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

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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).

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