SYN-004, an Oral β-lactamase to Prevent Clostridium difficile, Degrades Ceftriaxone Excreted in the Human Intestine in Phase 2a Clinical Trials

**ABSTRACT**

SYN-004 is a novel, orally administered, recombinant β-lactamase enzyme designed to degrade β-lactam antibiotics, including cephalosporins, in the human intestine. SYN-004 has clinical relevance as a prophylactic approach to prevent dysbiosis associated with β-lactam antibiotics in intestinal microflora. The efficacy of SYN-004 as an orally administered β-lactamase to degrade residual β-lactam antibiotic excreted into the intestine, either alone or in combination with proton pump inhibitors, was evaluated in a Phase 1 clinical study and in the absence of an ileostomy in a pilot study. SYN-004 was well tolerated in healthy subjects co-administered with 1 g IV ceftriaxone alone or in combination with two dose strengths of oral SYN-004 in a Phase 1 clinical study. In the absence of an ileostomy, SYN-004 was also well tolerated in otherwise healthy subjects co-administered with 1 g IV ceftriaxone alone or in combination with proton pump inhibitors. SYN-004 was generally well tolerated when administered with steady-state esomeprazole than when SYN-004 was administered alone over the course of the sampling period.

**RESULTS**

SYN-004 Phase 2a Clinical Experience

In the first study, SYN-004, as a Novel Recombinant β-lactamase, was evaluated in a single ascending dose (SAD) study up to 750 mg in normal healthy volunteers. SYN-004 was well tolerated in normal healthy volunteers. SYN-004 was well tolerated in 10 normal healthy volunteers co-administered with 1 g of IV ceftriaxone in combination with two doses of oral SYN-004 (75 mg and 150 mg) in 20 normal healthy volunteers. Phase 2a proof-of-concept studies have since been conducted in subjects with ileostomies to assess the potential for preventing Clostridium difficile infection (CDI) and antibiotic associated diarrhea (AAD) in ileostomy patients. SYN-004 is a novel recombinant β-lactamase that can degrade most β-lactam antibiotics excreted into the intestine thus preventing their excretion into the colon, and disrupting the gut microbiome. SYN-004 is released in the intestine of dogs in a fistulated dog model.

**CURRENT STUDY DESIGNS**

SYN-004 Phase 2a Clinical Mechanism of Action Studies

To advance the development of SYN-004, two Phase 2a clinical studies were undertaken in otherwise healthy subjects with functioning ileostomies. The use of this subject group allowed for serial sampling of their intestinal chyme to answer several questions regarding SYN-004.

SYN-004 Phase 2a Clinical Study in Ileostomy Subjects

Study 1: IV Ceftriaxone (CRO) +/- SYN-004 (n=10)

A phase II, randomized, single-blind, multi-center, placebo-controlled study to evaluate the effect of oral SYN-004 on the pharmacokinetics of ceftriaxone in healthy subjects with ileostomies. The study consisted of two periods, each of 14 days, with a washout period of 7 days between periods. SYN-004 was well tolerated in dogs when orally administered. SYN-004 was well tolerated in normal healthy volunteers. SYN-004 was well tolerated in subjects with ileostomies who were co-administered with 1 g IV ceftriaxone alone or in combination with 75 mg or 150 mg of SYN-004.

**CONCLUSIONS**

SYN-004 is well tolerated when co-administered with IV ceftriaxone. SYN-004 effectively degrades ceftriaxone in intestinal chyme to below the level of detection when SYN-004 is present. SYN-004 does not significantly alter the plasma PK of ceftriaxone. SYN-004 was not detected in the plasma of the subjects in Study 1. SYN-004 can be administered with a PPI, and this approach leads to earlier release of enzyme from the pH dependent formulation which may have earlier degradation of ceftriaxone after the 1st dose.

SYN-004 has now progressed into a Phase 2b clinical trial for prevention of CDI and AAD in patients being treated with ceftriaxone for LRTI.