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# 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), a first-in-class pleuromutilin antibiotic approved for intravenous (IV) and oral use in adults with community-acquired bacterial pneumonia (CABP),[1] inhibits protein synthesis by selectively binding to the 50S ribosomal subunit at the A- and P-sites in the peptidyl transferase center[2,3]
- The unique mode of action of LEF and its 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 to other antibiotic classes[1-4]
  - LEF has potent in vitro activity against pathogens that commonly cause CABP and is unaffected in vitro by an organism's resistance to other major antibiotic classes[5,6]
- Macrolides and fluoroquinolones, antibiotic classes commonly used to treat CABP,[7] are associated with QT prolongation that can potentially result in life-threatening cardiac arrhythmias[8,9]
- LEF has undergone extensive nonclinical testing, with results suggesting a potential for QT prolongation[10]
  - Further assessment in phase 1 studies of healthy volunteers demonstrated dose/exposure-related effects of LEF on QT interval
- The objective of this investigation was to assess cardiac safety in adults with CABP treated with LEF or moxifloxacin (MOX) based on analysis of the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 phase 3 clinical trials

## METHODS

### Study Design and Patients

- Both studies were prospective, randomized, double-blind, double-dummy, phase 3 trials[11,12]
  - In LEAP 1, patients with Pneumonia Outcomes Research Team (PORT) risk class III–V were randomized to receive LEF 150 mg IV every 12 hours (q12h) for 5–7 days or MOX 400 mg IV every 24 hours (q24h) for 7 days
    - Patients could switch to oral therapy (LEF 600 mg q12h or MOX 400 mg q24h) after 6 IV doses of study drug (~3 days) if predefined improvement criteria were met
  - In LEAP 2, patients with PORT risk class II–IV were randomized to receive oral LEF 600 mg q12h for 5 days or oral MOX 400 mg q24h for 7 days
- In both studies, patients with known QT prolongation or on a medication with the potential to prolong the QT interval were excluded as per MOX label[13]
- Please refer to **Poster 664** for further details on study design

### Cardiac Safety Assessments

- Vital sign measurements (heart rate, systolic and diastolic blood pressure [SBP/DBP], respiratory rate, body temperature) were recorded at baseline and throughout both studies
- After 5 minutes of rest in the supine position, triplicate 12-lead electrocardiograms (ECGs) were obtained with Mortara ELI™ 150 or ELI™ 250 ECG recorders (Welch Allyn, Skaneateles Falls, NY, USA) within a 5-minute interval at screening in both studies, on Days 1/3 in LEAP 1 (predose and ≤15 minutes after first IV dose), and on Days 1/4 in LEAP 2 (predose and 1–3 hours after first oral dose)
  - ECG recordings collected on Day 3 (LEAP 1) and Day 4 (LEAP 2) allowed evaluation of postdose ECG parameters around the peak LEF plasma concentration ($C_{max}$) and when LEF levels had reached steady state
  - Recordings were digitally transmitted to a central ECG laboratory (ERT, Philadelphia, PA, USA) for interval measurements and interpretation using a semiautomatic technique
  - Sites unable to digitally transmit an ECG provided hard copies that were scanned and digitized (ECGScan software, AMPS LLC, New York, NY, USA) for adjudication

## METHODS (continued)

- Cardiac safety was evaluated with descriptive statistics and a linear mixed-effects model using change in QT interval corrected according to Fridericia (QTcF) as a dependent variable
  - Linear mixed-effects model: ΔQTcF = time + treatment + (time × treatment) + baseline QTcF. An unstructured covariance structure was used to specify the repeated measures (time within patient and period)

