Transforming Medicine Through Synthetic Biology

Synpheny-1 Phase 2 Top-Line Results

October 18, 2022
Forward Looking Statements

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Speakers

Aoife Brennan, MB ChB
President & CEO

Molly Harper
Chief Business Officer

Caroline Kurtz, PhD.
Chief Development Officer
Opening Remarks

Dr. Aoife Brennan
President & CEO
PKU remains a profound burden

Phase 2 top-line data confirm transformative potential of SYNB1934

Expect to initiate Phase 3 with SYNB1934 in H1 2023
The Opportunity & Positioning for PKU

Molly Harper
Chief Business Officer
PKU: Universally Diagnosed, Underserved

Underserved Population

~75% remain untreated\(^1\)

Attractive Market Opportunity

- 17,000 in the US;\(^1\) >150,000 globally\(^2\)
- Kuvan\(^\circledR\) achieved $500mm/yr with ~15% share\(^3\)
- Palynziq\(^\circledR\): $300mm for 2022 with ~10% share\(^3\)

What Good Looks Like

Target threshold for plasma Phe reduction -20%

Per clinician, KOL input\(^4\)

Regulatory precedent for response target\(^5\)

Designed to Fit with PKU Patients

Patient Presentation, SYNB1618 & SYNB1934

- Potential clinical positioning: as both monotherapy and adjunctive* treatment options
- Lack of systemic absorption
- Convenient, oral administration
Synpheny-1
Phase 2 Top-Line Results

Caroline Kurtz, PhD.
Chief Development Officer
Phase 2 Synpheny-1 in Patients with PKU

**Study Design**

<table>
<thead>
<tr>
<th>Diet Run-In</th>
<th>Dose Ramp(^1)</th>
<th>Treatment Period</th>
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</thead>
<tbody>
<tr>
<td>Day -1</td>
<td>Day 1</td>
<td>Day 7</td>
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</table>

- **Fasting Plasma Phe**
- **D5-Phe Tracer Study**

**Dosing**

- Day -1: 1 x 10\(^{11}\)
- Day 1: 3 x 10\(^{11}\)
- Day 7: 1 x 10\(^{12}\)
- Day 14: 1 x 10\(^{12}\)

\(^1\) SYNB1618: Days 1-3: 1x10\(^{11}\), Days 4-6: 3x10\(^{11}\); SYNB1934: Days 1-3: 3x10\(^{11}\), Days 4-6: 6x10\(^{11}\)

**Disposition & Demographics**

- Enrolled **20 adults** with PKU (SYNB1618 =11, SYNB1934 = 9)

- All had **Phe > 600 \(\mu\)M** at screening, despite diet and/or sapropterin (Kuvan\(^\circledR\)), with mean of 1,041 \(\mu\)M and 987 \(\mu\)M for SYNB1618 and SYNB1934, respectively\(^2\)

- Baseline characteristics were evenly distributed across arms, with a representative mix by age, gender, Phe levels, and baseline treatment

\(^2\) Baseline Phe values per data for \(n=5\)
Robust Mean Reductions in Plasma Phe (“All Comers”*)

Plasma Phe Change vs. Baseline (Day 14)

Data are LS mean +/- 95% CI
SYNB1618 n=10; SYNB1934 n=5

* Defined as those that completed dosing
Note: The 95% confidence interval did not cross zero for either strain

% Change

-60%
-40%
-20%
0%
-20%
-34%

% change +/-95% CI

SYNB1618
SYNB1934
Robust Mean Reductions in Plasma Phe ("All Comers")*

Plasma Phe Change vs. Baseline (Day 14)

-20%  -34%

% Change

% change +/-95% CI

SYNB1618  SYNB1934

Kuvan® pivotal study
“All comers” benchmark¹

Robust Mean Reductions in Plasma Phe ("All Comers")*

Data are LS mean +/- 95% CI
SYNB1618 n=10; SYNB1934 n=5

* Defined as those that completed dosing
Note: The 95% confidence interval did not cross zero for either strain

Responder Data Show Clinical Significance of Phe Lowering

**SYNB1618**

6/10 achieved at least 20% Phe lowering

Range among responders -20% to -61%

**SYNB1934**

3/5 achieved at least 20% Phe lowering

Range among responders -29% to -80%

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1. Responder definition: >20% reduction vs. baseline in plasma Phe levels achieved on Day 7 or Day 14
2. Maximum Phe reduction by patient, Day 7 or Day 14
Results Across All Participants Support Strength of Profile

