The objectives of this analysis were to develop a population pharmacokinetic (PK) model to describe the absorption and disposition of fusidic acid after single and multiple doses and to determine the effect of food on the rate and extent of bioavailability.

Plasma PK data from three phase 1 studies (n = 75; n = 14 with and without food) in which healthy subjects received sodium fusidate (500 to 2,200 mg) as single or multiple oral doses every 8 h (q8h) or q12h for up to 7 days were modeled using S-ADAPT (MCPEM algorithm). Accumulation of fusidic acid after multiple doses was more than that predicted based on single-dose data. The PK of fusidic acid was best described using a time-dependent mixed-order absorption process, two disposition compartments, and a turnover process to describe the autoinhibition of clearance. The mean total clearance (% coefficient of variation) was 1.28 liters/h (33%) and the maximum extent of autoinhibition was 71.0%, with a 50% inhibitory concentration (IC50) of 46.3 mg/liter (36%). Food decreased the extent of bioavailability by 18%. As a result of the autoinhibition of clearance, steady state can be achieved earlier with dosing regimens that contain higher doses (after 8 days for 750 mg q12h and 1 day for 1,500 mg q12h on day 1 followed by 600 mg q12h versus 3 weeks for 500 mg q12h). Given that large initial doses autoinhibit the clearance of fusidic acid, this characteristic provides a basis for the administration of front-loaded dosing regimens of sodium fusidate which would allow for effective concentrations to be achieved early in therapy.

Although fusidic acid (or sodium fusidate) has been used for the treatment of staphylococcal infections in patients since the early 1960s outside the United States, an act of Congress was required to resurrect this agent from the “dead drug list” in the United States in order for it to be developed for the treatment of patients with chronic staphylococcal infections. The longstanding use of fusidic acid in other countries, including the United Kingdom, Australia, and Canada, for the treatment of staphylococcal infections has allowed a better understanding of the safety profile for this agent. In addition, clinical studies conducted over the last 2 decades (1–4), including recent phase 1 and 2 studies (5, 6), have shown fusidic acid to be safe and well tolerated.

Fusidic acid is orally bioavailable and extensively metabolized, with the metabolites predominantly eliminated by biliary excretion. While at least three of the seven identified fusidic acid metabolites have antimicrobial activity (7, 8), such activity is less than that of fusidic acid. Given that fusidic acid has never been evaluated according to the requirements of modern drug development, major clinically relevant gaps exist in our understanding of its pharmacokinetics (PK). Early PK studies for fusidic acid were based on data from bioassays (8), and, as such, these findings may be biased given the similarity in MIC values for active metabolites and fusidic acid against Staphylococcus aureus. Additionally, fusidic acid exhibits complex and nonlinear PK. Previous studies have demonstrated decreased apparent total clearance after dosing regimens containing multiple intermediate and high doses (500 mg every 12 h [q12h] or higher) compared to single doses, as assessed by the extent of fusidic acid accumulation (9–11). Such accumulation was evident after low doses (250 mg q12h) (12). Other PK features, such as a longer terminal half-life after multiple intravenous or oral doses than after a single dose, time to steady state exceeding five times the terminal half-life, and an effect of food on the rate and extent of bioavailability (8, 9, 11, 13, 14), are observed with fusidic acid. However, quantitative PK models describing such attributes have not been characterized. A population PK model, which describes the disposition of fusidic acid, together with the application of pharmacokinetic-pharmacodynamic (PK-PD) principles, would be a valuable tool that could be used to support the selection of optimal dosing regimens of sodium fusidate.

Using data from healthy subjects from three phase 1 studies, the objectives of this analysis were 2-fold. The first objective was to develop a population PK model to describe the absorption and disposition of fusidic acid after single and multiple oral doses. The second objective was to determine the effect of food on the rate and extent of fusidic acid bioavailability.

(Materials and methods are included in the full text of the article.)

Materials and methods
Subjects and study designs. Data were pooled from phase 1 studies, studies CE06-102A (study 102-A), CE06-102B (study 102-B), and CE06-
Population Pharmacokinetics of Fusidic Acid

103 (study 103), which were conducted in healthy adult subjects. All subjects gave their written informed consent prior to entering into the respective study. The studies were approved by the responsible Institutional Review Board and followed the Declaration of Helsinki.

Study 102-A was a 3-period, randomized, crossover study in which 28 subjects (23 males, 5 females) receiving single doses of sodium fusidate were evaluated in the fasted state and 14 of the 28 subjects were also evaluated in the fed state. For administration in the fasted state, subjects received 500 mg of sodium fusidate as the test formulation (CEM-102, equivalent to 480 mg fusidic acid) or reference formulation (Fucidin; Leo Pharma) in study periods 1 and 2. In study period 3, 3,500 mg of sodium fusidate was given under fed conditions (14 subjects) or as Fucidin (14 subjects). For dosing in the fed state, subjects consumed a high-fat, high-calorie breakfast within 30 min prior to dosing. While PK data from all 28 subjects in this study were available, data from the reference formulation arm were not used for the analysis described herein.

Study 102-B was a placebo-controlled, randomized study in 24 subjects (17 males, 7 females) who received 13 doses of 500 mg of sodium fusidate or placebo every 8 h (q8h) in the fasted state. Eighteen subjects received sodium fusidate and six subjects received placebo. Of the 24 subjects, one was discontinued from the study due to a macular rash which occurred after a dose of sodium fusidate. The rash was judged as probably related to sodium fusidate by the clinical investigator. Therefore, 17 subjects from this study were available for the population PK analysis.

