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Broad-Spectrum Fluorocycline TP-434 has Oral Bioavailability in Humans

A. Leighton[1], I. Zupanets[2], N. Bezugla[2], L. Plamondon[3], G. Macdonald[3], J. Sutcliffe[3,]*

[1]Medical Consultant, San Francisco, US; [2]National University of Pharmacy of Ministry of Health of Ukraine, Kharkov, UA;

[3]Tetraphase Pharmaceuticals, Watertown, Mass. US

Contact: Leland Webster
Tetraphase Pharmaceuticals
lwebster@tphase.com

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Abstract

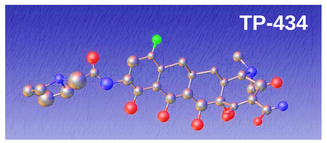
Background: TP-434 is a novel broad-spectrum fluorocycline antibiotic with potent activity and efficacy against multidrug-resistant (MDR) gram-negative and gram-positive aerobic and anaerobic pathogens, including *Enterobacteriaceae* expressing extended-spectrum beta-lactamases (ESβL) and/or carbapenemases, MRSA, and VRE; it has limited activity against *Pseudomonas* spp. The IV formulation of TP-434 is currently in Phase 2 clinical development. TP-434 had 29% oral bioavailability in chimpanzee.

Methods: A single-center, double-blinded, placebo-controlled single-ascending dose study with an oral solution of TP-434 was done in healthy men and women aged 18-50 years. Escalation of 50, 100, 200, and 300 mg doses was performed sequentially in Dose Groups (DG) of 8 subjects (6 TP-434 and 2 placebo). Safety panels included hematology, biochemistry, urinalysis, and for women, a pregnancy test, at screening, check-in, after dose administration and each of the 5 days the subjects were in the study unit as well as a follow-up assessment on Day 9. Electrocardiograms were collected in triplicate pre- and post-dosing and physical examinations were performed at screening, check-in, and at study exit (or early termination). Plasma concentration data from a total of 24 subjects who received study drug were included in the statistical analysis.

Results: No serious adverse events were reported over the course of this study. In general, doses up to 200 mg of TP-434 were well tolerated; 1 subject each receiving 200 mg reported dizziness or nausea. At a dose of 300 mg, increases in partial thromboplastin time were noted (<1.5 x upper limit of normal) in both placebo and subjects, and 1 subject each had increased alanine aminotransferase (<1.2 x ULN) and unconjugated bilirubin (<1.2 x ULN) or nausea and transient vomiting of mild severity. All AEs resolved spontaneously. Tmax was reached at approximately 2 hours for all DGs studied. The overall systemic exposure of TP-434 was dose-proportional and linear as doses increased from 50 mg to 300 mg. Exposures consistent with therapeutic efficacy were reached. Average oral bioavailability across DGs was 28%.

Conclusion: The feasibility of development of an oral formulation was confirmed. TP-434 showed promising oral bioavailability in humans, reaching exposures predicted to be therapeutically efficacious. The availability of an oral step-down option with a novel broad-spectrum antibiotic would fulfill an increasing medical need.

Introduction



TP-434 is an IV antibiotic with oral potential that is being developed to treat serious hospital infections. The potency of TP-434 against the 6 ESKAPE pathogens is excellent for all but *P. aeruginosa* (Tables 1-2).

Table 1. Activity of TP-434 against Gram-Negative "KAPE" (*K. pneumoniae, A. baumannii, P. aeruginosa, Enterobacter* spp.) Pathogens

Organism	N	MIC range MIC_{50}/MIC_{90} in µg/ml						
		TP-434	Tigecycline	Carbapenem	Levofloxacin	3rd Gen Ceph	Gentamicin	Piperacillin/ Tazobactam
Klebsiella pneumoniae	219	0.03 - 16 0.5/1	0.13 - 16 0.5/2	0.03 - >32 0.25/16	0.03 - >32 2/>32	0.03 - >64 32/64	≤0.25 - >32 4/>32	2 - >128 16/>64
ESβL+ *Klebsiella pneumoniae*	90	0.13 -16 0.5/2	0.25 - 16 1/4	0.03 - >32 ≤1/>32	≤0.25 - >32 >4/>32	0.25 - >64 >32/>64	≤0.2 5- >32 >8/>32	2 - >128 >64/>6128
Carbapenem-resistant *K. pneumoniae*	14	0.13 - 8 1/2	0.5 - 8 1/2	8 - >32 >32/>32	32 - >32 >32/>32	>32 >32/>32	2 - >32 8/>32	>32 - >32 >32/>32
Acinetobacter baumannii	89	≤0.016 - 4 0.5/2	≤0.016 - 8 0.5/4	0.13 - >32 2/>32	0.02 - >32 >2/16	0.12 - >16 >16/>16	0.5 - >32 32/>32	1 - >128 >128/>128
Pseudomonas aeruginosa	88	1 - >64 8/16	1 - >16 16/>16	0.12 - >32 1/16	0.06 - >2 0.25/>2	1 - >16 >16/>16	0.12 - >32 2/16	1 - >128 8/>128
Enterobacter cloacae	134	0.03 - 4 0.5/2	0.06 - 8 0.5/4	0.06 - 32 0.5/4	0.008 - >4 0.25/>4	0.03 - >164 >16/>64	0.25 - >32 0.5/>8	0.5 - >128 64/>128
Enterobacter aerogenes	30	0.25 - 2 0.25/0.25	0.25 - 4 0.5/0.5	≤1 - 2 ≤1/≤1	≤0.25 - 0.5 ≤0.25/≤0.25	≤0.5 - >64 ≤0.5/16	≤0.25 - 1 ≤0.25/0.5	≤0.5 - >64 2/16

