



# Neue Makrolide/Ketolide und Oxazine

# Neue Makrolide/Ketolide und Oxazine

| Code       | Name                | Gruppe                | Wirksam gegen  | Abstract  |
|------------|---------------------|-----------------------|--|---|
| CEM-101    | --                  | Ketolid               | Staphylokokken<br>Streptokokken<br><i>Chlamydia pneumoniae</i> | <a href="#">D-2250</a> ; <a href="#">F1-3974</a> ; <a href="#">F1-3975</a> ;<br><a href="#">F1-3976</a> ; <a href="#">F1-3977</a> ;<br><a href="#">F1-3978</a> ; <a href="#">F1-3979</a> ; <a href="#">F1-3980</a> ;<br><a href="#">F1-3981</a> ; <a href="#">F1-3982</a> ; <a href="#">F1-3984</a> |
| EDP-420    | Bicyclolid          | Bizyklisches Makrolid | <i>S. pyogenes</i><br><i>S. pneumoniae</i>                     | <a href="#">A-022</a> ; <a href="#">F1-3972</a>   |
| --         | Cethromycin         | Ketolid               | Streptokokken<br><i>Clostridium difficile</i>                  | <a href="#">A-3561</a> ; <a href="#">C1-1960</a> ; <a href="#">C1-3842</a> ;<br><a href="#">C2-256</a> ; <a href="#">L-683</a>  |
| RWJ-416457 | Oxazolidinon        | Oxazin                | <i>Chlamydia spp.</i>  | F1-205  |
| PA-824     | Nitroimidazo-oxacin | Oxazin                | Mykobakterien  | <a href="#">B-881</a>   |
| TR700      | TR701 Prodrug       | Oxazin                | Enterokokken<br>Staphylokokken                                 | <a href="#">F1-2060</a> ; <a href="#">F1-2061</a> ;<br><a href="#">F1-2068</a> ; <a href="#">F1-2069</a>  |
| TR701      | Oxazolidinon        | Oxazin                | Enterokokken<br>Staphylokokken                                 | <a href="#">F1-2063</a> ; <a href="#">F1-2064</a> ;<br><a href="#">F1-2065</a> ; <a href="#">F1-2066</a><br><a href="#">F1-2069a</a>  |

# A-022

## Comparative Efficacy of EDP-420, Telithromycin, Cethromycin and Linezolid Against Murine Skin Abscess Induced by *Streptococcus pyogenes*

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**Background:** The high incidence of resistance of *S. pyogenes* has limited the utility of existing macrolide antibiotics, left few empirical therapeutic options and challenged the newer class of macrolide agent development. EDP-420, a new bicyclolide (bridged bicyclic macrolide), is highly active against two principal mechanisms of macrolide resistance *in vitro*. **Methods:** Skin abscesses were induced in mice by subcutaneous inoculation of *S. pyogenes*. Treatment was initiated immediately, 24 and 48 hours after inoculation. Skin abscess protection rate and bacterial burden in abscesses were compared at the end of experiments. CFU reduction from established abscess (four days post inoculation) after four day treatments against *S. pyogenes* have been compared. Single dose pharmacokinetics of EDP-420 in plasma, normal skin and abscess tissue were also compared.

**Results:** EDP-420 was more effective than telithromycin, cethromycin and linezolid against *S. pyogenes* mefA abscess with PD<sub>50s</sub> of 16.3, >100, 50.1 and 85.2 mg/kg, respectively. PD<sub>50s</sub> of EDP-420, telethromycin, cethromycin and linezolid against *S. pyogenes* ermB abscess were 7.1, >100, 50.6 and 7.1 mg/kg, respectively. EDP-420 exhibited better bacterial clearance from the established abscess model than linezolid.

**Conclusions:** EDP-420 demonstrated better efficacy against two mechanisms of macrolide resistance strains of *S. pyogenes* in murine abscess than currently marketed ketolide and oxazolidinone. EDP-420 is potentially a potent antibiotic for treatment of skin and soft tissue infections.

# A-3561

## A Thorough QT Study to Define the ECG Effects of Cethromycin (CER) Using a Clinical and a Supratherapeutic Dose Compared to Placebo and Moxifloxacin (MFX) in Healthy Subjects (CL07-001)

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**Background:** The objective of this trial was to evaluate the effect of CER on cardiac repolarization, as measured by QTc prolongation in healthy subjects.

**Methods:** 238 subjects were randomly assigned to receive the therapeutic CER dose (300 mg QD), a supratherapeutic CER dose (900 mg QD), MFX (400 mg x1) or placebo. Digital ECGs were obtained on day -1 (baseline) and on day 5 of therapy. PK sampling took place on day 1 and day 5. The primary endpoint was the time-matched change from baseline in QTc interval based on an individual correction (QTcl) method that provides an optimization of QT correction for heart rate as compared to the fixed exponent approaches of Bazett or Fridericia.

**Results:** The ECG results summarizing the mean change from baseline at day 5 steady state are shown below. Assay sensitivity was demonstrated and no confidence intervals exceeded 10 ms in the CER dose groups. PK/PD modelling did not show any exposure effect relationship.

**Conclusions:** CER showed no signal of any effect on AV conduction, depolarization or cardiac repolarization as measured by the PR, QRS or QTcl or QTcF interval durations. There was no effect on heart rate in the CER therapeutic dose group at steady state. However, in the supratherapeutic dose group there was a 10 bpm increase requiring use of the primary QTcl endpoint for detection of any effect on cardiac repolarization.

The MFX positive control group demonstrated the expected small change in QTc duration and the placebo group's change from baseline was within 2 ms for QTcl.

|                         | All Subjects | Placebo | MFX<br>400 mg x1 | CER<br>300 mg QD | CER<br>900 mg QD |
|-------------------------|--------------|---------|------------------|------------------|------------------|
| Total N                 |              | 59      | 59               | 59               | 56               |
| $\Delta$ QTcl* (ms)     |              | -1.6    | 4.9              | -0.4             | 0.9              |
| Heart Rate in bpm       |              | 1.6     | 2.6              | 4.4              | 11.3             |
| QTcl new >500 ms N      |              | 0       | 1 (2%)           | 0                | 0                |
| QTcl new >480 ms N (%)  |              | 0       | 0                | 0                | 0                |
| QTcl 30-60 ms inc N (%) |              | 1 (2%)  | 4 (7%)           | 1 (2%)           | 1 (2%)           |
| QTcl >60 ms inc (N)     |              | 0       | 0                | 0                | 0                |

# B-881

## A Novel Phosphate-Starvation Model of *M. tuberculosis* Dormancy

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**Background:** *Mycobacterium tuberculosis* (*Mtb*) may encounter inorganic phosphate ( $P_i$ ) limitation in macrophage phagolysosomes. We studied *Mtb* growth during  $P_i$  limitation and susceptibility of  $P_i$ -starved bacilli to isoniazid (INH). We studied the *Mtb* transcriptome induced by  $P_i$  starvation and identified genes required for bacillary survival under  $P_i$ -limited conditions *in vitro*, and in mouse and guinea pig lungs.

**Methods:** *Mtb* CDC1551 was grown in 7H9 media containing a range of  $P_i$  concentrations. *Mtb* cultures were deprived of  $P_i$  for 21-42 days and treated with INH for 7 days before colony counting. *Mtb* RNA was extracted from cultures 24 and 72 hrs after  $P_i$  starvation, and genome-wide microarrays and quantitative RT-PCR were used to assess relative gene expression. A pool of 17 *Himar1* transposon (Tn) mutants was used in aerosol infections of mice and guinea pigs, and mutant survival was assessed by PCR.

**Results:**  $P_i$  limitation restricts *Mtb* growth in a dose-dependent manner. The minimum inhibitory concentration to INH is >100-fold higher for  $P_i$ -starved bacilli relative to log-phase-growing bacilli.  $P_i$  starvation leads to a doubling in bacillary length, as demonstrated by transmission electron microscopy. The *Mtb* regulatory genes *senX3*, *regX3*, *ppk*, *mprA*, *relA*, and *sigE*, and the phosphate transport genes *pstS1*, *pstS2*, and *pstA1* are induced after  $P_i$  starvation. Tn mutants with mutations in *senX3* and *regX3* showed a survival defect under  $P_i$ -limited conditions, and in mouse and guinea pig lungs.

**Conclusions:**  $P_i$  starvation of *Mtb* leads to dormancy, characterized by growth restriction, morphological changes, and phenotypic tolerance to INH. Gene expression analysis of  $P_i$ -starved bacilli suggests accumulation of inorganic polyphosphate, which has been implicated in bacterial growth restriction. The regulatory system *senX3-regX3* appears to be responsible for sensing and regulating the adaptive response to  $P_i$  limitation. This regulatory system is essential for *in vivo* survival of *Mtb*, suggesting that the microenvironment during *in vivo* infection is  $P_i$ -limited.

