synlogic

Transforming Medicine Through Synthetic Biology

Corporate Presentation

August 2023



Forward Looking Statements

This presentation contains "forward-looking statements" that involve substantial risks and uncertainties for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. All statements, other than statements of historical facts, included in this press release regarding strategy, future operations, clinical development plans, future financial position, future revenue, projected expenses, prospects, plans and objectives of management are forward-looking statements. In addition, when or if used in this press release, the words "may," "could," "should," "anticipate," "believe," "look forward," "estimate," "expect," "intend," "on track," "plan," "predict," "prepare" and similar expressions and their variants, as they relate to Synlogic, may identify forward-looking statements. Examples of forward-looking statements include, but are not limited to, statements regarding the potential of Synlogic's approach to Synthetic Biotics to develop therapeutics to address a wide range of diseases including: inborn errors of metabolism and inflammatory and immune disorders; our expectations about sufficiency of our existing cash balance; the future clinical development of Synthetic Biotics; the approach Synlogic is taking to discover and develop novel therapeutics using synthetic biology; and the expected timing of Synlogic's clinical trials of labafenogene marselecobac (SYNB1934), SYNB1353, SYNB8802 and SYNB2081 and availability of clinical trial data. Actual results could differ materially from those contained in any forward-looking statements as a result of various factors, including: the uncertainties inherent in the clinical and preclinical development process; the ability of Synlogic to protect its intellectual property rights; and legislative, regulatory, political and economic developments, as well as those risks identified under the heading "Risk Factors" in Synlogic's filings with the U.S. Securities and Exchange Commission. The forward-looking statements contained in this press release reflect Synlogic's current views with respect to future events. Synlogic anticipates that subsequent events and developments will cause its views to change. However, while Synlogic may elect to update these forward-looking statements in the future, Synlogic specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing Synlogic's view as of any date subsequent to the date hereof.



synlogic

Our Mission

To treat diseases underserved by other modalities by researching, developing and commercializing a new class of medicines through the application of synthetic biology to therapeutics.

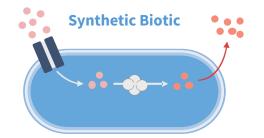
Synlogic: Now in Phase 3, with A Clinical Pipeline that Reflects Validated Synthetic Biotic Product Platform

Clinical stage pipeline of oral, non-systemic, novel biotherapeutics

- Late-stage programs
 focused on rare,
 metabolic disorders
- Lead drug candidate for PKU, labafenogene marselecobac, initiated
 Phase 3 June 2023; four current clinical programs, ~400 individuals dosed to date

Reproducible, **productive product platform** based on synthetic biology

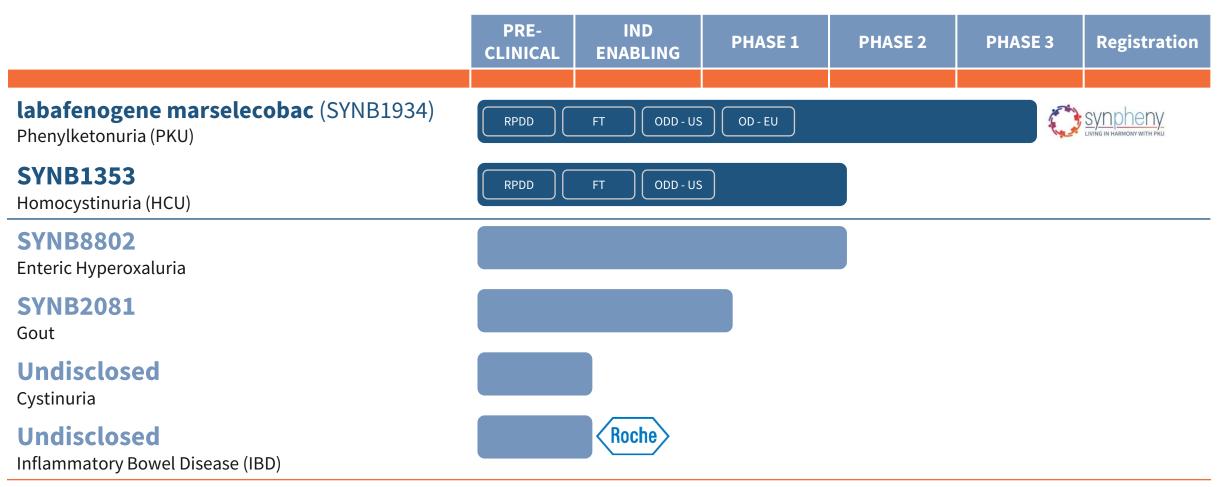
• **Synthetic Biotic platform:** drug candidates based on genetically engineered probiotics targeting validated, disease-specific metabolites:



- **Differentiated drug candidates:** GI-restricted, non-colonizing, reversible via GI clearance
- Integrated internal capabilities: development, manufacturing and discovery

Advancing a New Class of Biotherapeutics

Late-Stage Drug Candidates Focused on Rare Metabolic Diseases, PKU & HCU



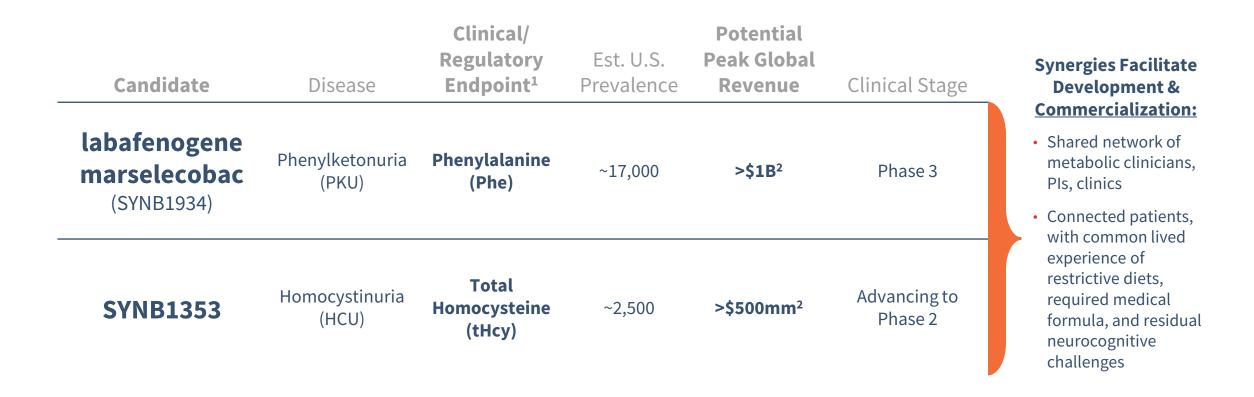
RPDD = Rare Pediatric Disease Designation granted by FDA | FT = Fast Track granted by FDA

ODD - US = Orphan Drug Designation granted by FDA | OD - EU = Orphan Designation granted by EMA



PKU, HCU Programs Benefit from Precedents and Synergies

Prior Approvals Provide De-Risked Paths Forward; Both Present Commercially Compelling Markets



1. For PKU: Kuvan, Palynziq both approved based on phenylalanine (Phe) change vs. PBO; For HCU: Cystadane approved based on change in total homocysteine (hTCY)

2. Assumes indicated for pediatric through adult

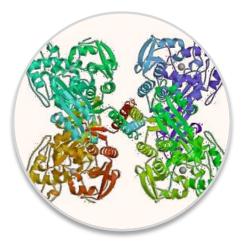
labafenogene marselecobac (SYNB1934)

Potential as first and only **oral, non-systemic** *biotherapeutic available as both* **monotherapy and adjunctive** *medical treatment for PKU*

Currently being evaluated in Synpheny-3, pivotal Phase 3 study

- Rare Pediatric Disease Designation (FDA)
- Orphan Drug Designation (FDA)
- Orphan Designation (EMA)

The Lifelong Burden of PKU Includes Both the Extreme Diet, and Neurocognitive Challenges of Uncontrolled Phe



PKU is **caused by defects in PAH enzyme** responsible for metabolizing Phe, amino acid in dietary protein



Built-up, **Phe becomes neurotoxic**, risking intellectual disabilities, deficits in mental processing, social engagement, emotional problems^{1,2,3}



PKU burdens include neurocognitive symptoms and lifelong diet requirements of:

Restricted protein (e.g. 4-6 g/day) Low protein/Low-Phe foods (e.g. pasta) Supplemental amino acid medical formula

Reflecting adherence challenges of diet, ~80% of patients' Phe levels > goals in a major US center studied



PKU Presents a Large Rare Disease Market, Across Geographies

Country/Territory	Estimated Prevalence ¹	 PKU is the most prevalent inborn error
**** ****	~1:10,000 (~25,000 patients)	of metabolism for which there is no cure
C×	~1:6,000 (~14,000 patients)	 Widespread newborn screening for PKU diagnoses patients, and connects families to clinics, starting in infancy
	~1:17,000 (~80,000 patients)	 Specific mutations affect degree of PAH enzyme functionality, disease prevalence and severity
	~1:125,000 (~1,000 patients)	 Diagnosis, monitoring and treatment
	~1:16,000 (~17,000 patients) ²	decisions based on plasma Phe levels (vs. genetic testing)

1. Hillert et al. Ajv The Genetic Landscape and Epidemiology of Phenylketonuria, AJHG 2020

2. Xiang L, Tao J, Deng K, et al. Phenylketonuria incidence in China between 2013 and 2017 based on data from the Chinese newborn screening information system: a descriptive study; 2. US data from NPKUA



PKU Patients and Clinicians are Connected, Facilitating Clinical Development & Commercialization

Concentrated Sites of Care

- Care for patients with inborn errors of metabolism like PKU is provided through a well-defined network of metabolic clinics¹
- After diagnosis during infancy, patients and families are connected to local and national organizations, for support and education



s://www.npkua.org/Resources/Find-a-Clinic; 2. GMDI; 3. US Government Accountability Services: Information on Genetic Counselor and Medical Geneticist Workforces, 2020.

