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BAY 73-7388, a novel aminomethylcycline, exhibits potent efficacy in pulmonary murine models of infection

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Objective: With the emergence of resistance to currently available antibiotics in the treatment of infectious diseases, the development of novel antibiotic classes has become of major importance. BAY 73-7388 is the first aminomethylcycline antibacterial agent and is characterised by potent activity *in vitro* against sensitive and multi-antibiotic resistant Gram-positive, Gram-negative and atypical bacteria. We have evaluated BAY 73-7388 in several murine pulmonary infection models with a range of pathogens in both neutropenic (Neut) and immunocompetent (IC) mice.

Methods: BAY 73-7388 and reference antibiotics were evaluated in acute, systemic lethal infections caused by multi-resistant (res) and susceptible (sus) *Streptococcus pneumoniae* (Spn); acute, lethal pulmonary Spn infection in Neut mice; chronic, Spn lung model in IC mice; and chronic *Haemophilus influenzae* (Hflu) infection model in IC mice. In each infection BAY 73-7388 and other antibiotics were administered i.v.

Results: PD50 (survival) and ED50 (bacterial burden) results for BAY 73-7388 and comparators, vancomycin (VAN), linezolid (LIN), ciprofloxacin (CIP), azithromycin (AZI) and doxycycline (DOX) against sus and res strains of Spn and Hflu (sus), are detailed in the table below.

	Efficacy (mg/kg)					
In Vivo model	BAY 73-7388	**AZI**	CIP	LIN	VAN	DOX
Acute, systemic Spn, IC(sus) (PD50)	0.09	2.21	>50	3.5	1.4	1.8
Acute, systemic Spn, Neut (res) (PD50)	0.14	18.9	21.3	7.1	0.14	>50
Chronic Spn,IC (ED50)	7.4	5.15	>50	>40	>40	31.6
Chronic Hflu,IC (ED50)	4.7	31.6	1.0	NA	NA	18.6
Acute, pulmonary Spn, Neut (PD50)	11.0	7.5	31.6	>40	7.2	>50
Acute, pulmonary Spn, Neut (res) (PD50)	8.5	>50	>50	>40	5.4	>50

Conclusions: Overall, BAY 73-7388 performed as well or better than the currently available therapeutic agents in all the models investigated in this study.

(BAY 73-7388 was discovered by Paratek Pharmaceuticals Inc., Boston, MA, and designated PTK 0796.)

BAY 73-7388, A NOVEL AMINOMETHYLCYCLINE, EXHIBITS POTENT EFFICACY IN PULMONARY MURINE MODELS OF INFECTION

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Abstract

Objective:

With the emergence of resistance to currently available antibiotics in the treatment of infectious diseases, the development of novel antibiotic classes has become of major importance. BAY 73-7388 is the first aminomethylcycline antibacterial agent and is characterised by potent activity *in vitro* against sensitive and multiantibiotic-resistant gram-positive, gram-negative atypical, and anaerobic bacteria. We have evaluated BAY 73-7388 in several murine pulmonary infection models with a range of pathogens in both neutropenic (Neut) and immunocompetent (IC) mice.

Methods:

BAY 73-7388 and reference antibiotics were evaluated in acute, systemic lethal infections caused by multiresistant (res) and susceptible (sus) *Streptococcus pneumoniae* (SPn); acute, lethal pulmonary SPn infection in Neut mice; chronic, SPn lung model in IC mice; and chronic *Haemophilus influenzae* (HFlu) infection model in IC mice. In each infection, BAY 73-7388 and other antibiotics were administered IV.

Results:

PD_{50} (survival) and ED_{50} (bacterial burden) results for BAY 73-7388 and comparators, vancomycin (VAN), linezolid (LZD), ciprofloxacin (CIP), azithromycin (AZI), and doxycycline (DOX), against susceptible and resistant strains of SPn and HFlu (sus) are detailed in the table below.

Conclusions:

Overall, BAY 73-7388 performed as well as or better than the currently available therapeutic agents in all the models investigated in this study.

