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A Phase 1b/2a Randomized Open-label Study Measuring Chyme Concentrations of Intravenously Administered Ceftriaxone in the Presence of the Oral Beta-lactamase SYN-004

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Background and Purpose

SYN-004 is an oral recombinant β-lactamase developed by Synthetic Biologics, Inc., and intended to degrade certain intravenous (IV) β-lactam antibiotics excreted into the gut, thereby mitigating their compromising effects on the gut microbiome, and correspondingly preventing opportunistic hospital-acquired, bacterial infections such as *C. difficile*.

In the U.S., the White House issued a National Action Plan for combating antibiotic-resistant infections including *C. difficile* infection (CDI) in March 2015 with the aim of reducing the incidence of CDI by 50% by 2020.

Antibiotics → ***C. difficile* Infection** → **Hospitalisation** → **Treatment**

The purpose of this study was to evaluate the ability of SYN-004 to degrade ceftriaxone secreted into the small intestine after IV administration without affecting antibiotic pharmacokinetics (PK) in the bloodstream.

Antibiotics + SYN-004 → **Prevention** → **Save Lives & Reduce Health Costs**

Methods

Nine otherwise healthy subjects with functioning ileostomies (see Figure 1) were enrolled at Algorithme Pharma Inc., a Phase 1 Clinical Research Organization based in Montreal, Canada. Seven male patients were aged between 24 and 74 years old, and two female patients were respectively of 53 and 60 years old.

In the first treatment period, all subjects received an infusion of ceftriaxone and, in the second treatment period, were randomized to receive one of the two single oral doses of SYN-004 (75 or 150 mg) twice in one day (early morning and early afternoon), with a single IV dose of 1g ceftriaxone, 30 minutes following the first dose of SYN-004 (see Figure 3).

Subjects were confined in the clinical unit for 24 hours, and medical monitoring lasted one week after the end of the second confinement period. PK sampling was up to 8.5 hours post-dose during Treatment Period 1 and Treatment Period 2, both in plasma and chyme, the semifluid mass expelled in the ostomy bag.

Results

Patients with functioning ileostomies were recruited by means of publicity in mass media and in collaboration with local ostomy associations.

Figure 1. Schematic Ileostomy

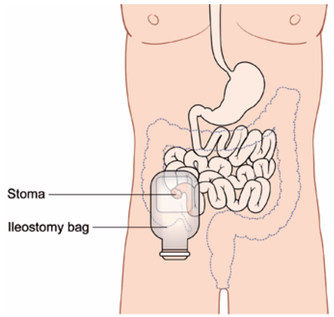

Figure 2. Patient Recruitment, Screening and Enrolment Activities

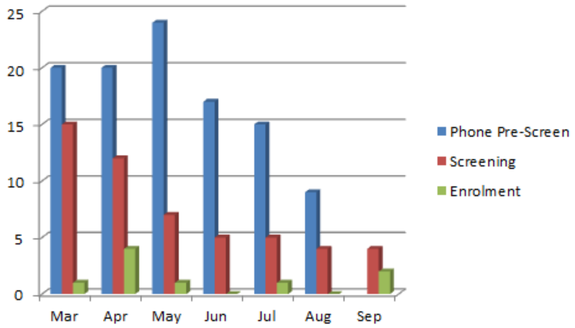

Figure 3. Design of Clinical Trial

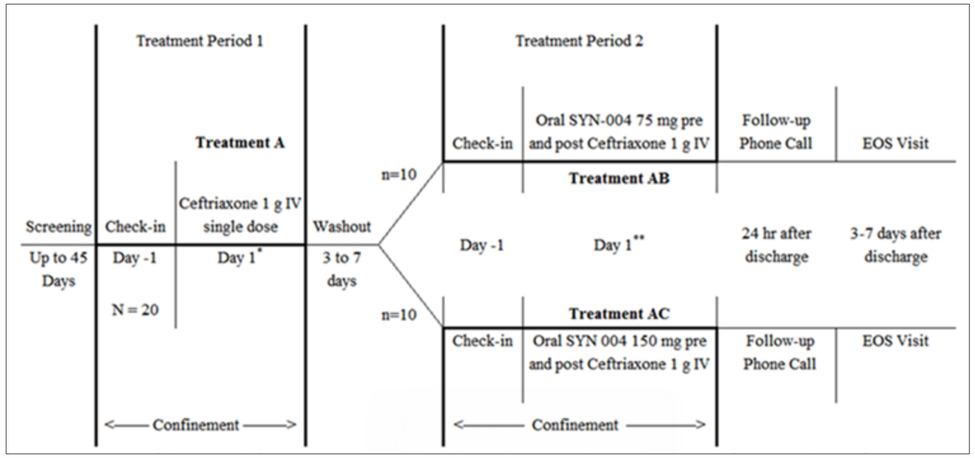

Table 1. Adverse Events Related to Treatment

Number of Treatment Emergent Adverse Events	Treatment AB: Ceftriaxone + 75 mg SYN-004 (N=6)	Treatment AC: Ceftriaxone + 150 mg SYN-004 (N=5)
GASTROINTESTINAL DISORDERS		
Abdominal pain	1	
NERVOUS SYSTEM DISORDERS		
Somnolence	1	
RENAL & URINARY DISORDERS		
Pollakiuria (frequent urination)		1

Results (continued)

To successfully enroll nine patients over a period of seven months (see Figure 2), Algorithme Pharma's recruitment team had a total of 105 prescreen phone conversations with prospective volunteers with ileostomy, and 52 screening appointments were completed. Main reasons for screening failure were concurrent medical conditions, safety laboratory parameters out of range, and use of prohibited medications.

Table 1 shows that the 75 and 150 mg single doses of SYN-004 as well as the single dose of ceftriaxone were very well tolerated. AEs were mostly mild to moderate in intensity, and all patients had recovered from their AEs at the end of their study participation.

The uniqueness of this study design resides in the special population that are patients with ileostomies. The presence of the ileostomy permits access to the chyme. This constitutes a direct measurement of the degradation of ceftriaxone in the small intestine.

Conclusion

The clinical portion of this Phase 1b/2a study was successfully completed. The methodology used in this trial of sequential sampling and analyzing the chyme should prove to be a powerful approach to allow the direct measurement of PK/PD for oral medications whose primary mechanism of action occurs in the gut.

Preliminary results from this study indicate that SYN-004 degrades residual ceftriaxone in the chyme while not impacting the systemic ceftriaxone plasma levels. SYN-004 is currently being investigated in a multicenter, placebo-controlled Phase 2b study in hospitalized patients being treated with IV ceftriaxone for lower respiratory infections. The primary outcome of the Phase 2b study will be prevention of *C. difficile* infection, with a secondary outcome of prevention of antibiotic-associated diarrhea.

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