Pharmacokinetics/Pharmacodynamics and Safety of 3 g Ceftolozane/Tazobactam in Critically Ill Adult Patients

INTRODUCTION

Ceftolozane/tazobactam (MRL-659/3354), a β-lactam/β-lactamase inhibitor (β-LA/B-LAI) combination with a well-established β-lactamase inhibitor, is approved for the treatment of adults with complicated urinary tract infections (cUTIs) and complicated intra-abdominal infections (cIAIs) at a dose of 1.5 g ceftolozane/1 g tazobactam every 8 hours (480 mg for 1 L and 6 g for 2 L) and every 12 hours for 4 L.

Ceftolozane/tazobactam is being evaluated in a phase 3 nosocomial pneumonia study (ClinicalTrials.gov identifier NCT02070757) at a higher dose of 3 g (2 g/1 g) every 8 hours (q8h) for up to 7 days for cUTI and up to 14 days for cIAI.

OBJECTIVE

†Presented herein are data from the first 18 patients enrolled in clinical studies.

The objectives of this study were to:

1. Evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of ceftolozane/tazobactam in critically ill patients receiving mechanical ventilation.

2. Assess the clinical efficacy of ceftolozane/tazobactam in critically ill patients with pneumonia receiving mechanical ventilation.

3. Evaluate the safety of ceftolozane/tazobactam in critically ill patients with pneumonia receiving mechanical ventilation.

METHODS

Study Design and Treatment

- Enrollment in the prospective, multicenter, noncomparative, open-label, phase 1b study (ClinicalTrials.gov identifier NCT02070757) was closed and analysis of data is ongoing.

- Preserved urine was the data from the first 18 patients enrolled.

- Encoded patients received 4–6 doses of 3-g ceftolozane/tazobactam in a 1:1 randomization of first dose, with the PK/PD assessment following the last dose.

Table 1. Ceftolozane/Tazobactam Dose According to Renal Function

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Dose</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Normal renal function</td>
<td>3 g</td>
<td></td>
</tr>
<tr>
<td>Moderate renal impairment (CrCl 30–59 mL/min)</td>
<td>3 g</td>
<td></td>
</tr>
<tr>
<td>Severe renal impairment (CrCl ≤ 29 mL/min)</td>
<td>1.5 g</td>
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Assessments

- Plasma PK samples were collected at 0 (before dose) and at 1, 2, 4, 6, and 8 hours after the start of the first and last doses.

- All patients received 4–6 doses of 3 g ceftolozane/tazobactam as a single oral dose.

- The following ceftolozane and tazobactam plasma PK parameters were calculated for total plasma concentrations using noncompartmental analysis with Phoenix WinNonlin (version 6.0).

- Area under the plasma concentration-time curve from 0 to infinity (AUC0–∞) was calculated for total plasma concentrations and was expressed as micrograms per milliliter per hour (μg·h/L).

- Peak plasma concentration (Cmax) was calculated for free drug concentrations.

- Probability of achieving efficacy was assessed by determining the percentage of patients achieving the ceftolozane/tazobactam PD target.

- Total concentrations of ceftolozane and tazobactam were adjusted to free drug concentrations by multiplying zero-time plasma concentrations by 0.033 and 0.0024 for ceftolozane and tazobactam, respectively.

- Urine samples were collected at 0–2, 2–4, 4–6, and 6–8 h postdose for determination of renal clearance (CLR).

- MIC of 4 μg/mL was selected based on Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint for P. aeruginosa.