

# synlogic

A photograph of three scientists in a laboratory setting. They are wearing white lab coats with 'synlogic' logos and safety glasses. One scientist is seated in the foreground, while two others stand behind him, engaged in conversation. The background shows laboratory equipment and shelves.

## **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

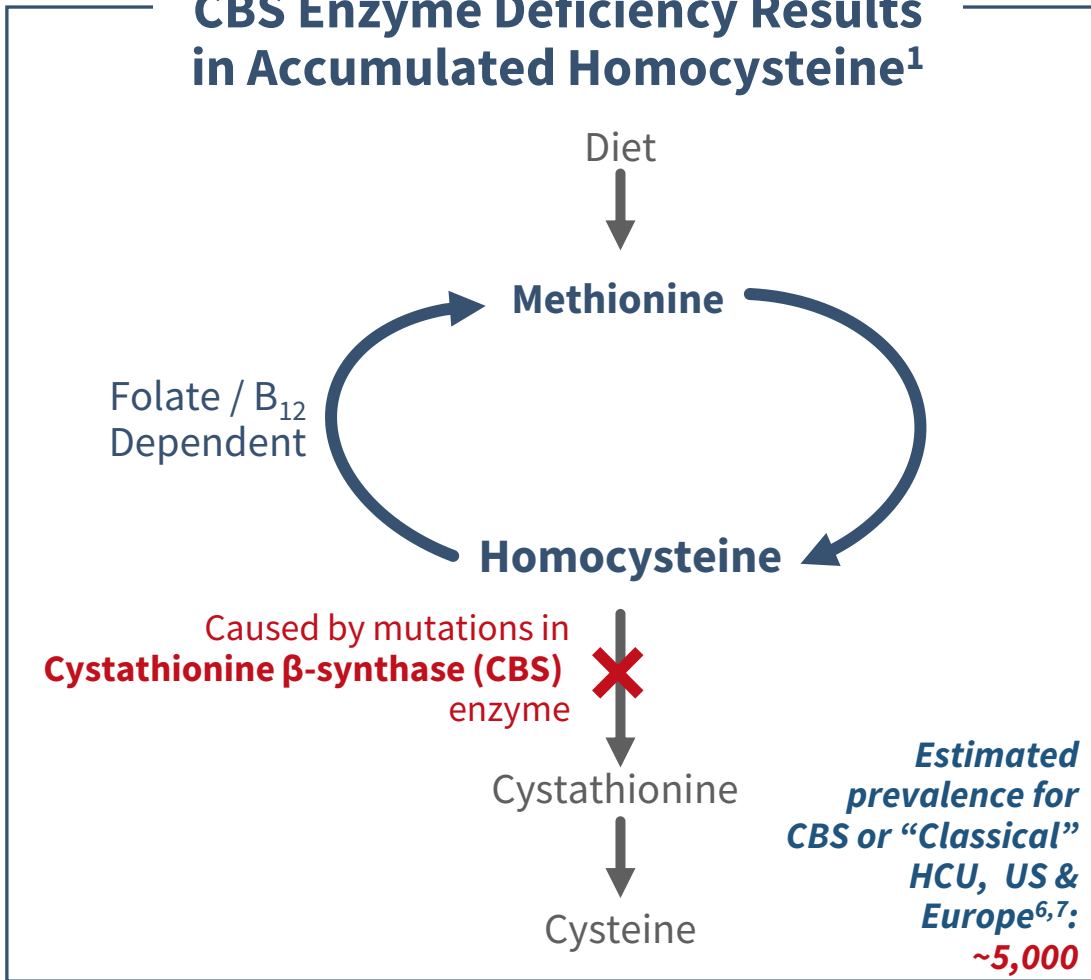
- A genetically engineered probiotic, **SYNB1353 is designed to consume methionine, a precursor to homocysteine**
- Patients and KOLs share enthusiasm for target product profile: **safe, orally-administered, convenient – and viable across age groups**
- **Proof of mechanism established:** Phase 1 results 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

