Proof-of-Concept Study of Oxalate-Consuming Synthetic Biotic Medicine SYNB8802 in Enteric Hyperoxaluria after Roux-en-Y Surgery

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Disclosures

- Puurunen M, Ndugga-Kabuye MK, Marsh A, Lubkowicz D, Kurtz C, Brennan A, Riese R are or were employees of Synlogic Inc.

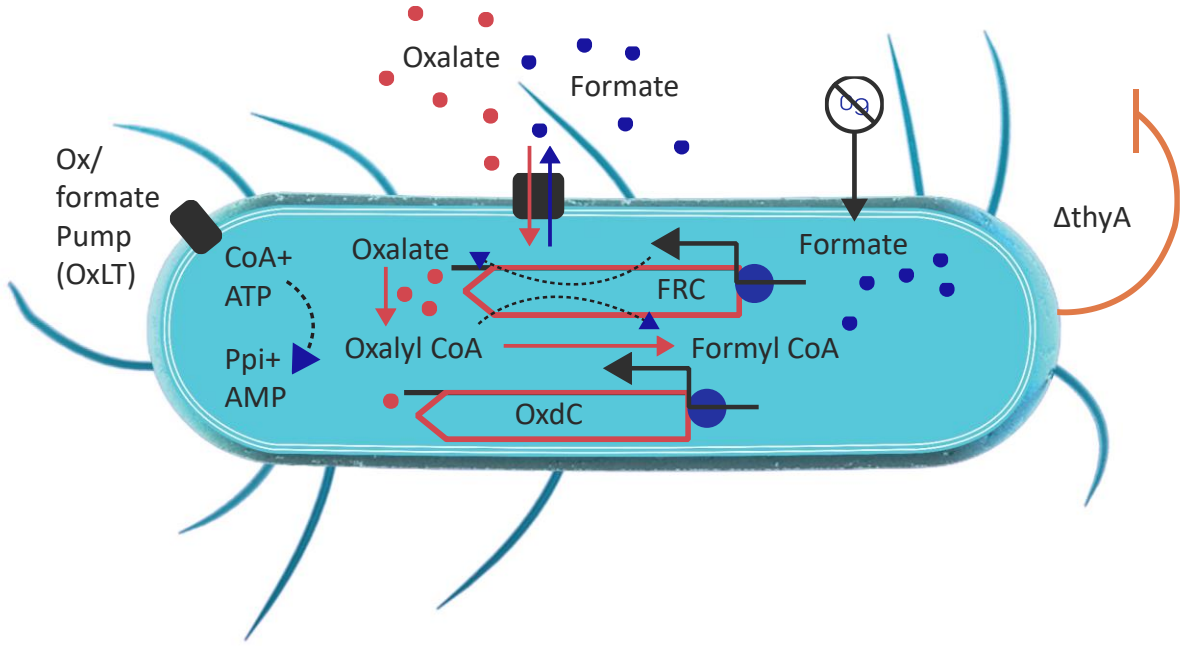
- Denney WS is consultant to Synlogic Inc.

Background

- Enteric hyperoxaluria (EH) is characterized by elevated urinary oxalate excretion due to increased gastrointestinal oxalate absorption
- Increased oxalate absorption is due to underlying fat malabsorption and/or increased intestinal permeability caused by inflammatory bowel disease, short bowel syndrome, celiac disease, cystic fibrosis and pancreatic insufficiency
- EH has been associated with recurrent kidney stones and adverse renal outcomes, including chronic kidney disease (CKD)
- No pharmacological therapies are currently available to treat EH

