Population pharmacokinetics, exposure-efficacy, and target attainment analyses of tedizolid in Japanese and Chinese subjects

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BACKGROUND

- Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a threat for healthcare systems globally.[1] MRSA frequently causes healthcare-associated infections and is associated with increased morbidity, mortality rate and length of hospital stay.[1]
- There are a number of antibiotics with high *in vitro* potency, which are approved for the treatment of MRSA infections, although many of these antibiotics have limitations due to increased risk of toxicity or dosing challenges in special populations.[2,3]
- In 2014, tedizolid phosphate, a novel oxazolidinone antibiotic, was approved by the US FDA for the treatment of acute bacterial skin and skin structure infections (ABSSSI) at the dose of 200 mg, once daily (QD) for 6 days.[4] Tedizolid phosphate has recently been investigated versus linezolid in two randomised Phase 3 clinical studies for 1) the treatment of skin and soft tissue infections (SSTI) in Japanese patients[5] and 2) the treatment of ABSSSI in Chinese patients.[6]
- Tedizolid phosphate is available in both intravenous (IV) and oral (PO) formulations at identical dosage (200 mg QD) and has a high oral bioavailability (i.e. Caucasian: 91.7%, Japanese: 82.6%, Chinese: 85.5%, Korean: 95.2% subjects).[7–10]
- Analyses of previous Phase 1 studies indicated that no dose adjustment is required for the treatment of patients with moderate-to-severe renal impairment or severe hepatic impairment, for obese or morbidly obese patients, or for elderly patients.[11–13]
- Population pharmacokinetic (popPK) analyses of pooled data from healthy subjects (who received single- or multiple-dose IV/PO tedizolid phosphate) and patients with ABSSSI who were treated with IV/PO tedizolid phosphate 200 mg QD supported that dose adjustments are not necessary based on patient age, sex, race, body weight, body mass index (BMI), renal function, or hepatic function.[14]
- Previous population PK/PD analyses did not reveal any relationship between tedizolid exposures and efficacy (likely due to the limited exposure range from 200 mg dose administered in the Phase 3 trials), and suggested a minimum inhibitory concentration (MIC) of 0.5 μg/mL as the susceptibility breakpoint for *S. aureus* infections,[14] which is approved by the US FDA, CLSI and EUCAST.

OBJECTIVES

1. The primary objectives of the current analyses were to utilise and refine a previously developed popPK model of tedizolid to characterise relationships between patient-specific factors and tedizolid exposure, and to describe the relationships between patient-specific exposures and clinical and/or microbiologic responses in Japanese patients diagnosed with SSTI or Chinese patients diagnosed with ABSSSI caused by Gram-positive pathogens, including MRSA.
2. The secondary objective was to perform target attainment analyses to predict tedizolid susceptibility breakpoints for 200 mg QD dosing for *S. aureus* in both Japanese and Chinese patients.

MATERIALS AND METHODS

- In the current popPK modelling, the previously developed popPK model[14] was applied to this Asian population as a 'base model' after exploratory data analysis, and was subsequently refined to develop the final popPK model (including further re-evaluation of relationships between covariates and PK parameters). PK and baseline demographic data obtained from three randomised, Phase 1 studies conducted in Japanese (n = 42; Study 16101: n = 26; Study 16102: n = 16) and Chinese (n = 16; Study 16411) healthy subjects,[8,9,15,16] and from two randomised Phase 3 studies conducted in Japanese SSTI (n = 83; Study 16099; NCT01967225[5]) and Chinese ABSSSI (n = 51; Study 16121; NCT02066402[6]) patients were pooled and used for model development.
  In the single-dose part of the Phase 1 studies, subjects received tedizolid phosphate 200 mg as an intravenous infusion or an oral tablet. In the multiple-dose Japanese Phase 1 study, subjects received IV or PO tedizolid phosphate 200 mg, QD for 7 days. In the multiple-dose Chinese Phase 1 study, subjects received tedizolid phosphate 200 mg, QD as IV infusion for 3 days and as oral tablet for 4 days (total: 7 days). In the Phase 3 studies, Japanese patients with SSTI received IV/PO tedizolid phosphate 200 mg, QD for 7–14 days and Chinese patients with ABSSSI received IV/PO tedizolid phosphate 200 mg, QD for 6 days, with a switch between IV and PO dosing at the discretion of the treating physician in both studies.
- The Phase 1 studies conducted in both Japanese and Chinese subjects used dense/rich blood sampling for collection and evaluation of plasma tedizolid exposures up to 72 hours after last dose, with subjects being followed for at least 7–9 days after the last dose of tedizolid phosphate to monitor safety of study drug. A sparse-sampling strategy was used in the Phase 3 studies for collection of plasma tedizolid concentrations.
- The demographic and clinical covariates assessed for their influence on tedizolid PK parameters included age, body weight, BMI, ideal body weight (IBW), total bilirubin, creatinine clearance (CrCL), sex, Japanese versus Chinese ethnicity, the presence of diabetes mellitus, and the presence of peripheral vascular disease (PVD). A standard forward selection-backward elimination method was used during the covariate analysis to identify statistically significant (α = 0.001) predictors of PK variability.
- The performance of the final popPK model was evaluated using visual predictive check (VPC) methodology to assess concordance between the model-based simulated/predicted tedizolid concentrations and the observed data in the Phase 1/3 studies.
- The popPK model for tedizolid was used to calculate the following (empiric Bayesian) individual tedizolid exposure parameters on Day 1 and Day 6 (steady state) for each patient assuming hypothetical once-daily 200 mg IV or oral tedizolid phosphate therapy: area under the plasma drug concentration-time curve from time 0 to 24 hours (AUC_{0-24}), minimum plasma drug concentration (C_{min}), and maximum plasma drug concentration (C_{max}).