- PKU clinicians represent a **focused potential prescriber universe,** including in the US:
 - ~150 metabolic dietitians²
 - ~1,000 medical geneticist physicians³
- Precedents de-risk the PKU opportunity: previously approved medicines (Kuvan,[®] Palynziq[®]) providing pathways for:
 - <u>Clinical:</u> Single registrational study with primary analysis conducted on subset of pre-defined responders
 - <u>Regulatory:</u> Full (vs. accelerated) approval based on Phe reduction vs. placebo as endpoint
 - <u>Reimbursement:</u> Payer coverage typically requires alignment with study population, and demonstration of benefit per pivotal study

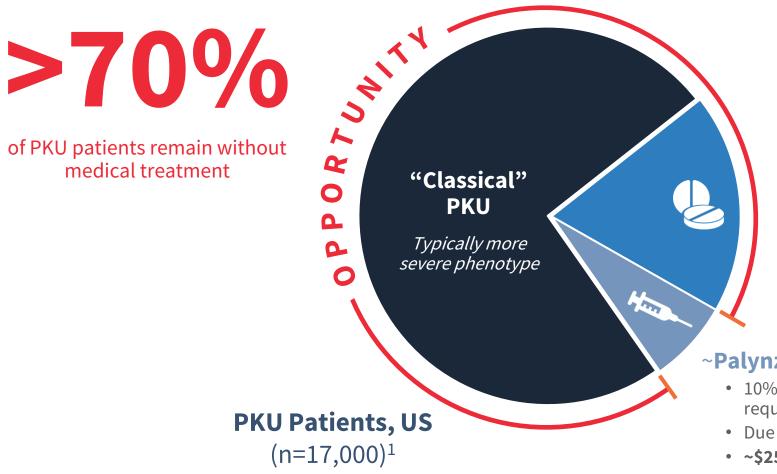
Reimbursement for PKU Medicines in the US is Straightforward

- Access: Through pharmacy benefit, typically at specialty tier, per each payer's medical policy for that product
- **Reimbursement:** Prior Authorization requirements typically follow product labeling, requiring:
 - Physician attestation
 - Clinical notes and lab values
 - Demonstration of response in Phe reduction for re-authorization¹
- **Distribution:** Through specialty pharmacy(ies) contracted with manufacturer

Drug	Indication	Annual Price (Adult, US)
Carbaglu (carglumic acid)	Hyperammonemia due to NAGS deficiency	~\$600,000
Ravicti (glycerol phenylbutyrate)	Urea cycle disorders (UCDs)	~\$700,000
Orfadin (nitisinone) ²	Hereditary tyrosinemia type 1 (HT-1)	~\$325,000
Lumizyme (alglucosidase alfa)	Pompe disease	~\$600,000
Palynziq (pegvaliase injection)	PKU	~\$200,000
Kuvan (sapropterin) ²	PKU	~\$200,000

Analog Pricing: Rare Metabolic Disease Drugs

Current Treatment Limitations Leave Need for New Approach



Sapropterin (Kuvan,[®] biopterin class)

- ~\$500mm/year revenue pre-genericization
- Limited to the BH4-responsive patient segment²
- Adjunctive medical treatment opportunity

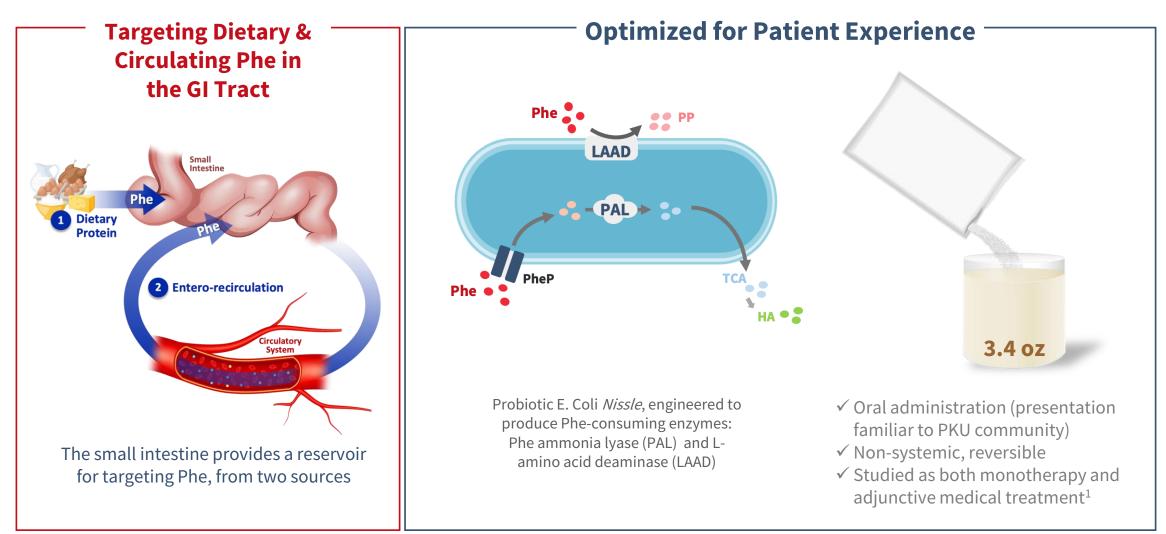
~Palynziq[®] (pegvaliase injection)

