The half-life of NAI-107 was determined by linear least-squares regression. The AUC was calculated from the mean concentrations using the trapezoidal rule. Pharmacokinetic
estimates for dose levels that were not measured were calculated using linear interpolation for dose levels between those with measured kinetics (e.g. between 5 and 20 mg/kg) and linear extrapolation for dose levels above or below the highest and lowest dose levels with kinetic measurements (i.e. 5 and 80 mg/kg).

In vivo time kill and PAE

Two hours after thigh infection with S. aureus ATCC 25923 mice were treated with single subcutaneous doses of NAI-107 (5, 20, 80 mg/kg). Groups of two treated and untreated mice were sacrificed at eight time points, every 3 to 24 hours over a 72 hour study period. The thighs (four per treatment group) were immediately removed upon euthanasia and processed for CFU determination. The burden of organisms in the thigh was measured by viable plate counts of tissue homogenates. The impact of each dose on the burden of organisms over time was measured. The time that drug concentrations would be expected to exceed the MIC was determined from the pharmacokinetic data. The postantibiotic effect (PAE) was calculated by subtracting the time that it took for organisms to increase 1 log in level in the thighs of saline-treated animals from the time that it took organisms to grow the same amount in treated animals after serum levels fell below the MIC for the infecting organism (PAE = T - C, where C is the time for 1-log_{10} control growth and T is the time for 1-log_{10} treatment growth after levels have fallen below MIC).

Pharmacokinetic/pharmacodynamics index determination
Neutropenic mice were similarly infected with *S. aureus* ATCC 25923. Treatment with NAI-107 was initiated 2 h after infection. Treatment included twenty administered over a 72 h study period using 12, 24, 36, and 72 hourly dosing intervals. Four thigh infections were included in each dosing group. The five total doses of NAI-107 ranged from 1.56 to 400 mg/kg/72 h. The drug doses were administered subcutaneously. Most of the mice were euthanized after 72 h of therapy, and the thighs were removed and processed for CFU determination. A few mice, at the lowest drug doses, were euthanized earlier than 72 h because of the development of signs of distress that required early euthanasia.

To determine which PK/PD index was most closely linked with efficacy, the number of bacteria in the thigh at the end of 72 h of therapy (or earlier for some of the lowest doses) was correlated with (i) the $C_{\text{max}}$/MIC ratio, (ii) the 24-hour AUC/MIC ratio, and (iii) the percentage of the dosing interval during which serum levels exceed the MIC for each of the dosage regimens studied. The correlation between efficacy and each of the three PK/PD indices was determined by nonlinear least-squares multivariate regression (Sigma Plot version 12.3; Systat Software, San Jose, CA). The model is derived from the Hill equation: 

$$E = \frac{E_{\text{max}} \times D}{ED_{50}^N \cdot D_{\text{N}}}$$

where $E$ is the effect or, in this case, the log change in CFU per thigh between treated mice and untreated controls after the 72-h period of study, $E_{\text{max}}$ is the maximum effect, $D$ is the 24-h total dose, $ED_{50}$ is the dose required to achieve 50% of $E_{\text{max}}$, and $N$ is the slope of the dose-effect curve. The indices $E_{\text{max}}$, $ED_{50}$, and $N$ were calculated using nonlinear least-squares regression. The coefficient of determination ($R^2$) was used to estimate the variance that could be due to regression with each of the PD parameters.
Pharmacokinetic/pharmacodynamic index target for efficacy

Five (four-fold) increasing doses of NAI-107 were used to treat neutropenic mice with thigh infections produced by nine strains of *S. aureus* (4 methicillin-susceptible strains and 5 methicillin-resistant strains). The subcutaneous doses of NAI-107 varied from 1.56 to 400 mg/kg/72 h fractionated into an every 12 h regimen. Four thigh infections were included in each dosing regimen group. Therapy was initiated 2 h after infection. The animals were euthanized at 72 h after infection, and the thighs were removed and immediately processed for CFU determination. A sigmoid dose-response model derived from the four-parameter Hill equation was used to calculate the dose of NAI-107 that produced a net bacteriostatic effect and 1 log₁₀ kill over 72 h (static and 1 log kill doses). The 24-h AUC/MIC and 72-h AUC/MIC values for the static and 1 log₁₀ kill doses were calculated using the sigmoid Emax model.

RESULTS

In vitro susceptibility testing

The MICs of NAI-107 for the nine *S. aureus* strain used in the studies are shown in Table 1 and ranged from 0.125 to 0.5 µg/ml. Resistance to methicillin did not impact the NAI-107 potency.

