Safety and Tolerability of an Oxalate-Consuming Synthetic Biotic Medicine: SYNB8802 in Healthy Volunteers with Induced Dietary Hyperoxaluria

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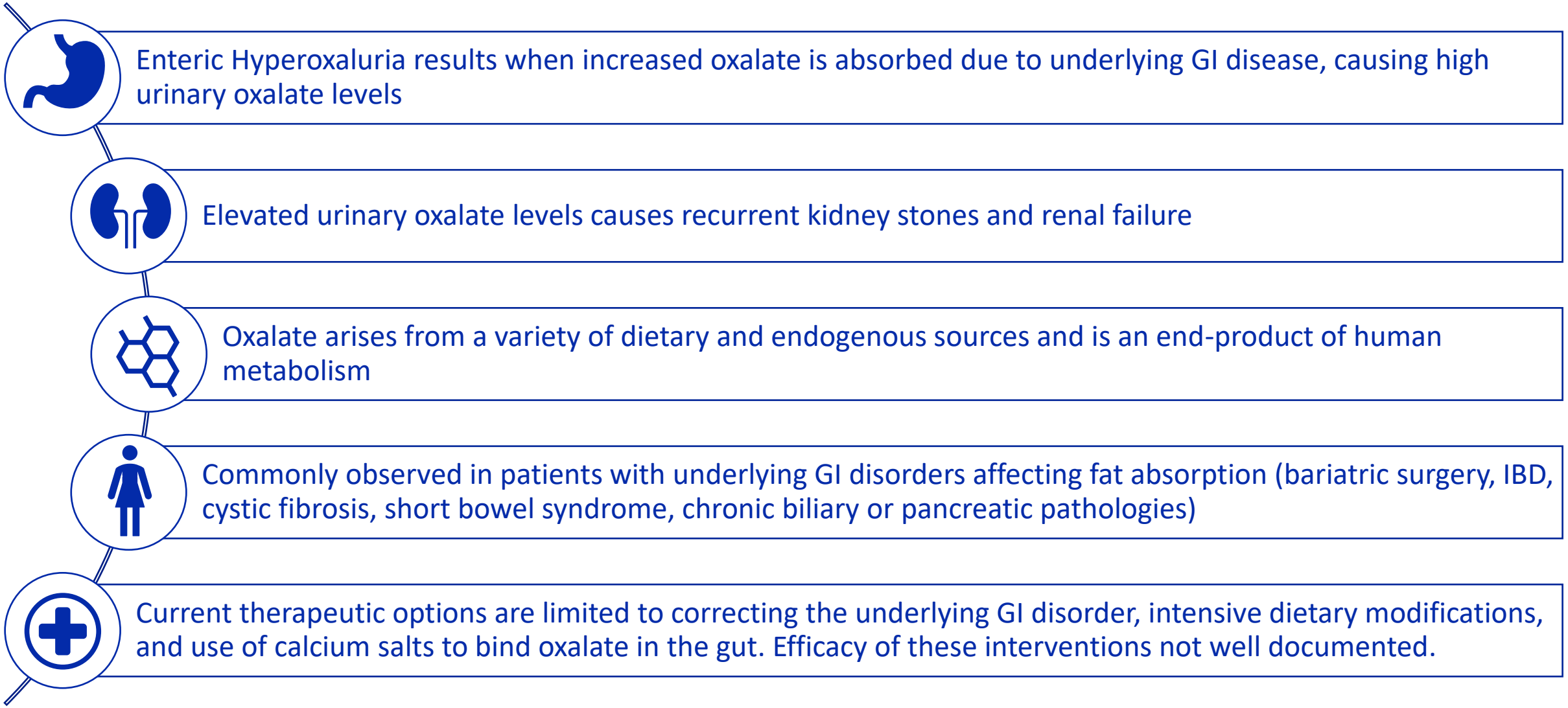
Disclosures

William S. Denney is a consultant for Synlogic and does not own stock or options in the Company.

