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EXPERIMENTAL THERAPEUTICS

Pharmacokinetic and Pharmacodynamic Analyses To Determine the Optimal Fixed Dosing Regimen of Iclaprim for Treatment of Patients with Serious Infections Caused by Gram-Positive Pathogens

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ABSTRACT Iclaprim is a bacterial dihydrofolate reductase inhibitor that is currently being evaluated in two phase 3 trials for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI). Prior animal infection model studies suggest that the pharmacokinetic/pharmacodynamic (PK/PD) drivers for efficacy are area under the concentration-time curve from 0 to 24 h at steady state (AUC_{0-24ss}), AUC/MIC, and time above the MIC during the dosing interval ($T > MIC$), while QTc prolongation was associated with the maximal concentration at steady state (C_{maxss}) in a thorough QTc phase 1 study. Using PK data collected from 470 patients from the previously conducted phase 3 complicated skin and skin structure infection (cSSSI) trials, population PK modeling and Monte Carlo simulation (MCS) were used to identify a fixed iclaprim dosage regimen for the ongoing phase 3 ABSSSI studies that maximizes AUC_{0-24ss}, AUC/MIC, and $T > MIC$ while minimizing the probability of a C_{maxss} of ≥800 ng/ml relative to the values for the previously employed cSSSI regimen of 0.8 mg/kg of body weight infused intravenously over 0.5 h every 12 h. The MCS analyses indicated that administration of 80 mg as a 2-h infusion every 12 h provides 28%, 28%, and 32% increases in AUC_{0-24ss}, AUC/MIC, and $T > MIC$, respectively, compared to values for the 0.8-mg/kg cSSSI regimen, while decreasing the probability of a C_{maxss} of ≥800 ng/ml, by 9%. Based on PK/PD analyses, 80 mg iclaprim administered over 2 h every 12 h was selected as the dosing scheme for subsequent phase 3 clinical trials.

KEYWORDS Monte Carlo simulation, PD, PK, iclaprim

Iclaprim is a diaminopyrimidine that is currently in phase 3 clinical development for the treatment of acute bacterial skin and skin structure infections (ABSSSI) as well as for hospital-associated bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) caused or suspected to be caused by susceptible Gram-positive pathogens (1, 2). Iclaprim selectively inhibits bacterial dihydrofolate reductase, a critical enzyme in the bacterial folate synthesis pathway, and displays bactericidal activity *in vitro* against Gram-positive organisms, including drug-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), linezolid-resistant *Staphylococcus aureus* (LRSA), daptomycin-nonsusceptible MRSA, vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-resistant *Staphylococcus aureus* (VRSA), vancomycin-resistant enterococcus (VRE), and multidrug-resistant *Streptococcus pneumoniae* (MDRSP) (3). To date, iclaprim has been evaluated in two phase 3 studies of patients with ABSSSI, two phase 3 studies of patients with complicated skin and skin structure infections

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(cSSSI), and one phase 2 study of patients with hospital-acquired and ventilator-associated bacteria pneumonia due to suspected or confirmed Gram-positive pathogens (1, 2, 4–7, 16). In the cSSSI clinical trials (ASSIST-1 and -2), patients received iclaprim at 0.8 mg/kg of body weight infused intravenously (i.v.) over 0.5 h every 12 h for 8 to 14 days.

In vivo studies of animal infections (thigh infection model, pneumonia model, and sepsis model) suggest that the pharmacokinetic/pharmacodynamic (PK/PD) drivers which are best correlated with efficacy are area under the concentration-time curve from 0 to 24 h at steady state (AUC_{0-24ss}), AUC_{0-24ss}/MIC, and time above the MIC during the dosing interval ($T > MIC$) (8, 9). The preclinical PK/PD work for iclaprim was conducted in animals (i.e., mouse and rat) that have considerably higher thymidine levels (i.e., ≥100-fold higher) than those observed in humans. Thymidine inhibits the action of iclaprim, making it difficult to quantify its definitive PK/PD target. Therefore, only qualitative PK/PD assessments were made, and iclaprim activity was judged to be both concentration and time dependent. The iclaprim half-life and twice-daily dosing confounded the ability to distinguish AUC, AUC/MIC, or $T > MIC$ as the optimal PK driver in previous animal studies.

While available data indicate that bacterial killing is related to AUC_{0-24ss}, AUC_{0-24ss}/MIC, and $T > MIC$ (8, 9), safety, namely, QTc prolongation, appears to be linked to the maximal concentration at steady state (C_{maxss}). A thorough QTc study indicated that there was an association between the maximum QTc value and higher values of C_{max} (10). Doses of 1 mg/kg and 2 mg/kg administered over 0.5 h led to dose-related increases in the QTc interval, whereas a dose of 0.5 mg/kg administered over 0.5 h did not. The increases in QTc interval for the 1-mg/kg dose were considered to be mild, with a mean (95% confidence interval) change in the placebo- and baseline-corrected QTcB of 10.3 (3.3–17.3) ms. This dose was associated with a geometric mean (95% confidence interval) C_{max} of 792 (682–919) ng/ml. A reference C_{max} of 800 ng/ml was therefore used for the evaluation of potential dosing regimens with respect to the risk of QTc prolongation.

