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Safety, Tolerability and Pharmacokinetics of Single Intravenous Doses of TP-271, a Novel Fluorocycline Antibiotic

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Abstract

This is the first report of clinical data for TP-271, a fully-synthetic fluorocycline antibiotic being developed for the treatment of serious bacterial infections including respiratory infections caused by multidrug-resistant pathogens.

This was a phase 1, single site, randomized, double-blind, placebo controlled dose-escalating, single dose study in healthy adults who provided informed consent prior to any study procedure. Seven cohorts of 8 subjects each (6 active and 2 placebo) received an intravenous dose of 0.15, 0.45, 1.0, 2.0, 3.0, 4.0 or 5.0 mg/kg TP-271 or placebo. Plasma and urine samples for pharmacokinetic (PK) analyses were collected immediately prior to dosing through 96 hours. Safety was assessed through collection of adverse events (AEs), clinical labs, vital signs, ECG and physical exam data.

The mean (CV) derived PK parameters for TP-271 were:

TP-271 Dose (mg/kg)	AUC_{inf} (µg*h/mL)	C_{max} (µg/mL)	$T_{1/2}$ (h)	Cl (L/h)
0.15	2.2 (22.2)	0.3 (19.3)	15.1 (14.8)	5.6 (20.9)
0.45	6.5 (17.6)	0.9 (18.0)	17.8 (6.0)	5.8 (14.0)
1.0	17.4 (31.6)	2.7 (15.3)	18.9 (23.6)	4.3 (24.0)
2.0	41.8 (17.5)	6.7 (13.4)	19.1 (8.9)	4.1 (19.3)
3.0	67.2 (18.0)	12.0 (13.8)	17.1 (15.2	3.7 (16.4)
4.0	107.8 (18.0)	18.5 (20.7)	17.1 (10.5)	2.9 (17.0)
5.0	175.0 (31.5)	27.6 (26.5)	17.9 (5.3)	2.3 (15.4)

Mean fractional excretion values for TP-271 ranged from 9.98% to 16.94%.

There were no serious or severe AEs reported and no AEs leading to early discontinuation. Treatment emergent AEs were reported by 39.5% of subjects who received TP-271 and 35.7% of subjects who received placebo. The most frequently reported AEs in the TP-271 groups were gastrointestinal: nausea was reported by 1 subject in the 4.0 mg/kg group and by 4 subjects in the 5.0 mg/kg group; vomiting was reported by one subject in the 4.0 mg/kg group and 3 subjects in the 5.0 mg/kg group. No placebo subjects reported nausea or vomiting. There were no clinically significant changes in lab values, ECG parameters or physical exam findings.

Following single IV doses of TP-271, plasma exposures increased as dose increased in a greater than dose-proportional manner and were well tolerated at doses that resulted in high plasma exposures. These results support continued clinical development of TP-271.

Introduction

TP-271 is a novel, fully-synthetic fluorocycline antibiotic being developed for the IV/oral treatment of serious bacterial infections, including respiratory infections caused by multidrug-resistant pathogens. In *in vitro* assays, TP-271 had potent activity against key community respiratory Gram-positive and Gram-negative pathogens, including *Streptococcus pneumoniae* (MIC_{90} 0.03 mg/L), methicillin-resistant *S. aureus* (MRSA; MIC90 0.12 mg/L), *Streptococcus pyogenes* (MIC_{90} 0.03 mg/L), *Haemophilus influenzae* (MIC_{90} 0.12 mg/L), and *Moraxella catarrhalis* (MIC_{90} 0.016 mg/L).[1] In addition, TP-271 has shown *in vivo* efficacy in neutropenic and immunocompetent animal pneumonia models.[1]

This phase 1 study was the first-in-human study for TP-271.

