Objective: To evaluate the activity of solithromycin, a fourth generation macrolide and a novel fluoroketolide, tested against a contemporary (2012) collection of serotyped United States (USA) macrolide-resistant \textit{S. pneumoniae} isolates associated with community-acquired bacterial pneumonia. Solithromycin was designed to overcome macrolide-resistant \textit{S. pneumoniae}. With the introduction of new pneumococcal conjugate vaccines, the serotype distribution of \textit{S. pneumoniae} has been dynamic in recent years, and hence monitoring the activity of new agents against circulating serotypes is prudent.

Methods: A total of 272 macrolide-resistant (erythromycin MIC, $\geq 1 \text{ mg/L}$) \textit{S. pneumoniae} collected during 2012 from 49 medical centers (35 states) across the USA were included (SENTRY Antimicrobial Surveillance Program). Isolates were recovered from lower respiratory tract specimens (82.7%) and blood cultures (17.3%) in patients across all age groups with a diagnosis of community-acquired bacterial pneumonia. Species identification was performed using biochemical test algorithms and/or PCR assays. Serotyping was performed by \textit{cpsB} sequencing and multiplex PCR methodology. Susceptibility testing applied CLSI methods (M07-A9) and interpretations were performed using CLSI M100-S23 (2013) breakpoint criteria.

Results: Against all 272 isolates, solithromycin demonstrated high potency (MIC$_{50/90}$, 0.06/0.25 mg/L) and inhibited all strains at MIC values $\leq 0.5$ mg/L. Although potency remained high, solithromycin activity was slightly lower against the two most prevalent serotypes - 19A (MIC$_{50/90}$, 0.25/0.25 mg/L) and 35B (MIC$_{50/90}$, 0.12/0.25 mg/L) compared to other serotypes and the overall population (Table). In total, 29 serotypes/serogroups were represented in this population. Penicillin resistance by CLSI oral penicillin V criteria ($\geq 2 \text{ mg/L}$) was high overall (39.0%) and extremely high in serotype 19A (91.2%) and serotype 35B (82.4%) isolates. Ceftriaxone-nonsusceptibility ($\geq 2 \text{ mg/L}$, CLSI non-meningitis criteria) was 19.9% overall and very high in serotype 19A (67.6%), but not serotype 35B (2.9%) isolates.

Conclusions: Solithromycin demonstrated sustained activity against a geographically diverse set of macrolide-resistant \textit{S. pneumoniae} isolated from patients with CABP across the USA in 2012. Solithromycin was shown to be very active against the two most prevalent macrolide-resistant serotypes (19A and 35B) in addition to the other prevalent serotypes/serogroups present in the overall population. These data support and encourage the continued clinical development of solithromycin for the treatment of multidrug resistant community-acquired bacterial pneumonia.