SYNB1353 for Homocystinuria (HCU)

Findings from Proof of Mechanism Phase 1 Study in Healthy Volunteers,

November 30, 2022
SYNB1353: Potential for a Breakthrough in HCU
Novel Mechanism Targets GI-Based Methionine for a Differentiated Treatment Approach

Rare metabolic disease with risks of acute and chronic complications - and severe need for new treatment options

- Elevated homocysteine (tHcy) in HCU can cause acute thromboemboli and chronic multisystem complications
- Methionine restricted diet is the mainstay of treatment but majority of patients above targets for tHcy
- Direct synergies with PKU for clinical development, commercial operations: shared KOLs, metabolic clinics, connected patient groups

SYNB1353 offers potential 1st-of-its-kind treatment option that works with HCU patients’ lives

- A genetically engineered probiotic, SYNB1353 is designed to consume methionine, a precursor to homocysteine
- Patients and KOLs share enthusiasm for target product profile: safe, orally-administered, convenient – and viable across age groups
- Proof of mechanism established: Phase 1 results in HVs confirmed that SYNB1353 can consume methionine in the GI tract and lower absorption
- Safety, tolerability profile consistent with other Synlogic programs: adverse events were all mild to moderate, no SAEs

Forward Development Planning Underway

- Planning for ph. 2 study in HCU patients underway
- CMC activities to support scale-up for phase 2 and registration studies underway

tHcy = total homocysteine
HCU: An Inborn Error of Metabolism Resulting in Multisystem Burden

CBS Enzyme Deficiency Results in Accumulated Homocysteine

Diet
Methionine
Homocysteine
Folate / B_{12} Dependent
Caused by mutations in Cystathionine β-synthase (CBS) enzyme

Cystathionine
Cysteine

Acute Risks, Progressive Complications

Central Nervous System
Developmental delays, intellectual disabilities, neuropsych/psychosocial challenges

Ophthalmological System
Dislocation or displacement of the natural lens

Circulatory System
Thromboembolism, resulting in stroke

Skeletal System
Reduction of bone mass and quality leading to scoliosis and osteoporosis

Estimated prevalence for CBS or “Classical” HCU, US & Europe: ~5,000

“I think about my HCU patients like potential time bombs due to their risk of acute events”
- HCU KOL

Total Homocysteine (tHcy): Clinical Biomarker to Manage HCU
Difficulties with Current Standard of Care Leave Levels Uncontrolled for Most Living with HCU

HCU Treatment Goal: Reduce, Control Total Homocysteine (tHcy)

Predictor of outcomes, treatment target
Treatment of HCU focuses on tHcy control;¹ Loss of tHcy control in later life is associated with serious complications²

“Lower is better”
Guidelines recognize -20% for clinical response¹
Normal (healthy) range: 5-15 μmol/L
In HCU, levels can be >200 μmol/L
Guidelines recommend <100 μmol/L if possible¹

Regulatory precedent as basis for approval
Per indication language for Cystadane® (betaine)³

Current Treatment Options Leave Majority with Uncontrolled tHcy

1) Low-methionine diet (low in natural protein), along with supplemental formula (Met-free L-AA mixture)
   • Complexity, difficulty yields poor adherence¹

2) Betaine (Cystadane®)
   • Fishy taste/odor hurts compliance¹

Majority of patients remain with tHcy levels far above goals⁴, at risk for both acute and chronic complications

¹. Morris AAM, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency
SYNB1353 for HCU: Targeting Methionine for a New Approach

Developed from Ginkgo Collaboration

- Optimized, engineered components identified:
  - MetDC methionine decarboxylase from protein engineering screen
  - MetP transporter from metagenomic screen

A Methionine-Consuming Synthetic Biotic

- Engineered probiotic E. coli Nissle, designed to metabolize methionine (Met) via the methionine decarboxylase (MetDC) pathway, preventing its conversion into homocysteine
- Converts Met to 3-methylthiopropylamine (3-MTP); YjeH gene deleted to prevent the release of methionine once it enters the cell

### A Differentiated Biotherapeutic for HCU

SYNB1353 Potentially Integrates Efficacy, Safety, Convenience to Enable Use Across Ages

