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SYN-004 (ribaxamase), an orally administered β-lactamase for prevention of antibiotic-mediated dysbiosis of the gut microbiome and *Clostridium difficile* infection in patients receiving intravenous β-lactam antibiotics

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SYN-004 (ribaxamase) is an orally administered β-lactamase to be given with IV β-lactam antibiotics. Ribaxamase remains localized in the intestine to degrade excreted β-lactam antibiotics which should protect the gut microbiome from disruption thus preventing deleterious effects including, *Clostridium Difficile* Infection (CDI), and colonization by opportunistic pathogens and emergence of antibiotic resistance in the gut. Ribaxamase was well tolerated in phase 1 studies and efficiently degraded ceftriaxone excreted into the human intestine in Phase 2a studies, where it did not alter the plasma pharmacokinetics of the ceftriaxone. A multinational phase 2b, double-blind, placebo-controlled, study was conducted to determine whether ribaxamase could prevent CDI with additional endpoints for antibiotic-associated diarrhea, colonization by antibiotic-resistant pathogens, changes in the gut micro biome and emergence of antibiotic resistance in the gut. The 412 patient ITT population, enriched for higher risk for CDI, were admitted to the hospital for ≥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 and for 72 h after. Fecal samples were collected at pre-specified points for determination of colonization by opportunistic pathogens and to examine changes in the gut microbiome. Patients were monitored for 6 weeks for CDI (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 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 significant protection of the gut microbiome in the ribaxamase group as compared with the placebo group. These data are consistent with ribaxamase maintaining the balance of the gut microbiome and thereby preventing opportunistic infections like CDI.

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Application of small synthetic antimicrobial peptides (ssAMP) to control antibiotics resistant pathogens of citrus canker disease

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Citrus canker caused by *Xanthomonas Citri* Subsp. Citri (Xcc) decreases the fruit quality and yield significantly. Emerging of *Streptomycin*-Resistant (SR) strains threatens the citrus industry seriously because of a lack of proper control agents. It has been suggested that ssAMPs could be a promising alternative. Over 50 potential hexapeptides were designed and synthesized based on the Positional Scanning of Synthetic Peptide Combinatorial Libraries (PS-SPCL). Majority of them showed antimicrobial activities against variety of microbes including *Bacillus, Pseudomonas, Xanthomonas* and *Candida* species. Three hexapeptides, BHC06 and 11, and KCM21 were selected and tested to control citrus canker using 5 years old sathuma mandarin leaves (*Citrus unshiu*). Each hexapeptide drastically reduce the canker symptom development caused by wild type as well as SR strains. The results showed great potential of ssAMPs to fight against emerging antibiotics-resistant pathogens in agriculture.

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