## RESULTS

### Patients

- The intent-to-treat population (all randomized patients; *n*=1289 [LEF, *n*=646; MOX, *n*=643]) included 551 patients in LEAP 1 (LEF, *n*=276; MOX, *n*=275) and 738 patients in LEAP 2 (LEF, *n*=370; MOX, *n*=368), and the safety analysis set (all randomized and treated patients; *n*=1282 [*n*=641 per group]) included 546 patients in LEAP 1 (*n*=273 per group) and 736 patients in LEAP 2 (*n*=368 per group)
- Demographics and baseline characteristics were generally well balanced between treatment groups in LEAP 1 and LEAP 2 **(Table 1)**
  - In LEAP 1, a higher proportion of patients had a history of arrhythmia in the LEF group compared with the MOX group
- Baseline mean heart rates **(Table 2)** and QTcF intervals **(Table 3)** were similar between treatment groups in both studies

### Cardiac Safety Analyses

- Changes in SBP, DBP, respiratory rate, and body temperature over time were generally comparable between treatment groups in both studies (data not shown)
- Baseline and postbaseline ECG assessments were available for 544 patients in LEAP 1 (LEF, *n*=273; MOX, *n*=271) and 730 patients in LEAP 2 (LEF, *n*=363; MOX, *n*=367)
- ECGs revealed decreases in mean heart rates in both treatment groups, with slightly smaller reductions recorded for LEF than MOX in both studies **(Table 2)**
  - Mean heart rate reduction for LEF patients was 7.9 bpm on Day 3 postdose in LEAP 1 and 6.6 bpm on Day 4 postdose in LEAP 2
  - MOX patients showed mean heart rate reductions of 8.2 bpm on Day 3 postdose in LEAP 1 and 8.4 bpm on Day 4 postdose in LEAP 2
- After dosing, the mean QTcF interval increased in both treatment groups, although the magnitude of the change was consistently smaller for LEF than MOX **(Table 3)**
  - 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 IV LEF and MOX, respectively) and on Day 4 postdose in LEAP 2 (9.3 [1.0] and 11.6 [1.0] msec with oral LEF and MOX, respectively)
- The proportion of patients meeting potentially important postbaseline QTcF values or changes was generally comparable between treatment groups, with fewer patients in the LEF group reaching threshold values compared with the MOX group **(Figure 1)**
  - The data demonstrated expected differences by route of administration, with more ECG changes meeting potentially important values or changes from baseline observed after IV dosing (LEAP 1) than after oral dosing (LEAP 2), which is consistent with a concentration-dependent effect given that $C_{max}$ (not AUC) is higher after IV dosing
  - In both studies, no LEF-treated patients and 1 MOX-treated patient (LEAP 2) had a postbaseline QTcF increase >60 msec that resulted in a value >500 msec

## RESULTS (continued)

- In the standardized Medical Dictionary for Regulatory Activities query of "torsade de pointes/QT prolongation (broad)," the most common treatment-emergent adverse event across both studies was ECG QT/QTc prolonged (LEF, *n*=4; MOX, *n*=5; **Table 4**)
  - In these patients, the maximum increase from baseline in QTcF interval ranged from 29.6–49.7 msec for LEF and 17.0–45.0 msec for MOX
  - All events were nonserious and mild or moderate in severity, 6 events were considered related to study drug (LEF, *n*=4; MOX, *n*=2), and 5 events led to study drug discontinuation (LEF, *n*=2; MOX, *n*=3)
- Two patients from LEAP 1 experienced fatal events (LEF, *n*=1; MOX, *n*=1); both patients had cardiovascular disease and neither fatal event was considered by the investigator to be related to study drug
  - The patient treated with LEF had ventricular arrhythmia on Day 20 (18 days after the last LEF dose)
  - The patient treated with MOX had cardiac arrest on Day 18 (9 days after the last MOX dose)

