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TP-434 Has Potential to Treat Complicated Urinary Tract Infections (cUTI)

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Abstract

Background. TP-434 is a novel broad-spectrum fluorocycline being developed by Tetraphase Pharmaceuticals for a wide range of infections, including cUTIs. Due to the growing prevalence of multidrug-resistant (MDR) *Enterobacteriaceae* and a growing high-risk (diabetic and aging) population, TP-434 could be an important addition for treatment of cUTIs.

Methods: MICs of TP-434 were done using CLSI standard procedures. Female BALB-c mice were infected with 10⁶ bacteria in 0.2% Carrageenan intravenously (IV) to establish pyelonephritis. TP-434 was administered IV 12 and 24 hours post-infection and 36 hours post-infection the kidneys were cultured for bacterial load. Pharmacokinetics (PK) of TP-434 in plasma and urine in healthy subjects after IV or oral administration were evaluated using validated bioanalytical procedures.

Results: TP-434 has an excellent spectrum for empiric treatment of cUTIs caused by either gram-negative or gram-positive bacteria, with MIC₅₀/MIC₉₀ values of 0.25/0.5 and 0.5/1 µg/ml against 176 *Escherichia coli* and 219 *Klebsiella pneumoniae* isolates, respectively, and MIC₉₀s of 0.12 µg/ml vs. vancomycin-susceptible (n=102) or -resistant (n=88) enterococci or MRSA (n=137). TP-434 was highly efficacious and comparable to or better than IV meropenem in reducing kidney bacterial burden by 3.8 and 2.4 logs when given at 5 and 20 mg/kg in mice challenged with uropathogenic extended-spectrum β-lactamase-producing *E. coli* or *Klebsiella pneumoniae*, respectively. The concentration of TP-434 in human urine 0-8 h post-dose of 1.5 mg/kg IV q24h was 6.9 and 13.3 µg/mL on Days 1 and 10, respectively. A single 300 mg oral dose of TP-434 provided urine levels in excess of 9 µg/mL over the 24-hour period following ingestion.

Conclusion: The combined potency/efficacy of TP-434 against key MDR uropathogens and in murine pyelonephritis along with its ability to provide urine concentrations in man by both IV and oral routes at multiples above targeted MIC₉₀s support further evaluation for its use as an IV/oral step-down therapy for cUTI/pyelonephritis.

Introduction

Incidence of cUTI and pyelonephritis. A recent population-based study noted an overall rate of pyelonephritis, the most severe manifestation of UTIs, of 15–17 cases per 10,000 women and 3–4 cases per 10,000 men [1]. The in-hospital mortality rate for pyelonephritis varies from 7.3 cases per 1000 hospitalized women to 16.5 cases per 1000 hospitalized men [2]. There has been an increase in trimethoprim-sulfamethoxazole (TMP-SMX) resistance, especially in *E. coli*, the most common cause of both nosocomial and community-acquired pyelonephritis [3]. Thus, the IDSA guidelines for treatment of uncomplicated pyelonephritis recommend a fluoroquinolone (FQ) as first-line therapy [4]. Given the 30% resistance to TMP-SMX, the use of FQs has significantly increased (doubled), and will undoubtedly result in FQ resistance being even more prevalent in UTI pathogens. The majority of these patients are seen in the emergency room where empiric therapy is utilized. The increasing rate of extended spectrum β-lactamase (ESBL-producing *Enterobacteriaceae* and FQ resistance in the predominant pathogens will severely limit, or eliminate, oral options for treatment of ambulatory patients with even uncomplicated UTIs/pyelonephritis.

Appropriate antibiotic choice and mortality. Choice of an appropriate antibiotic regimen in older patients is particularly important because of the high burden of morbidity and mortality that accompanies UTI in this population. In one single-center chart review study, over 70% of elders diagnosed with UTI in the emergency department (ED) were admitted (compared to an overall elder admission rate of 50%) with an average length of stay of 5.4 days, 6% mortality, and 13% intensive care unit admission rate [5]. This is consistent with the admission rate of 44% in the ED for the elder patients in the 1996–2005 National Hospital Ambulatory Medical Care Survey (NHAMCS) [6]. Bacteremic UTI is more frequently seen in this growing population and was associated with 33% mortality in one study of admitted older patients [7], emphasizing the need for good empiric therapy. Thus, the development of an IV/oral drug which empirically covers the key problematic organisms for both nosocomial and ambulatory hospitalized patients would be highly desirable.

