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SYN-004 (ribaxamase) Significantly Reduced the Incidence of Clostridium difficile Infection in a Phase 2b Clinical Study

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Background: SYN-004 (ribaxamase) is an orally administered β-lactamase designed to be given with intravenous β-lactam antibiotics. Ribaxamase remains localized in the intestine and is available to degrade β-lactam antibiotics which are excreted into the intestine before the antibiotic reaches the colon. Degradation of these excess antibiotics is expected to protect the gut microbiome from disruption and thus prevent deleterious effects including, secondary infections like *Clostridium difficile*, colonization by opportunistic pathogens and the emergence of antibiotic resistance in the gut microbiome. Ribaxamase was shown to be well tolerated in Phase 1 clinical studies and efficiently degrade ceftriaxone excreted into the human intestine in Phase 2a studies. Importantly, oral ribaxamase did not alter the plasma pharmacokinetics of the ceftriaxone as it was not systemically available.

Material/methods: A global Phase 2b, double blind, placebo controlled, multicenter study was conducted to determine whether ribaxamase could prevent *C. difficile* infection (CDI) with exploratory endpoints of antibiotic-associated diarrhea, colonization by opportunistic pathogens, changes in the balance of the gut microbiome and emergence of antibiotic resistant organisms. The modified intent to treat population was 412 patients who were admitted to the hospital for treatment of a lower respiratory tract infection. As treatment, the patients were expected to receive ≥5 days of IV ceftriaxone and were randomized 1:1 to receive either ribaxamase or placebo during ceftriaxone treatment and for 72h after. Fecal samples were collected at pre-specified points for determination of bacterial colonization by specific antibiotic resistant pathogens and to examine changes to the gut microbiome and resistome. The patients were also monitored for diarrhea for 6 weeks during which time CDI was defined as diarrhea plus the presence of *C. difficile* toxin (as determined by the local clinical laboratory and confirmed by a central laboratory). The study was powered at 80% for the reduction in CDI with 1-sided alpha = 0.05.

Results: Recently released topline data from the study revealed a statistically significant 71.4% relative risk reduction in CDI (1-sided p=0.0454) and a 43.9% relative risk reduction in new colonization by vancomycin resistant enterococci (1-sided p=0.0002) in the ribaxamase group as compared with the placebo group. Consistent with these results, ribaxamase also significantly protected the gut microbiome for antibiotic-mediated dysbiosis as compared with placebo.

Conclusions: These results are consistent with ribaxamase being capable of maintaining the balance of the gut microbiome thus preventing one of the most serious consequences of disruption of the gut microbiome, *C. difficile* infection. Protection of the gut microbiome from the deleterious effects of antibiotics should also have additional benefits including prevention of emergence of antibiotic resistance in the gut microbiome. Analysis of the data from the study, including changes to the gut resistome of the patients during the study, are ongoing.