# C1-1960

## Activity of Cethromycin and Comparators versus Defined Phenotypes of *Streptococcus pneumoniae* (SPN) Obtained from Hospitals Across Canada: Results from 2007 CANWARD Study

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**Background:** Cethromycin is a new ketolide, specifically designed to overcome macrolide resistance in SPN. The purpose of this study was to compare the activity of cethromycin to telithromycin and clarithromycin against SPN with various macrolide resistance phenotypes obtained from Canadian hospitals.

**Methods:** From Jan- Dec 2007, 12 sentinel hospitals across Canada submitted isolates from patients attending hospital clinics, emergency rooms, medical and surgical wards, and intensive care units. Each centre was asked to submit pathogens (consecutive, one per patient/infection site) from blood (360), respiratory (200), urine (100), and wound (50) infections. 7885 isolates were collected. Susceptibility testing was performed using CLSI broth microdilution methods against 439 SPN.

**Results:** In vitro activity of cethromycin, telithromycin and clarithromycin against SPN is listed below.

**Conclusions:** Cethromycin was more active than both telithromycin and clarithromycin versus all macrolide resistant phenotypes of SPN. Cethromycin was less active versus SPN with an M-phenotype than SPN with an MLS<sub>B</sub> phenotype.

|                | SPN phenotype, MIC <sub>50</sub> /MIC <sub>90</sub> (µg/ml) |                                  |                                 |                                     |   |
|----------------|---|----------------------------------|---------------------------------|-------------------------------------|---|
|                | ALL<br>(N= 439)   | Macro S <sup>1</sup><br>(N=341 ) | Macro R <sup>2</sup><br>(N= 70) | M-phenotype <sup>3</sup><br>(N= 39) | MLS <sub>B</sub> -phenotype <sup>4</sup><br>(N=31 ) |
| Cethromycin    | 0.015/0.015   | 0.015/0.015                      | 0.015/0.06                      | 0.03/0.06                           | 0.015/0.015   |
| Telithromycin  | 0.015/0.03  | 0.015/0.015                      | 0.03/0.25                       | 0.12/0.25                           | 0.015/0.06  |
| Clarithromycin | £0.03/2   | ≤0.03/0.03                       | 4/≥32                           | 2/8                                 | ≥32/ ≥32  |

<sup>1</sup>Clarithromycin MIC ≤1µg/ml; <sup>2</sup>Clarithromycin MIC ≥1µg/ml; <sup>3</sup>Clarithromycin MIC ≥1 µg/ml and clindamycin MIC ≤1 µg/ml; <sup>4</sup>Clarithromycin MIC ≥1µg/ml and clindamycin MIC ≥1µg/ml.

# C1-3842

## In Vitro Activity of Cethromycin (CER) Against Toxigenic *Clostridium difficile* Clinical Isolates

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**Background:** *C. difficile* is the major cause of antibiotic-associated diarrhea. CER, is a novel ketolide antibiotic with activity against gram-positive bacteria resistant to penicillin, macrolides and quinolones, and is in development for treatment of community acquired pneumonia. Ketolide antibiotics are less often associated with alteration of the intestinal microflora or with *C. difficile* colonization. With only vancomycin (VAN) and metronidazole (MTZ) as first line therapy, the search for new agents with activity against *C. difficile* is warranted. We investigated the *in vitro* activity of CER against *C. difficile* isolates.

**Methods:** 110 unique toxigenic *C. difficile* isolates of differing REA type known to have caused CDI were utilized for susceptibility testing. Inoculum preparation and agar dilution were performed according to the CLSI method for anaerobes (M11-A7). ATCC 700057 strain was included as the control and CER was assayed alongside VAN and MTZ.

**Results:** Cethromycin demonstrated *in vitro* activity with a geometric mean MIC and MIC<sub>50</sub> in between those of MTZ and VAN. 80% of the tested isolates had cethromycin MICs of 0.03 - 4 µg/mL with the MIC<sub>90</sub> being 128 µg/mL.

**Conclusions:** CER had good *in vitro* activity against a majority of *C. difficile* isolates tested. If confirmed in clinical trials, this activity, combined with the preservation of normal intestinal flora of ketolide antibiotics including CER, may lessen the likelihood of developing CDI while being treated with CER and reduce recurrence of CDI if it is treated with CER compared with other agents.

|     | MIC (µg/mL) |                |       |      |
|-----|-------------|----------------|-------|------|
|     | Range       | Geometric Mean | 50%   | 90%  |
| CER | 0.03 - 128  | 0.527          | 0.125 | 128  |
| VAN | 0.5 - 4     | 1.045          | 1     | 2    |
| MTZ | 0.125 - 2   | 0.248          | 0.25  | 0.25 |

# C2-256

## In Vitro Activity of Cethromycin Against a Collection of Viridans Group Streptococci and *Streptococcus bovis* Blood Isolates

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**Background:** Cethromycin is ketolide antibacterial agent with activity against clinically important Gram-positive bacteria including many macrolide-resistant strains. We determined the in vitro activity of cethromycin against a diverse collection of VGS and *S. bovis* blood isolates and compared its activity with that of another ketolide. **Methods:** The study includes a collection of 133 viridans group streptococci (VGS) (53 *S. mitis*, 48 *S. anginosus*, 18 *S. sanguinis*, 12 *S. salivarius* and 2 *S. mutans*) and 22 *S. bovis* strains isolated from 1998 to 2007 at our institution. The antimicrobial susceptibility for CTY, and telithromycin (TEL) was determined by the agar dilution method according to the CLSI methodology. The analysis was stratified according to penicillin (PEN) and erythromycin (ERY) susceptibility and ERY resistance phenotypes.

**Results:** Among the streptococci studied, seven strains (6 *S. bovis* and 1 *S. salivarius*) showed TEL resistance (8-128µg/ml) all exhibited the cMLSB

phenotype and harboured the *erm(B)* gene. The CTY MIC range for the TEL resistant strains was 0.5->64 µg/ml.

**Conclusions:** Cethromycin showed potent in vitro activity against VGS. Based on the MIC data cethromycin activity was comparable to telithromycin. and showed improved in vitro activity against telithromycin-resistant *S. bovis* and *S. salivarius* strains.

| Category (n)           | TEL               |                   |            | CTY               |                   |            |
|------------------------|-------------------|-------------------|------------|-------------------|-------------------|------------|
|                        | MIC <sub>50</sub> | MIC <sub>90</sub> | Range      | MIC <sub>50</sub> | MIC <sub>90</sub> | Range      |
| All (155)              | £0.03             | 0.25              | £0.03-128  | £0.06             | 0.12              | £0.06->64  |
| PEN S (110)            | £0.03             | 0.06              | £0.03-128  | £0.06             | 0.12              | £0.06->64  |
| PEN I (36)             | £0.03             | 0.12              | £0.03-1    | £0.06             | 0.12              | £0.06-4    |
| PEN R (8)              | £0.03             | 0.12              | £0.03-0.12 | £0.06             | £0.06             | £0.06      |
| ERY S (80)             | £0.03             | £0.03             | £0.03      | £0.06             | £0.06             | £0.06      |
| ERY R (75)             | 0.06              | 1                 | £0.03-128  | £0.06             | 1                 | £0.06->64  |
| M (28)                 | 0.06              | 0.12              | £0.03-0.25 | £0.06             | £0.06             | £0.06-0.12 |
| cMLS <sub>B</sub> (42) | 0.06              | 16                | £0.03-128  | £0.06             | 4                 | £0.06->64  |
| iMLS <sub>B</sub> (5)  | £0.03             | 0.06              | £0.03-0.06 | £0.06             | £0.06             | £0.06      |

# D-2250

## Proposed MIC Quality Control Ranges for CEM-101 Using the CLSI Multi-Laboratory M23-A2 Study Design

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**Background:** CEM-101 is a promising new macrolide in development for treating community-acquired (CA) macrolide-resistant and -susceptible bacteria. This study was performed to establish quality control (QC) ranges for CEM-101 for use in clinical or reference laboratories when performing Clinical and Laboratory Standards Institute (CLSI) broth microdilution MIC methods. QC strains included *S. aureus* ATCC 29213 (SA), *E. faecalis* ATCC 29212 (EF), *S. pneumoniae* ATCC 49619 (SPN) and *H. influenzae* ATCC 49247 (HI).

**Methods:** CLSI broth microdilution methods were utilized in an eight laboratory study design compliant with M23-A2 specifications. Four media lots (three manufacturers) of cation-adjusted Mueller-Hinton (MH) broth (with 2-5% lysed horse blood for testing SPN) or HTM broth were evaluated. Ten replicate MIC tests were performed for each QC organism generating 320 values for each strain (1,280 total). Azithromycin and/or erythromycin and/or clarithromycin were used as internal controls.

**Results:** The table lists the recommended QC MIC ranges for CEM-101. Modal MIC values (% of total) observed were: SA at 0.06 µg/ml (64.1), EF at 0.03 µg/ml (67.8), SPN at 0.008 µg/ml (85.3) and HI at 2 µg/ml (93.1). No significant differences were noted between media lots or testing site performance for either CEM-101 or the three control agents. All control agent MIC values were within CLSI published ranges.