Enteric Hyperoxaluria

Significant disease burden leading to kidney stones and chronic kidney disease



Reduction of urinary oxalate leads to reduced kidney stone events

Need for novel therapeutic options

Sources of Oxalate

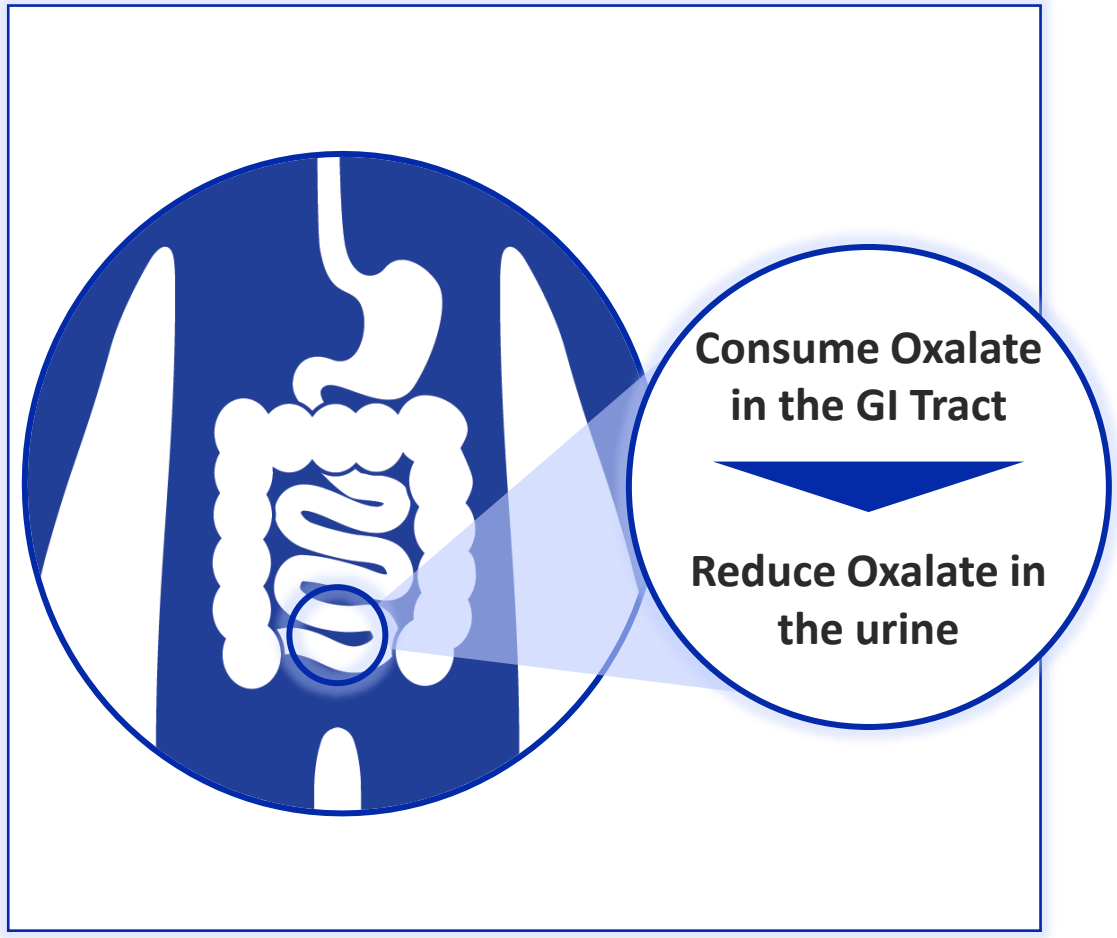
Pathophysiology of Malabsorption

- Under normal conditions, dietary calcium forms a complex with oxalate in the gut lumen and renders it insoluble.
- Increased free fatty acids in the gut can lead to increased soluble oxalate in the colon and increased colonic absorption by preventing the formation of the calcium-oxalate complex
- Result is elevated urinary oxalate levels

20% decrease in UOx was associated with 25% reduction in the annual odds of a future stone event in a large observational study [1]

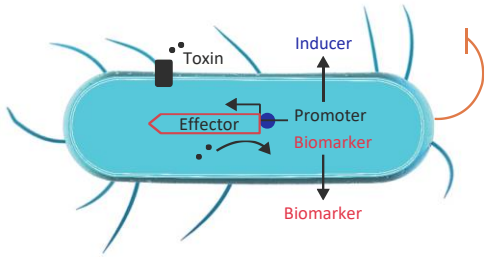
[1] D'Costa MR, Kausz AT, Carroll KJ, Ingimarsson JP, Enders FT, Mara KC, Mehta RA, Lieske JC. Subsequent urinary stone events are predicted by the magnitude of urinary oxalate excretion in enteric hyperoxaluria. Nephrol Dial Transplant. 2020 Dec 26:gfaa281. doi: 10.1093/ndt/gfaa281. Epub ahead of print. PMID: 33367720.