Based on the current understanding of iclaprim's PK/PD profile, the FDA recommended that a fixed dose of iclaprim be used in the ongoing iclaprim phase 3 clinical program, since previous PK studies demonstrated no relationship between weight and clearance (CL) (11). This investigation summarizes the PK/PD modeling studies used to determine the optimal fixed dosing regimen for the phase 3 ABSSSI trials (REVIVE trials) and for the planned HABP and VABP trial (INSPIRE trial) (1, 2, 16). A fixed dose of iclaprim, i.e., 80 mg administered over 2 h every 12 h, was selected for these phase 3 trials and is projected to maximize both efficacy and safety compared to those of the weight-based dosing regimen used in the previous phase 3 cSSSI trials.

(The data reported here were presented in part at IDWeek 2016 [12].)

RESULTS

Population PK model. A summary of significant steps in the model-building process is shown in Fig. S3 in the supplemental material. Compared with a one-compartment model, the two-compartment model resulted in a decrease in the minimum objective function (MOF) of over 500 points. Three attempts to run a three-compartment model did not successfully converge. When the proportional plus additive residual error model was compared to the proportional error model, the proportional plus additive error model lowered the MOF by 21.0 points. Incorporating interoccasion variability into the model decreased the MOF by 182 points. Scatterplots of Eta1 versus Eta2 versus Eta3 versus Eta4 justified the inclusion of the off-diagonal elements of the covariance matrix (Fig. S2). A two-compartment model with interoccasion variability and a proportional error term plus the full off-diagonal covariance matrix was initially chosen for further model development, i.e., as a basic model to which covariates would be added.

The full covariate model did not converge with the above basic model structure, indicating that the full covariate model needed simplification. Interoccasion variability

TABLE 1 Summary of final model parameters[a]

Parameter	Estimate	SE estimate	Lower CI	Upper CI
$\theta 1$	48.2	4.22	39.76	56.64
$\theta 2$	36.1	2.04	32.02	40.18
$\theta 3$	36.8	2.62	31.56	42.04
$\theta 4$	1.85	0.851	0.148	3.552
$\theta 5$	−0.210	0.031	−0.148	−0.272
$\theta 6$	0.353	0.046	0.261	0.445
$\theta 7$	2.78	1.06	0.66	4.90
$\theta 8$	13.5	2.29	8.92	18.08
$\theta 9$	3.97	0.694	2.58	5.36
CV%				
V_1	51		45	56
CL	41		38	44
V_2	86		65	104
Additive residual error	5.19	0.87	3.45	6.93
Residual error CV%	36.5	0.0935	36.31	36.69

[a]CI, confidence interval; CV, coefficient of variation; SE, standard error; V_1, volume in central compartment; V_2, volume in peripheral compartment; CL, clearance.

was removed from the model, and the resulting model converged successfully; however, the covariance step aborted. The Eta block 4 structure was then reduced to an Eta block 3 structure, retaining the Eta values for central volume, peripheral volume, and clearance. The Eta value for intercompartmental clearance (*Q*) was still in the model, but without covariance parameters. This model also converged, but the covariance step aborted. The Eta value for intercompartmental clearance was then removed, and this model converged with the covariance step.

The final irreducible model is as follows: method = conditional + interaction, with omega as a block. CL was modeled as follows: CL (liters per hour) = $\theta 2 + \theta 5 \times$ age (years) + $\theta 7 \times$ sex (0 for females and 1 for males) + $\theta 9 \times$ occasion (an indicator variable which is 0 if the day of sampling is day 1 or 2 and 1 if the day of sampling is day 4 [±1 day]), i.e., CL (liters per hour) = 36.1 + (−0.21) × age + 2.78 (for males only) + 3.97 (for day 4 only). The apparent volume of distribution in the central compartment (V_1) was modeled as follows: V_1 (liters) = $\theta 1 + \theta 6 \times$ weight (kilograms), i.e., V_1 (liters) = 48.2 + 0.353 × weight (kilograms). The apparent volume of distribution in the peripheral compartment (V_2) was modeled as follows: V_2 (liters) = $\theta 3$, i.e., V_2 (liters) = 36.8. *Q* was modeled as follows: *Q* (liters per hour) = $\theta 4 + \theta 8 \times$ SOI (an indicator of the severity of disease; 0 if disease is not severe and 1 if disease is classified as severe), i.e., *Q* (liters per hour) = 1.85 + 13.5 (for severe infection only). The parameter estimates after covariate building and backward elimination are shown in Table 1.