Study 103 was a double-blind, randomized, placebo-controlled, single- and multiple-dose dose escalation study in 32 subjects (17 males, 15 females) (6). This study was originally designed to contain four dose groups receiving 550, 1,100, 1,650, and 2,200 mg of sodium fusidate in the fasted state (cohorts 1, 2, 3, and 4, respectively). In each dose group, 6 subjects received sodium fusidate as a single dose and 2 subjects received placebo in period 1. After a 7-day washout period, cohorts 1, 2, and 3 received 11 doses of 550, 1,100, or 1,650 mg of sodium fusidate q12h, respectively, in period 2. Data from 1 subject in cohort 3 were not available for PK analysis due to nausea and vomiting in period 2. Given the dose-limiting gastrointestinal intolerance observed after the administration of the 1,650-mg q12h regimen in cohort 3, doses for cohort 4 were reduced in period 2. In this period, cohort 4 subjects received 2 doses of 1,100 mg q12h followed by 13 doses of 550 mg q12h. An additional group of 6 subjects (cohort 5), who received 2 doses of 1,650 mg q12h followed by 13 doses of 825 mg q12h, was studied.

For each of the phase 1 studies described above, film-coated tablets containing 250 or 275 mg of sodium fusidate were administered together with 240 ml of water at ambient temperature. Intake of water or other fluids was not permitted from 2 h before to 2 h after dosing (except for the water given during dosing and the milk given with the high-calorie breakfast). All subjects were nonsmokers, who had to abstain from caffeine from 24 h before dosing until the last blood sample for PK analysis in the respective period, and were not allowed to consume any products containing grapefruit from 7 days prior to the first dose to the last blood sample for PK analysis. For all single doses and for the last morning dose of multiple-dose regimens, subjects fasted for at least 10 h prior to and at least 4 h after dosing (with the exception of subjects studied under fed conditions). Lunch was provided approximately 4.5 h after the morning dose. For multiple-dose regimens with q12h dosing, the morning dose was given at least 30 min before breakfast and the evening dose was given at least 2 h after dinner.

PK sampling and analytical methods. All blood samples were collected using tubes with K$_2$-EDTA as the anticoagulant. The samples were immediately centrifuged, frozen, and stored at −80°C. Plasma samples were prepared for fusidic acid concentration determination by adding tetrahydrofusidic acid as the internal standard to a volume of 100 μl of plasma. An aqueous solution of 250 μl buffer (0.05 M citric acid, 0.2 M dibasic ammonium phosphate) was also added for extraction. Liquid/liquid extraction was then performed with a mixture of dichloromethane–hexane–methyl tert-butyl ether (1:1:1, vol/vol/vol). After centrifugation, the organic phase was concentrated and reconstituted in water-acetonitrile (1:1, vol/vol). A sample volume of 15 μl was injected into a reverse-phase high performance liquid chromatography (LC) system (HP1100 Series system; Agilent) using a Hydro-RP column (2.0 by 100 mm, 4-μm particle size; Phenomenex) that was maintained at 35°C. Retention times were 2.5 min for fusidic acid and 3.5 min for the internal standard. The mobile phase was nebulized by heated nitrogen gas in a Z-spray source/ interface. Ions were detected in negative mode by a tandem quadrupole mass spectrometer (MS/MS) (Quattro Ultima; Micromass). The mass-to-charge ratios were 515 to 453 for fusidic acid and 519 to 59.6 for the internal standard.

The assay was linear over a concentration range from 0.0200 to 50.0 mg/liter. The lower limit of quantification was 0.0200 mg/liter. The applicability of the assay to diluted samples was successfully tested using a 10-fold dilution. Interday precision was 12.3% at 0.0600 mg/liter, 8.9% at 2 mg/liter, and 8.5% at 40 mg/liter. Intraday precision ranged from 5.1 to 11.6% over the same concentration range. Accuracy ranged from −4.4 to 12.7%, and recovery was 101.6% for fusidic acid.

Noncompartmental PK analysis. A noncompartmental PK analysis (NCA) was conducted to provide insights about the structure of the PK model. The NCA was performed, as described previously (15), using WinNonlin Pro (version 5.2.1; Pharsight Corp., Mountain View, CA). Apparent terminal half-lives were determined only if the terminal slope could be reliably estimated for the respective profile. The area under the curve (AUC) was calculated using the linear up/log down trapezoidal method as implemented in WinNonlin. AUC$_{0\rightarrow t}$ was calculated as the area under the curve from time zero to infinity for a single dose, and AUC$_{0\rightarrow t}$ was calculated as the area under the curve during one dosing interval for a multiple-dose regimen. AUC$_{0\rightarrow t}$ was defined as the AUC$_{0\rightarrow t}$ for a single dose or the AUC$_{0\rightarrow t}$ after the last dose for a multiple-dose regimen. The mean input time was approximated as half of the time of peak concentration for the calculation of the apparent volume of distribution at steady state (V/$F$) (15).

Population PK analysis. Absorption. Population PK models considered included models with first-order, parallel first-order and Michaelis-Menten (MM), or multiple first-order absorption processes. As an alternative method to describe complex absorption profiles not adequately described by the aforementioned absorption processes, a previously described semiphysiological absorption model (16), which was based on data for single doses, was adapted for the single- and multiple-dose data described herein. For this absorption model, the rate of drug released from stomach [Rel($t$)] was allowed to change over time, as shown in equation 1:

$$\text{Rel}(t) = \frac{V_{\text{max}}(t) \cdot A_{\text{ stom}}}{K_m + A_{\text{ stom}}}$$

where $A_{\text{ stom}}$ represents the amount of drug in the stomach, $V_{\text{max}}(t)$ represents the maximum rate of drug release from stomach at time $t$, and $K_m$ is the amount of drug associated with a Rel($t$) equal to half of the maximal rate of $V_{\text{max}}(t)$ at time $t$. $V_{\text{max}}(t)$ is described by the Hill-type equation provided in equation 2:

$$V_{\text{max}}(t) = V_{\text{max}}(0) \cdot \left[1 + \frac{E_{\text{max}} \cdot TSD^\gamma}{TSD_{50} + TSD^\gamma}\right]$$

where TSD is the time since last dose, TSD$_{50}$ is the time since last dose associated with a half-maximal change of $V_{\text{max}}(t)$, $V_{\text{max}}(0)$ is the rate of drug release from the stomach at time zero, and $\gamma$ is the Hill coefficient. The change in $V_{\text{max}}(t)$ over time allows the population PK model to accommodate complex absorption PK profiles. The maximum change of $V_{\text{max}}(t)$ over time is characterized by $E_{\text{max}}$, which was modeled using a logistic transform with a lower and upper limit of −1 and 9. The lower-limit value of −1 for $E_{\text{max}}$ represents complete inhibition of gastric release, and the upper-limit value of 9 for $E_{\text{max}}$ represents a rapid maximum rate of gastric release [10 times $V_{\text{max}}(0)$], particularly when TSD is much larger than TSD$_{50}$. The $\gamma$ was fixed to 10 to support estimation (16).
Given that the time of peak concentration (\(T_{\text{max}}\)) is dose independent for sodium fusidate, as reported by MacGowan et al. (17), the rate of gastric release was assumed to be primarily determined by the stomach content and not by the amount of drug in stomach. To accommodate this, the \(V_{\text{max}}(0)/\text{dose}\) and \(K_{\text{inj}}/\text{dose}\) were estimated. These model parameters were subsequently multiplied by the administered dose to obtain \(V_{\text{max}}(0)\) and \(K_{\text{inj}}\) in equations 1 and 2.

The differential equations for absorption of fusidic acid, which reflect the change in the amount of drug in the stomach (\(A_{\text{stomach}}\)) and intestine (\(A_{\text{intestine}}\)) before transfer to the central compartment, are provided in equations 3 and 4:

\[
\frac{dA_{\text{stomach}}}{dt} = -\text{Rel}(t) \quad (3)
\]

\[
\frac{dA_{\text{intestine}}}{dt} = F_{\text{fed}} \cdot \text{Rel}(t) - k_{\text{abs}} \cdot A_{\text{intestine}} \quad (4)
\]

where \(F_{\text{fed}}\) represents the relative bioavailability of fusidic acid under fed compared to fasting conditions (\(F_{\text{fed}} = 1\) in the fasted state) and \(k_{\text{abs}}\) is the first-order absorption rate constant from the intestine to the central compartment. The mean absorption time (\(t_{\text{abs}}\)) was estimated using the inverse of \(k_{\text{abs}}\) \((t_{\text{abs}}/k_{\text{abs}})\).

**Disposition.** Population PK models with one or two disposition compartments and first-order, MM, or parallel first-order and MM elimination were considered. To account for the potential saturation of clearance at high fusidic acid concentrations and increasing accumulation with time, a model with autoinhibition of clearance was evaluated. Given that clearance was not anticipated to change instantaneously with drug concentration, as would be assumed with MM elimination, the time course of the inhibition of fusidic clearance was evaluated by a turnover process.

For the two-compartment disposition model with autoinhibition of clearance, the differential equations for the amount of drug in the central (A1) and peripheral (A2) compartments and extent of inhibition (INH), are provided in equations 5, 6, and 7, respectively:

\[
\frac{dA1}{dt} = k_{\text{obs}} \cdot A_{\text{intestine}} - [(1 - \text{INH}) \cdot CL + CLd] \cdot C1 + CLd \cdot C2 \quad (5)
\]

\[
\frac{dA2}{dt} = CLd \cdot (C1 - C2) \quad (6)
\]

\[
\frac{d\text{INH}}{dt} = k_{\text{out}} \cdot \left( \frac{l_{\text{max}} \cdot C_{\text{Hill}}}{I_{\text{max}} + C_{\text{Hill}}} + \text{INH} \right) \quad (7)
\]

where C1 and C2 are the drug concentrations in the central and peripheral compartments, respectively, and \(k_{\text{out}}\) describes the turnover rate constant for the inhibition compartment with a maximum extent of inhibition \(l_{\text{max}}\), CI is clearance, CLd is distribution clearance, IC50 is the drug concentration causing 50% of \(I_{\text{max}}\), and Hill is an estimated Hill coefficient.

While the unknown extent of bioavailability after oral dosing (\(F\)) was not included in the clearance and volume terms in above-described equations, such terms represent apparent clearances and volumes. All initial conditions for each of the compartments in the population PK model were zero.

**Parameter variability and residual error model.** The variability of all population PK parameters was described by a log-normal distribution with the exception of \(E_{\text{max}}\) and \(l_{\text{max}}\). For these two parameters, a normal distribution on a logistically transformed scale was applied. Between-occasion variability (BOV) (18) was considered for absorption parameters. The residual error was described by a proportional plus additive model. The Beal M3 method (19) was used to fit observations reported to be below the lower limit of quantification (BLQ). Using this approach, the algorithm considers the likelihood distribution of the BLQ value to be normally distributed and to be between negative infinity and the lower limit of quantification.

**Covariate effects.** Relationships between all PK parameters and select covariates, such as age, body size, and sex, were visually assessed for trends by plotting the post hoc individual PK parameter estimates or the individual random deviates from the population mean versus continuous or categorical covariates. Covariate evaluations for body size also included the evaluation of an allometric body size model to reduce the between-subject variability (BSV) of clearances and volumes of distribution (20-22). For these evaluations, the clearances and volumes of distribution were normalized using a standard total body weight of 70 kg and fixed allometric exponents of 0.75 and 1 for clearances and volumes of distribution, respectively.

**Model discrimination.** Model discrimination was carried out by conducting visual predictive checks and by evaluating standard diagnostic plots, the objective function (\(-\log\text{likelihood}\)), and normalized prediction distribution errors (23), as calculated in S-ADAPT 1.57 beta (24).