**Conclusions:** CEM-101 is a novel macrolide to be directed against CA respiratory tract infections and possibly other infections commonly treated with MLS<sub>B</sub>-class agents. Proposed MIC QC ranges will help guide clinical or reference laboratories involved in the testing of clinical trial isolates and facilitate the regulatory review process.

| CEM-101 MIC (mg/ml)             |   |            |
|---------------------------------|---|------------|
| QC Organism (ATCC no.)          | Proposed range (log <sub>2</sub> dilutions) | % in range |
| <i>S. aureus</i> ATCC 29213     | 0.03 - 0.12 (3)                             | 96.6       |
| <i>E. faecalis</i> ATCC 29212   | 0.015 - 0.06 (3)                            | 95.6       |
| <i>S. pneumoniae</i> ATCC 49619 | 0.004-0.015 (3)                             | 99.3       |
| <i>H. influenzae</i> ATCC 49247 | 1 - 4 (3)                                   | 99.7       |

# F1-2060

## MICs Of TR-700 - the Active Moiety of the Novel Oxazolidinone Prodrug TR-701- for Linezolid-Susceptible and -Resistant Enterococci and Staphylococci

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**Background:** Linezolid is an effective antibiotic but: (i) its modal MICs for susceptible staphylococci and enterococci are only 2- to 4- fold below CLSI and EUCAST breakpoints and (ii) resistance can emerge via 23S rRNA mutations (most often G2576T), and recombination among 23S rRNA gene copies. We investigated the activity of TR-700, the active component of the novel oxazolidinone pro-drug TR-701, vs linezolid-susceptible and -resistant bacteria.

**Methods:** MICs of linezolid and TR-700 were determined by CLSI agar dilution for: (i) linezolid-susceptible enterococci and staphylococci; (ii) linezolid-resistant clinical isolates, mostly with G2576T, and (iii) various linezolid-resistant laboratory mutants, including those with G2447T, A2503G and T2504C. Mutated gene copies were enumerated by pyrosequencing.

**Results:** For 48 linezolid-susceptible MRSA, including hospital and community strains, MICs of TR-700 were 0.25-0.5 mg/L compared with 2 mg/L linezolid. For 52 linezolid-susceptible enterococci, MICs were 0.25-0.5 mg/L for TR-700 and 1-2 mg/L for linezolid, irrespective of species and vancomycin status. For 16 linezolid-resistant staphylococci (MRSA or coagulase negative) -heterozygous, where tested, for G2576T- MICs of TR-700 were 1-4 mg/L vs 8-64 mg/L linezolid. For 36 linezolid-resistant enterococci, MICs of TR-700 were 1-16 mg/L (geom mean 2.2) vs 8-64 mg/L (geom mean 18.3) linezolid. Only 3 isolates, all *Enterococcus faecium*, required TR-700 MICs >4 mg/L: 2 of these, with MICs of 8 mg/L, were homozygous for G2576T; the other, with an MIC of 16 mg/L, lacked known 23S rRNA lesions and its mechanism remains uncertain. MICs of TR-700 for MRSA with other linezolid-compromising mutations besides G2576T were 1-2 mg/L vs 8-32 mg/L linezolid.

**Conclusions:** TR-700 is ca. 8-16 fold more active than linezolid vs staphylococci and enterococci and has the potential to overcome linezolid resistance, particularly where strains are heterozygous for G2576T.

# F1-2061

## TR-700, a Novel Oxazolidinone, Tested Against Linezolid-Resistant Gram-positive Species with Well-Characterized Resistance Mechanisms

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**Background:** TR-700 is the active component of orally administered prodrug TR-701. TR-700 has demonstrated potent activity against numerous Gram-positive species and in this study, a worldwide collection of linezolid-resistant (LZD-R) organisms was investigated.

**Methods:** 240 strains were susceptibility (S) tested by CLSI reference broth microdilution methods including 120 LZD-R and 120 controls, matched by species, geographic origin, site of infection and time. Species of LZD-S/LZD-R strains were: *E. faecalis* (16/16), *E. faecium* (EFM; 55/55), *S. aureus* (SA; 8/8), coagulase-negative staphylococci (CoNS; 8 spp., 40/40) and viridans group streptococci (VGS; 2 spp., 1/1). 23S rRNA target mutations or *cfr* genes were detected by PCR and sequencing.

**Results:** Among LZD-R strains, the R-mechanisms were G2576T (109), *cfr* (4) and unknown (7), with strains originating from Europe, Far East, North and South America. Most strains were multidrug-R (MDR) and *cfr* isolates exhibited the R to phenicols, clindamycin, LZD, pleuromutilins and streptogramin B. TR-700 MIC values, regardless of species, were 4- to 32-fold greater than LZD-S isolates. TR-700 MIC results were  $\leq 4$ ,  $\leq 8$  or  $\leq 16$   $\mu\text{g/ml}$  for 88, 96 and  $>99\%$  of LZD-R strains, respectively. TR-700 MIC<sub>50/90</sub> results were lower for LZD-R enterococci (1/2  $\mu\text{g/ml}$ ) compared to staphylococci (4/16  $\mu\text{g/ml}$ ).

**Conclusions:** TR-700 exhibits enhanced activity against LZD-R and control wildtype strains compared to LZD. A significant number (nearly 90%) of LZD-R strains were inhibited by achievable levels ( $\leq 4$   $\mu\text{g/ml}$ ) of TR-700. All strains with the emerging *cfr*-mediated R had TR-700 MICs at  $\leq 8$   $\mu\text{g/ml}$ .

| Organisms (no. tested) | Agent  | No. occurrences at MIC ( $\mu\text{g/ml}$ ): |    |    |                 |                 |    |           |
|------------------------|--------|--|----|----|-----------------|-----------------|----|-----------|
|                        |        | $\leq 0.5$                                   | 1  | 2  | 4               | 8               | 16 | $\geq 32$ |
| SA (8)                 | TR-700 | 2  | 3  | 3  | 0               | 0               | 0  | 0         |
|                        | LZD    | 0  | 0  | 0  | 0               | 4 <sup>a</sup>  | 3  | 1         |
| CoNS (40)              | TR-700 | 0  | 2  | 10 | 15              | 8               | 4  | 1         |
|                        | LZD    | 0  | 0  | 0  | 0               | 4 <sup>a</sup>  | 13 | 23        |
| EF, EFM and VGS (72)   | TR-700 | 6  | 26 | 34 | 5               | 1               | 0  | 0         |
|                        | LZD    | 0  | 0  | 0  | 14 <sup>b</sup> | 23 <sup>c</sup> | 30 | 5         |

# F1-2063

## Human Pharmacokinetics of TR-700 after Ascending Single Oral Doses of the Prodrug TR-701, a Novel Oxazolidinone Antibiotic

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**Background:** The prodrug TR-701 is a novel oxazolidinone antibiotic that is rapidly converted in vivo by phosphatases, to the microbiologically-active molecule TR-700. TR-700 is 4- to 8-fold more potent in vitro and in vivo than linezolid (the only currently marketed oxazolidinone) against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE).

**Methods:** A randomized, double-blind, placebo-controlled, ascending single-dose study was performed to assess the safety, tolerability and pharmacokinetics (PK) of TR-701 and TR-700 in healthy adult subjects. Cohorts of 8 subjects (6 active and 2 placebo) received single oral doses of 200, 400, 600, 800, or 1200 mg TR-701 after a 10-hr fast.

**Results:** TR-700 rapidly appeared in plasma with median  $T_{max}$  values that ranged from 3 to 4 hours, and was slowly eliminated with mean  $t_{1/2}$  values ranging from 8 to 8.8 hours. Mean  $C_{max}$  and  $AUC_{0-24}$  for TR-700 increased in a linear and approximately dose-proportional manner from 200-1200 mg (1.99-9.47  $\mu\text{g}/\text{mL}$  and 20.11-98.80  $\mu\text{g}\cdot\text{hr}/\text{mL}$ , respectively). TR-700 oral clearance (CL/F) was not affected by the dose levels examined. TR-701 was only detected above the 5 ng/mL limit of quantitation in a single subject in the 1200-mg cohort from 0.25-3 hr (range 5.9-16.9 ng/mL). TR-701 was well-tolerated and no significant clinical or laboratory abnormalities were reported.

**Conclusions:** Ascending single oral doses of TR-701 provided approximately dose-proportional increases in the peak ( $C_{max}$ ) and extent of TR-700 exposure (AUC). TR-700 plasma concentrations were above the  $MIC_{90}$  (0.5  $\mu\text{g}/\text{mL}$ ) for MRSA and VRE for an average of 15.3 hrs at 200 mg, and for at least 24 hrs at 400 mg and above. These PK data support a once-daily dosing regimen for TR-701.