- 10% rate of anaphylaxis (boxed warning, USPI), requires injectable epinephrine, 24/7, for life²
- Due to adverse event profile, 1-2 year titration period³
- ~\$250mm/year revenue⁵ with <10% share in US

*Responsive to BH4 (tetrahydrobiopterin) = molecule that the body produces to act as a cofactor with PAH, the enzyme that is impaired in PKU. Sapropterin is a synthetic form of BH4.

ightarrow 1. NPKUA, patient numbers for sapropterin, pegvaliase derived from Biomarin financials and disclosures; 2. USPIs for Kuvan, Palynziq 3. Synlogic Market Research 2021

labafenogene marselecobac (SYNB1934): Designed to Consume Phe, Meet Patient Needs



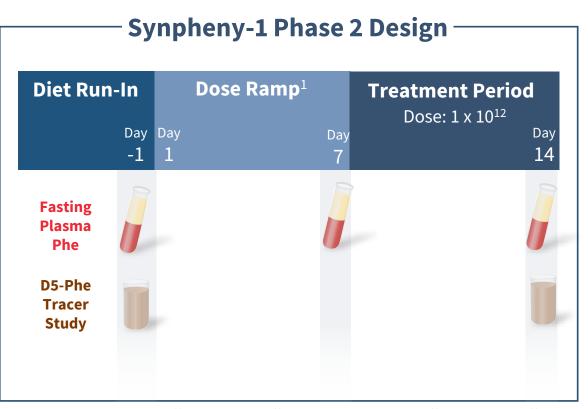
1. Phase 2 and Phase 3 study designs accept patients taking pterins (Kuvan/sapropterin and sepiapterin) at baseline

Synlogic's PKU Program Advanced to Phase 3 in 2Q 2023

<u>Stage</u>	<u>Modality</u>	<u>Company/Program</u>
Ph 3 Complete	Biopterin	PTC/PTC923
Ph 3 Study Ongoing	Synthetic Biotic	Synlogic / labafenogene marselecobac (SYNB1934)
Ph 1	Allosteric inhibitor of SLC6A19	Jnana/JNT-517
	Gene Therapy	Biomarin/ BMN 307 (Clinical Hold since Sept 2021)
Preclinical	Systemic mRNA for PAH	Moderna/mRNA-3283
	PAH stabilizer (oral)	Agios/NA
	Gene Therapy	Sangamo/ST101
		SOM-Biotech/SOM1311
		Generation Bio/NA
		American Gene Tech/NA



Phase 2 Study Design Provided Proof of Concept



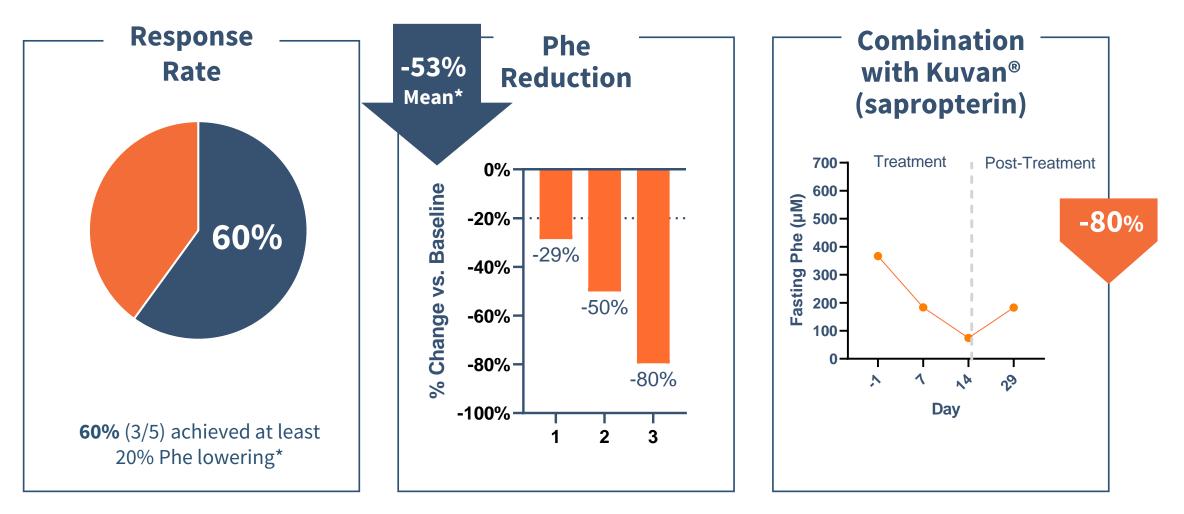
1. SYNB1618: Days 1-3: 1x10¹¹, Days 4-6: 3x10¹¹; SYNB1934: Days 1-3: 3x10¹¹, Days 4-6: 6x10¹¹ 2. Baseline Phe values per data for n=5