Frequency of uropathogen isolation in hospital-acquired cUTIs. A European multi-center 1-day prevalence study (pan European prevalence (PEP)-study) on healthcare-associated UTIs in urology tested 320 uropathogens from 232 urological departments in 42 European countries [8]. The following table provides their results in terms of frequency of isolation: *Escherichia coli* was responsible for 35% of UTIs, followed by *Pseudomonas* spp. (13%), *Klebsiella* spp. (10%), *Proteus* spp. (7%) and *Enterobacter* spp. (3%). Among Gram-positive uropathogens, *Enterococcus* spp. was isolated in 9% and *Staphylococcus* spp. in 4% of cases. *Candida* spp. was isolated in 3% of cases.

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Results

Table 1. TP-434 MIC₅₀/MIC₉₀ Values for Panels of Major cUTI Gram-negative and Gram-positive Isolates

| | | MIC _{50/90} (µg/ml) | | | | | | | | | | | | | |
|-------------------------|-----------------|------------------------------|-----------------|---------------------------|-----------------|-------------------------------|-----------------------------|--------------------------|-------------------------------|-----------------------------|----------------------------|------------------------------------|----------------------------------|-----------|-----------|
| <i>Escherichia coli</i> | | <i>Klebsiella pneumoniae</i> | | <i>Klebsiella oxytoca</i> | | <i>Enterobacter aerogenes</i> | <i>Enterobacter cloacae</i> | <i>Proteus mirabilis</i> | <i>Pseudomonas aeruginosa</i> | <i>Stenotr. maltophilia</i> | <i>Serratia marcescens</i> | Vancomycin-susceptible enterococci | Vancomycin-resistant enterococci | MSSA | MRSA |
| all n=176 | ESBL+ only n=97 | all n=219 | ESBL+ only n=90 | all n=41 | ESBL+ only n=11 | n=30 | n=134 | n=68 | n=88 | n=29 | n=30 | n=102 | n=88 | n=56 | n=137 |
| 0.25/0.5 | 0.25/0.5 | 0.5/1 | 0.5/2 | 0.25/1 | 0.5/1 | 0.25/0.25 | 0.5/2 | 2/4 | 8/16 | 0.25/1 | 1/1 | 0.06/0.12 | 0.06/0.12 | 0.25/0.25 | 0.06/0.12 |

Number of *E. coli* ESBL-producing (ESBL+) isolates: SHV (n=10), TEM (n=2), OXA (n=3), CTXM (30), DHA-1 (n=1), ACT (n=1), CMY (n=2)

Number of *K. pneumoniae* ESBL+ isolates: SHV (n=45), KPC (n=20), CTXM (n=19), DHA-1 (n=1), FOX (n=1), OXA (n=1), TEM (n=1)

Number of *K. oxytoca* ESBL+ isolates: SHV (n=4), CTXM (n=8), OXA (n=4), DHA (n=1)

Table 2. Mean ± SD Urine Concentrations of TP-434 (ng/mL) for IV SAD Cohorts

| Single IV Dose | Collection Interval | | | | |
|----------------|------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| | Day 1* 0 to 8 hours | Day 1* 8 to 24 hours | Day 2 24 to 48 hours | Day 3 48 to 72 hours | Day 4 72 to 96 hours |
| 0.1 mg/kg | 673 ± 292 | 355 ± 162 | 103 ± 64.0 | 34.3 ± 20.0 | 12.7 ± 9.6 |
| 0.25 mg/kg | 1728 ± 1025 | 1044 ± 405 | 279 ± 97.3 | 132 ± 58.7 | 42.7 ± 19.6 |
| 0.5 mg/kg | 3322 ± 1130 | 1515 ± 610 | 538 ± 134 | 211 ± 114 | 90.8 ± 44.5 |
| 1 mg/kg | 6878 ± 4212 | 3715 ± 1411 | 1151 ± 563 | 419 ± 243 | 180 ± 104 |
| 1.5 mg/kg | 8533 ± 4316 | 5467 ± 1534 | 1730 ± 482 | 863 ± 119 | 244 ± 94.4 |
| 2 mg/kg | 11715 ± 1915 | 5493 ± 364 | 2082 ± 791 | 883 ± 334 | 359 ± 129 |
| 3 mg/kg | 11573 ± 2778 | 18097 ± 8772 | 4835 ± 1550 | 1404 ± 494 | 538 ± 296 |