**Computation.** The population PK analysis was performed in S-ADAPT (versions 1.56 and 1.57 beta) (24) using the parallelized importance sampling Monte Carlo parametric expectation maximization algorithm (PMETHOD = 4 in S-ADAPT). Estimation settings that have been previously qualified for complex population PK-PD models (25) were used. A translator tool (SADAPT-TRAN) was used to facilitate model building, model evaluation, and automated plotting (26). The visual predictive checks evaluating the performance of the model relative to the observed data were performed in NONMEM VI (level 1.2), and deterministic simulations were conducted in Berkeley Madonna (version 8.3.14).

**RESULTS**

Demographic data, by study and overall, for all three phase 1 studies are provided in Table 1. The NCA PK parameter estimates for fusidic acid by study and dosing regimen are provided in Table 2. The geometric mean \(\tau_{\text{max}}\), normalized to a 500-mg dose of sodium fusidate ranging from 27 to 38 mg/liter after single doses ranging from 500 to 2,200 mg, thus indicating no apparent dose dependency. As shown in Table 2 for study 103, the median \(T_{\text{max}}\) which after morning sodium fusidate doses of 500 to 1,650 mg ranged from 1.5 to 4 h, appeared to be independent of dose. However, the median \(T_{\text{max}}\) associated with the morning 2,200-mg dose, which was 6 h, occurred modestly later. Compared to the morning doses of the same amount, the median \(T_{\text{max}}\) occurred 1 to 5 h later for the evening doses (3.5 to 8 h). Both the apparent terminal half-life and \(V_{\text{max}}/F\) were variable and showed no apparent dose dependency. There was a greater-than-dose-proportional increase in the \(\text{AUC}_{\text{Dose}}\) after a single dose in study 103, and the apparent total clearance (CL/F) decreased systematically with dose from 1.40 liters/h for 550 mg to 0.846 liters/h for 2,200 mg.

The impact of food on the PK of fusidic acid, as assessed by NCA using crossover data from 14 subjects who received sodium fusidate in both the fed and fasted state in study 102-A, is also shown in Table 2. Food decreased the \(C_{\text{max}}\) of fusidic acid by a mean of 23.2% and the \(\text{AUC}_{\text{Dose}}\) by a mean of 16.7%.

As part of the assessment of the extent of nonlinearity in the PK of fusidic acid, the ratios of \(C_{\text{max}}\) AUC, \(t_{1/2}\), and CL/F after multiple doses compared to those after single doses for each cohort in study 103 were calculated and are provided in Table 3. The ratios of the peak concentration after multiple doses to that after a single dose observed for sodium fusidate doses of 550, 1,100, and 1,650 mg were 3.35, 3.86, and 3.33, respectively. Substantial accumulation of fusidic acid was evident for all dose groups after multiple relative to single doses, as evidenced by the 2.19- to 2.35-fold increase in \(\text{AUC}_{\text{Dose}}\). In addition, the CL/F ratio, which ranged from 0.426 to 0.457, indicated that for single and multiple doses ranging from 550 to 1,650 mg, CL/F decreased after multiple...
TABLE 1 Summary statistics of demographic characteristics for phase 1 subjects included in the analysis data set by study and for all subjectsa

<table>
<thead>
<tr>
<th>Study and subject group</th>
<th>No. of subjects</th>
<th>Mean (SD)</th>
<th>Age (yr)</th>
<th>Ht (cm)</th>
<th>Wt (kg)</th>
<th>Body mass index (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Age (yr)</td>
<td>Ht (cm)</td>
<td>Wt (kg)</td>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>Study 102-A</td>
<td>23</td>
<td>5</td>
<td>42.4 (8.61)</td>
<td>173 (8.32)</td>
<td>74.2 (9.66)</td>
<td>24.7 (2.06)</td>
</tr>
<tr>
<td>Subjects only fasted</td>
<td>13</td>
<td>1</td>
<td>45.1 (8.33)</td>
<td>175 (7.35)</td>
<td>73.6 (9.11)</td>
<td>24.1 (1.90)</td>
</tr>
<tr>
<td>Subjects both fed and fasted</td>
<td>10</td>
<td>4</td>
<td>39.7 (8.29)</td>
<td>172 (9.2)</td>
<td>74.7 (10.5)</td>
<td>25.3 (2.10)</td>
</tr>
<tr>
<td>Study 102-B</td>
<td>12</td>
<td>5</td>
<td>39.8 (8.65)</td>
<td>170 (9.84)</td>
<td>72.4 (12.6)</td>
<td>24.8 (2.60)</td>
</tr>
<tr>
<td>Study 103</td>
<td>15</td>
<td>15</td>
<td>37.8 (10.5)</td>
<td>166 (8.38)</td>
<td>73.5 (10.5)</td>
<td>26.7 (2.44)</td>
</tr>
<tr>
<td>Cohort 1</td>
<td>4</td>
<td>2</td>
<td>35.5 (11.1)</td>
<td>168 (9.97)</td>
<td>76.8 (13.4)</td>
<td>26.9 (2.04)</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>3</td>
<td>3</td>
<td>37.7 (6.65)</td>
<td>163 (4.86)</td>
<td>75.5 (7.29)</td>
<td>28.4 (1.33)</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>4</td>
<td>2</td>
<td>38.8 (7.99)</td>
<td>168 (9.99)</td>
<td>76.8 (13.4)</td>
<td>26.9 (2.04)</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>2</td>
<td>4</td>
<td>40.7 (14.4)</td>
<td>162 (7.56)</td>
<td>71.2 (6.85)</td>
<td>27.1 (1.86)</td>
</tr>
<tr>
<td>Cohort 5</td>
<td>2</td>
<td>4</td>
<td>36.5 (13.5)</td>
<td>167 (9.35)</td>
<td>73.7 (10.1)</td>
<td>26.4 (1.93)</td>
</tr>
<tr>
<td>All subjects</td>
<td>50</td>
<td>25</td>
<td>40.0 (9.53)</td>
<td>170 (9.23)</td>
<td>73.5 (10.6)</td>
<td>25.5 (2.51)</td>
</tr>
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</table>

a Numbers in parentheses indicate standard deviations.
TABLE 2 Noncompartmental PK parameter estimates for fusidic acid

