\section*{INTRODUCTION}

Rezafungin (RZF) is a novel echinocandin antifungal being developed for single-agent prophylaxis against invasive fungal disease caused by \textit{Candida}, \textit{Aspergillus}, and \textit{Pneumocystis} species in patients at high risk of infection, such as blood and marrow transplant (BMT) recipients.

The long half-life of RZF (\(\sim 133\) h) in human enables administration of once-weekly dosing regimens.\(^1\) Prophylactic efficacy in a mouse \textit{Pneumocystis} model is achieved at a human equivalent dose of \(<50\) mg once-weekly.\(^2\) A dose of 400 mg followed by 200 mg once weekly achieved \(>90\%\) target attainment for treatment of \textit{Candida}.\(^3\)

Pharmacokinetic-pharmacodynamic (PK-PD) simulations were performed using the rezafungin dosing regimen for treatment of \textit{Candida} to evaluate the appropriateness for prophylaxis against \textit{A. fumigatus} among BMT patients.

\section*{METHODS}

\subsection*{Population Pharmacokinetic (PopPK) Model}

A previously developed PopPK model\(^1\) was updated with data from an additional Phase 1 trial and the Phase 2 STRIVE trial in patients with candidemia and/or invasive candidiasis. The PopPK model was refined using NONMEM Version 7.2.

The ability of covariates (eg, body size, age, sex, albumin, creatinine clearance, and infection status) to explain interindividual variability on select PK parameters was explored (stepwise forward selection \((\alpha = 0.01)\) and stepwise backward elimination \((\alpha = 0.001)\)).

\subsection*{Monte Carlo Simulations}

Baseline demographic data from 100 BMT recipients at Stanford and the PopPK model were used for Monte Carlo simulation (\(n=2,000\)) of expected RZF concentration-time profiles in BMT patients following RZF IV 400 mg on Week 1 and then 200 mg weekly x11.

Free-drug concentration-time profiles (plasma protein binding estimate of \(97.4\%\))\(^4\) were evaluated relative to the max observed minimal effective concentration to inhibit 100\% of isolates tested (MEC\(_{100}\) 0.03 mg/L) (Table 1).

\subsection*{RESULTS}

\subsubsection*{Final PopPK model}

linear, 4-compartment model with zero-order IV input; provided precise and unbiased fits to the observed data.

\subsubsection*{Monte Carlo simulations}

Across simulated patients (Table 2), exposures were highest during Week 1 (Figure 2). The percent of simulated patients with free-drug plasma concentrations above the MEC\(_{100}\) and MEC\(_{30}\) values for the entire dosing interval (one week) was 100\% and 98.0\% at Week 1, 99.9\% and 92.0\% at Week 4, and 90.2\% and 99.8\% at Week 12.

\subsection*{CONCLUSIONS}

These data support a weekly RZF dosing regimen for prevention of \textit{A. fumigatus} infections in BMT patients.

No clinically significant covariates were identified in infected patients, indicating consistent exposure across a wide range of subject factors.

The effectiveness of antifungal prophylactic regimens is often limited due to pill burden, adherence, safety, tolerability, and DDIs.

In addition to the excellent safety, tolerability, and lack of drug interactions exhibited by echinocandins, the favorable PK profile of RZF presents the opportunity to mitigate the typical challenges faced when administering antifungal prophylaxis in BMT patients.

\section*{REFERENCES}


\begin{table}[h]
\centering
\caption{RZF MEC distributions and cutoff values for \textit{A. fumigatus}}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{A. fumigatus} & \textbf{(60)} & \textbf{MEC\(_{100}\)} & \textbf{MEC\(_{30}\)} & \textbf{MEC\(_{0.015}\)} & \textbf{MEC\(_{0.03}\)} \\
\hline
\text{\(\leq 0.008\)} & 25 (41.7) & 29 (90.0) & 6 (100) & 0.015 & 0.015 & 0.03 \\
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\end{tabular}
\end{table}

\begin{figure}[h]
\centering
\caption{Covariate effects on rezafungin Week 1 plasma AUC}
\end{figure}

\begin{figure}[h]
\centering
\caption{Rezafungin free-drug plasma concentration–time profiles by week relative to \textit{A. fumigatus} MEC\(_{100}\) (0.03 mg/L, marked in red)}
\end{figure}