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Phase 1 Single and Multiple Ascending Dose Studies of a Broad-Spectrum Fluorocycline, TP-434

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Revised Abstract

Background: TP-434 is a broad spectrum fluorocycline with *in vitro* antimicrobial activity against all major pathogens except *Pseudomonas aeruginosa* and *in vivo* efficacy in murine infection models (septicemia, thigh, UTI, and pneumonia) challenged with MRSA, *Streptococcus pneumoniae, S. pyogenes* or multidrug-resistant gram-negative bacteria.

Objectives: Study objectives were exploration of safety, tolerability, plasma pharmacokinetics (PK) and urinary excretion of single and multiple ascending doses of TP-434 IV.

Methodology: Dose escalations were performed sequentially in 56 and 32 healthy adult volunteers (18-50 years old) in the single ascending dose (SAD) and multiple ascending dose (MAD) study, respectively. Each of the 7 Dose Groups (DGs) in the SAD study and 4 DGs in the MAD study consisted of 8 subjects (6 randomized to receive TP-434 and 2 matching placebo). In the MAD study, subjects received 30-minute (30') infusions of 0.50 mg/kg q24h and 1.50 mg/kg q24h or 60-minute (60') infusions of 1.5 mg/kg q24h and 1.0 mg/kg q12h.

Results: Plasma PK were dose-proportional and linear in the SAD study with respect to AUC, Cmax, and 0-8 h urine concentrations. All estimated half-lives (T½) were between 12-24 hours, with DG7 (3 mg/kg) having the largest estimated T½ while DG1 (0.10 mg/kg) had the smallest.

For the MAD study, the AUC increased proportionally with dose, reaching steady state values of ~8000 ng·h/mL when given once daily at 1.5 mg/kg and 12,688 ng·h/mL (over 24 hrs) when given 1.0 mg/kg twice daily. Clearance and volume of distribution at steady state averaged 14 L/h and 315.9 L, respectively. Based on PK population modeling, steady-state should be attained in 7 days. The mean half-life of TP-434 in plasma (all cohorts confounded) was 47.7 h, while the median value was 35.3 h. Renal clearance accounted for approximately 15.5 ± 2.4% of total clearance of TP-434.

No serious adverse events were reported in the SAD or MAD study. The most common adverse events by system organ class were gastrointestinal, administration site, and vascular disorders. No clinically significant safety lab values or significant changes in ECG readings were observed.

Conclusions: PK, safety and tolerability data indicate TP-434 may be of utility at dose regimens up to and including 2 mg/kg/day and are consistent with the potential utility of once-daily doses in the treatment of important bacterial infections, including those caused by multidrug-resistant gram-negative pathogens.

Introduction/Study Design

Exploratory compound. TP-434 is an experimental parenteral broad-spectrum fluorocycline made by total synthesis using a highly convergent route from two precursors rather than by semisynthetic modification of a tetracyclic core (see Poster F1-2157). TP-434 has activity against a broad range of Gram-positive (MIC_{90} values of ≤0.5 µg/ml) and Gram-negative bacterial pathogens (MIC_{90} values of ≤2 µg/ml) except *Pseudomonas aeruginosa* (MIC_{90} of 16 µg/ml) (see F1-2158). TP-434 retains activity against tetracycline-resistant strains carrying either single-component efflux pumps (e.g., Tet(A) or Tet(K)) and/or resistance mediated by ribosomal protection proteins that remove tetracycline from its ribosomal binding site (e.g., Tet(M) or Tet(O) (see F1-2160).

Study Design. Given the *in vitro* potency and efficacy in murine models of infection (see F1-2161), TP-434 was evaluated in Phase 1 SAD and MAD studies to determine the safety, tolerability, PK and urinary excretion of single and multiple ascending doses of TP-434 IV. Both studies were double-blind, placebo-controlled and conducted in a single Phase 1 unit (Cetero Research, Fargo, ND). Eight subjects were randomized to each dose group (DG). 6 randomized to TP-434 and 2 to placebo (saline or D5W [5% dextrose for injection]). The SAD DGs were 0.1, 0.25, 0.5, 1.0, 1.5, 2.0, and 3.0 mg/kg q24h (30 min. infusions). In the MAD study, subjects received either 30-minute infusions of 0.50 mg/kg q24h (DG1) or 1.50 mg/kg q24h (DG2) or 60-minute (60') infusions of 1.5 mg/kg q24h (DG3) or 1.0 mg/kg q12h (DG4) for 10 days. Sixteen PK samples per subject were taken after the first dose in both SAD and MAD studies to provide data out to 96 hrs. In the MAD study, another set of PK samples were taken after the last dose, with Cmin samples at intervening days. Urine excretion was measured for 5 days. Subjects were kept in the Phase 1 unit for 5d for the SAD and 14d for the MAD with a follow-up at 9 ±1d and 24 ± 2d.

