F1-2035

# First Year Antimicrobial Surveillance Results for CEM-101, a Novel Fluoroketolide with Potent Activity Against Pathogens Associated with Community-acquired Bacterial Pneumonia

*RN JONES, HS SADER, MJ JANECHEK, GJ MOET*
JMI Laboratories, North Liberty, Iowa, USA

ICAAC 2009
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, 319.665.3371
ronald-jones@jmilabs.com

## Abstract

**Background**: CEM-101 is a newly developed fluoroketolide with an unusually wide spectrum against pathogens associated with community-acquired bacterial pneumonia (CABP). CEM-101 has a potency generally equal to or 2-fold greater than telithromycin (TEL) or $MLS_B$ agents. We report results from a global study of CEM-101 potency and resistance (R) rates for 2008.

**Methods**: 2,901 CABP isolates of *S. pneumoniae* (SPN; 1738), *H. influenzae* (HI; 976) and *S. aureus* (SA; 187) were susceptibility (S) tested by CLSI broth microdilution methods with categorical interpretations (M07-A8, M100-S19) against CEM-101 and >25 comparators. The geographic samples included 1362 strains from the USA, 1273 from Europe (EU) and 266 from Latin America (LA).

**Results**: Organism population characteristics were: SPN penicillin-R (≥2 µg/ml) ranged from 15.9 (LA) to 23.0% (USA), HI β-lactamase production at 14.7 (EU) to 25.4% (USA), and MRSA rates at 40.9 (LA) to 55.0% (USA). Other SPN-R rates were (USA/EU/LA in %); erythromycin (40.0/36.3/20.0), levofloxacin (LEV; 0.6/1.8/0.7), amoxicillin/clavulanate (17.8/8.2/12.4) and ceftriaxone (CRO; 9.7/8.3/4.8). CEM-101 was very potent versus SPN ($MIC_{50}$, 0.015 µg/ml), more potent than TEL and against SA ($MIC_{50}$, 0.06 µg/ml). At the USA-FDA breakpoints for TEL, CEM-101 showed broader coverage for SPN (100.0 vs. 99.8%), HI (99.1 vs. 98.7%) and SA (70.1 vs. 69.5%). These ketolide-S rates were greater than LEV, CRO and all marketed $MLS_B$ agents.

| Pathogen (no. tested) | MIC (µg/ml) | | Cum. % inhibited at CEM-101 MIC: | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 50% | 90% | ≤0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 |
| HI (976) | 1 | 2 | 0.1 | 0.1 | 0.2 | 0.9 | 10.1 | 73.3 | 96.8 |
| SPN (1738) | 0.015 | 0.25 | 80.3 | 87.3 | 89.6 | 97.4 | 99.8 | 100.0 | - |
| SA (187) | 0.06 | >4 | 20.3 | 63.1 | 69.5 | 69.5 | 70.1 | 70.1 | 71.1 |

**Conclusions**: CEM-101 showed wide coverage of CABP pathogens in a three continent sample. High potency and spectrum of activity make CEM-101 a promising parenteral/oral candidate for further study as a therapeutic agent for CABP.

## Introduction

CEM-101 (formerly OP-1068) is a novel macrolide-ketolide class agent selected as a candidate for oral and parenteral therapy of community-acquired respiratory tract infections (CA-RTI). In vitro screening studies indiciated a potency comparable or superior to telithromycin, cethromycin, erythromycin, azithromycin and clarithromycin, as well as activity against Gram-positive isolates having documented resistances to macrolides or lincosamides.

CEM-101 activity is generally focused against Gram-positive pathogens, but it also possesses measurable potencies versus fastidious Gram-negative species (*Haemophilus, Moraxella*), some Enterobacteriaceae (Salmonella, Shigella), atypical respiratory tract species, *Helicobacter pylori*, telithromycin-resistant streptococci, and pathogens causing various sexually transmitted diseases (STD).

