Population Pharmacokinetics Study of Contezolid (MRX-I), a Novel Oxazolidinone Antibacterial Agent, in Chinese Patients

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ABSTRACT

Purpose: Contezolid (MRX-I) is a novel oxazolidinone with potent *in vitro* activity against gram-positive pathogens. The aim of this study was to establish the dose-pharmacokinetic (PK) exposure-pharmacodynamic (PD)—response relationship and to quantitatively evaluate the variability of MRX-I after continuous oral administration of 600 mg BID and 800 mg BID for 14 days under fed conditions in patients with skin and skin structure infections. Another goal was to evaluate the 2 dosing regimens against methicillin-resistant *Staphylococcus aureus* infections based on PK/PD analysis.

Methods: PK data from healthy volunteers and patients were pooled to develop a population PK model using a nonlinear mixed effect modeling method. Monte Carlo simulations were used to predict probability of target attainment (PTA) and cumulative fraction of response after single oral administration of 600 and 800 mg of MRX-I under fed conditions.

Findings: The PK profile of oral administration of MRX-I was described by using a 2-compartment model with first-order elimination. Absorption of MRX-I may be affected by food intake. Type of volunteers could affect absorption constant rate and volume of distribution in the peripheral compartment, and weight could affect volume of distribution in the central department. No obvious effect on PK parameters was identified for other factors such as age, sex, creatinine clearance, concomitant medicine, and baseline diseases. Based on Monte Carlo simulation, MRX-I 600 or 800 mg BID up to 14 days on ordinary fed status could produce satisfactory efficacy against methicillin-resistant *S aureus*, with cumulative fraction of response >90% for $fAUC_{0-24}$/MIC targeted at 2.3. At MIC ≤2.0 μg/mL for MRX-I 600 mg BID, or at MIC ≤4.0 μg/mL for MRX-I 800 mg BID, with continuous administration for 14 days at fed status, both regimens could obtain satisfactory clinical and antibacterial efficacy, with PTA >90%. Hence, the MRX-I regimen of 800 mg BID for 7—14 days can be recommended for confirmative clinical trials in patients with skin and skin structure infections.

Implications: PK profiles of MRX-I were well captured by using a 2-compartment PK model, and disease status, food intake, and weight were found to significantly affect PK profiles. A dosing regimen of 800 mg BID for 7—14 days with ordinary food intake was recommended for pivotal study based on simulated $fAUC_{0-24}$/MIC and PTA values. Results suggest that dose adjustments are not necessary for patient sex in confirmatory studies. Chinese Clinical

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Key words: healthy subjects, MRX-I, patients, pharmacodynamic pharmacokinetics, PD, PK.

INTRODUCTION

The recent occurrence of gram-positive, multidrug-resistant bacteria is a huge challenge to clinical therapeutics.[1] Oxazolidinones are a promising new antibiotic class for treating infections caused by gram-positive multidrug-resistant bacteria.[2] Linezolid was the first oxazolidinone approved by the US Food and Drug Administration. Adverse reactions such as thrombocytopenia and bone marrow suppression, however, are the biggest obstacles limiting its use in the clinic.[3−5] Tedizolid is another US Food and Drug Administration−approved oxazolidinone, although it has drawbacks due to limitations regarding safety.[6]

MRX-I is a novel oxazolidinone with potent *in vitro* activity against gram-positive pathogens, including pathogens involved in respiratory, skin and skin structure, and other community-acquired and nosocomial infections.[7,8] In particular, MRX-I displays potent antibacterial activity against common gram-positive pathogens that are resistant to currently available antibiotics, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, and penicillin-resistant *Streptococcus pneumoniae*. In general, the *in vitro* antibacterial profile of MRX-I is similar to or slightly better than that of linezolid, a currently available oxazolidinone. However, in long-term toxicity studies of rats, myelosuppression occurred significantly less with MRX-I than with linezolid, suggesting that MRX-I could offer superior clinical safety, tolerability, and compliance.[9]

Single and multiple ascending doses of MRX-I administered orally in healthy volunteers have been evaluated[10], and Phase II studies in patients with skin and skin structure infections were conducted. The purpose of the present study was to develop a population pharmacokinetic (PK) model to characterize the PK profiles of MRX-I and to assess the factors that might affect the PK profiles after single and multiple oral administration of MRX-I in healthy volunteers and patients. A PK/pharmacodynamic (PD) model was conducted to evaluate different dosing regimens and to provide suggestions for clinical studies in later phases of development.

