# *In vitro* activity of eravacycline and comparators against *Acinetobacter baumannii*, including carbapenem-resistant strains, and *Stenotrophomonas maltophilia* isolated from patients in Europe

**Matteo Bassetti[1], Ian Morrissey[2], Trudy Grossman[3], Katherine Luepke[3], Patrick Scoble[3], Joyce Sutcliffe[3]**

[1]Santa Maria Misericordia Hospital, Udine, Italy; [2]IHMA Europe Sarl, Epalinges, Switzerland; [3]Tetraphase Pharmaceuticals, Watertown, MA, USA

Contact:
Tetraphase Pharmaceuticals Medical Information (TPMI)
medinfo@tphase.com
617-715-3600

## Introduction

Eravacycline is a novel, fully-synthetic fluorocycline antibiotic of the tetracycline class with broad-spectrum activity in development for the treatment of serious infections, including those caused by MDR pathogens. Eravacycline has been evaluated in phase 3 studies for the treatment of cIAI and for cUTI, including pyelonephritis. It is important to evaluate the activity of eravacycline against European clinical isolates of key pathogens because eravacycline will be under review by the European Medicines Agency for potential approval in Europe.

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 Europe.

## Methods

In this study, a total of 249 clinical isolates (150 *A. baumannii* and 99 *S. maltophilia*) were collected from 2013-2014, including CR isolates.

- Minimum inhibitory concentration (MIC) endpoints were determined by broth microdilution according to CLSI guidelines (1).
- Quality control testing was performed each day of testing as specified by the CLSI using *E. coli* ATCC 25922 and *E. coli* ATCC 35218.
- Antibiotic susceptibility was determined using EUCAST break-points (2), when available.
- CR was defined as resistance to imipenem.

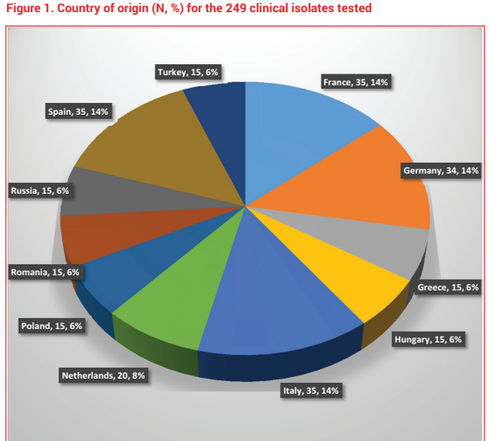
## Results

- The eravacycline $MIC_{50/90}$ for all *A. baumannii* and *S. maltophilia* isolates was 0.5/1 mg/L. The eravacycline $MIC_{50/90}$ for CR *A. baumannii* isolates was also 0.5/1 mg/L. The tigecycline and colistin $MIC_{50/90}$ for all *A. baumannii* was 1/2 mg/L, and 1/4 mg/L for the CR subset. The tigecycline $MIC_{50/90}$ for *S. maltophilia* was 0.5/2 mg/L. The colistin $MIC_{50/90}$ for *S. maltophilia* was 1/>4mg/L.
- Summary of $MIC_{50/90}$ for ERV, as well as cumulative MIC distribution for eravacycline against *A. baumannii* and *S. maltophilia*, including CR phenotypes are shown in Table 1. There were no CR *S. maltophilia* isolates.

## Results (cont'd)

- Country of origin for the clinical isolates is shown in Figure 1.
- Figure 2 shows the cumulative MIC distribution of eravacycline, tigecycline, and colistin against *A. baumannii*, while Figure 3 shows the cumulative MIC distribution for eravacycline, tigecycline, and colistin, against CR *A. baumannii*. Figure 4 shows the MIC distribution of eravacycline, tigecycline, and colistin for *S. maltophilia*.
- Figure 5 shows the isolate counts by source of infection (N=249)
- The antimicrobial activity of eravacycline and comparator agents against *A. baumannii* and *S. maltophilia*, including CR phenotypes, is shown in Table 2.
- The susceptibility of colistin for all *A. baumannii* isolates was 92%, while the susceptibility for the CR subset decreased to 88%.

**Figure 1. Country of origin (N, %) for the 249 clinical isolates tested**



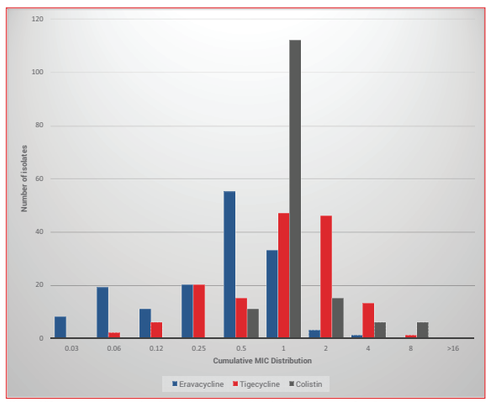

UK, United Kingdom of Great Britain and Northern Ireland; *Countries included as "Other" (Austria, Belgium, Denmark, and Greece) had less than 5 isolates each.

