Poster # 1371

Safety, Tolerability and Pharmacokinetics of Multiple Doses of TP-6076, a Novel, Fully Synthetic Tetracycline, in a Phase 1 Study

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Abstract

Background: TP-6076 is a novel, fully synthetic tetracycline being developed for the treatment of serious bacterial infections including those caused by multidrug-resistant *Acinetobacter baumannii*. TP-6076 has demonstrated potent activity *in vitro* against carbapenem-resistant strains of *A. baumannii*, with MIC_{90} 64 times lower compared to tigecycline and 256 times lower compared to minocycline. We now report the results of a multiple ascending dose study in normal healthy volunteers.

Methods: This was a phase 1, single site, randomized, double-blind, placebo-controlled dose-escalating, multiple dose study in healthy adults who met the inclusion/exclusion criteria and provided informed consent prior to any study procedure. Cohorts of 8 subjects each (6 active and 2 placebo) received daily doses of 6.0 to 40.0 mg TP-6076 or placebo for 7 days. Plasma and urine samples for pharmacokinetic (PK) analyses were collected starting immediately prior to dosing until 96 hours after the last dose. Safety was assessed through collection of adverse events (AEs), clinical laboratories, vital signs, ECG and physical exam data.

Results: The geometric mean derived PK parameters for TP-6076 were:

TP-6076 Dose (mg)	$AUC_{0\text{-}tau}$ (ng*h/mL)		$T_{1/2}$ (h)
	Day 1	Day 7	Day 7
6.0	1034	1621	21.2
20.0	4871	7139	27.7
30.0	6382	10149	28.4
35.0	7842	10825	28.8
40.0	9433	12698	25.8

There were no serious or severe AEs reported. The most frequently reported AEs were gastrointestinal events, including nausea and vomiting, and localized infusion site reactions. There were no clinically significant changes in clinical laboratory values, ECG parameters or physical exam findings.

Conclusion: Following multiple IV doses of TP-6076, plasma exposure increased as dose increased. Multiple IV doses of TP-6076 were generally well tolerated, with higher gastrointestinal adverse event rates in the higher dose groups.

Background

- TP-6076 is a novel, fully synthetic antibiotic of the tetracycline class being developed for the treatment of serious and life-threatening bacterial infections including those caused by multidrug-resistant *Acinetobacter baumannii.*
- Potent *in vitro* activity against Enterobacteriaceae (MIC_{90}, 0.5 mg/L) and *A. baumannii* (MIC_{90}, 0.06 mg/L) has been demonstrated for TP-6076. The MIC_{90} values for TP-6076 against *A. baumannii* were 64 times lower compared to tigecycline and 256 times lower compared to minocycline (Table 1).
- In addition, TP-6076 has shown *in vivo* efficacy against both carbapenem-resistant *A. baumannii* and carbapenem-resistant Enterobacteriaceae in neutropenic murine lung models
- Early Phase 1 SAD (single ascending dose) and MAD (multiple ascending dose) studies have been completed. Here we report the results of the MAD study in normal healthy volunteers

References

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Background (cont'd)

Table 1. ***In vitro*** **activity of TP-6076 and comparators against 55 XDR** ***A. baumannii*** **isolates**

Antibiotic	$MIC_{50/90}$ in µg/mL	Range
TP-6076	0.016 / 0.063	≤0.004 - 0.25
Tigecycline	2 / 4	0.031 - 2
Minocycline	8 / 16	≤0.016 - 32
Meropenem	>32 / >32	2 - >32
Meropenem/vaborbactam	>32/>32	8 - >32
Ceftazidime/avibactam	>32/>32	8 - >32
Gentamicin	>32 / >32	8 - >32
Colistin	0.5 / 4	0.063 - >32

Methods

- Phase 1, single site, randomized, double-blind, placebo-controlled dose-escalating, multiple dose study of TP-6076 in healthy adults

Primary Objective: To assess the safety and tolerability of multiple dose regimens of TP-6076

Secondary Objectives:

- To determine the plasma pharmacokinetic (PK) profile for TP-6076 and metabolites following multiple doses
- To determine the excretion of TP-6076 following multiple doses