Serum pharmacokinetics

Single dose pharmacokinetics of NAI-107 are shown in Figure 1. At the doses studied, exposure to NAI-107 increased in a dose-dependent manner across the dose range...
studies. Cmax concentrations ranged from 3.6 to 22.3 μg/ml. AUC values ranged from 26.8 to 276 mg*h/L. The elimination half-life ranged from 4.2 to 8.2 hours.

**In vivo time kill and PAE**

The effect of single doses of NAI-107 at 5, 20, and 80 mg/kg on the in-vivo killing and regrowth of a strain of *S. aureus* ATCC 25923 are shown in Figure 2. Rapid, dose-dependent killing of organisms occurred following the two highest dose levels. Prolonged growth inhibition was observed following administration of the lowest dose level. More than a 2 log$_{10}$ CFU/Thigh reduction was observed with two of the three dose levels and maximal killing was greater than 3 log$_{10}$ CFU/Thigh for the highest dose relative to the organism burden at the initiation of drug therapy. Organism regrowth was delayed for many hours with all of the dose levels with calculated PAEs ranging from 36 to more than 72 hours.

**Pharmacokinetic/pharmacodynamics index determination**

The relationship among the dose of NAI-107, dosing interval, and effect against *S. aureus* ATCC 25923 is shown in Figure 3. The dose response curves for the every 24, 36, and 72 h dosing regimens were very similar. For the two highest dose levels the every 12 h regimen was shifted somewhat to the left indicating enhanced effect. The similarity of dose response curves among the dosing intervals suggests that the AUC/MIC would be the predictive pharmacodynamic index.
The relationships between log_{10} CFU per thigh and the Cmax/MIC ratio, the AUC/MIC ratio and the percentage of time serum levels exceeded the MIC are illustrated in Figure 4a-c for S. aureus ATCC 25923, respectively. Analysis of these complementary analyses suggest the importance of AUC/MIC based upon visual data fit and the \( R^2 \) values.

**Pharmacokinetic/pharmacodynamic index Target for efficacy**

To determine if the AUC/MIC ratios required for effect were similar for multiple pathogens, we studied the activities of NAI-107 every 12 h dosing regimens against 8 additional strains of *S. aureus*. The dose response data for each of the nine *S. aureus* strains is shown in Figure 5. The dose response relationships were quite similar among the strains, which is not surprising given the relatively narrow MIC range. A 2- to more than 4- log reduction was observed with this strain collection over the dose ranged studies. The doses necessary to produce a bacteriostatic effect and a 1 log reduction in organism burden as well as the corresponding AUC/MIC values are shown in Table 2. The static doses varied from 9.6 mg/kg/24h to 46.1 mg/kg/24h. The doses associated with a 1 log kill were roughly 2-fold higher than those associated with stasis. The presence of beta-lactam resistance did not alter the pharmacodynamic target required to produce efficacy. The relationships between NAI-107 exposure (expressed as the AUC/MIC) and efficacy against all *S. aureus* strains are shown in Figure 6. The relationship among the data for each of the nine strains studied is extremely strong with an \( R^2 \) value of 0.89. The mean 24h AUC/MIC associated with stasis was 371 and that needed for a 1 log reduction was near 500.
Discussion

The emergence of treatment resistant pathogens is an escalating threat to public health (18-21). The increasing incidence of drug resistant bacteria, fungi, parasites, and viruses is evident from contemporary epidemiologic surveys in the U.S. and worldwide (4, 22-24). This change in microbial ecology is occurring at the same time as our at-risk patient populations continue to grow and effective antimicrobial drug discovery has been on the decline (1, 4, 5, 25-30).

The group of nosocomial bacterial pathogens of greatest concern has been termed the ESKAPE pathogens as they effectively "escape" the effects of common antibacterial drugs (1). This organism collection includes *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter* species. These bacteria are responsible for the majority of U.S. hospital infections. At least 70% of these hospital acquired bacterial infections are resistant to at least one commonly used antibiotic (FDA). Among the 2 million annual infections in hospitalized patients, death results in nearly 100,000 (24, 31). For example, more people now die of methicillin-resistant *S. aureus* (MRSA) in U.S. healthcare settings than of HIV and tuberculosis combined (32, 33). Additionally, resistance to the last line of antibiotics currently available for most gram-positive infections, glycopeptides and lipopeptides, are increasing (34-39). Thus, novel agents for gram-positive pathogens are urgently needed.