In this presentation, we report CEM-101 activity measured by reference Clinical and Laboratory Standards Institute (CLSI) methods when testing organisms associated with CA-RTI (streptococci, *Haemophilus* spp. and *Staphylococcus aureus*), emerging resistance subsets and various patterns of $MLS_B$-ketolide resistance found among the tested organisms collected from an international surveillance program in 2008.

## Materials and Methods

Organisms tested: All organisms tested in this 2008 CEM-101 surveillance program were collected from patients in the United States (USA), Europe and Latin America (LA). The sources of these strains were pathogens isolated from CA-RTI e.g. the most common bacterial species (*Streptococcus pneumoniae, H. influenzae* and *S. aureus*). The distribution of pathogens and the geographic contributions were:

- *S. pneumoniae* (1,738)
  - geography: USA (765), Europe (828), and LA (145)
  - penicillin-susceptible, ≤0.06 µg/ml (1,116)
  - penicillin-intermediate, 0.12-1 µg/ml (251)
  - penicillin-resistant, ≥2 µg/ml (371)
- *H. influenzae* (976)
  - geography: USA (448), Europe (429) and LA (99)
  - β-lactamase-positive (192), 19.7%
  - β-lactamase-negative (784)
- *S. aureus* (187)
  - geography: USA (149), Europe (16) and LA (22)
  - methicillin-resistant (MRSA; 99), 52.9%
  - methicillin-susceptible (MSSA; 88)

Susceptibility testing: All susceptibility tests were performed by CLSI broth microdilution methods (M07-A8, 2009) by a central monitoring CLIA/GLP-compliant laboratory (JMI Laboratories, North Liberty, Iowa, USA). Testing used three media types: cation-adjusted Mueller-Hinton broth (CA-MHB) with 2.5-5% lysed horse blood (for testing streptococci), Haemophilus Test Medium (HTM; for testing *H. influenzae*) and CA-MHB without supplements for *S. aureus*. CLSI M100-S19 was utilized to interpret MIC results to susceptibility categories and for quality control (QC) ranges, where criteria were available. Tested QC strains included: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619 and *H. influenzae* ATCC 49247 and 49677. All QC results were within published limits.

A wide variety of comparison agents were utilized including: amoxicillin/clavulanate, ceftriaxone, cefuroxime, penicillin, tetracycline, vancomycin, ampicillin, oxacillin, gentamicin, azithromycin, cefdinir, clarithromycin, clindamycin, erythromycin, levofloxacin, linezolid, quinupristin/dalfopristin, telithromycin and trimethoprim/sulfamethoxazole (TMP/SMX), all assessed by the broth microdilution method.

## Results

- Activity of CEM-101 was characterized against a recent *S. pneumoniae* collection (2008) that had the following resistance profile: erythromycin (36.4% resistant), clindamycin (20.0%), tetracycline (25.8%), TMP/SMX (21.7%), amoxicillin/clavulanate (8.6%; 14.0% in USA), and levofloxacin (1.1%); see Table 2.
- Direct comparison of CEM-101 versus another ketolide (telithromycin, Table 1), shows a potency advantage and pathogen coverages greater on a by weight basis. All telithromycin non-susceptible pneumoccocci (MIC, ≥2 µg/ml) had CEM-101 MIC values at ≤1 µg/ml. *H. influenzae* (two-fold) and *S. aureus* CA-RTI isolates were also more susceptible to CEM-101 when compared to telithromycin (Tables 1 and 2).
- CEM-101 demonstrated potency and/or spectrum improvements compared to all tested macrolides or clindamycin versus these three pathogens (Table 3).