Key Inclusion Criteria. Healthy males or females (surgically sterile); age ≥18 to 50.

Key Exclusion Criteria:

- Body mass index (BMI) <18.5 or >32 kg/m^2
- Clinically significant vital sign abnormalities (systolic BP< 90 or >140 mmHg; diastolic BP<50 or >90 mmHg; heart rate <45 or >100 bpm)
- Clinically significant ECG abnormalities; QTc ≥ 450 msec
- Clinically significant history or presence of any gastrointestinal pathology
- Clinically relevant medical conditions which were likely to interfere with the evaluation of the trial drug, e.g., chronic obstructive pulmonary disease (COPD), metabolic disorders (such as diabetes mellitus) malignancies, autoimmune diseases, cardiovascular disease
- Concurrent acute or chronic infections (e.g., viral infections, except chronic recurrent herpes simplex infections)
- Clinically abnormal safety labs, including ALT or AST > upper limit of normal (ULN) or bilirubin > ULN, differential blood count outside normal range
- Positive test results for HIV, Hepatitis B (HbsAg), or Hepatitis C (HCV) at the Screening Visit
- History of significant alcohol or drug abuse within one year prior to the Screening Visit and/or ongoing or positive test for drugs of abuse
- Tobacco use within last 3 months and/or ongoing
- Use of prescription medication with 14 days of dosing or OTC medications within 7 days of dosing
- Hemoglobin values ≤12.8 g/L (males) and ≤11.5 g/L (females), and hematocrit values ≤37% (males) and ≤ 32.0% (females)

References

1. Muralidharan, G. , et al. 2005. Pharmacokinetics of tigecycline after single and multiple doses in healthy subjects. Antimicrob. Agents Chemother. **49**:220-229.
2. Tygacil (tigecycline) for injection for intravenous use, package insert. Wyeth Pharmaceuticals, Philadelphia, PA, March 2009.

Demographics

Table 1. Demographics of TP-434 SAD Studies

Parameters	All Subjects (N=56)	Male Subjects (N=49)	Female Subjects (N=7)
Age	28.1 (18-48)	26.4 (18-44)	40.4 (29-48)
Weight (lbs)	176.7 (128.5-239.0)	180.6 (143.5-239.0)	149.6 (128.5-186.0)
Height (in.)	69.3 (62.9-77.1)	70.0 (63.9-77.1)	64.6 (62.9-67.1)
BMI	25.7 (19.6-31.5)	25.8 (19.6-31.4)	25.2 (21.9-31.5)
Race			
American Indian or Alaska Native	1 (1.8%)	1 (2.0%)	---
Asian	3 (5.4%)	3 (6.1%)	---
Black or African American	4 (7.1%)	4 (8.2%)	---
Black or African American and White	1 (1.8%)	1 (2.0%)	---
White	47 (84.0%)	40 (81.6%)	7 (100.0%)

Table 2. Demographics of TP-434 MAD Studies

Parameters	All Subjects (N=32)	Male Subjects (N=31)	Female Subjects* (N=1)
Age	30.8 (19-50)	30.3 (19-50)	46.0
Weight (lbs)	174.9 (115.5-255.5)	176.8 (131.0-255.5)	115.5
Height (in.)	69.0 (61.8-76.0)	69.2 (61.8-76.0)	64.5
BMI	25.7 (19.3-31.3)	25.9 (19.3-31.3)	19.5
Race			
American Indian or Alaska Native	1 (3.1%)	1 (3.2%)	---
Asian	1 (3.1%)	1 (3.2%)	---
Black or African American	1 (3.1%)	1 (3.2%)	---
Black or African American and White	---	---	---
White	29 (90.6%)	28 (90.3%)	1 (100.0%)

Pharmacokinetics

Table 3. Summary Statistics and Pharmacokinetic Parameter Values for TP-434 SAD Study Using Noncompartmental Methodology

