The Efficacy of PTK 0796 (BAY 73-6944) in Murine Models of *Streptococcus pneumoniae* Infections

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ABSTRACT

Background *Streptococcus pneumoniae* (Spn) is the most frequently isolated organism in community-acquired pneumonia, is a significant cause of hospitalization and mortality, and is becoming increasingly resistant to antibiotics. PTK 0796 (7-dimethylamino, 9-(2,2-dimethyl-propyl)-aminomethylcycline) is a novel antibacterial agent of the tetracycline family having broad and enhanced activity against susceptible and multi-antibiotic resistant gram-positive bacteria. PTK 0796 was tested in four Spn animal infection models to evaluate its potential as a therapeutic agent.

Methods Efficacy of PTK 0796 was evaluated in four models: Systemic Immunocompetent (IC) Infection, LRTI Neutropenic (Neut), LRTI Lung Burden (IC), Thigh Wound (Neut).

Results PD50 and ED50 results for PTK 0796 and comparators, Vancomycin (Vanco), Linezolid (Lin), and Minocycline (Mino) against tetracycline susceptible (Sus) and resistant (Res) strains of *Spn*

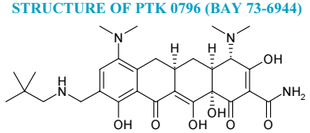
	Efficacy (mg/kg)			
In vivo model	**PTK 0796**	**Vanco**	**Lin**	**Mino**
Systemic (IC), Sus/Res, PD50	0.09/0.14	1.4/0.14	3.5/7.1	0.5/>100
LRTI (Neut) Sus/Res, PD50	11.0/27.1	7.2/5.4	>40/>40	>40/>40
LRTI (IC), ED50	7.4	>40	>20	35.4
Thigh Wound (Neut), Sus/Res, ED50	0.75/0.77	10.2/10.2	>40/>40	2.26/>50

Conclusions PTK 0796 exhibited excellent efficacy in four *Spn* infection models. Efficacy was demonstrated in systemic and organ-based infections, in normal and neutropenic animals, and irrespective of in vitro resistance to other antibiotics. PTK 0796 was comparable or superior to antibiotics currently available for the treatment of serious *Spn* infections.

INTRODUCTION

- *S. pneumoniae* remains the most frequently isolated organism in community-acquired pneumonia and continues to be a significant cause of mortality in humans.
- The prevalence of multi-drug resistant *S. pneumoniae* is increasing.
- PTK 0796 (BAY 73-6944) is a novel aminomethylcycline effective against respiratory pathogens including multi-resistant *S. pneumoniae,* as well as having broad and potent antibacterial activity including multi-antibiotic resistant bacteria.
- Characteristics of PTK 0796 (BAY 73-6944):
  - Structure: 7-dimethylamino, 9-(2,2-dimethyl-propyl)-aminomethylcycline).
  - Highly active against resistant gram-positive and gram-negative pathogens *in vitro*.
  - MIC90 for *S. pneumoniae* is 0.125 µg/ml (range of ≤0.06 – 0.25).

STRUCTURE OF PTK 0796 (BAY 73-6944)



METHODS

Animals Systemic and lung models: Male CD-1 mice (18-25g) were used. Female ICR (20–30g) mice were used for the neutropenic thigh model. Neutropenia was established by injecting cyclophosphamide IP at 150 and 100mg/kg doses on day 0 and 3, respectively.

Strains Systemic models: mice were infected intraperitoneally with tetracycline susceptible, 157E or resistant, 700905 strains of *S. pneumoniae* suspended in 5% mucin.
Lung models: mice were infected intranasally with 50µl of tetracycline susceptible GSK1629 or resistant PBS942 strains of *S. pneumoniae* suspended in PBS.

Thigh models: Immunocompromised mice were infected in the thigh muscles with tetracycline susceptible, 157E or resistant, 700905 strains of *S. pneumoniae* suspended in PBS.

Therapeutic assays: Survival rate

In the systemic IP challenge model, 5 mice per group were infected with 10^5 CFU/mouse (100 fold LD50) of tetracycline susceptible *S. pneumoniae* 157E and 10^6 CFU/mouse (100 fold LD50) of resistant *S. pneumoniae* suspended in 5 % bacteriological mucin. Following infection, increasing single doses of PTK 0796 or comparators were then administered IV, 1h post-infection. Survival of animals was then monitored for 7d and PD50s calculated.