Methods

- Phase 1, single site, randomized, double-blind, placebo-controlled, dose-escalating, single dose study in healthy adults

Primary Objective: determine the safety and tolerability of up to 7 different single IV doses of TP-271, ranging from 0.15 to 5.0 mg/kg, in healthy adult subjects

Secondary Objective: Determine the PK profile of TP-271

Key Inclusion Criteria

- Adult, age 18-50 years
- Non-obese; Body Mass Index (BMI) of 18.0 to 33.0 kg/m^2
- Non-childbearing potential
- Negative for HIV or Hepatitis (B,C)
- Signed consent form

Key Exclusion Criteria

- History or presence of clinically significant disease or disorder
- Lab, blood pressure, heart rate or ECG values abnormal or outside of reference ranges
- Use of medication within 7 days of dosing
- Consumption of nicotine, alcohol or drug abuse substances

- For each cohort, post-screening process, subjects were randomized 6:2 and dosed on Day 1 over a 60-minute infusion as described in Table 1. Subjects were discharged from the clinic at Day 5 and performed the return visit on Day 7-10.

Table 1. Seven cohorts of 8 subjects each received a single ascending intravenous dose of TP-271 (6 subjects) or placebo (2 subjects)

Cohort	Planned IV Dose
A	0.15 mg/kg or placebo
B	0.45 mg/kg or placebo
C	1.0 mg/kg or placebo
D	2.0 mg/kg or placebo
E	3.0 mg/kg or placebo
F	4.0 mg/kg or placebo
G	5.0 mg/kg or placebo

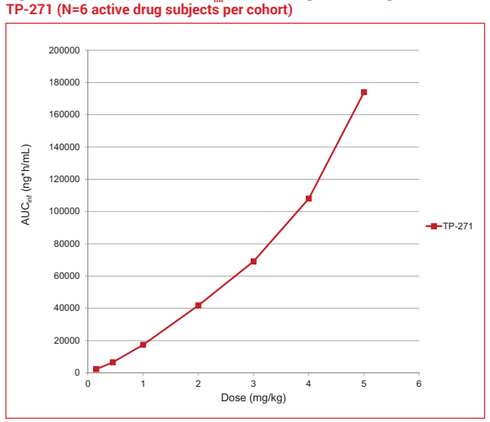
Methods (cont'd)

- Plasma and urine samples for pharmacokinetic (PK) analyses were collected immediately prior to dosing through 96 hours.
- Safety was assessed through collection of adverse events (AEs), clinical labs, vital signs, ECG and physical exam data.

Pharmacokinetic Results

- Fifty-seven (57) subjects were enrolled into the study, and 43 subjects received TP-271.
- Demographics and baseline characteristics were generally similar across treatment groups
  - Majority of subjects in this study were white (38 subjects, 66.7%); Fifty-two (52) subjects (91.2%) were male and 5 subjects (8.8%) were female; Mean age of all subjects was 30.8 years (range: 18 to 49 years); Mean BMI of all subjects was 26.83 kg/m^2
- The mean increases in AUC and C_{max} observed with increasing single doses of TP-271 were greater than dose proportional (Figure 1; Table 2). The half-life ranged from 15.13 – 19.05 hours. Mean plasma CL values of TP-271 ranged from 2.26 to 5.65 L/hr and mean V_d values ranged from 58.26 to 147.33 L, across all the doses tested (Table 2).
- Following a single infusion, mean total amount of drug excreted in the urine (Ae) generally increased as a function of dose. Mean fractional excretion (Fe) values for TP-271 ranged from 9.98% to 16.94% across treatment groups (Table 3).

Figure 1. Mean (CV) derived AUC_{inf} curve for single ascending IV doses of TP-271 (N=6 active drug subjects per cohort)



AUC_{inf} = area under the plasma concentration versus time curve extrapolated to infinity

Table 2. Mean (CV) derived PK parameters for single ascending IV doses of TP-271 (N=6 active drug subjects per cohort)

Cohort (TP-271 Dose (mg/kg))	AUC_{inf} (µg*h/mL)	C_{max} (µg/mL)	$T_{1/2}$ (h)	Cl (L/h)	V_d (L)
A (0.15)	2.2 (22.2)	0.3 (19.3)	15.1 (14.8)	5.6 (20.9)	121.4 (15.9)
B (0.45)	6.5 (17.6)	0.9 (18.0)	17.8 (6.0)	5.8 (14.0)	147.3 (9.0)
C (1.0)	17.4 (31.6)	2.7 (15.3)	18.9 (23.6)	4.3 (24.0)	115.7 (24.0)
D (2.0)	41.8 (17.5)	6.7 (13.4)	19.1 (8.9)	4.1 (19.3)	113.3 (20.0)
E (3.0)	67.2 (18.0)	12.0 (13.8)	17.1 (15.2	3.7 (16.4)	90.4 (26.3)
F (4.0)	107.8 (18.0)	18.5 (20.7)	17.1 (10.5)	2.9 (17.0)	72.7 (24.8)
G (5.0)	175.0 (31.5)	27.6 (26.5)	17.9 (5.3)	2.3 (15.4)	58.3 (14.5)

