
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.
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

### SYNB8802 Design

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapeutic strategy</strong></td>
<td>Metabolite consumption: Engineered to Convert Oxalate to Formate for the Treatment of Enteric Hyperoxaluria</td>
</tr>
<tr>
<td><strong>Bacterial Chassis</strong></td>
<td><em>E. coli Nissle</em> (probiotic chassis organism)</td>
</tr>
<tr>
<td><strong>Effector(s)</strong></td>
<td>OxDC and associated components: Catalyzes conversion of oxalate to formate</td>
</tr>
<tr>
<td><strong>Pump</strong></td>
<td>OxLT: Pumps oxalate in &amp; formate out</td>
</tr>
<tr>
<td><strong>Switch</strong></td>
<td>FNR promoter: Inducer-promoter pair</td>
</tr>
<tr>
<td><strong>Safety Features</strong></td>
<td>Δ thyA: Controls growth so strain does not colonize</td>
</tr>
</tbody>
</table>
Pathophysiology of Enteric Hyperoxaluria

Dietary Sources of Oxalate

- Oxalate
- Hyperoxaluria
- Kidney stones

Oxalate absorption

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Absorption</th>
<th>SYNB8802 Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary Oxalate</td>
<td>Healthy state</td>
<td>Healthy people absorb ~10% of dietary oxalate, mostly via stomach and small intestine</td>
</tr>
<tr>
<td></td>
<td>Disease state</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients absorb ~20-30% of dietary oxalate, through entire GI tract including colon

SYNB8802 Consumes Oxalate Throughout the GI Tract
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 $5 \times 10^{10}$ to $6 \times 10^{11}$ live cells, dosed TID with meals.
- Primary outcome is safety and tolerability; exploratory outcome includes pharmacodynamic effects of SYNB8802 on urine and fecal oxalate
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

• 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
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.

* outlier of 415% removed
Conclusions

• There is an unmet medical need for pharmacological therapies in EH

• SYN8802, an investigational synthetic biotic medicine, was safe and well-tolerated in healthy volunteers

• In a dietary-induced hyperoxaluria model in healthy volunteers SYN8802 lead to a consistent and significant reduction of urinary oxalate

• SYN8802 markedly reduced the amount of oxalate in feces in a dose-related manner, confirming strain ability to access dietary oxalate from within the gut

• SYN8802 has achieved proof-of-mechanism

• Further clinical development as a potential treatment for EH is warranted