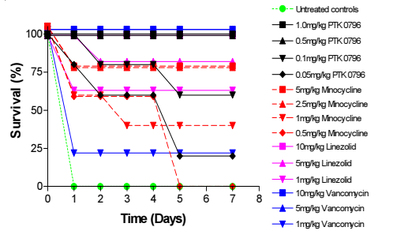
In the acute lower respiratory tract infection model, 5 neutropenic mice per group were infected intranasally with tetracycline susceptible *S. pneumoniae* GSK1629 or resistant *S. pneumoniae* PBS942 at an inoculum of 10^8CFU/mouse. Following infection, increasing single dose treatments of PTK 0796 or comparator drugs were then administered IV, 2h post-infection. Survival of animals was then monitored for 7d and PD50s calculated.

Reduction in CFU in Pulmonary and Thigh Wound Model

For the thigh model, 5 mice per group were infected with 10^4CFU/mouse of tetracycline susceptible *S. pneumoniae* IM in the left thigh and with 10^5CFU/mouse of resistant *S. pneumoniae* in the right thigh. Mice were then treated IV with increasing doses of PTK 0796 and comparators 2h post-infection. Bacterial burdens of the thighs were then evaluated at 24h post-infection. An ED50 was calculated as being the dose that reduced the number of bacteria in the thighs by 2logs.
In the chronic lung model, 5 mice per group were infected intranasally with tetracycline susceptible *S. pneumoniae* GSK1629 at an inoculum of 10^8CFU/mouse. After 24h post-infection, mice were then treated with increasing single doses of PTK 0796 or comparators. At 48h mice were sacrificed and bacterial burden of their lungs evaluated.

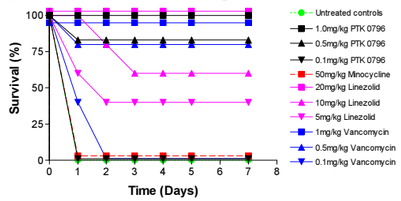
RESULTS

FIGURE 1. Efficacy of PTK 0796, Minocycline, Linezolid, and Vancomycin in the treatment of a systemic, tetracycline susceptible *S. pneumoniae* 157E infection



PTK 0796 showed greater efficacy in the tetracycline susceptible systemic model than all comparators tested.

FIGURE 2. Efficacy of PTK 0796, Minocycline, Linezolid, and Vancomycin in the treatment of a systemic, tetracycline resistant *S. pneumoniae* (700905) infection



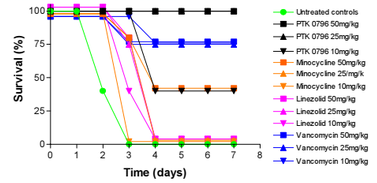
PTK 0796 showed greater efficacy in the tetracycline resistant systemic model compared to Minocycline and Linezolid, as well as equal efficacy to Vancomycin.

Table 1. The PD50s obtained in the systemic, tetracycline susceptible 157E, and resistant 700905 *S. pneumoniae* infection model

Compound	Strain	MIC	PD50 (mg/kg)
PTK 0796	**Susceptible**	**0.125**	**0.09**
	Resistant	**0.25**	**0.14**
Minocycline	Susceptible	0.125	0.50
	Resistant	8.0	>50
Linezolid	Susceptible	1.0	3.50
	Resistant	0.5	7.10
Vancomycin	Susceptible	0.25	1.40
	Resistant	0.25	0.14

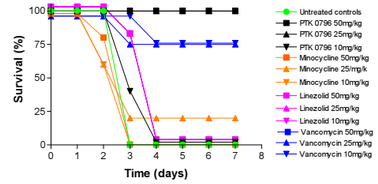
The PD50s of PTK 0796 were lower than all comparators tested in the tetracycline susceptible systemic *S. pneumoniae* infection model. Also, PTK 0796 performed better than or equal to all comparators tested in the tetracycline resistant systemic *S. pneumoniae* infection model.

FIGURE 3. Efficacy of PTK 0796, Minocycline, Linezolid, and Vancomycin in the treatment of an acute LRTI model in immunocompromised mice, by a tetracycline susceptible *S. pneumoniae* GSK1629 strain.



PTK 0796 showed greater efficacy in the tetracycline susceptible lower respiratory tract infection model than all comparators other than Vancomycin tested in this study.

FIGURE 4. Efficacy of PTK 0796, Minocycline, Linezolid, and Vancomycin in the treatment of an acute LRTI model in immunocompromised mice, by tetracycline resistant *S. pneumoniae* PBS942.



