

ASM General Meeting

May 30 to June 2, 2015, New Orleans, LA

Abstract deadline: January 27, 2015, 11:59 pm EST

No Late Breaker Abstracts

Title: Clinical Evaluation of SYN-004, an Oral Beta-Lactamase Therapy for the Prevention of Antibiotic-Induced Disruption of Intestinal Microflora

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Antibiotics that are excreted into the intestine, such as ceftriaxone (CRO), can damage the microflora and lead to serious illnesses such as *Clostridium difficile* infection. SYN-004 is a potent beta-lactamase enzyme for oral use with IV antibiotics to degrade antibiotics in the intestine. SYN-004 was engineered from the *Bacillus licheniformis* PenP enzyme to expand the hydrolysis of beta-lactams to cephalosporins, including CRO, while maintaining its anti-penicillin activity.

SYN-004, manufactured in *E. coli*, was formulated into enteric-coated pellets. *In vitro*, the pellets remained intact at low pH (0.1 N HCl) while complete dissolution occurred at pH >5.5. In human chyme, SYN-004 enzyme activity was maintained for at least 6 hrs, demonstrating enzyme stability in human intestinal contents. Efficacy studies were performed using jejunal-fistulated dogs (n=6). Following IV CRO (30 mg/kg), CRO was detected at high levels in the intestine (mean C_{max} of 1500 ug/g at 90 min), and a second CRO peak (mean 167 ug/g) was observed six hours later, after feeding. When SYN-004 was delivered ten minutes prior to CRO, intestinal CRO levels remained low (≤ 5 ug/g chyme) in 4/6 dogs. The second CRO peak was not detected in any SYN-004-treated animal demonstrating that SYN-004 was present, remained functional, and hydrolyzed the CRO in the intestines of all dogs. In a GLP toxicology study, dogs received SYN-004 capsules orally 3 times a day for 28 days at 0, 6.6, 18, and 57 mg/kg/day. Dosing was well tolerated with no indication of effects on any organ system and no histopathological findings. The NOAEL was 57 mg/kg/day. A second GLP dog study is in progress in which SYN-004 and CRO were administered concurrently.

Clinical evaluation of SYN-004 was initiated in late 2014 with single ascending and multiple ascending dose pharmacokinetic, safety and tolerability studies in humans. A proof-of-mechanism study in ileostomy subjects is expected to commence in Q1 2015 to assess intestinal CRO degradation. The clinical program for SYN-004 will investigate the prevention of the undesirable effects associated with IV beta-lactam antibiotics including antibiotic-associated diarrhea, *Clostridium difficile* infection, and intestinal colonization with resistant organisms and related infections. Clinical data will be presented.

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