- In the randomised Phase 3 studies, clinical and microbiological outcomes were assessed along with the MIC of baseline causative pathogens. The PK/PD modelling using logistic regression analysis evaluated the exposure estimates for their relationships with efficacy outcomes (i.e. clinical or microbiological success rates) at end-of-therapy or test-of-cure.
- The goals of the target attainment analyses were to estimate the probability of attaining the PK/PD target measure (AUC_{0-24}/MIC ratio of 15) associated with the efficacy of tedizolid against *S. aureus* in order to determine MIC susceptibility breakpoints in the Chinese and Japanese patient populations separately.
- The distribution of the percentage of observations above the target breakpoint for each MIC value was determined separately for Chinese and Japanese patients. Using the final popPK model, 100 trials of 500 virtual Japanese and 1000 virtual Chinese patients were simulated. Virtual patients were randomly re-sampled with replacement from the Phase 3 studies. The mean percentage of simulated AUC_{0-24}/MIC ratios above the target breakpoint, across all 100 datasets, was reported as the PK/PD target attainment for each MIC value. The MIC susceptibility breakpoint was determined to be the highest clinically relevant MIC value with a probability of PK/PD target attainment of at least 0.9.
- All exploratory analyses, statistical analyses, and graphical presentations of data were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA). Population modelling was performed using NONMEM, v7.3.0 (ICON Development Solutions, Hanover, MD, USA) and KIWI graphical interface, v1.6 (Cognigen Corp., Buffalo, NY, USA).

RESULTS

- The baseline demographic characteristics of the subjects/patients included in the popPK analysis are shown in **Table 1**.

Table 1. Baseline demographic parameters

Baseline characteristic		Study 16411	Study 16121	Chinese Overall	Study 16101	Study 16102	Study 16099	Japanese Overall
Number of subjects/patients included in the popPK analysis		16	51	67	26	16	83	125
Age (yrs)	Median	25.5	49.0	37.0	26.0	27.0	67.0	53.0
	Min; Max	19; 36	18; 79	18; 79	21; 37	21; 35	25; 94	21; 94
Body mass index (kg/m2)	Median	22.5	24.7	23.7	21.35	20.45	25.0	23.6
	Min; Max	19.4; 24.7	18.4; 35.9	18.4; 35.9	18.3; 25.5	18.3; 25.1	16.9; 47.9	16.9; 47.9
Weight (kg)	Median	62.15	68.0	67.0	64.25	62.85	67.0	65.0
	Min; Max	49.7; 76.6	47.0; 111.0	47.0; 111.0	53.5; 78.2	50.5; 75.4	38.8;109.4	38.8; 109.4
Ideal body weight (kg)	Median	62.25	62.3	62.3	66.7	66.6	60.8	62.8
	Min; Max	54.3; 73.2	47.1; 76.1	47.1; 76.1	58.1; 72.6	61.0; 73.2	40.1; 77.3	40.1; 77.3
Total bilirubin (mg/dL)	Median	0.69	0.58	0.64	1.10	1.20	0.50	0.78
	Min; Max	0.36; 1.13	0.23; 2.28	0.23; 2.28	0.80; 2.20	0.50; 1.80	0.20; 2.90	0.20; 2.90
Creatinine clearance (mL/min)*	Median	114.9	96.9	105.2	124.1	124.8	88.7	105.5
	Min; Max	83.8; 137.5	34.1; 235.1	34.1; 235.1	93.3; 198.6	98.2; 145.5	16.9; 249.0	16.85; 249.0
Sex, male	n (%)	16 (100)	35 (68.6)	51 (76.1)	26 (100)	16 (100)	54 (65.1)	96 (76.8)
Race, Asian	n (%)	16 (100)	51 (100)	67 (100)	26 (100)	16 (100)	83 (100)	125 (100)
Ethnicity, Chinese	n (%)	16 (100)	51 (100)	67 (100)	na	na	na	na
Ethnicity, Japanese	n (%)	na	na	na	26 (100)	16 (100)	83 (100)	125 (100)
Diabetes, n (%)	Yes	0 (0.0)	7 (13.7)	7 (10.4)	0 (0.0)	0 (0.0)	37 (44.6)	37 (29.6)
Peripheral vascular disease, n (%)	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (9.6)	8 (6.4)