Key Inclusion Criteria

- Healthy Adults, age 18-55 years
- Non-obese; Body Mass Index (BMI) of 18 to 35 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 another investigational drug or device
- Consumption of nicotine, alcohol or drug abuse substances

- Fifty-six (56) healthy subjects in cohorts of 8 each (6 active and 2 placebo) received daily doses of 6 to 40 mg TP-6076 or placebo for 7 days. One cohort received twice daily dosing and two cohorts also received a one-time loading dose of 40-45 mg on Day 1. The starting dose was determined based on the PK and tolerability results from the SAD study.
- Plasma samples for PK analyses were collected starting immediately prior to dosing until 96 hours after the last dose.
- Plasma concentration data for TP-6076 were analyzed using non-compartmental techniques.
- Safety was assessed through collection of adverse events (AEs), clinical laboratories, vital signs, ECG and physical exam data.

Results

Table 2. Demographics

Parameter	TP-6076 Dose							All Placebo N = 14
Median (range)	6 mg N = 6	20 mg N = 6	30 mg N = 6	35 mg N = 6	40 mg N = 6	40 mg +20 mg q12h N = 6	45mg +30 mg N = 6	
Age (yrs)	32 (21-44)	24 (18-30)	23 (20-34)	22 (19-49)	34 (19-53)	25 (18-28)	29 (24-54)	28 (20-54)
Height (cm)	173 (160-179)	168 (166-204)	179 (175-185)	174 (166-177)	171 (158-172)	171 (162-183)	168 (164-186)	174 (151-195)
Weight (kg)	66.5 (56.1-76.7)	71.5 (64.7-79.1)	72.3 (65.7-78.2)	76.6 (63.1-98.8)	74.3 (61.9-97.7)	65.4 (51.1-73.2)	68.7 (51.6-88.9)	74.5 (55.1-96.4)
BMI (kg/m^2)	22.7 (19.6-25.6)	24.4 (19.0-26.9)	22.4 (21.0-23.7)	25.5 (22.9-31.5)	28.1 (20.9-33.0)	21.4 (19.5-23.9)	22.8 (18.1-27)	24.8 (19.8-30.7)
Sex:								
Male (%)	1 (17)	3 (50)	5 (83)	3 (50)	2 (33)	2 (33)	1 (17)	3 (21)
Female (%)	5 (83)	3 (50)	1 (17)	3 (50)	4 (67)	4 (67)	5 (83)	11 (79)
Race:								
White (%)	6 (100)	5 (83)	5 (83)	5 (83)	3 (50)	5 (83)	5 (83)	12 (86)
Asian (%)	-	-	-	-	1 (17)	-	-	1 (7)
Black (%)	-	1 (17)	-	-	2 (33)	-	-	-
Other (%)	-	-	1 (7)	1 (7)	-	1 (7)	1 (7)	1 (7)

Disposition

- A total of 9 subjects (16%) who received TP-6076 were withdrawn due to TEAEs. Six subjects were withdrawn because of moderate vomiting and/or nausea (2 subjects on Day 2 and 3 subjects on Day 3) and 3 because of infusion site related reactions (2 subjects on Day 3 and 1 subject on Day 4). The TEAEs that resulted in withdrawal were considered possibly related to TP-6076.
- No subjects who received a dose of 30 mg q24h or less without a loading dose were withdrawn due to TEAEs.

Table 3. PK parameters

PK Parameter (CV%)	TP-6076 Dose						
	6.0 mg q24h	20 mg q24h	30 mg q24h	35 mg q24h	40 mg q24h	40 mg + 20 mg q12h	45 mg + 30 mg q24h
DAY 1							
N	6	6	6	6	6	6	6
T_{max} (h)	0.5	0.5	0.5	1.0	0.6	0.5	0.5
C_{max} (ng/mL)	248 (7.4)	1017 (19.2)	1500 (14.2)	1490 (21.0)	1743 (21.3)	1980 (16.7)	2069 (24.1)
$AUC_{0\text{-}T}$ (ng•h/mL)	1034 (10.7)	4871 (18.3)	6382 (16.1)	7842 (25.4)	9433 (22.0)	7611 (25.0)	11488 (31.5)
DAY 7							
N	6	5	6	4	3	-	2
C_{max} (ng/mL)	287 (18.1)	1293 (13.6)	1684 (17.4)	1607 (29.4)	1364 (200.6)	-	1460-1570
$AUC_{0\text{-}T}$ (ng•h/mL)	1621 (12.7)	7139 (18.8)	10149 (15.7)	10825 (29.6)	12698 (61.1)	-	9049-9940
$T_{1/2el}$ (h)	21.2 (5.6)	27.7 (13.5)	28.4 (6.0)	28.8 (7.6)	25.8 (2.8)	-	24.4-33.3
CL (L/h)	3.7 (12.7)	2.8 (18.8)	3.0 (15.7)	3.2 (29.6)	3.2 (61.1)	-	3.0-3.3
Vz (L)	113 (14.2)	112 (23.3)	121 (21.1)	134 (34.7)	117 (64.5)	-	106-159