*All pre-infusion values were below the limit of detection

Table 3. Mean ± SD Urine Concentrations of TP-434 (ng/mL) for IV MAD Cohorts on Days 1-4 and on Days 10-13

| 10-Day Dose | Collection Interval | | | | | | | | | | |
|----------------------------|---------------------|---------------|----------------|----------------|----------------|--------------|--------------|---------------|----------------|----------------|----------------|
| | Day 1 ^c | | Day 2 | Day 3 | Day 4 | Day 10 | | | Day 11 | Day 12 | Day 13 |
| | 0 to 8 hours | 8 to 24 hours | 24 to 48 hours | 48 to 72 hours | 72 to 96 hours | Pre-infusion | 0 to 8 hours | 8 to 24 hours | 24 to 48 hours | 48 to 72 hours | 72 to 96 hours |
| 0.5 mg/kg QD ^a | 2798 ± 1116 | 1537 ± 468 | 3133 ± 1374 | 3067 ± 1041 | 3002 ± 1054 | 3733 ± 1888 | 4577 ± 2652 | 2250 ± 701 | 913 ± 328 | 515 ± 235 | 281 ± 140 |
| 1.5 mg/kg QD ^a | 9890 ± 2904 | 4483 ± 2401 | 8103 ± 1965 | 9288 ± 1645 | 8662 ± 1618 | 5927 ± 4646 | 8629 ± 8287 | 4851 ± 5055 | 1678 ± 1782 | 936 ± 921 | 495 ± 494 |
| 1.5 mg/kg QD ^b | 6920 ± 1160 | 2873 ± 1779 | 6583 ± 1648 | 5985 ± 1786 | 6508 ± 2790 | 9188 ± 4966 | 13317 ± 3420 | 5565 ± 2180 | 2293 ± 989 | 1157 ± 562 | 575 ± 322 |
| 1.0 mg/kg BID ^b | 4508 ± 741 | 8132 ± 2268 | 10570 ± 1754 | 12860 ± 2282 | 14608 ± 5527 | 26275 ± 8718 | 25060 ± 5292 | 9230 ± 2411 | 4304 ± 1078 | 1928 ± 448 | 1010 ± 490 |

^aInfused over 30 minutes; ^bInfused over 60 minutes; ^cAll Day 1 pre-infusion values were below the limit of detection

Methods

Antibiotic Susceptibility. TP-434 was tested against panels of recent clinical aerobic isolates, including quality control strains according to methods published by Clinical and Laboratory Standards Institute (CLSI) [9]. Recent clinical isolate collections included strains from Micromyx LLC, (Kalamazoo, MI), Eurofins Medinet (Chantilly, VA) and IHMA (Schaumburg, IL), largely from 2008-2009.

Kidney infection models. Female BALB/c mice (18 to 20 g) were infected with 0.2 mL *E. coli* EC200 or *K. pneumoniae* KP453 in 0.2% Carrageenan via intravenous injection. At 12 and 24 hours post-infection, mice (6 per group) were dosed IV with TP-434 or control antibiotic. At 36 hours post-initiation of treatment, mice were euthanized by CO₂ inhalation. The kidneys were removed, weighed, homogenized, serially diluted, and plated on TSA medium. The plates were incubated overnight at 37°C in 5% CO₂. CFU/gram of kidney was calculated by enumerating the plated colonies then adjusting for serial dilutions and kidney weight.