# F1-2064

## Human Pharmacokinetics of the Prodrug TR-701 and TR-700, its Active Moiety, after Multiple Oral Doses of 200 and 400 mg TR-701, a Novel Oxazolidinone

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**Background:** TR-701 is a novel oxazolidinone prodrug antibiotic extensively converted in vivo by phosphatases to its microbiologically-active moiety, TR-700. TR-700 is 4- to 8-fold more potent in vitro and in vivo than linezolid against gram-positive bacteria including: methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE).

**Methods:** A randomized, double-blind, placebo-controlled, multiple-dose study was performed to determine the pharmacokinetics (PK) of TR-701 and TR-700 in healthy adults. Each cohort of 10 subjects (8 active and 2 placebo) received daily oral doses of 200 or 400 mg TR-701, up to 21 days.

**Results:** Day 1 and 15 TR-700 median  $T_{max}$  values ranged from 3.0 and 4.0 hrs, and mean half-life ( $t_{1/2}$ ) values ranged from 8.1 to 11.3 hrs after 200 and 400 mg TR-701 administration. On both Day 1 and 15, mean  $C_{max}$  and  $AUC_{0-24}$  values for TR-700 increased in a somewhat greater than dose-proportional manner from 200 to 400 mg.  $C_{max}$  and  $AUC_{0-24}$  increased by 1% and 34% at 200 mg, and by 8% and 15.3% at 400 mg, on Day 15 compared to Day 1. TR-700 mean oral clearance was marginally greater for the 200-mg cohort (10.0 and 9.5 L/hr on Day 1 and 15) vs the 400 mg cohort (7.5 and 7.7 L/hr on Day 1 and 15). At 200 mg, the apparent volume of distribution ( $V_z/F$ ) was 160 L on Day 1 and 128 L on Day 15. At 400 mg,  $V_z/F$  was 87 L and 90.5 L on Day 1 and 15, respectively. TR-701 was not detected for either cohort on Day 1 or Day 15.

**Conclusions:** TR-701 at 200 and 400 mg QD for 15 days provided approximately dose-proportional increases in the peak and extent of TR-700 exposure at steady state. Plasma concentrations of TR-700 were maintained at  $> 0.5 \mu\text{g/mL}$  (the  $MIC_{90}$  for MRSA and VRE) for  $>60\%$  of the dosing interval at 200 mg TR-701, and the entire 24 hr dosing interval at 400 mg.

# F1-2065

## ***In Vitro* and *in Vivo* Efficacy of TR-701 and TR-700 versus the Linezolid-and Methicillin-Resistant *Staphylococcus aureus cfr* Strain CM/05**

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**Background:** The detection of a plasmid-borne *cfr* (chloramphenicol-florfenicol resistance) gene in staphylococci recovered from human specimens in the USA adds a new dimension to the threat against the clinical utility of several antimicrobial classes, including the oxazolidinones. A clinical strain, MRSA CM/05, carries this *cfr* gene, which confers resistance to linezolid, chloramphenicol and clindamycin through modification of the ribosomal region involved in drug binding (A2503). TR-701 is the phosphate prodrug of the active antibacterial TR-700 currently in Phase 1 clinical trials. In this study, the activity of TR-700 and TR-701 were evaluated *in vitro* and *in vivo* versus the linezolid resistant MRSA CM/05 strain (L-MRSA).

**Methods:** MICs were determined by the broth microdilution method (CSLI) using a two-fold serial dilution range of test compound (64 to 0.002 µg/mL). Mouse septicemia studies were carried out using  $\sim 2 \times 10^7$  CFU/mouse, with doses of either TR-701 or linezolid from 1mg/kg to 50mg/kg.

**Results:** MIC values obtained for TR-700 and comparator antibiotics against L-MRSA CM/05 were as follows: TR700 = 0.5 µg/mL, linezolid = 8 µg/mL, daptomycin = 2 µg/mL, oxacillin >64 µg/mL; vancomycin = 1 µg/mL, trimethoprim = 1 µg/mL, ciprofloxacin = 16 µg/mL, and tetracycline = 0.125 µg/mL. A single oral dose of 20 mg/kg TR-701 provided 100% protection in animals 24 hours post-infection. In contrast, only 1 of 10 animals survived when treated with linezolid at 20 mg/kg.

**Conclusions:** TR-700 was 16-fold more potent than linezolid against CM/05, with ciprofloxacin and oxacillin having little or no antimicrobial activity against the isolate. In the mouse septicemia model, TR-701 was effective in protecting mice systemically infected with the L-MRSA CM/05 strain, whereas linezolid provided only marginal protection at the highest concentration evaluated.

# F1-2066

## Demonstration of TR-701 Efficacy in a Mouse Inhalation Anthrax Model

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**Background:** Research on new therapeutics for treating inhalation anthrax include reports on the oxazolidinone linezolid. In a mouse *B. anthracis* spore inhalation challenge model, linezolid was reported as comparable to ciprofloxacin in PO administered therapy. This report prompted investigation of TR-701, the phosphate prodrug of the active antibacterial oxazolidinone TR-700 currently in clinical trials. In this study, the efficacy of TR-701 was evaluated *in vivo* versus linezolid and ciprofloxacin in a mouse inhalation anthrax model.

**Methods:** BALB/c mice were infected intratracheally with *B. anthracis* (Ames) spores at  $1.58 \times 10^4$  spores/mouse ( $10 \times \text{LD}_{50}$ ). Oral drug treatments were 80 mg/kg ciprofloxacin, 80 mg/kg linezolid, or 80 mg/kg or 40 mg/kg TR-701, starting 1 hour post-infection. Additional treatments were given once-daily for 1-5 days post-infection. Survival was monitored for 2 weeks post-challenge. Results were analyzed by Kaplan-Meier and Logrank (Mantel-Cox) tests. Minimum inhibitory concentrations (MIC) for all drugs were conducted according to CLSI methods.

**Results:** By day 4, all vehicle control mice had died while all drug treated mice were still alive. Survival monitoring continuing through day 14 post infection showed 50% survival of mice receiving either 80 mg/kg ciprofloxacin or 80 mg/kg linezolid. Mice receiving TR-701 at 80 mg/kg or 40 mg/kg showed 90%, and 80% survival, respectively.

**Conclusions:** Oral dosing of TR-701 demonstrated significant long term protection in a mouse inhalation anthrax model. This data suggests that TR-701 has potential as a therapeutic for the treatment of inhalation anthrax.

# F1-2068

## Quality Control Parameters for TR-700 Broth Microdilution Susceptibility Tests

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**Background:** TR-701, a promising new oxazolidinone, is a prodrug under development by Trius Therapeutics; the active moiety is TR-700. TR-700 has activity against Gram-positive microorganisms.

**Methods:** An eight-laboratory study was conducted to generate data to determine quality control (QC) limits for five standard QC organisms when testing susceptibility to TR-700 by the broth microdilution method. Three different lots of Mueller-Hinton broth were used. The broth was supplemented with 3% lysed horse blood for testing *S. pneumoniae*. All susceptibility tests were performed by methods outlined by the CLSI. Each laboratory performed 30 MIC determinations for each QC strain.

**Results:** Colony counts ranged from  $1.5 \times 10^4$  to  $2.0 \times 10^6$ . Significant lot-to-lot variation was not observed. All tests were very reproducible and the following quality control limits are proposed (table).

**Conclusions:** Microbroth dilution quality control ranges are proposed for TR-700 against 3 quality control strains recommended by the CLSI. These ranges have been proposed and accepted by the CLSI Subcommittee on Antimicrobial Susceptibility Testing.

| <u>Organism (ATCC)</u>       | Proposed QC Limits ( $\mu\text{g/ml}$ ) | % in Range |
|------------------------------|---|------------|
| <i>S. aureus</i> (29213)     | 0.25 - 1                                | 99.2%      |
| <i>E. faecalis</i> (29212)   | 0.25 - 1                                | 100%       |
| <i>S. pneumoniae</i> (49619) | 0.12 - 0.5                              | 99.6%      |

# F1-2069

## Relative Potency of TR-700, the Active Moiety of Prodrug TR-701, against Selected Bacterial Pathogens and Provisional Disk Test Criteria

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**Background:** TR-701, a promising new oxazolidinone, is a prodrug under development by Trius Therapeutics; the active moiety is TR-700.

**Methods:** The in vitro activity of TR-700 was compared to that of linezolid (Lnz), cefotaxime (Ctx) and levofloxacin (Levo) against 900 bacterial pathogens representing 3 genera. CLSI broth microdilution and disk diffusion methodologies were used. Tentative microbiological MIC breakpoints are proposed. A 20 µg TR-700 disk was used to propose tentative disk diffusion breakpoints.

**Results:** MIC<sub>90s</sub> (µg/mL), MIC and disk diffusion breakpoints for 3 groups of microorganisms were (see table 1).

