SYN-004, A NOVEL STRATEGY TO PROTECT THE GUT MICROBIOME FROM THE DELETERIOUS EFFECTS OF RESIDUAL IV β-LACTAM ANTIBIOTICS

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Disruption of the Gut Microbiome Can Lead to *Clostridium difficile* Infection

- IV Antibiotics
- Biliary excretion
- Dysbiosis
- Probiotics
- Antibiotics & Vaccines
- mAbs & Vaccines
- FMT & Bacterial Replacement
- CDI
- SYN-004

*C. difficile* spores
SYN-004

• Orally administered, β-lactamase enzyme that degrades penicillins and cephalosporins, formulated for release at pH ≥ 5.5 (proximal small intestine)

• To be given during and after administration of intravenous (IV) β-lactam-containing antibiotics like ceftriaxone

• Degrade the excess antibiotics that are excreted into the small intestine via the bile

• Prevent disruption of the gut microbiome and thus protect from opportunistic GI pathogens like *C. difficile*
SYN-004 Non-clinical Studies

- Oral SYN-004 degrades IV ceftriaxone excreted into the dog small intestine
- Safe when dosed up to 57 mg/kg/day (19 mg/dose, t.i.d.) for 28 days in dogs
- Minimal and sporadic systemic absorption of SYN-004
- Safe when dosed up to 57 mg/kg/day with 300 mg/kg/day of IV ceftriaxone for 14 days in dogs

Ceftriaxone Plasma PK
Clinical Trials with SYN-004

- **Phase 1**-two studies in normal healthy volunteers
- Single ascending oral dose up to 750 mg
- Multiple ascending oral doses up to 300 mg q.i.d. for 7 days
- SYN-004 was safe and well tolerated with no systemic bioavailability of SYN-004 and no anti-drug antibodies
- Adverse events were mild and self-limiting
Clinical Trials with SYN-004

• **Phase 2a** - two studies in subjects with functioning ileostomies to obtain intestinal chyme samples-on-going

• Administering IV ceftriaxone with or without oral SYN-004, measuring chyme concentrations and plasma PK of ceftriaxone and SYN-004

• Administering IV ceftriaxone plus SYN-004 in the presence or absence of proton pump inhibitors, measuring chyme concentration and plasma PK of ceftriaxone and SYN-004
Clinical Trials with SYN-004

- **Phase 2b**: A Phase 2B, Parallel-Group, Double Blind, Placebo-Controlled, Multicenter Study of SYN-004 Compared to Placebo for the Prevention of *Clostridium difficile* Associated Diarrhea in Patients with a Diagnosis of a Lower Respiratory Tract Infection

- ~370 patients to be treated with IV ceftriaxone for lower respiratory tract infections will receive SYN-004 or PBO

- Will compare the incidence of CDI and AAD

- Will also look at changes in the gut microbiome

- Study has been initiated, ~75 global sites when fully active
SYN-004 Conclusions

- SYN-004 degrades IV penecillins and cephalosporins \textit{in vitro} and \textit{in vivo} in the small intestine in dogs when antibiotics are excreted via the bile

- Oral SYN-004 is safe and well tolerated in GLP toxicity studies in dogs and does not affect the plasma PK of IV ceftriaxone

- Oral SYN-004 is safe and well tolerated in normal human volunteers with no systemic bioavailability or immunogenicity

- Clinical studies to confirm the mechanism of action of oral SYN-004 and to examine its capacity to prevent dysbiosis and CDI are ongoing
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