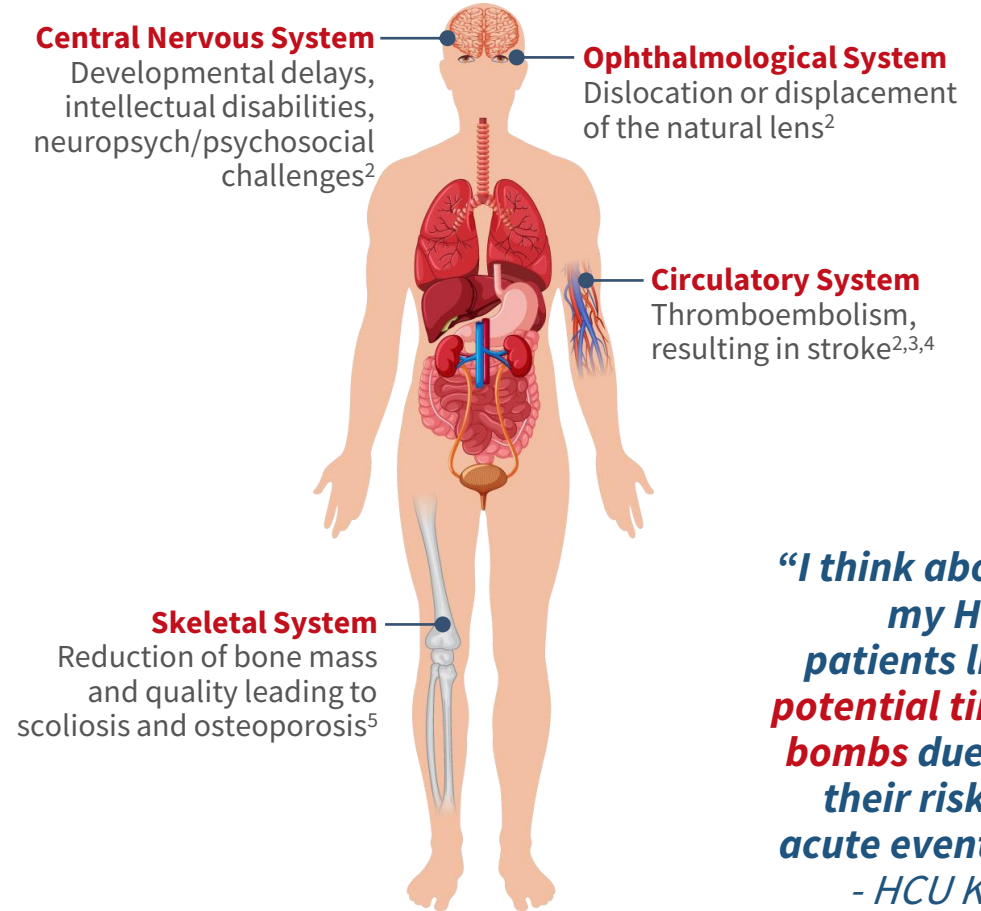
- **Planning for ph. 2 study in HCU patients underway**
- CMC activities to support scale-up for phase 2 and registration studies underway

# HCU: An Inborn Error of Metabolism Resulting in Multisystem Burden

## CBS Enzyme Deficiency Results in Accumulated Homocysteine<sup>1</sup>



## Acute Risks, Progressive Complications



1. Development of an Investigational Methionine-consuming Synthetic Biotic Medicine (SYNB1353) for the Treatment of Homocystinuria, International Congress of Inborn Errors of Metabolism, November 23, 2021; 2. Mudd SH. Disorders of transulfuration. In: Scriver CR (ed). *The Metabolic and Molecular Bases of Inherited Disease*, 8<sup>th</sup> ed. McGraw-Hill: New York, 2001, pp 2007–2205; 3. Saposnik G, et al. Heart Outcomes Prevention Evaluation 2 Investigators. Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from the HOPE 2 trial. *Stroke*. 2009;40(4):1365-1372; 4. Ding R, et al. The association of cystathionine β synthase (CBS) T833C polymorphism and the risk of stroke: a meta-analysis. *J Neurol Sci*. 2012;312(1-2):26-30; 5. reviewed in: Saito M, Marumo K. The Effects of Homocysteine on the Skeleton. *Curr Osteoporos Rep*. 2018;16(5):554-560. 6. Weber Hoss GR, Sperb-Ludwig F, Schwartz IVD, Blom HJ. Classical homocystinuria: A common inborn error of metabolism? An epidemiological study based on genetic databases. *Mol Genet Genomic Med*. 2020 Jun;8(6):e1214. doi: 10.1002/mgg3.1214. Epub 2020 Mar 30. PMID: 32232970; PMCID: PMC7284035. 7. Synlogic Data on File: Key Opinion Leader Conversations 2021-2022.