The lantibiotic class represents a novel group of naturally derived, ribosomal-synthesized peptides with potent gram-positive activity. The prototype molecule nisin was discovered in the 1920s and used as a food preservative for over 40 years (29).
Lantibiotics exert their antimicrobial activities by binding to lipid II at a site different from that affected by glycopeptides and are therefore active against MDR gram-positive pathogens. The result of binding to and sequestering lipid II is inhibition of bacterial cell wall biosynthesis at the transglycosylation step. There are additional proposed mechanisms of action after lipid II binding, which include membrane interaction with or without pore formation (12, 40, 41). Recently, a candidate lantibiotic, NAI-107 (Microbisporicin), emerged from a screening program designed to find new bacterial cell wall inhibitors (7, 13).

We report the in vivo pharmacodynamic activity of NAI-107 against *S. aureus*. NAI-107 demonstrated potent *in vitro* and *in vivo* efficacy against *S. aureus*, including isolates with resistance to beta lactams. The *in vitro* MIC varied only 4-fold against NAI-107 in this diverse group of *S. aureus* isolates despite the oxacillin activity varying over 128-fold. Numerically, NAI-107 MIC range in the study was lower than comparator drugs vancomycin and linezolid, and very similar to that of daptomycin, ceftaroline, and tedizolid. Isolates with demonstrated resistance to these comparator drugs were not tested in the current study, but previous studies have demonstrated a lack of cross resistance between lantibiotics and glycopeptide resistance (7, 13, 14, 42). The treatment studies demonstrated marked bactericidal activity that was dose dependent. In addition, we observed prolonged growth suppression (PAEs) of >35 h. Dose fractionation studies found the AUC/MIC was most closely linked to drug effect. Together, these complementary findings indicate that optimal dosing would include large, infrequent dosing.
An important consideration in PK/PD studies is the inclusion of multiple isolates with varying phenotypes and genotypes in order to form a robust PK/PD target estimate. The studies presented included 9 total isolates including 5 MSSA isolates, 4 MRSA isolates, both hospital- and community-acquired isolates, as well as three different USA genotypes. NAI-107 demonstrated potent efficacy in vivo against all of these isolates with a 2- to 5-log$_{10}$ CFU/thigh drop over a 72 h treatment period with an overall Emax of 8.6 log$_{10}$ CFU/thigh. This microbiological response in the animal model was similar to or in excess of currently approved MRSA drugs that have been studied in this same model: ceftaroline (43), daptomycin (44-46), oxazolidinones (46, 47), and vancomycin (46). The NAI-107 24 h target AUC/MIC associated with a net static and 1 log$_{10}$ killing effect against S. aureus was near 370 and 500, respectively. Once more, the AUC/MIC index was a very strong predictor of efficacy based on regression analysis of the treatment data against a relatively large strain set. One limitation of the current study is we were unable to perform protein binding studies given limited drug availability and therefore only total drug values were considered in these analyses. It will be important in future studies to determine protein binding and perform PK/PD analyses with both total and free drug exposures. Only one previous study of antimicrobial efficacy of NAI-107 is reported in the literature (42). Jabes and colleagues demonstrated efficacy against MRSA, GISA, and VRE isolates in a lethal murine model, rat granuloma pouch model, and rat endocarditis model. The S. aureus lethal murine model demonstrated an ED$_{50}$ of 25 mg/kg/24 h, which is similar to the static dose and ED$_{50}$ (25 and 30 mg/kg/24 h, respectively) identified in the current study. Outside of this single study, which was not
optimized to examine pharmacodynamic relationships, there are no other pre-clinical PK/PD studies for comparison purposes.

In conclusion, these studies demonstrate that NAI-107 has dose-dependent in vivo activity against various strains of \textit{S. aureus}. The AUC/MIC was the PK/PD index that best predicted efficacy. Both static and killing endpoints were achieved at relatively modest AUC/MIC targets. The targets identified in these studies and preliminary human PK data should be useful to guide appropriate dosing regimen design for clinical trials. These findings suggest NAI-107 is a promising and novel antibiotic candidate for further study and development for the treatment of gram-positive infections.

\textbf{Acknowledgements:} This study was funded by Sentinella Pharmaceuticals, Inc.

