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SYN-004 (ribaxamase), an orally administered β-lactamase for prevention of *Clostridium difficile* infection; colonization by antimicrobial resistant pathogens and preservation of the diversity of the gut microbiome

SYN-004 (ribaxamase) is an orally administered β-lactamase designed to be given with IV β-lactam antibiotics. Ribaxamase remains localized in the intestine where it is available to degrade excreted β-lactam antibiotics which protects the gut microbiome from disruption by these still functional antibiotics. This protection of the gut microbiome is expected to prevent the deleterious effects of the antibiotics including, *Clostridium difficile* infection (CDI), colonization by opportunistic pathogens and emergence of antibiotic resistance in the gut. Ribaxamase was well tolerated in Phase 1 clinical studies and efficiently degraded ceftriaxone excreted into the human intestine in Phase 2a clinical studies, where it also did not alter the plasma pharmacokinetics of the ceftriaxone. A global Phase 2b, double-blind, placebo-controlled study was conducted to determine whether ribaxamase could prevent *C. difficile* infection with additional endpoints for antibiotic-associated diarrhea, colonization by opportunistic pathogens, changes in the gut microbiome and emergence of antibiotic resistant organisms in the gut. Four hundred and twelve patients, a modified intent to treat population, enriched for higher risk for CDI, were admitted to the hospital for at least 5 days of IV ceftriaxone for treatment of a lower respiratory tract infection. Patients were randomized 1:1 to receive ribaxamase or placebo during treatment for 72 hours. Later fecal samples were collected at pre-specified points for determination of colonization by opportunistic pathogens and to examine changes to the fecal microbiome. Patients were monitored for 6 weeks after antibiotic treatment for CDI (as defined as diarrhea plus the presence of *C. difficile* toxin as determined by the local clinical laboratory). The study was powered at 80% for the reduction in CDI with a 1-sided alpha = 0.05. The study met its primary endpoint with a 71.4% relative risk reduction in CDI (1-sided p=0.0454), a statistically significant 43.9% relative risk reduction in new colonization by vancomycin resistant enterococci (1-sided p=0.0002) and demonstration of significant protection of the gut microbiome in the ribaxamase group as compared with the placebo group. These data support that ribaxamase maintains the balance of the gut microbiome, thereby preventing opportunistic infections like CDI and preventing colonization by opportunistic antibiotic-resistant pathogens.

Speaker Biography

John F Kokai-Kun is the Vice President of Non-clinical Affairs for Synthetic Biologics Inc. (Rockville, MD). He has received his BS in Biochemistry from Juniata College in Huntingdon, PA and he has completed his PhD in Microbiology from the University of Pittsburgh, School of Medicine. He served as a Post-doctoral Researcher at the Uniformed Services University of the Health Sciences in Bethesda, MD. He has 20 years of experience in the drug development industry and has held positions with several Biotechnology and Pharmaceutical companies where his research and development efforts have focused primarily on anti-bacterial drugs and vaccines. He is also an Adjunct Assistant Professor of Microbiology and Immunology at the Uniformed Services University.

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