**Conclusions:** TR-700 was very active against the majority of the strains tested. TR-700 tended to be 2- to 64-fold more active than Lnz, 4- to 256-fold more active than Ctx, and 4- to 64-fold more active than Levo against all species tested. Tentative disk diffusion breakpoints are proposed for the 20 µg TR-700 disk. Provisional interpretive criteria must await pharmacokinetic and clinical information.

**Table 1. MIC<sub>90</sub> & Proposed Breakpoints**

| Species               | MIC <sub>90</sub> µg/mL |     |     |      | TR-700 Proposed Breakpoints |                           |
|-----------------------|-------------------------|-----|-----|------|-----------------------------|---------------------------|
|                       | TR -700                 | Lnz | Ctx | Levo | MIC (µg/mL)<br>S, I, R      | Disk<br>(mm)<br>S, I, R   |
| Enterococci (n=203)   | 0.5                     | 2   | >64 | >16  | £2, -, -                    | <sup>3</sup> 15, -, -     |
| Staphylococci (n=336) | 0.5                     | 2   | >64 | >16  | £2, 4, <sup>3</sup> 8       | <sup>3</sup> 18,15-17,£14 |
| Streptococci (n=361)  | 0.25                    | 16  | 1   | 1    | £2, -, -                    | <sup>3</sup> 15, -, -     |

# F1-2069a

## Hematological Effects of TR-701, Linezolid and Placebo Administered for 21 Days in Healthy Subjects

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**Background:** Oxazolidinones are known to induce dose- and time-dependent reversible hematologic effects. TR-701 is a novel oxazolidinone prodrug of the microbiologically-active moiety, TR-700. Preclinical studies have shown that oral TR-701 is generally 6 times more efficacious than linezolid (LNZ) *in vivo*.

**Methods:** In order to maximize observable effects of TR-701 and LNZ on hematologic parameters, we conducted a 21 day Phase 1 study comparing the two drugs and placebo in healthy subjects. Each cohort (8 active and 2 placebos) received either single daily oral doses of 200, 300, or 400 mg QD TR-701, or 600 mg BID LNZ.

**Results:** Dose and time-dependent changes in hematologic parameters were observed with TR-701, compared to placebo. LNZ produced changes in hematologic parameters comparable to 400 mg QD TR-701. For both drugs, these effects generally appeared during the 2<sup>nd</sup> week, and stabilized during the 3<sup>rd</sup> week of drug administration.

**Conclusions:** Over 21 days of administration, biological evidence of oxazolidinone-induced effects on the hematopoietic system observed with 400 mg QD TR-701 were similar to those seen following 600 mg BID LNZ. If TR-701's 6-fold increased *in vivo* potency over LNZ translates to the clinical paradigm, a therapeutic dose with negligible potential for hematologic effects could be expected.

### Maximum % Decrease over 21 Days (Mean / Individual)

| Dose             | Platelets (%) | Neutrophils (%) | Reticulocytes (%) | RBCs (%)  |
|------------------|---------------|-----------------|-------------------|-----------|
| PLACEBO          | -5 / -23      | -2 / -57        | -8 / -38          | -3 / -11  |
| 200 mg TR-701 QD | -15 / -38     | -18 / -51       | -14 / -42         | -2 / -9   |
| 300 mg TR-701 QD | -23 / -43     | -4 / -44        | -5 / -57          | -3 / -7   |
| 400 mg TR-701 QD | -38 / -50     | -37 / -66       | -39 / -91         | -11 / -27 |
| 600 mg LNZ BID   | -22 / -54     | -38 / -66       | -21 / -95         | -7 / -13  |

# F1-3972

## Comparative Efficacy of EDP-420, Telithromycin, Azithromycin, Linezolid, Levofloxacin and Trimethoprim-Sulfamethoxazole against Murine Lethal Pneumonia Induced by Macrolide-Resistant *Streptococcus pneumoniae* P6254

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**Background:** *Streptococcus pneumoniae* is a common cause of severe community-acquired and nosocomial pneumonia and the leading cause of death in hospital settings. EDP-420, a new bicyclolide (bridged bicyclic macrolide) with unique structural features, exhibited effectiveness against both macrolide susceptible and resistant *S. pneumoniae in vitro*.

**Methods:** Pneumococcal pneumonia was induced by intranasal inoculation of *S. pneumoniae* P6254. For all animals, developed bacteremia within 24 hours, lung bacterial counts increased progressively and died within 4 days if left untreated. Two treatments were given at 3 and 24 hours after inoculation. Cumulative survival rates were recorded daily.

**Results:** EDP-420 was estimated PD<sub>50s</sub> of 6.2 and 1.8 mg/kg for oral and intravenous treatments respectively. Linezolid was estimated PD<sub>50</sub> of 11.0 mg/kg for both oral and intravenous treatments. Telithromycin and levofloxacin were estimated oral PD<sub>50s</sub> of 10.9 and 19.2 mg/kg respectively. Azithromycin and trimethoprim/sulfamethoxazole had an estimated PD<sub>50</sub> of >50 mg/kg.

**Conclusions:** The data demonstrates better efficacy of EDP-420 against macrolide resistant *S. pneumoniae* in murine lethal pneumonia in comparison with currently marketed macrolide, ketolide, oxazolidinone and fluoroquinolone, as well as dihydrofolate reductase inhibitor/sulfonamide classes antibiotics. EDP-420 is potentially a potent antibiotic for treatment of community-acquired pneumonia.

# F1-3974

## Comparative Activity of CEM-101 Against Macrolide-susceptible and -resistant Pneumococci

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**Background:** Drug-resistant pneumococcal strains occur worldwide. CEM-101 is a member of the macrolide-ketolide group that is 2-4 fold more active than telithromycin against macrolide R pneumococci. We tested activity of CEM-101 compared to erythromycin, azithromycin, clarithromycin, telithromycin, clindamycin, penicillin G, amoxicillin/clavulanate, levofloxacin, moxifloxacin against a range of pneumococci.

**Methods:** The 221 clinical isolates included 50 macrol S and 171 macrol R strains. Of these 53 were pen G S, 63 I and 105 pen G R (old CLSI breakpoints); 27 strains were quinolone R with defined QRDR mutations. Macrol R strains comprised 54 with *erm(B)*, 51 *mef(A)*, 4 *erm(A)*, 31 *erm(B)* + *mef(A)*, 27 with L4, and 4 with 23S rRNA ribosomal protein mutations. Agar dilution was with Mueller-Hinton agar + 5% sheep blood and inocula of 10<sup>4</sup> cfu/spot. Plates were incubated overnight in air for 35°C with usual QCs.

**Results:** MICs (µg/ml) were (see table). CEM-101 had an MIC range against macrol S pneumococci of 0.002-0.015 µg/ml and a range against macrol R pneumococci (all phenotypes) of 0.004-1 µg/ml. Only 3 strains with *erm(B)* [with and without *mef(A)*] had CEM-101s MIC of 1.0 µg/ml and 218/221 strains had CEM-101 MICs of ≤0.5 µg/ml. Telithro MIC ranges were 0.015-0.03 µg/ml for macrol S and 0.03-2 µg/ml for macrol R strains, resp. CEM-101 MICs were up to four

fold lower than those of telithro against macrol S and R strains. MICs of erythro, azithro, clarithro were highest in *erm(B)* [with and without *mef(A)*], L4 and 23s rRNA strains and clinda R only seen amongst strains containing *erm(B)* with or without *mef(A)*.

**Conclusions:** CEM-101 had the lowest MICs of all macrolides and ketolides against all strains including macrolide R phenotypes.

| Drug      | Macrolide susceptible (50) |       |       | Macrolide resistant (171) |       |       |
|-----------|----------------------------|-------|-------|---------------------------|-------|-------|
|           | Range                      | MIC50 | MIC90 | Range                     | MIC50 | MIC90 |
| CEM-101   | 0.002-0.015                | 0.03  | 0.25  | 0.004-1                   | 0.06  | 0.25  |
| Erythro   | 0.03-0.25                  | 0.06  | 0.125 | 1->64                     | >64   | >64   |
| Azithro   | 0.06-0.25                  | 0.125 | 0.125 | 1->64                     | >64   | >64   |
| Clarithro | 0.015-0.06                 | 0.03  | 0.06  | 0.25->64                  | 32    | >64   |
| Telithro  | 0.015-0.03                 | 0.03  | 0.03  | 0.03-2                    | 0.125 | 0.5   |
| Clinda    | 0.015-0.06                 | 0.03  | 0.06  | 0.03->64                  | 0.125 | >64   |
| Amox/clav | 0.015-8                    | 0.5   | 2     | 0.015-16                  | 1     | 8     |
| Pen G     | 0.015-8                    | 1     | 2     | 0.008->16                 | 1     | 4     |
| Levo      | 1-32                       | 1     | 16    | 0.06-32                   | 1     | 2     |
| Moxi      | 0.125-8                    | 0.25  | 4     | 0.125-4                   | 0.25  | 0.5   |

# F1-3975

## Antimicrobial Characterization of CEM-101 Activity Against 331 Respiratory Tract Pathogens Including Multidrug-Resistant Pneumococcal Serogroup 19A (MDR-19A) Isolates

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**Background:** CEM-101 (CEM), a novel macrolide-ketolide, has potent activity against bacterial pathogens susceptible (S) or resistant (R) to other MLS<sub>B</sub>-ketolide agents. Projected for use in therapy of respiratory tract infections (RTI), CEM was tested against contemporary RTI isolates.