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>N</th>
<th>Dose (mg)</th>
<th>Dosing interval</th>
<th>Dose no.</th>
<th>C_{max} (mg/liter)</th>
<th>T_{max} (h)</th>
<th>t_{1/2} (h)</th>
<th>AUC_{T=12 h} (mg · h/liter)</th>
<th>AUC_{\text{clearance}} (mg · h/liter)</th>
<th>Cl/F (liters/h)</th>
<th>V_{ss}/F (liters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>103</td>
<td>1</td>
<td>6</td>
<td>550</td>
<td>Single</td>
<td>1</td>
<td>31.2 (32)</td>
<td>2.0 (2.0, 3.0)</td>
<td>20.4 (25)</td>
<td>222 (42)</td>
<td>377 (59)</td>
<td>1.40 (59)</td>
<td>22.5 (40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>550</td>
<td>12 h</td>
<td>2</td>
<td>30.7 (35)</td>
<td>2.0 (1.5, 2.0)</td>
<td>193 (41)</td>
<td>239 (53)</td>
<td>866 (50)</td>
<td>0.596 (65)</td>
<td>12.8 (60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>550</td>
<td>12 h</td>
<td>11</td>
<td>31.1 (45)</td>
<td>7.0 (1.0, 8.0)</td>
<td>2.0 (1.0)</td>
<td>886 (50)</td>
<td>1.072 (23)</td>
<td>0.984 (20)</td>
<td>15.5 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>650</td>
<td>12 h</td>
<td>11</td>
<td>105 (40)</td>
<td>3.0 (1.5, 4.0)</td>
<td>13.5 (25)</td>
<td>866 (50)</td>
<td>0.596 (65)</td>
<td>12.8 (60)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>6</td>
<td>1,100</td>
<td>Single</td>
<td>1</td>
<td>71.5 (15)</td>
<td>3.5 (1.0, 4.0)</td>
<td>17.7 (9)</td>
<td>561 (15)</td>
<td>1,072 (23)</td>
<td>0.984 (20)</td>
<td>15.5 (8)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1,100</td>
<td>12 h</td>
<td>1</td>
<td>82.7 (18)</td>
<td>1.5 (1.5, 3.0)</td>
<td>536 (7)</td>
<td>737 (20)</td>
<td>2,483 (16)</td>
<td>0.425 (22)</td>
<td>14.2 (16)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1,100</td>
<td>12 h</td>
<td>2</td>
<td>102 (48)</td>
<td>4.0 (3.0, 11.5)</td>
<td></td>
<td>808 (28)</td>
<td>1,662 (39)</td>
<td>0.952 (49)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>6</td>
<td>1,650</td>
<td>Single</td>
<td>1</td>
<td>99.4 (25)</td>
<td>3.0 (2.0, 4.0)</td>
<td>15.1 (15)</td>
<td>1,072 (23)</td>
<td>1,072 (23)</td>
<td>0.984 (20)</td>
<td>15.5 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>1,650</td>
<td>12 h</td>
<td>1</td>
<td>90.8 (20)</td>
<td>4.0 (2.0, 8.0)</td>
<td></td>
<td>808 (28)</td>
<td>1,662 (39)</td>
<td>0.952 (49)</td>
<td>17.8 (18)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1,650</td>
<td>12 h</td>
<td>2</td>
<td>105 (7)</td>
<td>8.0 (2.0, 11.5)</td>
<td></td>
<td>799 (8)</td>
<td>862 (12)</td>
<td></td>
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<tr>
<td></td>
<td>4</td>
<td>6</td>
<td>2,200</td>
<td>Single</td>
<td>1</td>
<td>126 (22)</td>
<td>6.0 (3.0, 8.0)</td>
<td>16.3 (26)</td>
<td>981 (23)</td>
<td>2,493 (39)</td>
<td>0.846 (47)</td>
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<td></td>
<td></td>
<td></td>
<td>1,100</td>
<td>12 h</td>
<td>1</td>
<td>64.5 (22)</td>
<td>2.5 (1.5, 4.0)</td>
<td></td>
<td>507 (27)</td>
<td>1,030 (26)</td>
<td>0.466 (25)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1,100</td>
<td>12 h</td>
<td>2</td>
<td>82.7 (31)</td>
<td>7.0 (2.0, 11.5)</td>
<td></td>
<td>767 (31)</td>
<td>1,030 (26)</td>
<td>0.466 (25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6</td>
<td>500</td>
<td>12 h</td>
<td>15</td>
<td>141 (26)</td>
<td>4.0 (3.0, 6.0)</td>
<td>18.0 (40)</td>
<td>1,370 (25)</td>
<td>1,370 (25)</td>
<td>0.385 (21)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1,100</td>
<td>12 h</td>
<td>2</td>
<td>91.8 (21)</td>
<td>2.5 (2.0, 6.0)</td>
<td></td>
<td>819 (16)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,650</td>
<td>12 h</td>
<td>2</td>
<td>157 (11)</td>
<td>3.5 (1.5, 8.0)</td>
<td></td>
<td>1,537 (11)</td>
<td>1,537 (11)</td>
<td>0.310 (12)</td>
<td>14.3 (29)</td>
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<tr>
<td></td>
<td>6</td>
<td>825</td>
<td>12 h</td>
<td>15</td>
<td>259 (12)</td>
<td>3.5 (3.0, 4.0)</td>
<td>29.3 (35)</td>
<td>2,551 (13)</td>
<td>2,551 (13)</td>
<td>0.310 (12)</td>
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</tbody>
</table>

