TP-6076

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Tetraphase Pharmaceuticals

TETRAPHASE
PHARMACEUTICALS

Tetraphase Pharmaceuticals Overview

- Tetraphase is developing novel antibiotics for serious and life-threatening Gram-negative MDR infections
- Pipeline of differentiated antibiotics created by proprietary chemistry platform

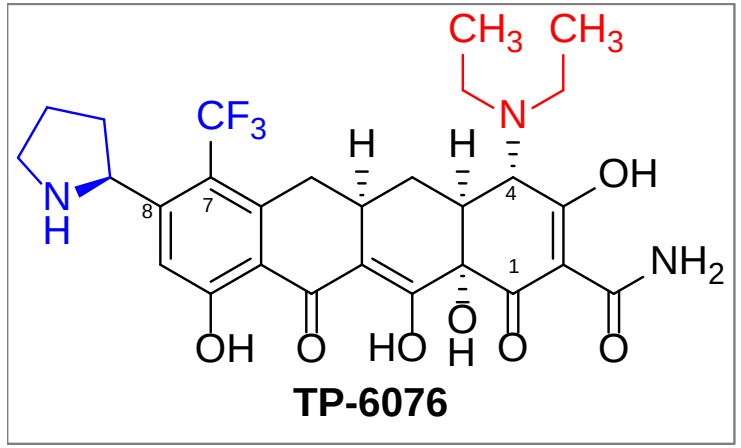
XERAVA™ (eravacycline)

TP-271

TP-6076

TP-6076: Product Overview

- TP-6076 is a novel, synthetic, broad-spectrum antibacterial of the tetracycline class
- In development for the treatment of serious and life-threatening bacterial infections, including those caused by
  - Carbapenem-resistant *Enterobacteriaceae*
  - Multidrug-resistant *Acinetobacter baumannii*
- TP-6076 disrupts bacterial protein synthesis by binding to the 30S ribosomal subunit
- Research funding provided by a **CARB-X grant**



TP-6076

Sun C, Deng Y, Hunt D, Fyfe C, Kerstein K, Xiao X. TP-6076, A Fully Synthetic Tetracycline Antibacterial Agent, Is Highly Potent against a Broad Range of Pathogens, including Carbapenem-resistant Enterobacteriaceae, abstr. SUN-332. Poster presented at ASM Microbe; June 1-5, 2017; New Orleans, LA, USA.

TP-6076 *In Vitro* Activity Against *E. coli* Recombinantly Expressing Tetracycline Resistance Genes

Antibiotic	MIC (µg/mL)								
	EC107	EC969	EC2152	EC970	EC1082	EC1083	EC1827	EC1153	EC971
	25922	tet(M)	tet(Q)	tet(K)	tet(A)	tet(B)	tet(D)	tet(X)	lacZ
TP-6076	0.0078	0.0312	0.0312	0.00039	0.0625	0.0312	0.0156	0.25	0.0078
Tetracycline	1	>64	64	>64	>64	>64	>64	>64	2
Minocycline	0.25	>32	>32	1	8	4	8	2	0.5
Doxycycline	1	32	32	8	32	32	32	8	1
Tigecycline	0.0312	0.25	0.125	0.125	1	0.5	0.25	2	0.125
Ceftriaxone	0.0625	0.125	0.125	0.0625	0.0625	0.0625	0.0625	0.125	0.125

Sun C, Deng Y, Hunt D, Fyfe C, Kerstein K, Xiao X. TP-6076, A Fully Synthetic Tetracycline Antibacterial Agent, Is Highly Potent against a Broad Range of Pathogens, including Carbapenem-resistant Enterobacteriaceae, abstr. SUN-332. Poster presented at ASM Microbe; June 1-5, 2017; New Orleans, LA, USA.

TP-6076 *In Vitro* Activity against *Enterobacteriaceae* spp., Including Resistant Phenotypes and Genotypes

- TP-6076 *in vitro* activity was investigated against *Enterobacteriaceae* spp. (n=221) from organism panels from the available CDC/FDA Antibiotic Resistance (AR) Isolate Bank*
  - *Enterobacteriaceae* genotypes/phenotypes included the following (isolate could have >1 resistance type)
    - MBL+ (n=47)
    - NDM+ (n=37)
    - Caz-Avi Resistant (n=47)
    - RNA methylase+ (30)
    - Fos(A)+ (n=23)
    - Δomp (n=33)
    - $TetR^{+}$ (n=71)