Parameter	Arithmetic Mean (%CV) Median (Range) for T_{max}						
	DG1 (0.10 mg/kg)	DG2 (0.25 mg/kg)	DG3 (0.50 mg/kg)	DG4 (1.00 mg/kg)	DG5 (1.50 mg/kg)	DG6 (2.00 mg/kg)	DG7 (3.00 mg/kg)
AUC_t (ng·hr/mL)	433.56 (21.27%)	1174.87 (16.58%)	2552.98 (25.76%)	5400.14 (22.02%)	8633.03 (17.02%)	12204.11 (14.14%)	22852.88 (19.89%)
AUC_{inf} (ng·hr/mL)	557.18 (23.41%)	1326.06 (15.98%)	2721.96 (25.35%)	5613.03 (21.25%)	8983.82 (17.95%)	12541.24 (15.01%)	23518.39 (20.05%)
C_{max} (ng/mL)	227.00 (24.45%)	466.50 (22.70%)	993.50 (17.50%)	1888.33 (27.84%)	3233.33 (22.60%)	4916.67 (16.99%)	9793.33 (16.44%)
T_{max} (hr)	0.50 (0.50-0.50)	0.50 (0.25-0.50)	0.50 (0.50-0.55)	0.50 (0.50-0.53)	0.50 (0.50-0.50)	0.50 (0.50-0.50)	0.50 (0.50-0.58)
λ_z (1/hr)	0.0594 (26.88%)	0.0435 (10.21%)	0.0394 (32.39%)	0.0375 (37.77%)	0.0320 (19.18%)	0.0343 (10.70%)	0.0296 (20.80%)
$T_{1/2}$ (hr)	12.39 (26.39%)	16.09 (9.80%)	19.03 (28.68%)	20.28 (28.86%)	22.34 (18.23%)	20.41 (10.60%)	24.18 (18.68%)
CL[a] (L/hr/kg)	6.41 (17.31%)	7.21 (14.64%)	7.21 (15.03%)	6.41 (13.23%)	5.61 (13.97%)	5.61 (7.67%)	4.81 (21.78%)
V_{ss}[a] (L)	84.9 (23.06%)	122.6 (7.33%)	123.4 (16.86%)	118.5 (25.87%)	116.9 (15.08%)	105.7 (12.18%)	78.5 (19.84%)
C_{min} (ng/mL)	6.91 (22.17%)	6.45 (15.14%)	6.37 (21.29%)	7.60 (26.81%)	10.69 (36.32%)	11.24 (43.57%)	18.98 (22.59%)
MRT (hr)	13.11 (24.19%)	16.66 (15.12%)	18.36 (26.57%)	17.89 (23.62%)	19.94 (17.17%)	18.12 (10.55%)	16.13 (13.59%)

[a]Based on average body weight of 80.1 kg

- **Total exposure and peak plasma concentrations increased with dosage as observed by larger observed AUC and Cmax for larger doses.**
- **All estimated half-lives were between 12-24 hours.**

Table 4. Summary Statistics and Pharmacokinetic Parameter Values for TP-434 MAD Study Using Population PK Modeling (see A1-028)

Parameter	Arithmetic Mean (%CV) Median (Range) for T_{max}			
	30 min infusion		60 min infusion	
	DG1 0.5 mg/kg q24h	DG 2 1.5 mg/kg q24h	DG 3 1.5 mg/kg q24h	DG4 1.0 mg/kg q12h
AUC_{0-24} (ng·hr/mL)	1991.3 (20.3%)	5903.0 (9.4%)	6449.0 (13.9%)	3937.3 (11.7%)
$AUC_{0\text{-}tau(ss)}$ (ng·hr/mL)	2992.4 (28.0%)	7803.0 (11.9%)	8670.8 (16.0%)	6667.4 (10.0%)
C_{max} (ng/mL)	227.00 (18.0%)	3446.7 (7.1%)	2785.0 (22.0%)	2125.0 (15.3%)
C_{max} (D10) (ng/mL)	931.3 (16.6%)	3403.3 (9.3%)	1891.7 (10.2%)	1825.0 (15.5%)
T_{max} (hr)	0.50 (0.50-0.50)	0.50 (0.50-0.50)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
$T_{1/2}$ (hr)	35.3 (27.6-53.4)	32.3 (29.8-38.9)	40.2 (27.9-108.9)	59.3 (35.0-107.4)
CL (L/hr)	12.1 (26.0%)	16.5 (10.6%)	13.9 (18.8%)	11.7 (9.7%)
V_{ss} (L)	315.0 (8.9%)	322.4 (6.6%)	319.6 (8.8%)	321.1 (6.31%)
C_{min} (ng/mL)	27.92 (42.0%)	63.8 (18.7%)	72.18 (26.8%)	105.2 (17.1%)
C_{min} (D10) (ng/mL)	54.55 (40.4%)	140.3 (31.3%)	129.9 (20.4%)	286.8 (20.6%)

- **The mean half-life of TP-434 in plasma (all cohorts confounded) was 47.7 h, while the median value was 35.3 h.**
- **Renal elimination of TP-434 accounts for approximately 15.5 ± 2.4 % of overall elimination.**