**Methods:** A worldwide sample of organisms included *S. pneumoniae* (SPN; 168, 59.3% erythromycin [ERY]-R and 18 MDR-19A strains), *M. catarrhalis* (MCAT; 21, 11  $\beta$ -lactamase[+]), *H. influenzae* (HI; 100, 48  $\beta$ -lactamase[+]), *H. parainfluenzae* and *H. haemolyticus* (12) and *L. pneumophila* (LPN; 30). All S tests were by reference CLSI methods (M7-A7, M100-S18) and breakpoints per CLSI (2008) for comparison agents such as azithromycin (AZ), clarithromycin (CLA), ERY, telithromycin (TEL), clindamycin (CC), Synecid (SYN), levofloxacin (LEV), linezolid, and rifampin (RIF).

**Results:** SPN were very S to CEM (MIC<sub>90</sub>, 0.25  $\mu$ g/ml; highest MIC at 0.5  $\mu$ g/ml) and CEM was 2- and 8-fold more potent than TEL and CC, respectively. MDR-19A replacement strains were also CEM-S (MIC<sub>90</sub>, 0.5  $\mu$ g/ml). LPN were most S to CEM with all MIC values at  $\leq$ 0.015  $\mu$ g/ml (TEL MIC<sub>90</sub>, 0.03  $\mu$ g/ml). *Haemophilus* RTI pathogens were less CEM-S (MIC<sub>90</sub>, CEM/TEL): HI (2/4  $\mu$ g/ml) and others (2/4  $\mu$ g/ml) with no variations for  $\beta$ -lactamase (+) strains. MCAT CEM-101 MICs were all at  $\leq$ 0.5  $\mu$ g/ml, equal to TEL.

**Conclusions:** CEM exhibited the widest spectrum/activity against RTI pathogens among the tested MLS<sub>B</sub>-ketolide agents (AZ, CLA, ERY, TEL, CC, SYN) and comparable to LEV. All CEM MIC values were at  $\leq$ 0.5 and  $\leq$ 4  $\mu$ g/ml for SPN or LPN and HI, respectively; expanded studies should be considered.

| Organism (no.)                | CEM MIC ( $\mu$ g/ml) |              |                  | TEL MIC ( $\mu$ g/ml) |                   |                        |
|-------------------------------|-----------------------|--------------|------------------|-----------------------|-------------------|------------------------|
|                               | 50%                   | 90%          | Range            | 50%                   | 90%               | Range                  |
| SPN (150)                     | 0.015                 | 0.25         | $\leq$ 0.008-0.5 | 0.03                  | 0.5               | $\leq$ 0.008-1         |
| MDR-19A (18)                  | 0.25                  | 0.5          | 0.06-0.5         | 0.5                   | 1                 | 0.12-1                 |
| MCAT (21)                     | 0.12                  | 0.12         | $\leq$ 0.008-0.5 | 0.12                  | 0.25              | $\leq$ 0.015-0.5       |
| HI (100)                      | 1                     | 2            | 0.12-4           | 2                     | 4                 | 0.25-16                |
| Other <i>Haemophilus</i> (12) | 2                     | 2            | 0.12-2           | 2                     | 4                 | 0.25-8                 |
| LPN (30)                      | $\leq$ 0.015          | $\leq$ 0.015 | $\leq$ 0.015     | 0.03 <sup>a</sup>     | 0.03 <sup>a</sup> | 0.03-0.06 <sup>a</sup> |

# F1-3976

## Antimicrobial Characterization of CEM-101: Activity Against Enterococci, Uncommon Gram-positive Pathogens, *N. gonorrhoeae* and Anaerobes

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**Background:** CEM-101, a new macrolide-ketolide, has potency advantages over other MLS<sub>B</sub>-ketolides against pathogens causing respiratory tract and cutaneous infections. However, expanded activity vs. other species may be clinically helpful, and those species were tested.

**Methods:** 4 major organism groups (244 strains) were processed including: enterococci (99 [Table]; 39 *E. faecalis*, 40 *E. faecium*, 20 VRE), *N. gonorrhoeae* (34; 44% ciprofloxacin [CIP]-resistant [R]), anaerobes (71; 7 genus or species groups) and unusual Gram-positive species (40; 4 genus groups). All susceptibility (S) testing used CLSI broth microdilution or agar dilution methods and interpretations. 5-11 comparison agents were tested including telithromycin (TEL) and azithromycin (AZ).

**Results:** CEM-101 potency against enterococci showed a bimodal distribution (0.03 and 2 µg/ml), and that activity was 2- and 32-fold superior to TEL and AZ, respectively. Against *E. faecalis* CEM-101 activity (MIC<sub>90</sub>, 2 µg/ml) was like amoxicillin/clavulanate (MIC<sub>90</sub>, 1 µg/ml) and linezolid (MIC<sub>90</sub>, 2 µg/ml). CEM-101 MIC<sub>90</sub> for *Bacillus* spp., *Listeria* spp. and *Micrococcus* spp. was 0.03 µg/ml, but 0.5 µg/ml for *Corynebacterium* spp. Gonococci had all CEM-101 MIC results at £0.25 µg/ml, 4-fold more potent than AZ. Anaerobe CEM-101 MIC<sub>90</sub> results varied from >32 (*B. fragilis*, *C. difficile*) to (*Prevotella* spp.) £0.25 µg/ml (Gram-positive [GP] spp).

**Conclusions:** CEM-101 exhibited varied activity against tested species, however clinical utility could be expected against most enterococci, *N. gonorrhoeae*, GP anaerobes and most uncommonly isolated GP species. Wider CEM-101 clinical applications should be considered.

| Organism/resistance (no.) | CEM-101 MIC (µg/ml) |     |         | TEL MIC (µg/ml) |     |         |
|---------------------------|---------------------|-----|---------|-----------------|-----|---------|
|                           | 50%                 | 90% | Range   | 50%             | 90% | Range   |
| <i>E. faecalis</i>        |                     |     |         |                 |     |         |
| Vancomycin-S (29)         | 0.03                | 2   | 0.015-2 | 0.06            | 4   | 0.03-8  |
| Vancomycin-R (10)         | 0.25                | 2   | 0.015-2 | 0.5             | 4   | 0.03-4  |
| <i>E. faecium</i>         |                     |     |         |                 |     |         |
| Vancomycin-S (30)         | 0.25                | 2   | 0.03-2  | 0.5             | 4   | 0.03-8  |
| Vancomycin-R (10)         | 2                   | 2   | 0.25-2  | 4               | 4   | 2-4     |
| Other enterococci (20)    | 0.03                | 1   | 0.015-2 | 0.06            | 2   | 0.015-4 |

# F1-3977

## Antimicrobial Characterization of CEM-101: Potential Application Against Species Causing Enteritis/Gastroenteritis

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**Background:** MLS<sub>B</sub>-ketolides have been considered for expanded use against gastroenteritis disease pathogens (GDP) such as *H. pylori* (HP) gastritis, and diarrheal illness associated with *Campylobacter jejuni* (CJ), *Salmonella* spp. (SAL) and *Shigella* spp. (SHI). CEM-101, a novel macrolide-ketolide, was screened against contemporary GDP isolates and reported here.

**Methods:** SAL (20 strains, representing 11 serotypes) and SHI (40; four species) were tested by CLSI broth microdilution methods with M100-S18 breakpoints applied. CJ (20) and HP (23) were tested by Mueller-Hinton agar dilution method, supplemented with sheep blood, and CJ results were confirmed by Etest (AB BIODISK, Solna, Sweden). Key comparison agents were tested: azithromycin (AZ), clarithromycin (CLA), telithromycin (TEL), levofloxacin (LEV), amoxicillin/clavulanate (A/C) and trimethoprim/sulfamethoxazole (TMP/SMX).

**Results:** CEM-101 demonstrated activity against food-borne GDPs SAL (MIC<sub>50</sub>, 4 µg/ml), SHI (MIC<sub>50</sub>, 8 µg/ml) and CJ (MIC<sub>50</sub>, 1 µg/ml). This was comparable or superior (MIC<sub>50</sub> ranges) to: TEL (8-16 µg/ml), erythromycin (2->4 µg/ml), AZ (4 µg/ml) and A/C (2-8 µg/ml). CLA results were diverse (MIC<sub>50</sub> range 0.015->16 µg/ml) as well as were TMP/SMX; LEV was most active (MIC<sub>50</sub>, £0.12 µg/ml). HP CEM-101 MIC results were grouped from 0.03-0.25 µg/ml and at 2 or 4 µg/ml; the latter corresponding to CLA-R (>16 µg/ml) strains.