The apparent V_1 was influenced by body weight. Age, gender, and time (day 1 versus day 4) had a slight influence on clearance (CL), and "severe cSSSI" had some influence on the intercompartmental clearance (*Q*) between the central volume and the peripheral volume of distribution. Body mass index (BMI), ethnicity, total bilirubin (TBili), alanine transaminase (ALT), and creatinine clearance, investigated for inclusion into the model, were found to have no influence on the population pharmacokinetic parameters.

Population predicted concentrations versus the observed concentrations for the base and final models are shown in Fig. 1a and b. For the base model, the fitted line had a slope of 1.02, an intercept of 24.6, and an r^2 value of 0.57; these values modestly improved in the final irreducible model, to a slope of 1.11, an intercept of 2.26, and an r^2 value of 0.58. Therefore, the irreducible model had a better fit relative to the intercept and a modest increase in r^2. It can also be seen that the final irreducible model allowed for the prediction of higher concentrations. Likewise, the Bayesian fit of the individual PK parameters by use of the final population PK model as the prior distribution was modestly better than that for the base model (Fig. 2a and b). The best-fit line for the

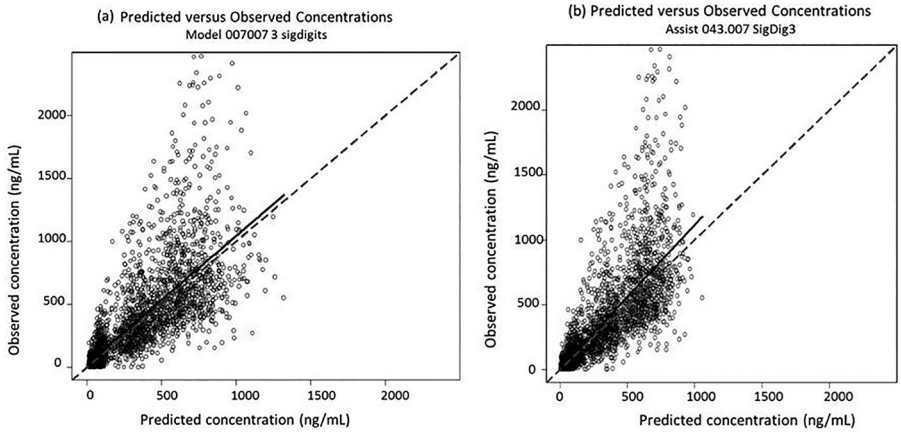

FIG 1 Population predicted concentrations versus measured concentrations for the basic structural model (a) and the final irreducible model (b). The fitted line is shown as a solid line, and the line of identity is shown as a dashed line from corner to corner.

base model had a slope of 1.00, an intercept of 9.77, and an r^2 value of 0.83, while the final model had a slope of 1.09, an intercept of −12.72, and an r^2 value of 0.85. The base model and the final model provided equivalent predictions, with the final model having a slight improvement in r^2.

Plots of the weighted residuals versus predicted concentrations are shown in Fig. 3a and b, while plots of the weighted residuals versus time since the most recent dose for the basic and final models are shown in Fig. 4a and b. In comparing the base and final model weighted residual plots, the locally weighted scatterplot smoother (LOESS) procedure suggested that the final model is well balanced. Both plots support the underlying assumption of homoscedasticity (or homogeneity of variance).

Individual iclaprim concentration-time profiles. A summary of the PK and PK/PD profiles of the different iclaprim dosing regimens evaluated is shown in Table 2. While the predicted PD indices for the 64-mg/2-h dosing regimen were similar to those for the base case (0.8 mg/kg over 0.5 h), those for the 72- and 80-mg/2-h regimens were substantially higher. For example, the AUC/MIC ratio for the 80-mg regimen was 1.3-fold higher. At the same time, all of the simulated regimens were associated with lower C_{maxss} values than those for the base case, suggesting that 14.5%, 21.49%, and 29.4% of patients who received the 64-mg, 72-mg, and 80-mg fixed dosing strategies, respectively, would have C_{maxss} values of >800 ng/ml.