MATERIALS AND METHODS

The protocol and informed consent form of these studies were approved by the Ethics Committee in Huashan Hospital, Shanghai, China. Guidelines from the National Medical Products Administration, the International Conference on Harmonisation, the Declaration of Helsinki, and Good Clinical Practice were applied during the conduct of these studies. All subjects signed the informed consent form and were instructed regarding the purposes, risks, and benefits of these studies. These clinical trials were registered at the Center for Drug Evaluation of the National Medical Products Administration (identifier: CTR20131214).

Study Designs and Subjects

PK data from 5 separate studies were included in this research. Three of these studies were conducted in healthy volunteers, and 2 were performed in patients. A detailed overview of study design, treatment, population, and PK sampling for the 5 studies included in these analyses is presented in Table I. Study data from healthy volunteers have been published elsewhere.[10]

Sample Collection and Quantification

Blood samples were collected in heparin sodium tubes and stored on ice until centrifugation. Plasma samples were then stored at approximately –20°C until analysis. Samples from all studies were analyzed for plasma concentrations of MRX-I by using a validated HPLC-MS/MS detection assay.[11] QTRAP 4000 (AB Sciex, Framingham, Massachusetts) and an ultra-high performance liquid chromatogram (Waters Corporation, Milford, Massachusetts) with a Waters ACQUITY UPLC BEH C_8 column (1.7 μm, 2.1 × 100 mm) and a guard column were applied. The assay was validated over the nominal MRX-I concentration range from 0.00500 to 1.00 mg/L with a lower limit of quantitation of 0.00500 mg/L. The maximum variability was 5.8% and 9.9% for intrabatch and interbatch detections, respectively.

Table I. Overview of study design, treatment, population, and pharmacokinetic sampling for the 5 studies included in the present analyses.

Study No.	No. of Subjects	Dose Regimen	Pharmacokinetic Sampling
1 (healthy volunteers)*	24	50, 100, 200, 400, 800, 1200, 1600, and 1800 mg	0, 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 h
2 (healthy volunteers)*	12 12	300, 600, 900 mg 900 mg	0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h
3 (healthy volunteers)*	24	600 mg q12h and 800 mg q12h, 15 days (single dose on day 1 and day 15)	0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 h after first dose on day 1; 0 h before dose and 1.5 h after dose on day 2; 3, 4, 8, 12, and 6 h after dose and 1.5 h after the next dose on days 13 and 14; 0, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h after the last dose on day 15
4 (adult patients)	28	600 mg q12h and 800 mg q12h, 7–14 days	Sparse blood sampling group were 0 h before the first dose on the day of visit 2a, 0.5–1 h, 3–4 h, 6–8 h after dosing, and follow-up 3
5 (adult patients)	16	600 mg q12h and 800 mg q12h, 7–14 days	Intensive blood sampling group was 0.5, 1, 2, 4, 6, 8, and 12 h after the first dose on the third day of administration and follow-up 3

* Study data from healthy volunteers have been published elsewhere.[10]

Population PK Model Development

MRX-I plasma PK data collected from 5 clinical studies were analyzed with a nonlinear mixed effects modeling approach using NONMEM version 7.3 (Icon Development Solutions, LLC, Dublin, Ireland). The PK models were fit to the data by using the first-order conditional estimation with interaction method. One- and two-compartment PK models were explored. Interindividual variability was assessed for PK model parameters using an exponential relationship (equation (1)). Proportional, additive, and combined (additive plus proportional) residual error models were explored. Relations between individual PK parameter estimates and possible covariates were explored by using graphical techniques. The covariates that were screened included demographic information (age, weight, and sex), renal (creatinine clearance and glomerular filtration rate) and liver (aspartate aminotransferase and alanine aminotransferase) function, subject type (healthy volunteers vs patients with infectious diseases), co-medications, and fed status.[12] When objective function value (OFV) was reduced by ≥ 3.84 ($P < 0.05$; $df = 1$), the covariate was kept in the model. After forward inclusion, the full model will remain by subtracting each covariate using a backward elimination process. When OFV was increased by ≥ 6.63 ($P < 0.01$; $df = 1$), the subtracted covariate was kept in the model. Standard model diagnostic methods were used, including successful minimization, diagnostic plots, plausibility, and precision of parameter estimates, as well as OFV and shrinkage values.

Fed status exhibited an impact on bioavailability (F1) of MRX-I according to covariate analysis. It was assumed that F1 = 100% in the condition of a high-fat meal, F1 = 45.4% if fasting, and F1 = 57.0% if ordinary food intake.[10]

Final Model Evaluation

Bootstrap analysis was performed for the final model with 1000 times resampling. The calculated 95% CI of model parameters from successfully minimized runs were included in the final model parameters. Visual predictive check (VPC) was also performed to evaluate predictive performance. For VPC, 1000 simulated replicates of the pharmacokinetic dataset were generated. The simulated data were compared with the observed data by superimposing the median, 5%, and 95% of the observed data with 95% prediction bands of each of these percentiles from the simulations.

