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Designed for Life

Phenylketonuria Clinical Program Update

20 September 2021

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 presentation regarding strategy, future operations, 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 presentation, the words “may,” “could,” “should,” “anticipate,” “believe,” “estimate,” “expect,” “intend,” “plan,” “predict” and similar expressions and their variants may identify forward-looking statements. Examples of forward-looking statements include, but are not limited to, the approach we are taking to discover and develop novel therapeutics using synthetic biology; statements regarding the potential of our platform to develop therapeutics to address a wide range of diseases, including: metabolic diseases, inflammatory and immune disorders, and cancer; the future clinical development of Synthetic Biotic medicines; the potential of our technology to treat phenylketonuria and cancer; the expected timing of our anticipated clinical trial initiations and availability of clinical data; the benefit of orphan drug and fast track status; the adequacy of our capital to support our future operations and our ability to successfully initiate and complete clinical trials; the results of our collaborations; and the difficulty in predicting the time and cost of development of our product candidates. Actual results could differ materially from those contained in any forward-looking statement as a result of various factors, including, without limitation: the uncertainties inherent in the preclinical development process; our ability to protect our intellectual property rights; and legislative, regulatory, political and economic developments, as well as those risks identified under the heading “Risk Factors” in our filings with the SEC. The foregoing review of important factors that could cause actual events to differ from expectations should not be construed as exhaustive and should be read in conjunction with statements that are included herein and elsewhere, including the risk factors included in our quarterly report on Form 10-Q filed with the SEC on August 12, 2021, and in any subsequent filings we make with the SEC. The forward-looking statements contained in this presentation reflect our current views with respect to future events. We anticipate that subsequent events and developments could cause our views to change. However, while we may elect to update these forward-looking statements in the future, we specifically disclaim any obligation to do so. These forward-looking statements should not be relied upon as representing our view as of any date subsequent to the date hereof.

Our Program Today

01

Interim Analysis of SYNB1618 Phase 2 SynPheny-1 Study
Dr. Aoife Brennan, CEO

02

SYNB1934 Phase I Data, Dose Cohorts 1-3
Dr. David Hava, CSO

03

Platform Implications and Next Steps in PKU
Dr. Aoife Brennan, CEO

04

Q&A
Management Team

Progress in Phenylketonuria

Dr. Aoife Brennan, MB CHB
President & CEO

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Synthetic Biotic Medicines: a novel approach in Phenylketonuria (PKU)

PKU

Current and emerging treatment options leave many patients behind

Synthetic Biotic Medicines

Potential to treat all PKU patients with a safe oral approach

Today: two trials with interim results

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LIVING IN HARMONY WITH PKU

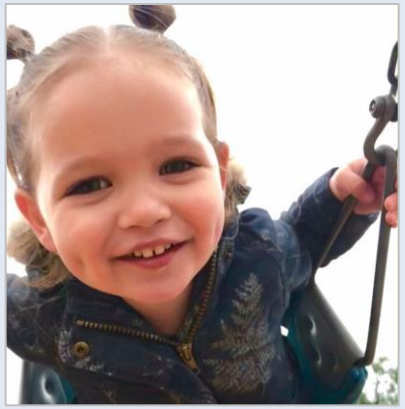
SYNB1618 strain achieved prespecified 20% Phe lowering target in PKU patients

Ph. 1 HV

SYNB1934 strain demonstrated two-fold greater activity than SYNB1618 in healthy volunteers

PKU remains an area of high unmet need

Patients



Julia,
living with PKU

Pediatrics
~5,000 U.S.

25% out of Phe control

Adults
~12,300 U.S.

65% out of Phe control

90% of patients and caregivers express need for greater natural protein intake [(1)]

Challenges

- Extremely challenging low protein diet with **low compliance**
- Substantial need for increased intake of **natural protein** enabled by Phe reductions
- Significant risk of **neurocognitive impairment** in patients with elevated Phe levels

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[(1)] Puurunen et al, Global PKU Patient Meeting, September 2021

PKU patients are poorly served today

Disease State	Patient Goal
Out of Phe Control (>360 µmol/L of Phe)	**Lower blood Phe** to reduce risk of neurocognitive impairment
In Phe control (<360 µmol/L of Phe)	**Enable greater dietary protein intake** while maintaining Phe control

Limited Therapeutic Options

Palynziq™ (pegvaliase-pqpz) Injection

- Daily injection
- Allergic reactions
- REMS
- Adults only

KUVAN® (sapropterin dihydrochloride) Tablets

- 70% fail to respond
- Only 10% all-comers fasting Phe reduction [2]

Significant market opportunity, large unmet need, with potential for new products to capture share

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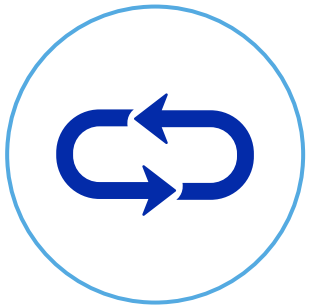
[2] Kuvan FDA statistical review, 25 Nov 2007

Synthetic Biotic Medicines: Differentiated product candidates for the treatment of PKU

Designed for PKU

Oral



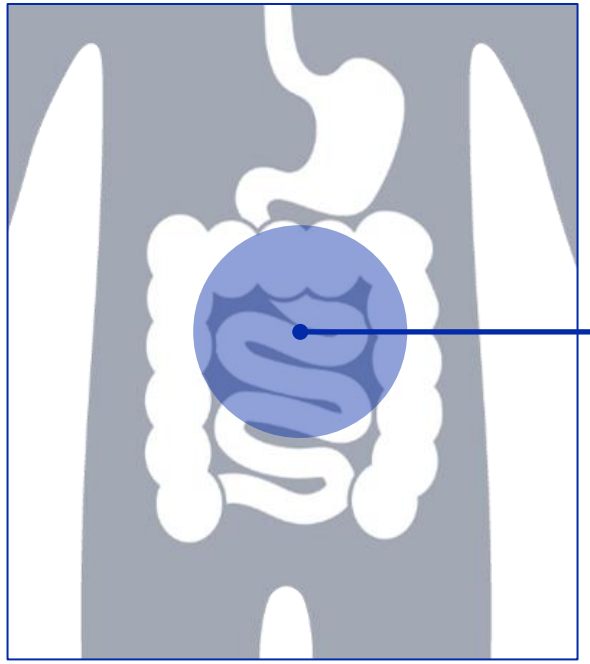
Reversible

Gut Restricted

Synthetic Biotic medicines for the treatment of PKU present a compelling opportunity to change patients' lives