Safety and Tolerability in MAD

No SAEs were observed. No clinically significant safety lab values or significant changes in ECGs were observed. Five subjects were discontinued from study drug due to AEs. Four of these were due to superficial phlebitis; of these, three subjects were in DG2 (1.5 mg/kg q24h; 30 minute infusion at drug concentration of 1.0 mg/mL). In contrast, no subject was discontinued in DG3 (1.5 mg/kg q24h; 60 minute infusion with TP-434 concentration of 0.4 mg/mL). One subject in DG4 [1.0 mg/kg q12h; 60 minute infusion at drug concentration of 0.4 mg/mL) was discontinued from study drug due to decreased appetite, nausea, and vomiting and 1 subject was discontinued on Day 9 due to bilateral superficial phlebitis. All AEs were mild to moderate in intensity and were resolved before or by scheduled study end.

Table 5. Treatment-Related (Possibly or Likely Related) Adverse Events by Subject – N (%)

Adverse Event (AE) MedDRA SOC / Preferred Term	MAD Study – AEs Across Dose Groups					
	0.50 mg/kg (30 min/24 hr) N = 6	1.50 mg/kg (30 min/24 hr) N = 6	1.50 mg/kg (60 min/24 hr) N = 6	1.00 mg/kg (60 min/12 hr) N = 6	Placebo N = 8	Overall N = 32
Gastrointestinal disorders						
Abdominal pain upper	--	--	1 (16.7%)	--	--	1 (3.1%)
Diarrhoea	--	3 (50.0%)	--	1 (16.7%)	--	4 (12.5%)
Nausea	--	2 (33.3%)	5 (83.3%)	4 (66.7%)	1 (12.5%)	12 (37.5%)
Vomiting	--	1 (16.7%)	--	1 (16.7%)	--	2 (6.3%)
General disorders and administration site conditions						
Feeling hot	--	1 (16.7%)	--	--	--	1 (3.1%)
Infusion site discomfort	--	--	1 (16.7%)	3 (50.0%)	--	4 (12.5%)
Infusion site erythema		1 (16.7%)	1 (16.7%)	4 (66.7%)		6 (18.8%)
Infusion site extravasation	--	1 (16.7%)		--	--	1 (3.1%)
Infusion site pain		4 (66.7%)	2 (33.3%)	1 (16.7%)	--	7 (21.9%)
Oedema peripheral	--	--	--	1 (16.7%)	--	1 (3.1%)
Tenderness	--	1 (16.7%)	--	--	--	1 (3.1%)
Metabolism and nutrition disorders						
Decreased appetite	--	--	--	2 (33.3%)	--	2 (6.3%)
Musculoskeletal and connective tissue disorders						
Pain in extremity	--	3 (50.0%)	1 (16.7%)	1 (16.7%)	--	5 (15.6%)
Nervous system disorders						
Dizziness	--	1 (16.7%)	2 (33.3%)	--	--	3 (9.4%)
Headache	1 (16.7%)	2 (33.3%)	2 (33.3%)	1 (16.7%)	--	6 (18.8%)
Psychiatric disorders						
Insomnia	--	--	--	1 (16.7%)	--	1 (3.1%)
Skin and subcutaneous tissue disorders						
Hyperhidrosis	--	2 (33.3%)	--	--	--	2 (6.3%)
Vascular disorders						
Phlebitis superficial	1 (16.7%)	5 (83.3%)	2 (33.3%)	6 (100.0%)	--	14 (43.8%)

Conclusions

- **PK was linear and dose-proportional in both the SAD and MAD studies**
- **TP-434 demonstrated dual elimination, with the primary route via biliary tract**
- **TP-434 had a lower incidence and severity of nausea and vomiting than reported in Phase 1 studies for tigecycline[1]**
- **Dose concentration will be reduced and infusion times can be prolonged in future clinical studies**
- **1.5 mg/kg q24h x 10 days achieved steady state AUC of 8670 ng·h/mL and Cmax of 1891.7 ng/mL in contrast to that reported for tigecycline at approved q12h regimen (4700 ng·h/mL and Cmax of 630 ng/mL[2])**
- ***In vitro* potency against MDR gram-negative and gram-positive aerobic, facultative, and anaerobic pathogens (F1-2155 – F1-2158), Phase 1 PK profile (A1-028), and safety and tolerability support advancement of TP-434 into Phase 2**
- **Additionally, results from an oral Phase 1 SAD study demonstrate AUCs consistent with therapeutic coverage, thus offering potential for IV - oral step down treatment with TP-434**