Engineering a non-pathogenic bacteria to consume oxalate



Non-pathogenic **bacterial chassis**

+

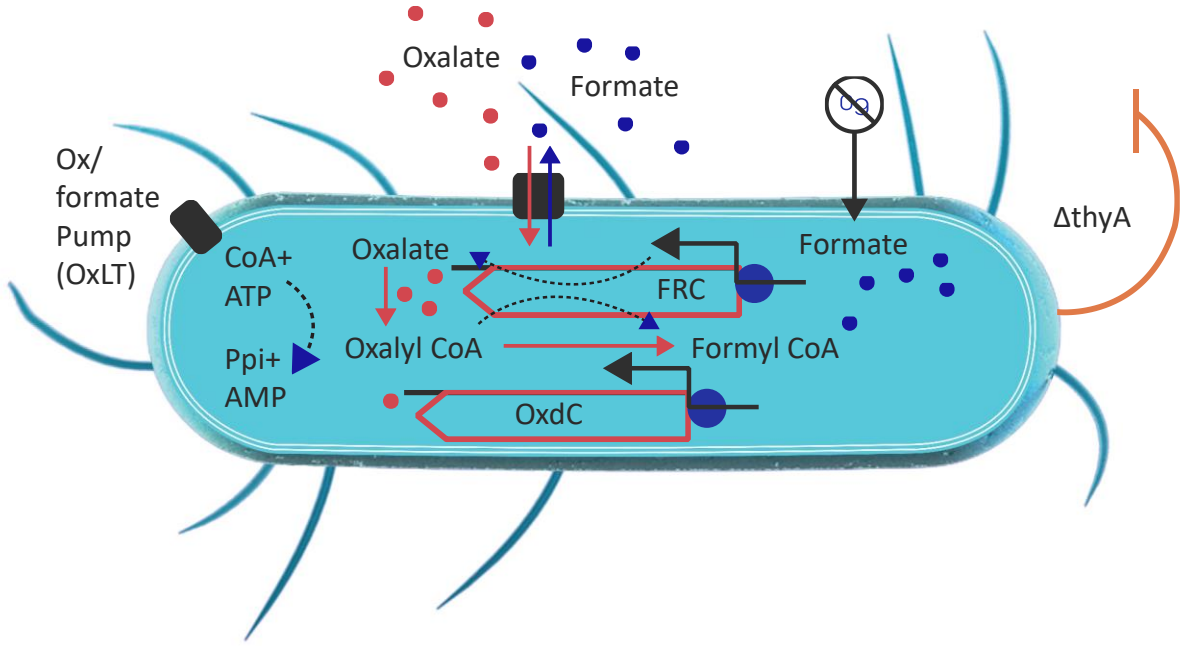


Programable, engineering

Designed to consume oxalate in each GI compartment, throughout GI tract

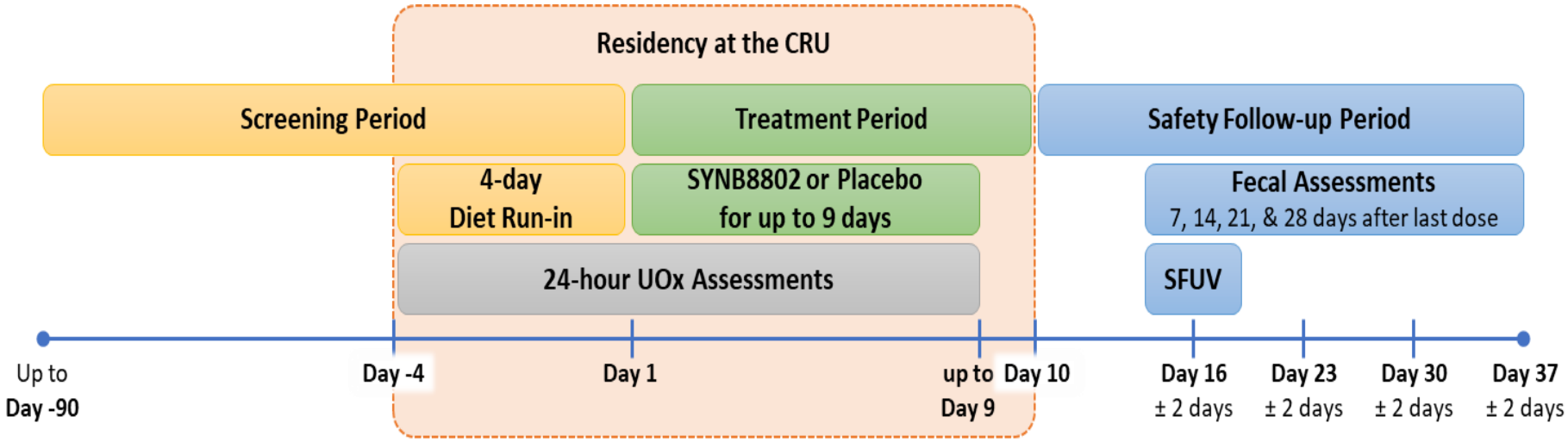
SYNB8802 Design

Component	SYNB8802 Design
Therapeutic strategy	**Metabolite consumption:** Engineered to Convert Oxalate to Formate for the Treatment of Enteric Hyperoxaluria
Bacterial Chassis	***E. coli* Nissle** (probiotic chassis organism)
Effector(s)	***OxdC and associated components:*** Catalyzes conversion of oxalate to formate
Pump	***OxLT:*** Pumps oxalate in & formate out
Switch	**FNR promoter:** Inducer-promoter pair
Safety Features	***Δ thyA:*** Controls growth so strain does not colonize