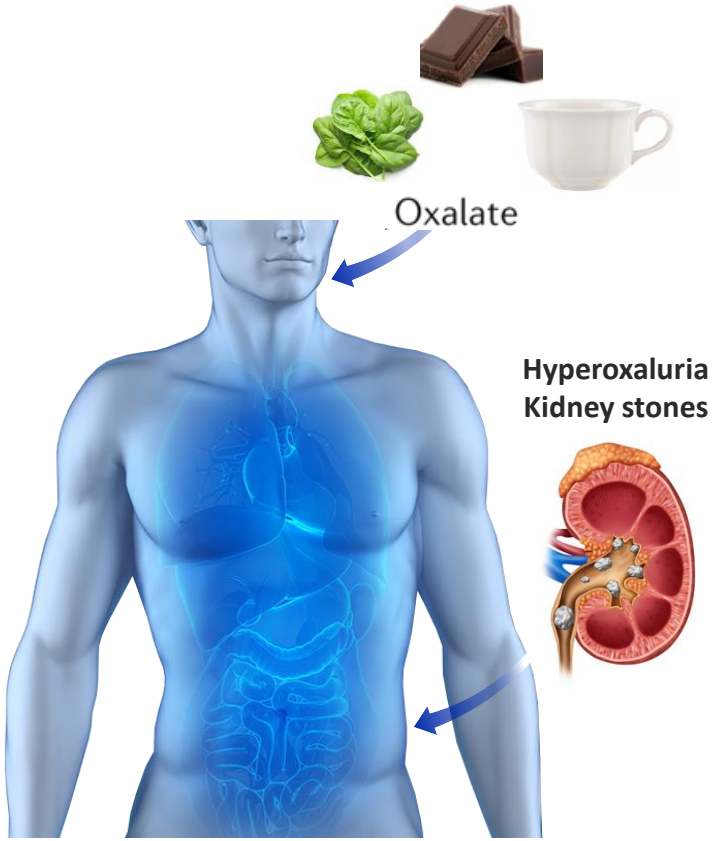
SYNB8802, a genetically engineered non-colonizing strain to convert oxalate to non-toxic metabolites

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



Pathophysiology of Enteric Hyperoxaluria

Dietary Sources of Oxalate



Oxalate absorption

Pathway	Absorption			SYNB8802 Activity
	Healthy state	Disease state		
Dietary Oxalate				
Stomach	✓	✓	Healthy people absorb ~10% of dietary oxalate, mostly via stomach and small intestine	✓
Small intestine	✓	✓		✓
Colon		✓	Patients absorb ~20-30% of dietary oxalate, through entire GI tract including colon	✓

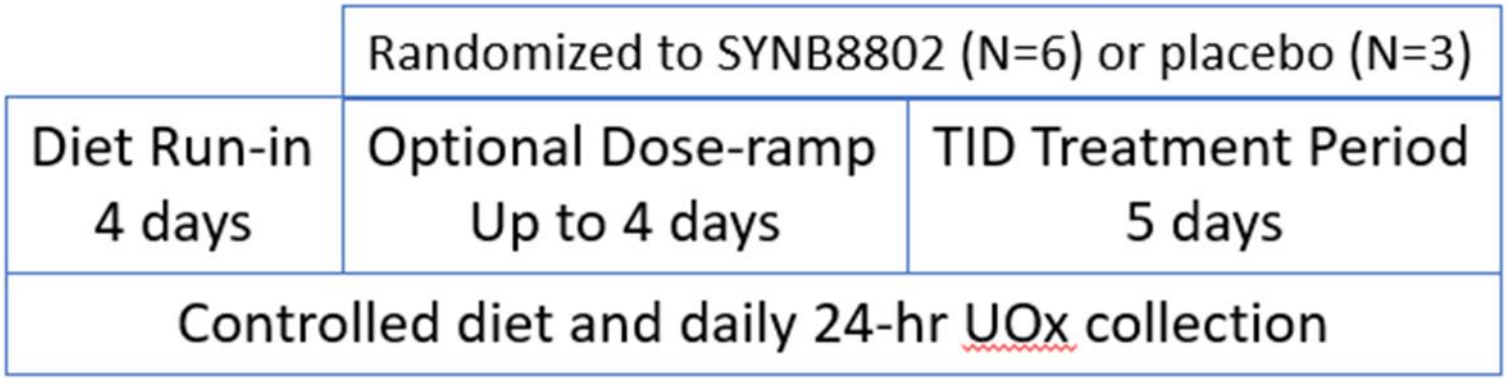
SYNB8802 Consumes Oxalate Throughout the GI Tract