AUC_{inf} = area under the plasma concentration versus time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration; $T_{1/2}$ = elimination half-life; Cl = volume of plasma cleared per unit time; V_d = volume of distribution

Table 3. Mean (CV) urine PK parameters for single ascending IV doses of TP-271 (N=6 per cohort)

Cohort (TP-271 Dose (mg/kg))	Ae (mg)	Fe (%)	CLr (L/h)
A (0.15)	1.6 (26.8)	13.0 (19.8)	0.7 (9.1)
B (0.45)	4.9 (39.6)	12.7 (34.3)	1.1 (64.6)
C (1.0)	9.8 (28.4)	13.4 (15.6)	0.6 (15.3)
D (2.0)	28.2 (34.9)	16.9 (38.8)	0.7 (28.2)
E (3.0)	24.8 (45.0)	10.0 (43.7)	0.4 (47.0)
F (4.0)	36.1 (19.7)	11.6 (12.4)	0.3 (10.2)
G (5.0)	52.8 (42.4)	13.7 (25.8)	0.3 (11.4)

Ae = amount of drug excreted in the urine over 96 h; Fe = fractional excretion;
CLr = renal clearance
Note: all TP-271 urine concentrations taken pre-dose were below the limit of quantification

Table 4. Mean (SD) urine concentrations following single IV doses of TP-271 (N=6 per cohort)

Cohort (TP-271 Dose (mg/kg))	Urine Concentration (µg/mL)				
	0-12h	>12-24 h	>24-48 h	>48-72 h	>72-96h
A (0.15)	0.81 (0.13)	0.41 (0.25)	0.17 (0.06)	0.07 (0.04)	0.04 (0.02)
B (0.45)	1.80 (0.54)	1.29 (0.61)	0.46 (0.16)	0.19 (0.15)	0.08 (0.05)
C (1.0)	5.57 (2.70)	2.75 (1.66)	1.22 (0.66)	0.48 (0.43)	0.19 (0.20)
D (2.0)	6.25 (2.40)	5.16 (2.51)	2.31 (1.32)	0.56 (0.29)	0.31 (0.25)
E (3.0)	11.88 (4.08)	8.12 (3.37)	3.51 (1.12)	1.02 (0.42)	0.46 (0.18)
F (4.0)	14.51 (5.97)	8.57 (5.07)	3.53 (1.60)	0.98 (0.43)	0.45 (0.29)
G (5.0)	17.57 (5.22)	15.77 (5.48)	6.47 (5.34)	4.06 (5.80)	0.79 (0.67)

Safety Results

- Overall, 38.6% subjects reported 37 TEAEs during the study (35.7% of the placebo arm and 39.5% of the treatment arm reported TEAEs).
  - Except for 1 moderate TEAE (abdominal discomfort) reported by 1 subject (1.8%), all TEAEs were mild in severity
  - No clinically significant changes in lab values, ECG parameters, or physical exam findings occurred
- There were no deaths, serious or severe AEs, or discontinuations during the study
- The most frequently reported AEs in the TP-271 groups were gastrointestinal: nausea was reported by 1 subject in the 4.0 mg/kg group and by 4 subjects in the 5.0 mg/kg group; vomiting was reported by one subject in the 4.0 mg/kg group and 3 subjects in the 5.0 mg/kg group. No placebo subjects reported nausea or vomiting.

Conclusions

- Following single IV doses of TP-271, plasma exposures increased as dose increased in a greater than dose-proportional manner
- TP-271 was well tolerated at single doses that resulted in high plasma exposures
- The results of this phase 1 SAD study support the continued clinical development of TP-271

References

1. Grossman et al., Fluorocycline TP-271 Is Potent against Complicated Community-Acquired Bacterial Pneumonia Pathogens. *mSphere* 2017;2(1):1-11.

Disclosures

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