Presentation 007
Monday

# *In Vitro* Activity of Eravacycline and Comparators Against *Acinetobacter baumannii*, Including Carbapenem-Resistant Strains, and *Stenotrophomonas maltophilia* Isolated from Patients in the US


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## Abstract

**Background:** Eravacycline (ERV) is a novel, fully-synthetic fluorocycline antibiotic of the tetracycline class in development for the treatment of serious infections, including those caused by multidrug-resistant (MDR) pathogens. The purpose of this study was to evaluate in vitro activity of ERV and comparators against *Acinetobacter baumannii* (AB), including strains with a carbapenem-resistant (CR) phenotype, and *Stenotrophomonas maltophilia* (SM) isolated from US patients.

**Methods:** Non-duplicate, non-consecutive, single-patient clinical isolates of AB and SM were collected from US patients in 2013-2014. MICs for ERV and comparators against 380 isolates from both species were determined by CLSI broth microdilution. Susceptibility was determined with CLSI 2015 breakpoints, where available. CR in AB (CRAB) was defined as resistant to imipenem.

**Results:** ERV *in vitro* activity against AB and SM is shown in the following Table. ERV $MIC_{90}$ for all AB and SM isolates was 1 mg/L, and 2 mg/L for CRAB. TGC, imipenem (IPM), and colistin (CST) $MIC_{90}$ for AB were 4, >8, and 2 mg/L, respectively, and remained consistent for CRAB. Susceptibility to CST for all AB was 95%, while for CRAB was 93%. Susceptibility to IPM for all AB and CRAB was poor (39.4%, 0%, respectively). TGC, IPM, and CST $MIC_{90}$ for SM were 2, >8, and 4 mg/L, respectively.

| Organism (N) | ERV | TGC | IPM | CST |
|---|---|---|---|---|
| | $MIC_{50/90}$ | $MIC_{50/90}$ | $MIC_{50/90}$ | $MIC_{50/90}$ |
| *A. baumannii* (349) | 0.5/1 | 1/4 | >8/>8 | 1/2 |
| CRAB (207) | 0.5/2 | 2/4 | >8/>8 | 1/2 |
| *S. maltophilia* (31) | 0.5/1 | 1/2 | >8/>8 | 1/4 |

$MIC_{50/90}$ = minimal inhibitory concentration required to inhibit growth of 50/90% of isolates (mg/L).

**Conclusion:** Overall, ERV $MIC_{90}$ for AB and SM was 1 mg/L (2 mg/L for CRAB), and was 2-4 fold more potent than TGC or CST, and up to 8-fold more potent than IPM. ERV shows promising activity against AB and SM, including CRAB, isolated from US patients.


## Introduction

Gram-negative bacteria are common causes of intra-abdominal infections, urinary tract infections, and other serious infections. Moreover, resistance amongst Gram-negative pathogens is increasing. Eravacycline is a novel, fully-synthetic fluorocycline antibiotic of the tetracycline class in development for the treatment of serious infections, including those caused by multidrug-resistant (MDR) pathogens. ERV is in phase 3 clinical development for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis.

The pharmacokinetics and pharmacodynamics of eravacycline have been studied in animals and during clinical trials. Two doses of eravacycline were used in clinical trials of cIAI that produced favorable results in terms of efficacy, safety and pharmacokinetic evaluations: 1.5 mg/kg q24h and 1 mg/kg q12h (1, 2). In a phase 1 multiple-ascending dose study in healthy volunteers, the $C_{max}$ values after a 60-minute infusion were 2.7 and 2.1 mg/L at day 1, respectively, and 1.9 and 1.8 mg/L at day 10, respectively, based on a four-compartment model (3). $AUC_{ss}$ values were 8.7 and 12.7 mg·hr/L for the 1.5 mg/kg q24h dose and 1 mg/kg q12h dose, respectively (3).

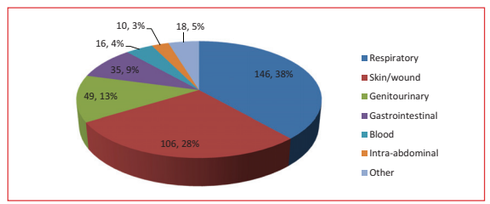
Renal clearance of 3.0-3.5 L/h was reported in healthy volunteers with approximately 16% excreted unchanged in the urine. In healthy subjects who received multiple IV doses of 1.5 mg/kg q24h over 60 minutes, eravacycline concentrations in urine collected from 0–8 h were 6.9 ± 1.2 mg/L on day 1 and 13.3 ± 3.4 mg/L on day 10 (2).

The purpose of this study was to evaluate the *in vitro* activity of eravacycline and comparators against *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*, including strains with a carbapenem-resistant (CR) phenotype, isolated from patients in the US.