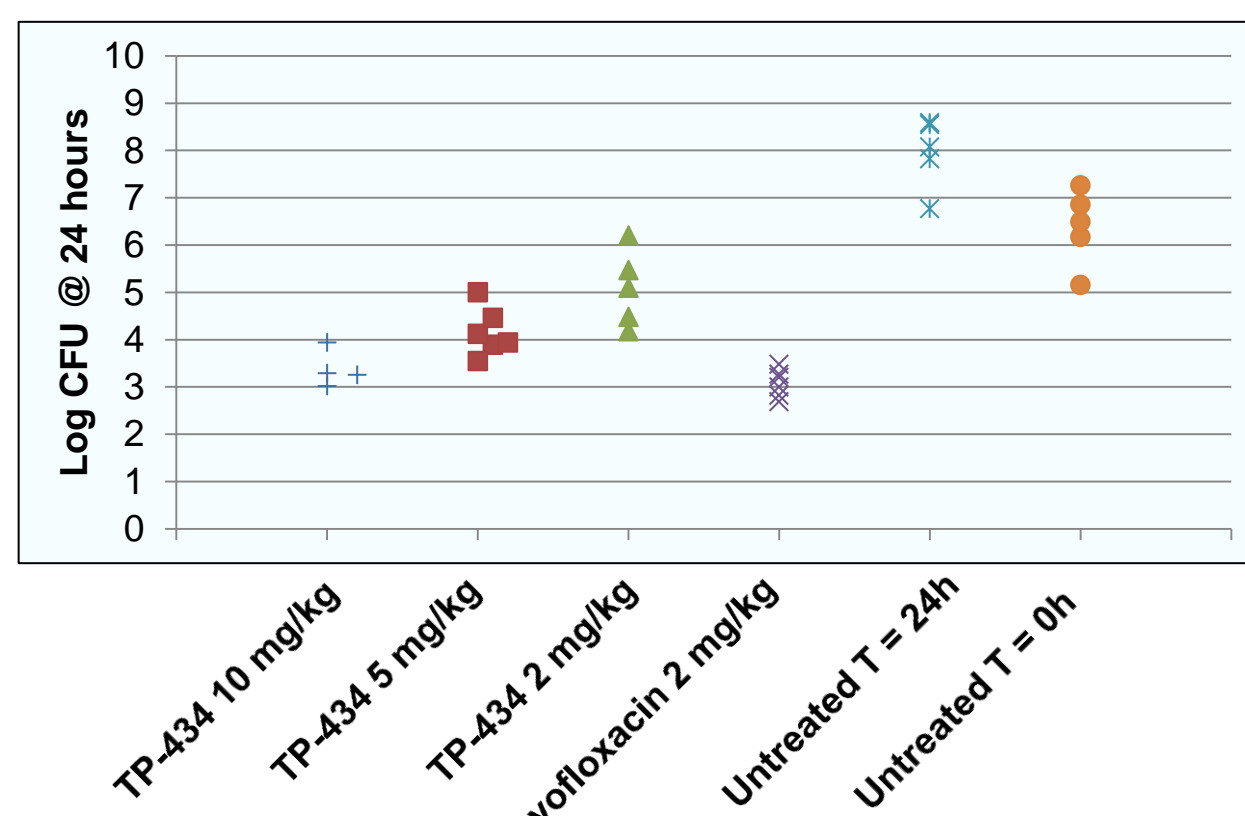
Study design for Phase 1 Studies. All clinical trials were single-center, double-blind, randomized, placebo-controlled studies conducted under GCP guidelines to investigate the safety, tolerability and pharmacokinetics of TP-434 given intravenously (IV) as a single or repeat dose or orally as a single dose. All subjects were screened and monitored for changes in hematology, urinalysis, serum biochemistries, and electrocardiograms. Robust PK sampling was done: 1) collection of blood predose and at 15 time points post-dose and up to 96h after IV or oral ingestion of single dose of compound; or 2) for the 10 day multiple-ascending dose (MAD) study, there was collection of blood predose every day of dosing with 10 additional samples drawn on Days 1 and 10, and sampling predose on Days 11 (+ 36h post-dose on Day 10) through Day 14. In addition, urine was collected predose and 0-8h, 8-24h, 24-48, 48-72, and 72-96 hours post-dose for single-ascending dose (SAD) studies. In addition to the urine sampling schedule of the SAD study, in the MAD IV study a predose urine sample was collected on Day 10, and samples 0-8 hours, 8-24 hours, 24-48, 48-72, and 72-96 hours after the start of the infusion on Day 10 were pooled and collected. TP-434 and its C-4 epimer, TP-498, were analyzed by validated LC-MS/MS methods, with limits of quantitation of 5 ng/mL in both plasma and urine. All dose groups consisted of 8 subjects, 6 randomized to TP-434 and 2 to placebo. Available adverse events, safety laboratories, and electrocardiograms, including Day 5 or Day 14 assessments were reviewed before the next sequential dose group was administered study drug.

Phase 1 IV SAD Study. Subjects were screened within 21 days prior to a baseline period (Day -1, start of hospitalization), followed by single 30-minute IV infusion dose (D1) and 96 hours of post-dose follow-up at Cetero Research, Fargo, ND. An End of Study (EOS) visit was performed 9 ± 1 days after dosing (10).

Phase 1 IV MAD Study. Subjects were screened within 21 days prior to a baseline period (Day -1, start of hospitalization), followed by 10 days of a 30-minute IV infusion of 0.5 mg/kg or 1.5 mg/kg q24h or a 60-minute IV infusion of either 1.5 mg/kg q24h or 1.0 mg/kg q12h at Cetero Research, Fargo, ND. An End of Study (EOS) visit was performed 24 ± 2 days after dosing (12).

