Synpheny-1: A Phase 2 Study of the Efficacy and Safety of SYNB1618 and SYNB1934 in Patients with Phenylketonuria

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SIMD 2023 Meetings

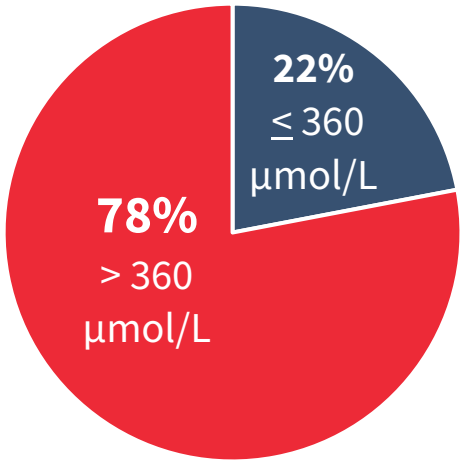
Disclosures

- Current and former employees of Synlogic, Inc.: Neal Sondheimer, Chrisie Ding, Kristina Humphries, Vasu Sethuraman, Casey Woodbury, Marja Puurunen, Caroline Kurtz, and Aoife Brennan
- William Denny, Sharon Ernst, and Nicole McWhorter are consultants to Synlogic, Inc.
- Jerry Vockley, George Diaz, Hope Northrup and John Philips have acted as paid advisors to Synlogic, Inc.
- Jerry Vockley, George Diaz, Ilona Ginevic, Dorothy K. Grange, Hope Northrup, John Phillips, Shawn Searle, Janet Thomas, and Roberto Zori received research funding from Synlogic, Inc.
- Study was sponsored and funded by Synlogic, Inc.

PKU: Despite Progress, Significant Needs Remain

Lifelong Phe Control is the Key to Risk Reduction

Most patients have Phe levels >360 µmol/L [1, 5, 6]



Patients (N=82) aged 18 - 40

Phe levels collected from electronic medical records at two US clinics over a 5-year period[1]

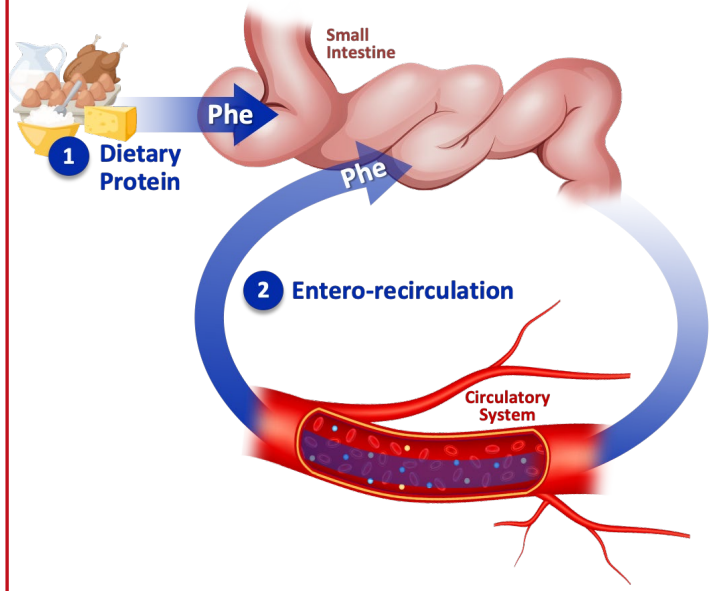
- Phe build-up in the brain can cause neurologic damage and neurocognitive defects, affecting daily living and independence[2-4]
- In multiple studies, most patients remain above goal despite dietary management and pharmacotherapies[1, 5, 6]
- Less than 25% of patients receive available pharmacotherapies[7]

PKU = Phenylketonuria; Phe = Phenylalanine, an amino acid found in all natural sources of dietary protein

1. Levy H et al. *Mol Gen Met* 2020; 129, 177-185. 2. Vockley J, et al. *Genetics Medicine* 2014;16:188-200. 3. Bilder DA, et al. *Mol Gen Metabol*. 2017;121:1-8. 4. Hillert A et al. *Am J Hum Gen* 2020; 107, 234-250. 5. Jurecki E et al., *Mol Gen and Met*. 2017;120:190-197. 6. Brown, Licter-Konecki., *Mol Gen and Met.* 2016. 6, 8-12. 7. US Data estimate NPKUA

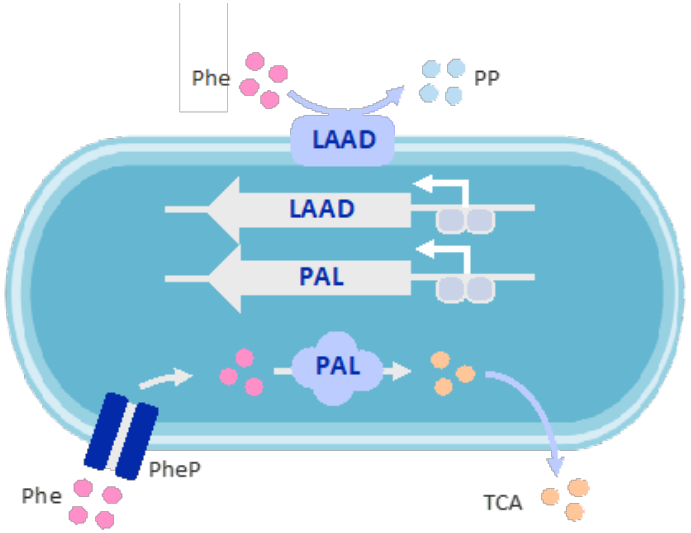
A Genetically-Engineered Probiotic, Designed to Consume Phe

