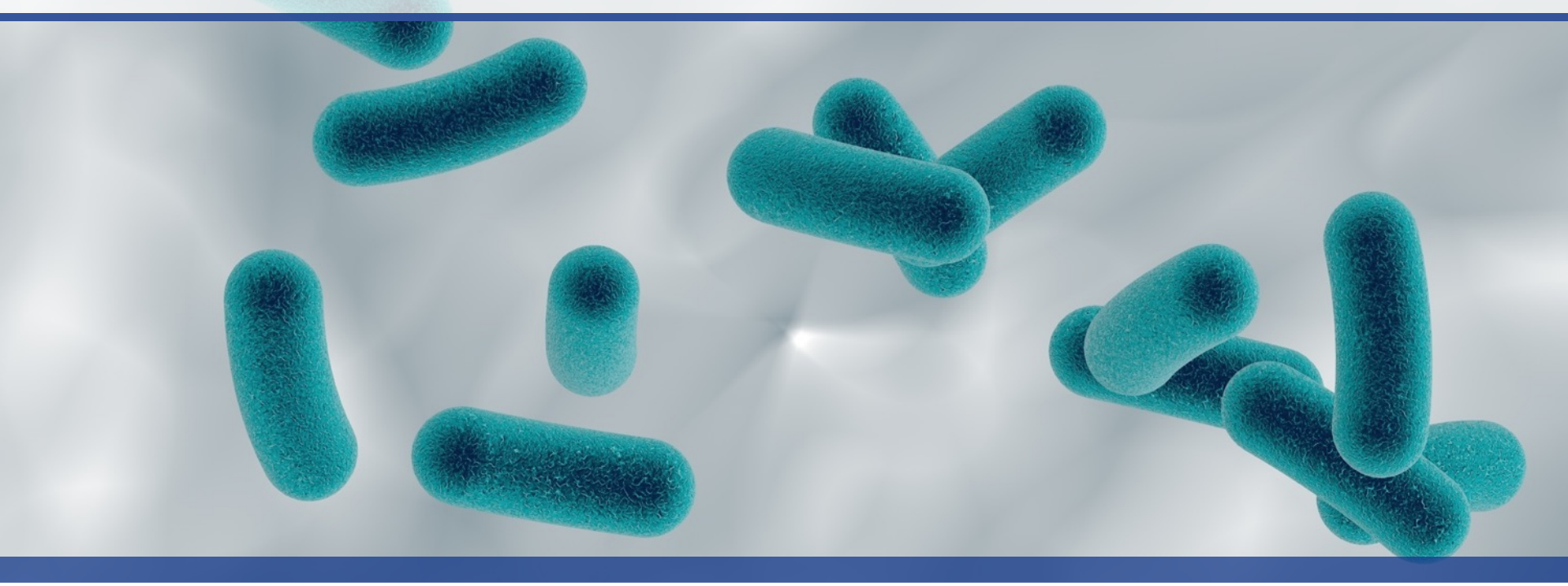
TETRAPHASE PHARMACEUTICALS



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

Larry Tsai, Susan Redican, Patrick Horn

Disclosures

- Larry Tsai is a full time employee of Tetraphase Pharmaceuticals, Inc.
- Susan Redican is a full time employee of Tetraphase Pharmaceuticals, Inc.
- Patrick Horn is a full time employee of Tetraphase Pharmaceuticals, Inc.

Introduction

- TP-6076 is a novel, fully synthetic broad-spectrum antibiotic of the tetracycline class
- TP-6076 is being developed for the treatment of serious and life-threatening bacterial infections including those caused by carbapenem-resistant *Enterobacteriaceae* and multidrug-resistant *Acinetobacter baumannii*
- TP-6076 disrupts bacterial protein synthesis by binding to the 30S ribosomal subunit and interfering with the access of aminoacyl-transfer ribonucleic acid to the A-site on the messenger ribonucleic acid-ribosome complex, preventing addition of amino acids to the growing peptide chain
- Structure and characterization will be presented in Poster SUNDAY-332, “TP-6076, a Fully Synthetic Tetracycline Antibacterial Agent, is Highly Potent against a Broad Range of Pathogens, Including Carbapenem-Resistant Enterobacteriaceae,” Session 351, 6/4/2017 12:15PM