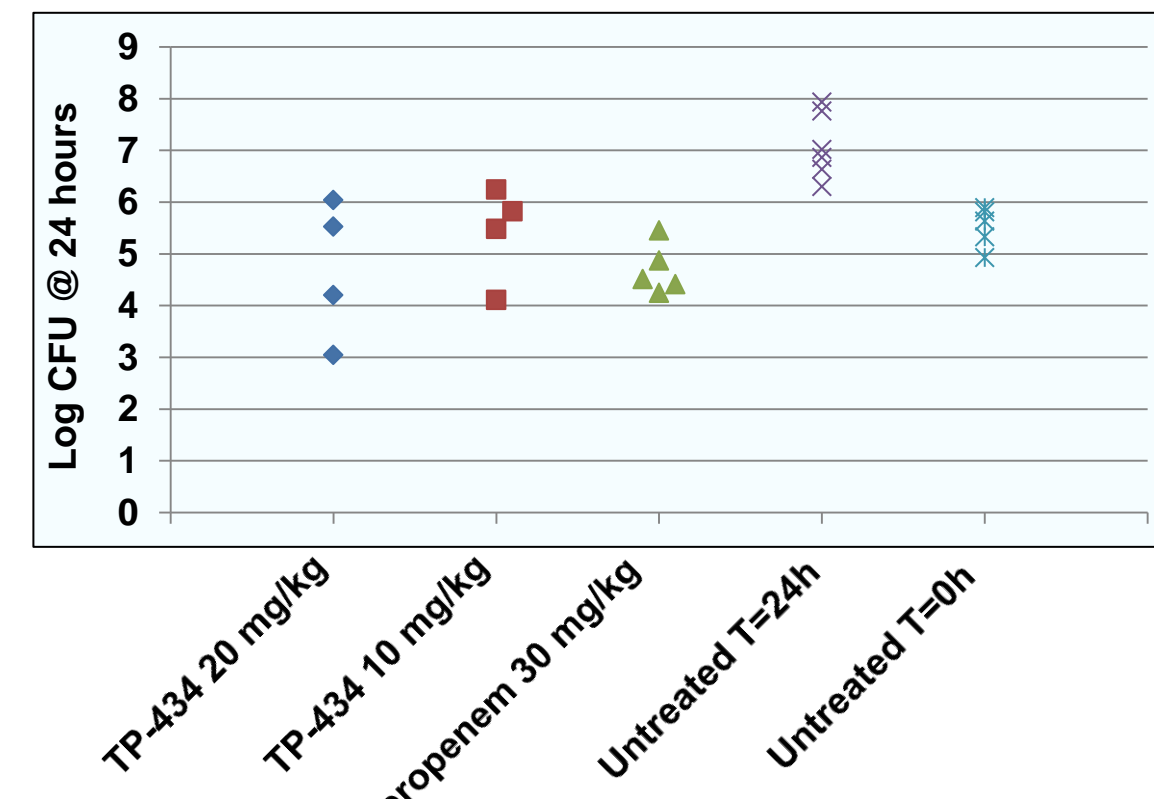
Study design for Phase 1 Oral SAD Study. Subjects were screened within 10 days prior to a baseline period (Day -1, start of hospitalization), followed by single oral dose (D1) and 96 hours of post-dose follow-up in the Phase 1 unit in Kharkov, Ukraine. An End of Study (EOS) visit was performed 9 ± 1 days after dosing (11).

E. coli EC200 Pyelonephritis/Descending UTI Murine Model



MICs of TP-434 and levofloxacin against EC200 are 0.13 and 0.03 µg/ml

K. pneumoniae KP453 Pyelonephritis/Descending UTI Murine Model



MICs of TP-434 and meropenem against KP453 are 0.5 and 0.03 µg/ml

| Single Oral Dose | Collection Interval | |
|------------------|------------------------|---------------|
| | Day 1* 0 to 8 hours | 8 to 24 hours |
| 50 mg | 1604 ± 909 | 1325 ± 1207 |
| 100 mg | 3646 ± 3182 | 2375 ± 768 |
| 200 mg | 5483 ± 1849 | 5922 ± 961 |
| 300 mg | 9468 ± 5374 | 9350 ± 1610 |

*All pre-infusion values were below the limit of detection

Conclusions

- TP-434 has excellent *in vitro* potency against MDR gram-positive and gram-negative uropathogens causing cUTI/pyelonephritis, including ESBL+ and carbapenem-resistant *Enterobacteriaceae*, excepting *P. aeruginosa*.
- TP-434 was efficacious against common uropathogens *E. coli* and *K. pneumoniae* in murine pyelonephritis models.
- TP-434 produced human urine concentrations by both the IV and oral route in sufficient excess of targeted MIC₉₀ of 2 µg/ml.
- TP-434 has the potential to be used as IV/oral step-down therapy for cUTIs and moderate-to-severe ambulatory UTIs.