Table 1. Direct comparisons of two ketolides (CEM-101 and telithromycin) tested against CABP pathogens (2,901 strains overall).

| Pathogen (no. tested)/ Ketolide | Cumulative % inhibited at MIC (µg/ml): | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | ≤0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 |
| *S. pneumoniae* (1,738) | | | | | | | | | |
| CEM-101 | 80.3 | 87.3 | 89.6 | 97.4 | 99.8 | 100.0[b] | 100.0 | 100.0 | 100.0 |
| Telithromycin | -[a] | 80.8 | 85.0 | 94.4 | 99.0 | 99.9[b] | 100.0 | 100.0 | 100.0 |
| *H. influenzae* (976) | | | | | | | | | |
| CEM-101 | 0.1 | 0.1 | 0.2 | 0.9 | 10.1 | 73.3 | 96.8 | 99.1[b] | 99.5 |
| Telithromycin | - | 0.1 | 0.1 | 1.3 | 4.9 | 48.1 | 89.3 | 98.7[b] | 99.2 |
| *S. aureus* (187) | | | | | | | | | |
| CEM-101 | 20.3 | 63.1 | 69.5 | 69.5 | 70.1 | 70.1[b] | 71.1 | 71.1 | - |
| Telithromycin | - | - | - | 67.9 | 69.0 | 69.5[b] | 70.3 | - | - |

a. - = untested concentration.
b. Existing or projected susceptible breakpoint MIC.

Table 2. Comparative in vitro activity of CEM-101 tested against *S. pneumoniae* (1,738 strains), *H. influenzae* (976 strains) and *S. aureus* (187 strains) isolated from patients with respiratory tract infections (CABP) in 2008.

| Organism (no. tested)/ Antimicrobial agent[a] | MIC (µg/ml) | | | % by category:[b] |
|---|---|---|---|---|
| | 50% | 90% | Range | Susceptible/Resistant |
| *S. pneumoniae* (1,738) | | | | |
| CEM-101 | 0.015 | 0.25 | ≤0.008-1 | 100.0/0.0 |
| Amox/Clav | ≤1 | 4 | ≤1-16 | 87.2/8.6 |
| Cefdinir | ≤0.06 | 8 | ≤0.06->8 | 74.2/23.8 |
| Ceftriaxone | ≤0.25 | 1 | ≤0.25-8 | 91.4/1.4 |
| Cefuroxime | ≤1 | 8 | ≤1->8 | 87.2/3.3 |
| Clindamycin | ≤0.25 | >2 | ≤0.25->2 | 79.6/20.0 |
| Erythromycin | ≤0.06 | >8 | ≤0.06->8 | 63.4/36.4 |
| Levofloxacin | 1 | 2 | ≤0.5->4 | 98.8/1.1 |
| Penicillin | ≤0.03 | 4 | ≤0.03->4 | 64.2/21.3 |
| Telithromycin | ≤0.06 | 0.25 | ≤0.06-2 | 99.0/0.0 |
| Tetracycline | ≤2 | >8 | ≤2->8 | 73.2/25.8 |
| TMP/SMX | ≤0.5 | >2 | ≤0.5->2 | 66.7/21.7 |
| Vancomycin | ≤1 | ≤1 | ≤1 | 100.0/- |
| *H. influenzae* (976) | | | | |
| CEM-101 | 1 | 2 | 0.03->16 | 99.1/0.5 |
| Amox/Clav | ≤1 | ≤1 | ≤1-8 | 99.9/0.1 |
| Ampicillin | ≤1 | 16 | ≤1->16 | 80.0/18.9 |
| Azithromycin | 1 | 2 | ≤0.5->4 | 98.9/- |
| Cefdinir | 0.12 | 0.5 | ≤0.06-4 | 98.5/- |
| Ceftriaxone | ≤0.25 | ≤0.25 | ≤0.25-0.5 | 100.0/- |
| Cefuroxime | ≤1 | 2 | ≤1->8 | 99.2/0.1 |
| Clarithromycin | 8 | 16 | ≤0.25->32 | 83.1/2.2 |
| Levofloxacin | ≤0.5 | ≤0.5 | ≤0.5-4 | 99.7/- |
| Telithromycin | 2 | 4 | ≤0.06->8 | 98.7/0.8 |
| Tetracycline | ≤2 | ≤2 | ≤2->8 | 98.5/1.1 |
| TMP/SMX | ≤0.5 | >2 | ≤0.5->2 | 79.4/17.5 |
| *S. aureus* (187) | | | | |
| CEM-101 | 0.06 | >4 | ≤0.03->4 | 70.1/28.9 |
| Oxacillin | >2 | >2 | ≤0.25->2 | 47.1/52.9 |
| Ceftriaxone | 16 | >32 | 1->32 | 47.1/52.9 |
| Clindamycin | ≤0.25 | >2 | ≤0.25->2 | 69.5/29.9 |
| Erythromycin | >4 | >4 | ≤0.25->4 | 32.6/66.8 |
| Gentamicin | ≤2 | ≤2 | ≤2->8 | 95.2/4.8 |
| Levofloxacin | 4 | >4 | ≤0.5->4 | 48.1/51.9 |
| Linezolid | 2 | 2 | 0.5-4 | 100.0/- |
| Quin/Dalfo | 0.5 | 1 | ≤0.25-1 | 100.0/0.0 |
| Telithromycin | ≤0.25 | >2 | ≤0.25->2 | 69.5/29.9 |
| Tetracycline | ≤2 | ≤2 | ≤2->8 | 93.1/5.9 |
| TMP/SMX | ≤0.5 | ≤0.5 | ≤0.5->2 | 97.3/2.7 |
| Vancoymcin | 1 | 1 | 0.5-2 | 100.0/0.0 |

