Cardiac Safety in Adults With Community-Acquired Bacterial Pneumonia Treated With Lefamulin or Moxifloxacin: Analysis of Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Study Results

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INTRODUCTION & PURPOSE

Lefamulin (LEF) is a pleuromutilin antibiotic approved for intravenous and oral use in adults with community-acquired bacterial pneumonia (CABP); intravenous preparations may also be used for adults with moderate-to-severe community-acquired respiratory tract infections (CARTI) or hospital-acquired pneumonia (HAP) in the inpatient setting; LEF is a dihydropeptidyl transferase (DHP) inhibitor (DHPase)

• The micromolar mode of action at a distinct binding to a highly conserved ribosomal region may confer a broad spectrum of antibacterial activity and suggest a low potential for development of resistance in other major antibiotic classes

• Metabolites and fluoroquinolones, antibiotic classes commonly used to treat CABP, are associated with QT prolongation and torsade de pointes

• LEF has a prolonged elimination half-life of 68–72 hours, consistent with drug accumulation

• LEF has catheter-related veno-occlusive nonclinical toxicity, with results suggesting a potential for QT prolongation

METHODS

Study Design and Patients

• Both studies were prospective, randomized, double-blind, double-layer, phase 3 trials in adults infected with CABP

• In LEAP 1, patients with Pneumonia Outcomes Research Team (PORT) risk class I (n = 370) MOX (n = 367) and LEAP 2 (n = 738) patients in LEAP 1 (PORT risk class II) and 736 patients in LEAP 2 (n = 370) MOX (n = 367) and LEAP 2 Study Results

• In LEAP 1, a higher proportion of patients had a history of arrhythmia in the LEF treatment group compared with the MOX treatment group

• In both studies, no LEF-treated patients and 1 MOX-treated patient (LEAP 2) had a serious adverse event related to QT prolongation

• LEF has potent in vitro activity against pathogens that commonly cause CABP and cytokine-mediated antimicrobial resistance in the peptidyl transferase center

• The largest least square mean (SE) change in QTcF from baseline to postbaseline was observed on Day 3 postdose in LEAP 1 (13.6 [1.2] and 16.4 [1.2] msec with LEF and MOX, respectively) and on Day 3/4 postdose (339 –6.6 [12.8] 348 –8.4 [13.8] msec with LEF and MOX, respectively)

• In LEAP 1, a higher proportion of patients had heart rate increases of ≥60 msec in the LEF group compared with the MOX group

• In the standardized Medical Dictionary for Regulatory Activities query of “torsade de pointes,” no LEF-treated patients and 1 MOX-treated patient (LEAP 2) had a serious adverse event related to torsade de pointes

• In both studies, patients treated with LEF had statistically significant, clinically meaningful decreases from baseline in a number of patient-reported outcomes (PROs) compared with patients treated with MOX

• The only noteworthy change in vital signs was the increase in heart rate in both the LEF and MOX treatment groups, which is consistent with recovery after the infection

• Consistent with nonclinical and phase 1 findings, LEF caused mild QT prolongation in some patients with CABP

• Mild prolongation of the QT interval was seen with LEF at clinically relevant doses in the phase 3 CABP program, but the observed effect was smaller than that observed with the comparator, MOX

• Given the small effect, LEF is unlikely to pose a clinically significant risk of ventricular proarrhythmia with short-term or long-term use (e.g., LEF is not recommended to be given to patients on other drugs with known effects on QT interval)

RESULTS

Table 1. Demographics and Baseline Characteristics (Intention-to-Treat Population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LEAP 1</th>
<th>LEAP 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>68.4 (15.6)</td>
<td>68.4 (15.3)</td>
<td>0.91</td>
</tr>
<tr>
<td>Baseline mean heart rate, bpm</td>
<td>76 (11)</td>
<td>76 (10)</td>
<td>0.72</td>
</tr>
<tr>
<td>Furosamide use (%)</td>
<td>0.9%</td>
<td>0.9%</td>
<td>0.97</td>
</tr>
<tr>
<td>Baseline QTcF, msec</td>
<td>375 ± 11.4</td>
<td>376 ± 11.5</td>
<td>0.61</td>
</tr>
<tr>
<td>Baseline QT, msec</td>
<td>367 ± 11.7</td>
<td>368 ± 11.7</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Table 2. Change From Baseline in Heart Rate (Safety Analysis Set)

