INTRODUCTION

Plazomicin is a novel aminoglycoside antibiotic that has potent bactericidal activity against Gram-negative bacteria as well as enterobacteria that possess a broad range of antibiotic resistance mechanisms such as aminoglycoside-modifying enzymes, β-lactamases, and fluoroquinolone target-site mutations. Plazomicin was well tolerated in Phase 1 studies and a Phase 2 study in patients with complicated urinary tract infections (cUTI) or acute pyelonephritis (AP).

A Phase 3 study (CARE) was conducted to evaluate the efficacy and safety of plazomicin in patients with pneumonia complicated with community-acquired pneumonia (CAP), hospital-onset ventilator-acquired pneumonia (HAP), or hospital-acquired pneumonia (VAP) due to Gram-negative bacteria (GNB) such as Pseudomonas aeruginosa, Acinetobacter baumannii, and carbapenem-resistant Enterobacteriaceae (CRE). This study was designed to achieve a mean steady-state AUC0–24 exposure of 262 mg·L/h in critically-ill patients with normal renal function administered 15 mg/kg/day.

The CL due to CRRT (CLCRRT) was set to the sum of the actual patient-specific sieving coefficient (SC); dialysis CL was set to 0 when CRRT was not utilized. A population PK model previously developed using NONMEM® 7.2 based on data from TDM using protocol-specified dose adjustment equations.

RESULTS

Population Pharmacokinetic Analysis

- A population PK model previously developed using NONMEM® 7.2 based on data from TDM using protocol-specified dose adjustment equations.
- Data from 22 patients enrolled in CARE, including 5 patients undergoing slow continuous renal replacement therapy (CRRT) were included in the interim PK analysis.
- A 3-compartment (CMT) model with zero-order input (k0) and first-order elimination (k1) was developed to allow for implementation of therapeutic drug management (TDM) to guide dose adjustments.
- TDM was used to achieve target plazomicin in steady-state AUC0-24 exposures within a precise range than what could have been achieved using the initial dosing table had been used on all PK sampling days versus using TDM to adjust dose during treatment for patients who were enrolled in CARE.

CONCLUSIONS

- A previously-developed population PK model was refined in order to describe plazomicin in critically-ill patients with CRE infections.
- Use of TDM appeared to reduce the inter-day differences in AUC0-24 and resulted in more precise target AUC0-24 values than what could have been achieved had only the initial dosing table been utilized.

REFERENCES


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