Disposition, Demographics Reflected Target PKU Population

- 20 adults with PKU (SYNB1618 =11, labafenogene marselecobac (SYNB1934) = 9)
- Phe > 600 μM at screening, despite diet and/or sapropterin (Kuvan[®]); mean 1,041 μM and 987 μM for SYNB1618 and SYNB1934, respectively²
- Baseline characteristics evenly distributed, with a representative mix by age, gender, Phe levels, and baseline treatment



Phase 2 Data Demonstrated Potential Phe Reduction witn labafenogene marselecobac (SYNB1934)





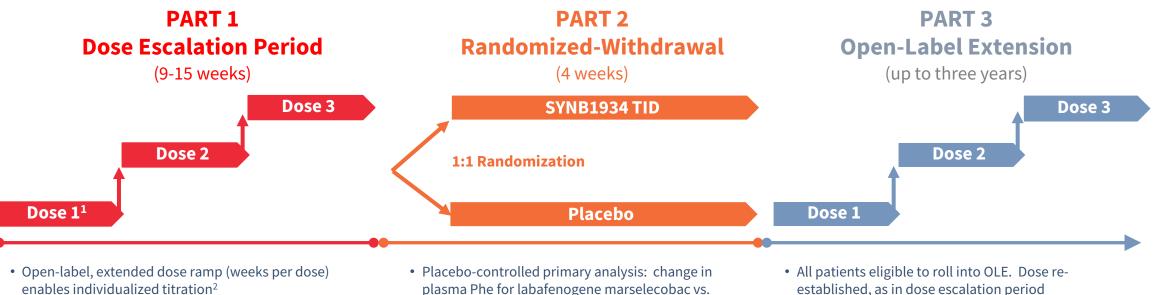
Favorable Safety & Tolerability Profile Across PKU Program

- ✓ No serious adverse events (SAEs)
- Adverse events all **mild to moderate**, predominantly GI in nature, and consistent with those described in the dosing of probiotics
 - Across both arms, 3 patients discontinued due to GI-related AEs. One patient withdrew consent at the baseline visit and one reported facial flushing which was attributed to a potential allergic reaction
- ✓ The study design for the labafenogene marselecobac (SYNB1934) Phase 3 incorporates these learnings through
 - 1. Low starting dose
 - 2. An extended, slower dose ramp, with more time at each dose prior to advancing



Synpheny-3: Global, Pivotal, Phase 3 Study of labafenogene marselecobac (SYNB1934)

Three-Part Design Reflects Input from Regulators, Clinicians and Patient Community



- Informs responder population³ for Part 2
- To enroll ~150 patients with Phe >360 μM^1
- For patients currently without medical treatment or those on pterins;
- Study participants may follow their usual diet while participating in the trial

- Placebo-controlled primary analysis: change in plasma Phe for labafenogene marselecobac vs. placebo during withdrawal among responders (from Part 1)
- Change in Phe tolerance (i.e. dietary liberalization)



- 1. For patients ages 18 years and older; an initial subset of data from patients in Part 1 will be used to assess the opportunity to lower the age of enrollment to 12
- 2. Dose levels for ramp are: 3x10¹¹, 6x10¹¹ and 1x10¹¹; each begins with once/daily and increases frequency to three times daily, with meals
- 3. 20% reduction vs. baseline in plasma Phe during Part 1 is responder definition