TABLE 3 Ratio of noncompartmental PK analysis parameter estimates after multiple doses to those after single doses for fusidic acid by cohort for study 103

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose (mg)</th>
<th>C_{max} (mg/liter)</th>
<th>AUC_{0–12 h} (mg · h/liter)</th>
<th>AUC_{\text{clearance}} (mg · h/liter)</th>
<th>t_{1/2} (h)</th>
<th>Cl/F (liters/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>550</td>
<td>3.35 (28)</td>
<td>3.99 (26)</td>
<td>2.35 (21)</td>
<td>0.663 (36)</td>
<td>0.426 (23)</td>
</tr>
<tr>
<td>2</td>
<td>550</td>
<td>3.86 (13)</td>
<td>4.43 (12)</td>
<td>2.32 (15)</td>
<td>0.945 (33)</td>
<td>0.452 (17)</td>
</tr>
<tr>
<td>3</td>
<td>1,650</td>
<td>3.33 (30)</td>
<td>4.40 (26)</td>
<td>2.19 (46)</td>
<td>1.80 (65)</td>
<td>0.457 (36)</td>
</tr>
</tbody>
</table>

a N, number of healthy subjects; Dose no., number of doses administered; Single, single dose; C_{max} maximum observed concentration; T_{max} time of C_{max} postdose; t_{1/2}, apparent half-life during the terminal phase; AUC_{T=12 h}, area under the curve from time zero to 12 h; AUC_{\text{clearance}} area under the curve from time zero to infinity for a single dose or area under the curve during one dosing interval after the last dose for multiple-dose regimen; F, (unknown) extent of bioavailability after oral dosing; Cl/F, apparent total clearance; V_{ss}/F, apparent volume of distribution at steady state.

b Dose numbers 1, 11, 13, and 15 refer to morning doses; dose number 2 refers to evening doses.

c Median (minimum, maximum) is reported for T_{max}.

d The comparison of AUC_{\text{clearance}} after single and multiple doses assumes that steady state was achieved after multiple dosing. If steady state had not been achieved, AUC_{\text{clearance}} would be expected to be even higher and Cl/F lower after multiple doses compared to the estimates reported.

e Please note that multiple doses were lower than single dose for cohorts 4 and 5. For cohorts 1, 2, and 3, single and multiple doses administered were the same.

f Data for the 14 subjects who received sodium fusidate in the fasted and fed state within study 102-A are reported in this row to support the conclusions for the effect of food on the rate and extent of bioavailability. These 14 subjects are part of the 28 subjects receiving sodium fusidate in the fasted state.

g Area under the curve from 0 to 8 h.

ied sodium fusidate dosing regimens in study 103 were very well predicted by the model with autoinhibition of clearance implemented but poorly predicted by the model with parallel linear and MM elimination. For dosing regimens of approximately 400 mg q12h or lower, the accumulation ratio was small due to a lack of clearance inhibition at steady state. For dosing regimens of approximately 450 to 500 mg q12h, higher clearances were evident, a finding that was likely due to limited saturation with initial doses and achievement of clearance inhibition only at steady state. Doses of approximately 750 mg q12h or higher led to notable clearance inhibition, both after a single dose and at steady state. The results of the simulations conducted demonstrated that significant accumulation of fusidic acid occurred with the administration of dosing regimens of approximately 500 mg q12h or total daily doses of 1,000 mg or greater, regardless of schedule of administration, due to the inhibition of clearance.

To illustrate the effect of front-loaded dosing regimens on the time to steady state, plasma concentration-time profiles for such dosing regimens were simulated using the population mean PK parameters.
parameters provided in Table 4. Simulated plasma concentration-time profiles for various sodium fusidate q12h dosing regimens without (Fig. 4A) and with (Fig. 4B) front loading, the latter of which involved the administration of two large doses at 0 and 12 h, along with a comparison of the average steady-state concentration ($C_{ss}$) expected with each dose (Fig. 4C), are shown in Fig. 4. As shown in Fig. 4A, the simulation results indicated that the time to steady state was dose dependent and was approximately 3 weeks or longer for q12h dosing regimens with intermediate doses of 500 mg. Times to steady state were approximately 8 and 3 days for q12h dosing regimens with intermediate doses of 500 mg or less, respectively. However, as shown in Fig. 4B, the front-loaded dosing regimen of 1,200 mg q12h or greater on day 1 followed by 600 mg q12h allowed for steady state to be achieved rapidly (24 h or less).

The autoinhibition of clearance of fusidic acid resulted in a
high clearance state for dosing regimens containing low doses of sodium fusidate (less than approximately 400 mg q12h) and a low clearance state for dosing regimens containing high doses (greater than approximately 550 mg q12h). As shown in Fig. 4C, the high clearance state at low doses resulted in a gradual increase in the $C_{ss}$ of fusidic acid whereas the low clearance state resulted in a rapid increase in the $C_{ss}$. These two clearance states transitioned from one to the other over a relatively narrow dose range due to the high Hill coefficient of 4.61. For smaller Hill coefficients, the dose range between a low and a high clearance state would be wider. For dosing regimens of approximately 400 mg q12h or less, the $CL/F$ was approximately 1.27 liters/h with an apparent terminal half-life of 14.0 h. For dosing regimens of approximately 550 mg q12h or higher, the $CL/F$ of fusidic acid was approximately 0.370 liters/h with an apparent terminal half-life of 38.9 h. The $C_{ss}$ of fusidic acid for low concentrations ($C1 < IC_{50}$) in a high clearance state ($CL_{high}/F$) can be approximated and is provided in equation 8:

$$C_{na} = \frac{\text{Daily dose}}{24 \text{ h} \cdot CL_{high}/F} = \frac{\text{Daily dose}}{24 \text{ h} \cdot 1.27 \text{ liters/h}}$$  \hspace{1cm} (8)$$