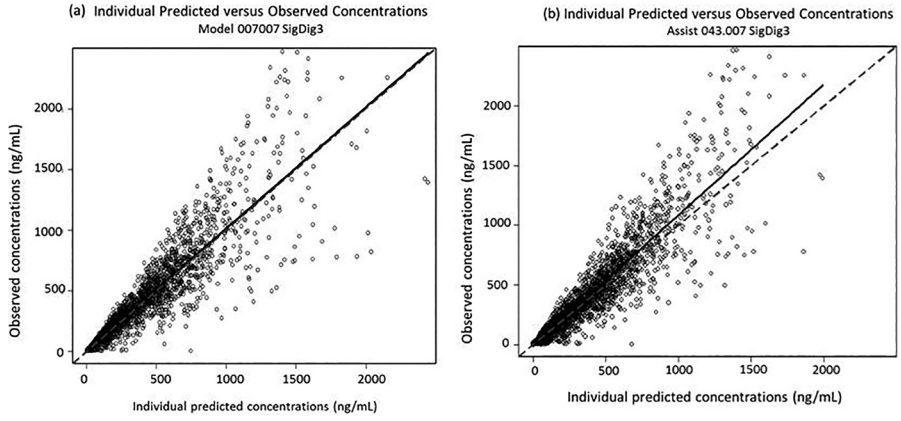

FIG 2 Individual predicted concentrations versus measured concentrations for the basic structural model (a) and the final (b). The fitted line is shown as a solid line, and the line of identity is shown as a dashed line from corner to corner.

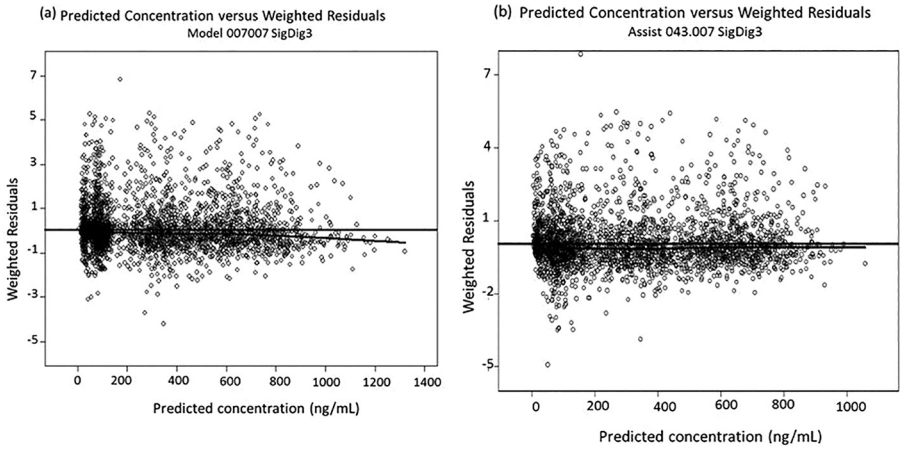

FIG 3 Weighted residuals versus population predicted concentrations, with LOESS smoothing, for the basic (a) and final (b) models.

DISCUSSION

The purpose of this study was to detail the PK/PD modeling used for the selection of the fixed dosing scheme of iclaprim employed in the REVIVE-1 and -2 phase 3 ABSSSI studies (1, 2, 16). The goal was to identify an iclaprim dose regimen that maximized AUC_{0-24ss}, AUC/MIC, and $T >$ MIC (efficacy parameters) while minimizing the probability of a C_{maxss} of ≥800 ng/ml (parameter associated with QTc prolongation in a thorough QTc phase 1 study) relative to the values for 0.8 mg/kg infused i.v. over 0.5 h every 12 h. Based on the data included in a previous New Drug Application (NDA), the FDA recommended that a fixed instead of weight-based iclaprim dosing regimen be considered given that the clearance and apparent volume of distribution appeared to be independent of body weight in previous PK analyses. The FDA also suggested that any candidate fixed dosing scheme selected for consideration in phase 3 studies should avoid achievement of C_{maxss} values in excess of the range associated with QTc prolongation (11). There was no formal recommended percent reduction in C_{maxss} values of >800 ng/ml by the FDA. The 0.8-mg/kg dose in the ASSIST-1 and -2 pooled studies had a mean change of 4.0 (standard deviation, 17.0) ms from after infusion to baseline and a 3.5-ms difference compared to that for linezolid, an antibiotic not associated with QTc prolongation (13). Therefore, any improvement over the 0.8-mg/kg dose, which was approximately a 9% reduction in C_{max} with the 80-mg/2-h fixed dose, was considered an acceptable percentage of improvement.

Based on the FDA's request, a PK model was fit to the iclaprim PK data collected

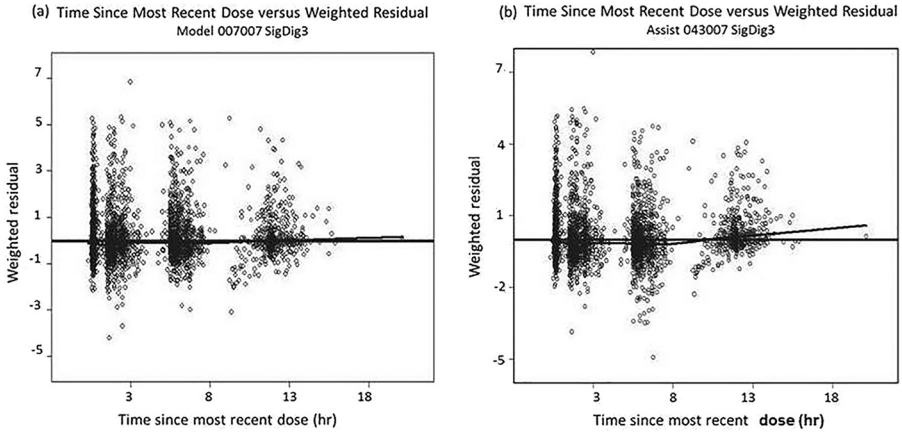

FIG 4 Weighted residuals versus time since the most recent dose for the basic (a) and final (b) models.

