**BACKGROUND**

Omadacycline (OMC), a new tetracycline agent, was approved in both oral and intravenous (IV) formulations by the US Food and Drug Administration (FDA) in October 2018 for treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) in Europe, and for CABP in the United States.

In pivotal Phase 3 studies, OMC dosing regimens included a loading dose of 500 mg IV every 12 hours (q12h) on Day 1 of therapy for both CABP and ABSSSI, or 450 mg oral on day 1 and 2 of therapy for ABSSSI only.

However, if the loading dose was accidentally omitted, patients would receive only the maintenance dose, which could adversely affect clinical outcomes. The objective of this study was to determine the impact of omission of the loading dose on OMC exposure and pharmacodynamics (PD).

**METHODS**

**Pharmacokinetics**

- Pharmacokinetic (PK) data from two studies in healthy volunteers were used:
  - One study investigated IV OMC administration (N=26).
  - One investigator used IV administration (500 mg, N=8).

- Extensive PK sampling was performed (13) samples collected over 24 hours in each subject.

- Data were fit using noncompartmental methods.
- Area under the concentration-time curve (AUC) was calculated using the linear trapezoidal rule.
- PK profiles were simulated on Days 2 and 5, and AUCs were calculated.
- The following dose regimens were simulated using actual PK profiles from clinical studies:
  - IV load: 500 mg IV q12h on Day 1, followed by 100 mg IV every 24 hours (q24h) on Days 2-5.
  - No load: 100 mg IV every 24 hours on Days 2-5.
  - Oral load: 450 mg oral q4h on Day 1 and 2, followed by 300 mg oral q4h on Days 3-5.
  - Oral load: 300 mg oral q4h on Days 1-5.
- AUCs for the final model were calculated for each subject for four protein binding (PB) values (0, 25%, 50%, and 100%), and subsequently used in all analyses.
- 95% confidence intervals (CI) generated around the mean PK profile were used in subsequent analyses to explore the PK/PD target attainment.

**Pharmacodynamics**

- The PD parameter associated with efficacy for OMC is AUC/MIC.
- Table 1 summarizes the MIC kill thresholds for OMC, AUC/MIC杀 thresholds for OMC, and the one investigator used in these studies, which correlated with early clinical response, both the IV and oral regimens.
- For S. aureus, the AUC/MIC threshold was met or exceeded regarding the use of a loading dose for S. aureus; however, for S. pneumoniae, the AUC/MIC threshold was met only at MIC values ≥0.25 µg/mL.
- Using the AUC/MIC threshold (0.5) identified in the Phase 3 ABSSSI studies, which correlated with early clinical responses, both the IV and oral regimens would be expected to exceed this threshold for S. aureus, the pathogen most frequently associated with ABSSSI.
- The MIC50 thresholds were each used for calculations.

**RESULTS**

- Table 1. PK/PD Thresholds for Omadacycline

**REFERENCES**

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