T-20

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) pleuromutilin, is approved for the treatment of adults with community-acquired bacterial pneumonia (CABP).[1]
- 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.[2-4]

METHODS

- Data were obtained from patients who received IV and/or PO LEF in 2 phase 3 studies conducted in patients with CABP[2,3] and 1 phase 2 study conducted in patients with acute bacterial skin and skin structure infections (ABSSSIs).[4]
- Repeated measures multiple linear regression was used to evaluate factors predictive of ALT, including LEF area under the concentration-time curve (AUC) measures prior to each ALT assessment, with interactions and covariates selected stepwise.
  - Measures of LEF total-drug AUC were determined using a population pharmacokinetic model developed using phase 1, 2, and 3 data.[5]
  - Candidate independent variables evaluated included age; sex; body mass index (BMI); baseline gamma-glutamyl transferase (GGT); baseline alkaline phosphatase; baseline aspartate aminotransferase (AST); baseline albumin; baseline bilirubin; pneumonia pathogen; concomitant metformin use; concomitant statin use; history of diabetes; history of liver disease; CURB-65 criteria (confusion, urea >7 mmol/L, respiratory rate ≥30 breaths per min, low blood pressure, and age ≥65 years), Pneumonia Patient Outcomes Research Team (PORT), and American Thoracic Society (ATS) severity scores; and route of LEF administration.
    - Baseline values for factors representing markers of liver function, including those known to be collinear with ALT, were included as candidate independent variables to investigate the impact of baseline liver function on the relationship between LEF AUC and ALT.
- Using the final model, percent probabilities of ALT elevation >1, 1.5, 2, 3, 5, and 10× upper limit of normal (ULN) post-baseline up to 2 days after the end of therapy were calculated among analysis patients at fixed post-baseline LEF AUC values, and among simulated patients after administration of LEF IV and PO dosing regimens.
  - Simulated patients received LEF 150 mg IV every 12 hours (q12h), 600 mg PO q12h for 5 days under fasting conditions, and 600 mg PO q12h for 5 days under fed conditions.

RESULTS

- The final repeated measures multiple linear regression model, which was based on data from 653 patients with complete covariate information, is shown in **Table 1**.
  - Increased BMI, increased baseline GGT, increased baseline AST, and decreased age were factors for which model main effects were predictive of increased ALT ($P \leq 0.0002$).
  - Increased prior cumulative AUC was associated with increased ALT, although the magnitude of the slope of the association was altered through interactions with sex and baseline AST.
    - Male patients had higher slopes than female patients, and patients with lower baseline AST had higher slopes than those with higher baseline AST ($P < 0.0001$ for each interaction).
    - Positive slope estimates for the association between cumulative AUC and ALT resulted for patients with baseline AST ≤59 U/L among male patients and ≤35 U/L among female patients.

RESULTS (continued)

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

Variable	Parameter estimate	SE	Means ratio (95% CI)	*P* value
Intercept	–0.0809	0.2271		
Prior cumulative total AUC, mg•h/L*	0.1363	0.0141	1.099 (1.078, 1.120)	<0.0001
Age, per 10-year increase	–0.0568	0.0138	0.961 (0.943, 0.980)	<0.0001
Male	0.0426	0.0576	1.030 (0.953, 1.114)	0.46
BMI, per 5 kg/m^2 increase	0.0715	0.0191	1.051 (1.024, 1.078)	0.0002
Baseline GGT, per doubling	0.2106	0.0228	1.157 (1.122, 1.194)	<0.0001
Baseline AST, per doubling	0.7362	0.0443	1.666 (1.569, 1.769)	<0.0001
Interaction between baseline AST and prior cumulative total AUC	–0.0265	0.0030	0.982 (0.978, 0.986)	<0.0001
Interaction between male and prior cumulative total AUC	0.0201	0.0044	1.014 (1.008, 1.020)	<0.0001

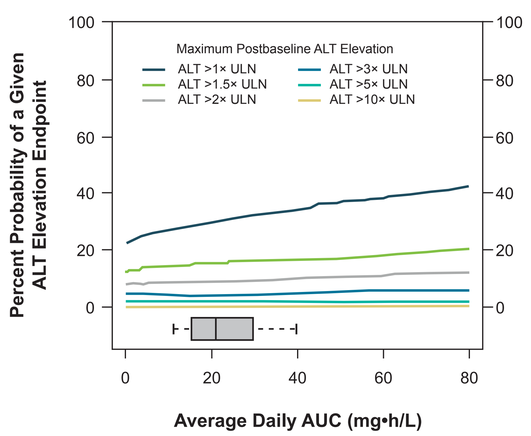
Model AIC = 3840.85

AIC=Akaike information criterion; ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the concentration-time curve; BMI=body mass index; GGT=gamma-glutamyl transferase.

*Prior cumulative total AUC was evaluated on the square root transformation scale.

- Across fixed average daily AUC values, the model-predicted impact of LEF on clinically 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 as 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)**.