TABLE 2 PK analyses of different iclaprim dosing regimens

Parameter	Value for iclaprim dosing regimen (median [IQR][a])			
	0.8 mg/kg over 0.5 h	64 mg over 2 h	72 mg over 2 h	80 mg over 2 h
C_{maxss} (ng/ml)	702 (572–953)	524 (411–679)	590 (462–764)	655 (514–849)
% C_{maxss} of >800 ng/ml	38.5	14.5	21.5	29.4
AUC_{0-24ss}	3,865 (2,992–5,394)	3,970 (3,092–5,540)	4,466 (3,479–6,233)	4,962 (3,865–6,926)
AUC/MIC (h)	32 (24–45)	33 (26–46)	37 (29–52)	41 (32–58)
$T >$ MIC (%)	39.2 (27.5–55.0)	45.0 (35.0–60.8)	48.3 (38.3–65.0)	51.7 (40.8–70.0)

[a]Unless noted otherwise. IQR, interquartile range.

from 470 patients in the ASSIST studies. The final model resulted in a structural PK model with parameter estimates that were highly consistent with previous analyses. Although several covariates were related to clearance, apparent central volume of distribution, and intercompartmental clearance, most covariate parameter associations were subtle in nature. The modest contributions of covariates to the final PK model were reflected in the nearly identical fits and model diagnostics between the base and final PK models. Most importantly, no relationship was observed between total body weight and clearance and between creatinine clearance and clearance.

The findings from the population PK analyses had important implications for the iclaprim dosing regimen selected for the subsequent Monte Carlo simulation analyses. It is only necessary to dose a drug based on total body weight when key pharmacokinetic parameters, namely, drug clearance and volume of distribution, change proportionately with total body weight (14, 15). The lack of association between weight and clearance allowed for the exploration of fixed iclaprim dosing regimens, as requested by the FDA, in Monte Carlo simulation analyses to maximize AUC, AUC/MIC, and $T >$ MIC, the PD parameters associated with efficacy in animal infection models (8, 9). The ability to use a fixed dose was also beneficial from a PK/PD perspective, as C_{max} was linked to QTc prolongation in a thorough QT study and use of a fixed dose minimizes the potential for the higher C_{max} values that are often observed with a weight-based dosing approach, particularly among obese patients. This is especially true for drugs in which clearance does not increase in proportion to total body weight. Conversely, the use of a fixed-dose strategy ensures that smaller patients (<50 kg) are not provided with a dose that results in suboptimal AUC/MIC and $T >$ MIC exposures and, consequently, potentially less efficacious outcomes. The lack of an association between renal function and clearance also negated the need to consider renal dose adjustment regimens for patients with various degrees of renal function.

In the subsequent Monte Carlo simulation analyses, 80 mg iclaprim infused over 2 h every 12 h was identified as the optimal regimen because it provided the optimal balance in maximizing PK/PD parameters associated with both efficacy and safety. Iclaprim at 80 mg infused over 2 h every 12 h had the most favorable values for AUC, AUC/MIC, and $T >$ MIC, the PD parameters associated with iclaprim's efficacy, of all simulated regimens. In addition, this dosing regimen had a favorable reduction of C_{max} (nearly 10%), the pharmacokinetic parameter associated with iclaprim's dose-limiting toxicity of QTc prolongation. Relative to the regimen used in the ASSIST studies (iclaprim at 0.8 mg/kg infused i.v. over 0.5 h every 12 h), iclaprim administered as an 80-mg infusion over 2 h is projected to result, on average, in 30% increases in AUC/MIC and $T >$ MIC. The projected AUC values with the 80-mg i.v. dose every 12 h are somewhat higher than those achieved in phase 1 clinical studies in which iclaprim was considered safe and well tolerated, and they represent 1.15-fold and 1.28-fold increases over those calculated for the base case exposure from the ASSIST trials (4, 6, 7). However, these levels are significantly below the AUCs achieved at the no-observed-adverse-effect level (NOAEL) in 13-week toxicology studies (26,900 ng · h/ml [males] and 26,600 ng · h/ml [females] in the marmoset and 7,260 ng · h/ml [males] and 20,400 ng · h/ml [females] in the rat). In addition, the median C_{maxss} for the 80-mg/2-h infusion regimen was projected to be 655 ng/ml, which is lower than the 702 ng/ml predicted

