SYNB8802v1 Lowers Urinary Oxalate Using a Controlled Dietary Model of Hyperoxaluria in Patients with Roux-en-Y Gastric Bypass

SA-PO307

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INTRODUCTION

Disease State[1,2]

- In Enteric Hyperoxaluria (EH), prior insult to the bowel results in GI malabsorption, including excessive absorption of oxalate and elevated urinary oxalate (UOx) levels
- Elevated UOx can result in crystal formation and painful, recurrent kidney stones, impaired renal function and deposition of oxalate in other tissues and organs
- EH most commonly occurs in adults who have had prior insult to the bowel, such as inflammatory bowel disease (IBD) or bariatric surgery including Roux-en-Y (RnY) Gastric Bypass
- Current treatment is limited to dietary restrictions with limited success; there are no approved treatments for EH

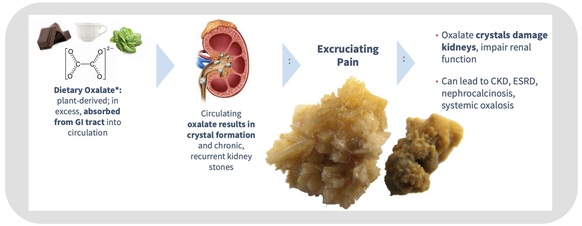

Figure 1: EH etiology and progression.

Study Objectives

- The Synthetic Biotic, SYNB8802v1, is a potential orally-administered, non-systemically absorbed treatment for EH based on an engineered probiotic designed to consume oxalate in the GI tract
- To establish Proof-of-Concept plus safety and tolerability, we selected a population of patients with a history of Roux-en-Y (RnY) gastric bypass surgery, reflecting the abnormal GI physiology typical of EH, and utilized a controlled, inpatient dietary setting to induce hyperoxaluria

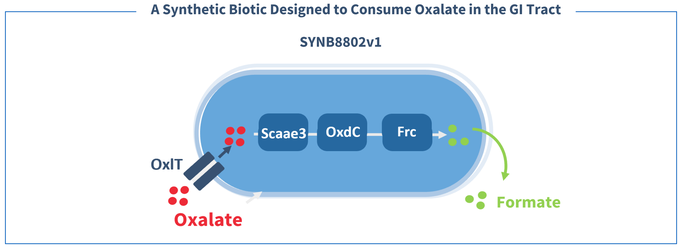

Figure 2: SYNB8802v1 is an engineered bacteria derived from E. coli Nissle that consumes oxalate in the GI tract to prevent absorption. In addition to the genes for oxalate degradation, SYNB8802v1 has a deletion of the *pks* island, encoding colibactin.

METHODS

- Study SYNB8802-CP-002 was a Phase 1b, randomized, placebo-controlled, single-center inpatient study, enrolling 11 adults (median [SD] age 56 [8.6], 1 M/10 F) with a history of RnY gastric bypass, and no prior kidney stones
- Seven participants received SYNB8802v1 and four received placebo
- Participants were admitted to a phase 1 unit and placed on a controlled diet consisting of 300 mg of dietary oxalate and 400 mg of calcium plus PPI (40 mg QD) at baseline for three days, and during dosing on days 1-12
- Days 1-7 dosing was at the $1x10^{11}$ SYNB8802v1 or placebo (QD d1, BID d2, TID d3-6), and Days 8-12 were at $3x10^{11}$ SYNB8802v1 or placebo (QD d7, BID d8, TID d9-12)
- 27 participants were screened, 11 were enrolled (seven randomized to SYNB8802v1 and four to placebo); 10 completed (seven on SYNB8802v1 and three on placebo)

RESULTS

Reduction of Urinary Oxalate at Both Dosing Levels

- The oxalate diet resulted in a baseline mean (SD) UOx of 29.4 (2.3) mg/24h for the placebo group and 32.5 (9.0) mg/24h for the SYNB8802v1 group
- SYNB8802v1 lowered UOx by -37.3 % (p<0.01) at the 3e11 dose and -27.7% (p<0.01) at the 1e11 dose relative to placebo, analyzed using a pharmacometric model factoring in dose level and frequency

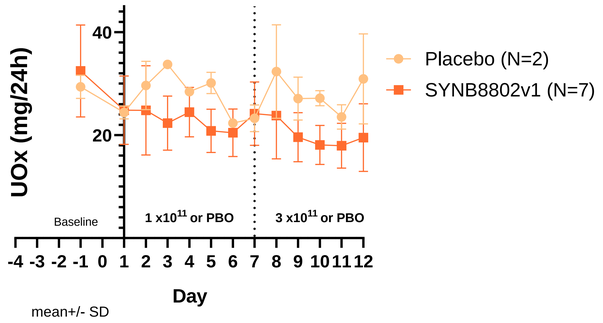

Figure 3: UOx reduction at two dosing levels.

RESULTS (cont'd)

SYNB8802v1 POC Achieved by Lowering of Urinary Oxalate

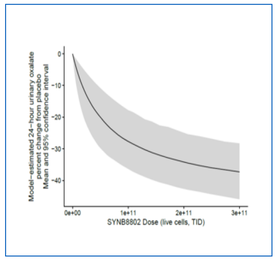

Figure 4: Pharmacometric model with estimated percent change from baseline in 24-hour urinary oxalate. Mean percent change (line) ±95% confidence interval (gray shading).

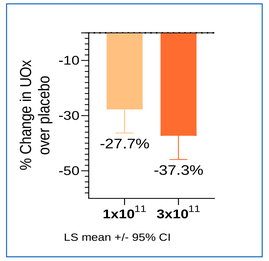

Figure 5: UOx reduction over placebo in participants treated with 1e11 and 3e11 doses of SYNB8802v1.

SYNB8802v1 Adverse Event Summary

System Organ Class Preferred Term	SYNB8802v1 (N=7) n (%)	Placebo (N=4) n (%)	Total (N=11) n (%)
Any TEAE	6 (85.7)	2 (50.0)	8 (72.7)
Gastrointestinal disorders	5 (71.4)	2 (50.0)	7 (63.6)
Abdominal pain	3 (42.9)	0	3 (27.3)
Nausea	2 (28.6)	0	2 (18.2)
Vomiting	2 (28.6)	0	2 (18.2)
Musculoskeletal and connective tissue disorders	3 (42.9)	1 (25.0)	4 (36.4)
Back pain	2 (28.6)	0	2 (18.2)

Table 1: SYNB8802-CP-002 adverse event summary.

CONCLUSIONS

- SYNB8802v1 demonstrated the capacity to lower UOx in RnY patients, providing proof of concept as a potential therapeutic for Enteric Hyperoxaluria (EH)
- SYNB8802v1 was well tolerated in patients with RnY gastric bypass, with no serious adverse events; one placebo patient discontinued due to antibiotic use
- SYNB8802v1 should be further evaluated in subjects afflicted with kidney stone disease and EH

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For additional information, please contact Caroline Kurtz at caroline@synlogictx.com

References: 1. Puurunen et al., Relationship between 24-hr urinary oxalate and incident chronic kidney disease among patients with and without underlying gastrointestinal disease. Presented at American Society of Nephrology; November 2021.
2. D'Costa MR, Kausz AT, Carroll KJ, et al. Subsequent urinary stone events are predicted by the magnitude of urinary oxalate excretion in enteric hyperoxaluria. *Nephrol Dial Transplant*. 2021;36(12):2208-2215. doi:10.1093/ndt/gfaa281.