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

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Disruption of the Gut Microbiome Can Lead to *C. difficile* Infection

IV Antibiotics

Probiotics and prebiotics

Dysbiosis

FMT & Bacterial Replacement Therapy

C. difficile spores

Biliary excretion

Antibiotics (Vaccines)

mAbs & Vaccines

CDI

ribaxamase

*CDI is serious, deadly, and expensive*

29,000 US deaths/year within 10 days of diagnosis

1 in 5 (8,000) recurrences within 2 months

CDI adds up to:

12 days in the hospital

$27,160 per case in direct costs

Synthetic Biologics
SYN-004 (ribaxamase)

rye bak’ sa mase

- An orally administered, β-lactamase (an enzyme of 29 kDa) that is designed to degrade penicillins and cephalosporins (engineered from P1A)

- Formulated for pH-dependent release at ≥ 5.5 (proximal small intestine)

- Expected to be orally administered during and after administration of certain intravenous (IV) β-lactam-containing antibiotics like ceftriaxone

- Intended to degrade the excess antibiotics that are excreted into the small intestine via the bile (ribaxamase is stable in human intestinal chyme)

- Designed to prevent disruption of the gut microbiome and thus protect from opportunistic GI pathogens like *C. difficile*
Pre-clinical Animal Models

Demonstrate the tolerability and *in vivo* activity of ribaxamase

**• Fistulated dog model**
- Ribaxamase degraded IV β-lactam antibiotics excreted into the dog intestine

**• Nonclinical toxicology in dogs**
- Ribaxamase was well tolerated up to 57 mg/kg/day
- Ribaxamase was well tolerated when administered with IV ceftriaxone
- Ribaxamase was not absorbed and did not change the plasma PK of the ceftriaxone

**• Piglet Model of Antibiotic-Mediated Dysbiosis**
- Ribaxamase protected the gut microbiome from disruption by β-lactam antibiotics
- Ribaxamase prevented the propagation of antibiotic resistance genes
Clinical development
Early Phase Clinical Studies
Phase 1 and Phase 2a

• **Phase 1**-two studies in normal, healthy volunteers
  - Well tolerated up to 750 mg single dose and 300 mg q.i.d. – 7 days
  - Not absorbed and no anti-drug antibodies were detected

• **Phase 2a**-two studies in subjects with ileostomies, IV ceftriaxone ± ribaxamase
  - Ribaxamase degraded all ceftriaxone in the intestine
  - Ribaxamase did not affect the plasma PK of the ceftriaxone
  - Ribaxamase can be administered in the presence of proton pump inhibitors
Ribaxamase: Phase 2b Proof-of-Concept Study

54 Multinational Clinical Sites Enrolled Patients

Patients admitted to the hospital for treatment of a lower respiratory tract infection

mITT 412 patients

1:1

Ceftriaxone + Ribaxamase *(plus a macrolide)*

Ceftriaxone + Placebo *(plus a macrolide)*

Primary Endpoint:
- Prevention of *C. difficile* infection (CDI)

Secondary Endpoint:
- Prevention of *non-C. difficile*, antibiotic-associated diarrhea (AAD)

Exploratory Endpoints:
- Evaluate ability to limit disruption of the gut microbiome
Enriching for a Population at Risk for *C. difficile* Infection

- Patient were admitted to a hospital for several days
- At least 5 days of ceftriaxone use expected
- Patients > 50 years old
- Patients with higher PORT scores
  (a measure of the severity of the primary infection)
Phase 2b Proof of Concept Study

Study Design

Randomized 1:1, 150 mg ribaxamase or placebo

- US
- Canada
- Romania
- Bulgaria
- Hungary
- Poland
- Serbia

Fecal microbiome and fecal colonization samples taken for analysis

Diarrhea = 3 or more loose or watery stools in a 24 hour period, samples collected
CDI = local lab results for presence of *C. difficile* toxins A and/or B by an approved test (confirmed at a central lab by toxin ELISA)
Study Demographics and Safety Outcomes

• 206 patients per group in mITT
• Average age of patients ~70 years old
• ~2/3 males
• ~1/3 of patients received macrolides
• ~1/3 patients received concurrent drugs for stomach acid
• TEAEs and SAEs were similar between active and placebo and there was no trend associated with ribaxamase use
• Cure rate for the LRTI to the ceftriaxone treatment was ~99% in both groups at 72 hours post treatment and at 2 weeks post treatment
**Clostridium difficile** Infection

- No CDI patients reported previous CDI
- P-values are 1-sided based on the pre-specified Z-test
- The study was powered at 80% with 1-sided alpha=0.05
Antibiotic-associated Diarrhea

- P-values are 1-sided based on the pre-specified Z-test
New *C. difficile* Colonization at 72 hrs & 4 weeks

- P-values are 1-sided based on the pre-specified Z-test
New VRE Colonization at 72 hrs & 4 weeks

- P-values are 1-sided based on the pre-specified Z-test
Conclusions

• Ribaxamase reduced the incidence of new onset CDI by 71% as compared with placebo (confirmed at the central lab), p=0.045

• Ribaxamase appeared to be well tolerated and not affect the cure rate for the primary infection

• Ribaxamase did not significantly reduce AAD as defined in the protocol, but there was a reduction in all cause diarrhea

• Ribaxamase reduced new colonization with *C. difficile* and VRE

• Analysis of fecal samples for changes in the gut microbiome and gut resistome (CDC contract) are on-going
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