

Title: Results of a Global Phase 3 Trial Comparing Oral Solithromycin versus Oral Moxifloxacin for Treatment of Community-acquired Bacterial Pneumonia (CABP) in Adults

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Objective: Despite guidelines for antibiotic stewardship, antibiotic resistance in CABP is a looming problem. This study compares solithromycin, a fourth generation macrolide and the first fluoroketolide, to moxifloxacin.

Methods: This was a double-blind, randomized controlled trial enrolling adults with CABP, PORT Risk Class II, III or IV (NCT#01756339). Patients were randomized 1:1 to oral solithromycin (5 days) or oral moxifloxacin (7 days), with evaluations at Baseline, Day 4 to assess early clinical response (ECR), Day 7, Day 12-17 (short-term follow-up, or SFU visit), and Day 28 (long-term follow-up). An early clinical response was defined as improvement in at least 2 of 4 cardinal symptoms (cough, chest pain, dyspnea, sputum production) without worsening in any. Success at SFU was determined by investigators. Primary objectives were demonstration of non-inferiority (10% NI margin) at ECR in the intent to treat (ITT) population (FDA guidance) and at SFU in the ITT and clinically evaluable (CE) populations (EMA guidance).

Results: 860 patients from 16 countries were randomized (ITT population); 856 received at least one dose of study drug (safety population); a microbiological diagnosis was established in 54% (mITT population); and 90% met key study inclusion and exclusion criteria without confounding diagnoses and within pre-specified protocol windows for follow-up (CE population). Mean age of solithromycin patients was 58.5 years, with 36.4%  $\geq$  age 65, versus 56.7 years with 31.6%  $\geq$  age 65 for moxifloxacin. 50.7% of solithromycin patients had PORT III/IV disease (11.3% PORT IV), versus 48.6% of moxifloxacin patients (8.8% PORT IV). *Streptococcus pneumoniae* was the most commonly diagnosed pathogen (23%), followed by *Haemophilus influenzae* (16%), *Legionella pneumophila* (15%), *Mycoplasma pneumoniae* (9%), *Moraxella catarrhalis* (6%), and *Staphylococcus aureus* (4%).

Solithromycin was non-inferior to moxifloxacin in the ITT in ECR (78.2% versus 77.9%) and SFU success (84.5% versus 86.6%) and in the CE-SFU success (88.1% versus 91.3%). Comparative ECR success for solithromycin was more favorable among the pre-defined sub-group of patients  $\geq$  age 75 (83.9% vs 69.8%). Solithromycin demonstrated comparable safety to moxifloxacin in the occurrence of adverse events (AEs) (36.6% versus 35.6%), study-drug related AEs (10.1% versus 12.5%), Serious AEs (6.6% versus 6.3%; none attributed to study drug) and deaths (1.4% in both groups). Grade 4 ALTs ( $>8$ xULN) were observed in 5 moxifloxacin patients and 2 solithromycin patients. Two episodes of *Clostridium difficile* diarrhea were diagnosed, both in moxifloxacin recipients.

Conclusions: Oral solithromycin, the first fluoroketolide, was non-inferior to oral moxifloxacin for treatment of CABP, with greater relative success among older patients, despite treatment for 5 versus 7 days. Safety outcomes were comparable, although among moxifloxacin patients there were more Grade 4 ALT elevations and 2 episodes of *C. difficile* diarrhea. A return to macrolide monotherapy for CABP might be feasible in the future.