TABLE 3 Summary of subject characteristics[a]

Parameter	Mean	SD	Quartile 1	Median	Quartile 3	Range
wt (kg)	79	17.1	67	76	90	42.0–143.0
ht (m)	1.72	0.1	1.65	1.72	1.78	1.29–1.96
BMI (kg/m^2)	26.8	5.6	22.9	26	30	16.8–54.7
Ideal wt (kg)	65.9	10.2	58.5	66	73.2	28.8–89.5
Age (yr)	47.8	15.3	38	47.5	58	18.0–87.0
Creatinine CL (ml/min)	99	29	78	102	120	18–172
ALT level (SI)	13.4	21.6	0.21	1.21	19	0.04–245
Total bilirubin level (SI)	7.5	5.4	3.6	6	9.6	1.7–40.9

[a]SI, International System of units.

for the base case (ASSIST trial regimen) and lower than the observed mean values for C_{max} observed at doses associated with QTc prolongation in the QTc studies (10). Importantly, the upper limit of the 95% confidence interval for C_{max} for the 1-mg/kg dose in the QTc study, 919 ng/ml, was not exceeded until the 90th percentile, suggesting a good safety margin (10). Note that 1-h infusions were also considered, but a 2-h infusion was selected to minimize the potential for adverse events related to elevated C_{max} values. Conversely, 3- and 4-h infusions were also considered, but their resultant improvement in the iclaprim PK/PD profile (C_{maxss} values of $<$800 ng/ml) over that for 2-h infusions was not deemed clinically meaningful. It was also felt that 2-h infusions were more practical than 3- or 4-h infusions (data not shown).

Several things should be noted in interpreting these findings. Similar to most phase 3 trials involving patients with skin and soft tissue infections, the ASSIST-1 and ASSIST-2 study populations may not be reflective of the broad range of patients who have ABSSSI in clinical practice. Most notably, patients with a body mass index of $>$40 and patients with estimated creatinine clearance of $<$30 ml/min were excluded from the ASSIST studies. Given that these patient populations were not reflected in the simulations used to determine the fixed dosing scheme for the ongoing phase 3 ABSSSI trials (REVIVE-1 and -2 trials) and the planned HABP and VABP trial (INSPIRE trial) (1, 2), it will be important to assess the viability of the selected regimen as data become available. Finally, the PK/PD drivers for iclaprim are based on *in vivo* animal infection model studies and will need to be revisited once human exposure-response data are available.

In summary, the data from the population PK analyses indicate that a fixed instead of weight-based dosing regimen is optimal for iclaprim, since there is no meaningful relationship between body weight and clearance. In the dose selection simulation analyses, iclaprim at 80 mg over a 2-h infusion every 12 h was identified as the optimal regimen. Relative to the weight-based dosing scheme used in the ASSIST-1 and ASSIST-2 trials, this regimen should confer, on average, 30% increases in AUC/MIC and $T >$ MIC while decreasing the probability of C_{max} values of $\geq$800 ng/ml by 9%. The results of these simulations form the basis for the selection of the dose for treatment of serious Gram-positive infections, including in the ongoing pivotal phase 3 ABSSSI REVIVE clinical trials, as the iclaprim regimen of 80 mg administered over 2 h every 12 h for 5 to 14 days is expected to maximize the likelihood of antibacterial efficacy while reducing the potential for adverse events.

MATERIALS AND METHODS

Study population. Pharmacokinetic (PK) data were obtained from patients from the previously conducted phase 3 ASSIST trials. The two ASSIST trials were phase 3, double-blind, randomized, multicenter cSSSI studies of nearly identical design. Across both trials, iclaprim was administered as a dose of 0.8 mg/kg over 0.5 h every 12 h for 8 to 14 days (4, 6, 7). In accordance with the study protocols, pharmacokinetic samples were obtained from each patient on two occasions: the first occasion after the first dose and the second occasion on the 4th day ($\pm$1 day) of treatment. Of the 492 patients who received iclaprim, PK data were available for 476 patients (241 patients from ASSIST-1 and 235 patients from ASSIST-2). Baseline characteristics of patients with PK data in the ASSIST trials are shown in Table 3. There were 1,528 concentrations from patients in ASSIST-1 and 1,533 concentrations from patients in ASSIST-2. The distribution of measured concentrations versus time since the most recent dose is shown in Fig. S1 in the supplemental material.

Population PK model. The concentration-time data were modeled using NONMEM, version VI (Iconus, Ellicott City, MD), software in conjunction with WINGS for NONMEM, version 613 (Auckland, New Zealand), an interface to run the program and extract the results. NONMEM VI was installed under NMQUAL, version 6.2.0 (Metrum Institute, Augusta, ME), which executes bug fixes and program validation. Diagnostic plots were executed in SPlus 6.2 (Insightful, Seattle, WA), and the bootstrap of the generalized additive model was run under Xpose3.1 (Department of Biopharmaceutics, Uppsala University, Sweden), which interfaces with SPlus 6.2 (Insightful, Seattle, WA).