Targeting Phe in the Small Intestine



The small intestine provides a reservoir for targeting Phe, from two sources

SYNB1618 / 1934



Oral administration, TID with meals

- Live Biotherapeutic, derived from *E. coli* Nissle 1917, a probiotic
- Engineered to produce Phe-consuming Phe ammonia lyase (PAL) and L-amino acid deaminase (LAAD)
- GI restricted, non-colonizing, reversible via GI clearance

PKU Program Clinical Studies to Date

In all studies (Ph 1 & Ph 2), 240 participants have been dosed to date, including > 30 PKU participants*

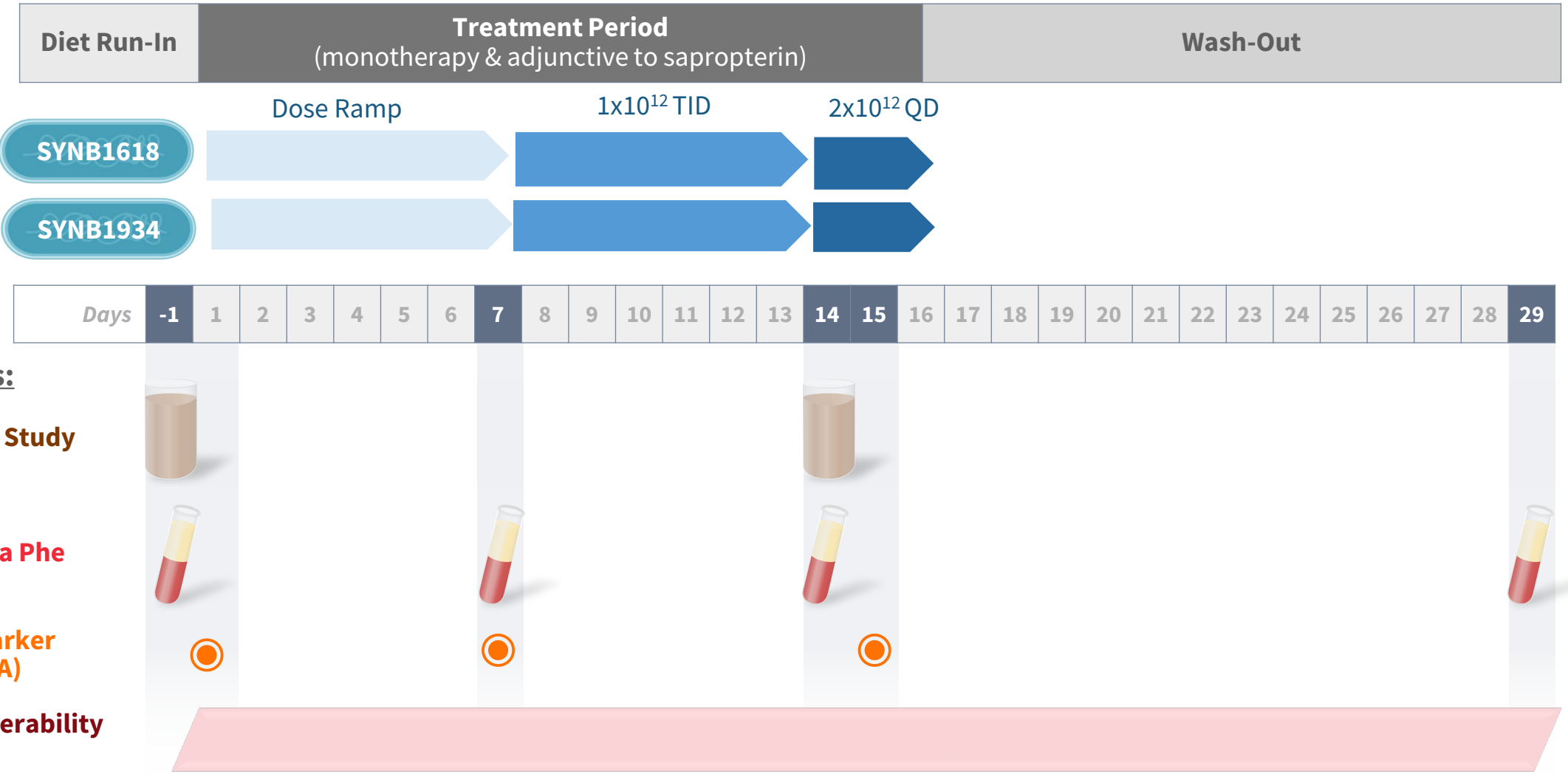
Study	Population	Key Findings
Phase 1 SYNB1618	56 HVs and 14 PKU participants	○ **Established safety and dose-response with frozen liquid formulation, HVs and PKU participants**
Phase 1 SYNB1618	88 HVs	○ **Solid oral/lyophilized formulation matched prior dose response in HVs**
Phase 1 SYNB1934 (with both SYNB1618 and SYNB1934)	62 HVs	○ **Demonstrated ~2x increased activity for SYNB1934 vs. SYNB1618 in HVs** ○ **Established safety bridge to SYNB1934**