First-in-human study in Hyperoxaluria

Part A – Dietary-induced hyperoxaluria in healthy volunteers

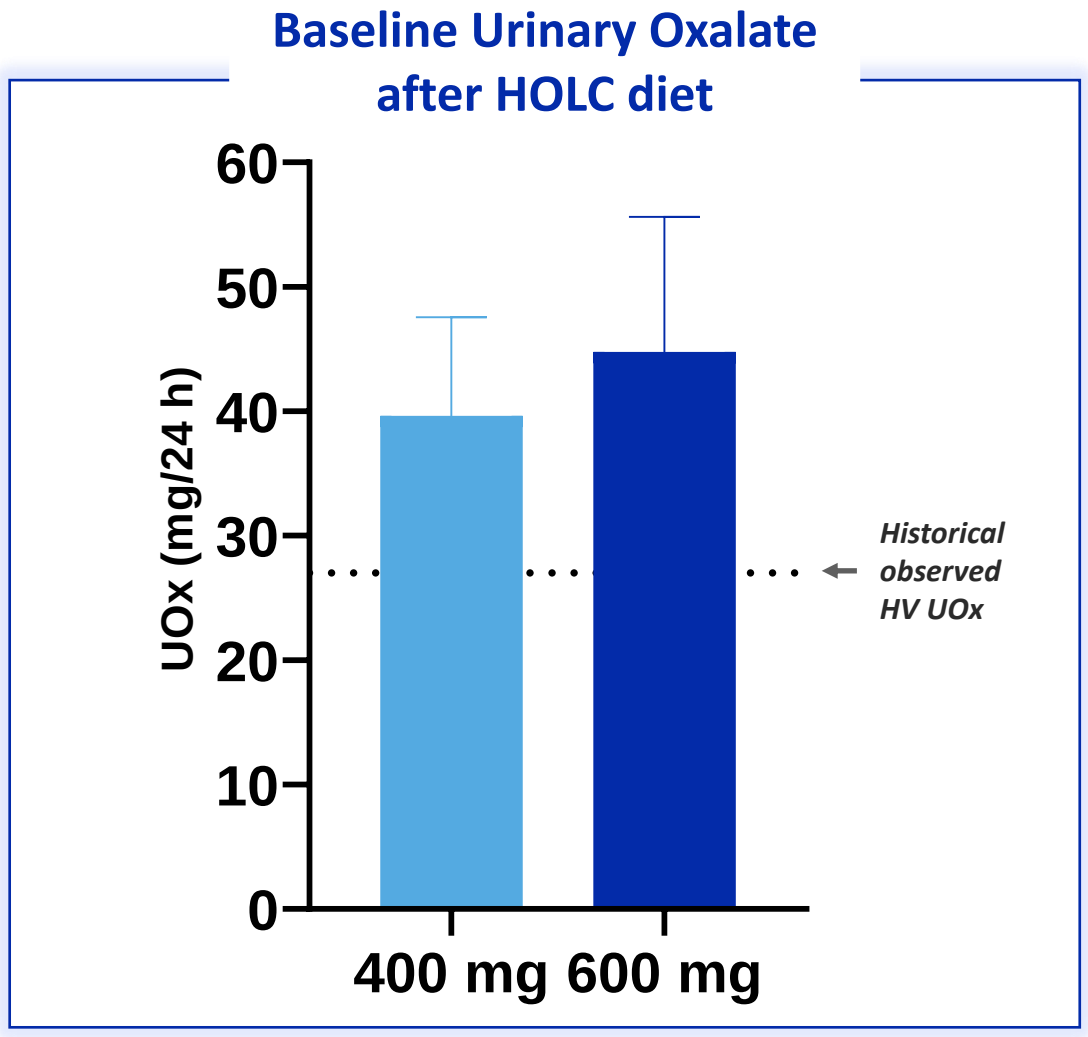


CRU = Clinical Research Unit; TID = three times per day; SFUV = Safety Follow-up Visit; UOx = urinary oxalate

Data presented from 5 cohorts of N=9 healthy volunteers (6 active:3 placebo) each

High oxalate diet successfully elevated UOx levels in HV

- American diet contains approx. 200-250 mg oxalate/day