PK/PD Analysis

Once the population PK model was finalized, individual concentration–time profile of the adult patients with complex skin and skin structure infections were simulated for the MRX-I dose regimens of 600 mg or 800 mg BID, continuous administration for 14 days after ordinary food intake. PK parameters such as AUC_{0-24} were calculated according to the simulated PK profiles. Combined with the MIC results of MRX-I for 218 gram-positive strains, including *S aureus* (methicillin-sensitive bacteria and drug-resistant bacteria), *S pneumoniae*, and enterococcus, the PK/PD index was calculated by using the single point estimation method.

The target value of $fAUC_{0-24}/MIC_{90} = 2.3$ (*S aureus*) was taken as the standard,[13] and the Monte Carlo simulation was used to calculate the PD compliance probability and cumulative response percentage of MRX-I dosing (600 mg or 800 mg dosing interval was every 12 h, repeat administration). The probability was used to evaluate the optimal clinical and microbial efficacy of MRX-I against common pathogenic bacteria.

Population PK Model

A 2-compartment disposition model with first-order elimination best described the data. Interindividual variability of all PK parameters was described by using the exponential model. The residual variability was described by a combined-error (additive plus proportional) model. The statistically significant covariate effects were identified and retained in the final model: fed status on F1, subject type on absorption constant rate (K_a) and apparent volume of the peripheral compartment (V_3), and weight on apparent volume of the central compartment (V_2). The final model parameter estimates and the precision associated with their estimation are shown in Table III. Typical values of apparent clearance from the central compartment (CL) and apparent intercompartmental clearance were 2.30 L/h and 0.787 L/h, respectively. Typical values of V_2 and V_3 were 4.37 L and 2.58 L; the typical value of K_a was 1.05 h^{-1}. The final equations for the structural model parameters (with BW indicating weight) are presented in Equations (1)–(6).

$$CL = 2.30 \times e^{\eta_1} \tag{1}$$

$$V_2 = 4.37 \times \left(\frac{BW}{62.2}\right)^{1.15} \times e^{\eta_2} \tag{2}$$

$$Ka = 1.05 \times 0.617^{TYPE} \times e^{\eta_3} \tag{3}$$

$$V_3 = 2.58 \times 0.342^{TYPE} \times e^{\eta_4} \tag{4}$$

$$Q = 0.787 \tag{5}$$

$$F1 = \frac{e^{-0.000762*DOSE}}{1+e^{-0.000762*DOSE}} \times F1FOOD, \text{ if fasting,}$$
$$\text{F1FOOD} = 0.454; \text{ if ordinary food,}$$
$$\text{F1FOOD} = 0.570; \text{ if high} - \text{fat meal, F1FOOD} = 1 \tag{6}$$

RESULTS

Dataset and Demographic Summary

The MRX-I plasma concentration below the lower limit of quantitation and missing values were removed from the original database. A total of 2092 plasma concentrations from 116 subjects were included in the analysis. A summary of the baseline demographic characteristics and other intrinsic or extrinsic factors of interest for the study subjects are shown in Table II.

Covariate Analysis

Table IV presents a summary of the empiric Bayesian estimation of individual PK parameters of studies 3, 4, and 5 (CL/F, V_2/F, V_3/F, and K_a) of healthy subjects or patients and exposure parameters calculated from simulated drug concentration–time curves using noncompartmental analysis (Phoenix WinNonlin version 7.0; Certara L.P. [Pharsight], Princeton, New Jersey); these variables were also compared between the 2 doses

Table II. Demographic characteristics and other intrinsic or extrinsic factors of interest for subjects who participated in the studies.

Variable	Healthy Volunteers (n = 72)	Patients (n = 44)
Age, median (range), y	24 (18, 32)	41 (18, 70)
Sex		
Male	35	31
Female	37	13
Weight, median (range), kg	59.6 (50.1, 77)	65 (47.5, 122)
Height, median (range), cm	168 (150, 185)	170.5 (150, 190)
BMI, median (range), kg/m^2	21.84 (19.09, 25.02)	23.475 (16.42, 41.24)
Creatinine clearance, median (range), mL/min	122.095 (98.57, 176.98)	109.61 (56.79, 257.55)
GFR, median (range), mL/min/1.73 m^2	133.805 (94.27, 223.04)	113.8 (77.24, 206.51)
ALT, median (range), U/L	1.1 (0.73, 1.67)	0.796 (0.47, 4.29)
AST, median (range), U/L	0.48 (0.24, 1.08)	0.864 (0.14, 3.16)
Food intake state: 0, 1*	48, 36	0, 44
Type of food: 0, 1, 2†	48, 24, 12	0, 44, 0
Concomitant drug: 0, 1‡	71, 1	31, 13
History of present illness: 0, 1‡	72, 0	24, 20

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; GFR = glomerular filtration rate.
* 0, fasting; 1, fed.
† 0, fasting; 1, ordinary food; 2, high-fat meal.
‡ 0, without; 1, with food.