Transformative Potential in PKU with labafenogene marselecobac

- Large orphan disease population: majority remain without treatment due to limitations of today's options
 - Commercially validated by currently approved medications, but safety/efficacy leaves need for new approaches)
 - Diagnosed, connected patients and concentrated sites of care facilitate clinical development and commercial launch
- Phase 3 initiated; prior regulatory approvals de-risk path forward
 - Two prior FDA approvals with full approval (not accelerated) based on biomarker in single registrational study
- **Compelling expected product profile** meets patient needs
 - Orally-administered, powder/sachet presentation consistent with standard of care medical formula
 - Non-systemic; Reversible, non-colonizing; favorable safety and tolerability profile with no SAEs, and
 - Efficacy as monotherapy or adjunct to biopterins (-53% average Phe reduction in responders; -29 -80% range)
- Pursuing **broad US and Ex-US patent protection** (e.g., composition of matter patent exclusivity to 2041)
 - Composition of matter directed to the engineered bacterium and its drug formulation; coverage will continue to grow
 - Methods of treatment and administration & manufacturing methods

Potential as 1st and only orally-administered biotherapeutic for both monotherapy and adjunctive treatment in PKU

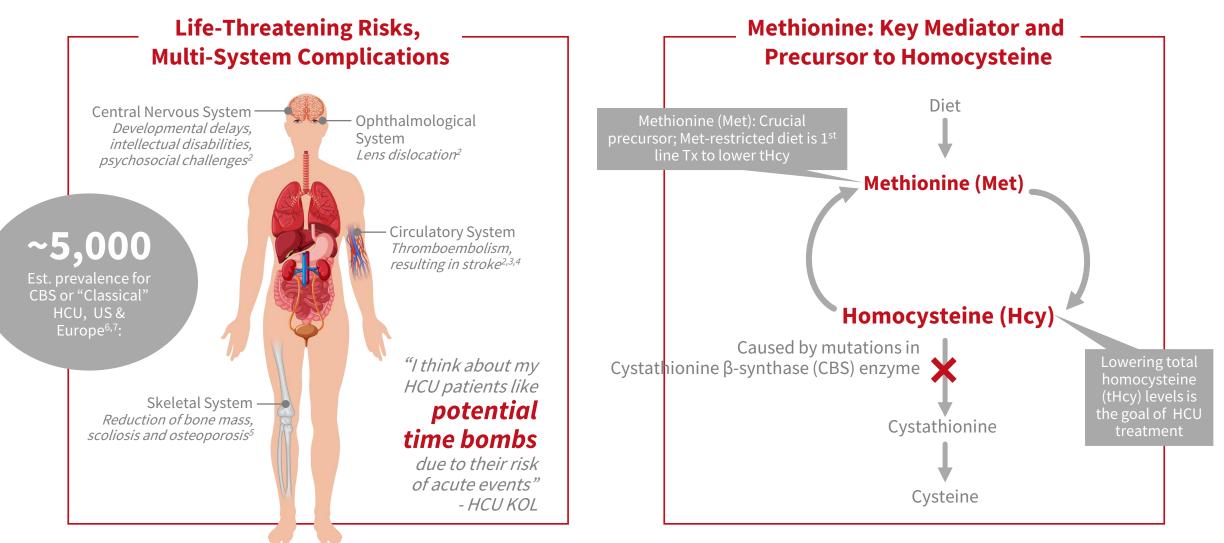
>\$1B revenue opportunity globally



SYNB1353 for Homocystinuria (HCU)

- Rare Pediatric Disease Designation (FDA)
- Orphan Drug Designation (FDA)
- Fast Track Designation (FDA)

HCU: Multi-System Burden, Acute Risks due to Uncontrolled Homocysteine



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*, 8th 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.



SYNB1353: New Approach to Lowering tHcy through Methionine

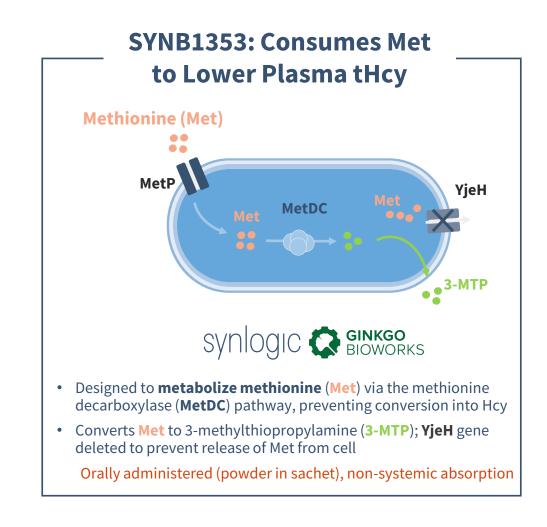
Current Options Leave Majority of HCU Patients Behind

- **Total homocystinuria (tHcy):** HCU treatment target (*"lower is better"*)^{1, 2}
 - Guidelines: -20% for clinical response, <100 μmol/L if possible¹
 - Normal (healthy) range: 5-15 μmol/L
 - In HCU, levels can be >200 μ mol/L
 - Regulatory precedent for approval (per Cystadane®)