- HV subjects were given a high oxalate, low calcium diet (HOLC) during the diet run-in and treatment phases of the study
- HV subjects absorb approx. 10% of dietary oxalate
- Urinary oxalate levels elevated to >1.5X typically observed in healthy volunteers
- Dietary intake carefully measured on in-patient unit, incl. weighing of meals consumed

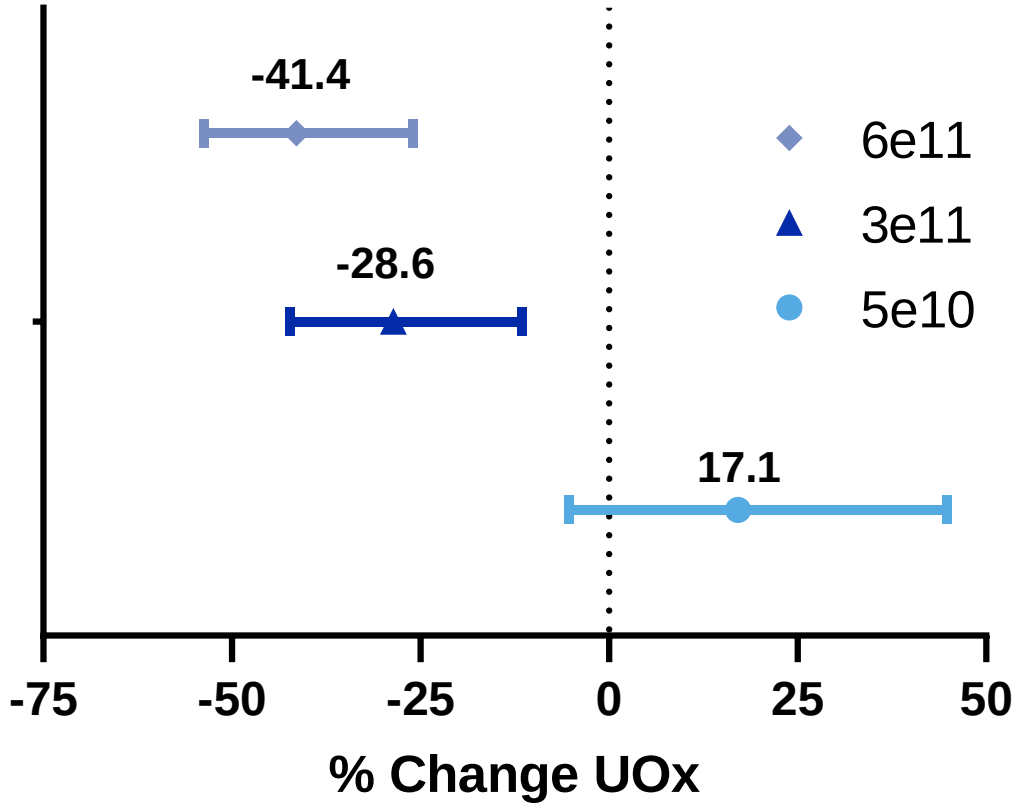


Historically Uox in HV is <40 mg/24h. Examples: Langman 2018, (27 mg), Quintero 2020, (19.8mg), Captozyme 2018 (28 mg). Mean +/- SD shown.