The equation for high plasma concentrations ($C1 \gg IC_{50}$), which results in an apparent low clearance state ($CL_{low}/F$), is provided in equation 9:

$$C_{na} = \frac{\text{Daily dose}}{24 \text{ h} \cdot CL_{low}/F} = \frac{\text{Daily dose}}{24 \text{ h} \cdot 0.370 \text{ liters/h}}$$  \hspace{1cm} (9)$$

It is important to note that the daily dose is the amount of fusidic acid and the $C_{na}$ needs to be multiplied by $F_{fed}$ for administration in the fed state. The $C_{na}$ predicted from equations 8 and 9 are consistent with that predicted by the full model for all doses except 450 to 500 mg of sodium fusidate q12h (Fig. 4C).
DISCUSSION

Using data from healthy subjects from three phase 1 studies, the objectives of this analysis were to develop a population PK model to describe the absorption and disposition of fusidic acid after single and multiple oral doses and to determine the effect of food on the rate and extent of fusidic acid bioavailability. As a result of the wide dose range of the single and multiple oral sodium fusidate doses studied in the fed and fasted state, a robust population PK model that accommodated the PK characteristics of fusidic acid, including complex absorption and nonlinearity in clearance, was successfully developed.

The final population PK model was a semiphysiological model, which described the absorption of fusidic acid using a time-dependent mixed-order absorption process and which contained two disposition compartments and a turnover process to describe the autoinhibition of clearance. The above-described autoinhibition of clearance implemented in the final population PK model is similar to the semiphysiological turnover model (i.e., indirect-response model) approach proposed by Gordi et al. (27, 28) to describe the auto-induction of hepatic metabolism by artemisinin. Both models, however, differ from those for clarithromycin (29) and linezolid (30), the clearance of which was also described to be autoinhibited. While the models for clarithromycin and linezolid describe the time delay between plasma concentrations and inhibition of clearance by drug penetration to an effect compartment, the indirect response model proposed by Gordi et al. (27, 28) and the model for fusidic acid described herein are based on the assumption that this time delay is caused by the turnover rate of hepatic enzymes.

An important implication of the autoinhibition of clearance of fusidic acid is the presence of two clearance states for sodium fusidate dosing regimens containing high and low doses. For dosing regimens containing low doses (250 mg or less q12h), a high clearance state was evident with little to no accumulation. For dosing regimens containing high doses (750 mg q12h or higher), a low clearance state was evident with long terminal half-lives. Given the BSV of fusidic acid, intermediate doses of sodium fusidate (450 to 500 mg q12h) may result in either low or high clearance states.

Another important implication of the autoinhibition of clearance of fusidic acid is that the administration of sodium fusidate q12h dosing regimens containing high doses without front loading result in the achievement of steady state in approximately 8 days compared to approximately 3 weeks for dosing regimens containing intermediate doses. Such a delay in time to achieving steady-state concentrations may increase the risk of failure to therapy and increased emergence of bacterial resistance. Administration of front-loaded dosing regimens, such as 1,500 mg q12h on day 1 followed by 600 mg q12h, which involve delivering a large amount of the total drug exposure early in therapy, would allow for a low clearance state to be achieved. As a result, high fusidic acid exposures would be achieved on day 1. A maintenance dose of 600 mg sodium fusidate every 12 h is proposed to maintain the low clearance state and provide high fusidic acid concentrations throughout the therapy.

The impact of the front-loaded dosing regimens and those with-
out front loading on the bacterial burden of methicillin-resistant *Staphylococcus aureus* (MRSA) and suppression of the emergence of resistance during therapy was evaluated using a one-compartment in vitro infection model which contained physiologic concentrations of albumin to account for protein binding (31, 32). In this 48-h study, regrowth of MRSA was associated with fusidic acid at 550 mg q12h and 1,100 mg q24h while suppression of bacterial regrowth was achieved by 550-mg and 1,100-mg fusidic acid front-loaded dosing regimens for which front-loaded doses were 2.3 and 4.4 times the maintenance dose, respectively. Data from a 240-h experiment using a hollow-fiber in vitro infection model (which also contained physiologic concentrations of albumin to account for protein binding) evaluating the activity of three fusidic acid dosing regimens, 600 mg q12h, 1,200 mg q12h on day 1 followed by 600 mg q12h, and 1,500 mg q12h on day 1 followed by 600 mg q12h, against MRSA provided further support for front-loaded dosing regimens. In contrast to the non-front-loaded dosing regimen, both front-loaded dosing regimens were associated with a delay in the emergence of resistant subpopulations over the study period (31, 32). Thus, the autoinhibition of clearance of fusidic acid described herein provides the opportunity to use front-loaded dosing regimens to achieve exposures associated with efficacy earlier in therapy, a strategy that has demonstrated pharmacodynamic benefits using data from in vitro infection models. Subsequent use of parameter estimates from a PK-PD model based on the above-described one-compartment in vitro infection model data and the final population PK model described herein, together with Monte Carlo simulation which allowed for the assessment of the impact of PK variability on achieving relevant bacterial reduction endpoints, provided further support for the use of front-loaded sodium fusidate dosing regimens (31, 32).

Recent findings of a phase 2 study in patients with acute bacterial skin and skin structure infections, for which comparable efficacy was observed for sodium fusidate at 550 mg q12h and linezolid 600 mg q12h, each administered for 10 to 14 days, provide further support for the use of front-loaded sodium fusidate dosing regimens (5).