In vitro activity of TP-6076

- TP-6076 has demonstrated potent activity in vitro against Gram-negative organisms including carbapenem and multidrug-resistant strains of *Enterobacteriaceae* and *A. baumannii*

55 XDR *Acinetobacter baumannii*

Antibiotic	$MIC_{50/90}$ µg/mL
TP-6076	0.016/0.063
Tigecycline	2/4
Minocycline	8/16
Tetracycline	>32
Colistin	0.5/4
Meropenem	>32
Gentamicin	>32

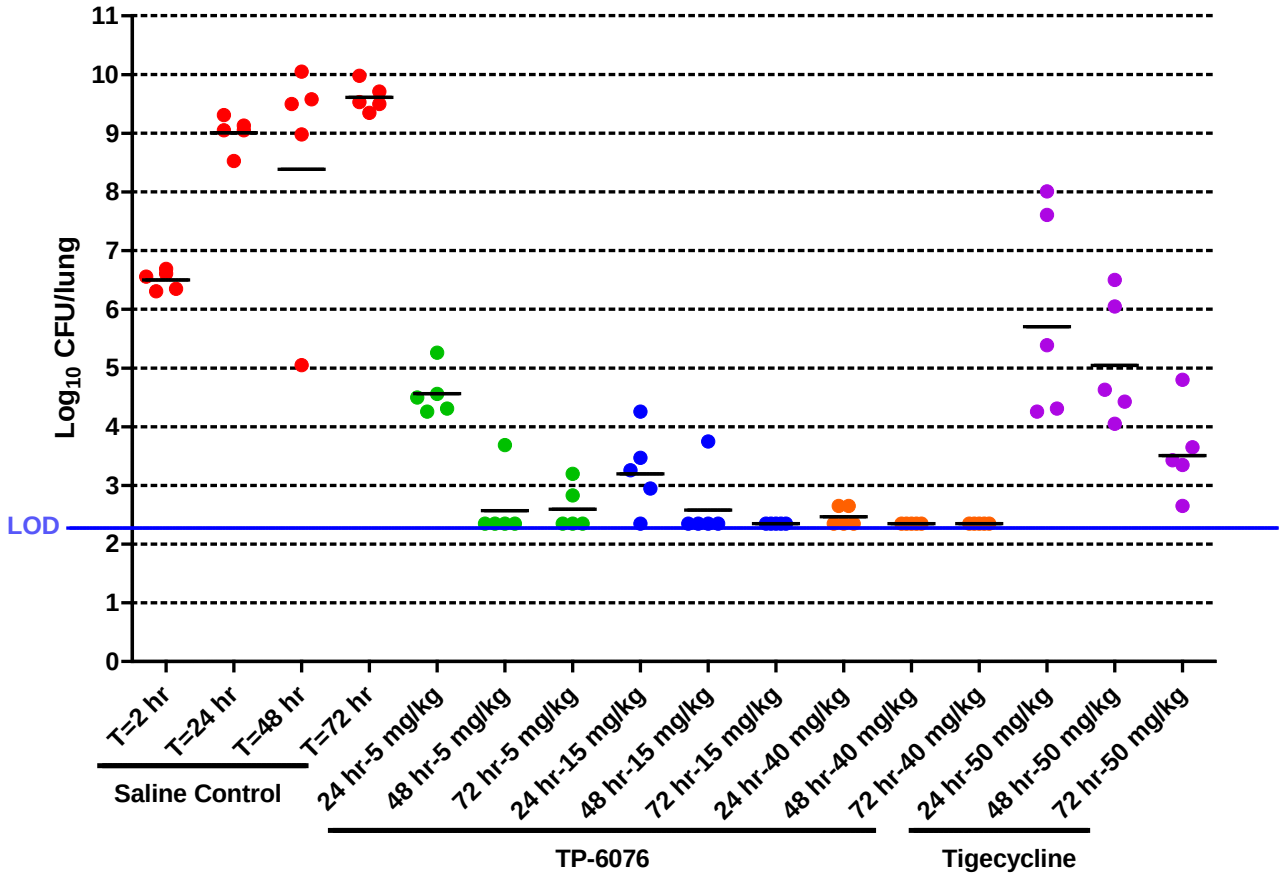
141 resistant *Enterobacteriaceae* spp.