Intuitive and direct approach to treating PKU

Oral therapy,
3 x day with meals



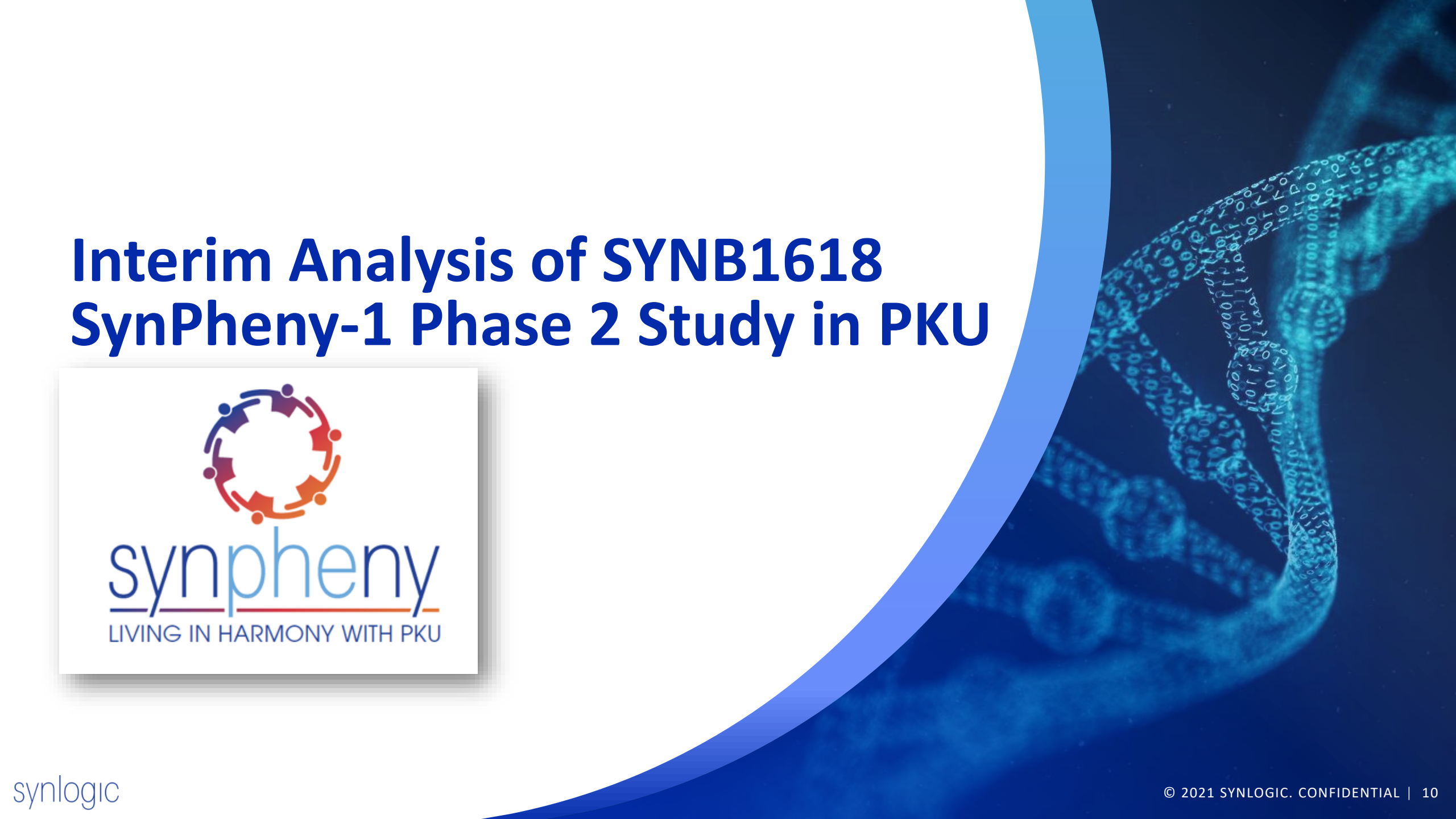
Dietary Phe

Converted by Synthetic Biotic to harmless metabolites (TCA)

Reduce plasma Phe *or* enhance protein tolerance

Unique mechanism of action generates quantitative, measurable biomarker of Phe metabolism: TCA (trans-cinnamic acid)

Interim Analysis of SYNB1618 SynPheny-1 Phase 2 Study in PKU



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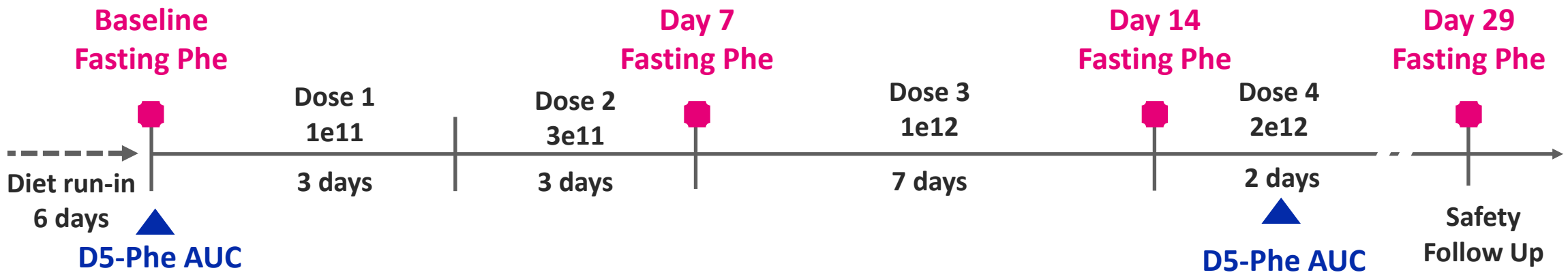
SYNB1618 Phase 2 SynPheny-1 study in PKU: Design



Population

- IA of 8 subjects receiving SYNB1618
- Adult PKU patients, plasma Phe levels ≥ 600 µmol/L
- Stable diet
- No use of Kuvan or Palynziq

Endpoints

- Fasting Plasma Phe levels (day -1, 7, 14, 29)
- Labelled D5-Phe 24hr AUC, change from baseline after meal challenge (day -1, 15)

Diet Control

- 6-day diet run in
- Individualized diet plan to match baseline Phe intake
- Stable study diet: diet run-in through 2 weeks post treatment

SYNB1618 metabolized Phe into TCA and prevented Phe absorption after meal challenge

