Poster No. 1971: Use of Pharmacokinetic/Pharmacodynamic (PK/PD) Analyses to Determine the Optimal Fixed Dosing Regimen of Iclaprim (ICL) for Phase III ABSSSI Clinical Trials

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Abstract

Background: ICL is a novel dihydrofolate reductase inhibitor antibiotic that is currently in Phase 3 clinical development. Studies indicated that PK/PD drivers for efficacy are $AUC_{0\text{-}24hss}$, AUC/MIC, and T > MIC while adverse events may be linked to $Cmax_{ss}$. This analysis employed PK/PD modeling and simulation to estimate an optimal fixed dosing scheme for the Phase III ABSSSI trials designed to maximize both efficacy and safety.
Methods: Using PK data collected from 470 patients from the previously conducted Phase 3 ABSSSIs trials (ASSIST-1 & -2) population PK modeling and Monte Carlo simulation (MCS) were used to identify a fixed ICL dose regimen that maximized $AUC_{0\text{-}24hss}$, AUC/MIC, and T > MIC (efficacy parameters) while minimizing probability of a $Cmax_{ss} \geq 800$ ng/mL (parameter that may be associated with adverse events) relative to 0.8 mg/kg IV, infused over 0.5 hrs, Q12H ("base case" regimen used in ASSIST-1 & 2). For these analyses, the *S. aureus* MIC_{90} of 120 ng/mL identified in worldwide surveillance studies from patients with SSSI and hospital acquired bacterial pneumonia was employed.
Results: Comparison of median (IQR) PK/PD metrics for the candidate fixed and based ICL dosing regimens were analyzed. The MCS analyses indicate that administration of 80 mg as a 2 hr infusion Q12H provides a 28%, 28%, 32%, increase in $AUC_{0\text{-}24hss}$, AUC/MIC, & T > MIC, respectively, compared to base case regimen while decreasing the probability of $Cmax_{ss} \geq 800$ ng/mL by 9%.
Conclusion: Based on PK/PD system analyses, ICL 80 mg administered over 2 hr Q12H was selected as the dosing regimen for ABSSSI Phase 3 studies. This regimen conferred a greater likelihood of antibacterial efficacy while minimizing peak plasma levels relative to the dosing regimen used in previous phase III trials.

Background

- ICL is a new generation diaminopyrimidine is that is currently in Phase 3 clinical development.
- ICL inhibits bacterial dihydrofolate reductase, a critical enzyme in the bacterial folate synthesis pathway.
- Studies indicated that PK/PD drivers for ICL efficacy are $AUC_{0\text{-}24hss}$/MIC and and T > MIC while adverse events may be linked to $Cmax_{ss}$.
- PK/PD modeling and simulation were used to determine the optimal fixed dosing scheme for the ongoing Phase ABSSSI trials (REVIVE trials) that maximized both efficacy and safety relative to the weight-based dosing scheme used in the previous phase III skin trials (ASSIST).

Methods

- Pharmacokinetic (PK) data were obtained from 470 patients from the previously conducted Phase 3 ASSIST trials.
  - ASSIST 1 & 2 were randomized, multi-center, double-blind, Phase 3 cSSSI studies of essentially identical design.
  - Iclaprim was administered as a dose of 0.8 mg/kg over 0.5h Q12h.
- A two-compartment population pharmacokinetic model was fit to Day 4 PK data.
- Bayesian estimates of the individual PK parameters were derived and these were used to generate the individual concentration-time profiles at day 4.
- Based on these individual values, the derived parameters AUC0-24hss, Cmaxss, Cminss, AUC/MIC, and T > MIC were calculated for candidate fixed dose ICL dosing regimens and for ICL 0.8 mg/kg IV, infused over 0.5 hrs, Q12H ("base case" regimen used in ASSIST).
- The goal was to identify a fixed ICL dose regimen that maximized $AUC_{0\text{-}24hss}$, AUC/MIC, and T > MIC (efficacy parameters) while minimizing probability of a $Cmax_{ss} \geq 800$ ng/mL (parameter that may be associated with adverse events) relative to 0.8 mg/kg IV, infused over 0.5 hrs, Q12H.
- For these analyses, the *S. aureus* MIC_{90} of 120 ng/mL identified in worldwide surveillance studies from patients with SSSI and hospital acquired bacterial pneumonia was employed.