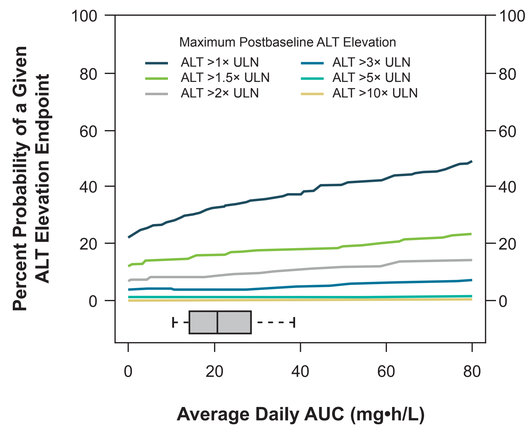
Figure 1. Model-Predicted Percent Probabilities of Achieving ALT Elevation Endpoints Among All Patients Across a Range of Average Daily LEF AUC Values*



ALT=alanine aminotransferase; AUC=area under the concentration-time curve; LEF=lefamulin; ULN=upper limit of normal.

*The boxplot represents the distribution (10th, 25th, 50th, 75th, and 90th percentiles) of cumulative average AUC among all postbaseline ALT observations for the analysis population. The axis maximum of 80 mg•h/L was the 99.7th percentile among all such observations.

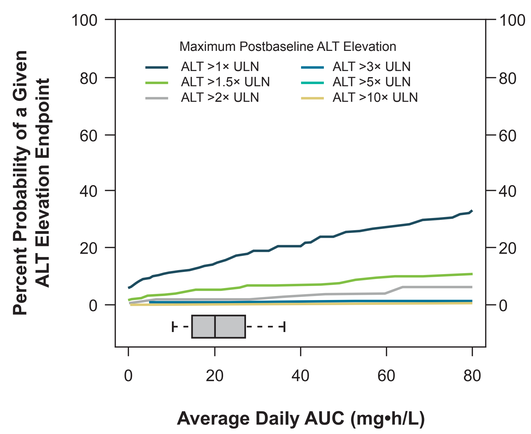
Figure 2. Model-Predicted Percent Probabilities of Achieving ALT Elevation Endpoints Among Male Patients Across a Range of Average Daily LEF AUC Values*



ALT=alanine aminotransferase; AUC=area under the concentration-time curve; LEF=lefamulin; ULN=upper limit of normal.

*The boxplot represents the distribution (10th, 25th, 50th, 75th, and 90th percentiles) of cumulative average AUC among all postbaseline ALT observations for male patients in the analysis population.

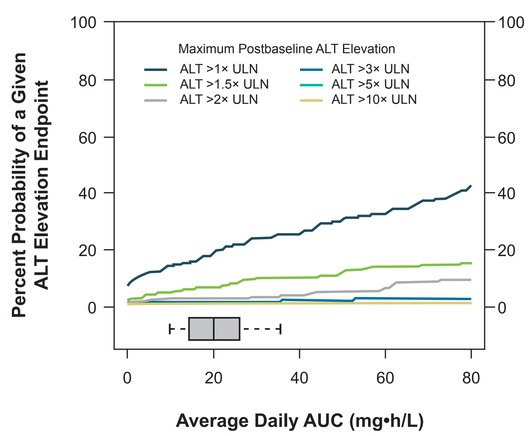
Figure 3. Model-Predicted Percent Probabilities of Achieving ALT Elevation Endpoints Among Patients With Baseline AST <20 U/L Across a Range of Average Daily LEF AUC Values*



ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the concentration-time curve; LEF=lefamulin; ULN=upper limit of normal.

*The boxplot represents the distribution (10th, 25th, 50th, 75th, and 90th percentiles) of cumulative average AUC among all postbaseline ALT observations for patients in the analysis population with baseline AST <20 U/L.

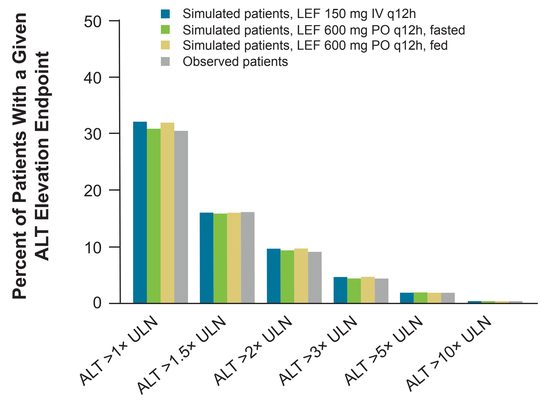
Figure 4. Model-Predicted Percent Probabilities of Achieving ALT Elevation Endpoints Among Male Patients With Baseline AST <20 U/L Across a Range of Average Daily LEF AUC Values*



ALT=alanine aminotransferase; AST=aspartate aminotransferase; AUC=area under the concentration-time curve; LEF=lefamulin; ULN=upper limit of normal.

*The boxplot represents the distribution (10th, 25th, 50th, 75th, and 90th percentiles) of cumulative average AUC among all postbaseline ALT observations for males in the analysis population with baseline AST <20 U/L.

Figure 5. Percentage of ALT Elevation Endpoints Among Simulated Patients and Observed Patients From the Analysis Dataset After Administration of LEF IV and PO Dosing Regimens



ALT=alanine aminotransferase; IV=intravenous; LEF=lefamulin; PO=oral; q12h=every 12 hours; ULN=upper limit of normal.

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.

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