Transforming Medicine Through Synthetic Biology

Proof of Concept for SYNB8802 for Enteric Hyperoxaluria
Top-Line Results from Phase 1b Study

December 15, 2022
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Speakers

Aoife Brennan, MB ChB  
President & CEO

Kyle Wood, MD  
Associate Professor, Urology, University of Alabama at Birmingham

Caroline Kurtz, PhD  
Chief Development Officer

Dave Hava, PhD  
Chief Scientific Officer
Opening Remarks

Dr. Aoife Brennan
President & CEO
Enteric Hyperoxaluria & the Burden of Recurrent Kidney Stones

POC Achieved with Urinary Oxalate Lowering from Phase 1b Study

SYNB8802: Potential for First Approved Treatment for Enteric Hyperoxaluria
Enteric Hyperoxaluria & Recurrent Kidney Stones: An Overview

Dr. Kyle Wood
Associate Professor, Urology
University of Alabama at Birmingham
Enteric Hyperoxaluria (EH) & Recurrent Kidney Stones

Dietary Oxalate*: plant-derived; in excess, absorbed from GI tract into circulation

Oxalate crystals damage kidneys, impair renal function

Can lead to CKD, ESRD, nephrocalcinosis, systemic oxalosis

Circulating oxalate results in crystal formation and chronic, recurrent kidney stones

Excruciating Pain

Higher urinary oxalate (UOx) levels predict stone events in EH patients, with ~20% decrease in UOx associated with ~25% reduction in annual stone event risk¹

Urinary Oxalate Levels – and GI Malabsorption - Also Increase Risk for CKD

**Findings**
- Largest population-based study on the relationship of urinary oxalate levels and incident CKD to date
  - Dataset includes 426,896 patients without CKD at baseline and includes 12,522 with GI malabsorption
- Among patients without a history of CKD, higher urine oxalate is associated with higher risk of developing incident CKD
  - Prevalence of CKD was twice as high in patients with UOx ≥ 80 mg/d compared with < 20 mg/d
  - Risk is substantially higher among those with an underlying malabsorptive condition

**Methodology**
- Largest population-based study on the relationship of urinary oxalate levels and incident CKD to date
  - Dataset includes 426,896 patients without CKD at baseline and includes 12,522 with GI malabsorption

**Puurunen et al, Data presented at ASN in November 2021**

![Incident CKD Risk vs. Baseline Urinary Oxalate & GI Malabsorption](image-url)
# Hyperoxaluria May Have Genetic or Enteric Etiology

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Primary Hyperoxaluria (PH)</th>
<th>Enteric Hyperoxaluria (EH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology</td>
<td>Rare genetic condition</td>
<td>Dietary oxalate hyperabsorption</td>
</tr>
<tr>
<td>Onset</td>
<td>Pediatric</td>
<td>Adult</td>
</tr>
<tr>
<td>Etiology</td>
<td>Genetic liver enzyme deficiency</td>
<td>Underlying insult to bowel: including IBD, bariatric surgery, other chronic GI conditions</td>
</tr>
</tbody>
</table>

**UOx. Levels**
- 90 – 500 mg / 24 hrs (~10x normal) for Primary Hyperoxaluria (PH)
- 45 – 130 mg / 24 hrs (~3x normal) for Enteric Hyperoxaluria (EH)
Clinical Path: Differential Diagnosis to Enteric Hyperoxaluria

Clinical Presentation
- High Risk of Recurrent Kidney Stones
  (“annual stone formers”)¹

Stone Composition
- Calcium Oxalate Stones¹
- Other

Etiology of Oxalate Malabsorption
- Genetic
- Idiopathic
- Enteric²

Source of GI Injury
- Surgery
- IBD/Crohn’s
- Other Medical² (e.g. CF)

Estimated U.S. Population:¹,²

| (>3mm) x (~75%) x (~10%) | = ~200,000-300,000 |

¹. Ziemba 2017 ². Synlogic 2022 Qualitative Market Research & Real World Evidence analyses by Trinity Partners

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Today, Treatment for EH is Limited to Dietary Restrictions

<table>
<thead>
<tr>
<th>Stone Etiology</th>
<th>Current Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Volume</td>
<td>Increase fluid intake</td>
</tr>
<tr>
<td>Hypocitraturia</td>
<td>Citrate supplements</td>
</tr>
<tr>
<td><strong>Hyperoxaluria</strong></td>
<td>Low oxalate diet, calcium supplements, change IBD Tx (if applicable)</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>May include low sodium diet or thiazide diuretics</td>
</tr>
<tr>
<td>High Uric Acid</td>
<td>Increase fluid intake</td>
</tr>
</tbody>
</table>

- Modest efficacy
- Avoids healthy foods (e.g. green vegetables)
- Calcium supplements can exacerbate hypercalciuria
- Treatment is even less effective for enteric hyperoxaluria

Source: Synlogic 2022 Qualitative Market Research, In-depth interviews with U.S. stone clinic physicians treating patients with recurrent stones
Proof of Concept
Data for SYNB8802

Caroline Kurtz, PhD.
Chief Development Officer
SYNB8802: Consuming Oxalate in the GI Tract to Prevent Absorption

**Our Approach**
- Oral therapy
  - Consume oxalate in the GI tract
  - Reduce oxalate in the urine

**Precision Engineering of Probiotic**
- Scaae3, OxdC, Frx
- Oxalate
- Formate

**Consume Oxalate Throughout GI Tract**

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## SYNB8802 Differentiation: Targeting Oxalate Throughout the GI Tract