Phase 1 Study Design

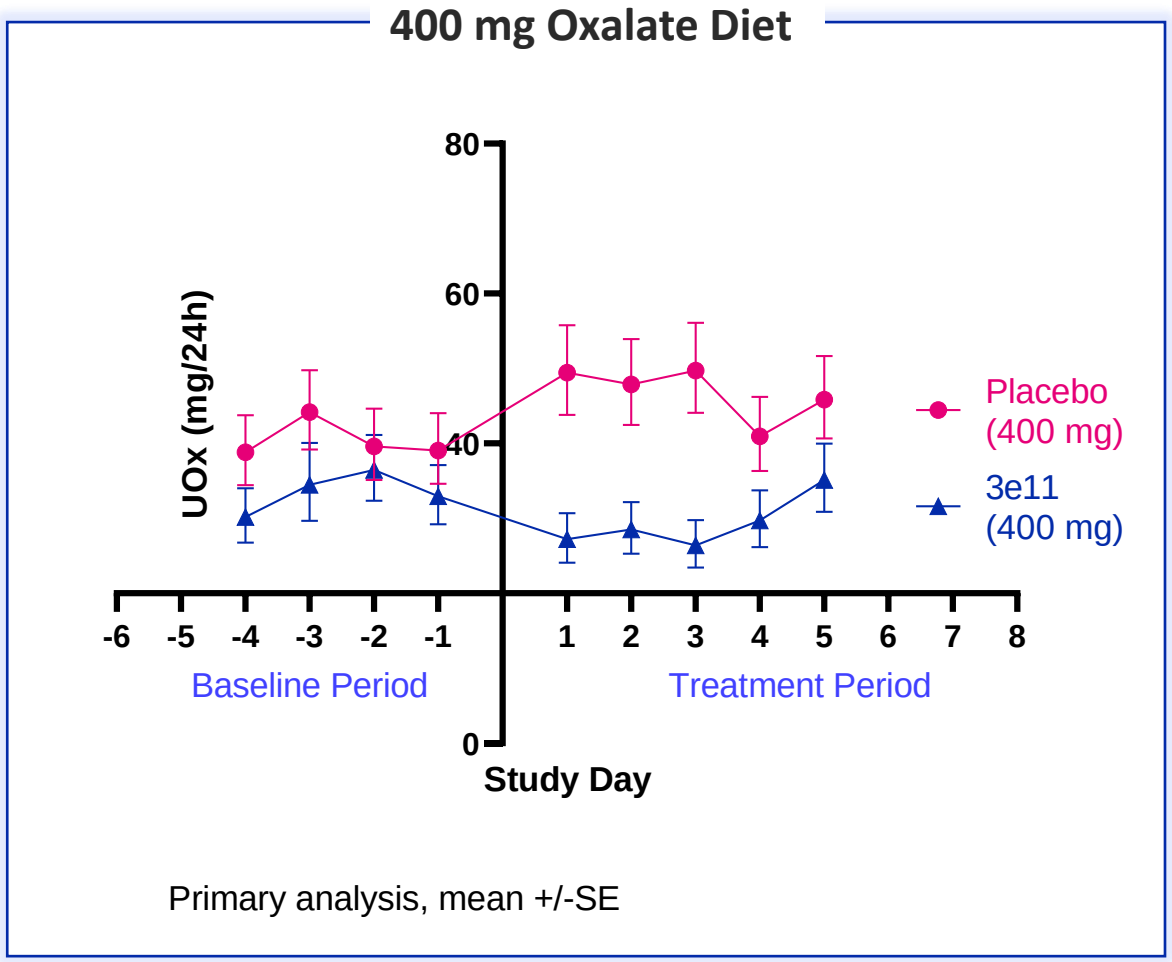
SYNB8802 is being investigated in an ongoing Phase 1a/b study