Antibiotic	$MIC_{50/90}$ µg/mL
TP-6076	0.063/0.5
Tigecycline	0.5/2
Minocycline	8/>32
Tetracycline	16/>32
Colistin	0.25/>32
Meropenem	8/>32
Gentamicin	8/>32

TETRAPHASE

Fyfe C, LeBlanc G, Close, Newman JV. 2017. 27th ECCMID, Poster P1365.

TP-6076 is Efficacious against Carbapenem-resistant *Acinetobacter baumannii* in a Mouse Pneumonia Model



Compound	MIC (μg/mL)
TP-6076	0.008
Tigecycline	1

TETRAPHASE

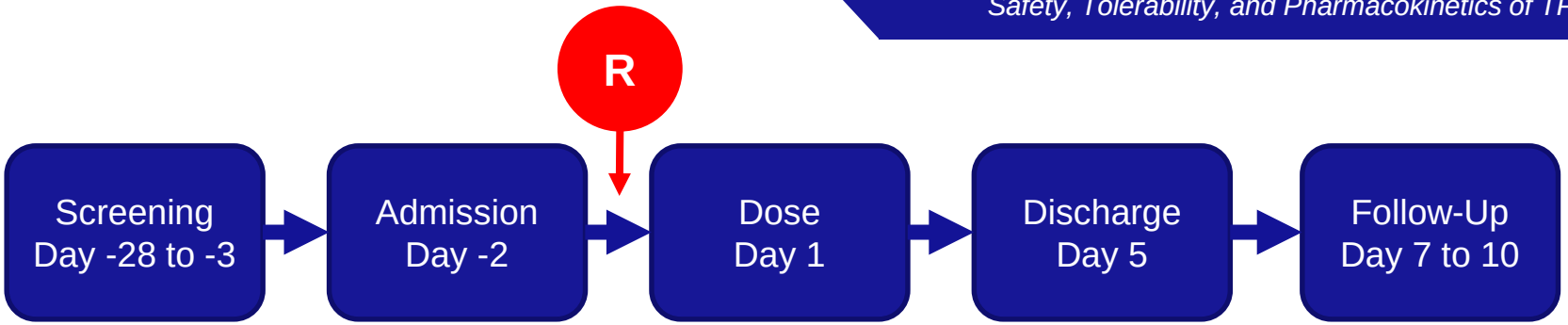
Grossman TH, Fyfe C, Kerstein K, Xiao X, Sun C, Newman J, Weiss WJ, Dumas J, Sutcliffe JA. 2016. 26th ECCMID, poster P1310

TP-6076-001 Study Design

- First in human
- Randomized, double-blind, placebo controlled, single-center
- **Primary objective:** determine the safety and tolerability of single ascending doses of TP-6076 in healthy subjects
- **Secondary objective:** determine the PK profile of TP-6076
- 5 sequentially-enrolled cohorts:

Cohort	TP-6076 IV Dose (single IV infusion over 30 minutes)
1	1.8 mg
2	6.0 mg
3	19.2 mg
4	40.0 mg
5	60.0 mg

TP-6076-001 Study Design



- Plasma concentrations of TP-6076 were measured pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2.5, 4.5, 8.5, 12.5, 24, 48, 72, and 96 hours after the start of the infusion
- Urine collected pre-dose, 0-12, 12-24, 24-48, 48-72, and 72-96 hours after the start of the infusion
- Adverse events, physical exams, vital signs, ECGs, clinical pathology (chemistry, hematology, coagulation and urinalysis) assessed
- Blinded interim assessments of safety and pharmacokinetics conducted after the completion of each dose cohort prior to dosing the next cohort