## Methods

- A total of 380 clinical isolates (349 *A. baumannii* and 31 *S. maltophilia*) were collected from various body sites from 2013-2014, including CR isolates (breakdown by site of infection is given in Figure 1).
- Minimal inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines (4).
- Quality control testing was performed each day of testing as specified by the CLSI using *E. coli* ATCC 25922, *E. coli* ATCC 35218 and *P. aeruginosa* ATCC 27853.
- Antibiotic susceptibility was determined using CLSI 2015 break-points (5), where available.
- Carbapenem-resistant (CR) was defined as resistance to imipenem.

**Figure 1. Isolate counts (n, %) by source of infection (N=380)**




Other = HEENT (Head, Eyes, Ears, Nose, and Throat), Instrument, Muscular, or Skeletal sources

## Results

- The eravacycline $MIC_{50/90}$ values for all *A. baumannii* and *S. maltophilia* isolates were 0.5/1 mg/L. The eravacycline $MIC_{50/90}$ values for CR *A. baumannii* were 0.5/2 mg/L (Table 1).
- The antimicrobial activity of eravacycline and comparators is shown in Table 2. MIC distributions for eravacycline, tigecycline, colistin and imipenem for *A. baumannii*, CR *A. baumannii*, and *S. maltophilia* are shown in Figures 2, 3, and 4, respectively.
- The tigecycline $MIC_{90}$ was 4 mg/L for *A. baumannii*, including the CR *A. baumannii* subset, and 2 mg/L for *S. maltophilia*. The colistin $MIC_{90}$ was 2 mg/L for *A. baumannii*, including the CR *A. baumannii* subset, and 4 mg/L for *S. maltophilia*. Both *A. baumannii*, including the CR *A. baumannii* subset, and *S. maltophilia* isolate groups had overall $MIC_{90}$ values of >8 mg/L for imipenem.
- Based on $MIC_{90}$ values, the potency of eravacycline was 4-fold greater than that of tigecycline against *A. baumannii* overall and *S. maltophilia*, and 2-fold greater than tigecycline against carbapenem-resistant *A. baumannii*. The potency of eravacycline was up to 2-fold greater than colistin against *A. baumannii* overall and up to 4-fold greater than colistin against *S. maltophilia*.

**Table 1. MIC Distribution (Cumulative %) for Eravacycline against *Acinetobacter baumannii*, including CR phenotype, and *Stenotrophomonas maltophilia***

| Organism (n) | Number of isolates (cumulative %) inhibited at eravacycline MIC (mg/L) of: | | | | | | | | | MIC (mg/L) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | $MIC_{50}$ | $MIC_{90}$ | Range |
| *A. baumannii* (349) | 34 (9.7%) | 40 (21.2%) | 25 (28.4%) | 59 (45.3%) | 113 (77.2%) | 49 (91.7%) | 27 (99.4%) | 2 (100%) | | 0.5 | 1 | 0.03-4 |
| CR *A. baumannii* (207) | | 2 (1%) | 7 (4.4%) | 42 (24.6%) | 86 (66.2%) | 42 (86.5%) | 26 (99%) | 2 (100%) | | 0.5 | 2 | 0.06-4 |
| *S. maltophilia* (31) | | 1 (3.2%) | 2 (9.7%) | 10 (41.9%) | 10 (74.2%) | 5 (90.3%) | 3 (100%) | | | 0.5 | 1 | 0.06-2 |

Underlined = $MIC_{50}$; Red text = $MIC_{90}$; CR = Carbapenem-resistant

**Table 2. Antimicrobial activity of eravacycline and comparator agents against *Acinetobacter baumannii*, including CR phenotype, and *Stenotrophomonas maltophilia***