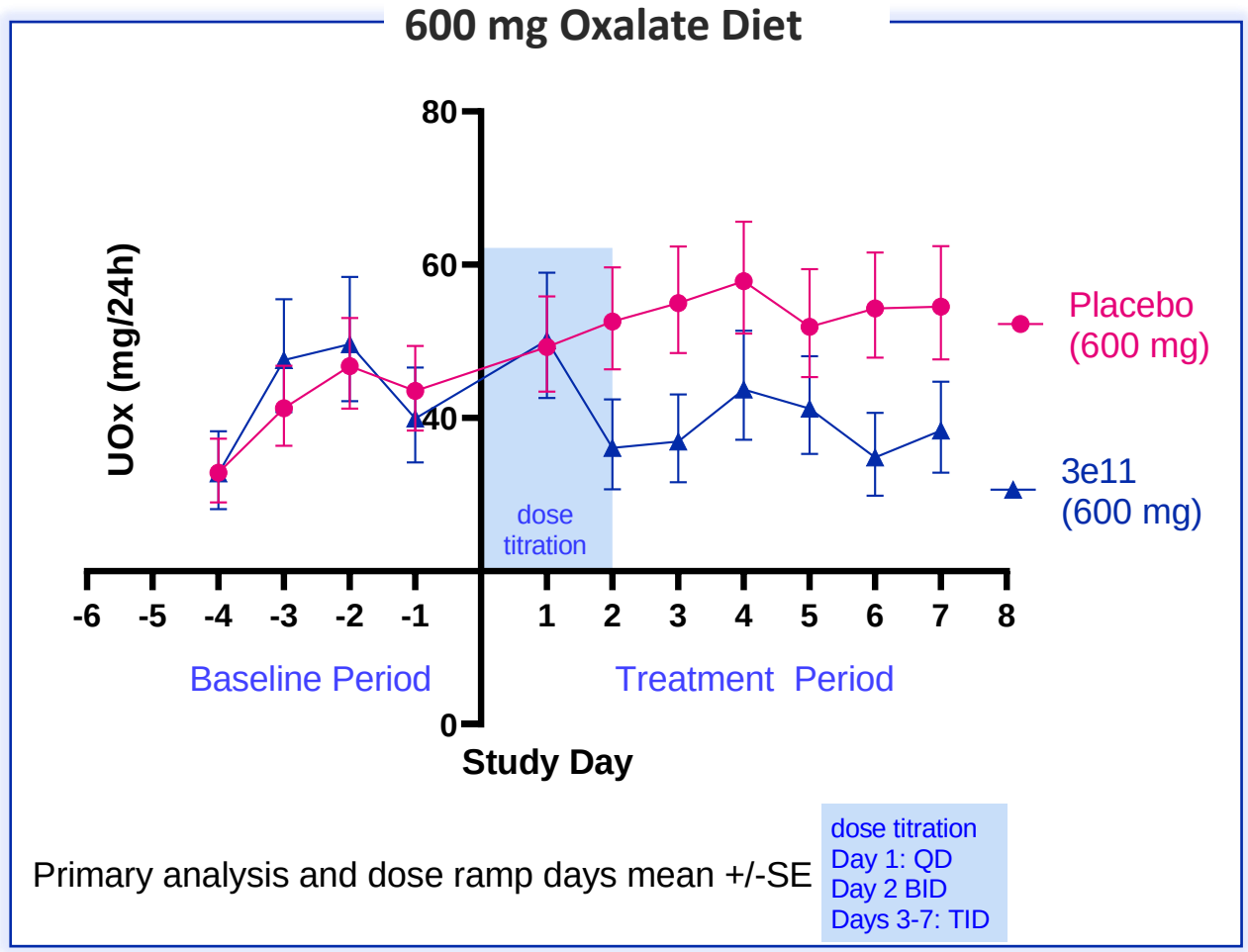
- In the Phase 1a part healthy volunteers consume a high oxalate (400-600mg/day), low calcium (400mg/day) diet and provide daily 24 hour urine collection and fecal samples
- Following a run in period, they are randomized to SYNB8802 or placebo
- Cohorts of N=9 (6 active: 3 placebo) are enrolled in a multiple ascending dose (MAD) study. Study doses range from $5x10^{10}$ to $6x10^{11}$ live cells, dosed TID with meals.
- Primary outcome is safety and tolerability; exploratory outcome includes pharmacodynamic effects of SYNB8802 on urine and fecal oxalate

Study Design



Separation of UOx in active and placebo groups started from the BID day and was maintained throughout dosing period