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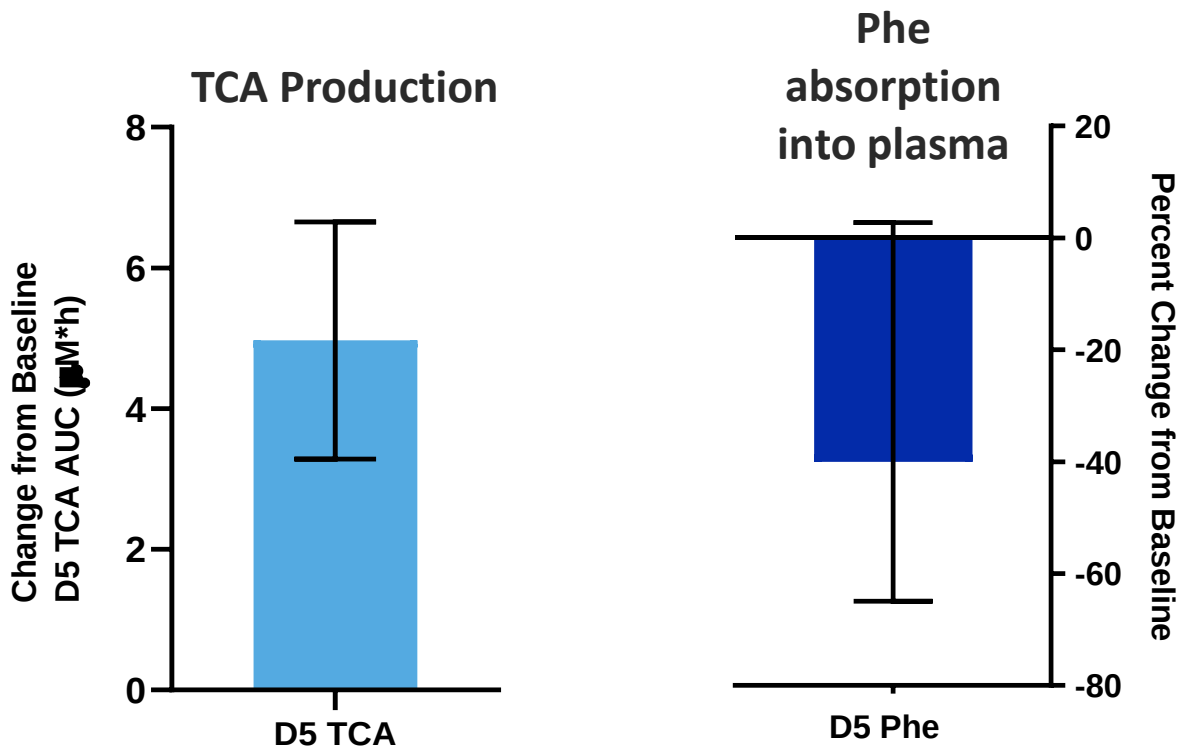
D5 Phe Meal Challenge
(2e12 dose, N=8, Days -1 and 15)



4 of 8 patients experienced >40% D5-Phe lowering after meal challenge

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Percent change from baseline +/- 95% confidence interval. TCA = trans-cinnamic acid. AUC = Area under curve.

SYNB1618 reduced fasting plasma Phe levels

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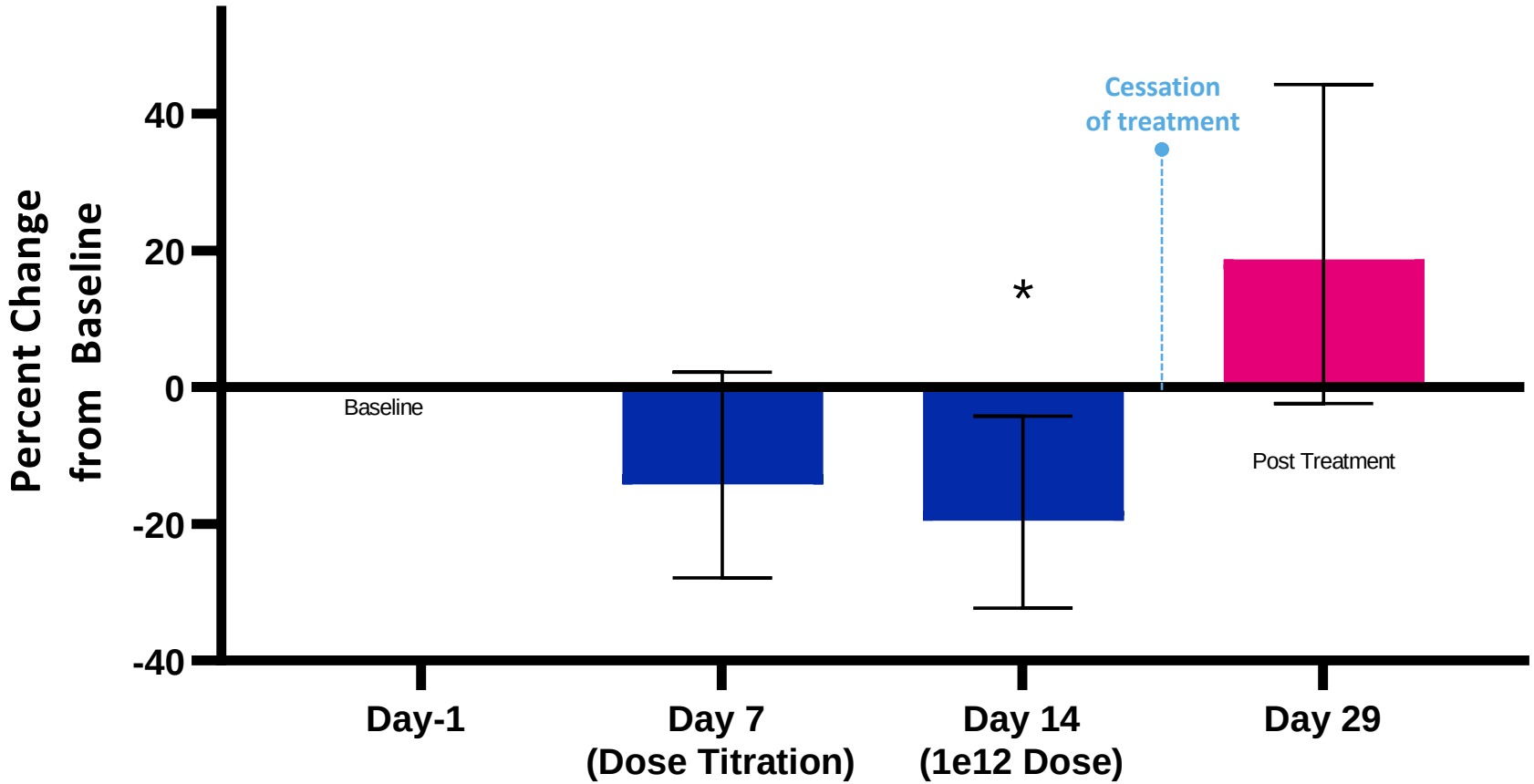
Fasting Plasma Phe Levels (N=8)



