Development of SYNB1934 for the Treatment of Phenylketonuria: Phase 2 Data and Phase 3 Design

Caroline Kurtz, Neal Sondheimer, David Hava, Aoife Brennan

Synlogic Inc., Cambridge, MA

synlogic

Introduction

Despite the introduction of adjunctive therapies, there remains an unmet medical need in phenylketonuria (PKU). Phe control by dietary management is difficult and many patients are unable to reach goals, risking cognitive impairment and supporting the need for novel treatment approaches.

Synthetic biotics are a new class of investigational medicines, designed to carry out beneficial activities within patients. Two synthetic strains, SYNB1618 and SYNB1934 were engineered from Escherichia coli Nissle 1917, expressing phenylalanine ammonia lyase (PAL), L-amino acid deaminase (LAAD) and a Phe transporter with auxotrophy to prevent replication in the body.

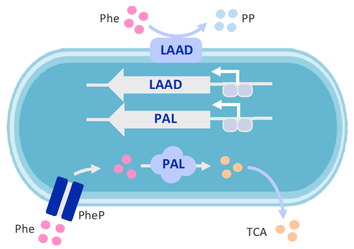


Figure 1. SYNB1618/SYNB1934. SYNB1934 contains a modified version of PAL with enhanced Phe consumption activity compared with SYNB1618. In vitro studies showed an approximate two-fold elevation in PAL activity in SYNB1934 compared to SYNB1618. Studies in healthy human volunteers and patients with PKU evaluated the metabolism of deuterated Phe (*d5*-Phe) and confirmed greater potency of SYNB1934.

Phase 2 Synpheny-1 Study[1]

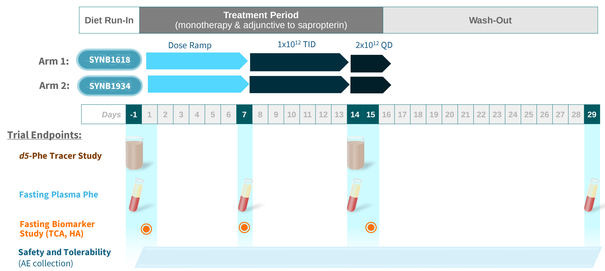


Figure 2. Synpheny-1 was an open-label Ph2 study to evaluate safety and efficacy of SYNB1618 (arm-1) and SYNB1934 (arm-2) in 20 adult PKU patients. 24h *d5*-Phe was AUC evaluated, d-1, 14 (at $2x10^{12}$ dose). Fasting Phe: evaluated in AM pre-dose on Days -1, 7, 14, 29. Biomarkers (TCA, HA): evaluated d1, 7, 15. Safety and tolerability: AEs collected throughout treatment and at Day 29.

Patient Disposition

- 28 patients screened
- 20 patients enrolled (11 in arm 1, 9 in arm 2)
- 15 patients completed
- 5 patients discontinued (1 in arm 1, 4 in arm 2)

References:

1. Vockley J, Sondheimer N, Ginevic I, Grange D, Northrup H, Phillips J, Searle S, Thomas J, Zori R, Denny W, Ding C, Ernst S, Humphries K, McWhorter N, Sethuraman V, Woodbury C, Puurunen M, Kurtz C, Brennan A. Synpheny-1: A phase 2 study of the efficacy and safety of SYNB1618 and SYNB1934 in patients with phenylketonuria. Presented at Society for Inherited Metabolic Disorders (SIMD); 2023 March 18-21; Salt Lake City, UT.

Results

Reduction in *d5*-Phe

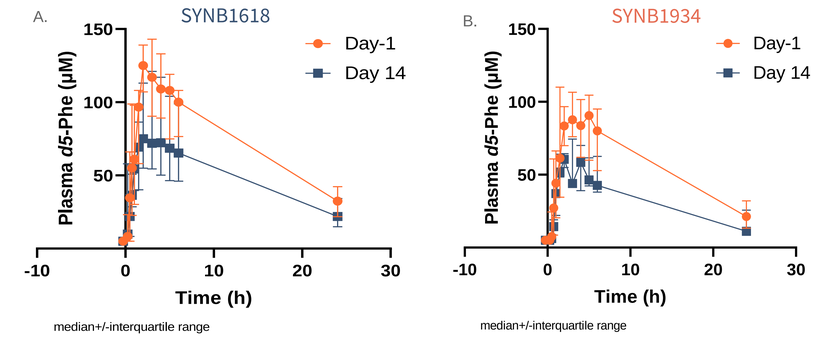


Figure 3. Plasma *d5*-Phe measured over 24 hours (-15, 15, 30, 45, 60, 120, 180, 240, 360, 1440 min), on Days –1 and 14 for all patients with complete samples on these days. A) Arm 1 (SYNB1618) Day-1 n=11, Day 14, n=9-10; B) Arm 2 (SYNB1934): day-1 n=8-9, day 14 n=5. Median values and interquartile range shown at each timepoint for Day -1 (orange) and Day 14 (blue).