\textbf{References}


16. **National Research Council Committee on the Care and Use of Laboratory Animals Institute of Laboratory Animal Resources and Commission on Life Sciences.**


46. Lee DG, Murakami Y, Andes DR, Craig WA. 2013. Inoculum effects of ceftobiprole, daptomycin, linezolid, and vancomycin with Staphylococcus aureus and Streptococcus pneumoniae at inocula of 10(5) and 10(7) CFU injected into
opposite thighs of neutropenic mice. Antimicrobial agents and chemotherapy 57:1434-1441.

Figure Legends

**Figure 1.** Single dose serum pharmacokinetics of NAI-107 in neutropenic mice. Three different doses of NAI-107 that varied by 4-fold concentration on a mg/kg basis were administered by subcutaneous route. Serum drug concentrations were measured by the sponsor. Groups of three mice were sampled for each time point. Samples were collected every 3 to 24 hours over 72 hours. Each symbol represents the mean value from three animals. The error bars represent the standard deviation. The 72 h time point for the 5 mg/kg dose was below the limit of detection. PK parameters listed in the box include maximum drug concentrations (Cmax), the AUC from 0-∞ (AUC), and elimination half-life (T1/2) for each dose.

**Figure 2.** In vivo time kill experiment with NAI-107 using a neutropenic mouse thigh model. Each symbol represents the mean and standard deviation from four thighs infected with *S. aureus* ATCC 25923. The error bars represent the standard deviation. Three single subcutaneous doses of NAI-107 were administered to mice. The solid symbols represent organism burden from untreated control animals. The burden of organisms was measured every 3-24 h over the 72 hour study. The first symbol in time (0 hour) represents the burden at the time of dosing. The black horizontal bars represents the time that serum concentrations would be estimated to remain above the MIC of the infecting organism. The duration of the postantibiotic effect (PAE) was calculated and is reported above.
Figure 3. In vivo dose fractionation with NAI-107 using a neutropenic mouse thigh model. Each symbol represents the mean and standard deviation from four thighs infected with S. aureus ATCC 25923. The error bars represent the standard deviation. Five total drug (mg/kg/72 h) dose levels were fractionated into one of four dosing regimens. The burden of organisms was measured at the start and end of therapy. The study period was 72 hours. The horizontal dashed line at 0 represents the burden of organisms in the thighs of mice at the start of therapy. Data points below the line represent killing and points above the line represent growth.

Figure 4. Impact of pharmacodynamic regression of the in vivo dose fractionation study with NAI-107 against S. aureus ATCC 25923. Each symbol represents the mean and standard deviation from four thighs. The dose data is expressed as either the [A] Cmax:MIC, [B] AUC:MIC, or [C] Percent time drug concentrations exceed the MIC over the dosing period (% Time Above MIC). The R^2 represents the coefficient of determination. The ED50 represents the PD index associated with 50% of the maximal effect (Emax) and N is the slope of the relationship or the Hill coefficient. The line drawn through the data points is the best fit line based upon the sigmoid Emax formula. The horizontal dashed line at 0 represents the burden of organisms in the thighs of mice at the start of therapy. Data points below the line represent killing and points above the line represent growth.

Figure 5. In vivo dose effect of NAI-107 against nine select S. aureus isolates using a neutropenic mouse thigh model. Each symbol represents the mean and standard
deviation from four thighs. Five total drug dose levels were fractionated into an every 12 hourly regimen. The burden of organisms was measured at the start and end of therapy. The study period was 72 hours. The horizontal dashed line at 0 represents the burden of organisms in the thighs of mice at the start of therapy. Data points below the line represent killing and points above the line represent growth.

Figure 6. In vivo dose effect of NAI-107 against nine S. aureus isolates using a neutropenic mouse thigh model. Each symbol represents the mean and standard deviation from four thighs. Five total drug dose levels were fractionated into an every 12 hourly regimen. The study period was 72 hours. The NAI-107 exposure is expressed as the total drug 72h AUC/MIC. The burden of organisms was measured at the start and end of therapy. The horizontal line at 0 represents the burden of organisms in the thighs of mice at the start of therapy. Data points below the line represent killing and points above the line represent growth. The R^2 represents the coefficient of determination. The ED50 represents the AUC/MIC associated with 50% of the maximal effect (Emax) and N is the slope of the relationship or the Hill coefficient. The line drawn through the data points is the best fit line based upon the sigmoid Emax formula.
Table 1. *In vitro* Activity of NAI-107 Against Select *S. aureus* Isolates Using CLSI Methods

