O1068

Oral Lefamulin Demonstrates Favorable Safety and Tolerability in Adults With Community-Acquired Bacterial Pneumonia (CABP) in the Phase 3 Lefamulin Evaluation Against Pneumonia (LEAP 2) Study

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BACKGROUND

- Need for new effective empiric monotherapy options without the safety issues of fluoroquinolones (**Table 1**)

Table 1. Fluoroquinolone-Associated Disability

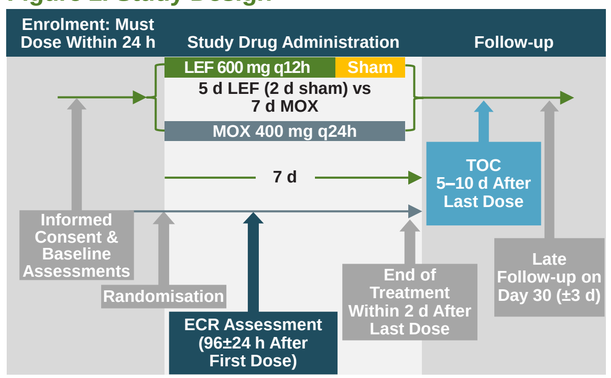
- **Disabling and potentially irreversible serious adverse reactions:**
  - **Tendinitis and tendon rupture**
  - **Peripheral neuropathy**
  - **CNS effects**
- **Exacerbation of myasthenia gravis**
- **Aortic rupture**
- **Hypoglycaemia (potential coma)**
- **QT prolongation**
- ***Clostridium difficile*–associated diarrhoea**
- **Hypersensitivity**
- **Hematologic, hepatic, and renal toxicity (levofloxacin)**

- Lefamulin (LEF) is the first systemic pleuromutilin
  - Evaluated in 2 phase 3 CABP trials:
    - LEAP 1 (ECCMID 2018): LEF was generally well tolerated in patients when initiated IV with oral switch option for PORT risk class ≥III
    - LEAP 2: here we report safety and tolerability of oral LEF in patients with PORT risk class II–IV

METHODS

- Multicentre, double-blind, double-dummy (NCT02813694; EudraCT 2015-004782-92; **Figure 1**)

Figure 1. Study Design



ECR=early clinical response; IACR=investigator assessment of clinical response; LEF=lefamulin; MOX=moxifloxacin; TOC=test of cure.

METHODS (continued)

- Treatment-emergent adverse events (TEAEs), labs, 12-lead EKGs, and 28-day all-cause mortality were evaluated

RESULTS

- Demographic and baseline characteristics were representative of the general CABP population
  - Overall: 62% <65 y; 16% ≥75 y; 88% PORT II–III; 38% vascular; 19% CrCl <60 mL/min; 13% DM; 13% cardiac; 40% smoking history

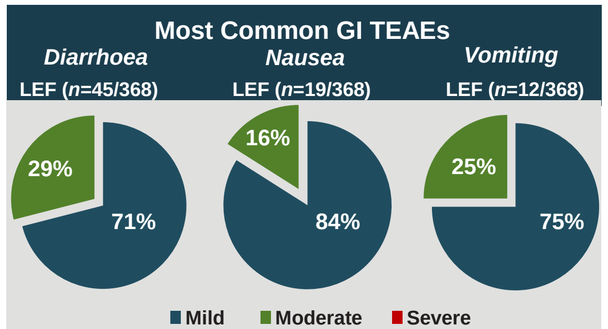
Table 2. Overview of TEAEs (Safety Analysis Set)

Patients, *n* (%)	LEF *n*=368	MOX *n*=368
TEAE	120 (32.6)	92 (25.0)
TEAE leading to discontinuation of study drug	12 (3.3)	9 (2.4)
Serious TEAE	17 (4.6)	18 (4.9)
Deaths within 28 d	3 (0.8)	3 (0.8)
Most common TEAEs (≥1%)		
Gastrointestinal SOC		
Diarrhoea	45 (12.2)	4 (1.1)
Nausea	19 (5.2)	7 (1.9)
Vomiting	12 (3.3)	3 (0.8)
Gastritis	4 (1.1)	2 (0.5)
Vascular disorders SOC		
Hypertension	5 (1.4)	5 (1.4)
Infections and infestations SOC		
Respiratory tract viral infection	5 (1.4)	1 (0.3)
Pneumonia	4 (1.1)	1 (0.3)
Urinary tract infection	3 (0.8)	6 (1.6)
Nervous system disorders SOC		
Headache	4 (1.1)	6 (1.6)
Respiratory, thoracic and mediastinal disorders SOC		
COPD	4 (1.1)	0
Investigations SOC		
ALT increased	3 (0.8)	4 (1.1)
AST increased	2 (0.5)	4 (1.1)
Blood and lymphatic system disorders SOC		
Anaemia	0	4 (1.1)
Psychiatric disorders SOC		
Insomnia	0	4 (1.1)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; COPD=chronic obstructive pulmonary disease; LEF=lefamulin; MOX=moxifloxacin; SOC=system organ class; TEAE=treatment-emergent adverse event.

RESULTS (continued)

Figure 2. Gastrointestinal (GI) Tolerability



- Diarrhoea was generally of short duration (median, 2 days) and did not lead to discontinuation of LEF
- Nausea and vomiting were generally mild
  - No patients discontinued because of nausea
  - 3 patients discontinued because of vomiting (2 LEF/1 MOX)
- 1 case of *C. difficile* infection was reported with LEF

LEF=lefamulin; MOX=moxifloxacin; SOC=system organ class; TEAE=treatment-emergent adverse event.

- Hepatobiliary events
  - TEAEs in 1.1% and 0.5% of patients receiving LEF and MOX, respectively
  - Postbaseline elevations of transaminases were infrequent and transient, with similar incidences
    - ALT levels were >3 × ULN in 4.2% and 4.7% of patients receiving LEF and MOX, respectively
  - No Hy's law criteria met
- Cardiac disorders (**Figure 3**)
  - TEAEs in 2.2% and 2.4% of patients receiving LEF and MOX, respectively
  - On day 4 postdose (steady state), mean change from baseline in QTcF interval was 9.5 msec with LEF and 11.6 msec with MOX

RESULTS (continued)

Figure 3. Cardiac Disorders

Changes in QTcF	LEF, *n* (%)	MOX, *n* (%)
Patients with both baseline and postbaseline values	363	367
Any postbaseline increase >30 msec	56 (15.4)	68 (18.5)
Any postbaseline increase >60 msec	4 (1.1)	7 (1.9)
Any postbaseline value >480 msec	7 (1.9)	9 (2.5)
Any postbaseline value >500 msec	1 (0.3)	2 (0.5)

LEF=lefamulin; MOX=moxifloxacin; SOC=system organ class; TEAE=treatment-emergent adverse event.

CONCLUSIONS

- 5-day oral LEF monotherapy was generally well tolerated with low discontinuation rates due to TEAEs
- The most frequent LEF TEAEs were GI, predominantly diarrhoea, which were mostly mild and rarely led to discontinuation
  - This contrasts with LEAP 1 in which diarrhoea was more common with MOX
- QTc prolongation was shorter with LEF than MOX with no associated cardiac arrhythmias
- These results add to the developing favourable safety/tolerability profile of IV and oral LEF

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