# 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;<sup>1</sup> Loss of tHcy control in later life is associated with serious complications<sup>2</sup>

**“Lower is better”**

Guidelines recognize -20% for clinical response<sup>1</sup>

Normal (healthy) range: 5-15  $\mu\text{mol/L}$

In HCU, levels can be  $>200 \mu\text{mol/L}$

Guidelines recommend  $<100 \mu\text{mol/L}$  if possible<sup>1</sup>

### Regulatory precedent as basis for approval

Per indication language for Cystadane<sup>®</sup> (betaine)<sup>3</sup>

## 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 adherence<sup>1</sup>

**2) Betaine (Cystadane<sup>®</sup>)**

- Fishy taste/odor hurts compliance<sup>1</sup>



Majority of patients remain with tHcy levels far above goals<sup>4</sup>, at risk for both acute and chronic complications

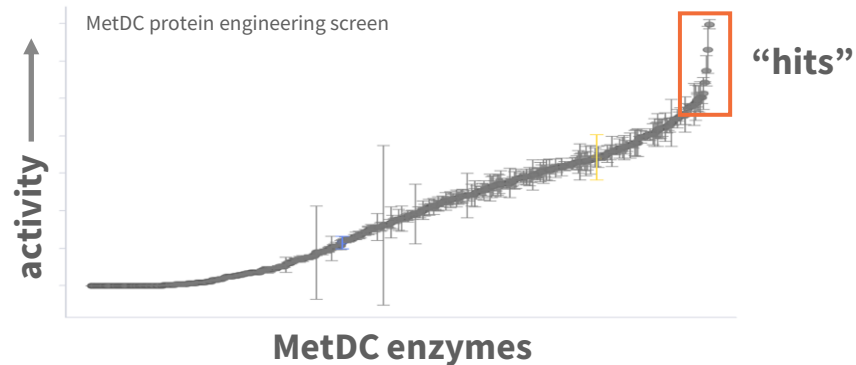
1. Morris AAM, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency

2. Walter 1998 3.. U.S. Prescribing Information for Cystadane<sup>®</sup> (betaine) 4. De Biase et al. 2020 & Synlogic patient & KOL Insights

# SYNB1353 for HCU: Targeting Methionine for a New Approach

## Developed from Ginkgo Collaboration

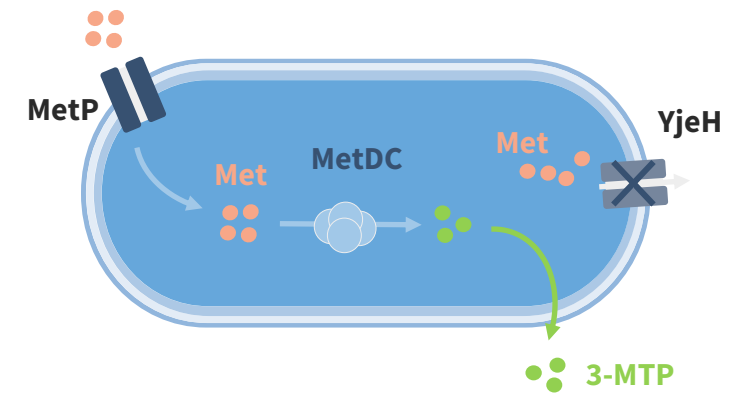
synlogic +  GINKGO BIOWORKS



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

## A Methionine-Consuming Synthetic Biotic

Methionine (Met)










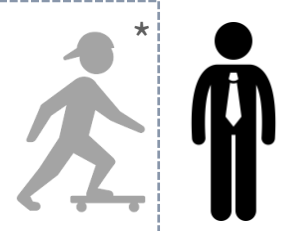
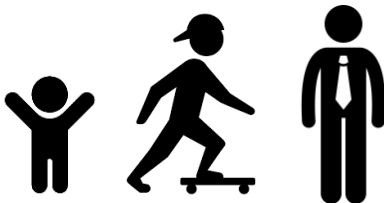
Gut lumen

Intestinal epithelium

- 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

	 <p>Pegtibatinase (TVT-058) <b>Phase 1/2</b></p>	 <p>Pegtarviliase (AGLE-177) <b>Phase 1/2</b></p>	 <p>SYNB1353 <b>✓ Phase 1, Proof of Mechanism</b></p>
Dosing & Administration <sup>1, 2, 3</sup>	 1.5 mg/kg biweekly Injection	 1.35 mg/kg weekly Injection	 <i>Sachet of lyophilized powder mixed with ~3 oz liquid taken with meals</i>
Safety Considerations	ERT mechanism associated with potential for allergic/immunological challenges		Transient/reversible, mild GI-related side effect
Potentially Applicable Patient Population <sup>1, 2, 3</sup>			