a. Amox/Clav = amoxicillin/clavulanate, TMP/SMX = trimethoprim/sulfamethoxazole, - = no interpretive criteria for this category, and Quin/Dalfo = quinupristin/dalfopristin.
b. Interpreive criteria as published in CLSI M100-S19 (2009) with telithromycin breakpoints applied to CEM-101 for comparison purposes only. Penicillin criteria are those listed for oral penicillin V therapy.

- Tables 3 and 4 show modest differences between geographic sampling, where *S. pneumoniae* from the USA ($MIC_{90}$, 0.25 µg/ml) were slightly more resistant to CEM-101 and telithromycin compared to strains from Europe and LA. Furthermore, telithromycin was less active against *H. influenzae* from the USA, while CEM-101 and azithromycin had equal potency across all sampled regions.
- CEM-101 activity was not adversely influenced by β-lactamase production in *H. Influenzae*; however, penicillin-non-susceptible *S. pneumoniae* and MRSA trended toward higher $MIC_{50}$ and $MIC_{90}$ values (Table 4). This was also noted for macrolides, clindamycin and telithromycin (data not shown).

Table 4. CEM-101 results comparing effect of various resistance phenotypes on potency.

| Pathogen/resistance subset (no. tested) | CEM-101 MIC (µg/ml) | | | % inhibited at MIC (µg/ml): | | | |
|---|---|---|---|---|---|---|---|
| | 50% | 90% | Range | ≤0.5 | 1 | 2 | 4 |
| *S. pneumoniae* | | | | | | | |
| USA (765) | 0.015 | 0.25 | ≤0.008-0.5 | 100.0 | - | - | - |
| Europe (828) | 0.015 | 0.06 | ≤0.008-1 | 99.5 | 100.0 | - | - |
| LA (145) | 0.015 | 0.06 | ≤0.008-0.5 | 100.0 | - | - | - |
| Penicillin-susceptible (1,116) | 0.015 | 0.03 | ≤0.008-1 | 99.9 | 100.0 | - | - |
| Penicillin-intermediate (251) | 0.015 | 0.12 | ≤0.008-0.5 | 100.0 | - | - | - |
| Penicillin-resistant (371) | 0.06 | 0.25 | ≤0.008-1 | 99.2 | 100.0 | - | - |
| *H. influenzae* | | | | | | | |
| USA (448) | 1 | 2 | 0.03-8 | 9.2 | 67.0 | 95.5 | 99.6 |
| Europe (429) | 1 | 2 | 0.12->16 | 11.7 | 76.7 | 97.9 | 98.6 |
| LA (99) | 1 | 2 | 0.5->16 | 8.1 | 86.9 | 98.0 | 99.0 |
| β-lactamase-positive (192) | 1 | 2 | 0.03-4 | 10.9 | 72.9 | 98.4 | 100.0 |
| β-lactamase-negative (784) | 1 | 2 | 0.12->16 | 10.0 | 73.3 | 96.4 | 98.9 |
| *S. aureus* | | | | | | | |
| USA (149) | 0.06 | >4 | ≤0.03->4 | 69.1 | 69.1 | 69.8 | 69.8 |
| Europe (16) | 0.06 | 0.12 | ≤0.03->4 | 93.8 | 93.8 | 93.8 | 93.8 |
| LA (22) | 0.06 | >4 | ≤0.03->4 | 59.1 | 59.1 | 63.6 | 63.6 |
| MRSA (99) | 0.12 | >4 | ≤0.03->4 | 53.5 | 53.5 | 53.5 | 53.5 |
| MSSA (88) | 0.06 | 2 | ≤0.03->4 | 88.6 | 88.6 | 90.9 | 90.9 |