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***In Vivo* Model**	**BAY 73-7388**	**VAN**	**LZD**	**CIP**	**AZI**	**DOX**
Acute, systemic SPn, IC (sus) (PD_{50})	0.09	1.4	3.5	>50	2.21	1.8
Acute, systemic SPn, Neut (res) (PD_{50})	0.14	0.14	7.1	21.3	18.9	>50
Chronic SPn, IC (ED_{50})	1.4	>40	>40	>50	5.15	1.2
Chronic HFlu, IC (ED_{50})	4.7	NA	NA	1.0	31.6	18.6
Acute, pulmonary SPn, Neut (PD_{50})	11.0	7.2	>40	31.6	7.5	>50
Acute, pulmonary SPn, Neut (res) (PD_{50})	8.5	5.4	>40	>50	>50	>50

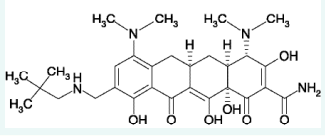
Introduction

- *Streptococcus pneumoniae* and *Haemophilus influenzae* are important causes of upper and lower respiratory tract infections. Indeed, *S.pneumoniae* remains the most frequently isolated organism in community-acquired pneumonia and continues to cause significant mortality
- The prevalence of multidrug resistance among these pathogens is increasing
- BAY 73-7388 is a novel aminomethylcycline active against gram-positive, gram-negative,anaerobic, and atypical bacteria, including those resistant to currently available classes of antibiotics

This study investigated the efficacy of BAY 73-7388 in pulmonary models of infections caused by *S.pneumoniae* and *H.influenzae.*

- Characteristics of BAY 73-7388
  - Structure: 7-dimethylamino,9-(2,2-dimethyl-propyl)-aminomethylcycline
  - Highly active against resistant gram-positive and gram-negative pathogens *in vitro*
  - MIC_{90} for *S.pneumoniae* is 0.125 mg/L (range, ≤0.06-0.25 mg/L)
  - MIC_{90} for *H.influenzae* is 2.0 mg/L (range, 0.5-8.0 mg/L)

Structure of BAY 73-7388



Methods

Animals Male, CD-1 mice (18-25 g) were used in systemic and lung models.

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 50 µL of tetracycline-susceptible (PBS1339) or -resistant (PBS942) strains of *S. pneumoniae* suspended in PBS. In the chronic *H. influenzae* model, mice were infected intranasally with 50 µL of a tetracycline-susceptible strain (PBS981) suspended in PBS.

Comparators Linezolid,azithromycin,ciprofloxacin,doxycycline, or vancomycin

Therapeutic Assays

Survival Rate

In the systemic IP challenge model, 5 mice per group were infected with 10^5 CFU/mouse (100-fold LD_{50}) of tetracycline-susceptible *S.pneumoniae* 157E and 10^6 CFU/mouse (100-fold LD_{50}) of resistant *S. pneumoniae* suspended in 5% bacteriologic mucin. Increasing single doses of BAY 73-7388 or comparators were administered IV, 1 h postinfection. Survival of animals was monitored for 7 d and PD_{50}s calculated.

In the acute lower respiratory tract infection model, mice were rendered neutropenic by injecting cyclophosphamide IP at 150- and 100-mg/kg doses on day 0 and 3, respectively. Five neutropenic mice per group were infected intranasally with tetracycline-susceptible *S.pneumoniae* PBS1339 or -resistant *S.pneumoniae* PBS942 at an inoculum of 10^6 CFU/mouse.Following infection, increasing single dose treatments of BAY 73-7388 or comparator drugs were then administered IV, 2 h postinfection. Survival of animals was then monitored for 7 d and PD_{50}s calculated.

Reduction in CFU in Pulmonary Infection

In the chronic *S.pneumoniae* lung model, 5 mice per group were infected intranasally with tetracycline-susceptible *S.pneumoniae* PBS1339 at an inoculum of 10^6 CFU/mouse. After 24 h postinfection, mice were then treated IV with increasing single doses of BAY 73-7388 or comparators.At 48 h, mice were sacrificed and the bacterial burden of their lungs was evaluated. In the chronic *H.influenzae* lung model, 5 mice per group were infected intranasally with tetracycline-susceptible *H.influenzae* PBS981 at an inoculum of 10^6 CFU/mouse. Mice were then treated IV in a dose response with BAY 73-7388 and comparators at 6, 24, and 30 h postinfection. At 48 h, mice were sacrificed and the bacterial burden of their lungs was evaluated.