4 of 8 patients experienced **>30% reduction** in fasting Plasma Phe at Day 7 or Day 14

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Percent change from baseline +/- 95% confidence interval. * = Statistically significant

Summary of interim safety analysis

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Gut restricted

Clearance upon cessation of dosing as expected

Generally well tolerated

Tolerability profile **consistent with experience** in healthy volunteers

Mild to Moderate GI AEs

No treatment-related discontinuations

No SAEs or new safety issues identified

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Safety analysis cut-off: 30 July 2021. Includes all patients (N = 9) through Day 15. Does not include Day 29 assessments for all patients. One discontinuation for anxiety, not drug related.

SYNB1934 Phase 1 Study Results

Dr. David Hava, PhD
Chief Scientific Officer

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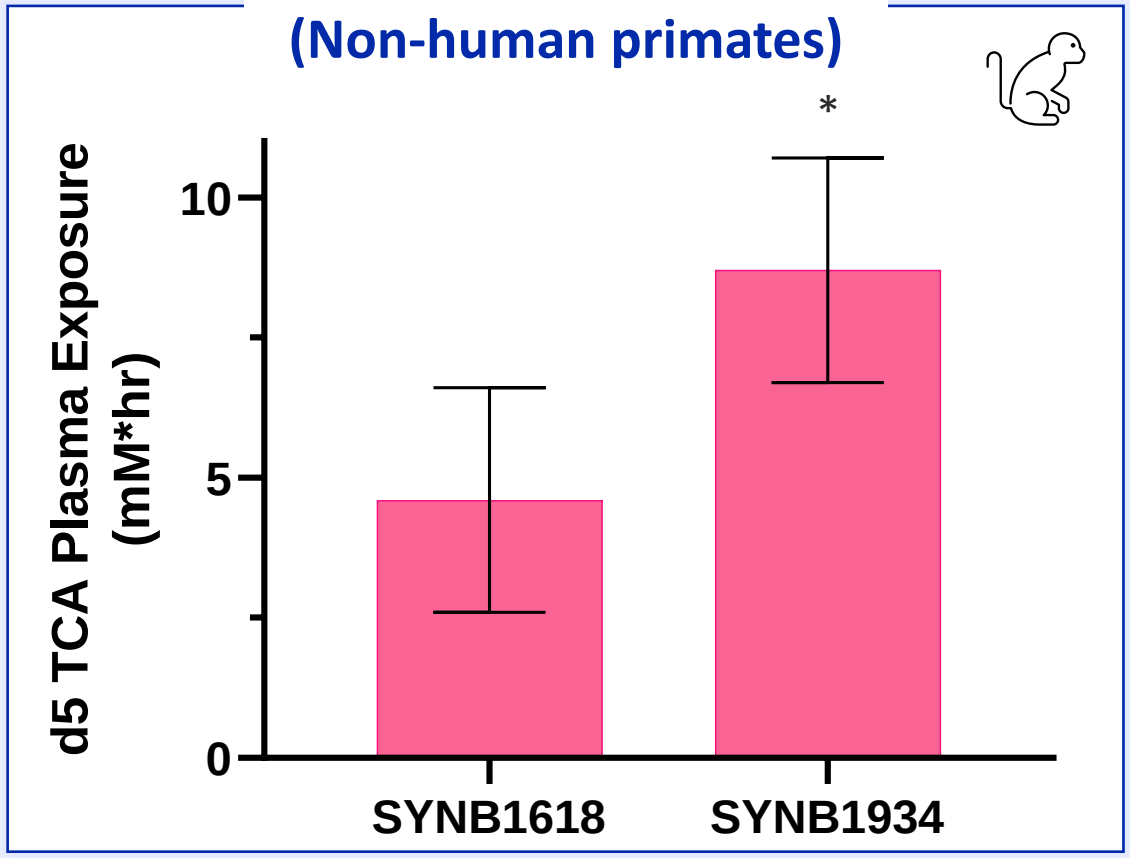
Synthetic biology platform optimized activity of therapeutic strain

SYNB1934

- Developed from SYNB1618 using directed evolution of PAL3 enzyme in whole cell assay
- Potential to provide increased Phe lowering activity and flexibility to optimize clinical profile

Increased activity *in vivo* (Non-human primates)



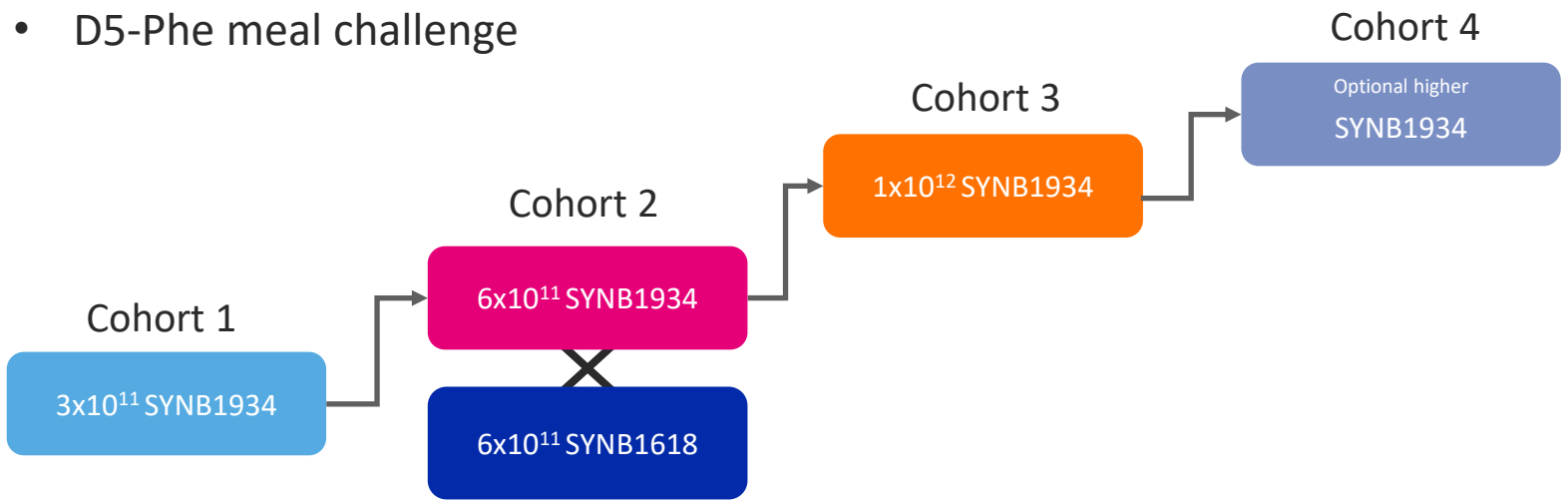
Increased activity two-fold in non-human primates using directed evolution approach

Monahan et al, SEED 2021. * = Statistically significant. Error bar is mean +/- standard deviation.