* calculated by the Cockroft-Gault formula
Max: maximum; Min: minimum; n: number of subjects; na: not applicable; SD: standard deviation.

- The final popPK model applied to the pooled dataset comprised of three Phase 1 and two Phase 3 studies and was a two-compartment model with sigmoidal absorption, absolute bioavailability (F1, for oral dose data) and linear elimination kinetics. The model was parameterised in terms of F1, with the oral absorption process described by an absorption lag time (ALAG1), duration of zero-order release of prodrug *in vivo* after administration of the tablet (D1), and first-order absorption rate constant (k_a); the disposition of tedizolid was parameterised using apparent clearance (CL/F), apparent inter-compartmental clearance (Q/F), apparent central volume of distribution (V_c/F), and apparent peripheral volume of distribution (V_p/F), where F represents the fraction of dosed prodrug that is metabolically converted to tedizolid.
- Body weight was identified as a statistically significant predictor of CL/F, V_c/F and V_p/F. Total bilirubin and Japanese ethnicity (versus Chinese ethnicity) were statistically significant predictors of CL/F and V_p/F, respectively. These statistically significant covariates are unlikely to lead to clinically relevant changes in steady state AUC_{0-24} and C_{max}, except of total bilirubin effects on C_{min}, because their geometric mean ratios, derived from model-based simulations, were within the 0.8–1.25 boundaries (**Figure 1**). No statistically significant influence of sex, age, BMI, IBW, CrCL, diabetes mellitus, or PVD on tedizolid exposure parameters was found.

Figure 1. Forest plot of geometric mean ratios (90% confidence intervals) of estimated covariate effects on tedizolid AUC_{0-24}, C_{max}, C_{min} at steady state following tedizolid phosphate, 200 mg, IV, QD dosing

AUC_{0-24}: area under the plasma drug concentration-time curve from time 0 to 24 hours; C_{max}: maximum plasma drug concentration; C_{min}: minimum plasma drug concentration; IV: intravenous; QD: once daily. Note: Comparator groups for each continuous covariate were defined by the lower, middle, and upper tertile ranges of the observed baseline covariate distribution in the analysis population. Ranges of body weight in comparator groups: 38.8kg to 61.5kg (Low), > 61.5kg to < 70.0kg (Reference), ≥ 70.0kg to 111.0kg (High). Ranges of total bilirubin concentrations in comparator groups: 0.2mg/dL to ≤ 0.5mg/dL (Low), > 0.5mg/dL to ≤ 0.9mg/dL (Reference), > 0.9mg/dL (High). The reference for ethnicity is Chinese subjects.

- The VPC plots demonstrated the validity of the final popPK model. The appropriate amount (~90%) of observed data fell within the prediction intervals. The central tendency and the magnitude of the variability of the data were well described for both the Japanese and Chinese Phase 3 studies, with good correspondence of the median lines and 5th/95th percentiles between the simulated and the observed data (**Figure 2**).

Figure 2. Median and 90% prediction intervals of simulated data from the prediction-corrected visual predictive check of the final population pharmacokinetic model overlaid on the median (5th/95th percentiles) of observed tedizolid data

DATA:
- Observations
- Median
- 5th and 95th percentiles

PREDICTIONS:
- 95% CI of prediction percentiles
- Median
- 5th and 95th percentiles

Medians and percentiles are plotted at the median time since previous dose of the data observed within each time since previous dose interval. CI: confidence interval; IV: intravenous

- Model-predicted tedizolid exposures at steady state were similar between Japanese and Chinese populations (**Table 2**).