Dose-responsive and reproducible UOx lowering demonstrated

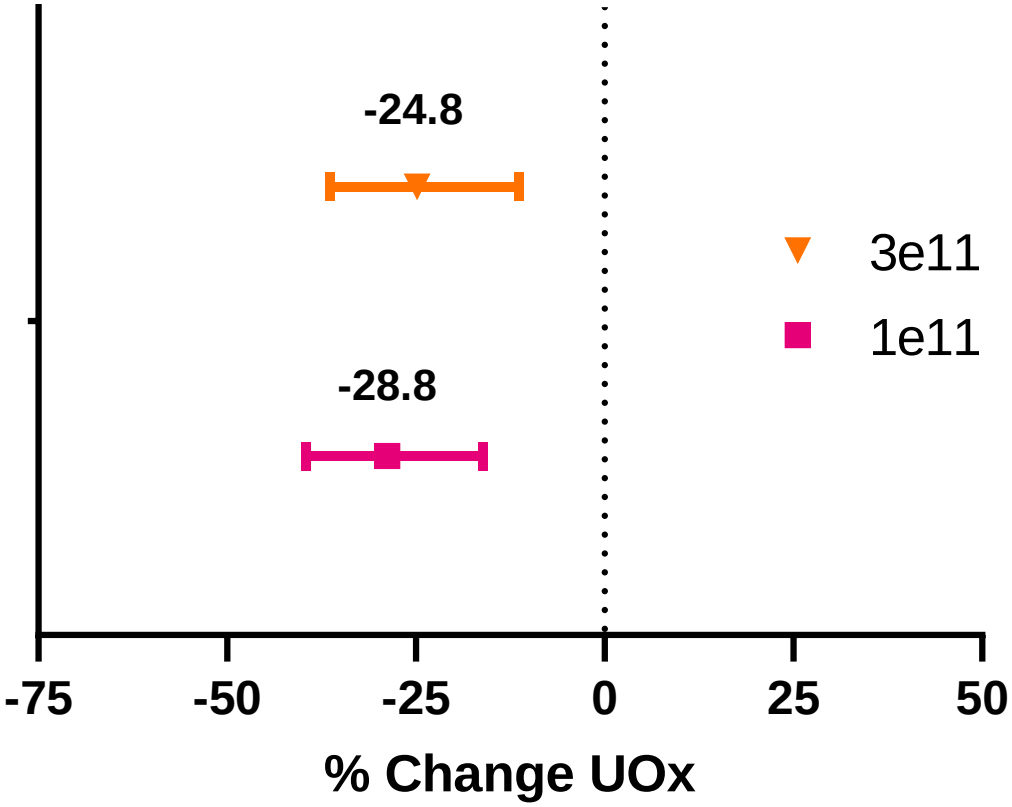
Efficacy Analysis (% Change from Baseline in 24h UOx over Pbo)