SYNB1934 Ph. 1 study allows head-to-head comparison of strains

Study Design

- Four-day dose ramp, two days dosing
- D5-Phe meal challenge

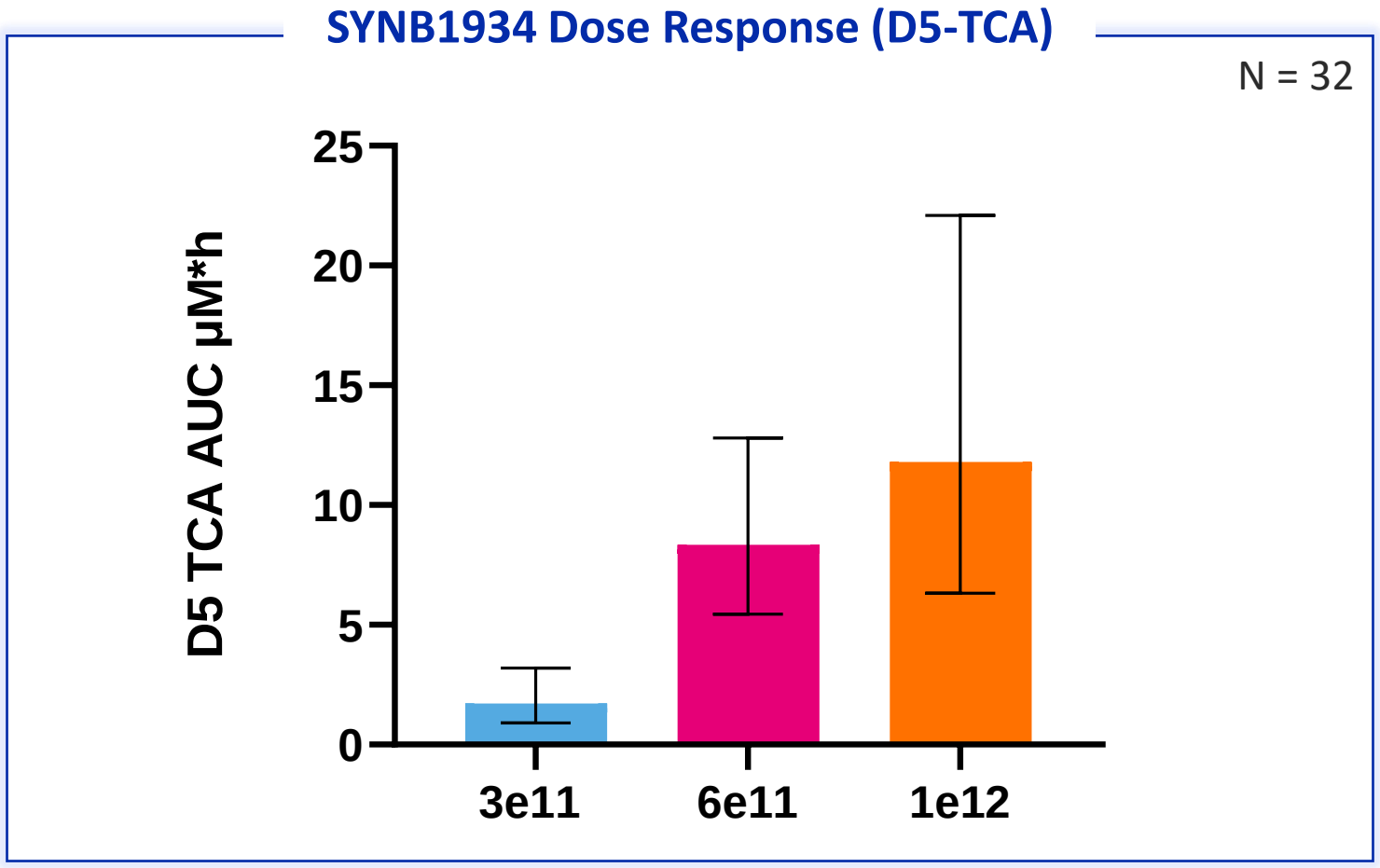


Endpoints

- Safety and tolerability
- Biomarkers of Phe consumption
- SYNB1934 clearance after cessation of dosing

