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
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

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

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

Ph. 1 HV
PKU remains an area of high unmet need

Patients

Julia, living with PKU

Pediatrics
~5,000 U.S.
25% out of Phe control
90% of patients and caregivers express need for greater natural protein intake (1)

Adults
~12,300 U.S.
65% out of Phe control

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

(1) Puurunen et al, Global PKU Patient Meeting, September 2021
PKU patients are poorly served today

**Disease State**
- **Out of Phe Control** (>360 μmol/L of Phe)
- **In Phe control** (<360 μmol/L of Phe)

**Patient Goal**
- **Lower blood Phe** to reduce risk of neurocognitive impairment
- **Enable greater dietary protein intake** while maintaining Phe control

**Limited Therapeutic Options**
- Daily injection
- Allergic reactions
- REMS
- Adults only
- 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

\(^{(2)}\) 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

Dietary Phe

Converted by Synthetic Biotic to harmless metabolites (TCA)

Reduce plasma Phe or enhance protein tolerance

Oral therapy, 3 x day with meals

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
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

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

Percent change from baseline +/- 95% confidence interval. TCA = trans-cinnamic acid. AUC = Area under curve.
SYNB1618 reduced fasting plasma Phe levels

Fasting Plasma Phe Levels (N=8)

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

Percent change from baseline +/- 95% confidence interval. * = Statistically significant
Summary of interim safety analysis

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
SYNB1934 Phase 1 Study Results

Dr. David Hava, PhD
Chief Scientific Officer
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

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 = \textit{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

**SYNB1934 and SYNB1618**

D5-TCA and D5-HA

Favors SYNB1618  Favors SYNB1934

N = 12

Fold Difference

-4 -3 -2 -1 0 1 2 3 4

Favors SYNB1618  Favors SYNB1934

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

D5 Phe Reduction:
SYNB1934

N = 32

D5 Phe Reduction:
SYNB1618

N = 88

Placebo SYNB1934: 6e11
SYNB1934: 1e12

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)

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

**Healthy volunteers**

- **SYNB1618**
  - 1e12 dose
  - 7% D5-Phe reduction post-meal

**PKU Patients**

- **SYNB1934**
  - 1e12 dose
  - 27% D5-Phe reduction post-meal
  - 20% Fasting plasma Phe

*Expectation of improved clinical profile*
Portfolio Implications and Next Steps in PKU
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

Synthetic Biotic Platform

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

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- **Phenylketonuria (PKU)**
  - SYNB1618
  - IA Data: Today
  - Head-to-Head Data: Today
  - Phase 2 Data: H1 2022

- **Enteric Hyperoxaluria**
  - SYNB8802
  - Phase 1B Data: 2022

- **Undisclosed Metabolic #1**
  - IND Filing: 2022

- **Undisclosed Metabolic #2**
  - Candidate Declaration: 2022

We are applying biomarker driven predictive modelling and strain optimization across the portfolio of metabolic indications.
PKU program to rapidly advance towards pivotal program

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<td>Ph. 2 SynPheny Interim Analysis (DELIVERED)</td>
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<td>Head-to-head data in HV (SYNB1618 &amp; SYNB1934 strain) (DELIVERED)</td>
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<td>H2 2022</td>
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<td>Start of pivotal program (with best strain)</td>
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Significant additional value inflection points in PKU program in 2022
Synthetic Biotic Medicines: a novel approach in Phenylketonuria (PKU)

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

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
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