Background: IV beta-lactam antibiotics, excreted via bile into the gastrointestinal (GI) tract, can damage the intestinal microbiome and lead to opportunistic Clostridium difficile infections (CDI). SYN-004, a novel oral antibiotic, is designed to protect the gut microbiome from these antibiotics. SYN-004 has completed two clinical studies. Phase 2 clinical trials are in progress.

Methods: SYN-004 was engineered from the penicillin (pen) enzyme, named PTA1, the first generation predecessor, by introducing a tinoamide acid change, DTPTK. SYN-004 displays a broader antibacterial degradation profile than PTA1 and efficiently degrades the cephalosporin, ceftiofur. Use of ceftiofur is a major risk factor for CDI infection.

RESULTS

SYN-004 Degradated Ceftriaxone in the GI Tract of Dogs

Jejunal-fistulated dogs (n=6) received SYN-004 (0.44 mg/kg) PO and IV ceftriaxone (30 mg/kg). SYN-004 delivered orally 10 min prior to IV ceftriaxone eliminated the initial peak of CRO in the intestine of 4/6 dogs (graph displays data from the 4 dogs). The second peak of CRO in 6/6 dogs, demonstrating that SYN-004 hydrolyzed the CRO in the intestines of all treated dogs. SYN-004 Did Not Affect Systemic Ceftriaxone Levels

Two QLP toxicity studies conducted in dogs demonstrated that SYN-004 was well tolerated. In one of the studies, SYN-004 (6.25 mg/kg or 57 mg/kg; PO; TID) was delivered with IV ceftriaxone (350 mg/kg) for 14 days.Serum samples, collected on Days 1 and 13, were analyzed for ceftiofur metabolites.

CONCLUSIONS

Phase 004 is a Phase 1 Clinical Trials Summary

Two Phase 1 studies were completed.

Study 1: Single-ascending sequential dose safety, tolerability, and PK study (40 subjects). This study was conducted as a double-blind, randomized, placebo-controlled (6 active and 2 placebo cohorts) study. SYN-004 (40, 75, 150, 300; 600, or 750 mg capsule) was given as a single oral administration, to assess the safety, tolerability, and PK profile of SYN-004.

Results: There were no serious adverse events (SAEs), no discontinuations due to an AE, and no deaths. All treatment-emergent adverse events (TEAEs) were reported as Grade 1 intensity (does not interfere with normal activities) and resolved without intervention. SYN-004 taken orally was not systemically bioavailable and no anti-SYN-004 antibodies were detected in any subject.

Study 2: Multiple-ascending sequential dose safety, tolerability, and PK study (24 subjects). This study was conducted as a double-blind, randomized, placebo-controlled (4 active and 2 placebo cohorts) study. SYN-004 was delivered orally QD for 7 days at 75, 150, or 300 mg.

Results: Six subjects reported 7 TEAEs; all Grade 1 intensity that resolved without intervention. SYN-004 was not systemically bioavailable even with dosing four times a day for 7 consecutive days and no SYN-004 antibodies were detected in any subject.

DISCLOSURES

All authors except MS are employees of Synthetic Biologics, Inc. MS is a paid consultant for Synthetic Biologics, Inc.

SYN-004 Phase 2 Clinical Trials

Two Phase 2a and a Phase 2b studies are in progress. Phase 2a: SYN-004 mechanism of action studies are being conducted in various models with patients with a function to determine the ability of SYN-004 to prevent CDI. In study 1, subjects received ceftriaxone (CRO) 1 g alone or in combination with SYN-004. In study 2, CRO was administered systemically and SYN-004 was catheterized in the absence or presence of a protamine pump inhibitor to determine the effect of pH change on SYN-004 function. In both studies, plasma and urine samples are analyzed for the concentrations of CRO and SYN-004. Study 1 is complete and the results are in progress.

Phase 2b: SYN-004 proof-of-concept study is being conducted in ~372 patients being treated with CRO for a lower respiratory tract infection. Study is conducted as a double-blind, placebo-controlled in patients randomized to receive 150 mg of oral SYN-004 or placebo QD during CRO treatment and continuing for 72 hrs after treatment. Patients are monitored for diarrhea over the next 6 weeks. The primary endpoints of the study are prevention of death, invasive infection (CDI) and Clostridium difficile-associated adenocarcinoma (CDAD) with secondary endpoints of prevention of antibiotic-associated diarrhea (AAD) and protection of the gut microbiome.

C O N C L U S I O N S

SYN-004 efficiently degraded penicillins and a panel of cephalosporins, including ceftiofur, ceftriaxone, and cefotaxime.

In dogs, oral delivery of SYN-004 pellets resulted in efficient degradation of intestinal ceftriaxone.

In dogs, SYN-004 did not affect systemic ceftriaxone levels.

SYN-004 was well tolerated in dogs at doses up to 75 mg/kg/day.

SYN-004 protected the intestinal microbiota from dysbiosis caused by ceftriaxone in pigs.

In Phase 1 clinical studies, SYN-004 was well tolerated at a single dose of up to 750 mg and multiple doses of 300 mg QD for 7 days.

SYN-004 is systemically bioavailable when administered orally.

Phase 2 clinical trials are in progress.