Results

Table 1: PK Analyses of Different Iclaprim Dosing Regimens

	Iclaprim Dosing Regimens			
Parameter	0.8 mg/kg/0.5 hr	64 mg/2hr	72 mg/2hr	80 mg/2hr
$Cmax_{ss}$, ng/mL (IQR)	702 (572-953)	524 (411-679)	590 (462-764)	655 (514-849)
$AUC_{0\text{-}24ss}$ (IQR)	3865 (2992-5394)	3970 (3092-5540)	4466 (3479-6233)	4962 (3865-6926)

Table 2: PD Analyses of Different Iclaprim Dosing Regimens

	Iclaprim Dosing Regimens			
Parameter	0.8 mg/kg/0.5 hr	64 mg/2hr	72 mg/2hr	80 mg/2hr
AUC/MIC (hr)	32 (24-45)	33 (26-46)	37 (29-52)	41 (32-58)
T > MIC (%) (IQR)	39.2 (27.5 – 55.0)	45.0 (35.0-60.8)	48.3 (38.3–65.0)	51.7 (40.8-70.0)

Results

Figure 1: Concentration distributions for 0.8 mg/kg/0.5hr

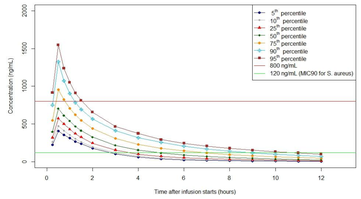


Figure 2: Concentration distributions for 64 mg/2hr

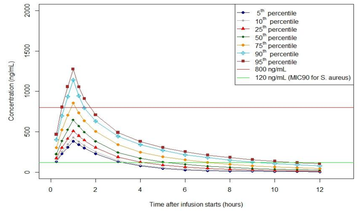


Figure 3: Concentration distributions for 72 mg/2hr

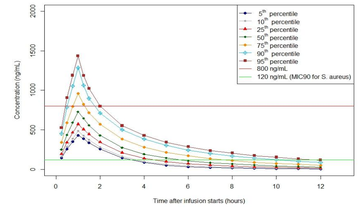
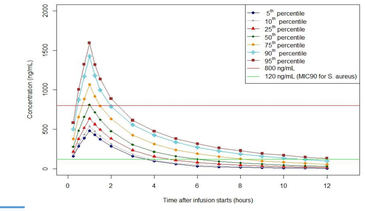


Figure 4: Concentration distributions for 80 mg/2hr



Conclusions

- Iclaprim was well tolerated in both of the ASSIST trials.
- A population PK analysis of the data from the ASSIST studies demonstrated no relationship between the clearance (CL) of iclaprim and body weight, suggesting that a fixed dose rather than weight-based dose should be used.
- ICL administered as an 80 mg 2 hr infusion provides a 28% increase in AUC/MIC and a 32% increase in the T > MIC compared to the dosing regimen used in the ASSIST trial (Tables 1-2; Figures 1-4)
- This dosing regimen maintains $Cmax_{ss}$ below the Cmax achieved in the ASSIST studies. Although ICL was safe and well-tolerated in the ASSIST studies, the new dose should further reduce adverse events (Tables 1-2); Figures 1-4).
- The ICL regimen of 80 mg administered over 2 hr Q12H is expected to maximize the likelihood of antibacterial efficacy while reducing the potential for adverse events and is selected as the dosing regimen for the ongoing pivotal ABSSSI REVIVE clinical trials.

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