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Evaluation of early clinical response (ECR) as a primary endpoint for CABP: pooled analysis of phase 3 studies comparing solithromycin, a new macrolide, and moxifloxacin

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Background: Community-acquired bacterial pneumonia (CABP) is a common and serious infection requiring antibiotic therapy. There have been no new oral antibiotics approved for CABP in over a decade, although increasing resistance to existing macrolides and other classes of antibiotics has created a medical need for new treatments. Traditionally, primary endpoints in CABP studies have focused on investigator determination of response 10-14 days after initiation of treatment. This is the first set of studies conducted in CABP prospectively utilizing Early Clinical Response [ECR], a programmatic, symptom-based endpoint assessed 3-4 days after initiation of treatment, as the primary endpoint. Historical data have shown that the treatment effect of an antibiotic is most pronounced at an early time point.

Material/methods: Pooled analyses of two Phase 3, randomized, double-blind, noninferiority studies in CABP were conducted. In the first study, adult patients were randomized to oral solithromycin for 5 days (+2 days placebo) or oral moxifloxacin for 7 days. In the second study, adult patients received IV solithromycin or IV moxifloxacin for 7 days and were eligible to be switched to oral therapy within the 7 day treatment period when clinically stable. The primary endpoint for both studies was ECR, defined as improvement at 72 [-12/+36] hours after the first dose in at least 2 of the following 4 cardinal symptoms: cough, shortness of breath, chest pain, and difficulty with sputum production. Study

investigators also assessed patient clinical response at a follow-up visit 5-10 days after last dose as a secondary endpoint.

Results: Overall, 78.7% of patients in the solithromycin group (676/859) and 78.8% of patients in the moxifloxacin group (678/860) achieved ECR (treatment difference: -0.16; 95% CI: -4.0, 3.7) in the pooled studies. Solithromycin met the pre-specified non-inferiority margin of 10% in each trial. Results for the investigator assessment of clinical response also demonstrated that comparable percentages of solithromycin patients (84.6%, 727/859) and moxifloxacin patients (87.6%, 753/860) achieved clinical success 5-10 days following treatment. In a concordance analysis of these endpoints, ECR had a high positive predictive value (94.8%) for predicting clinical success at the later time point.

Conclusions: Solithromycin was non-inferior to moxifloxacin, a potent fluoroquinolone, in the treatment of CABP utilizing the ECR endpoint. Concordance analyses support the utility of this objective, symptom-based endpoint in assessing treatment effect at an earlier time point.