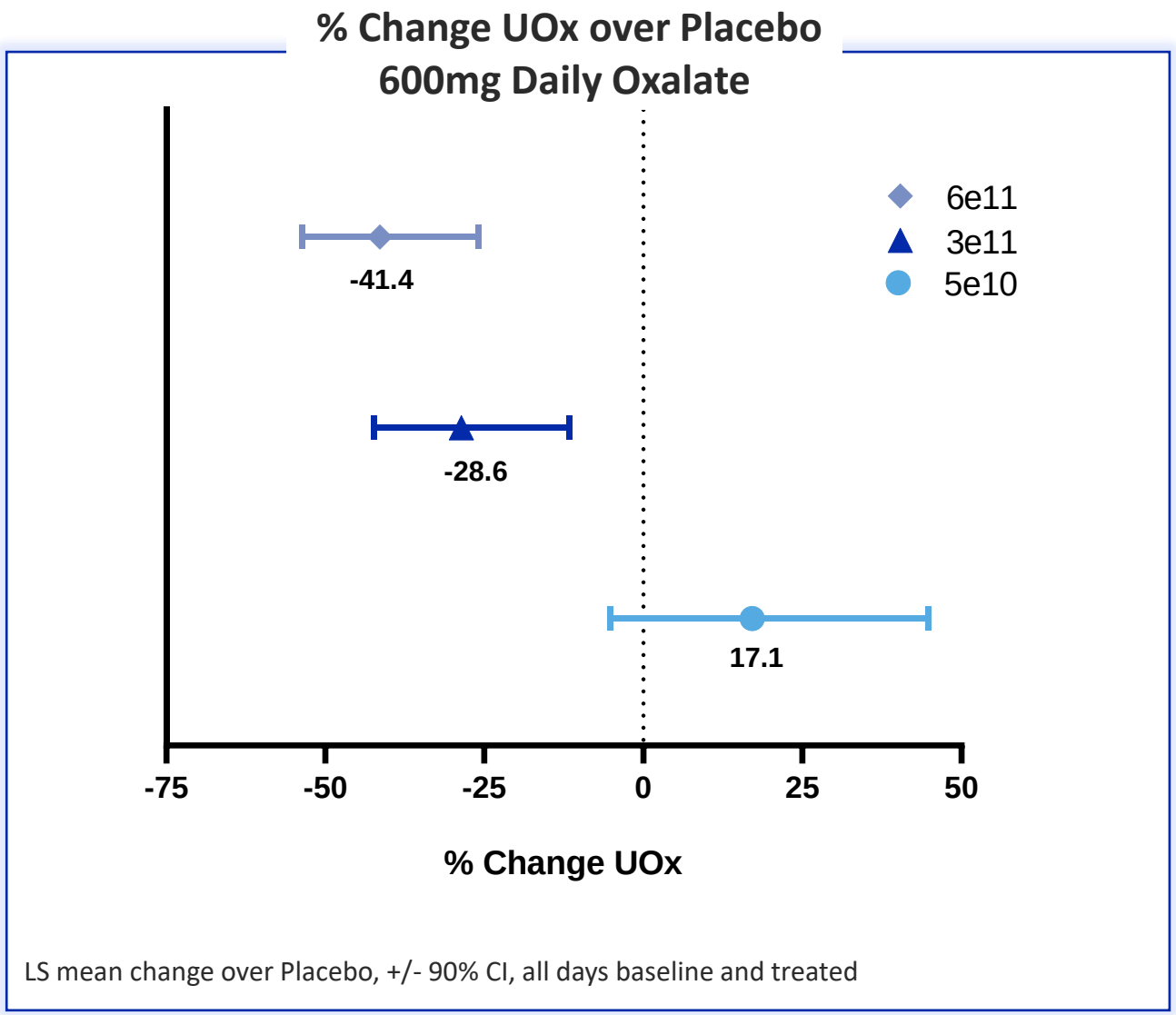




Dietary hyperoxaluria reaches steady state after 6 days of diet (on Day 2 of dosing)