Table 4. Summary of safety

Subjects (%) reporting:	TP-6076 Dose							All Placebo N = 14
	6 mg N = 6	20 mg N = 6	30 mg N = 6	35 mg N = 6	40 mg N = 6	40/20 mg q12h N = 6	45/30 mg N = 6	
At least 1 AE	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	14 (100)
IMP-related AEs	-	5 (83)	6 (100)	4 (67)	6 (100)	6 (100)	6 (100)	9 (64)
AEs leading to IMP withdrawal	-	-	-	2 (33)	2 (33)	1 (17)	4 (67)	-
Severe AEs	-	-	-	-	-	-	-	-
Serious AEs	-	-	-	-	-	-	-	-
AEs leading to death	-	-	-	-	-	-	-	-

Table 5. TEAEs occurring in more than one subject in any group

System Organ Class / Preferred term / Subjects (%)	TP-6076 Dose							All Placebo N = 14
	6 mg N = 6	20 mg N = 6	30 mg N = 6	35 mg N = 6	40 mg N = 6	40/20 mg q12h N = 6	45/30 mg N = 6	
Gastrointestinal Disorders								
Nausea	-	4 (67)	6 (100)	5 (83)	5 (83)	6 (100)	5 (83)	4 (29)
Vomiting	-	-	1 (17)	2 (33)	2 (33)	3 (50)	2 (33)	-
Diarrhea	-	1 (17)	-	1 (17)	2 (33)	1 (17)	2 (33)	3 (21)
Abdominal pain	-	2 (33)	1 (17)	2 (33)	2 (33)	-	4 (67)	2 (14)
Abdominal discomfort	-	-	2 (33)	-	2 (33)	-	-	2(14)
Flatulence	-	-	-	2 (33)	-	-	1 (17)	1 (7)
General Disorders and Administration Site Conditions								
Infusion Site Events	6 (100)	5 (83)	5 (83)	3 (50)	6 (100)	5 (83)	5 (83)	10 (71)
Fatigue	1 (17)	2 (33)	2 (33)	2 (33)	1 (17)	-	1 (17)	1 (7)
Nervous System Disorders								
Dizziness	-	2 (33)	2 (33)	1 (17)	2 (33)	1 (17)	4 (67)	5 (36)
Headache	-	1 (17)	5 (83)	2 (33)	-	2 (33)	3 (50)	4 (29)
Somnolence	-	1 (17)	2 (33)	-	-	-	-	-
Metabolism and Nutrition Disorders								
Decreased Appetite	-	1 (17)	-	3 (50)	2 (33)	-	-	1 (7)
Musculoskeletal and Connective Tissue Disorders								
Back Pain	-	-	-	-	1 (17)	-	1 (17)	2 (14)
Respiratory, Thoracic and Mediastinal Disorders								
Oropharyngeal pain	-	-	-	2 (33)	-	-	-	-
Renal and Urinary Disorders								
Pollakiuria	-	-	-	-	-	-	-	2 (14)

Conclusions

- Multiple IV doses of TP-6076 were generally well tolerated, with higher gastrointestinal adverse event rates in the higher dose groups and with loading doses.
- There were no clinically significant findings in any laboratory assessments, vital signs, ECGs or physical examinations.
- Following multiple IV doses of TP-6076, plasma exposure increased as dose increased.
- Many antibacterials directed at Gram-negative pathogens are in development, but few have potent activity against *A. baumannii*. TP-6076 holds the potential to effectively treat infections caused by this organism. Further clinical study is warranted.