(600 and 800 mg). There were slight differences in K_a and V_3 between patients and healthy subjects. Compared with healthy subjects, the average $t_{1/2}$ of patients decreased and the average C_{max} decreased by ~35%, which was statistically significant. Compared with healthy subjects, patients' mean AUC_{ss} value decreased by 18% in the 600-mg group and by 4% in the 800-mg group, with no statistically significant differences.

As presented in Table III, weight has a certain influence on V_2, and the introduction of weight reduced the interindividual variation of V_2 to 15.8%, but there was no variable significant effect on CL/F and the related parameters of exposure level (C_{max} and AUC_{ss}). Based on the simulations, the exposure of subjects with weight ranging from 46.7 to 112.0 kg was predicted to be 71.8%−196.6% of a typical subject (with a weight of 62.2 kg).

Other factors such as age, sex, creatinine clearance, and co-medications exhibited no significant effects on the PK parameters.

Model Diagnosis and Evaluation

As depicted in Figure 1, there was no major bias for the goodness-of-fit plots of individual- and population-predicted concentrations versus observed concentrations, conditional weighted residuals versus population predicted concentrations, or versus time after dose.[12] The bootstrap analysis validation results with 1000 times resampling (906 times resampling calculations were successful) are summarized in Table III. The typical values of parameters in the final model were close to the median values estimated from the bootstrap methods and were within the 95% CI of estimates by the bootstrap method; these findings indicate the stability and reliability of the original sample parameter value and were less affected by the sample distribution. VPC plots are presented in Figure 2. Because the 5th, 50th, and 95th percentiles of observed data and predicted data were fairly consistent, and the 90% CI of simulated data covered most of the observed concentrations, the prediction of the model was favorable, and it

Table III. Final model parameter estimates and bootstrap results.

Variable		Final Model			Bootstrap	
		Estimate	SE	RSE (%)	Estimate	95% CI
Typical value						
Theta	Description					
θ1	CL (L/h)	2.30	0.280	12	2.30	1.91 to 2.75
θ2	V_2 (L)	4.37	0.528	12	4.33	3.55 to 5.16
θ3	K_a (1/h)	1.05	0.0864	8	1.05	0.880 to 1.24
θ4	V_3 (L)	2.58	0.454	18	2.58	1.93 to 3.35
θ5	Q (L/h)	0.787	0.128	16	0.778	0.594 to 1.02
θ6	Ordinary food on F1	0.570	0.0472	9	0.571	0.485 to 0.664
θ7	Fast on F1	0.454	0.0326	8	0.456	0.390 to 0.512
θ8	Alpha	0.000762	0.000153	20	0.000781	0.000511 to 0.00100
θ9	TYPE* on K_a	−0.383†	0.0720	19	−0.376	−0.517 to −0.197
θ10	TYPE on V_3	−0.658‡	0.0905	14	−0.657	−0.927 to −0.435
θ11	Weigh on V_2	1.15	0.319	28	1.15	0.582 to 1.76
Interindividual variability						
Eta	Description					
η_1	ω^2_{CL}	0.101 (%CV = 31.8%)	0.0211	21 (Shr = 5%)	0.101	0.0663 to 0.186
η_2	ω^2_{V2}	0.0251 (%CV = 15.8%)	0.0133	53 (Shr = 58%)	0.0244	0.00201 to 0.0760
η_3	ω^2_{Ka}	0.179 (%CV = 42.3%)	0.0571	32 (Shr = 24%)	0.180	0.0632 to 0.323
η_4	ω^2_{V3}	0.651 (%CV = 80.7%)	0.177	27 (Shr = 19%)	0.616	0.273 to 1.01
Residual variability						
Epsilon	Description					
ε_1	Proportional error	0.182	0.0124	7 (Shr = 5%)	0.181	0.156 to 0.208
ε_2	Additive error	$8.87e^{-5}$	$4.75e^{-5}$	53 (Shr = 5%)	$8.91e^{-5}$	$2.79e^{-5}$ to $2.37e^{-4}$

CL = apparent clearance from the central compartment; K_a = absorption constant rate; V_2 = apparent volume of the central compartment; V_3 = apparent volume of the peripheral compartment; RSE = relative SE.
* TYPE value took 1 for patients, and 0 was assigned to healthy volunteers.
† θ9 estimated value was −0.383, in equation (3), the base for TYPE on Ka was calculated by 'θ9+1'in programming code, which made base by 0.617.
‡ θ10 estimated value was −0.658, in equation (4), the base for TYPE on V_3 was calculated by 'θ10+1' in programming code, which made base by 0.342.

could thoroughly describe the PK characteristics of MRX-I.