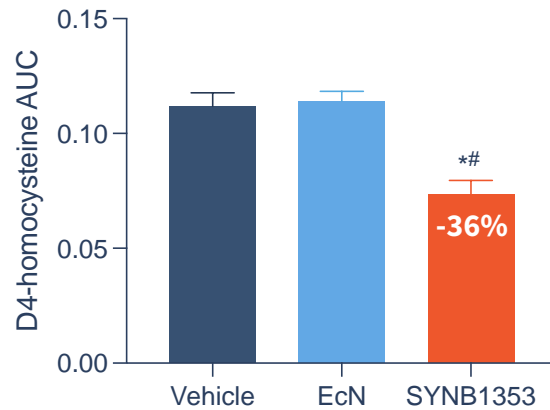
\*>12 in UK/Australia only, >18 in US <https://www.aeglea.com/clinical-trials/>

1. <https://hcuconnection.com/trials/1>. 2. <https://www.aeglea.com/clinical-trials/> 3. Synlogic data on file.

# SYNB1353: Program Progress to Date

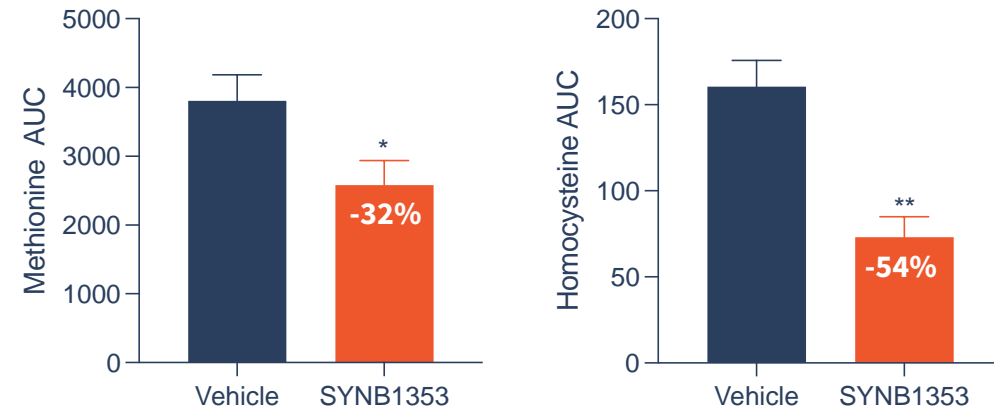
## Validated Preclinically in Multiple Models