<table>
<thead>
<tr>
<th>Oxalate Absorption Site</th>
<th>Absorption</th>
<th>Sites of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary Oxalate</td>
<td></td>
<td>synlogic</td>
</tr>
<tr>
<td>Stomach</td>
<td>Healthy</td>
<td>populated</td>
</tr>
<tr>
<td></td>
<td>State</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease</td>
<td>populated</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>Healthy</td>
<td>populated</td>
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<td></td>
<td>State</td>
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<tr>
<td></td>
<td>Disease</td>
<td>populated</td>
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<tr>
<td>Colon</td>
<td>Healthy</td>
<td>populated</td>
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<td></td>
<td>State</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease</td>
<td>populated</td>
</tr>
</tbody>
</table>

- SYNB8802 consumes oxalate throughout the GI tract
- Extends duration of action, increasing oxalate-lowering efficacy potential

**GI=gastrintestinal**
SYNB8802-CP-002 Phase 1b Study Design

**Randomized, placebo-controlled**
parallel arm, in-patient study

**Primary endpoint:** safety and tolerability

**Controlled diet:** Standardized dietary oxalate intake¹

**Patient population:** prior Roux-en-Y gastric bypass, with abnormal GI physiology typical of EH

**Disposition:** 11 patients, 7 received SYNB8802 and 4 received placebo, 1 patient discontinued during placebo treatment

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<table>
<thead>
<tr>
<th>Day</th>
<th>-3</th>
<th>-2</th>
<th>-1</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<th>5</th>
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<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>Run-In</td>
<td>Treatment</td>
<td>Treatment</td>
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<tr>
<td><strong>Placebo</strong></td>
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</tbody>
</table>

**Treatment:**
- Placebo 1 x 10¹¹
- Treatment 3 x 10¹¹

**Frequency**

**24h urine**

**Plasma**

**Fecal**

¹ Meals contained an average level of oxalate and low calcium, divided over 3 meals a day during in patient stay
Urinary oxalate levels at screening were consistent with diet and patient population (at ~30), and generally remained consistent with baseline values during the treatment period for placebo patients.

For both treatment periods, at both dose levels, dose-related reduction in urinary oxalate levels in response to SYNB8802 were observed.

* Per pharmacometrics analysis including data from 7 patients receiving SYNB8802 at both the $1 \times 10^{11}$ and $3 \times 10^{11}$ dose levels and 4 patients receiving placebo
POC Achieved by Lowering of Urinary Oxalate

Findings demonstrate that by consuming oxalate in the GI tract to prevent its absorption, SYNB8802 resulted in changes in urinary oxalate in gastric bypass patients.

Data analyzed using a pharmacometric model that enabled use of data from all patients on all study days.

SYNB8802 Urinary Oxalate Lowering vs. Baseline Compared to Placebo*

Phase 1b SYNB8802-CP-002 Study

-28.3
-37.8

* Per pharmacometrics analysis including data from 7 patients receiving SYNB8802 at both the 1x10^{11} and 3x10^{11} dose levels and 4 patients receiving placebo.

CFB=change from baseline, CFP=change from placebo.
Safety and Tolerability Findings
SYNB8802 – Proof of Concept from 002 Study Top-Line Results

- SYNB8802 was well tolerated, with no serious adverse events
- The most common adverse events were GI-related, mild, and transient
- The GI-related AEs occurred at a similar frequency in active and placebo groups
- One patient in the placebo group discontinued during dosing due to the need for antibiotics
• **EH:** Well-recognized burden of recurrent stones, with no FDA approved specific medical treatment options

• **SYNB8802:** POC data shows potential for a **powerfully differentiated** treatment
  - Dose related lowering of UOx established in patients with gastric bypass
  - Validated mechanism of metabolizing oxalate in GI tract to prevent its absorption
  - Both $1 \times 10^{11}$ and $3 \times 10^{11}$ doses exceeded -20% threshold for clinically meaningful reduction in recurrent stone risk, with urinary oxalate lowering of -38% vs. placebo at the $3 \times 10^{11}$ dose TID

• **Enriched, concentrated target patient population:** EH with highly recurrent stones
  - Profoundly affected by pain, interventions of recurrent stones
  - Connected to specialists (e.g. stone clinics)

• **Path forward:** plan to advance towards registrational trial, likely clinical endpoint of stone disease progression
Cross-Platform Implications

Dave Hava, PhD
Chief Scientific Officer
SYNB8802 POC: A Milestone for Synthetic Biotic Platform

✓ 3rd positive data readout in 4Q 2022, following proof of concept in PKU, and proof of mechanism in HCU

✓ 2nd disease state with POC achieved

✓ Platform experience accelerates learnings, for dosing, tolerability
Concluding Remarks

Dr. Aoife Brennan
President & CEO
## Advancing a New Class of Biotherapeutics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
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</tr>
<tr>
<td>Phenylketonuria (PKU)</td>
<td>SYNB1934*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homocystinuria (HCU)</td>
<td>SYNB1353</td>
<td>FT</td>
<td>ODD</td>
</tr>
<tr>
<td>Enteric Hyperoxaluria</td>
<td>SYNB8802</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gout</td>
<td>SYNB2081</td>
<td></td>
<td></td>
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<tr>
<td><strong>Immunology</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Inflammatory Bowel Disease (IBD)</td>
<td></td>
<td>FT</td>
<td></td>
</tr>
<tr>
<td>IBD Program - Single Target</td>
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</tbody>
</table>

*First generation SYNB1618 for PKU received both ODD and FT designations by the FDA and orphan medicinal product designation by the EMA.

FT = Fast Track granted by FDA  
ODD = Orphan Drug Designation granted by FDA

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Available For Questions

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Kyle Wood, MD
Associate Professor, Urology, University of Alabama at Birmingham

Michael Jensen
Chief Financial Officer

Molly Harper
Chief Business Officer

Antoine Awad
Chief Operating Officer
Thank You