PK/PD simulation

The PK/PD indices of MRX-I with the oral multidose of 600 mg and 800 mg q12h for adult patients with complex skin and skin structure infection are shown in Table V. As pictured in Figure 3, after the 600 mg q12h multiple dosing, the $fAUC_{0-24}/MIC_{90}$ values of MRX-I to *S aureus* (methicillin-sensitive strains or drug-resistant strains), coagulase-negative *Staphylococcus*, *Streptococcus*, and *Enterococcus* were 5.1−20.6; with the 800 mg q12h multidose administration regimen, the $fAUC_{0-24}/MIC_{90}$ value was 7.8−31.3, slightly higher than that of the 600-mg dose. Both regimens exceeded the PK/PD target value ($fAUC_{0-24}/MIC_{90}$ value = 2.3). For *S aureus*, the cumulative fraction of response (CFR) with $fAUC_{0-24}/MIC$ reaching 2.3 with the 600 mg q12h multidose administration

Table IV. Pharmacokinetic parameters of healthy subjects or patients. Values are given as mean (SD).

Parameter	MRX-I 600 mg		MRX-I 800 mg	
	Healthy Volunteers (n = 12)	Patients (n = 19)	Healthy Volunteers (n = 12)	Patients (n = 25)
CL/F, L/h/kg	0.16 (0.04)	0.19 (0.06)	0.18 (0.04)	0.18 (0.10)
V_2/F, L/kg	0.31 (0.028)	0.32 (0.01)	0.33 (0.035)	0.35 (0.026)
V_3/F, L/kg	0.22 (0.077)	0.07 (0.040)*	0.33 (0.15)	0.12 (0.10)*
K_a, h^{-1}	1.48 (0.19)	0.70 (0.20)*	1.52 (0.31)	0.70 (0.29)*
C_{max}, mg/L	16.88 (3.76)	10.85 (1.80)*	22.48 (4.38)	14.61 (3.63)*
AUC_{ss}, mg · h/L	62.71 (20.96)	51.43 (14.61)	81.25 (22.43)	78.37 (31.90)
$t_{1/2}$, h	4.14 (0.94)	1.86 (0.46)*	5.10 (1.46)	2.73 (1.70)*

CL = apparent clearance from the central compartment; K_a = absorption constant rate; V_2 = apparent volume of the central compartment; V_3 = apparent volume of the peripheral compartment.
*Statistically significant ($P < 0.001$).

regimen and the 800 mg q12h multidose administration regimen were both >90%. When the PTA was >90%, the corresponding MIC values were MIC ≤2.0 μg/mL and MIC ≤4.0 μg/mL, respectively.

DISCUSSION

A population PK model was built for the first time in this analysis for MRX-I in both healthy volunteers and patients with skin and skin structure infections. A 2-compartment model with first-order elimination and first-order absorption rate (K_a) captured their PK profiles well, followed by validation of the bootstrap and VPC methods. Possible effects of potential covariates on PK profile were assessed and quantified. A final population PK model was used to simulate patients' PK profiles after receiving different dose regimens. Monte Carlo simulations were used to predict PTA and CFR after single oral administration of MRX-I 600 mg and 800 mg under fed conditions.