SYNB8802 3e11 dose TID normalizes UOx levels

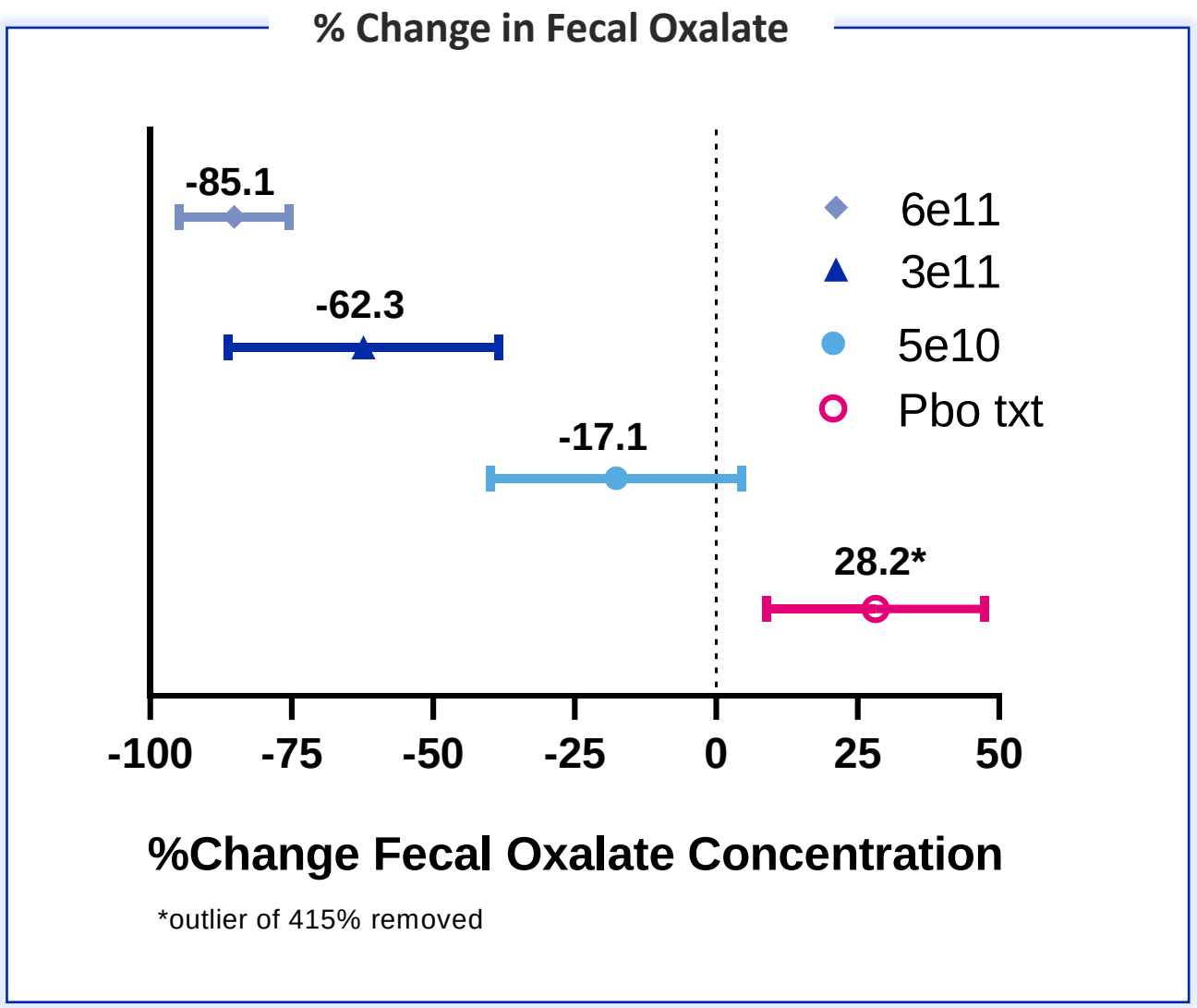
Dose-related Reduction of Urinary Oxalate at Well-tolerated Doses



LS mean change over Placebo, +/- 90% CI, all days baseline and treated

- SYNB8802 showed dose-related reduction of UOx
- SYNB8802 was generally well tolerated in healthy volunteers
- No serious or systemic adverse events were observed
- Most frequent AEs mild or moderate, transient, and GI-related
- A dose-ramp improved tolerability

Dose-related Reduction of Fecal Oxalate



- Total fecal oxalate was quantified using a high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS) method
- SYNB8802 led to dose-related reduction of fecal oxalate confirming that changes in UOx were related to consumption of oxalate by SYNB8802 in the GI tract

Conclusions

- There is an unmet medical need for pharmacological therapies in EH
- SYNB8802, an investigational synthetic biotic medicine, was safe and well-tolerated in healthy volunteers
- In a dietary-induced hyperoxaluria model in healthy volunteers SYNB8802 lead to a consistent and significant reduction of urinary oxalate
- SYNB8802 markedly reduced the amount of oxalate in feces in a dose-related manner, confirming strain ability to access dietary oxalate from within the gut
- SYNB8802 has achieved proof-of-mechanism
- Further clinical development as a potential treatment for EH is warranted