Table 3. Regional variations in the actiivty of CEM-101, telithromycin, clindamycin and macrolides when testing three CABP pathogens by reference broth microdilution methods.

| Organism/ antimicrobial agent | MIC (µg/ml) results by region: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | USA | | | Europe | | | Latin America | | |
| | 50% | 90% | %susceptible[a] | 50% | 90% | %susceptible | 50% | 90% | %susceptible |
| *S. pneumoniae* (no. tested) | (765) | | | (828) | | | (145) | | |
| CEM-101 | 0.015 | 0.25 | 100.0 | 0.015 | 0.06 | 100.0 | 0.015 | 0.06 | 100.0 |
| Telithromycin | ≤0.06 | 0.25 | 100.0 | ≤0.06 | 0.12 | 99.9 | ≤0.06 | 0.12 | 100.0 |
| Clindamycin | ≤0.25 | >2 | 78.0 | ≤0.25 | >2 | 78.1 | ≤0.25 | ≤0.25 | 95.9 |
| Erythromycin | ≤0.06 | >8 | 60.0 | ≤0.06 | >8 | 63.7 | ≤0.06 | >8 | 80.0 |
| *H. influenzae* (no. tested) | (448) | | | (429) | | | (99) | | |
| CEM-101 | 1 | 2 | 99.6 | 1 | 2 | 98.6 | 1 | 2 | 99.0 |
| Telithromycin | 2 | 4 | 99.1 | 1 | 2 | 98.6 | 1 | 2 | 97.0 |
| Azithromycin | 1 | 2 | 99.3 | 1 | 2 | 98.4 | 1 | 2 | 99.0 |
| Clarithromycin | 8 | 16 | 77.0 | 8 | 16 | 88.1 | 8 | 16 | 88.9 |
| *S. aureus* (no. tested) | (149) | | | (16) | | | (22) | | |
| CEM-101 | 0.06 | >4 | 69.1 | 0.06 | 0.12 | 93.8 | 0.06 | >4 | 59.1 |
| Telithromycin | ≤0.25 | >2 | 68.5 | ≤0.25 | 1 | 93.8 | ≤0.25 | >2 | 59.1 |
| Clindamycin | ≤0.25 | >2 | 68.5 | ≤0.25 | ≤0.25 | 93.8 | ≤0.25 | >2 | 59.1 |
| Erythromycin | >4 | >4 | 28.2 | 0.5 | >4 | 50.0 | 0.5 | >4 | 50.0 |

a. All susceptibility criteria are those published by the CLSI (2009) and for CEM-101 the telithromycin breakpoints were applied for comparison purposes only.