Considering that the bioavailability of MRX-I in mice, rats, and dogs is 69.2%, 109.0%, and 36.9% (data unpublished), respectively, and high-fat food could increase MRX-I bioavailability by 120% in humans, MRX-I could be deemed a low-to-medium absorption availability drug. Fed status exhibited a significant impact on bioavailability (F1) of MRX-I according to covariate analysis. If we assume that bioavailability of MRX-I administered with a high-fat meal is 100%, then the bioavailability under fasting and light-food status was 45.4% and 57.0%, respectively. MRX-I is a Biopharmaceutical Class System (BCS) II drug with low solubility and good permeability according to the BCS definition.[14] Food can reportedly increase solubilization and dissolution of BCS II and IV drugs (poorly water soluble) by stimulation of bile acid secretion, delayed gastric emptying, and gastric fluid volume, which could further increase drug absorption extent and rate.[15] Although the real mechanism of increased bioavailability is currently not clear, a positive effect of food is generally expected considering its BCS II property. The characteristics of BCS II drugs also could explain the nonlinearity in bioavailability, which was fitted by using dose-dependent bioavailability function. Disease status was found to significantly affect absorption rate and periphery volume of distribution, although the reason was not clear; possibilities include that disease status could lead to less physical activity, which decreases gastric emptying followed by a decreased absorption rate.[16] Body weight was found to be an intrinsic factor which may affect central compartment volume; however, the influence was found to be limited because the exposure of subjects with body weight ranging from 46.7 to 112.0 kg was within 71.8%−196.6% of the exposure of a person with typical weight (62 kg), which usually won't be considered clinically significant. Because the predicted exposure in subjects dosing with the suggested clinical effective dose (800 mg) was