**Table 1. Cumulative MIC distribution for eravacycline for *A. baumannii* and *S. maltophilia* including drug resistant phenotypes (n>5)**

| | Number of isolates (cumulative %) inhibited at eravacycline MIC (mg/L) of: | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Organism (n)** | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | ≥16 | $MIC_{50}$ | $MIC_{90}$ |
| *Acinetobacter baumannii* (150) | 8 (5.33) | 19 (18) | 11 (25.3) | 20 (38.7) | 55 (75.3) | 33 (97.3) | 3 (99.3) | 1 (100) | | | 0.5 | 1 |
| *A. baumannii* CR (99) | | 2 (2.02) | 7 (9.09) | 13 (22.2) | 46 (68.7) | 27 (96) | 3 (99) | 1 (100) | | | 0.5 | 1 |
| *Stenotrophomonas maltophilia* (99) | 1 (1.01) | | 11 (12.1) | 32 (44.4) | 33 (77.8) | 15 (92.3) | 5 (98) | 1 (99) | 1 (100) | | 0.5 | 1 |

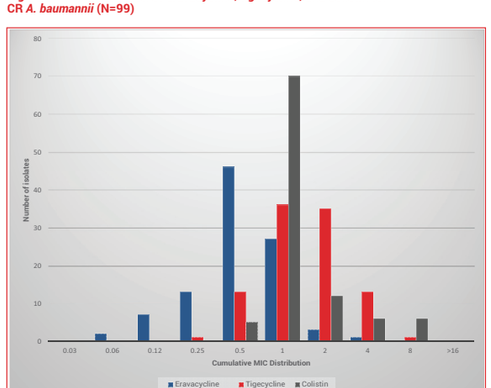
Underlined = MIC50; Red text = MIC90

**Figure 2. MIC distribution of eravacycline, tigecycline, and colistin for *A. baumannii* (N=150)**



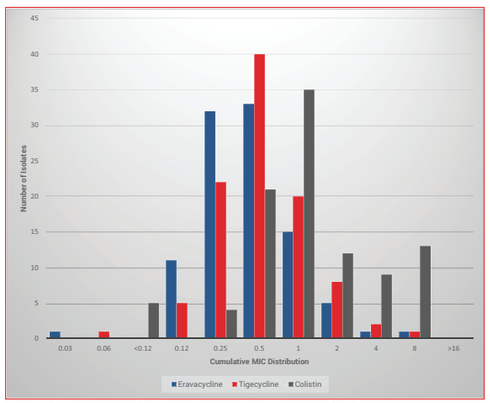

*Highest MIC tested for colistin was 4 mg/L, so isolates represented as >4 mg/L are graphed as 8 mg/L

**Figure 3. MIC distribution of eravacycline, tigecycline, and colistin for CR *A. baumannii* (N=99)**



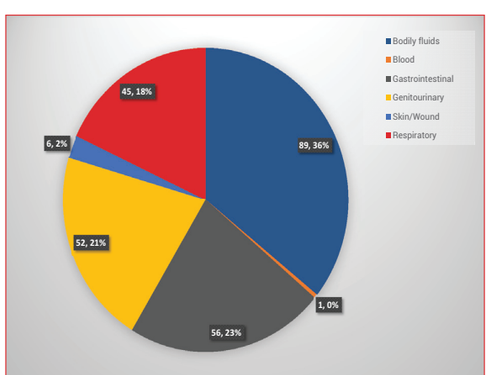

*Highest MIC tested for colistin was 4 mg/L, so isolates represented as >4 are graphed as 8 mg/L

**Figure 4. MIC distribution of eravacycline, tigecycline, and colistin for *S.maltophilia* (N=99)**




*Highest MIC tested for colistin was 4 mg/L, so isolates represented as >4 are graphed as 8 mg/L

**Figure 5. Isolate counts by source of infection (N=249)**




Bodily fluids Sources: Abscess/Pus, Abdominal Fluid, Peritoneal Fluid, Tissue, and Ulcer