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

| Parameter | LEAP 1 | | LEAP 2 | |
|---|---|---|---|---|
| | LEF (*n*=276) | MOX (*n*=275) | LEF (*n*=370) | MOX (*n*=368) |
| Age, y, mean (SD) | 61.0 (16.3) | 59.6 (14.9) | 57.4 (16.4) | 57.7 (16.2) |
| Male, *n* (%) | 170 (61.6) | 160 (58.2) | 207 (55.9) | 180 (48.9) |
| BMI, kg/m$^2$, mean (SD) | 26.5 (6.0) | 26.3 (6.3) | 26.5 (5.7) | 26.5 (5.8) |
| PORT risk class,* *n* (%) | | | | |
| I/II | 0 | 1 (0.4) | 184 (49.7) | 191 (51.9) |
| III | 196 (71.0) | 201 (73.1) | 145 (39.2) | 133 (36.1) |
| IV/V | 80 (29.0) | 73 (26.5) | 41 (11.1) | 44 (12.0) |
| History of hypertension, *n* (%) | 118 (42.8) | 112 (40.7) | 130 (35.1) | 141 (38.3) |
| History of arrhythmia, *n* (%) | 27 (9.8) | 15 (5.5) | 16 (4.3) | 15 (4.1) |

BMI=body mass index; LEAP=Lefamulin Evaluation Against Pneumonia; LEF=lefamulin; MOX=moxifloxacin; PORT=Pneumonia Outcomes Research Team.
*PORT risk class was calculated programmatically using data obtained at the site and reported in the electronic case report form and was not always consistent with the site-reported PORT risk class used for enrollment/stratification; as a result, 3 patients with PORT risk class I (LEF, *n*=1; MOX, *n*=2) were enrolled in LEAP 2.

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

| Time Point* | LEAP 1 | | | | LEAP 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | LEF | | MOX | | LEF | | MOX | |
| | *n* | Mean (SD) | *n* | Mean (SD) | *n* | Mean (SD) | *n* | Mean (SD) |
| Baseline, bpm† | 273 | 84.8 (15.9) | 272 | 84.0 (15.7) | 365 | 81.6 (15.2) | 368 | 82.2 (15.7) |
| Change from baseline, bpm‡ | | | | | | | | |
| Day 1 postdose | 271 | –2.2 (8.8) | 267 | –2.2 (8.3) | 357 | –0.9 (7.7) | 367 | –0.8 (9.3) |
| Day 3/4 predose | 265 | –5.8 (14.0) | 263 | –7.7 (13.2) | 341 | –6.2 (12.8) | 352 | –7.1 (14.3) |
| Day 3/4 postdose | 264 | –7.9 (14.0) | 262 | –8.2 (13.2) | 339 | –6.6 (12.8) | 348 | –8.4 (13.8) |

LEAP=Lefamulin Evaluation Against Pneumonia; LEF=lefamulin; MOX=moxifloxacin.
*Measurements were taken at baseline and on Days 1 and 3 in LEAP 1 and at baseline and on Days 1 and 4 in LEAP 2. Postdose measurements were performed in LEAP 2 within 1–3 hours after the first dose of study drug on the specified study day. For LEAP 2 outpatients, Day 4 measurements were performed 72–120 hours after the first dose.
†Last assessment before first dose of study drug.
‡Includes all patients with heart rate values at both baseline and the specified time point.

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

| Time Point* | LEAP 1 | | | | LEAP 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | LEF | | MOX | | LEF | | MOX | |
| | *n* | Mean (SD) | *n* | Mean (SD) | *n* | Mean (SD) | *n* | Mean (SD) |
| Baseline, msec† | 273 | 411.4 (25.9) | 272 | 411.4 (24.6) | 365 | 409.3 (23.1) | 368 | 410.9 (25.8) |
| **Change from baseline, msec‡** | ***n*** | **LSM (SE)** | ***n*** | **LSM (SE)** | ***n*** | **LSM (SE)** | ***n*** | **LSM (SE)** |
| Day 1 postdose | 271 | 8.8 (0.9) | 268 | 10.7 (0.9) | 357 | 1.7 (0.7) | 367 | 6.1 (0.7) |
| Day 3/4 predose | 265 | 5.9 (1.1) | 262 | 8.8 (1.1) | 341 | 8.5 (1.0) | 352 | 7.7 (0.9) |
| Day 3/4 postdose | 264 | 13.6 (1.2) | 263 | 16.4 (1.2) | 339 | 9.3 (1.0) | 348 | 11.6 (1.0) |