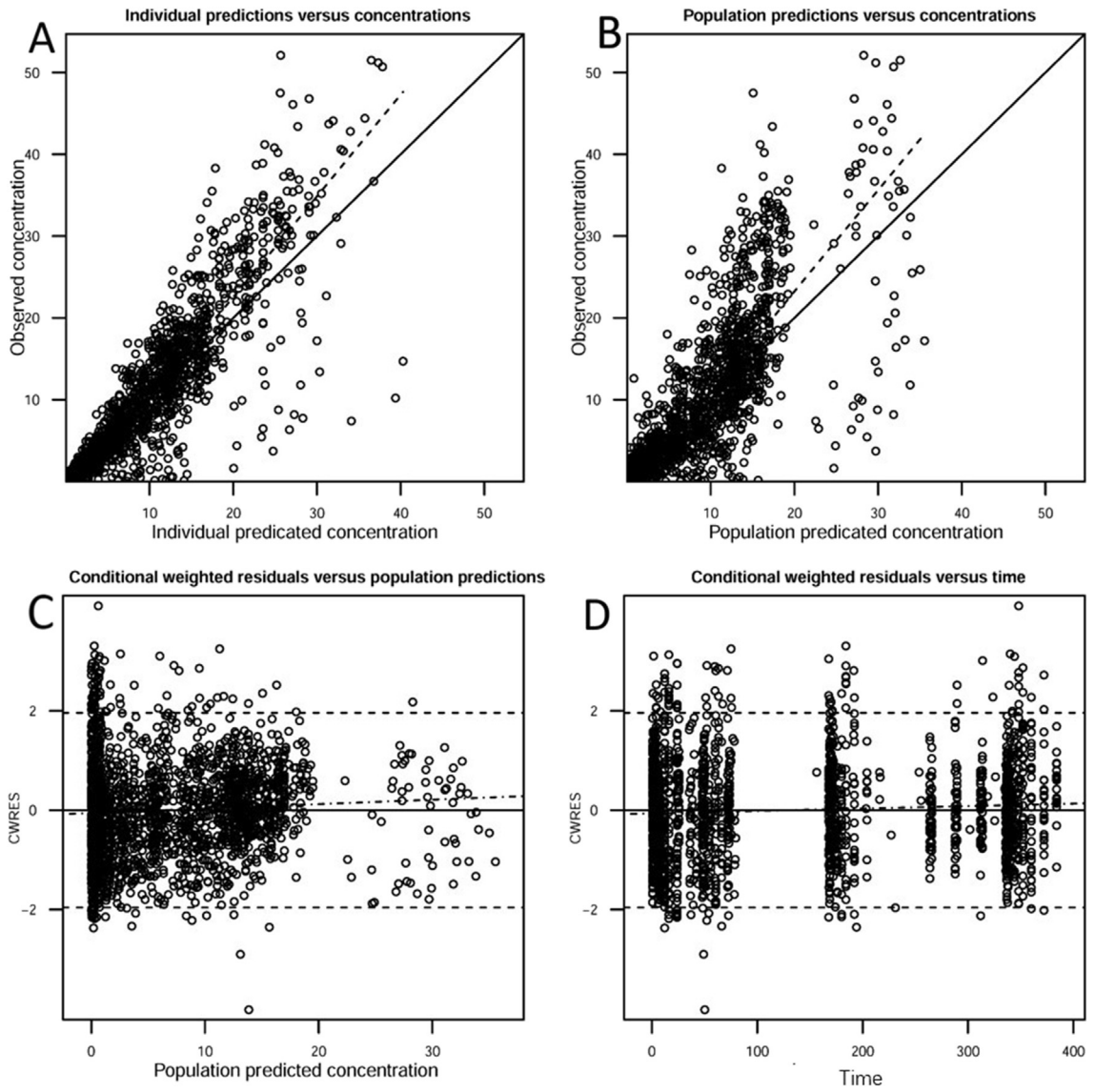

Figure 1. Goodness-of-fit plots for the final population pharmacokinetic parameter model. (A) Individual-predicted concentration versus observed concentration. (B) Population-predicted concentration versus observed concentration. (C) Conditional weighted residuals (CWRES) versus population-predicted concentration. (D) CWRES versus time. The solid line and dash line in (A), (B) represent the line of identity and regression line, respectively, whereas in (C) and (D) the solid lines denote the position where CWRES is equal to 0, while the middle dash lines are regression lines.

comparable with the maximum dose (1800 mg), for which safety characteristics were well established,[11] dose optimization was not considered necessary for subjects with body weight within 46.7–112.0 kg.

Currently, Phase III clinical study of MRX-I is on going. Previous Phase I and II clinical trials had well captured the PK and PD parameters and safety characteristics of MRX-I in healthy subjects and patients. MRX-I was quickly absorbed, with

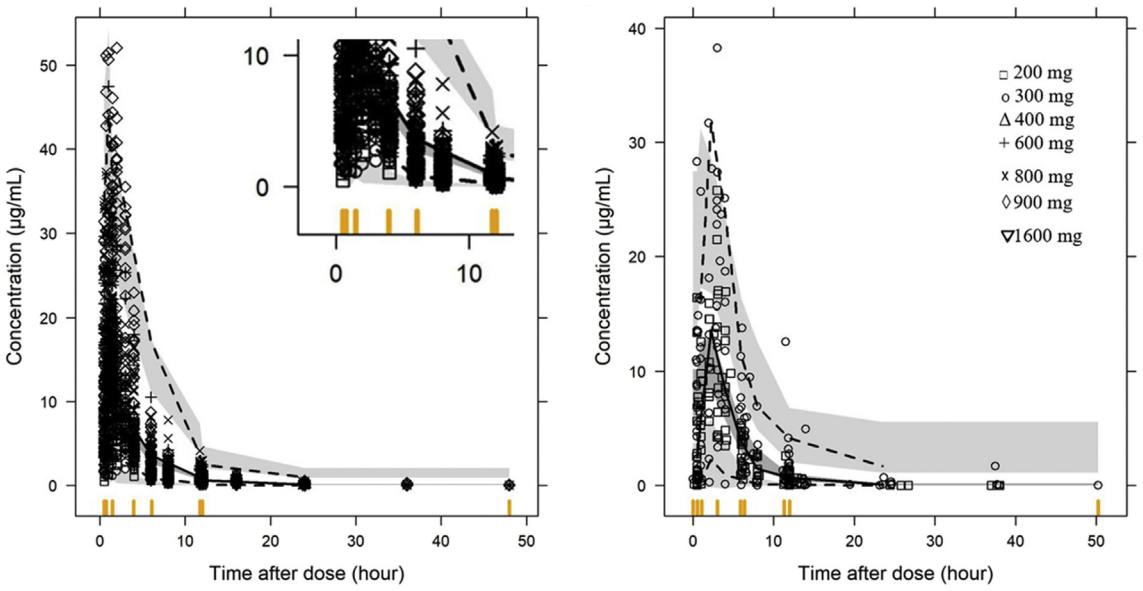

Figure 2. Visual predictive check (VPC) plots for the final population pharmacokinetic model. Left and right pictures show VPC results for healthy volunteers and patients, respectively. The raw data are shown as different symbles according to dose groups. square represents concentration value from 200 mg dosing group, circle is from 300 mg group, triangle from 400 mg group, cross from 600 mg group, x from 800 mg, diamand from 900 mg group, and inverted triangle from 1600 mg group. The upper dash line, solid line, and lower dash line indicate 95th, 50th, and 5th percentile of observed values, respectively. The upper, middle, and lower shades indicate 95th, 50th, and 5th percentile of predicted values, respectively.

nonlinear and susceptible bioavailability by high-fat food. After quick distribution, MRX-I was predominantly eliminated by metabolism with multiple non−cytochrome P450 enzymes, such as flavin-containing monooxygenase 5, short-chain dehydrogenase/reductase, aldehyde ketone reductase, and aldehyde dehydrogenase, which reduced the possibility of drug−drug interactions based on metabolism.[7] Meng et al[7] also recognized M2 as an inactive and predominant metabolite in circulation; its PK characteristics were investigated in a clinical trial of regular food effects.[13] MRX-I was also studied in white subjects to bridge clinical trials of Chinese and white subjects.[6] All Phase I and II clinical trials showed that MRX-I could be maximally well tolerated over the dose range of 50−1800 mg, which is better than linezolid.