Several aspects of the basic model were investigated, including whether the data were explained better by a one- versus two- versus three-compartment model, whether including an interoccasion variability factor improved the fit of the model, and the nature of the residual error model. Once the base model was identified, covariates were investigated for their influence on pharmacokinetic parameters, such as clearance (CL), apparent volume of distribution of the central compartment (V_1), apparent volume of distribution of the peripheral compartment (V_2), and intercompartmental clearance (Q). Covariates investigated for inclusion in the model were age, weight, body mass index (BMI), total bilirubin (TBili), alanine transaminase, creatinine clearance, gender, ethnicity, and day 1 versus day 4 sampling. It was also noted that there was a high degree of correlation between the intersubject variability parameters (Eta1, Eta2, Eta3, and Eta4) (Fig. S2). Therefore, a block structure for the between-subject random effects was included in the model. The residual error was investigated by use of proportional, power, and proportional plus additive error terms.

The construction of a full model was done with all variables, as indicated by multivariable exploration, generalized additive modeling plus bootstrap, and graphical exploration, included in the model. In the final step, the irreducible model was identified. This was done by removing covariates and error terms from the model one at a time. Each covariate was removed, and the impact on the minimum objective function (MOF) and changes in random effects were observed. At each step, the covariate that caused the MOF to increase the least upon its removal was eliminated from the model. This was repeated until the removal of any covariate increased the MOF by 6.63, which is equivalent to retaining covariates at a level where $\alpha = 0.01$. The critical value for significance was set to 0.01 to account for the multiplicity and the asymptotic approach of the test statistic to the chi-square distribution. This was the process of backward elimination.

Simulation studies. With the final irreducible model, Bayesian estimates of each patient's individual pharmacokinetic parameters were derived, and these were used to generate the individual concentration-time profiles at day 4 for the following four different dosing strategies: 0.8 mg/kg given i.v. over 30 min every 12 h, 64 mg given i.v. over 120 min every 12 h, 72 mg given i.v. over 120 min every 12 h, and 80 mg given i.v. over 120 min every 12 h. The 64-mg fixed dosing regimen was chosen based on the average weight of 80 kg in the ASSIST-1 and -2 trials. Based on a thorough QTc study of healthy volunteers, 96 mg of iclaprim was associated with QTc prolongation. Therefore, doses of 64, 72, and 80 mg were studied.

Concentration-time curve data could be calculated for 470 patients. While PK data were available for 476 patients in the ASSIST studies, six patients had no day 4 concentrations for estimation of the individual pharmacokinetic parameters. The derived parameters AUC_{0-24ss}, C_{maxss}, minimum concentration at steady state (C_{minss}), AUC/MIC, and $T >$ MIC were calculated for the candidate fixed-dose iclaprim regimens and for iclaprim at 0.8 mg/kg infused i.v. over 0.5 h every 12 h ("base case" regimen used in the ASSIST studies). The simulated AUC_{0-24ss} was calculated as follows for dosing every 12 h: $AUC_{0-24ss} = 2 \times$ dose/CL. For calculation of C_{maxss}, it was assumed that this occurred at the end of the infusion.

Pharmacokinetic/pharmacodynamic analyses. The goal of the PK/PD analyses was to identify a fixed iclaprim dose regimen that maximized AUC_{0-24ss}, AUC/MIC, and $T >$ MIC (efficacy parameters) while minimizing the probability of a C_{maxss} value of $\geq$800 ng/ml (parameter associated with QTc prolongation in the thorough QTc phase 1 study) relative to the values for 0.8 mg/kg infused i.v. over 0.5 h every 12 h. The *S. aureus* MIC_{90} of 0.12 μg/ml identified in a 2012-2014 worldwide surveillance study of patients with skin and skin structure infections and hospital-acquired bacterial pneumonia was employed (D. Huang, T. File, Jr., M. Dryden, G. R. Corey, A. Torres, and M. Wilcox, submitted for publication).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01184-17.

SUPPLEMENTAL FILE 1, PDF file, 0.5 MB.

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REFERENCES

1. Motif Bio. 2015. Phase 3 study to evaluate safety and efficacy of iclaprim versus vancomycin for ABSSSI: REVIVE-1 (REVIVE-1). ClinicalTrials.gov identifier NCT02600611. https://clinicaltrials.gov/ct2/show/NCT02600611?term=iclaprim&rank=2.

2. Motif Bio. 2015. Phase 3 study to evaluate safety and efficacy of iclaprim versus vancomycin for ABSSSI: REVIVE-2 (REVIVE-2). ClinicalTrials.gov identifier NCT02607618. https://clinicaltrials.gov/ct2/show/NCT02607618?term=iclaprim&rank=1.

