PHARMACOKINETICS, SAFETY AND TOLERABILITY OF A NOVEL FLUOROCYCLINE, TP-434, FOLLOWING MULTIPLE DOSE ADMINISTRATION

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REVISED ABSTRACT

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. TP-434 is currently being evaluated intravenously (IV) in a phase 2 study for the treatment of community-acquired complicated intra-abdominal infections. The current phase 1 study investigated the safety, tolerability and pharmacokinetic (PK) profile of TP-434 when administered orally after multiple daily doses.

Methods: Unformulated TP-434 was administered orally as single daily doses of 50, 100, 200 and 300 mg in a gelatin capsule for 7 days. Routine safety assessments and blood samples for PK analyses were obtained. The 100 mg dose was also administered as a single dose in both the fasting and fed states to determine the effect of food on the PK parameters. One group received 100 mg twice daily for 7 days.

Results: AUC and C_{max} are listed below; $T_{1/2}$ was 14-21 hours on Day 1 and 17-36 hours on Day 7

Dose (mg)		Day 1		Day 7	
		C_{max} (ng/mL)	AUC[a] (ng*hr/mL)	C_{max} (ng/mL)	AUC[a] (ng*hr/mL)
100	fast (n=8)	117	1924		
	fed (n=8)	41	724		
	light (n=6)	43	496	48	902
200 (100 BID)	fast	99	1001	164	3079
300	fast (n=6)	206	3154	342	9511
400	fast (n=6)	158	3183	Not done	Not done

light = light breakfast, fed = FDA specified breakfast, fast = minimum 8 hour fast
[a] Value reported is the AUC_{inf} from the time of the last dose administered. For the 100 mg q12h Dose Group, only 12 hours of dosing are included in the calculation.

No SAEs were reported. No significant safety signals were observed. No nausea was reported in the 50-200 mg once daily dose groups. Three subjects in the 300 mg group reported nausea, 2 of whom had at least 1 episode of emesis – all mild and transient.
Conclusions:
•TP-434 is orally bioavailable, indicating the potential for IV/oral step-down therapy, or oral therapy alone
•There is a significant effect of food on the oral absorption of TP-434
•No significant safety signals were observed
•TP-434 is tolerated at doses producing what is expected to be therapeutic levels

BACKGROUND

TP-434 is a fully synthetic fluorocycline antibiotic with a broad range of organism coverage, including MDR gram-negative (with the sole exception of *Pseudomonas* spp.), gram-positive, anaerobic, and atypical bacteria. It demonstrates potent, rapid antibacterial activity across a wide spectrum of fluoroquinolone-resistant and ESβL- and carbapenemase-producing resistant organisms. MIC values for TP-434 are shown below.

Pathogen Type	Panel Size	MIC50 (µg/mL)	MIC90 (µg/mL)
Gram negatives (19 species) (excluding *Pseudomonas* spp.)	14 - 208	<0.016 - 1	0.063 - 4
Pseudomonas aeruginosa	88	8	16
Gram Positive (10 species)	18 – 107	0.015 – 0.25	0.015 – 0.25
Anaerobes (21 species)	5 - 20	0.015 - 1	0.12 - 4

A phase 2 study evaluating the safety and efficacy of TP-434 in the treatment of complicated intra-abdominal infections is currently underway. Two dose regimens of TP-434 are being evaluated. The pharmacokinetic parameters that were observed for these two IV doses of TP-434 in phase 1 studies are shown below.

IV TP-434	Day 1		Day 10	
	Mean (%CV)			
	C_{max} (ng/mL)	AUC (ng*hr/mL)	C_{max} (ng/mL)	$AUC_{tau(ss)}$ (ng*hr/mL)
1.5 mg/kg q24h N=6	2785.0 (22.0)	7339.5 (15.4)	1891.7 (10.3)	7858.2 (11.5)
1.0 mg/kg q12h N=6	2125.0 (15.3)	4385.6 (13.9)	1825.0 (15.5)	6344.4 (14.9)

Methods

The study was conducted at a single phase 1 unit in the UK with healthy subjects. For all dosing cohorts, TP-434 was administered as simple powder in hard gelatin capsules.

For the Food Effect arm, 8 subjects received a single dose of TP-434 following an eight hour fast. Blood samples were obtained for PK analysis through 96 hours post dosing. After an additional 24 hour washout period, the same subjects received a second dose of 100 mg TP-434 30 minutes after the start of a standardized high-fat breakfast. Blood samples for PK analysis were obtained through 96 hours post dosing. Urine was also collected for analysis of TP-434 concentrations.

