BAY 73-7388 is highly efficacious in animal models of intra-abdominal infections caused by a range of aerobic and anaerobic organisms, including VRE

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Objective: BAY 73-7388, a novel antibiotic compound from the aminomethylcycline class, has an antibacterial spectrum encompassing Gram-positive, Gram-negative and anaerobic bacteria, including those resistant to currently available antibiotics. The efficacy of BAY 73-7388 in four different mouse infection models with pathogens causing intra-abdominal infections was compared with that of vancomycin (VAN), linezolid (LIN), imipenem (IMI) and metronidazole (MTN).

Methods: For systemic infections (sepsis), enterococci (tetracycline (TET)-resistant Enterococcus faecalis or Enterococcus faecium VRE) were administered intraperitoneally, and i.v. treatment was started 30 min post-infection; survival of the infected mice until day 5 was used as read-out. In the pouch model using Bacteroides fragilis as infecting pathogen, therapeutic efficacy of BAY 73-7388 compared with MTN was determined as reduction of CFU. The mouse model of caecal ligation was used as a model for polymicrobial peritonitis after surgical intervention and 10 days survival used as read-out.

Results: In systemic infections with TET-resistant E. faecalis or E. faecium VRE, efficacy of BAY 73-7388 was superior to VAN or LIN: 100% survival was observed at 1 mg/kg BAY 73-7388, 10 mg/kg VAN and 3 mg/kg LIN. For the E. faecium septicaemia model, 100% survival was found at 15 mg/kg BAY 73-7388, while neither VAN nor LIN treatment resulted in 100% survival, even at 50 mg/kg, the highest dose tested. In the pouch model with B. fragilis, the CFU reduction caused by BAY 73-7388 was superior to MTN (CFU reduction >6 log compared with 4 log at 25 mg/kg, respectively). Therapy (2 × 10 mg/kg i.v. on day 1) of intra-abdominal infections and post-operative polymicrobial peritonitis with BAY 73-7388 showed increased survival compared with IMI or LIN (80 vs. 70 vs. 30%, respectively).

Conclusions: Against pathogens causing intra-abdominal infections (including VRE and TET-resistant strains), BAY 73-7388 demonstrated superior therapeutic efficacy compared with VAN, LIN, MTN or IMI.

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

**Objective**

BAY 73-7388, a novel antibiotic compound from the aminomethylcycline class, has an antibacterial spectrum encompassing gram-positive, gram-negative, and anaerobic bacteria, including those resistant to currently available antibiotics. The efficacy of BAY 73-7388 in 4 different mouse infection models with pathogens causing intra-abdominal infections was compared with that of vancomycin (VAN), linezolid (LZD), imipenem (IMI), and metronidazole (MTN).

**Methods**

For systemic infections (sepsis), enterococcal (tetraycline [TET]-resistant Enterococcus faecalis, VAN-resistant Enterococcus faecium) (VRE) were administered intraperitoneally (IP) treatment was started 30 min postinfection, and survival of the infected mice until day 5 was monitored. In the pouch model using Bacteroides fragilis as the infecting pathogen, therapeutic efficacy of BAY 73-7388 was compared with MTN as determined by reduction of colony forming units (CFU). The mouse model of caecal ligation was used as a model for polymicrobial peritonitis after surgical intervention and 10-day survival was monitored.

**Results**

In systemic infections with TET-resistant E. faecalis or E. faecium, efficacy of BAY 73-7388 was superior to VAN or LZD (100% survival was observed at 1 mg/kg BAY 73-7388, 20 mg/kg VAN and 100 mg/kg LZD). For the E. faecium septicaemia model, 100% survival was found at 15 mg/kg BAY 73-7388, while neither VAN nor LZD treatment resulted in 100% survival, even at 50 mg/kg. The highest mortality rates were found in the TET-resistant E. faecalis model with 1 mg/kg BAY 73-7388 compared with 20 mg/kg VAN (75%) and 100 mg/kg LZD (50%).

**Conclusions**

In a mouse model of enterococcal (tet Res, VRE) septicemia, efficacy of BAY 73-7388 was superior to vancomycin or linezolid (80% vs 70% vs 30%, respectively). In a polymicrobial peritonitis mouse model, BAY 73-7388 demonstrates superior efficacy compared with imipenem or linezolid (80% vs 70% vs 30%, respectively).

**Results**

Among animals infected with E. faecalis strain 27159 (tet-Rev), efficacy of BAY 73-7388 was superior to that of VAN or LZD (Figure 1). 100% survival was observed at 3 mg/kg BAY 73-7388, 10 mg/kg VAN, and 3 mg/kg LZD. Treatment at 1 mg/kg BAY 73-7388, 10 mg/kg VAN, and 3 mg/kg LZD resulted in 100% survival, even at 50 mg/kg, the highest dose tested (Figure 2).

**Conclusions**

BAY 73-7388 demonstrated superior therapeutic efficacy against pathogens causing intra-abdominal infections (including VRE and TET-resistant strains) compared with VAN, LZ21, or IMI.

**Structure of BAY 73-7388**

BAY 73-7388 is the first compound selected from the novel class of aminomethylcyclines. BAY 73-7388 exhibits excellent activity against susceptible and resistant gram-positive and gram-negative pathogens as well as significant activity against anaerobic pathogens.

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**Figure 1.** Efficacy in E. faecalis (tet-Rev) mouse bacteremia model.

**Figure 2.** Efficacy in E. faecium bacteremia model in neutropenic mice.

**Figure 3.** Efficacy in the B. fragilis granuloma pouch model. Depicted are the reductions of viable bacterial load (CFU) at day 4 post infection (PI) of antibiotic-treated mice as compared with untreated control animals.