**Table 2. Antimicrobial activity of eravacycline and comparator agents against *A. baumannii* and *S. maltophilia*, including CR phenotypes**

| Organism/Antimicrobial Agent (No. Tested) | MIC (mg/L) | | %S / %I / %R[a] | |
|---|---|---|---|---|
| | $MIC_{50}$ | $MIC_{90}$ | Range | EUCAST |
| ***A. baumannii* (150)** | | | | |
| Aztreonam | > 16 | > 16 | 1->16 | --/--/-- |
| Cefepime | > 16 | > 16 | ≤ 0.25->16 | --/--/-- |
| Ceftazidime | > 16 | > 16 | ≤ 0.5->16 | --/--/-- |
| Ceftriaxone | > 32 | > 32 | 2->32 | --/--/-- |
| Colistin | 1 | 2 | 0.5->4 | 92/--/8 |
| **Eravacycline** | **0.5** | **1** | **0.03-4** | **--/--/--** |
| Gentamicin | > 8 | > 8 | 1->8 | 24.7/--/ 75.3 |
| Imipenem | > 8 | > 8 | ≤0.25->8 | 32/2/66 |
| Levofloxacin | > 4 | > 4 | ≤ 0.25->4 | 16.7/--/ 83.3 |
| Piperacillin/tazobactam | > 64 | > 64 | ≤ 0.5->64 | --/--/-- |
| Tetracycline | > 8 | > 8 | 1->8 | --/--/-- |
| Tigecycline | 1 | 2 | 0.06-8 | --/--/-- |
| ***A. baumannii* CR (99)** | | | | |
| Aztreonam | > 16 | > 16 | 16->16 | --/--/-- |
| Cefepime | > 16 | > 16 | 8->16 | --/--/-- |
| Ceftazidime | > 16 | > 16 | 8->16 | --/--/-- |
| Ceftriaxone | > 32 | > 32 | 32->32 | --/--/-- |
| Colistin | 1 | 4 | 0.5->4 | 87.9/--/ 12.1 |
| **Eravacycline** | **0.5** | **1** | **0.06-4** | **--/--/--** |
| Gentamicin | > 8 | > 8 | 2->8 | 8.08/--/ 91.9 |
| Imipenem | > 8 | > 8 | > 8->8 | 0/0/100 |
| Levofloxacin | > 4 | > 4 | 4->4 | 0/0/100 |
| Piperacillin/tazobactam | > 64 | > 64 | 64->64 | --/--/-- |
| Tetracycline | > 8 | > 8 | 2->8 | --/--/-- |
| Tigecycline | 1 | 4 | 0.25-8 | --/--/-- |
| ***S. maltophilia* (99)** | | | | |
| Aztreonam | > 16 | > 16 | 1->16 | --/--/-- |
| Cefepime | > 16 | > 16 | 0.5->16 | --/--/-- |
| Ceftazidime | 8 | > 16 | ≤ 0.5->16 | --/--/-- |
| Ceftriaxone | > 32 | > 32 | 1->32 | --/--/-- |
| Colistin | 1 | > 4 | ≤ 0.12->4 | --/--/-- |
| **Eravacycline** | **0.5** | **1** | **0.03-8** | **--/--/--** |
| Gentamicin | > 8 | > 8 | ≤ 0.25->8 | --/--/-- |
| Imipenem | > 8 | > 8 | 4->8 | --/--/-- |
| Levofloxacin | 1 | 4 | ≤ 0.25->4 | --/--/-- |
| Piperacillin/tazobactam | 64 | > 64 | 2->64 | --/--/-- |
| Tetracycline | > 8 | > 8 | 2->8 | --/--/-- |
| Tigecycline | 0.5 | 2 | 0.06-8 | --/--/-- |

Criteria as published by the EUCAST (2015); "--" defined as no breakpoint defined

## Conclusions

- Overall, the eravacycline $MIC_{90}$ for *A. baumannii* (including the CR subset) and *S. maltophilia* was 1 mg/L, and was found to be 2-4 fold more potent than tigecycline and colistin, comparatively.
- Based on $MIC_{90}$ values, the potency of eravacycline was 2-4-fold greater than that of tigecycline.
- The origin of country of the bacterial isolate was widely diverse throughout Europe, with the source of infection for the majority of the isolates coming from bodily fluids, respiratory, gastrointestinal, and the genitourinary regions.
- Eravacycline shows promising activity against *A. baumannii*, including CR-resistant isolates, and *S. maltophilia* from European patients.

**References**

(1) CLSI, 2015. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Eighth Edition M07-A10. Clinical and Laboratory Standards Institute (CLSI), Wayne, PA 19087-1898 USA.

(2). The European Committee on Antimicrobial Susceptibility testing, 2015. Breakpoint tables for interpretation of MICs and zone diameters. Version 5.0 http://www.eucast.org

**Presented at the 26th ECCMID, April 9 - 12, 2016, Amsterdam, Netherlands**