A Phase 3 community-acquired bacterial pneumonia (CABP) study of oral solithromycin (SOLI) versus oral moxifloxacin (MOXI) was successfully completed in 2015. This was the first oral CABP trial conducted under the new FDA and EMA guidances and also the first to use several molecular methods coupled with traditional culture and serology to identify pathogens. CABP is a significant cause of mortality and morbidity worldwide and is a serious infection requiring systemic antibiotic therapy. Antibacterial agents used to treat CABP include the penicillins, cephalosporins, fluoroquinolones, and macrolides. The current Infectious Diseases Society of America and American Thoracic Society (ATS) treatment guidelines generally recommend a β-lactam as monotherapy or in combination with a fluoroquinolone alone. Macrolides, such as clarithromycin and azithromycin, are well-tolerated and safe therapeutic agents and have been noted to have beneficial anti-inflammatory/immunomodulatory effects in addition to antibacterial effects.

The emergence and spread of respiratory pathogens resistant to macrolides and other classes of antibiotics has led to less therapeutic options for treatment of CABP, resulting in the need for newer agents that are active against resistant strains (File 2004; Neu 2004). A macrolide with improved activity, a better safety profile and available in both intravenous (IV) and oral formulations would be a significant therapeutic advance in the treatment of CABP.

Solithromycin is a fourth-generation macrolide antibiotic, and the first fluoroketolide, that has completed two global Phase 3 trials in patients with CABP. The objective was to describe the diagnostic methods used, the variety of bacteria isolated and their susceptibility in the global, oral Phase 3 CABP trial.

This randomized, double-blind Phase 3 trial was conducted in 16 countries on 4 continents with 860 patients dosed once a day for 5 days with oral solithromycin or 7 days with oral moxifloxacin. The severity of pneumonia in the enrolled patients was as follows: 50% PORT, 50% PORT II, 50% PORT III.

Pathogen identification: Multiple molecular and microbiological methods were used to identify causative CABP pathogens. Every effort was made to collect the following samples: nasal, oropharyngeal, sputum, pleural/brochial lavage fluids for Gram stain and culture. Two qPCR for detection of pathogens by the Cempra University® qPCR Application (Cempra, AG, Holzgerlingen, Germany). The pneumococcal positives were confirmed by a required positive result from culture (swabbing positive PCR targeting the pneumococcal surface protein A gene (spa)) (2), and PCR assay on nasopharyngeal swab samples. This assay was established by Altwegg et al. (2012) that a 60 qPCR cycle density 8000 copies/µL (equivalent to ≥2CFUs) distinguished between pneumococcal colonization and asymptomatic respiratory tract infection in patients presenting with CABP. This assay was modified to reduce the threshold to ≥1000 copies/µL, for diagnosis as the original threshold was in immunocompromised patients with HIV. Compared to the former threshold, a cutoff of 1000 copies/µL provided greater sensitivity to detect pneumococcal infection (99.30% vs. 98.36%) with retention of high specificity (98.44% vs. 98.56%) (6). Asphyxiating (OPH)-PCR assay on Mycoplasma culture and PCR identification (University of Alabama, Birmingham, Diagnostic Mycoplasma Laboratory). Presumptive positive based on colony morphology in pH color change of broth were subjected to qPCR analysis utilizing primers that target the repetitive element repMp1 (Donka 2007), to differentiate M. pneumoniae from commercial Mycoplasma species. Additionally, DNA extracted directly from the transport media inoculated by OP swab specimens was subjected to qPCR analysis to detect and identify M. pneumoniae. For blood, (5) Blood for Legionella serology. Due to the high rate of Legionella detection by serology, only a four-fold rise in titer ≥128 from acute to convalescent phase was accepted as positive. (7) Blood for mycoplasma serology (40-fold rise in IgG titer), (8) Urine for detection of S. mutans (Alere EinSawn®), (9) Urine for Legionella pneumophila serogroup 1 antigen detection (Alere BinaxNOW®).

Any pathogens isolated at the local laboratories were identified whenever possible to the genus and species level and submitted to the central microbiology laboratory for confirmatory identification and antibiotic susceptibility testing.

The distribution of pathogens identified at baseline from Blood Specimens, Respiratory Specimens, Urinary Antigen Tests, and Serology are shown below (Table 1).

### Table 1

**Pathogen Identification**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Solithromycin</th>
<th>Moxifloxacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>(107)</td>
<td>0.015</td>
</tr>
<tr>
<td>L. pneumophila</td>
<td>(64)</td>
<td>0.000032</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>(24)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

The most frequently identified pathogens were S. pneumoniae (23%), L. pneumophila (15%), M. catarrhalis (9%) and M. pneumoniae (9%).

**Susceptibility of the Most Frequently Identified CABP Pathogens (µg)**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>MIC Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>≤0.0008 - 0.50</td>
</tr>
<tr>
<td>L. pneumophila</td>
<td>≤0.000032 - 0.0025</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>≤0.12</td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>≤0.00006 - 32</td>
</tr>
</tbody>
</table>

The susceptibility of these isolates did not increase (4 µg/mL at baseline and 2 µg/mL on Day 7).

**Results**

When diagnosis was restricted to culture of blood, good quality respiratory specimens, and Legionella urinary antigen (the mITT-2 population), the following were observed: (File 2004; Neu 2004; 13. 24th Eur Congr Clin Microb Infect Dis; May 10-14, 2014; Barcelona, Spain, P1584).

- **Study Population**
  - Solithromycin: 800 (40%) vs. Moxifloxacin: 800 (40%)
  - Solithromycin: 800 (40%) vs. Moxifloxacin: 800 (40%)

- **ITT (Total study population)**
  - Solithromycin: 800 (40%) vs. Moxifloxacin: 800 (40%)

- **mITT (ITT population)**
  - Solithromycin: 800 (40%) vs. Moxifloxacin: 800 (40%)

### Conclusions

- In recent years, CABP caused by multi-drug resistant pathogens has been observed more frequently. Pneumococcal macrolide resistance, in particular, is now approximately 50% in the US (Morrissey 2014; Jones 2013). Therefore, there is an urgent need for additional antibacterial drugs with activity against these pathogens.
- This Phase 3, randomized, double-blind, multicenter, non-inferiority efficacy and safety study was conducted to evaluate oral solithromycin compared with oral moxifloxacin in the treatment of adult patients with CABP. Solithromycin demonstrated NI to moxifloxacin and a comparable treatment effect to moxifloxacin against the most frequently observed CABP pathogens.
- Using traditional and molecular methods, 54% of patients in the trial had a bacterial pathogen identified. Culture and serology confirmed many of the results from molecular methods, which supplemented the overall bacterial identification in this oral CABP trial, the first to use the new FDA guidance. Allowing many diagnostic methods enhanced the quality of the mITT population.
- Given its activity against common typical and atypical CABP pathogens including those with macrolide-resistance, solithromycin has the potential to restore macrolide activity for the effective treatment of CABP.