Table 2. Model-estimated tedizolid exposure parameters at steady state in Japanese and Chinese subjects/patients

Parameter	Intravenous (IV) route*		Oral (PO) route**	
	Japanese	Chinese	Japanese	Chinese
AUC_{0-24} (μg·h/mL)				
Mean ± SD	27.05 ± 6.68	25.73 ± 5.89	22.98 ± 5.67	21.86 ± 5.01
(Min; Max)	(12.01; 48.54)	(12.17; 37.09)	(10.20; 41.24)	(10.4; 31.51)
C_{max} (ng/mL)				
Mean ± SD	3381.15 ± 647.35	3249.64 ± 575.20	2158.34 ± 424.62	2056.59 ± 352.49
(Min; Max)	(2090.80; 5123.54)	(1876.01; 4434.19)	(1332.08; 3308.33)	(1233.73; 2796.15)
C_{min} (ng/mL)				
Mean ± SD	349.57 ± 162.33	313.33 ± 136.64	330.07 ± 146.52	300.07 ± 125.79
(Min; Max)	(49.44; 901.45)	(43.59; 639.51)	(64.20; 815.83)	(43.21; 558.92)

*n =1683 IV concentrations [Japanese: 1041; Chinese: 642]; **n =877 PO concentrations [Japanese: 388; Chinese: 489]; AUC_{0-24}: area under the plasma drug concentration-time curve from time 0 to 24 hours; C_{max}: maximum plasma concentration; C_{min}: minimum plasma drug concentration; Max: maximum; Min: minimum; SD: standard deviation.

- The model-predicted tedizolid PK parameters at steady state were compared with those previously described in non-Hispanic and Hispanic patient populations.[17] The data demonstrate that no clinically meaningful differences in tedizolid PK are expected based on ethnicity because the exposure levels overlap across Japanese, Chinese, Hispanic and non-Hispanic populations (**Figure 3**).

Figure 3. Boxplots of model-predicted steady-state tedizolid exposure parameters in Chinese, Japanese, non-Hispanic and Hispanic populations following hypothetical tedizolid phosphate 200 mg QD administration

Boxes are 25th, 50th, 75th percentiles; whiskers are 5th to 95th percentiles. Asterisks show data points outside this range. The number of subjects is shown above each box. AUC_{0-24}: area under the plasma drug concentration-time curve from time 0 to 24 hours; C_{max}: maximum plasma drug concentration; C_{min}: minimum plasma drug concentration; QD: once daily.

- No significant (i.e. P > 0.05) relationships were found between tedizolid exposure parameters and clinical or microbiological efficacy at end-of-therapy or test-of-cure visits in either Japanese or Chinese patients enrolled in the Phase 3 studies.
- In Japanese SSTI and Chinese ABSSSI patients infected by *S. aureus*, the probability of target attainment at the MIC value of 0.5μg/mL was 99.9%, and at the MIC value of 1.0μg/mL it was 90.8% and 92.2%, respectively (**Figure 4**).

Figure 4. Probability of PK/PD target attainment for tedizolid against *S. aureus* at the AUC_{0-24}/MIC ratio breakpoint of 15 in Japanese (N = 500) and Chinese (N = 1000) patients from 100 virtual trials

AUC_{0-24}: area under the plasma drug concentration-time curve from time 0 to 24 hours; MIC: minimum inhibitory concentration; PD: pharmacodynamic; PK: pharmacokinetic; the bars represent the observed distribution of MIC values in patients enrolled into Phase 3 studies.

CONCLUSIONS

- Based on the current analyses, none of the assessed covariates is expected to significantly influence tedizolid exposures at steady state, supporting administration of tedizolid phosphate without dose adjustments based on age, sex, ethnicity, body weight, BMI, renal/hepatic function, or the presence of comorbidities.
- None of the tedizolid exposure parameters examined was found to be a clinically significant predictor of the probability of achieving clinical and/or microbiological response in Japanese SSTI or Chinese ABSSSI patients.
- No ethnic differences could be identified in the tedizolid exposure levels in the current analysis when compared with the previously observed levels in non-Hispanic and Hispanic ABSSSI patients.
- The current analyses suggest that no dose adjustment is needed for the treatment of SSTI in Japanese patients or ABSSSI in Chinese patients if switching from IV to PO treatment.
- A susceptibility breakpoint of 0.5μg/mL for *S. aureus* or MRSA infections has a high probability of attaining the PK/PD target (AUC/MIC) in Japanese patients with SSTI or Chinese patients with ABSSSI, caused by *S. aureus*, administered 200 mg QD tedizolid phosphate.

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