Data Based on Integrated Analysis with Arms 1 & 2 (n=15)

Responders

- 60% (9/15) achieved at least 20% Phe lowering*

Response

- 42% mean Phe lowering in responders (n=9 responders)

Threshold Lowering

- 7/9 of the responders achieved Phe levels ≤600 µM

* Responder definition: ≥20% reduction vs. baseline in plasma Phe levels achieved on Day 7 or Day 14

SYNB1618 n=10; SYNB1934 n=5
Data Confirm Potential as Adjunctive Treatment Option

• Data included patients who received study drugs as an adjunct to ongoing treatment with sapropterin (Kuvan®)

• Adjunctive data for patients for both strains were consistent with broader findings
  • Phe reductions were 26% and 80%
  • In line with expectations given independent mechanism

• This experience confirms potential as an adjunctive treatment option
Biomarkers Confirm Phe Metabolism in GI Tract by Both Strains

**Inhibition of Phe Absorption**

- **Plasma D5-Phe**
  - Data are LS mean +/- 95% CI; SYNB1618 n=10; SYNB1934 n=5

**Biomarkers of Strain Activity in GI Tract**

- **Plasma D5-TCA**
- **Urinary D5-HA**

*Primary Endpoint*

TCA = trans-cinnamic acid; HA = hippuric acid; AUC = area under the curve; AeT = total amount excreted
Safety & Tolerability – Summary of Top-Line Findings
Favorable profile, consistent with program findings to date

Adverse events were all **mild to moderate**, predominantly GI in nature, and similar across SYNB1618 and SYNB1934.

- 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.

There were **no serious adverse events** (SAEs)

Expected Phase 3 plans incorporate these learnings through (1) Starting with a low dose and (2) A slower ramp, with more time at each dose prior to advancing
Phase 2 Top-Line Results Support Potential to Transform PKU

The **vast majority of PKU patients need a medical treatment** to lower Phe, with 75% untreated

- **Clinically meaningful Phe reduction**: SYNB1934 “All-comers” mean Phe reduction of -34%
- **Strong response**: 60% achieved clinical response across both strains, with -42% Phe lowering among responders
- **Potential for adjunctive therapy**: Additional Phe-lowering when provided to Kuvan-treated patients confirms potential for adjunctive use
- **Favorable safety profile**: Across Phase 2, all adverse events were mild or moderate in severity and were predominantly gastrointestinal (GI) in nature. There were no serious adverse events (SAEs).

With >230 patients dosed across 4 clinical trials, PKU Program advances to Ph. 3 with SYNB1934

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

Dr. Aoife Brennan
President & CEO
PKU Program Has Clear Path to Phase 3

**H2 2021**
- **SYNB1618**: POC established
- **SYNB1934**: Greater potency confirmed in Phase 1
- **Committed to Ph. 3** based on strength of POC

**H2 2022**
- **SYNB1618**: Completed Ph. 2
- **SYNB1934**: Generated data in PKU patients
- **Monotherapy and adjunctive potential positioning confirmed**

**H1 2023***
- **Ph. 3 initiation** with SYNB1934
  - Single, registrational study
  - Primary endpoint: plasma Phe reduction (vs. placebo) in responder population
  - Low dose to start, slower ramp, and flexible titration to optimize tolerability

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1. 20% reduction vs. baseline in plasma Phe was used as the responder definition for Palynziq (pegvaliase injection), the most recent PKU approval by the EMA and FDA, per Palynziq USPI

* Anticipated timing and study design
PKU remains a profound burden.

Phase 2 top-line data confirm transformative potential of SYN1934.

Expect to initiate Phase 3 with SYN1934 in H1 2023.
Advancing a New Class of Biotherapeutics

**Metabolic**

<table>
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<th>Phenylketonuria (PKU)</th>
<th>Homocystinuria (HCU)</th>
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<tr>
<td>SYN1934</td>
<td>SYN1353</td>
<td>Ph 1 HV Data H2 2022</td>
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<td>SYN8802</td>
<td></td>
<td>Proof of Concept H2 2022</td>
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<td>SYN2081</td>
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**Enteric Hyperoxaluria**

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<tr>
<th>Gout</th>
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<td>SYN1353</td>
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**Immunology**

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<th>Inflammatory Bowel Disease (IBD)</th>
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<td>IBD Program - Single Target (Roche)</td>
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HV = Healthy Volunteers

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Available For Questions

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Michael Jensen
Chief Financial Officer

Dave Hava, PhD
Chief Scientific Officer

Antoine Awad
Chief Operating Officer
Thank You