<table>
<thead>
<tr>
<th><em>S. aureus</em> strain</th>
<th>NAI-107 (μg/ml)</th>
<th>Oxacillin (μg/ml)</th>
<th>Comment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATCC 29213</td>
<td>0.25</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>ATCC 33591</td>
<td>0.5</td>
<td>&gt;16</td>
<td>USA 200</td>
</tr>
<tr>
<td>307109</td>
<td>0.5</td>
<td>&gt;16</td>
<td>USA 200</td>
</tr>
<tr>
<td>MW2</td>
<td>0.5</td>
<td>&gt;16</td>
<td>USA 300</td>
</tr>
<tr>
<td>R-2527</td>
<td>0.5</td>
<td>&gt;16</td>
<td></td>
</tr>
<tr>
<td>ATCC 25923</td>
<td>0.5</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>6538P</td>
<td>0.125</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Smith</td>
<td>0.25</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>WIS-1</td>
<td>0.5</td>
<td>&gt;16</td>
<td></td>
</tr>
</tbody>
</table>

*Pulsed-field gel electrophoresis genetic lineage

Table 2. *In vitro* and *In vivo* Efficacy of NAI-107 Against Select *S. aureus* Isolates Using AUC/MIC as the Predictive Pharmacodynamic Index

<table>
<thead>
<tr>
<th><em>S. aureus</em> strain</th>
<th>MIC (μg/ml)</th>
<th>Static Dose (mg/kg/24h)</th>
<th>1 Log Kill Dose (mg/kg/24h)</th>
<th>Static Dose 24h AUC/MIC</th>
<th>Static Dose 72h AUC/MIC</th>
<th>1 log kill 24h AUC/MIC</th>
<th>1 log kill 72h AUC/MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>29213</td>
<td>0.25</td>
<td>25.7</td>
<td>35.2</td>
<td>623</td>
<td>1080</td>
<td>692</td>
<td>1454</td>
</tr>
<tr>
<td>33591</td>
<td>0.5</td>
<td>25.4</td>
<td>44.2</td>
<td>310</td>
<td>536</td>
<td>379</td>
<td>913</td>
</tr>
<tr>
<td>307109</td>
<td>0.5</td>
<td>29.0</td>
<td>40.8</td>
<td>323</td>
<td>600</td>
<td>366</td>
<td>843</td>
</tr>
<tr>
<td>MW2</td>
<td>0.5</td>
<td>46.1</td>
<td>74.5</td>
<td>386</td>
<td>952</td>
<td>490</td>
<td>1539</td>
</tr>
<tr>
<td>R-2527</td>
<td>0.5</td>
<td>35.6</td>
<td>64.1</td>
<td>348</td>
<td>737</td>
<td>452</td>
<td>1326</td>
</tr>
<tr>
<td>25923</td>
<td>0.5</td>
<td>14.6</td>
<td>19.7</td>
<td>205</td>
<td>406</td>
<td>286</td>
<td>469</td>
</tr>
<tr>
<td>6538P</td>
<td>0.125</td>
<td>9.6</td>
<td>17.4</td>
<td>500</td>
<td>1382</td>
<td>998</td>
<td>1761</td>
</tr>
<tr>
<td>Smith</td>
<td>0.25</td>
<td>14.7</td>
<td>24.3</td>
<td>412</td>
<td>814</td>
<td>612</td>
<td>1045</td>
</tr>
<tr>
<td>WIS-1</td>
<td>0.5</td>
<td>16.2</td>
<td>27.1</td>
<td>230</td>
<td>425</td>
<td>316</td>
<td>559</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td></td>
<td><strong>24.1</strong></td>
<td><strong>38.6</strong></td>
<td><strong>371</strong></td>
<td><strong>770</strong></td>
<td><strong>510</strong></td>
<td><strong>1101</strong></td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td></td>
<td><strong>11.7</strong></td>
<td><strong>19.8</strong></td>
<td><strong>130</strong></td>
<td><strong>325</strong></td>
<td><strong>227</strong></td>
<td><strong>447</strong></td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td></td>
<td><strong>25.4</strong></td>
<td><strong>35.2</strong></td>
<td><strong>345</strong></td>
<td><strong>737</strong></td>
<td><strong>452</strong></td>
<td><strong>1045</strong></td>
</tr>
</tbody>
</table>

SD = standard deviation
5 mg/kg
Cmax 3.55 mg/l
AUC 26.76 mg.h/l
T1/2 4.2 h

20 mg/kg
Cmax 17.3 mg/l
AUC 155.26 mg.h
T1/2 5.0 h

80 mg/kg
Cmax 22.3 mg/l
AUC 275.59 mg.h
T1/2 8.2 h