Study will determine if SYNB1934 has improved activity over SYNB1618

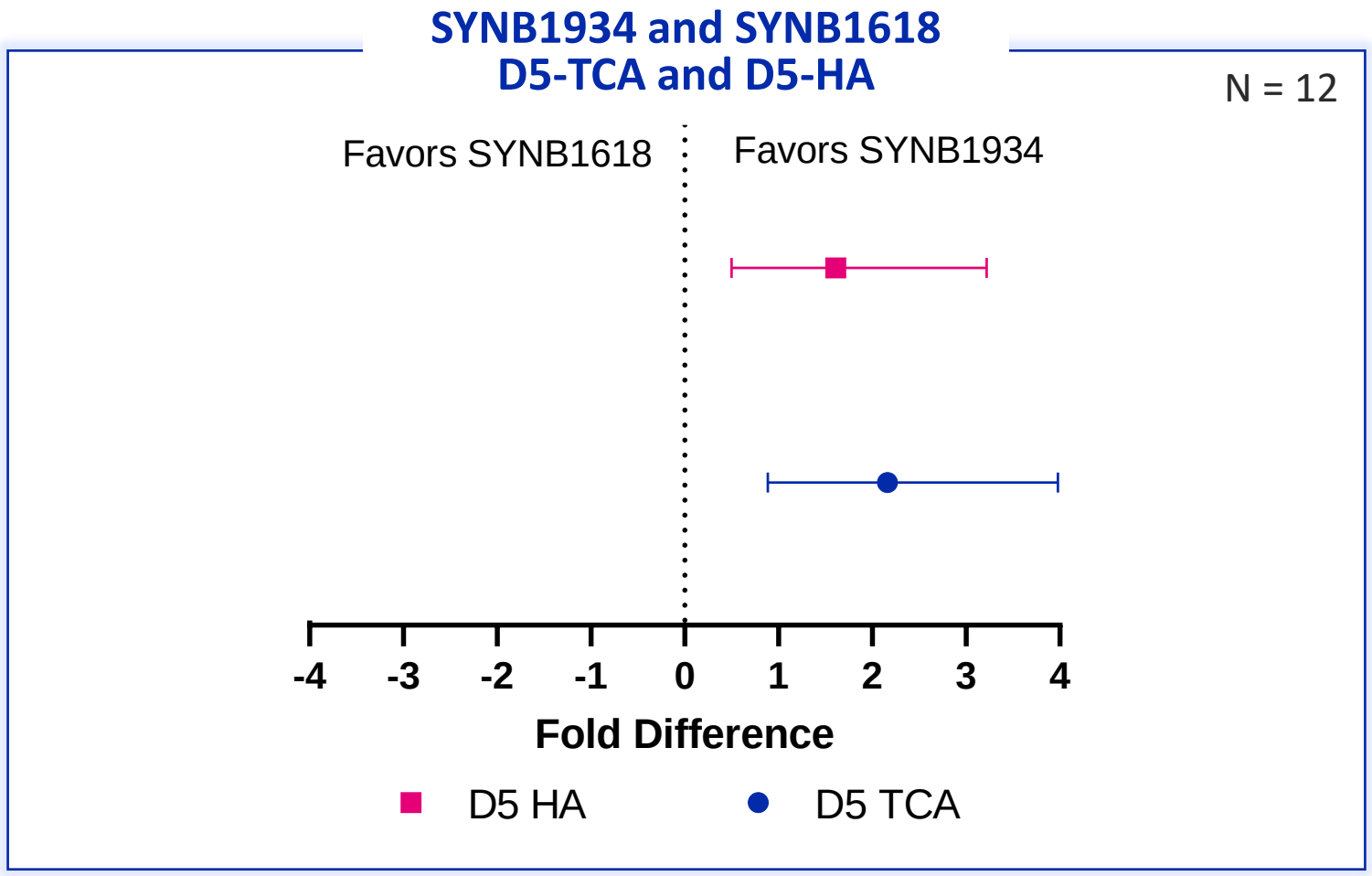
SYNB1934 metabolized labeled D5-Phe in a dose dependent manner



SYNB1934 exhibited clear and consistent dose responsive activity in humans

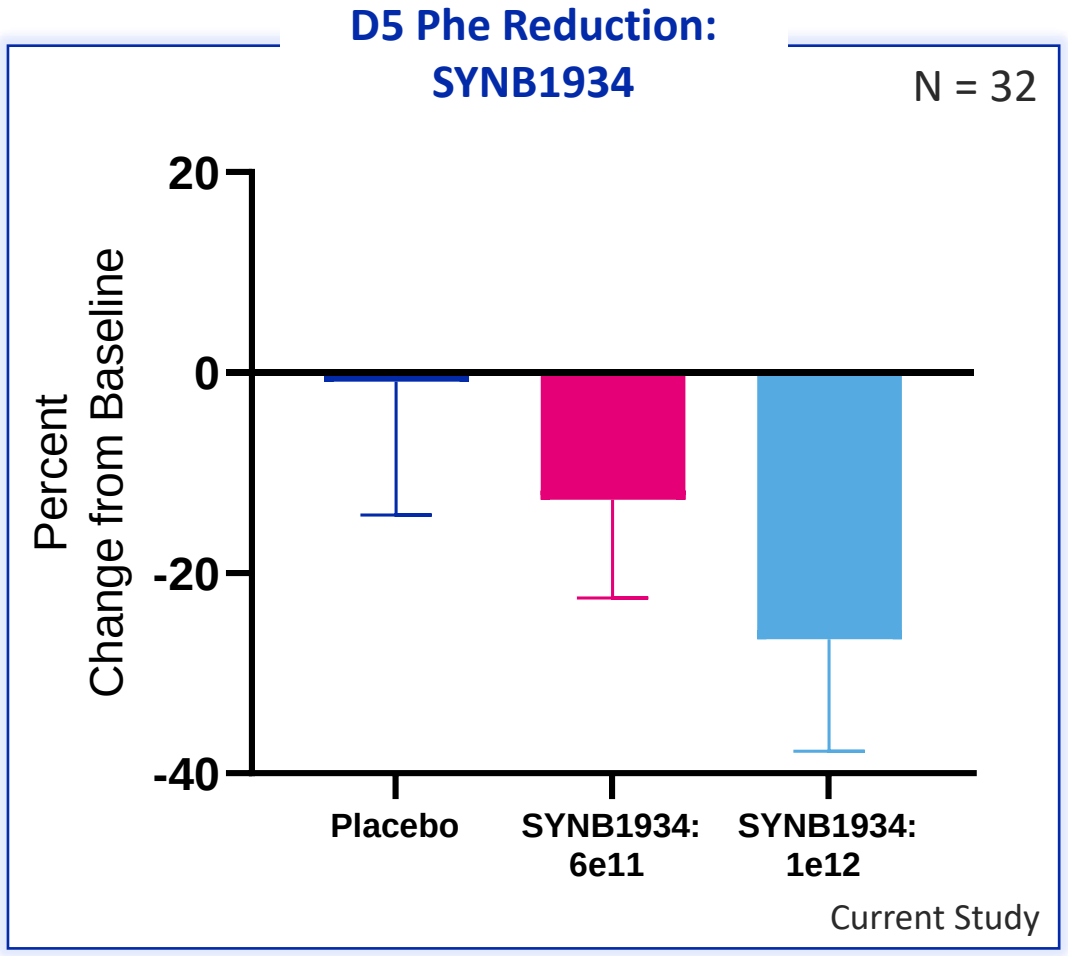
Mean +/- 90% confidence interval. TCA = *trans*-cinnamic acid