Results

Table 1. Efficacy in the tetracycline-susceptible *S.pneumoniae* chronic LRTI model in immunocompetent mice

Compound	Strain	MIC (mg/L)	PD_{50} (mg/kg)
BAY 73-7388	Susceptible	0.125	0.09
	Resistant	0.25	0.14
Vancomycin	Susceptible	0.25	1.40
	Resistant	0.25	0.14
Linezolid	Susceptible	1.0	3.50
	Resistant	0.5	7.10
Ciprofloxacin	Susceptible	0.5	>50
	Resistant	1.0	21.3
Azithromycin	Susceptible	0.06	2.21
	Resistant	>64	18.90
Doxycycline	Susceptible	0.06	1.8
	Resistant	4	>50

The PD_{50}s of BAY 73-7388 were lower than all comparators tested in the tetracycline-susceptible systemic S. pneumoniae *infection model.Also, BAY 73-7388 performed better than or equal to all comparators tested in the tetracycline-resistant systemic* S. pneumoniae *infection model.*

Table 2. Efficacy in tetracycline-susceptible PBS1339 *H.influenzae* chronic LRTI model of immunocompetent mice

Compound	Strain	MIC (mg/L)	PD_{50} (mg/kg)
BAY 73-7388	Susceptible	≤0.06	11.0
	Resistant	0.25	8.5
Vancomycin	Susceptible	0.5	7.2
	Resistant	0.5	5.4
Linezolid	Susceptible	1.0	>40
	Resistant	1.0	>40
Ciprofloxacin	Susceptible	0.25	31.6
	Resistant	0.5	>50
Azithromycin	Susceptible	0.03	7.5
	Resistant	>64	>50
Doxycycline	Susceptible	≤0.06	31.6
	Resistant	4	>50

The PD_{50} of BAY 73-7388 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 1. Efficacy in the tetracycline-susceptible *S.pneumoniae* chronic LRTI model in immunocompetent mice

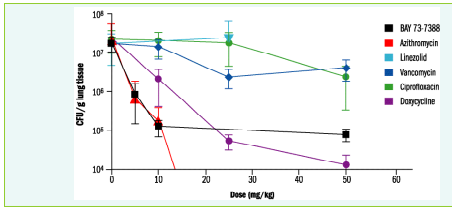


Table 3. Efficacy in the chronic LRTI model with tetracycline-susceptible PBS1339 *S.pneumoniae*

Compound	MIC (mg/L)	ED_{50} (mg/kg)
BAY 73-7388	≤0.06	7.4
Vancomycin	0.5	>40
Linezolid	1.0	>20
Ciprofloxacin	0.25	28.0
Azithromycin	0.03	5.15
Doxycycline	≤0.06	7.2

The ED_{50} of BAY 73-7388 was lower or comparable to any of the comparators tested in the chronic LRTI model infecting with susceptible S. pneumoniae *PBS1339.*

Figure 2. Efficacy in tetracycline-susceptible PBS981 *H.influenzae* chronic LRTI model in immunocompetent mice

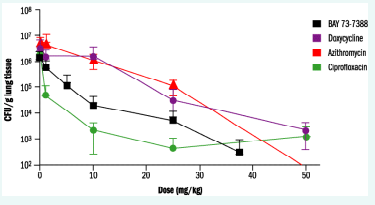


Table 4. Efficacy in the chronic LRTI model with tetracycline-susceptible PBS981 *H.influenzae*

Compound	MIC (mg/L)	ED_{50} (mg/kg)
BAY 73-7388	1.0	4.7
Ciprofloxacin	≤0.06	1.0
Azithromycin	1.0	31.6
Doxycycline	0.25	18.6

The ED_{50} of BAY 73-7388 was far lower than most of the comparators tested and comparable to ciprofloxacin in the chronic LRTI model infecting with susceptible H.influenzae *PBS981.*

Conclusions

- BAY 73-7388, a novel aminomethylcycline antibiotic, demonstrated efficacy equal or superior to all five currently available antibiotics tested in immunocompetent mice with systemic infection due to tetracycline-susceptible and -resistant strains of *S.pneumoniae*.
- BAY 73-7388 demonstrated efficacy comparable or superior to all five comparator antibiotics in immunocompromised and immunocompetent mice with pulmonary infection due to tetracycline-susceptible and -resistant clinical strains of *S.pneumoniae*.
- BAY 73-7388 demonstrated efficacy comparable or superior to all three comparator antibiotics in immunocompetent mice with pulmonary infection due to *H.influenzae*.
- In summary, BAY 73-7388 was consistently effective in treating common pulmonary pathogens in four different murine models investigated.