ESβL+ = extended-spectrum β-lactamase producing

Table 2. Activity of TP-434 against Gram-Positive "ES" (*E. faecium, S. aureus*) Pathogens

Organism	N	MIC range MIC_{50}/MIC_{90} in µg/ml				
		TP-434	Tigecycline	Linezolid	Vancomycin	Levofloxacin
***E. faecium* vancomycin-susceptible**	51	0.03-0.5 0.06/0.12	0.03-0.25 0.06/0.12	1-4 2/2	0.25-42 1/1	0.25->32 >32/>32
***E. faecium* vancomycin-resistant**	43	0.03-0.12 0.06/0.06	0.03-0.12 0.06/0.06	2-4 4/4	>64->64 >64->64	>32 >32/>32
MRSA	137	≤0.015-0.5 0.06/0.12	0.06-0.5 0.12/0.12	1-4 2/4	0.5-1 1/1	0.12->32 >32/>32

Introduction

Multidrug-resistant bacteria pose a significant threat to global health. Antimicrobial resistance and its global spread threaten the continued effectiveness of many medicines used today, while at the same time it risks jeopardizing important medical advances that also require concomitant antimicrobial therapy. In 2004, WHO provided a list of the top 10 diseases for which there will be inadequate therapies in the near future. Infection by resistant bacteria topped the list, ahead of cancer and diabetes. In the U.S., methicillin-resistant *Staphylococcus aureus* alone annually infects more than 94,000 people and kills nearly 19,000—more deaths than from homicides, HIV/AIDS, Parkinson disease, or emphysema. Additionally, resistant bacteria create an immense economic burden. One study suggested that such infections cost a staggering $21–34 billion in the U.S. alone. For World Health Day 2011, WHO launched a worldwide campaign to safeguard these medicines for future generations.

Study Design

TP-434-Oral-P1-SAD-1 was a single-center, double-blind, randomized, placebo-controlled Phase 1 clinical trial to investigate the safety, tolerability and pharmacokinetics of TP-434 administered as a single ascending oral dose to 32 healthy subjects (30 males and 2 females divided in 4 equal cohorts, with 6:2 receiving TP-434:placebo. All subjects received a 150 ml oral solution of D5W (5% dextrose in water) containing 50, 100, 200, or 300 mg of TP-434 free base equivalents in a stainless steel cup following a light breakfast of toast with apple jam. Subjects were screened within 10 days prior to a baseline period (Day -1, start of hospitalization), followed by single P.O. 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.

To provide a robust PK profile, blood was collected predose and at 15 time points post-dose encompassing up to 96h after oral ingestion of compound. In addition, urine was collected predose and 0-8h, 8-24h, 24-48h, 48-72h, and 72-96h post-dose. 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.

Demographics

Table 3. Demographics

Parameter	50 mg (N=6)	100 mg (N=6)	200 mg (N=6)	300 mg (N=6)	Placebo (N=8)
Mean Age (yrs)	32.2	34.5	31.3	37.3	37.1
Min- Max	19 - 50	21 - 46	21 - 39	27 - 49	23 - 50
Mean BMI (kg/m^2)	24.5	25.4	23.7	26.6	25.2
Min - Max	22.8 – 26.0	21.5 – 27.8	19.3 – 26.8	24.0 – 28.9	23.2 – 27.9
Mean Height (cm)	172.8	177.2	177.2	174.8	179.6
Min - Max	159 - 184	173 - 182	160 - 183	163 - 184	174 - 188
Mean Weight (kg)	73.5	79.8	74.4	81.6	81.4
Min - Max	63.5 – 87.4	64.2 – 89.3	62.5 – 89.8	67.7 – 89.5	73.4 – 89.3
Gender, % Females	16.7	0	16.7	0	0
% Males	83.3	100.0	83.3	100.0	100.0
Race, % White	100.0	100.0	100.0	100.0	100.0