3. Sader HS, Fritsche TR, Jones RN. 2009. Potency and bactericidal activity of iclaprim against recent clinical Gram-positive isolates. Antimicrob Agents Chemother 53:2171–2175. https://doi.org/10.1128/AAC.00129-09.
4. Dryden M, O'Hare MD, Sidarous E, Hadváry P, Islam K. 2008. Clinical efficacy of iclaprim in complicated skin and skin structure infection (cSSSI): preliminary results from the ASSIST-2 clinical trial, poster P545. Abstr 18th Annu Eur Congr Clin Microbiol Infect Dis Meet, 19 to 22 April 2008, Barcelona, Spain.
5. Huang DB, File TM, Jr, Torres A, Shorr AF, Wilcox MH, Hadvary P, Dryden M, Corey GR. 2017. A phase II randomized, double-blind, multicenter study to evaluate efficacy and safety of intravenous iclaprim versus vancomycin for the treatment of nosocomial pneumonia suspected or confirmed to be due to Gram-positive pathogens. Clin Ther 39:1706–1718. https://doi.org/10.1016/j.clinthera.2017.07.007.
6. Stevens D, Leighton A, Dankner WM, Islam K, Hadváry P. 2007. Efficacy of iclaprim in complicated skin and skin structure infections: preliminary results of ASSIST-1, poster 1079. Abstr 45th Annu Meet Infect Dis Soc Am, 4 to 7 October 2007, San Diego, CA.
7. Hadváry P, Stevens D, Solonets M, Jones ME, Sahm DF, O'Hare MD, Dankner W, Leighton A, Dryden M, Islam K. 2008. Clinical efficacy of iclaprim in complicated skin and skin structure infection (cSSSI): results of combined ASSIST phase III studies, poster L-1512. Abstr 48th Annu Intersci Conf Antimicrob Agents Chemother/46th Infect Dis Soc Am Annu Meet, 25 to 28 October 2008, Washington, DC. http://www.abstractsonline.com/viewer/SearchResults.asp.
8. Candiani GP, Romano G, Jabes D, Islam K. 2002. AR-100, a novel diaminopyrimidine compound: in vivo efficacy in a murine model of staphylococcal septicaemia, poster F-2030. Abstr 42nd Annu Intersci Conf Antimicrob Agents Chemother, 27 to 30 September 2002, San Diego, CA.
9. Murphy TM, Little S, Gordon L, McKenney D, Haldimann A, Hawser S, Lociuro S. 2008. Comparative efficacy of iclaprim against wild-type and thymidine kinase-deficient Staphylococcus aureus in a mouse abscess model, poster P1909. Abstr 18th Annu Eur Congr Clin Microbiol Infect Dis Meet, 19 to 22 April 2008, Barcelona, Spain.
10. Hadváry P, Leighton A, Wargenau M, Thomsen T, Islam K. 2007. Evaluation of the effect of iclaprim on the QT interval in healthy volunteers, poster 432. Abstr 45th Annu Meet Infect Dis Soc Am, 4 to 7 October 2007, San Diego, CA.
11. Anonymous. 14 April 2015. FDA letter. Type C meeting minutes. FDA, Office of Communications, Division of Drug Information, Center for Drug Evaluation and Research, Silver Spring, MD, USA.
12. Huang D, Lodise T. 2016. Use of pharmacokinetic/pharmacodynamics (PK/PD) analyses to determine the optimal fixed dosing regimen of iclaprim for phase 3 ABSSSI clinical trials, poster 1971. IDWeek 2016, New Orleans, LA.
13. Leighton A, Stevens D, Islam K, Dryden M, Dankner W, Hadvary P. 2008. Iclaprim effect on the QT interval: results of combined ASSIST phase III studies, abstr L-1513. Abstr 2008 IDSA Meet, 26 October 2008.
14. Pai MP. 2012. Drug dosing based on weight and body surface area: mathematical assumptions and limitations in obese adults. Pharmacotherapy 32:856–868. https://doi.org/10.1002/j.1875-9114.2012.01108.x.
15. Pai MP. 2015. Treatment of bacterial infections in obese adult patients: how to appropriately manage antimicrobial dosage. Curr Opin Pharmacol 24:12–17. https://doi.org/10.1016/j.coph.2015.06.004.
16. Huang DB, O'Riordan W, Overcash S, Heller B, Amin F, File TM, Wilcox MH, Torres A, Dryden M, Holland TL, McLeroth P, Shukla R, Corey GR. Phase 3, randomized, double-blind, multicenter study to evaluate the safety and efficacy of intravenous iclaprim versus vancomycin for the treatment of acute bacterial skin and skin structure infections suspected or confirmed to be due to Gram-positive pathogens: REVIVE-1. Clin Infect Dis, in press.