TETRAPHASE

TP-6076-001 Statistical Methods

- Demographics, prior and concomitant meds listed and summarized
- AEs coded and tabulated by dose group, all placebo, all IMP, severity, and relationship
- Laboratory values, vital signs, and ECG parameters listed and summarized, out of reference range values flagged
- Plasma concentration data for TP-6076 analyzed using Phoenix WinNonlin v 6.3 with non-compartmental techniques
- PK parameters listed and summarized using descriptive statistics
- Dose proportionality assessed using the power model: 'log(AUC or C_{max}) = μ (intercept of model) + ß (slope of model) × log(dose)', which included a term for dose fitted as a fixed (continuous) effect

TP-6076-001 Results – Disposition

- All subjects received a single IV infusion according to the assigned dose group
- All subjects completed the study through the Follow-Up visit
- All subjects included in the safety population and in the TP-6076 PK population

TP-6076-001 Study Results – Demographics

		TP-6076 Dose					All Active	All Placebo
		1.8 mg N = 6	6.0 mg N = 6	19.2 mg N = 6	40.0 mg N = 6	60.0 mg N = 6	N = 30	N = 10
Age (yrs)	Mean	36.3	33.7	31.8	33.3	43.8	35.8	40.6
	SD	10.5	9.9	14.7	7.8	9.1	10.8	12.8
Height (cm)	Mean	167.2	177.0	167.5	175.3	172.2	171.8	169.5
	SD	9.1	9.4	8.3	10.1	5.2	8.9	10.4
Weight (kg)	Mean	76.93	85.07	75.40	78.17	83.80	79.87	82.40
	SD	12.24	9.22	7.99	12.74	9.92	10.57	9.53
BMI (kg/m^2)	Mean	27.53	27.30	26.95	25.45	28.37	27.12	28.72
	SD	4.07	3.77	3.10	3.87	4.08	3.65	2.95
Sex:								
Male	n (%)	1 (16.7)	5 (83.3)	3 (50.0)	5 (83.3)	4 (66.7)	18 (60.0)	7 (70.0)
Female	n (%)	5 (83.3)	1 (16.7)	3 (50.0)	1 (16.7)	2 (33.3)	12 (40.0)	3 (30.0)
Race:								
White	n (%)	6 (100.0)	5 (83.3)	6 (100.0)	4 (66.7)	3 (50.0)	24 (80.0)	9 (90.0)
Black	n (%)	0	0	0	1 (16.7)	3 (50.0)	4 (13.3)	0
Asian	n (%)	0	0	0	0	0	0	1 (10.0)
Other	n (%)	0	1 (16.7)	0	1 (16.7)	0	2 (6.7)	0

TETRAPHASE

TP-6076-001 Study Results – Pharmacokinetics

PK Parameter	TP-6076 Dose				
	1.8 mg N = 6	6.0 mg N = 6	19.2 mg N = 6	40.0 mg N = 6	60.0 mg N = 6
T_{max} (h)	0.50	0.50	0.50	0.50	0.50
C_{max} (ng/mL)	67.2 (15.3)	310 (17.3)	1220 (21.9)	2660 (12.1)	3720 (14.0)
$AUC_{0\text{-}inf}$ (ng.h/mL)	NC	1780 (11.0) [n=5]	7290 (20.7)	17600 (16.8)	24400 (12.6)
$T_{1/2el}$ (h)[b]	6.94 (0.47) [n=3]	21.46 (4.37)	24.46 (4.58)	28.06 (3.31)	26.35 (4.15)
CL (mL/min)	NC	56.1 (11.0) [n=5]	43.9 (20.7)	37.9 (16.8)	41.0 (12.6)
V_d (L)	NC	97.7 (23.5) [n=5]	91.5 (22.8)	91.7 (20.1)	92.6 (24.8)