Safety

Table 4. Adverse Events

Adverse Event (AE) MedDRA SOC / Preferred Term	Treatment Arm					
	50 mg N = 6	100 mg N = 6	200 mg N = 6	300 mg N = 6	Placebo N = 8	Overall N = 32
Total Number of Subjects with AEs	0	0	2	5	2	9
Gastrointestinal disorders						
Nausea	--	--	1	1	--	2
Vomiting	--	--	--	1	--	1
Investigations						
Activated partial thromboplastin time prolonged (PTT)[a]	--	--	--	5	2	7
Alanine aminotransferase increased (ALT)	--	--	--	1	--	1
Blood bilirubin increased	--	--	--	1	--	1
Nervous system disorders						
Dizziness	--	--	1	--	--	1

[a]PTT prolongation was present in both treatment arms (e.g., patients that received placebo and TP-434).

Pharmacokinetics

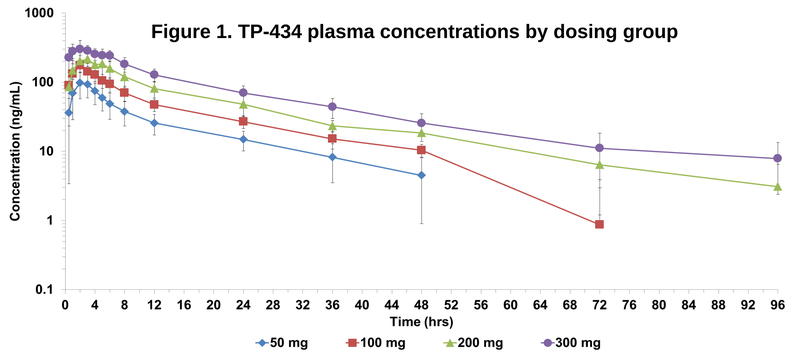


Table 5. PK Parameter Values for TP-434

Parameter	Arithmetic Mean (% CV) of PK Parameter Values for TP-434 Median (Range) for T_{max}			
	50 mg Dose Group 1	100 mg Dose Group 2	200 mg Dose Group 3	300 mg Dose Group 4
AUC_{0-t} (ng·hr/mL)	1077.1 (40.82)	2023.72 (24.45)	3775.94 (27.15)	6044.10 (24.96)
AUC_{0-inf} (ng·hr/mL)	1241.49 (35.79)	2252.66 (23.72)	3335.47 (33.22)	5653.28 (23.86)
C_{max} (ng/mL)	99.63 (39.97)	174.83 (38.38)	226.67 (19.70)	332.83 (25.21)
T_{max} (hr)	2.50 (2.00-3.00)	2.00 (2.00-2.00)	2.50 (2.00-4.00)	2.00 (1.00-6.00)
λ_z (1/hr)	0.0432 (17.90)	0.0414 (17.68)	0.0298 (21.21)	0.0266 (21.17)
$T_{1/2}$ (hr)	16.47 (17.72)	17.16 (16.73)	24.06 (18.70)	26.93 (19.43)
CL/F (L/hr)	47.07 (50.76)	46.31 (21.37)	55.86 (23.29)	52.00 (22.01)
V_z/F (L)	1093.26 (45.78)	1133.58 (22.58)	1889.90 (20.08)	1999.21 (27.05)
% F[a]	32.34 (35.80)	29.34 (23.71)	24.59 (27.15)	26.24 (24.97)
Renal Clearance (L/hr)	3.54 (29.04)	3.16 (15.52)	3.17 (25.64)	3.03 (27.90)

[a] % F was calculated using an average body weight of 78 kg (Phase 1 Oral study) and the AUC_{0-inf} for the 1.5 mg/kg q24h IV SAD dose (8983.82 ng·h/mL).

Table 6. Comparison of Single Dose of TP-434 Administered Orally or IV

Dose of TP-434	Arithmetic Mean (% CV)	
	Cmax (ng/mL)	AUC_{0-24} (ng·h/mL)
1.5 mg/kg IV dose, Day 1	2785.0 (22.0)	6449.0 (13.9)
300 mg single oral dose	332.83 (25.2)	6044.10 (25.0)

Conclusions

- TP-434 was well tolerated as single oral doses of 50, 100, 200, and 300 mg
- Exposures after 300 mg oral dosing were consistent with exposures seen in 1.5 mg/kg IV single doses
- Further studies to confirm the feasibility of TP-434 for oral step-down therapy are on-going
- TP-434 IV is currently being investigated in a Phase 2 trial for the treatment of community-acquired complicated intra-abdominal infections