Omadacycline is a novel aminomethylcycline with in vitro activity against Gram-positive and negative organisms, including *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Given its favorable pharmacokinetic properties, it is being developed to treat patients with community-acquired bacterial pneumonia (CABP).

Collection of pharmacokinetic (PK) data from omadacycline-treated patients with CABP allowed for refinement of a previously-described population PK model based on Phase 1 data [1, 2].

As described herein, the above-described population PK model [2], non-compartmental analysis [3], and in vitro antibacterial susceptibility testing [4] in vitro, in situ, and animal studies, were used to evaluate the efficacy and safety of IV and PO omadacycline dosing regimens for CABP and interpretive criteria for the in vitro activity testing of omadacycline against *S. pneumoniae* and *H. influenzae*.

### INTRODUCTION

#### Population Pharmacokinetic Model

A linear, three-compartment model with epithelial lining fluid (ELF) as a sub-compartment of portal compartment 1 was utilized to simulate IV and PO omadacycline concentration-time profiles (2).

Monte Carlo Simulations

Using the above-described omadacycline population PK model [2], total-drug ELF AUC concentrations between 0- to 120-hours were generated for 5,000 simulated patients following two omadacycline dosing regimens.

#### IV to PO Dosing Regimen

- 100 mg IV q12h on Day 1, followed by 100 mg IV q24h on Day 2 and 300 mg PO q24h on Days 3-5
- 400 mg IV q24h on Days 1-4 followed by 300 mg PO q24h on Days 5-9

#### PO Dosing Regimen

- 24-hour total-drug ELF and plasma AUC concentrations (AUC) were calculated for each simulated patient.
- Total-drug plasma AUC values were adjusted to free-drug plasma AUC values using a free-fraction of 0.79 based on protein binding [5].
- AUC values were divided by the minimum inhibitory concentration (MIC) to calculate the ratio of the MIC to AUC (MIC/AUC, ratio).

### METHODS

#### PK-PD Target Attainment Analyses

- **Percent probabilities** of PK-PD target attainment by MIC and weight over omadacycline MIC distributions for each pathogen based on average 24-hour AUC values on Days 1 to 2 and the 24-hour AUC on Day 3 (the combination of PO and PO switch) were determined for simulated patients after administration of each omadacycline dosing regimen.

- **The MIC** was randomly assigned based on an estimated log normal distribution of targets associated with a 1-log10 CFU reduction from baseline.

#### Pharmacokinetic-Pharmacodynamic Target Attainment Analyses Evaluating Omadacycline Dosing Regimens for the Treatment of Patients With Community-Acquired Bacterial Pneumonia

#### RESULTS

#### CONCLUSIONS

- These data provide support for improved omadacycline dosing regimens and the evaluation of omadacycline susceptibility breakpoints against *S. pneumoniae* and *H. influenzae*.

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**Table 1.** Omadacycline total-dug ELF/AUC/MIC ratio targets for *S. pneumoniae* and *H. influenzae* (1) and one-compartment in vivo (4) infection models, respectively

<table>
<thead>
<tr>
<th>Pathogen (MIC range)</th>
<th>MIC target (µg/mL)</th>
<th>AUC/MIC target</th>
<th>Total-dug ELF/AUC/MIC target</th>
<th>AUC/MIC target</th>
<th>Total-dug ELF/AUC/MIC target</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>0.005 - 0.125</td>
<td>10 - 44</td>
<td>0.6 - 14</td>
<td>1.2 - 28</td>
<td>9 - 32</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>0.01 - 0.06</td>
<td>100 - 600</td>
<td>0.001 - 0.02</td>
<td>100 - 600</td>
<td>0.001 - 0.02</td>
</tr>
</tbody>
</table>

**Table 2.** Percent probabilities of PK-PD target attainment by MIC and weight over omadacycline MIC distributions for each pathogen based on average 24-hour AUC values on Days 1 to 2 and the 24-hour AUC on Day 3 (the combination of PO and PO switch) were determined for simulated patients after administration of each omadacycline dosing regimen.

**Figure 2.** Percent probabilities of attaining randomly assigned total-dug ELF/AUC/MIC ratio targets for *S. pneumoniae* on Days 1 to 2 among simulated patients after administration of the IV to PO (A) and PO (B) omadacycline dosing regimens, overlaid on the MIC distributions for *S. pneumoniae*.

**Table 3.** Percent probabilities of PK-PD target attainment by MIC and weight over omadacycline MIC distributions for each pathogen based on average 24-hour AUC values on Days 1 to 2 and the 24-hour AUC on Day 3 (the combination of PO and PO switch) were determined for simulated patients after administration of each omadacycline dosing regimen.

**Figure 3.** Percent probabilities of attaining randomly assigned total-dug ELF/AUC/MIC ratio targets for *H. influenzae* on Days 1 to 2 among simulated patients after administration of the IV to PO (A) and PO (B) omadacycline dosing regimens, overlaid on the MIC distributions for *H. influenzae*.

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**REFERENCES**