Current HCU treatments are limited

- 1. Low-Met diet (low in natural protein),
- 2. Supplemental formula (Met-free L-AA mixture)
- 3. Betaine (Cystadane®)

Majority of HCU patients are far above goals, despite current options⁴



Morris AAM, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency
 Walter 1998 3.. U.S. Prescribing Information for Cystadane[®] (betaine) 4. De Biase et al. 2020 & Synlogic patient & KOL Insights

SYNB1353: Designd for Safety, Efficacy, and Convenience

Product Presentation and Expected Profile to Enable Use Across Age Spectrum in PKU

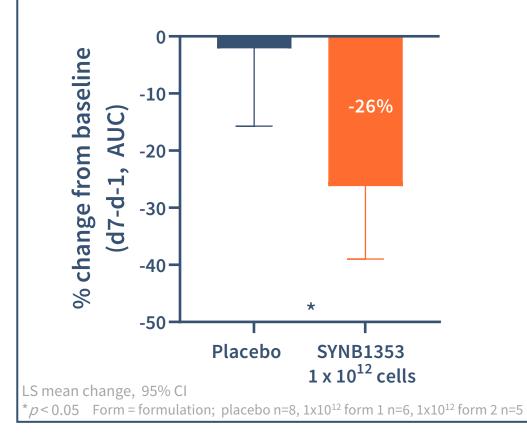
Therapeutic Class	Enzyme Replacement Therapy (ERT)		Synthetic Biotic	
Manufacturer <i>Drug/Status</i>	Pegtibatinase (TVT-058) Phase 1/2	Beglea Pegtarviliase (AGLE-177) Paused Ph 1/2*	SYNlOGIC ^{SYNB1353} ✓ Phase 1, Proof of Mechanism	
Dosing & Administration ^{1, 2, 3, 4}	1.5 mg/kg biweekly Iyophilized Injection	Up to 1.35 mg/kg weekly Injection	Powder mixed with ~3 oz liquid taken with meals	
Safety Considerations	ERT mechanism associated with potential for allergic/immunological challenges		Non-systemic. Transient/reversible, mild GI-related side effect	
Potentially Applicable Patient Population ^{1, 2, 3}	ź f		¥ Ż Î	

1. https://hcuconnection.com/trials/1. 2. https://www.aeglea.com/clinical-trials/ 3. Synlogic data on file. 4. Travere Corporate Presentation, March 2023

*Patients developed anti-drug antibodies at 1.35 mg/kg dose, Aeglea BioTherapeutics Press Release (12 April 2023); **>12 in UK/Australia only, >18 in US https://www.aeglea.com/clinical-trials/

SYNB1353 Phase 1 Study Demonstrated Proof-of-Mechanism in Healthy Volunteers

Significant Change in Plasma Met Confirmed SYNB1353 Activity as Intended



. Sondheimer et al., SIMD 2023

- Phase 1 study used healthy volunteer dietary model for (methionine meal challenge) to assess SYNB1353 ability to affect plasma Met levels
- November 2022: **proof of mechanism achieved** in HVs using a meal challenge by data showing:
 - Lowering plasma methionine and
 - Producing strain-specific biomarker (3MTP-glycine)
- Previously presented mechanistic modeling data suggests that SYNB1353 may lower plasma Hcy by up to 58% and may increase protein intake and in HCU patients¹
- Based on this proof of mechanism, SYNB1353 will advance to a Phase 2 proof of concept study in patients with HCU

SYNB1353 Phase 1 Safety & Tolerability 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 for HCU: Potential for Differentiated Convenience & Safety Across the Full Age Spectrum

- HCU is a rare metabolic disease caused by an inborn error of metabolism with well-recognized need for new treatment options
 - Burden includes life-threatening acute risks of ischemic stroke and chronic, multi-system complications
 - Large majority of patients with severely elevated total homocysteine levels, in need of new treatment options
- Commonalities and synergies with PKU, facilitating clinical, regulatory and commercial paths
 - Precedent in HCU for regulatory approval based on biomarker endpoint (total homocysteine or tHcy)
 - Shared sites of care, investigator and clinician community with PKU; connected patient communities
- Differentiated target product profile offers potential for patient convenience, safety tHcy lowering across the full age spectrum of PKU
 - Engineered probiotic designed to consume methionine, a precursor to homocysteine, in the GI tract
 - Orally-administered, non-systemically absorbed powder easily mixed with water or juice
 - Mechanism and safety profile expected to support use across the full age spectrum
- Based on positive proof of mechanism, will advance to Phase 2 proof of concept study in HCU patients



Additional Pipeline Programs



Additional Clinical Candidates Target Validated Metabolites

All Programs Benefit from Cross-Platform Synergies in Discovery, Development, & CMC