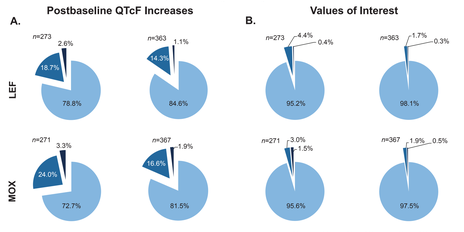
LEAP=Lefamulin Evaluation Against Pneumonia; LEF=lefamulin; LSM=least squares mean; MOX=moxifloxacin; QTcF=QT interval corrected according to Fridericia.
*Measurements were taken within 15 minutes of end of infusion on Days 1 and 3 in LEAP 1 and 1–3 hours postdose on Days 1 and 4 in LEAP 2. For LEAP 2 outpatients, Day 4 measurements were performed 72–120 hours after the first dose.
†Last assessment before first dose of study drug.
‡Based on a linear mixed-effects model.

**Table 4. QT/QTc Prolongation TEAEs* (Pooled Safety Analysis Set)**

| TEAE Preferred Term | LEF (*n*=641) | MOX (*n*=641) |
|---|---|---|
| QT prolongation,† *n* (%) | 5 (0.8) | 6 (0.9) |
| Electrocardiogram QT prolonged | 4 (0.6) | 5 (0.8) |
| Ventricular arrhythmia | 1 (0.2) | 0 |
| Cardiac arrest | 0 | 1 (0.2) |

LEF=lefamulin; MedDRA=Medical Dictionary for Regulatory Activities; MOX=moxifloxacin; SMQ=standard MedDRA query; TEAE=treatment-emergent adverse event.
*TEAEs started on or after the first dose of study drug. If the start date was unknown or was a partial date such that it could not be determined if the adverse event started on or after the first study drug administration, it was categorized as a TEAE. The same patient may contribute to ≥2 preferred terms in the same category. Patients with multiple TEAEs were counted once for each preferred term. Adverse events were coded according to MedDRA version 20.0.
†QT prolongation included the MedDRA SMQ "Torsade de pointes/QT prolongation" (broad).

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




LEAP=Lefamulin Evaluation Against Pneumonia; LEF=lefamulin; MOX=moxifloxacin; QTcF=QT interval corrected according to Fridericia.

## CONCLUSIONS

- The only noteworthy change in vital signs was the expected decrease in heart rate in both the LEF and MOX treatment groups, which is consistent with recovery from the infection
- Consistent with nonclinical and phase 1 findings, LEF caused mild QT prolongation in some patients with CABP
- Mild prolongation of the QTcF interval was seen with LEF at clinically relevant doses in the phase 3 CABP program, but the observed effect was smaller than that associated with the comparator, MOX
- Given the small effect, LEF is unlikely to pose a clinically significant risk of ventricular proarrhythmia with appropriate precautions and use (eg, LEF is not recommended to be given to patients on other drugs with known effects on QT interval)

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## Acknowledgments


Funding for development of this poster was provided by Nabriva Therapeutics to C4 MedSolutions, LLC (Yardley, PA), a CHC Group company.


## Disclosures

Borje Darpo is a consultant for ERT, which was contracted by Nabriva Therapeutics to perform the cardiac safety analyses. Anita F. Das has served as a consultant for Achaogen, AntibioTx, Boston Pharmaceuticals, Cempra, ContraFect, InterumTx, Nabriva Therapeutics, Paratek, Tetraphase, Theravance, UTILITY, Wockhardt, and Zavante. Daniel S. Stein, Jennifer Schranz, and Steven P. Gelone are employees of/stockholders in Nabriva Therapeutics plc.

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