**Conclusions:** CEM-101 exhibited activity against GDP strains like that of other macrolide-ketolides that have been applied for treatment (CLA, AZ), and this novel compound (CEM-101) should be studied alone or in combination at the clinical level, especially versus CLA-R gastric disease.

| Organism (no.)              | CEM-101 |      |        | Comparator (drug) <sup>a</sup> |      |                  |
|-----------------------------|---------|------|--------|--------------------------------|------|------------------|
|                             | 50%     | 90%  | Range  | 50%                            | 90%  | Range            |
| <i>C. jejuni</i> (20)       | 1       | 4    | 1-8    | 2                              | 4    | 1-8 (CLA)        |
| <i>H. pylori</i> (23)       | 0.06    | 0.25 | 0.03-4 | 0.03                           | 0.12 | £0.015->16 (CLA) |
| <i>Salmonella</i> spp. (20) | 4       | >16  | 1->16  | 4                              | 8    | 2-8 (AZ)         |
| <i>Shigella</i> spp. (40)   | 8       | 16   | 1->16  | 4                              | 8    | 1->16 (AZ)       |

a. Comparator drug in parentheses (azithromycin [AZ] or clarithromycin [CLA]).

# F1-3978

## In Vitro Activity of CEM 101, a New Ketolide Antibiotic against, *Chlamydia trachomatis* and *Chlamydia pneumoniae*

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*Chlamydia pneumoniae* is well recognized as an important pathogen of respiratory tract infections worldwide, being responsible for almost 10% of cases of community-acquired pneumonia. *In vitro* activity of the macrolides against *C. pneumoniae* varies, with clarithromycin showing the lowest MICs followed by, azithromycin. The ketolides are a new class of macrolide antibiotics with a 3-keto function instead of the cladinose sugar. The ketolides are acid stable and have activity against a broad range of respiratory pathogens, including multi-resistant pneumococci, *H. influenzae*, *Legionella* species, *M. pneumoniae*, and *Chlamydia sp.* Available data on the *in vitro* activity of a new ketolide, CEM 101 (Cempra Pharmaceuticals), are limited. We therefore compared the *in vitro* activities of CEM 101 with those of azithromycin, clarithromycin, telithromycin and doxycycline against 10 isolates of *Chlamydia pneumoniae* and 10 strains of *C. trachomatis* in HEp-2 cells. The MIC at which 50% and 90% of the isolates of *Chlamydia pneumoniae* are inhibited by CEM 101 was 0.25 µg/ml (range: 0.25 to 1.0 µg/ml). The MIC at which 50% and 90% of the strains of *C. trachomatis* were inhibited was 0.25 µg/ml (range: 0.125 to 0.5 µg/ml). The MIC<sub>90</sub>s for both *C. trachomatis* and *C. pneumoniae* against azithromycin, clarithromycin, telithromycin, and doxycycline were 0.125, 0.06, 0.06, 0.06 µg/ml, respectively. The MICs of CEM 101 were very consistent from isolate to isolate, varying by only one or two dilutions. This is especially impressive in view of the wide geographical distribution of the isolates tested. These results appear to indicate that CEM-101 is an effective antibiotic that should play a role in the treatment of *C. trachomatis* and respiratory tract infections caused by *C. pneumoniae*.

# F1-3979

## Comparative In Vitro Susceptibilities of a New Investigational Macrolide CEM-101 Against Human Mycoplasmas and Ureaplasmas

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**Background:** CEM-101 (Cempra Pharmaceuticals, Inc.) is a promising new macrolide in development for treating community acquired macrolide-resistant bacteria as well as macrolide-susceptible bacteria. We performed an in vitro study to determine the activity of CEM-101 in comparison to azithromycin (AZI), telithromycin (TEL), doxycycline (DOX), levofloxacin (LEV), clindamycin (CL), and linezolid (LZD) against clinical isolates of 6 human mycoplasma and ureaplasma species. Organisms tested included 38 *Mycoplasma pneumoniae* (MP), 5 *Mycoplasma genitalium* (MG), 13 *Mycoplasma hominis* (MH), 15 *Mycoplasma fermentans* (MF), 10 *Ureaplasma parvum* (UP) and 10 *Ureaplasma urealyticum* (UU).

**Methods:** Microbroth dilution was used to determine MICs using 10B broth for ureaplasmas and SP4 broth for mycoplasma species. MBCs were determined for 9 MP isolates.

**Results:** MP MICs for CEM-101 ranged from 0.000000063 - 0.5 µg/ml with MIC<sub>90</sub> = 0.25, making its activity equivalent to DOX, 2-fold > TEL and LEV, and 32-fold > AZI. LZD was the least active agent tested against MP with MIC<sub>90</sub> = 128 µg/ml. Two macrolide-resistant MP with AZI MICs > 32 µg/ml were inhibited by CEM-101 at 0.5 µg/ml. MBCs were ≥ 16-fold greater than MICs for 9 MP indicating the drug is bacteriostatic. All mycoplasmas and ureaplasma isolates were inhibited by CEM-101 at concentrations ≤ 0.5 µg/ml, making it the most potent compound tested overall. Excluding 4 macrolide-resistant MP, no isolate of any species tested had an MIC > 0.063 µg/ml for CEM-101.

**Conclusions:** CEM-101 showed excellent activity in vitro against human mycoplasmas and ureaplasmas, including macrolide-resistant MP, doxycycline-resistant UP and UU and was more potent than comparator drugs.

# F1-3980

## Antimicrobial Activity of CEM-101 a New Macrolide, Tested Against Diverse Collections of Bacterial Biowarfare/Bioterrorism(BW/BT) Agents

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**Background:** There continues to be a feared scenario of terrorist attacks with aerosolized microorganisms leading to mass infections. Given the added possibility of resistance to current treatments through genetic engineering or natural emergence, identifying effective antibiotics with novel mechanisms of action is critical to counter such an attack. In this study, we determined the minimum inhibitory concentrations (MICs) of a new macrolide CEM-101 against genotypic and geographic diverse collections of five BW/BT agents; *Bacillus anthracis*(BA), *Yersinia pestis*(YP), *Franciella tularensis*(FT), *Burkholderia mallei*(BM) and *B. pseudomallei*(BP).

**Methods:** Inoculum preparation and antibiotic microdilution were performed according to CLSI methods. MICs for 30 strains of each agent were determined by the microdilution method in 96-well plates, after an 18- or 42-hr incubation at 35°C.

**Results:** CEM-101, MIC ranges, MIC<sub>50</sub>, and MIC<sub>90</sub> (µg/ml) were; BA <0.008-0.015, <0.008, <0.008, YP 0.25-2, 1, 2, FT <0.08-4, 0.03, 2, BM 0.25-2, 1, 1, and BP 16,16,16.

**Conclusions:** CEM-101 a new macrolide antibiotic had significant *in vitro* activity against many of the BW/BT agents tested, with the exception of the BP strains. It has been shown that many macrolides preferentially accumulate intracellularly, which may enhance efficacy when used as a postexposure prophylaxis for preventing pneumonic disease among individuals exposed to aerosolized BW/BT agents. The potential broad-spectrum activity along with oral bioavailability makes CEM-101 an attractive candidate for treatment of BW/BT exposures and infections. Efficacy of CEM-101 in the animal-infection models for these agents should be evaluated.

# F1-3981

## Antimicrobial Characterization of CEM-101: PAE, Bactericidal Activity and Combinations

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**Background:** CEM-101, a new macrolide-ketolide for respiratory tract infection therapy, was tested to determine its killing activity (MBC and kill curves [KC]), post-antibiotic effect (PAE) and potency in combination with other agents (gentamicin [GEN], ceftriaxone [CRO], trimethoprim/sulfamethoxazole [TMP/SMX], vancomycin [VAN], levofloxacin [LEV]).

**Methods:** MBC determinations for CEM-101, telithromycin (TEL) and clarithromycin (CLA) used CLSI methods for 40 strains (6 species groups). KC used 8 strains (6 species groups). PAE was tested (5 strains) at 4x concentration for 1 or 2 hours exposure; TEL control. Drug interaction (synergy) tests were performed by checkerboard on 20 strains (*S. aureus* [SA], 7;  $\beta$ -streptococci [BSA] 6; *S. pneumoniae* [SPN] 7, see Table).

**Results:** CEM-101 exhibited low MBC/MIC ratios ( $\leq 4$ ) for BSA, SA and coagulase-negative staphylococci; and 2-fold greater potency than TEL. SA, enterococci and some macrolide/clindamycin-resistant (R) strains had higher ratios. KC results showed more rapid and greater cidal activity (concentration dependant) for CEM-101 compared to TEL. CEM-101/TEL PAE was: SA (2.3/2.6 hours), SPN (3.0/1.9), BSA (6.1/3.4), *H. influenzae* (3.7/1.2), *M. catarrhalis* (5.3/4.0). Interaction results with CEM-101 showing no antagonism and dominant additive or indifferent effects (Table).