In summary, a population PK model that described the disposition of fusidic acid was successfully developed. This model accommodated the complex PK characteristics of fusidic acid, including complex absorption and nonlinearity in clearance. The autoinhibition of clearance of fusidic acid provides a rationale for the administration of front-loaded dosing regimens for sodium fusidate. Such a population PK model, which can be used with data from nonclinical and clinical PK-PD models, provides an important foundation to support the selection of sodium fusidate dosing regimens for further study.

**APPENDIX**

This appendix presents the mathematical derivation for the model with autoinhibition of clearance that was incorporated into the final population PK model. The autoinhibition of clearance of fusidic acid described herein represents an expansion of a model with parallel first-order and Michaelis-Menten elimination. As shown below, this is demonstrated for a one-compartment intravenous bolus model with autoinhibition of clearance. This model converges to a parallel first-order and Michaelis-Menten elimination model when \( k_{\text{aut}} \) is large (i.e., rapid turnover) and if Hill is 1.

The differential equations for the amount of drug in the central compartment (A) and for the inhibition compartment (INH) are as follows:

\[
\frac{dA}{dt} = -\left[ CL \cdot (1 - INH) \right] \cdot C1 \cdot \text{IC:Dose} \quad (A1)
\]

\[
\frac{dINH}{dt} = k_{\text{aut}} \cdot \left( \frac{I_{\text{max}}} {IC_{50} + C1} \right) \cdot (1 - \frac{C1 \cdot C1_{\text{Hill}}}{IC_{50} + C1}) \quad (A2)
\]

An equivalent parameterization of this model would be to use \( CL \cdot \text{INH} \) instead of \( CL \cdot (1 - \text{INH}) \) in equation A1 and to write the differential equation for \( \text{INH} \) as follows:

\[
\frac{dINH}{dt} = k_{\text{aut}} \cdot \left( \frac{I_{\text{max}}} {IC_{50} + C1} \right) \cdot (1 - \frac{C1 \cdot C1_{\text{Hill}}}{IC_{50} + C1}) \quad (A2b)
\]

The \( I_{\text{max}} \) can take values from 0 to 1 (bounds included). If the turnover rate constant \( (k_{\text{aut}}) \) of the inhibition compartment is much faster than the elimination rate constant \( (k_{\text{el}} = CL/\text{V}1) \), the differential equation A2 can be set to zero and the steady-state solution for \( \text{INH} \) becomes:

\[
\text{INH} = \frac{I_{\text{max}} \cdot C1_{\text{Hill}}}{IC_{50} + C1_{\text{Hill}}} \quad (A3)
\]

With the assumption that Hill equals 1 as described above, equations A3 and A1 yield:

\[
\text{INH} = \frac{I_{\text{max}} \cdot C1}{IC_{50} + C1} \quad (A4)
\]

This equation can be reparameterized to yield the equation for a model with parallel first-order (clearance: \( CL_{\text{lin}} \)) and Michaelis-Menten elimination as described below. The maximum rate of elimination \( (V_{\text{max}}) \) is parameterized as the product of intrinsic clearance \( (CL_{\text{ic}}) \) and the Michaelis-Menten constant \( (K_{\text{m}}) \):

\[
\frac{dA}{dt} = -\left[ CL \cdot (1 - \frac{C1 \cdot C1_{\text{Hill}}}{IC_{50} + C1}) \right] \cdot C1 \cdot \text{IC:Dose} \quad (A5)
\]

\[
\frac{dA}{dt} = -\left[ \frac{CL_{\text{lin}} + CL_{\text{ic}} \cdot K_{\text{m}}}{K_{\text{m}} + C1} \right] \cdot C1 \cdot \text{IC:Dose} \quad (A6)
\]

For \( C1 \ll K_{\text{m}} \) and \( C1 \ll IC_{50} \), the square brackets in equations A5 and A6 yield the maximum achievable total clearance at low drug concentrations:

\[
CL = CL_{\text{lin}} + CL_{\text{ic}} \quad (A7)
\]

For \( C1 \gg K_{\text{m}} \) and \( C1 \gg IC_{50} \), the lowest clearance at high drug concentrations is as follows:

\[
CL \cdot (1 - \frac{I_{\text{max}}}{IC_{50} + C1}) = CL_{\text{lin}} \quad (A8)
\]

Rearranging equation A8 and inserting equation A7 yields the following:

\[
I_{\text{max}} = 1 - \frac{CL_{\text{lin}}}{CL_{\text{lin}} + CL_{\text{ic}}} = 1 - \frac{CL_{\text{lin}}}{C1_{\text{lin}} + CL_{\text{lin}}} \quad (A9)
\]

With equation A9 the square bracket in equation A5 yields the following:

\[
\frac{CL \cdot (1 - \frac{I_{\text{max}} \cdot C1}{IC_{50} + C1})}{IC_{50} + C1} = \frac{CL \cdot (1 - \frac{CL_{\text{lin}} + CL_{\text{ic}} \cdot K_{\text{m}}}{IC_{50} + C1})}{IC_{50} + C1} \quad (A10)
\]

Inserting equation A7 into equation A10 yields the following:

\[
\frac{CL \cdot IC_{50} + C1 \cdot C1}{IC_{50} + C1} = \frac{(CL_{\text{lin}} + CL_{\text{ic}}) \cdot IC_{50} + C1 + CL_{\text{ic}} \cdot IC_{50}}{IC_{50} + C1} \quad (A11)
\]

With \( K_{\text{m}} = IC_{50} \), equation A11 is identical to the square bracket for the
apparent total clearance in equation A6. Thus, the inhibition compartment model converges to a model with parallel first-order and Michaelis-Menten elimination when $k_{in}$ is large (i.e., rapid turnover) and the Hill coefficient is 1.

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REFERENCES