- **All participants completing day 14 dosing demonstrated strain-specific Phe metabolism through *d5*-Phe reduction and production of metabolites *d5*-TCA and *d5*-HA**

Reduction in Mean Fasting Plasma Phe

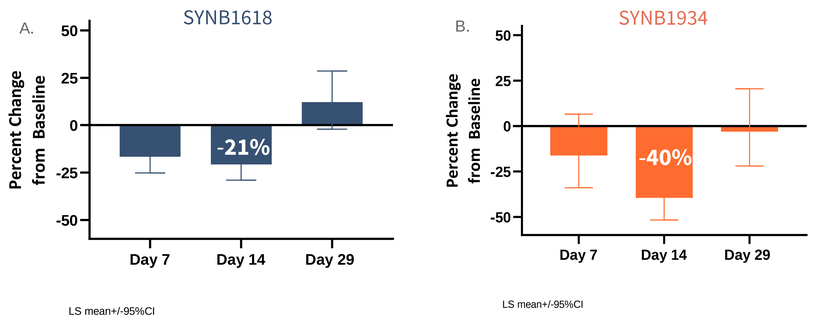


Figure 4. Percent change from baseline in fasting Phe values taken from blood draws before breakfast on Days –1 (baseline), 7, 14, and 29. LS mean change from baseline was calculated for days 7, 14, 29 using a mixed model of repeated measures. Estimates were performed on a log scale and back transformed to ratios for reporting. A) Arm 1, SYNB1618 (n=11); B) Arm 2 SYNB1934 (n=9). CI = confidence interval; LS = least squares.

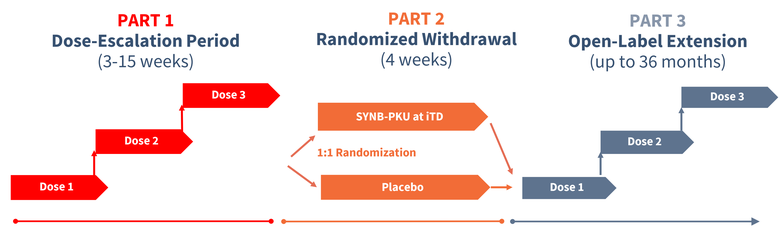
- **60% (n=9) of patients completing the study achieved Phe reduction ≥ 20%**
- Of this group, there was an average reduction of -36% in SYNB1618 group and -53% in SYNB1934

Safety and Tolerability Were Comparable Across Both Strains

- There were no SAEs
- TEAEs were all mild to moderate
- GI adverse events were the most common AEs (e.g., nausea, vomiting, abdominal pain, diarrhea) and similar in frequency and severity between the two strains
- Five patients discontinued due to TEAEs (one on SYNB1618 and four on SYNB1934)

Proposed Phase 3 Clinical Trial Design: Synpheny-3

- **Synpheny-3 is designed as a single, registrational study:** in PKU patients ages ≥ 12+ yrs*, with plasma Phe levels at baseline of ≥ 360 µM; N~150



- Individualized titration to find patient's optimal dose (iTD)
- Confirms "responders" for primary analysis period (in randomized withdrawal)

- Evaluates primary endpoint of plasma Phe reduction in treated vs. placebo among responders (from Part 1)

- Patients re-establish iTD, and collect long term safety data

* Pending data generated in adults first.

Phase 3 Endpoints

	Part 1/Dose-Escalation	Part 2/Randomized Withdrawal	Part 3/Open-Label Extension
Primary	To assess the percentage change in blood phenylalanine (Phe) level	To evaluate efficacy of **SYNB1934** versus placebo in the responder population through the change from baseline to Week 4 in blood Phe level	
Secondary	To assess the absolute change in Phe level	To evaluate the efficacy of **SYNB1934** versus placebo in the responder population with regard to the proportion of patients with a blood Phe level ≤ 360 µmol/L	To assess safety and tolerability
	To assess proportion of patients with a ≥20% reduction in blood Phe level	To evaluate the efficacy of **SYNB1934** versus placebo in the responder population with regard to change from DEP baseline in blood Phe level	To assess absolute and relative changes in blood Phe
		To evaluate efficacy of **SYNB1934** versus placebo in the responder population with regard to percent change from DEP baseline in blood Phe level at Week 4	To assess dietary protein intake

Conclusions

- Consistent with HV studies, SYNB1618 and SYNB1934 metabolize Phe in the GI tract in patients with PKU
- Phe lowering was seen with both SYNB1618 and SYNB1934 in a dose dependent manner
- There were no serious adverse events or deaths related to SYNB1618 or SYNB1934
- The most commonly observed AEs were mild to moderate gastrointestinal symptoms
- Consistent with preclinical data and head-to-head data in healthy volunteers, SYNB1934 has greater Phe metabolizing activity than SYNB1618
- A Phase 3 Trial has been designed based on the results of Synpheny-1 to further evaluate SYNB1934 safety and efficacy in patients with PKU

Disclosure: Studies referenced herein are funded by Synlogic, Inc.
Presented at NPKUA, Denver, CO, April 21, 2023.

synpheny
LIVING IN HARMONY WITH PKU