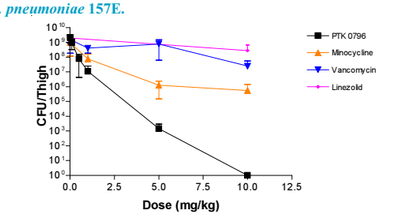
PTK 0796 showed greater efficacy in the tetracycline resistant lower respiratory tract infection model than all comparators other than Vancomycin tested in this study.

Table 2. The PD50s obtained in the acute, lower respiratory tract infection model infecting immunocompromised mice with either tetracycline susceptible or resistant *S. pneumoniae*.

Compound	Strain	MIC	PD50 (mg/kg)
PTK 0796	**GSK1629**	**≤0.06**	**11.0**
	Resistant PBS942	**0.25**	**27.1**
Minocycline	GSK1629	<0.06	>40
	Resistant PBS942	8.0	>40
Linezolid	GSK1629	1.0	>40
	Resistant PBS942	1.0	>40
Vancomycin	GSK1629	0.5	7.2
	Resistant PBS942	0.5	5.4

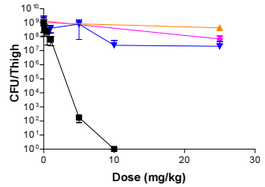
The PD50 of PTK 0796 showed greater efficacy in the tetracycline susceptible and resistant lower respiratory tract infection models than all comparators other than Vancomycin tested in this study.

FIGURE 5. Efficacy of PTK 0796, Minocycline, Linezolid, and Vancomycin in the treatment of a thigh wound model in immunocompromised mice, by tetracycline susceptible *S. pneumoniae* 157E.



The ED50 of PTK 0796 was much lower than any of the comparators tested in the thigh wound model in immunocompromised mice, by tetracycline susceptible *S. pneumoniae* 157E.

FIGURE 6. Efficacy of PTK 0796, Minocycline, Linezolid, and Vancomycin in the treatment of a thigh wound model in immunocompromised mice, by tetracycline resistant *S. pneumoniae* 700905.



The ED50 of PTK 0796 was much lower than any of the comparators tested in the thigh wound model in immunocompromised mice, by tetracycline resistant *S. pneumoniae* 700905.

Table 3. The ED50s obtained in the thigh wound model infecting immunocompromised mice with either tetracycline susceptible or resistant *S. pneumoniae*.

Compound	Strain	MIC	ED50 (mg/kg)
PTK 0796	**157E**	**0.125**	**0.75**
	Resistant 700905	**0.25**	**0.14**
Minocycline	157E	0.125	2.26
	Resistant 700905	8.0	>50
Linezolid	157E	1.0	>40
	Resistant 700905	0.5	>40
Vancomycin	157E	0.25	10.2
	Resistant 700905	0.25	10.2

The ED50 of PTK 0796 was much lower than any of the comparators tested in the thigh wound model in immunocompromised mice, by both a tetracycline susceptible and resistant *S. pneumoniae.*

FIGURE 7. Efficacy of PTK 0796, Minocycline, Linezolid, and Vancomycin in the treatment of a chronic, tetracycline susceptible *S. pneumoniae* GSK1629 LRTI model in immunocompetant mice.

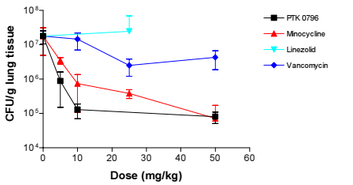


Table 4. The ED50s obtained in the chronic LRTI model infecting male CD1 mice with tetracycline susceptible *S. pneumoniae* GSK1629.

Compound	MIC	ED50 (mg/kg)
PTK 0796	**≤0.06**	**7.4**
Minocycline	<0.06	35.4
Linezolid	1.0	>20
Vancomycin	0.5	>40

The ED50 of PTK 0796 was far lower than any of the comparators tested in the chronic LRTI model infecting with susceptible *S. pneumoniae* GSK1629.

CONCLUSIONS

PTK 0796 (BAY 73-6944) a novel aminomethylcycline

- Exhibited good efficacy compared to standard antibiotics in systemic *S. pneumoniae* infections in immunocompetent mice against both tetracycline susceptible and resistant strains.
- In an acute lung model in immunocompromised mice, and in the chronic lung infection model in immunocompentent mice, demonstrated greater or equal efficacy to all comparators.
- In the neutropenic thigh model, was superior to comparators when the thighs were infected with either the resistant or susceptible strains of *S. pneumoniae.*

In summary, PTK 0796 (BAY 73-6944) exhibited excellent efficacy in four *S. pneumoniae* infection models.