Antibiotic	$MIC_{50/90}$ in µg/mL	Range
TP-6076	0.031/0.25	0.004 - 1
Tigecycline	0.25/2	0.016 – 8
Minocycline	8/>32	0.25 - >32
Meropenem	4/>32	≤0.016 - >32
Meropenem/ vaborbactam	0.063/>32	≤0.016 - >32
Ceftazidime/ avibactam	1/>32	0.063 - >32
Gentamicin	4/>32	0.125 - >32
Levofloxacin	16/>32	0.031 - >32
Colistin	0.25/>32	0.063 - >32

*CDC has one of the largest collections of isolates gathered from national reference labs and tracking activities, taken from specimens in healthcare, food, and the community; Collection panels provided free of charge

Includes *E. coli* (63), and species of *Klebsiella* (73*), Enterobacter* (30), *Proteus* (7), *Citrobacter* (7), *Salmonella* (13), *Shigella* (7*), Serratia* (12), *Morganella* (6), *Providencia* (2), *Kluyvera* (1)

Fyfe C, Barry R, Close B, Kerstein K, Nordmann P, Newman J. TP-6076 is active against bacterial isolates carrying emergent resistance types, P655. Poster presented at ASM Microbe; June 7-11, 2018; Atlanta, GA.; https://www.cdc.gov/drugresistance/resistance-bank/index.html

TP-6076 *In Vitro* Activity against XDR *Acinetobacter baumannii*

- Fifty-five XDR *A. baumannii* from organism panels from the available CDC/FDA Antibiotic Resistance (AR) Isolate Bank*
- Genotypes/phenotypes included the following (isolate could have >1 resistance type)
  - Caz-Avi resistant (OXA identified) (n=54)
  - RNA methylase+ (n=21)
  - TetR+ (n=28)
  - Colistin resistance (n=3)

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
Levofloxacin	16 / >32	4 - >32
Colistin	0.5 / 4	0.063 - >32

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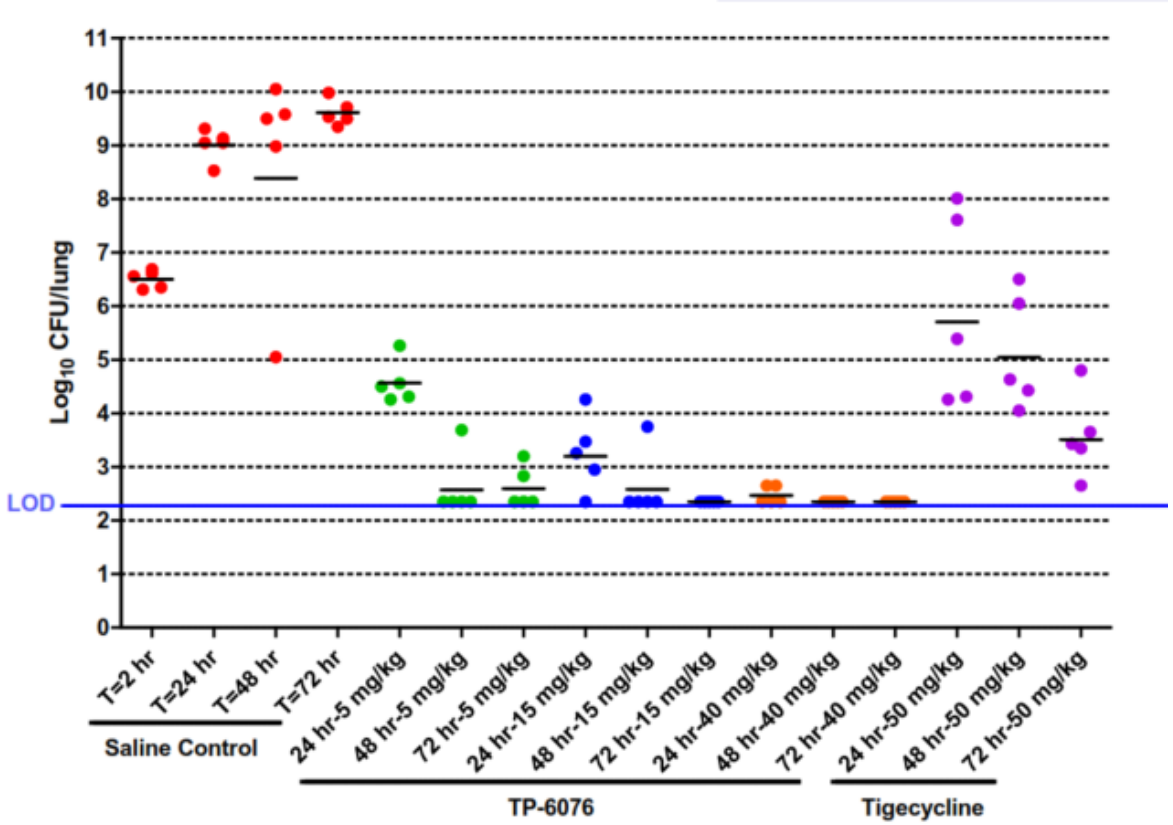
TP-6076 *In Vivo* Activity