Program	<u>Enteric Hyperoxaluria</u>	Gout	<u>Cystinuria</u>	
Candidate	SYNB8802	SYNB2081	Undisclosed	
Target Metabolite within the GI Tract	Dietary oxalate	Uric acid	Methionine	
Clinical Biomarker	Urinary oxalate	Plasma uric acid	Urinary cystine concentration	
Status	Clinical proof of concept established	IND enabling studies ongoing	Preclinical	
Shared <i>chassis</i> of Synthetic Biotic				

Industry-Leading Partners Reflect Synlogic Expertise, Progress to Date



- Established June 2021
- Research collaboration for discovery of novel Synthetic Biotic addressing novel single target for the treatment of inflammatory bowel disease (IBD)
- Roche has exclusive option to enter a licensing and collaboration agreement for further development and commercialization
- Synlogic achieved prespecified research milestones and payments in Q3 2021 and Q3 2022



- Established 2019
- Five-year, \$30 million strategic research collaboration
- Accelerates expansion and development of Synlogic's pipeline, based on Synlogic's product engine and Ginkgo's discovery capabilities
- Synlogic retains exclusive marketing rights
- Results to date include:
 - SYNB1353 for HCU
 - SYNB2081 for gout

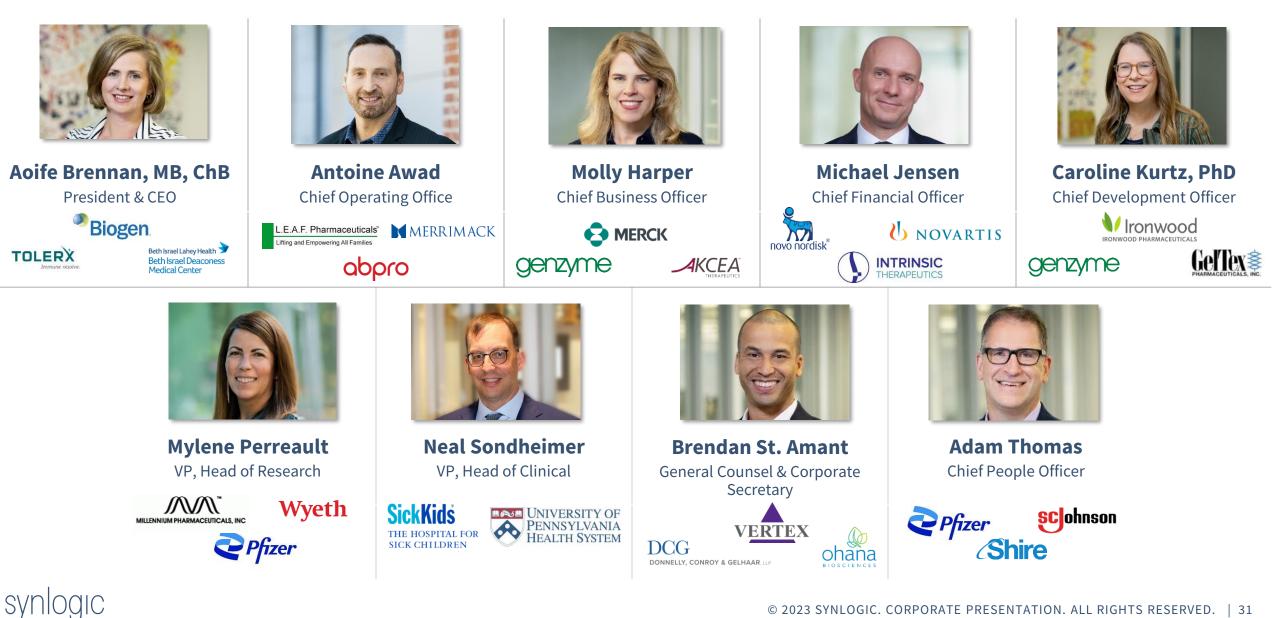


Corporate





Leadership Strength Brings Depth Across Biopharma



Financial Results for Second Quarter 2023

Summary Results

Balance Sheet (unaudited)		30 June 202	3 31 D	31 December 2022	
Cash, Cash Equivalents, and Marketable Securities		\$46.3M		\$77.6M	
(in thousands, except share and per share data)	Three Months Ended June 30		Six Months Ended June 30		
Financial Performance (unaudited)	2023	2022	2023	2022	
Revenue	\$ 35	\$ 152	\$ 209	\$ 396	
R&D Expenses G&A Expenses Net loss	\$ 11,765 \$ 3,924 \$ (15,048)	\$ 12,057 \$ 4,112 \$ (15,842)	\$24,215 \$7,891 \$(30,670)	\$23,795 \$8,383 \$(31,539)	
Net loss per share - basic and diluted* Weighted Average Shares Outstanding*	\$ (0.21) 70.2M	\$ (0.22) 72.1M	\$ (0.44) 69.7M	\$ (0.44) 72.0M	

Thank You