## Conclusions

- CEM-101, a novel fluoroketolide, when tested against contemporary CA-RTI pathogens (2008) demonstrated greater potency and potential spectrum coverage compared to macrolides, clindamycin and telithromycin
  - *S. pneumoniae*: $MIC_{50}$, 0.015 µg/ml and all MIC values at ≤1 µg/ml
  - *H. influenzae*: $MIC_{50}$, 1 µg/ml and 99.1% of strains inhibited at ≤4 µg/ml (telithromycin breakpoint)
  - *S. aureus*: $MIC_{50}$, 0.06 µg/ml, 70.1% inhibited at ≤1 µg/ml and a coverage (70.1% susceptible) equal to clindamycin.
- CEM-101 appears to be a very promising agent for therapy of CABP (CA-RTI) pending further studies of pharmacokinetic/pharmacodynamic features (parenteral and oral therapy), class-related adverse events and toxicities. Atypical pathogens associated with CABP/CA-RTI have also been documented as markedly susceptible to CEM-101 (Waites et al., 2009).

## References

1. Brinker AD, Wassel RT, Lyndly J, Serrano J, Avigan M, Lee WM, Seeff LB (2009). Telithromycin-associated hepatotoxicity: Clinical spectrum and causality assessment of 42 cases. *Hepatology* 49: 250-257.
2. Clinical and Laboratory Standards Institute (2009). *M07-A8. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - eighth edition.* Wayne, PA: CLSI.
3. Clinical and Laboratory Standards Institute (2009). *M100-S19. Performance standards for antimicrobial susceptibility testing. 19th informational supplement* Wayne, PA: CLSI.
4. Farrell DJ, Klugman KP, Pichichero M (2007). Increased antimicrobial resistance among nonvaccine serotypes of *Streptococcus pneumoniae* in the pediatric population after the introduction of 7-valent pneumococcal vaccine in the United States. *Pediatr Infect Dis J* 26: 123-128.
5. Glocker E, Bogdan C, Kist M (2007). Characterization of rifampicin-resistant clinical *Helicobacter pylori* isolates from Germany. *J Antimicrob Chemother* 59: 874-879.
6. Jones RN, Biedenbach DJ, Rhomberg PR, Fritsche TR, Sader HS (2008). Antimicrobial characterization of CEM-101 activity against 331 respiratory tract pathogens including multidrug-resistant pneumococcal serogroup 19A (MDR-19A) isolates. Abstr. F1-3975. *48th ICAAC*, Washington, D.C., USA.
7. Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A, Thomas AR, Harrison LH, Bennett NM, Farley MM, Facklam RR, Jorgensen JH, Besser J, Zell ER, Schuchat A, Whitney CG (2006). Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med* 354: 1455-1463.
8. McGhee P, Nagai K, Appelbaum PC (2008). Activity of CEM-101 compared to other agents against macrolide-susceptible and resistant streptococci. abstr. F1-3974. *48th ICAAC, October 25-28, 2008*, Washington DC, USA.
9. Raney PM, Tenover FC, Carey RB, McGowan JE, Jr. Patel JB (2006). Investigation of inducible clindamycin and telithromycin resistance in isolates of beta-hemolytic streptococci. *Diagn Microbiol Infect Dis* 55: 213-218.
10. Waites KB, Crabb DM, Duffy LB (2009). Comparative in vitro susceptibilities of human mycoplasmas and ureaplasmas to a new investigational ketolide, CEM-101. *Antimicrob Agents Chemother* 53: 2139-2141.
11. Wierzbowski AK, Karlowsky JA, Hoban DJ, Zhanel GG (2009). In vitro activity of the investigational ketolide cethromycin against macrolide- and penicillin-resistant *Streptococcus pneumoniae*: review of the 1998 to 2006 Canadian Respiratory Organism Susceptibility Study (CROSS). *J Antimicrob Chemother* 63: 620-622.
12. Young H, Moyes A, McMillan A (1997). Azithromycin and erythromycin resistant *Neisseria gonorrhoeae* following treatment with azithromycin. *Int J STD AIDS* 8: 299-302.