In Silico Simulation to Predict Activity of a Synthetic Biotic, SYNB8802, in Healthy Volunteers and Patients with Enteric Hyperoxaluria

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Synlogic, Inc.
**Enteric Hyperoxaluria Disease Pathogenesis**

Dietary Oxalate Distributes Throughout the Body Leading to Renal Complications

<table>
<thead>
<tr>
<th>Dietary Sources of Oxalate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxalate</td>
</tr>
<tr>
<td>Hyperoxaluria</td>
</tr>
<tr>
<td>Kidney stones</td>
</tr>
</tbody>
</table>

### Enteric Hyperoxaluria

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Pathogenic hyperabsorption of dietary oxalate, often accompanies bowel disease or bariatric surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Oxalate Levels</td>
<td>45 – 130 mg / 24 hrs (up to 3x normal)</td>
</tr>
<tr>
<td>Onset</td>
<td>Adult</td>
</tr>
<tr>
<td>Clinical Mgmt</td>
<td>Limited nutrition options; treatment of kidney stones as they occur; nephrocalcinosis; dialysis</td>
</tr>
<tr>
<td>U.S. Epidemiology</td>
<td>200,000 – 250,000</td>
</tr>
</tbody>
</table>
SYNB8802 Design
Engineered to Convert Oxalate to Formate for the Treatment of Enteric Hyperoxaluria

<table>
<thead>
<tr>
<th>Component</th>
<th>Approach</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial Chassis</td>
<td><em>E. coli</em> Nissle</td>
<td>Decades of human use</td>
</tr>
<tr>
<td>Switch</td>
<td>FNR promoter</td>
<td>Inducer-promoter pair</td>
</tr>
<tr>
<td>Pump</td>
<td>OxLT</td>
<td>Pumps oxalate in &amp; formate out</td>
</tr>
<tr>
<td>Effector 1</td>
<td>OxdC and associated components</td>
<td>Catalyzes conversion of oxalate to formate</td>
</tr>
<tr>
<td>Safety Features</td>
<td>Δ thyA</td>
<td>Controls growth</td>
</tr>
</tbody>
</table>

Switch

FNR promoter

Pump

OxLT

OxdC and associated components

Effector 1

OxdC

Safety Features

Δ thyA

Component Approach Benefit

Bacterial Chassis *E. coli* Nissle Decades of human use

Switch FNR promoter Inducer-promoter pair

Pump OxLT Pumps oxalate in & formate out

Effector 1 OxdC and associated components Catalyzes conversion of oxalate to formate

Safety Features Δ thyA Controls growth
*In Silico Simulation (ISS): a Mechanistic Modeling Approach*

Physiological Basis for Gastrointestinal Transit and Strain Activity

**Strain Activity in GI**

- **Stomach**
  - Ox
  - SYN
  - Consumption

- **Small intestine**
  - Ox
  - SYN
  - Consumption

- **Colon**
  - Ox
  - SYN
  - Consumption

**Strain Transit**

- **Stomach**
- **Small intestine**
- **Colon**

**Diagram:**

- Chyme progression

**Graph:**

- Strain (x10^11 Cells)
- Time (hr)

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In Silico Simulation (ISS): a Mechanistic Modeling Approach

Two Components: Gastrointestinal Strain Activity and Human Disease Biology
Establishing Confidence in the *In Silico* Simulation (ISS) Approach
Validation Using Clinical Data from Allena Oral Enzyme Study

Phase 1 study by Allena of their oral enzyme for oxalate degradation (ALLN-177)

The study began with a 3-day period on a high-oxalate low-calcium (HOLC) diet, before the drug was administered.

Simulations of the disease biology model agree with the observed impact of high dietary oxalate.

Predicting Synthetic Biotic Potential

Urinary Oxalate Reduction as a Function of SYNB8802 Dose

In Silico Simulations (ISS) predict a change in baseline of the clinical endpoint (urinary oxalate)

Urinary oxalate lowering by various doses can be compared to target product profile to inform candidate selection
Enteric Hyperoxaluria: Hyperabsorption of Dietary Oxalate Leading to Renal Complications

SYNB8802 Predicted to Meaningfully Lower Urinary Oxalate in EH Patients

SYNB8802 Phase 1 Clinical Study Initiated Ahead of Schedule