- TP-6076 was shown efficacious against carbapenem-resistant *Acinetobacter baumannii* in a Mouse Pneumonia Model



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

Grossman TH, Fyfe C, Kerstein K, Xiao X, Sun C, Newman J, Weiss WJ, Dumas J, Sutcliffe JA. TP-6076 is efficacious in a mouse pneumonia model with carbapenem-resistant Acinetobacter baumannii (CRAB) and retains potency against common tetracycline-resistance mechanisms, abstr. 1731, poster P1310. Poster presented at 26th European Congress of Clinical Microbiology and Infectious Diseases; April 9-12, 2016; Amsterdam, Netherlands.

TP-6076-001 – Study Overview

- Randomized, double-blind, single ascending dose study of TP-6076 IV administered to healthy subjects
- Pharmacokinetics results:

PK Parameter	TP-6076 Dose				
	1.8 mg N = 6	6 mg N = 6	19.2 mg N = 6	40 mg N = 6	60 mg N = 6
T_{max} (h)	0.50	0.50	0.50	0.50	0.50
C_{max} (µg/mL)	0.0672 (15.3)	0.310 (17.3)	1.220 (21.9)	2.660 (12.1)	3.720 (14.0)
AUC_{0-24} (µg.h/mL)	0.241 (30.0)	1.190 (15.5)	5.170 (22.7)	12.500 (14.2)	17.500 (15.2)
$T_{1/2el}$ (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

- Following single IV doses of TP-6076, exposure to TP-6076 increased with dose
- Peak (C_{max}) and total exposure (AUC_{0-inf}) increased in a slightly greater than dose proportional manner over the 1.8 mg to 60 mg dose range

Tsai L, Redican S, Horn P. Safety, Tolerability and Pharmacokinetics of Single Doses of TP-6076, a Novel Fully Synthetic Tetracycline, in a Phase 1 Study, abstr. #Oral8. Oral presentation presented at ASM Microbe; June 1-5, 2017; New Orleans, LA, USA.

TP-6076-001 Study Results – Safety and Tolerability

System Organ Class Preferred term	TP-6076 Dose					All Active	All Placebo
	1.8 mg N = 6	6 mg N = 6	19.2 mg N = 6	40 mg N = 6	60 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)
Feeling hot	0	0	0	0	0	0	1 (10.0)
Medical device site reaction	0	0	1 (16.7)	0	0	1 (3.3)	0
Vessel puncture site bruise	0	0	0	0	0	0	1 (10.0)
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)
Myalgia	0	0	0	0	0	0	1 (10.0)
Pain in extremity	0	0	0	1 (16.7)	0	1 (3.3)	0
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)

- TP-6076 was well tolerated when administered as a single IV dose up to 60 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

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TP-6076 Multiple Ascending Dose (MAD) Study

- Randomized, double-blind, multiple ascending dose study of TP-6076 IV administered to healthy subjects
- The geometric mean derived PK parameters for TP-6076 were:

TP-6076 Dose (mg)	$AUC_{0\text{-}tau}$ (µg*h/mL)		$T_{1/2}$ (h)
	Day 1	Day 7	Day 7
6	1.034	1.621	21.2
20	4.871	7.139	27.7
30	6.382	10.149	28.4
35	7.842	10.825	28.8
40	9.433	12.698	25.8

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

Full study results to be presented at IDWeek 2018
Friday, October 5 12:30-1:45 PM
Novel Agents Poster Session
Poster #1371

TP-6076 Summary

- TP-6076 exhibits low MICs against MDR Gram-negative organisms
  - *Enterobacteriaceae* MIC_{90} = 0.5 µg/mL
  - *A. baumannii* MIC_{90} = 0.06 µg/mL
- TP-6076 is minimally affected by major mechanisms of tetracycline efflux and ribosomal protection
- TP-6076 MICs are largely unaffected by common mechanisms of resistance (KPC, MBL, OXA, RNA methylases)
- *In vivo* activity against both CRAB in neutropenic murine lung models
- Completed Phase 1 SAD and MAD clinical studies
- Clinical development plan will target patients with serious infections caused by *A. baumannii*

- TP-6076 occupies a unique space in the current development pipeline
  - Multiple Gram-negative agents in development, but they are not always effective against *Acinetobacter*
  - Heavy use of BLI combinations and colistin expected to drive resistance towards MBL, OXA and/or *mcr-1* producers
  - TP-6076 holds the potential to address these resistance mechanisms