<table>
<thead>
<tr>
<th>Time Point*</th>
<th>Baseline mean (SD)</th>
<th>Day 3/4 postdose mean (SD)</th>
<th>Day 1 postdose mean (SD)</th>
<th>Day 3/4 predose mean (SD)</th>
<th>Change from Baseline (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 predose</td>
<td>77.1 ± 11.5</td>
<td>78.6 ± 11.9</td>
<td>77.3 ± 11.7</td>
<td>77.1 ± 11.7</td>
<td>–2.2 ± 11.7</td>
</tr>
<tr>
<td>Day 3/4 predose</td>
<td>74.1 ± 11.4</td>
<td>74.9 ± 11.5</td>
<td>73.7 ± 11.5</td>
<td>73.2 ± 11.6</td>
<td>–2.8 ± 11.5</td>
</tr>
<tr>
<td>Day 1 postdose</td>
<td>77.3 ± 11.7</td>
<td>78.6 ± 11.8</td>
<td>77.3 ± 11.4</td>
<td>76.7 ± 11.4</td>
<td>–2.7 ± 11.8</td>
</tr>
<tr>
<td>Day 3/4 postdose</td>
<td>74.9 ± 11.5</td>
<td>75.2 ± 11.4</td>
<td>73.9 ± 11.4</td>
<td>73.3 ± 11.4</td>
<td>–1.5 ± 11.4</td>
</tr>
</tbody>
</table>

Table 3. Change From Baseline in QTcF (Safety Analysis Set)

<table>
<thead>
<tr>
<th>Time Point*</th>
<th>Baseline mean (SD)</th>
<th>Day 3/4 postdose mean (SD)</th>
<th>Day 1 postdose mean (SD)</th>
<th>Day 3/4 predose mean (SD)</th>
<th>Change from Baseline (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 predose</td>
<td>375 ± 11.4</td>
<td>375 ± 11.4</td>
<td>375 ± 11.4</td>
<td>375 ± 11.4</td>
<td>0 ± 11.4</td>
</tr>
<tr>
<td>Day 3/4 predose</td>
<td>373 ± 11.3</td>
<td>381 ± 11.2</td>
<td>372 ± 11.7</td>
<td>372 ± 11.7</td>
<td>8 ± 11.3</td>
</tr>
<tr>
<td>Day 1 postdose</td>
<td>374 ± 11.2</td>
<td>382 ± 11.1</td>
<td>372 ± 11.4</td>
<td>372 ± 11.4</td>
<td>8 ± 11.3</td>
</tr>
<tr>
<td>Day 3/4 postdose</td>
<td>372 ± 11.1</td>
<td>381 ± 11.2</td>
<td>371 ± 11.3</td>
<td>371 ± 11.3</td>
<td>9 ± 11.3</td>
</tr>
</tbody>
</table>

Table 4. QTCF Prolongation Trigger (Pooled Safety Analysis Set)

- **Baseline QTcF increase \( \geq 30 \) msec (61.6% vs 58.2%)**
- **Baseline QTcF increase \( \leq 60 \) msec (27.8% vs 30.5%)**
- **Baseline QTcF increase \( >60 \) to \( \leq 120 \) msec (2.6% vs 1.9%)**
- **Baseline QTcF increase \( >120 \) msec (6.0% vs 8.1%)**

Figure 1. Proportions of Patients With Postbaseline QTcF Increases (A) and Values of Interest (B) (Safety Analysis Set)

CONCLUSIONS

- The only noteworthy change in vital signs was the expected increase in heart rate in both the LEF and MOX treatment groups, which is consistent with recovery after the infection

- Consistent with nonclinical and phase 1 findings, LEF caused mild QT prolongation in some patients with CABP

- Mild prolongation of the QT interval was seen with LEF at clinically relevant doses in the phase 3 CABP program, but the observed effect was smaller than that observed with the comparator, MOX

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REFERENCES

- Ixora Darpo, Full Publishing Information, Nabriva Therapeutics US, Inc., King of Prussia, PA, USA. 1


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Disclosures

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*Presented by