Values presented are Geometric Mean (Geometric CV%)
NC = not calculated

TETRAPHASE

TP-6076-001 Study Results – Safety and Tolerability

Safety, Tolerability, and Pharmacokinetics of TP-6076

Subjects (%) reporting:	TP-6076 Dose					All Active N = 30	All Placebo N = 10
	1.8 mg N = 6	6.0 mg N = 6	19.2 mg N = 6	40.0 mg N = 6	60.0 mg N = 6		
At least 1 AE	1 (16.7)	0	2 (33.3)	2 (33.3)	5 (83.3)	10 (33.3)	6 (60.0)
IMP-related AEs	1 (16.7)	0	0	1 (16.7)	5 (83.3)	7 (23.3)	1 (10.0)
AEs leading to IMP withdrawal	0	0	0	0	0	0	0
Severe AEs	0	0	0	0	0	0	0
Serious AEs	0	0	0	0	0	0	0
AEs leading to death	0	0	0	0	0	0	0

TETRAPHASE

TP-6076-001 Study Results – Safety and Tolerability

Safety, Tolerability, and Pharmacokinetics of TP-6076

System Organ Class Preferred term	TP-6076 Dose					All Active	All Placebo
	1.8 mg N = 6	6.0 mg N = 6	19.2 mg N = 6	40.0 mg N = 6	60.0 mg N = 6	N = 30	N = 10
Gastrointestinal Disorders	1 (16.7)	0	0	1 (16.7)	4 (66.7)	6 (20.0)	2 (20.0)
Nausea	1 (16.7)	0	0	1 (16.7)	3 (50.0)	5 (16.7)	2 (20.0)
Constipation	0	0	0	0	1 (16.7)	1 (3.3)*	0
Vomiting	0	0	0	0	0	0	1 (10.0)
Nervous System Disorders	0	0	1 (16.7)	1 (16.7)	1 (16.7)	3 (10.0)	1 (10.0)
Headache	0	0	1 (16.7)	0	0	1 (3.3)	1 (10.0)
Dizziness	0	0	0	0	1 (16.7)	1 (3.3)	0
Restless legs syndrome	0	0	0	1 (16.7)	0	1 (3.3)	0
General Disorders and Administrative Site Conditions	0	0	1 (16.7)	0	0	1 (3.3)	2 (20.0)
	0	0	0	0	0	0	1 (10.0)
Feeling hot	0	0	1 (16.7)	0	0	1 (3.3)	0
Medical device site reaction	0	0	0	0	0	0	1 (10.0)
Vessel puncture site bruise							
Metabolism and Nutrition Disorders	0	0	0	1 (16.7)	1 (16.7)	2 (6.7)	0
Decreased appetite	0	0	0	0	1 (16.7)	1 (3.3)	0
Dehydration	0	0	0	1 (16.7)	0	1 (3.3)	0
Musculoskeletal and Connective Tissue Disorders	0	0	0	1 (16.7)	0	1 (3.3)	1 (10.0)
	0	0	0	0	0	0	1 (10.0)
Myalgia	0	0	0	1 (16.7)	0	1 (3.3)	0
Pain in extremity							
Reproductive System and Breast Disorders	0	0	1 (16.7)	0	0	1 (3.3)	1 (10.0)
Dysmenorrhoea	0	0	1 (16.7)	0	0	1 (3.3)	1 (10.0)
Infections and Infestations	0	0	0	0	0	0	1 (10.0)
Nasopharyngitis	0	0	0	0	0	0	1 (10.0)

TETRAPHASE

Conclusions

- TP-6076 was well tolerated when administered as a single IV dose of up to 60.0 mg
- There were no deaths and no serious or severe TEAEs reported during the study, and no subject was withdrawn as a result of a TEAE
- There were no clinically significant findings in any laboratory assessments, vital signs, ECGs or physical examinations
- Following single IV doses of TP-6076, exposure to TP-6076 increased with dose; peak (C_{max}) and total exposure ($AUC_{0\text{-}inf}$) increased in a slightly greater than dose proportional manner over the 1.8 mg to 60.0 mg dose range
- Given the *in vitro* potency of TP-6076 against multidrug-resistant Gram-negative pathogens, the systemic exposures observed, and the favorable safety and tolerability observed after single dose IV administration of TP-6076, continued clinical development is warranted and is ongoing

TETRAPHASE