| Organism (n)/ Antimicrobial Agent | MIC (mg/L) | | | %S / %I / %R[a] |
|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | Range | CLSI |
| ***A. baumannii* (349)** | | | | |
| Aztreonam | > 16 | > 16 | ≤ 0.5->16 | –/–/– |
| Cefepime | 16 | > 16 | ≤ 0.25->16 | 32.7/23.8/43.6 |
| Ceftazidime | > 16 | > 16 | ≤ 0.5->16 | 31.5/4/64.5 |
| Ceftriaxone | > 32 | > 32 | ≤0.5->32 | 16.3/16.1/67.6 |
| Colistin | 1 | 2 | 0.25->4 | 94.6/–/5.4 |
| **Eravacycline** | **0.5** | **1** | **0.03-4** | **–/–/–** |
| Gentamicin | > 8 | > 8 | 0.5->8 | 36.4/4.6/59 |
| Imipenem | > 8 | > 8 | ≤0.25->8 | 39.5/1.2/59.3 |
| Levofloxacin | > 4 | > 4 | ≤ 0.25->4 | 24.1/3.7/72.2 |
| Piperacillin/tazobactam | > 64 | > 64 | ≤ 0.5->64 | 28.7/6.6/64.8 |
| Tetracycline | > 8 | > 8 | 0.25->8 | 28.4/11.5/60.2 |
| Tigecycline | 1 | 4 | 0.06-8 | –/–/– |
| **CR *A. baumannii* (207)** | | | | |
| Aztreonam | > 16 | > 16 | 8->16 | –/–/– |
| Cefepime | > 16 | > 16 | 2->16 | 7.3/31.9/60.9 |
| Ceftazidime | > 16 | > 16 | 4->16 | 5.8/4.8/89.4 |
| Ceftriaxone | > 32 | > 32 | 8->32 | 1/5.3/93.7 |
| Colistin | 1 | 2 | 0.25->4 | 92.3/–/7.7 |
| **Eravacycline** | **0.5** | **2** | **0.06-4** | **–/–/–** |
| Gentamicin | > 8 | > 8 | 0.5->8 | 16.4/4.8/78.7 |
| Imipenem | > 8 | > 8 | 8->8 | –/–/100 |
| Levofloxacin | > 4 | > 4 | 1->4 | 1/3.9/95.2 |
| Piperacillin/tazobactam | > 64 | > 64 | 16->64 | 0.5/1.5/98.1 |
| Tetracycline | > 8 | > 8 | 2->8 | 2.9/15.5/81.6 |
| Tigecycline | 2 | 4 | 0.25-8 | –/–/– |
| ***S. maltophilia* (31)** | | | | |
| Aztreonam | > 16 | > 16 | 4->16 | –/–/– |
| Cefepime | 16 | > 16 | 2->16 | –/–/– |
| Ceftazidime | 4 | > 16 | 1->16 | 74.2/3.2/22.6 |
| Ceftriaxone | > 32 | > 32 | 32->32 | –/–/– |
| Colistin | 1 | 4 | ≤ 0.12->4 | –/–/– |
| **Eravacycline** | **0.5** | **1** | **0.06-2** | **–/–/–** |
| Gentamicin | > 8 | > 8 | 1->8 | –/–/– |
| Imipenem | > 8 | > 8 | >8->8 | –/–/– |
| Levofloxacin | 1 | 4 | ≤ 0.25->4 | 74.2/22.6/3.2 |
| Piperacillin/tazobactam | 64 | > 64 | 4->64 | –/–/– |
| Tetracycline | 8 | > 8 | 1->8 | –/–/– |
| Tigecycline | 1 | 2 | 0.12-2 | –/–/– |

[a]Criteria as published by the CLSI (2015); "–" = No breakpoint defined; CR = Carbapenem-resistant

**Figure 2. MIC distribution of eravacycline, tigecycline, colistin and imipenem against *A. baumannii* (N=349)**

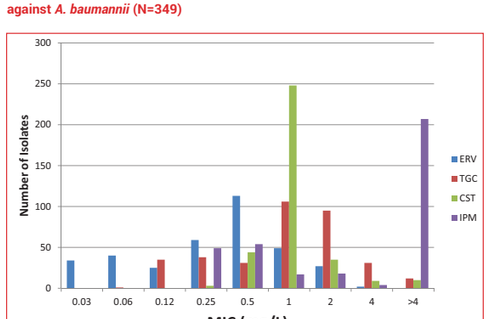



**Figure 3. MIC distribution of eravacycline, tigecycline, colistin and imipenem against CR *A. baumannii* (N=207)**

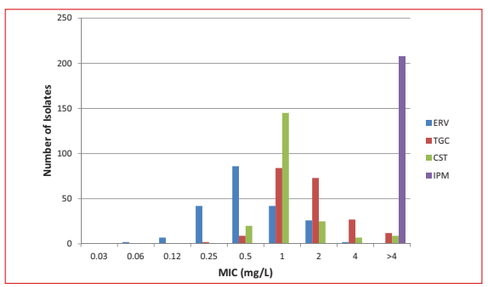
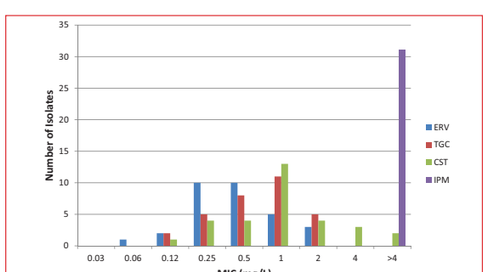



**Figure 4. MIC distribution of eravacycline, tigecycline, colistin and imipenem against *S. maltophilia* (N=31)**




## Conclusions

- Eravacycline was active against isolates of *Acinetobacter baumannii*, including carbapenem-resistant strains, and *Stenotrophomonas maltophilia* collected within the US.


**References**

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