**Conclusions:** CEM-101 exhibited cidal activity against several Gram-positive species at rates and an extent greater than TEL. PAE for CEM-101 was 2.3-6.1 and 3.7-5.3 hours for Gram-positive and -negative strains, respectively. No antagonism was found in synergy analyses, with enhanced inhibition most noted for combinations with CRO, GEN and TMP/SMX.

| Co-drug | Synergy  |         |          |             |            |               |
|---------|----------|---------|----------|-------------|------------|---------------|
|         | Complete | Partial | Additive | Indifferent | Antagonism | Indeterminate |
| CRO     | 0        | 2       | 5        | 12          | 0          | 1             |
| GEN     | 2        | 2       | 4        | 12          | 0          | 0             |
| LEV     | 0        | 0       | 3        | 17          | 0          | 0             |
| TMP/SMX | 0        | 2       | 4        | 14          | 0          | 0             |
| VAN     | 0        | 1       | 6        | 13          | 0          | 0             |
| All     | 2        | 7       | 22       | 68          | 0          | 1             |

# F1-3982

## Antimicrobial Characterization of CEM-101: Single Step, Selection by Passaging and Inducible Resistances

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**Background:** CEM-101, an orally administered macrolide-ketolide for respiratory tract infections (RTI), has potent activity against Gram-positive pathogens, *H. influenzae* and *M. catarrhalis*. To further define resistance (R) potential to CEM-101, 3 studies determined single step mutational rates, passaging selection and R induction by erythromycin (ERY).

**Methods:** Single step R used 1 *S. aureus* (SA), 1 *E. faecalis*, 2 *S. pneumoniae* (SPN), exposed to 4X, 8X and 16X MIC of CEM-101. Selection by passaging (7 days), used subinhibitory concentrations of CEM-101 and 3 comparators (azithromycin, clarithromycin, telithromycin [TEL]) with 18 strains including SA, CA-MRSA USA300, enterococci and SPN with various ERY-R patterns. Induction experiments with D-test (ERY inducer + CEM-101, clindamycin [CC] and TEL) tested 81 ERY-R, CC-S strains (17 spp).

**Results:** In R selection passaging, no significant variation was observed for 8 strains (44.4%; 4 spp). The remaining 10 strains exhibited modest CEM-101 MIC increases of 4- (7 strains) or 8-fold (3) without reversion of the MIC in drug-free media. R-selection during passaging was less for CEM-101 compared to other agents evaluated. No CEM-101 single-step mutations were observed at 4X, 8X or 16X CEM-101 MIC using inocula of  $6.5 \times 10^8$  (SPN) to  $6.0 \times 10^9$  (SA; see Table). Four patterns of ERY induction of CEM-101/TEL/CC-R were noted as follows: +/+ (39; 10 spp, *erm* A, B and C); -/+ (7; 2 spp, *erm* A); +/- (10; 4 spp, *msr* A) and -/- (25; 10 spp, none).

**Conclusions:** CEM-101 propensity for R was considered low for single step at  $<10^{-8}$  or  $10^{-9}$ ; infrequent by selection (passaging) and induction was comparable to CC but less than TEL. CEM-101 warrants further consideration as a RTI treatment agent.

**Table. Results of the single-step mutation studies**

| Organism                                      | Single step mutation rate <sup>a</sup> |
|---|--|
| <i>E. faecalis</i> ATCC 29212                 | $<4.0 \times 10^{-9}$                  |
| <i>S. aureus</i> ATCC 29213                   | $<6.0 \times 10^{-9}$                  |
| <i>S. pneumoniae</i> 063-1085A (wild-type)    | $<1.4 \times 10^{-9}$                  |
| <i>S. pneumoniae</i> 075-241B ( <i>erm</i> B) | $<6.5 \times 10^{-8}$                  |

a. Strains were exposed at 4X, 8X and 16X CEM-101 MIC.

# F1-3984

## Assessment of CEM-101 Susceptibility Testing Conditions and Optimization of Disk Diffusion Methods

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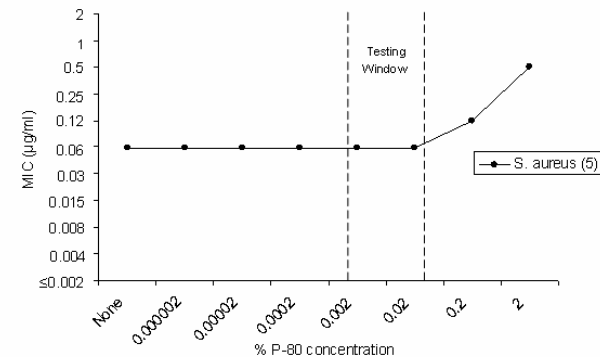
**Background:** CEM-101, a novel macrolide-ketolide, potent activity has against susceptible (S) and resistant (R) respiratory tract infection pathogens. To prepare it for clinical trials, in vitro S testing details for MIC methods and the selection of disk diffusion (DD) CEM-101 content were established.

**Methods:** CLSI broth microdilution (BMD) was used and test conditions were modified to determine effects on CEM-101 activity; anaerobic and CO<sub>2</sub> atmosphere; 5 x 10<sup>3</sup> and 5 x 10<sup>7</sup> inoculum; LHB and HTM; pH 5, 6 and 8; human serum protein at 5, 10 and 20%; calcium at 3.7 and 50 mg/L and use of polysorbate-80 (P-80) surfactant. Simultaneous changes in the pH and protein were also tested. CEM-101 DD tests with 2-, 5-, 10-, 15- and 30-µg versus 70 selected S and R strains.

**Results:** By changing BMD test conditions only the following resulted in significantly (34-fold) elevated CEM-101 MIC results: high inoculum (5 x 10<sup>7</sup>), P-80 at 2% (see Figure) and pH 5 or 6. pH effect was muted for pH 6 by presence of 10% human serum protein. Scattergrams with CEM-101 MIC values and zone diameters produced r values of 0.93-0.97 and the 15-µg disk (like other macrolides) provided best discrimination of S and R strains of staphylococci, enterococci and *H. influenzae*.

**Conclusions:** CEM-101 S testing by CLSI methods appears to be optimized for clinical trials using published BMD procedures without P-80. The 15-µg CEM-101 DD test accurately assesses this new agent's activity.

Figure. Average MIC values for five tested *S. aureus* strains when combined with various concentrations of a surfactant (polysorbate-80, P-80 at 0.000002 to 2%).



# L-683

## A Comparative Study of the Safety and Efficacy of Cethromycin (CER) to Clarithromycin (CLR) for the Treatment of Community Acquired Pneumonia (CAP) in Adults (CL05-001)

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**Background:** CAP is a major cause of death globally and is the sixth most common cause of death in the US. CER is a new ketolide having a potent antibacterial spectrum with activity against penicillin- and macrolide-resistant Gram-positive bacteria.

**Methods:** A phase III, double-blind, randomized, parallel group, multi-center study, conducted in the US, Canada, and South Africa, compared the safety and efficacy of CER 300 mg QD to CLR (BIAXIN® Filmtab®) 250 mg BID, for 7 days. Subjects were ambulatory adults with mild-to-moderate CAP, as evidenced by appropriate signs and symptoms, and by a positive chest x-ray as interpreted by a radiologist. The primary end point was clinical response at the test-of-cure (TOC) visit (days 14 to 22) in the intent-to-treat (ITT) and per protocol (PP) populations.

**Results:** A total of 584 subjects were randomized, and 582 were treated. In the PP population, 142 subjects were identified with a pre-treatment pathogen; the most common were *H. influenzae*, *M. pneumoniae*, *S. pneumoniae*, and *S. aureus*. The bacteriological cure rates in this population were 97.3% and 97.1% for CER and CLR, respectively. The incidence of treatment emergent adverse events was 38.9% and 38.8% for CER and CLR, respectively. The most commonly reported adverse events were dysgeusia (7.6%), diarrhea (4.5%), and nausea (4.5%) for CER.

**Conclusions:** CER achieved non-inferiority of clinical response in CAP compared to CLR. CER demonstrated safety results that were similar to those observed with CLR and were consistent with the favorable safety profile seen with CER in previous clinical trials.

|     | Clinical Cure (%) |      |                           | Radiographic Cure (%) |      |                           |
|-----|-------------------|------|---------------------------|-----------------------|------|---------------------------|
|     | CER               | CLR  | CI                        | CER                   | CLR  | CI                        |
| ITT | 83.1              | 81.1 | [-4.8%, +8.9%] (p=0.5667) | 82.4                  | 81.5 | [-6.0%, +7.7%] (p=0.8195) |
| PP  | 94.0              | 93.8 | [-4.5%, +5.1%] (p>0.9999) | 92.7                  | 92.3 | [-4.9%, +5.6%] (p>0.9999) |