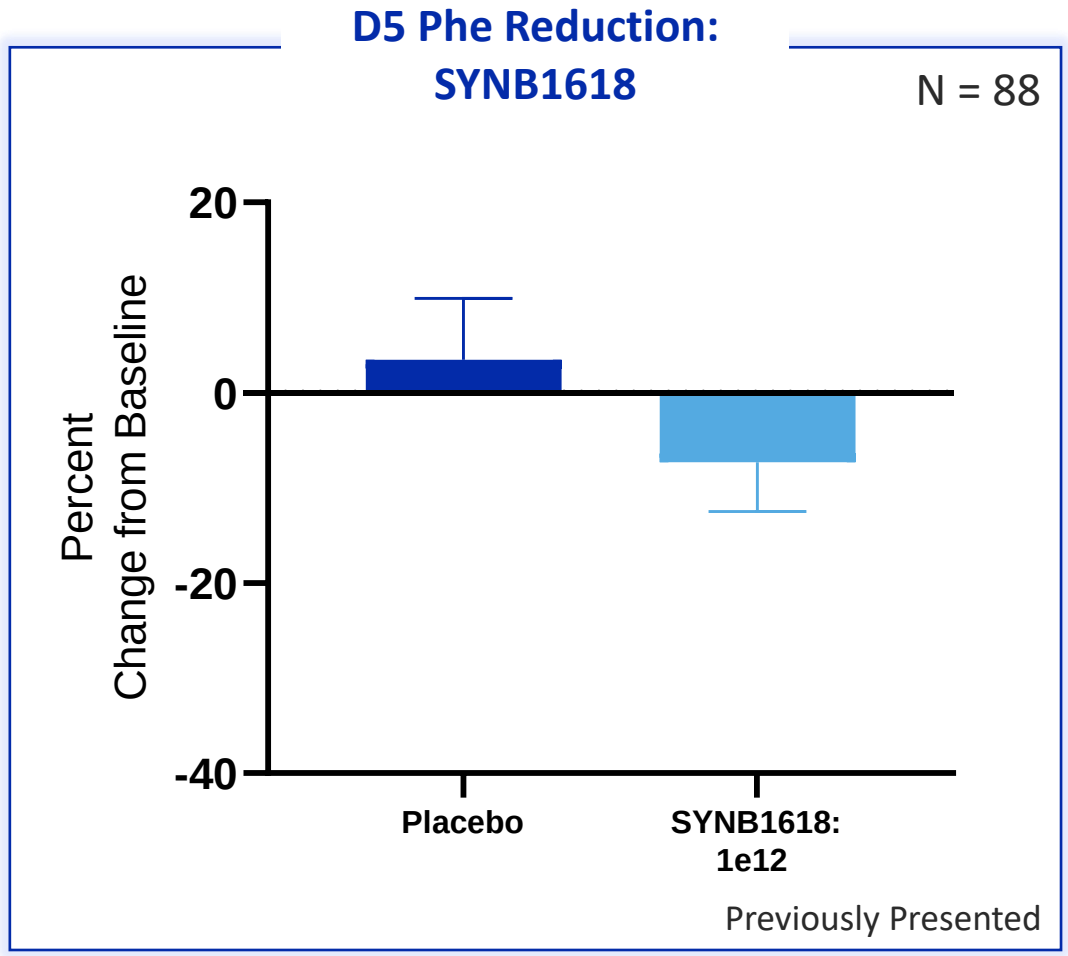
SYNB1934 demonstrated two-fold improvement over SYNB1618 in biomarkers of Phe metabolism



Mean +/- 90% confidence interval. TCA = *trans*-cinnamic acid HA = hippuric acid

Robust labeled D5-Phe reduction in healthy volunteers at multiple dose levels



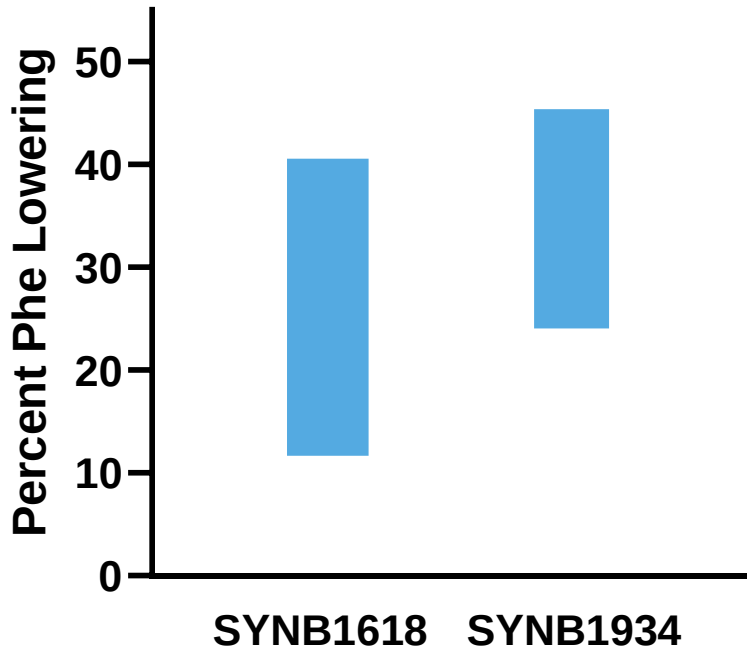


Percent change from baseline +/- 90% confidence interval. Cross study comparison. N = total study (all cohorts)

Prospective modeling for SYNB1618 predicted clinical activity

Prospective Model Results

(1e12 Live Cells)



Previously Presented

SYNB1618 Modeling

- Model predicted **15-40%** Phe lowering with SYNB1618 1e12 dose
- Model predicted **20-45%** Phe lowering with SYNB1618 at 2e12 dose

Clinical Observation

- Mean **20%** Phe lowering with SYNB1618 at 1e12 dose
- Mean **40%** Phe lowering with SYNB1618 at 2e12 dose after meal challenge

Prospective biomarker driven modeling suggests SYNB1934 provides opportunity for increased Phe lowering

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Model range represents relative activity of enzymes: PAL and LAAD

SYNB1934 to be evaluated in new arm of SynPheny-1 study

	Healthy volunteers	PKU Patients
SYNB1618 1e12 dose	**7%** D5-Phe reduction post-meal	**20%** Fasting plasma Phe
SYNB1934 1e12 dose	**27%** D5-Phe reduction post-meal	***Expectation of improved clinical profile***

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Portfolio Implications and Next Steps in PKU

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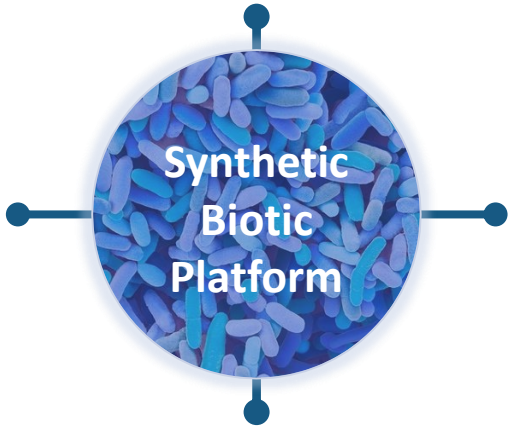
Synthetic Biotic Platform is enabling engine for drug development

