The Oral β-Lactam SYN-004 (ribazamase), Designed to Protect the Gut Microbiome from Biliary Excreted IV Antibiotics, Effectively Degradates Ceftriaxone in Two Phase 2a Clinical Trials

John R. Kakal-Kuhn¹, Tracey Roberts¹, Erci Seckard, Marianne Rutangle¹, Richard Fedorak¹, Christian Carte¹, Olivia Coughlin¹, Heidi Whalen¹, Klaus Gottlieb¹, John Simman²

¹Synthetic Biologics, Inc., Rockville, MD, ²Algorithme Pharma, Laval, QC, ³University of Alberta- Alberta Health Services, Edmonton, AB.

SYN-004 Phase 1 Clinical Experience

SYN-004 was well tolerated in a Single Ascending Dose (SAD) study up to 750 mg in normal healthy volunteers.

- There was intestinal and systemic absorption of SYM-004 detected (δAUC = 8 ng h/ml) and no anti-drug antibodies were detected in the SAD study.
- SYM-004 was well tolerated in a Multiple Ascending Dose (MAD) study up to 300 mg for 7 days in normal healthy volunteers.
- There was negligible systemic absorption of SYM-004 detected and no anti-drug antibodies were detected in the MAD study.

SYN-004 Phase 2a Clinical Mechanism of Action Studies

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

1. Is SYM-004 well tolerated in humans when co-administered with IV ceftriaxone?
2. Does SYM-004 effectively degrade IV administered ceftriaxone excreted into the intestine?
3. Does SYM-004 affect the plasma concentrations of IV ceftriaxone?
4. Can SYM-004 be detected in the plasma of the ileostomy subjects?

SYN-004 Phase 2a Clinical Studies in Ileostomy Subjects

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

An IRB reviewed, HIPAA compliant, single-center, open-label, placebo-controlled, Phase 2a clinical study to evaluate the effect of oral SYM-004 on the pharmacokinetics of ceftriaxone in Ileostomy subjects. Subjects were evenly randomized to receive 150 mg of SYM-004 or placebo orally with one daily dose of 2 g of ceftriaxone over three days. The study objectives were to determine the pharmacokinetics of ceftriaxone in ileostomy subjects following oral SYM-004 administration.

Study 2: IV Ceftriaxone & SYM-004 +/- Esomeprazole (n=14)

A Phase 2b, multi-center, double-blind, placebo-controlled, randomized, clinical trial conducted to determine the comparative pharmacokinetics of ceftriaxone and SYM-004 and the effect of esomeprazole on pharmacokinetics and drug interaction in subjects with functioning ileostomies. Subjects were evenly randomized to receive 150 mg of SYM-004 or placebo orally with one daily dose of 2 g of ceftriaxone over three days. The study objectives were to determine the pharmacokinetics of ceftriaxone in ileostomy subjects following oral esomeprazole or placebo administration.

Conclusions

- SYM-004 is well tolerated when co-administered with IV ceftriaxone.
- SYM-004 effectively degrades ceftriaxone in intestinal chyme to below the level of detection when SYM-004 is present.
- SYM-004 does not significantly alter the plasma PK of ceftriaxone when co-administered.
- SYM-004 was not detected in the plasma of the subjects in Study 1.
- SYM-004 can be administered with a PPI, and this appears to lead to earlier release of enzyme from the pH dependent formulation which allows for earlier degradation of ceftriaxone after the 1st dose.
- SYM-004 (ribazamase) is now in a Phase 2b clinical trial for prevention of CDI and AAD in patients being treated with ceftriaxone for a LRTI.