Pharmacokinetic-Pharmacodynamic (PK-PD) Analyses for Alanine Aminotransferase (ALT) Using Phase 2 and 3 Data From Lefamulin-Treated Patients

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INTRODUCTION & PURPOSE

• Lefamulin (LEF), a semi-synthetic intravenous (IV) and oral (PO) pleuromilin, is approved for the treatment of adults with community-acquired bacterial pneumonia (CABP).3

• Mild, transient, and asymptomatic elevations of hepatic aminotransferases, without bilirubin elevations, were observed in some patients with CABP treated with LEF.2,3

• Pharmacokinetic-pharmacodynamic (PK-PD) relationships for alanine aminotransferase (ALT) were evaluated using phase 2 and 3 data from patients treated with LEF.4,5

RESULTS (continued)

Table 1. Repeated Measures Multiple Linear Regression Model for ALT With Prior Cumulative Total AUC Evaluated as an Independent Variable

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>SE</th>
<th>Mean ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.0809</td>
<td>0.2271</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior cumulative total AUC, mg•h/L</td>
<td>0.1363</td>
<td>0.0414</td>
<td>1.069 (1.078, 1.20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, per 10-year increase</td>
<td>-0.0658</td>
<td>0.0138</td>
<td>0.941 (0.934, 0.948)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>0.0426</td>
<td>0.0576</td>
<td>1.040 (0.953, 1.14)</td>
<td>0.46</td>
</tr>
<tr>
<td>BMI, per 5 kg/m2 increase</td>
<td>0.0715</td>
<td>0.0191</td>
<td>1.051 (1.024, 1.079)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Baseline GGT, per doubling</td>
<td>0.2106</td>
<td>0.0228</td>
<td>1.257 (1.122, 1.394)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Baseline AST, per doubling</td>
<td>0.7362</td>
<td>0.0443</td>
<td>2.066 (1.569, 1.769)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Across fixed average daily AUC values, the model-predicted impact of LEF on relevant ALT elevation endpoints of 3× ULN or higher was minimal among all patients (Figure 1) and among patient subsets defined as male (Figure 2), as having reduced baseline AST (Figure 3), or both (Figure 4).
- Median (interquartile range) average daily LEF AUC values over the first 120 hours from start of treatment were 24.0 (20.2, 31.0) and 24.3 (18.0, 33.2) mg•h/L for the phase 3 patients with CABP who received LEF 150 mg IV q12h followed by 600 mg PO q12h PO and 600 mg PO q12h, respectively; for the phase 2 patients with ABSSSI who received LEF 100 mg IV q12h and 150 mg IV q12h, median (interquartile range) average daily LEF AUC values were 10.8 (9.25, 12.4) and 15.3 (13.5, 18.1) mg•h/L, respectively. At such average daily AUC values, no appreciable difference in ALT elevation endpoints of at least 3× ULN relative to no LEF exposure was estimated based on the final model for ALT.
- Percent probabilities were within 1.65% when comparing simulated patients and observed patients from the analysis dataset after IV and PO dosing regimens (Figure 5).

Figure 1. Model-Predicted Percent Probabilities of Achieving ALT Elevation Endpoints Among All Patients Across a Range of Average Daily LEF AUC Values

Figure 2. Model-Predicted Percent Probabilities of Achieving ALT Elevation Endpoints Among Male Patients Across a Range of Average Daily LEF AUC Values

CONCLUSIONS

- While a covariate-adjusted relationship between increased ALT and increased LEF AUC was found, model-predicted ALT elevation endpoints across fixed LEF AUC values, or among simulated patients after administration of LEF IV or PO dosing regimens relative to observed patients, were minimal.

REFERENCES


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