Platform

Deep synthetic biology expertise: Internal + Ginkgo Bioworks

Prospective, biomarker driven modeling predictive of therapeutic effect



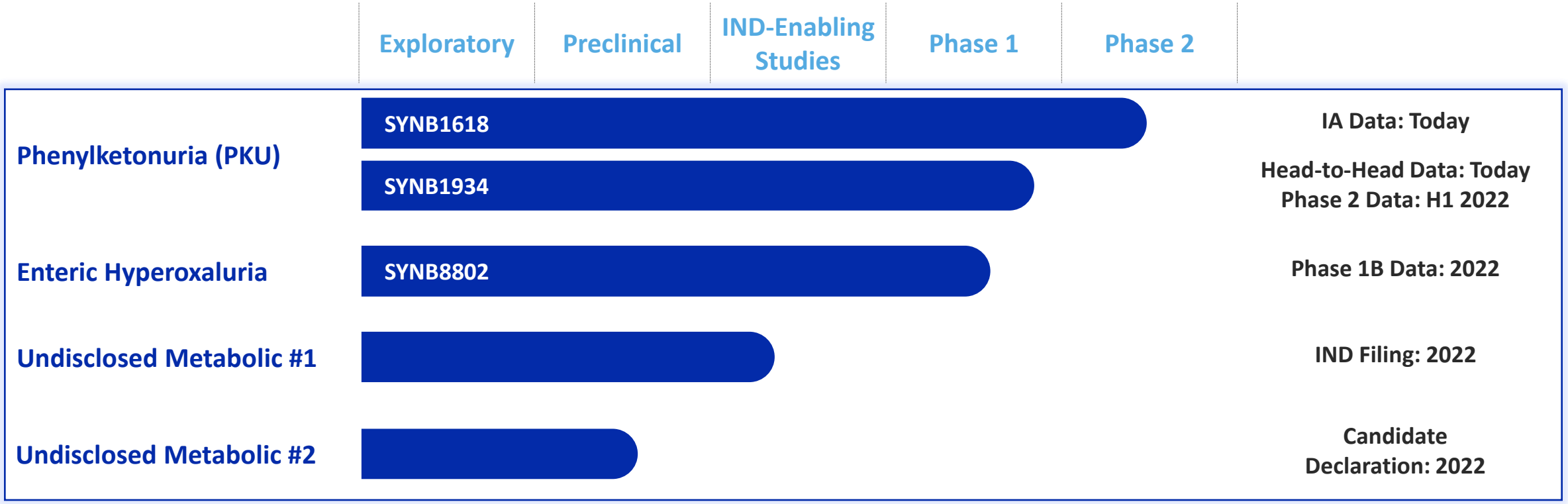
Modular SynBio components enables rapid, iterative product development

Internal process development and GMP manufacturing of live biotherapeutic

- Prospective modeling defines target product profiles
- Optimization of strains creates compelling clinical profiles
- Integrated translational and manufacturing capabilities enables rapid path to and through clinic

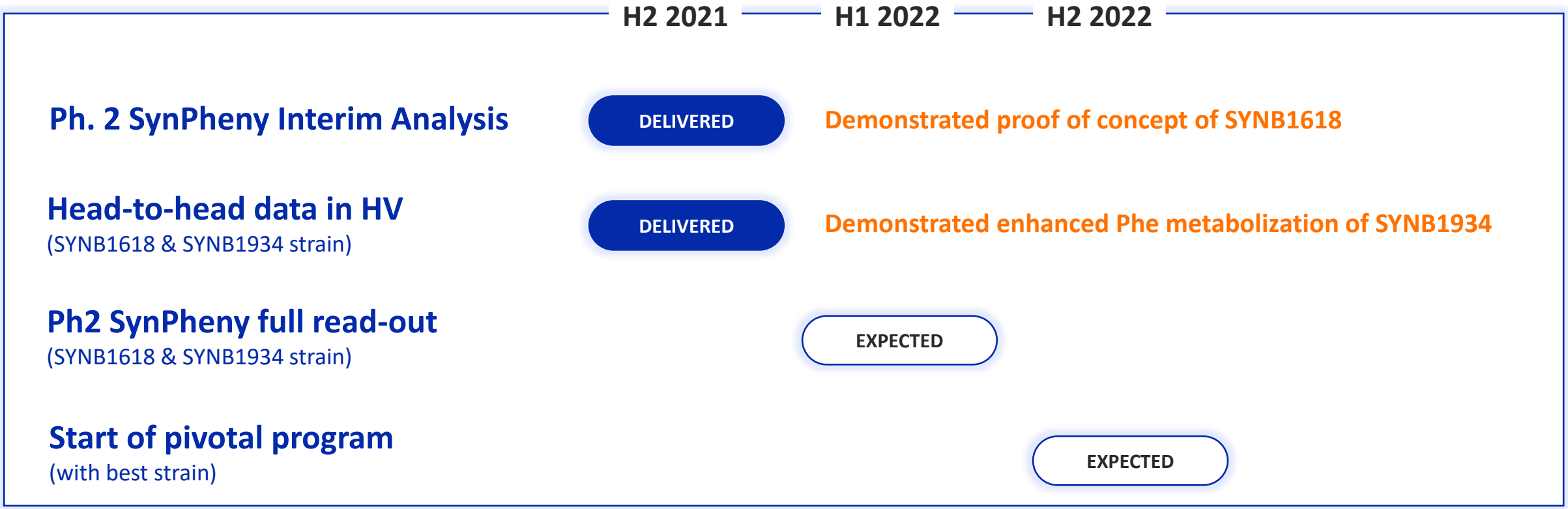
Integrated platform can repeatedly and rapidly generate optimized clinical candidates

Synthetic Biotic platform enables portfolio of high value metabolic indications



We are applying biomarker driven predictive modelling and strain optimization across the portfolio of metabolic indications

PKU program to rapidly advance towards pivotal program



Significant additional value inflection points in PKU program in 2022

Synthetic Biotic Medicines: a novel approach in Phenylketonuria (PKU)

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SYNB1618 strain achieved prespecified 20% Phe lowering target in PKU patients

SYNB1934 Ph. 1 HV

SYNB1934 strain demonstrated two-fold greater activity than SYNB1618 in healthy volunteers

Synlogic intends to begin pivotal study planning and advance the best asset into Phase 3 in 2022

Thank you to our study sites, patients, and investigators

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Available For Questions

Aoife Brennan, MB ChB
President & CEO

Daniel Rosan
Head of Finance & Investor Relations

Dave Hava, PhD
Chief Scientific Officer

Antoine Awad
Chief Operating Officer

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