**The Novel Broad-Spectrum Fluorocycline TP-434 is Active Against MDR Gram-Negative Pathogens**


Tetraphase Pharmaceuticals, Watertown, Mass., US

Contact: Leland Webster
Tetraphase Pharmaceuticals
lwebster@tphase.com

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### Revised Abstract

**Background:** TP-434 is a novel broad-spectrum (Vrial) fluorocycline antibiotic being developed by Tetraphase Pharmaceuticals. It has potent activity against multidrug-resistant (MDR) gram-negative pathogens associated with complicated nosocomial and community infections, including Enterobacteriaceae such as Escherichia coli and Klebsiella spp.; extended-spectrum beta-lactamases (ESBLs), and carbapenemases, MDR Acinetobacter baumannii, and anerobic bacteria such as Bacteroides fragilis.

**Methods:** Using standard CLSI methodology, TP-434 and clinical isolates were tested against recent isolates of E. coli (n=116), 97 were ESBL, K. pneumoniae (n=219, 90 were ESBL), K. oxytoca (n=41, 11 were ESBL), A. baumannii (n=8) and B. fragilis (n=30). The ESBL genotype of select isolates was characterized by PCR. In vitro bactericidal activity over 24 hours was determined using standard time-kills with vigorously aerated in rich media. In vivo drug activity was assessed in murine salmonella model challenged intraperitoneally with ESBL (SIV) producing E. coli strain EC134 and TP-434 administered intravenously, measuring survival at 48 hours.

**Results:** TP-434 showed MIC/\(\text{MIC}_90\) values (microgram/ml) of 0.39/0.5, 0.52/0.5, 0.52/0.5 and 0.51/0.5 against extended-spectrum beta-lactamase (ESBL) isolates of E. coli, K. pneumoniae, K. oxytoca, A. baumannii and B. fragilis, respectively. The presence of TEM, SHV, CTX-M, OXA, DHA, FOX, MOX, ACT, KPC, and ESBL genes has no impact on TP-434:MIC/\(\text{MIC}_90\) values (microgram/ml) against ESBL isolates. TP-434 was bactericidal in vitro against E. coli, K. pneumoniae, and A. baumannii, including ESBL-expressing isolates, showing 3-4 log reductions in colony forming units over 24 hours. The IC\(_50\) of TP-434 in a mouse sepsis model was 1.7 mg/kg versus a 3.5 mg/kg for tigecycline.

**Conclusions:** TP-434 shows superior activity in vitro versus clinical comparisons against problematic gram-negative bacteria, supporting its advancement into a Phase 2 clinical trial for complicated intra-abdominal infections.