For the Multiple Dose arms, 8 subjects received study drug (6 TP-434 and 2 placebo) for 7 consecutive days. Three dose groups were studied: 300 mg once daily, 400 mg once daily, or 100 mg every 12 hours. Blood samples for PK analysis were collected throughout the dosing period and for 96 hours following the final dose. Urine was collected for analysis of TP-434 concentrations.

TP-434 concentrations in plasma and urine were analyzed using previously developed and validated methodology.

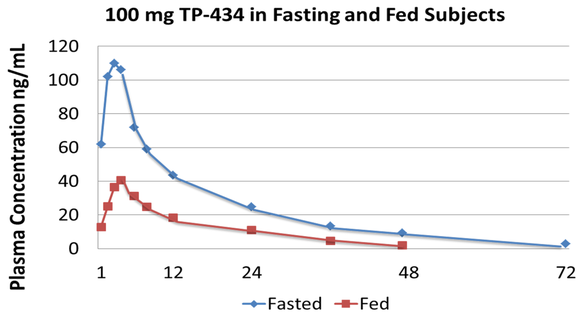
Throughout the study, standard phase 1 safety parameters were monitored: these included hematology, clinical chemistry and urinalysis parameters, physical examination findings, vital signs, electrocardiograms and adverse events.

Results

Demographics: Mean (range)

	Placebo (n=8)	Food Effect (n=8)	TP-434 Multiple Dose		
			100 mg q 12h (n=6)	300 mg q24h (n=6)	400 mg q24h (n=6)
Age (yrs)	27.8 (18-44)	25.1 (18-34)	27.5 (19-47)	33.5 (22-46)	32.7 (26-39)
Height (m)	1.8 (1.7-1.9)	1.8 (1.6-2.0)	1.8 (1.7-1.9)	1.8 (1.7-1.8)	1.8 (1.7-1.9)
Weight (kg)	77.5 (69.0 – 84.6)	71.8 (60.4-79.9)	77.9 (74.2-83.6)	75.1 (71.4-82.1)	76.1 (69.3-88.4)
Gender (% M)	100	100	100	100	100

Effect of Food on the Pharmacokinetics of TP-434



Urine Concentrations of TP-434 Following Oral Administration of 100 mg

Urine concentrations of TP-434 were measured for the initial 24 hours after dosing in the Food Effect dose group. For the 8 subjects in that cohort, the urine concentrations of TP-434 following dosing in the fasted state were:

- 0-8 hrs after dosing = 4074 ±3343 mg/mL
- 8-24 hrs after dosing = 2967 ± 662 ng/mL

Results

Pharmacokinetics of TP-434 Following Multiple Dose Administration

Dose Group (n=6)	Day 1			Day 7		
	C_{max} (ng/mL)	AUC_{inf} [a] (ng*hr/mL)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{inf} [a] (ng*hr/mL)	$T_{1/2}$ (hr)
100 mg q12h	100 ± 22	1001 ± 224	10 ± 2	164 ± 39	3079 ± 703	18 ± 3
300 mg q24h	206 ± 38	3154 ± 981	14 ± 3	342 ± 81	9511± 2450	36 ± 8
400 mg q24h	158 ± 101	3183 ± 910	13 ± 2			

[a] Value reported is the AUC_{inf} from the time of the last dose administered. For the 100 mg q12h Dose Group, only 12 hours of dosing are included in the calculation.

Safety Findings

No safety signals were identified following review of clinical chemistry, hematology, urinalysis, coagulation, liver function, renal function, vital signs, electrocardiogram and physical examination findings.

Adverse Events

Adverse events in the gastrointestinal system were observed at the highest doses of TP-434. Dosing was discontinued on Day 5 in the 400 mg q24h dose group because of tolerability issues (nausea and vomiting).

Adverse Events Reported by 2 or More Subjects in any Dose Group

	Placebo (n=6)	TP-434		
		100 mg q12h (n=6)	300 mg q24h (n=6)	400 mg q24h (n=6)
Abdominal pain		-	-	3
Abdominal pain (upper)	-	-	-	5
Nausea	1	1	3	4
Vomiting	-	-	2	5
Headache	1	-	-	3

Conclusions

- **TP-434 is orally bioavailable and plasma levels likely to be therapeutic were observed following doses that were generally well tolerated in healthy subjects.**
- **Oral bioavailability of TP-434 is reduced following administration to fed subjects (AUC_{inf} reduced ~62%).**
- **Urine concentrations of TP-434 above MICs for the majority of urinary tract pathogens were observed following oral administration of a single 100 mg dose.**
- **No significant safety signals were observed in this phase 1 study.**