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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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Introduction and Objective

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 CAP 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 discernment of the differential treatment effects of antibiotics in non-fatal pneumonia are effectively accomplished at an early time point.

Solithromycin is a fourth-generation macrolide antibiotic, and the first fluoroketolide, and has been evaluated in two global Phase 3 CABP trials. These randomized, blinded trials enrolled >1700 adults with CABP between 2013 and 2015. SOLITAIRE-Oral evaluated a 5-day oral solithromycin regimen compared to a 7-day oral moxifloxacin regimen[1]. SOLITAIRE-IV evaluated 7-day IV or IV-to-Oral regimens of solithromycin compared to moxifloxacin[2].

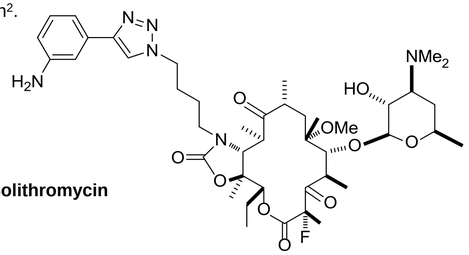

Figure 1: Solithromycin

Methods

Pooled analyses of two Phase 3, randomized, double-blind, noninferiority studies in CABP were conducted. Both studies enrolled adult patients with a diagnosis of CABP; randomization was stratified by geographic area, history of asthma and/or COPD, and PORT Risk Class (II vs III/IV). In SOLITAIRE-Oral, patients received oral solithromycin for 5 days (+2 days placebo) or oral moxifloxacin for 7 days. In SOLITAIRE-IV, 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 Early Clinical Response (ECR), defined as improvement at 72 [-12/+36] hours after the first dose in at least 2 of the following cardinal symptoms: cough, shortness of breath, chest pain, and difficulty with sputum production. Study investigators also assessed patient clinical response at a short-term follow-up (SFU) visit 5 to 10 days after last dose as a secondary efficacy endpoint.

Results

The SOLITAIRE Phase 3 trials were the first pneumonia studies to utilize the new FDA endpoint of ECR. Table 1 shows the symptom scoring used in these trials to programmatically determine the rate of early clinical response. Patients needed to improve in 2 of these symptoms, without worsening in any, to be considered a responder. Table 2 shows the pooled results at ECR as well as at SFU.

Table 1: Symptom Scores Used to Determine Early Clinical Response

Symptom	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
Cough	Resolution (to pre-CABP baseline) or absence of cough	Transient, did not interfere with normal activity	Frequent, interferes with normal activity or sleep	Constant, interferes with most or all activities or sleep
Dyspnea/ Shortness of Breath	Resolution (to pre-CABP baseline) or absence of dyspnea	Dyspnea on exertion (eg, climbing stairs)	Dyspnea with normal/routine activities (eg, walking)	Dyspnea at rest or requiring oxygen therapy
Chest Pain due to Pneumonia	Resolution or absence of chest pain related to CABP	Transient, does not interfere with normal activity	Frequent, interferes with normal activity or sleep	Constant, interferes with most or all activities or sleep
Difficulty with Sputum Production	Resolution (to pre-CABP baseline) or absence of sputum production	Sputum production rarely causes difficulty or distress	Sputum production often causes difficulty or distress	Constant difficulty with sputum production

Table 2: Response Rates at ECR and Investigator-assessed Clinical Responses at SFU

	Solithromycin		Moxifloxacin	
ITT population (overall) [a]	n/N	%	n/N	%
Early Clinical Response (ECR)	676/859	**78.7**	678/860	**78.8**
Clinical Response (SFU)	727/859	**84.6**	753/860	**87.6**

[a] Pooled data from two Phase 3 studies with similar designs and identical endpoints

A concordance analysis was performed looking at the results from each of these 2 timepoints, and is presented in Table 3. Positive and Negative Predictive Values, as well as sensitivity and specificity, were calculated and are presented in Table 4.

Table 3: Concordance Analysis, Comparing Outcomes between Early (ECR) and Late (SFU) Timepoints

	Investigator-assessed Clinical Response			
Early Clinical Response	Clinical Success	Clinical Failure	Indeterminate	Total
Responder	**1232 (71.6)**	68 (4.0)	42 (2.4)	1342
Non-Responder	222 (12.9)	**102 (5.9)**	6 (0.4)	330
Indeterminate	18 (1.1)	4 (0.2)	**26 (1.5)**	48
Total	1472	174	74	1720

Table 4: Predictive Values, Sensitivity and Specificity

Positive Predictive Value	**94.8%** 1232/(1232+68)
Negative Predictive Value	**31.5%** 102/(102+222)
Sensitivity	**84.7%** 1232/(1232+222)
Specificity	**60.0%** 102/(102+68)

Positive predictive value (PPV): of those patients who were an ECR responder, the percentage that were also a success at SFU

Negative predictive value (NPV): of those patients who were an ECR nonresponder, the percentage that were also a failure at SFU

Sensitivity: of those patients who were a clinical success at SFU, the percentage that were also an ECR responder

Specificity: of those patients who were a clinical failure at SFU, the percentage that were also an ECR nonresponder

Conclusions

- ECR was demonstrated to robustly predict treatment success with a Positive Predictive Value of 94.8%
- The low Negative Predictive Value (31.5%) is expected, as many patients who are not improved at an early time point are expected to improve by a later time point
- 12.9% of patients were non-responders at ECR who were considered successes at SFU. This result leads to the somewhat low overall concordance rate of 79% (71.6% + 5.9% + 1.5%)

References

1. Barrera CM, Mykietiuk A, Metev H, Nitu MF, Karimjee N, Doreski PA, et al. Efficacy and safety of oral solithromycin versus oral moxifloxacin for treatment of community-acquired bacterial pneumonia: a global, double-blind, multicentre, randomised, active-controlled, non-inferiority trial (SOLITAIRE-ORAL). *Lancet Infect Dis* 2016 16(4):421:430.
2. File TM, Rewerska B, Vucinic-Mihailovic V, Gonong JR, Das AF, Keedy K, Taylor D, Sheets A, Fernandes P, Oldach D, Jamieson BD. SOLITAIRE-IV: A Randomized, Double-Blind, Multi-Center Study Comparing the Efficacy and Safety of Intravenous-to-Oral Solithromycin to Intravenous-to-Oral Moxifloxacin for Treatment of Community-acquired Bacterial Pneumonia. *Clin Infect Dis.* 2016 Oct 15;63(8): 1007-1016.

Disclosures

These phase 3 CABP trials were conducted by and funded by Cempra, Inc. Brian Jamieson and David Oldach are employees of Cempra, Inc. Kavita Aggarwal and Prabhavathi Fernandes are former employees of Cempra, Inc.