### Hcy Lowering in CBS-Knockdown Mice



\*p<0.05 versus vehicle, #p<0.05 versus EcN

### Met and Hcy Lowering in Met-Challenged NHPs<sup>†</sup>



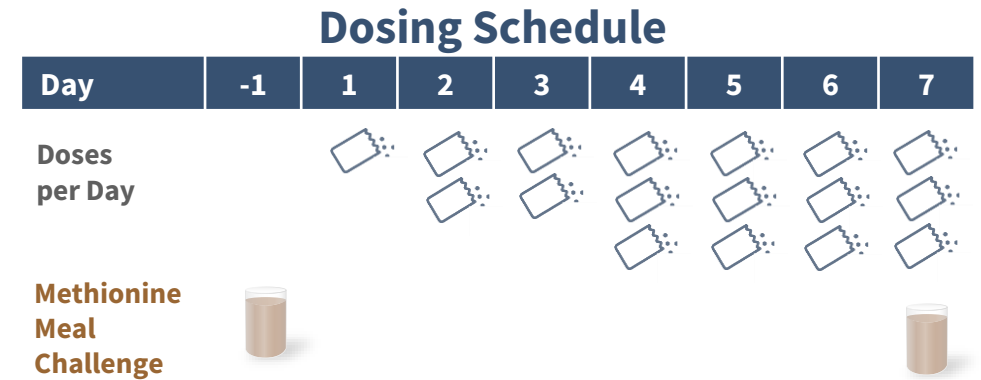
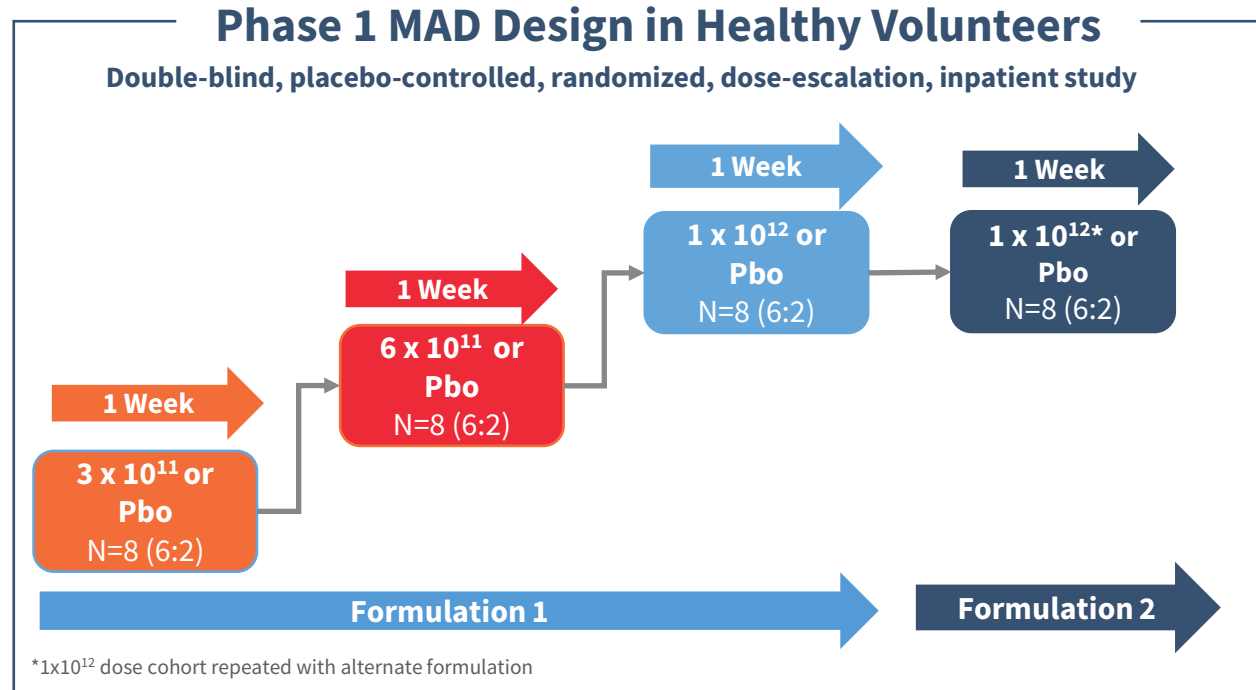
\*p<0.05 versus vehicle, \*\*p<0.01 versus EcN

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



# Study Design for SYN1353 Phase 1 in Healthy Volunteers

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

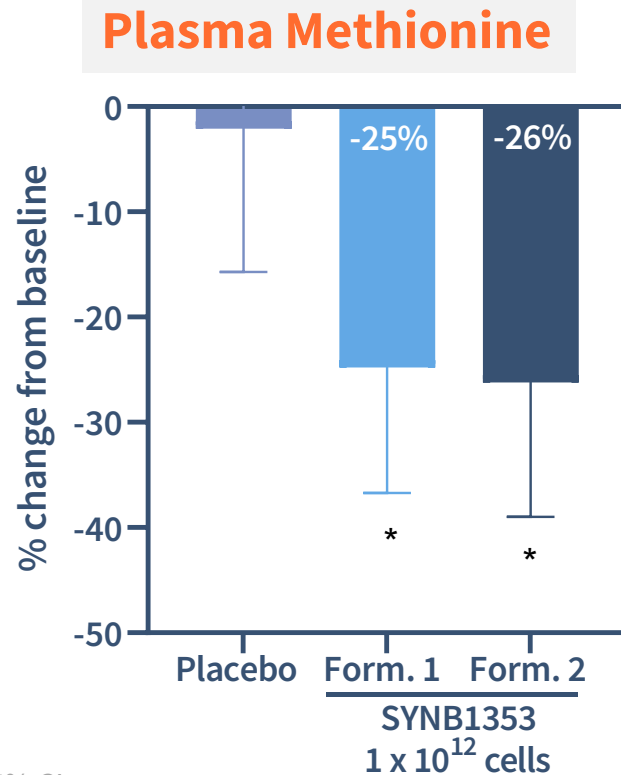


- **Objectives:** To assess the safety, tolerability, and PD of SYN1353 in HVs, in a dietary model of homocystinuria (HCU), and to evaluate two different formulations at the maximum dose.
- **Endpoints for Each Cohort & Dose Level Studied:**
  - Safety and tolerability
  - Clearance of SYN1353 by day 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



*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<sup>12</sup> form 1 n=6, 1x10<sup>12</sup> form 2 n=5

# Safety & Tolerability – Summary of Top-Line Findings

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

# SYNB1353 & HCU: Program Summary and Key Highlights

- 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**

