Omadacycline Pharmacokinetics: Impact of Comorbidities

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INTRODUCTION

• Omadacycline, a novel aminomethylcycline antibiotic with activity against many Gram-positive, Gram-negative, anaerobic, and atypical pathogens, was recently approved in the U.S. for the treatment of adults with community-acquired bacterial pneumonia and acute bacterial skin and skin structures infections.

• During drug development, robust population PK analyses based on Phase 1, 2, and 3 data were undertaken to characterize the disposition of omadacycline [1].

OBJECTIVES

• The objective of this analysis was to evaluate differences in omadacycline clearance among subjects stratified by comorbidities not previously evaluated.

METHODS

• The omadacycline PK model has previously been shown to be a linear, three-compartment model with zero-order IV input and first-order absorption using transit compartments to account for a delay in oral absorption following administration of the tablet or capsule formulations [1].

• Distributions of omadacycline clearance by the comorbidity are provided in Table 1.

• Summary statistics of baseline subject descriptors for the analysis population are presented in Table 1.

• Distributions of omadacycline clearance by the comorbidity are provided in Figure 1.

• Summary of omadacycline clearance estimates by comorbidity along with possible confounding variables are presented in Table 2.

• Omadacycline dose adjustments based on these covariates are likely not warranted.

RESULTS

Table 1. Summary of omadacycline clearance estimates by comorbidity

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Omadacycline CL (L/h)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smokers</td>
<td>Yes</td>
<td>11.2</td>
</tr>
<tr>
<td>History of chronic lung disease</td>
<td>No</td>
<td>9.8</td>
</tr>
<tr>
<td>History of coronary artery disease</td>
<td>No</td>
<td>9.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>No</td>
<td>7.9</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>No</td>
<td>7.6</td>
</tr>
<tr>
<td>History of stroke</td>
<td>No</td>
<td>10.4</td>
</tr>
</tbody>
</table>

INCREASES IN OMADACYCLINE CLEARANCE

• In a history of diabetes, chronic lung disease, coronary artery disease, or hypertension did not impact clearance. Omadacycline dose adjustments based on these comorbidities are likely not warranted.

• Current smokers had statistically significant increases in omadacycline clearance compared to non-smokers after accounting for the effect of sex. The difference was < 15% and, thus, is unlikely to be clinically relevant.

REFERENCES

1. Lakota EA, Van Wart SA, Tzian D, Jeffrey R., et al. For their scientific and editorial assistance. Funding for this analysis was provided by Paratek Pharmaceuticals, Inc., King of Prussia, PA, USA

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CONCLUSIONS

• Omadacycline, a novel aminomethylcycline antibiotic with activity against many Gram-positive, Gram-negative, anaerobic, and atypical pathogens, was recently approved in the U.S. for the treatment of adults with community-acquired bacterial pneumonia and acute bacterial skin and skin structures infections. During drug development, robust population PK analyses based on Phase 1, 2, and 3 data were undertaken to characterize the disposition of omadacycline [1]. The objective of this analysis was to evaluate differences in omadacycline clearance among subjects stratified by comorbidities not previously evaluated. The omadacycline PK model has previously been shown to be a linear, three-compartment model with zero-order IV input and first-order absorption using transit compartments to account for a delay in oral absorption following administration of the tablet or capsule formulations [1]. Distributions of omadacycline clearance by the comorbidity are provided in Table 1. Summary statistics of baseline subject descriptors for the analysis population are presented in Table 1. Distributions of omadacycline clearance by the comorbidity are provided in Figure 1. Summary of omadacycline clearance estimates by comorbidity along with possible confounding variables are presented in Table 2. Omadacycline dose adjustments based on these covariates are likely not warranted. Current smokers had statistically significant increases in omadacycline clearance compared to non-smokers after accounting for the effect of sex. The difference was < 15% and, thus, is unlikely to be clinically relevant.