Before new drugs enter into Phase III clinical trials, the risk of QTc prolongation should also be evaluated. Therefore, a large sample size, thorough QT study was conducted over 800−1600 mg under regular food status,[13] and it found that MRX-I had no effect on QTc prolongation with a concentration-QTc analysis.[17] Due to limitations of patient data, dose−response relations between PK/PD study results and clinical outcome were not able to be determined. Fortunately, the available *in vitro* and in vivo animal efficacy data[18,19] suggest a MIC cutoff value (~1 mg/L) for MRX-I to treat moderate to severe bacterial infections caused by gram-positive pathogens, most notably MRSA and other drug-resistant gram-positive cocci. Supporting this suggestion, the Monte Carlo simulation with a population PK model found that a dose regimen of 600 or 800 mg BID after continuous dosing of 14 days with regular food could produce satisfactory efficacy against MRSA with a 90% or higher CFR and PTA. Hence, the regimen of 800 mg BID up to 7−14 days can be

Table V. Gram-positive bacteria pharmacokinetic/pharmacodynamic index after administration of 600 and 800 mg of MRX-I.

Bacteria (No. of Strains)	MIC_{90} (μg/mL)	$fAUC_{0-24}/MIC_{90}$ (600 mg)	$fAUC_{0-24}/MIC_{90}$ (800 mg)
Methicillin-resistant *Staphylococcus aureus* (45)	1	10.3	15.7
Methicillin-sensitive *S aureus* (35)	1	10.3	15.7
Methicillin-resistant coagulase-negative *Staphylococcus* (16)	1	10.3	15.7
Methicillin-sensitive coagulase-negative *Staphylococcus* (13)	1	10.3	15.7
Enterococcus faecalis (15)	2	5.1	7.8
Enterococcus faecalis (15)	1	10.3	15.7
Penicillin-sensitive *Streptococcus pneumoniae* (39)	0.5	20.6	31.3
Penicillin-resistant *S pneumoniae* (15)	1	10.3	15.7
Other *Streptococcus* (39)	1	10.3	15.7

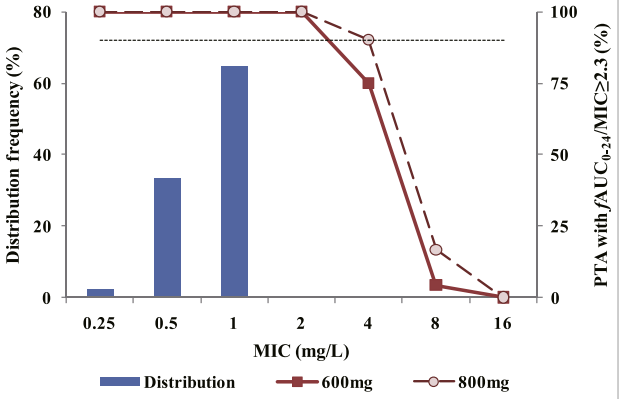

Figure 3. Distribution of methicillin-resistant *Staphylococcus aureus* in terms of MIC level and probability of target attainment (PTA) of $fAUC_{0-24}/MIC$ for MRX-I after multiple dosing. The dosing regimen of MRX-I is 600 or 800 mg BID for 14 consecutive days. f indicates the unbound fraction, the value of which is 0.1. Histograms and lines represent the distribution frequency of MIC and PTA values, respectively. In the graph, the distribution data of MIC for methicillin-resistant *S aureus* were obtained from *in vitro* studies in Huashan Hospital.

recommended in confirmative clinical trials in patients with skin and skin structure infections.

Although an optimized dosing regimen was suggested based on in vivo PK trial and PK/PD modeling method and several clinical pharmacology-related safety characteristics (eg, metabolite safety, QTc prolongation, drug–drug interactions) were well established, the inclusion and exclusion criteria of Phase III clinical trials remained a concern because the requirement of establishing drug efficacy in a limited sample size requires us to thoroughly understand PK variability. The current population PK study found that the PK variability was heavily influenced by weight, food effect, and disease status rather than liver or renal function. Thus, there is no reason yet to exclude patients with mild or moderate renal or liver impairment from participating in Phase III clinical trials. Regular food administration with MRX-I was suggested for dosing, which could offer substantial evidence in designing Phase III clinical trials.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

The sponsor MicuRx Pharmaceuticals Inc was responsible for the study design and data collection. They agreed to submit the article for publication.

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