<table>
<thead>
<tr>
<th><strong>Dosing &amp; Administration</strong></th>
<th><strong>Safety Considerations</strong></th>
<th><strong>Potentially Applicable Patient Population</strong></th>
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</thead>
<tbody>
<tr>
<td>Pegibatinase (TVT-058)</td>
<td>ERT mechanism associated with potential for allergic/immunological challenges</td>
<td><img src="img1" alt="1.5 mg/kg biweekly Injection" /> <img src="img2" alt="1.35 mg/kg weekly Injection" /> <img src="img3" alt="Sachet of lyophilized powder mixed with ~3 oz liquid taken with meals" /> <img src="img1" alt="1.5 mg/kg biweekly Injection" /> <img src="img2" alt="1.35 mg/kg weekly Injection" /> <img src="img3" alt="Sachet of lyophilized powder mixed with ~3 oz liquid taken with meals" /></td>
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<tr>
<td><strong>Phase 1/2</strong></td>
<td>Transient/reversible, mild GI-related side effect</td>
<td><img src="img1" alt="1.5 mg/kg biweekly Injection" /> <img src="img2" alt="1.35 mg/kg weekly Injection" /> <img src="img3" alt="Sachet of lyophilized powder mixed with ~3 oz liquid taken with meals" /> <img src="img1" alt="1.5 mg/kg biweekly Injection" /> <img src="img2" alt="1.35 mg/kg weekly Injection" /> <img src="img3" alt="Sachet of lyophilized powder mixed with ~3 oz liquid taken with meals" /></td>
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SYNB1353

✓ Phase 1, Proof of Mechanism

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* >12 in UK/Australia only, >18 in US [https://www.aeglea.com/clinical-trials/](https://www.aeglea.com/clinical-trials/)
  1. [https://hcuconnection.com/trials/](https://hcuconnection.com/trials/)
  2. [https://www.aeglea.com/clinical-trials/](https://www.aeglea.com/clinical-trials/)
SYNB1353: Program Progress to Date

Valuated Preclinically in Multiple Models

**Hcy Lowering in CBS-Knockdown Mice**

- Vehicle
- EcN
- SYNB1353

**Met and Hcy Lowering in Met-Challenged NHPs**

- Vehicle
- SYNB1353

*Similar design and model as used in Phase 1 healthy volunteer (HV) study*

**Rapid Progress: Candidate to POM in ~12 Months**

- **November 2021**
  - Candidate announced
  - Preclinical data presented at ICIEM 2021

- **July 2022**
  - First dose in Phase 1 HV Study

- **August 2022**
  - Granted Fast Track Designation by FDA

- **November 2022**
  - Proof of Mechanism achieved in Phase 1

*Similar design and model as used in Phase 1 healthy volunteer (HV) study*
Study Design for SYNB1353 Phase 1 in Healthy Volunteers

Methionine Meal Challenge Used to Simulate Severely Elevated Methionine, Homocysteine in HCU

**Objectives:**
- To assess the safety, tolerability, and PD of SYNB1353 in HVs, in a dietary model of homocystinuria (HCU), and to evaluate two different formulations at the maximum dose.

**Endpoints for Each Cohort & Dose Level Studied:**
- Safety and tolerability
- Clearance of SYNB1353 by day 28 (measured in feces)
- Plasma methionine, measured over 24 hours as area under the curve (AUC) following a methionine meal challenge
SYNB1353: Proof-of-Mechanism Achieved via Met Meal Challenge

Change vs. Baseline, Measured Following a Methionine Meal Challenge as Area Under the Curve (AUC) over 24 hours

Plasma Methionine

Data provided proof of mechanism by demonstrating the effects of SYNB1353’s GI-based metabolism of methionine on plasma methionine, in healthy volunteers

LS mean change, 95% CI
*p < 0.05
Form = formulation; placebo n=8, 1x10^{12} form 1 n=6, 1x10^{12} form 2 n=5
SYNB1353 was generally well-tolerated in healthy volunteers.

There were no serious adverse events (SAEs)

Adverse events (AEs) were all mild to moderate, transient, and predominantly GI in nature.
  • One subject discontinued dosing due to an adverse event.

Frequency and severity of GI-related AEs were similar in the active and control group
  • 7 of 22 SYNB1353 compared to 3 of 8 placebo subjects had at least 1 GI-related AE

All subjects completing the 28-day analysis cleared SYNB1353 in feces
The goal of treatment in HCU is to lower plasma levels of total homocysteine (tHcy), reducing the risk of acute and chronic, multisystem complications. tHcy has been accepted as a regulatory endpoint for efficacy in HCU patients.

SYNB1353 is an engineered probiotic designed to consume methionine, a precursor to homocysteine, in the GI tract and lower total plasma homocysteine for patients with HCU.

SYNB1353 has achieved FDA Fast Track designation (August 2022), and Orphan Drug designation (November 2022).

SYNB1353 has demonstrated methionine consumption in the GI tract of healthy volunteers, resulting in a lowering of plasma methionine, assessed following a meal challenge to elevate methionine levels.

SYNB1353 was well tolerated in healthy volunteers with GI adverse event rates and severity similar between active and placebo groups.

Based on this proof of mechanism in healthy volunteers, SYNB1353 will be advanced to a Phase 2 proof of concept study in patients with HCU.
Thank You