600mg Daily Oxalate



Lower is better

400mg Daily Oxalate



Lower is better

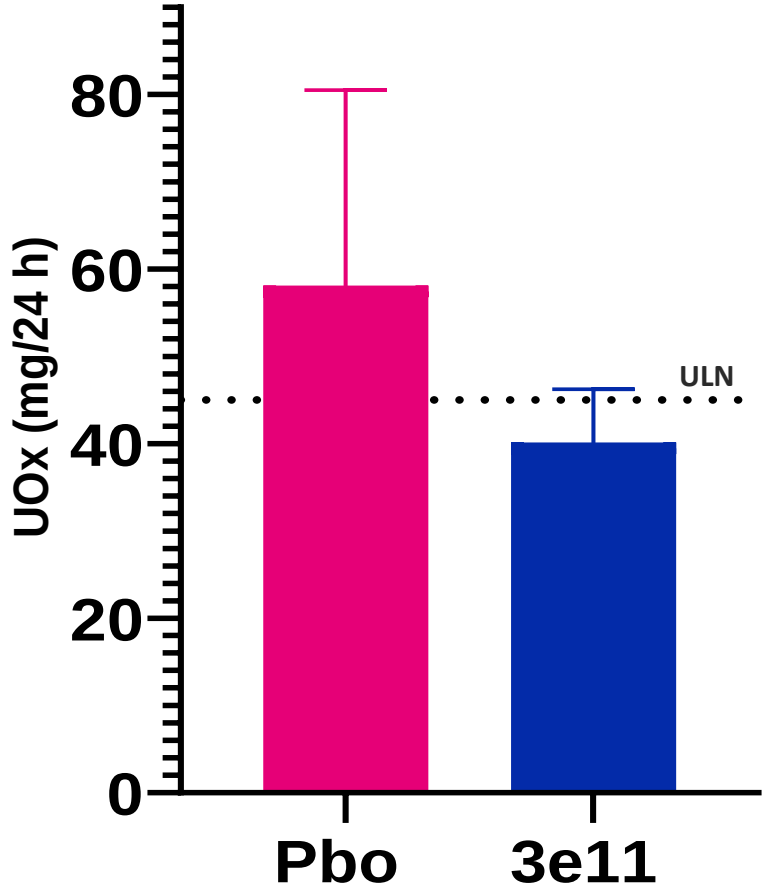
LS-mean change from baseline, change from placebo and 90% confidence interval; all days baseline and treated

3e11 Dose Chosen for Further Evaluation

Safety

- SYNB8802 was generally well tolerated in healthy volunteers (N=45).
- There were no serious or systemic adverse events.
- The most frequent adverse events were mild or moderate, transient, and GI-related.
- 3e11 live cells administered three times daily with meals was selected as the dose for part B of the study.

UOx Levels at End of Dosing Period

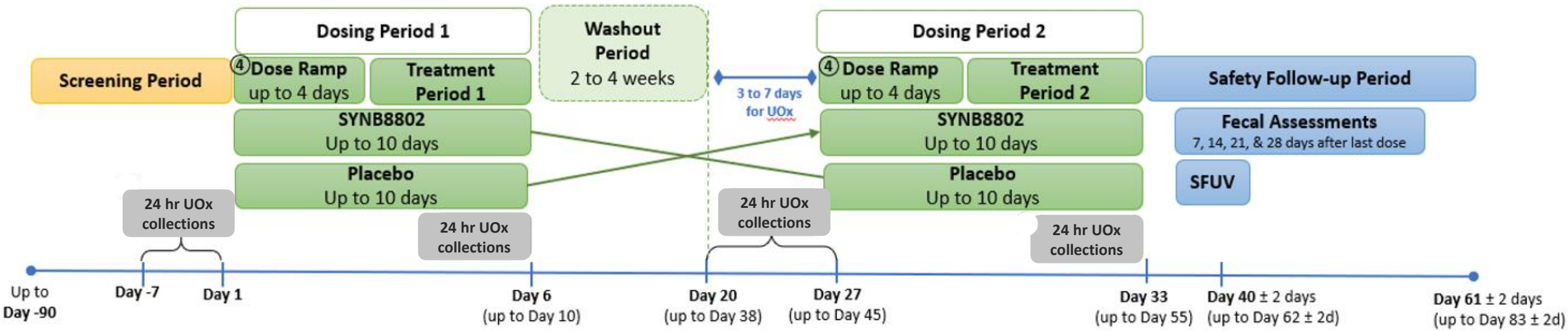


LS-mean change from baseline, change from placebo and 90% confidence interval; all days baseline and treated.
Mean and 90% confidence interval after 5 days of dosing with 600 mg daily dietary oxalate.

Ph1 B: Proof-of-concept study in EH patients

Study open to enrollment

Enrolling patients with EH due to malabsorptive bariatric surgery or surgical short bowel syndrome and UOx ≥50 mg/day



TID = three times per day; SFUV = Safety Follow-up Visit; UOx = urinary oxalate

ClinicalTrials.gov
ct.gov #: NCT04629170

Thank you to study participants

Study Sponsor:

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