* Includes HVs and PKU participants from all Phase 1 studies and Synpheny-1

HV = healthy volunteer; Phe = phenylalanine; PKU = phenylketonuria

Phase 2 Synpheny-1 Study Design

synpheny
LIVING IN HARMONY WITH PKU

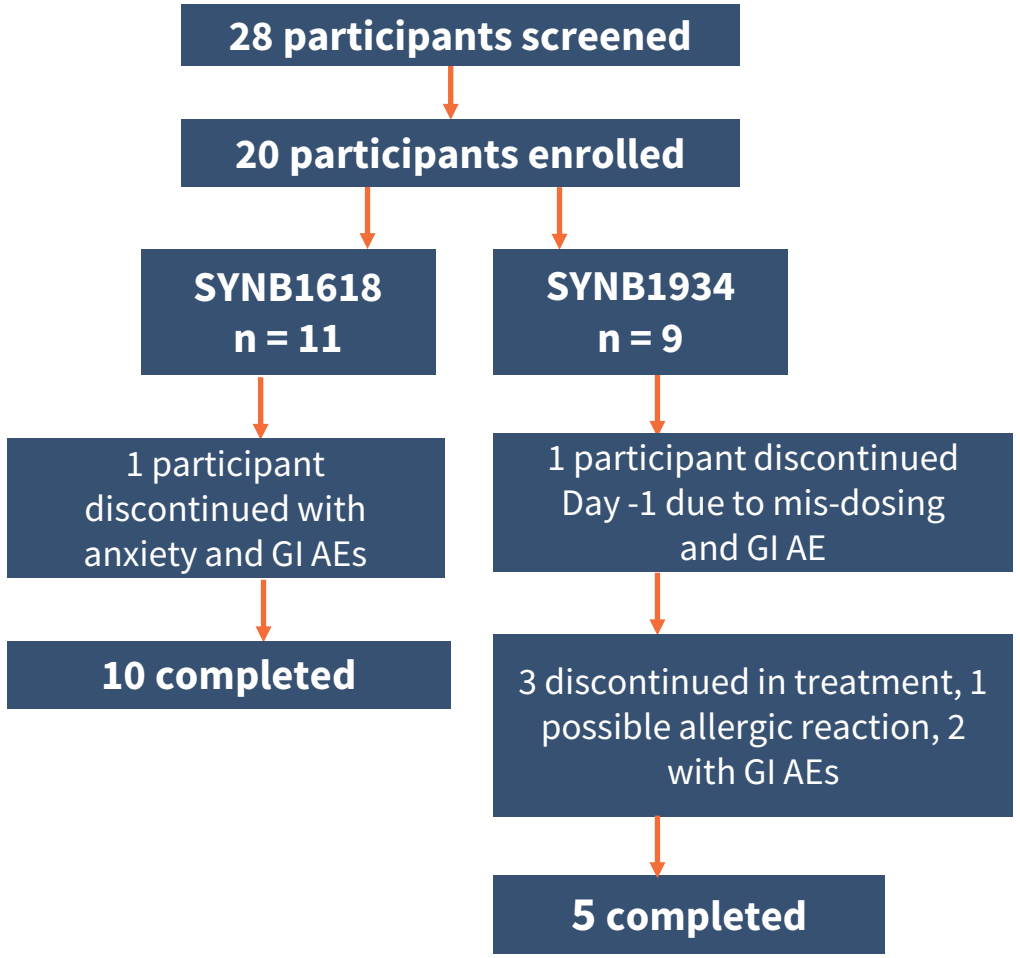


24h AUC evaluated, d-1, 14 (at $2x10^{12}$ dose); Fasting Phe: Evaluated in AM pre-dose on Days -1, 7, 14, 29; Biomarkers (TCA, HA): Evaluated d1, 7, 15; Safety & tolerability: AEs collected throughout treatment and at Day 29

Patient Demographics and Enrollment

Patient characteristics were representative of the PKU population

Demographics / Variables		Arm 1 SYNB1618 (n = 11)	Arm 2 SYNB1934 (n = 9)
Age (years)	**Mean ± SD** **Range**	29.4 ± 10.9 18 - 50	32.2 ± 8.9 23 - 47
Sex (female, male)		6, 5	4, 5
Baseline Phe level (µM)	**Mean ± SD** **Range**	1052.4±481.6 507.0 – 1950.0	938.3 ± 651.4[a] 367 – 2350[a]
Baseline Phe intake (mg)	**Mean ± SD** **Range**	1818.8 ± 1928.3 595 – 7155	2209.2 ± 2585.5[b] 550 – 8943[b]
Concomitant sapropterin use (n)		1	1



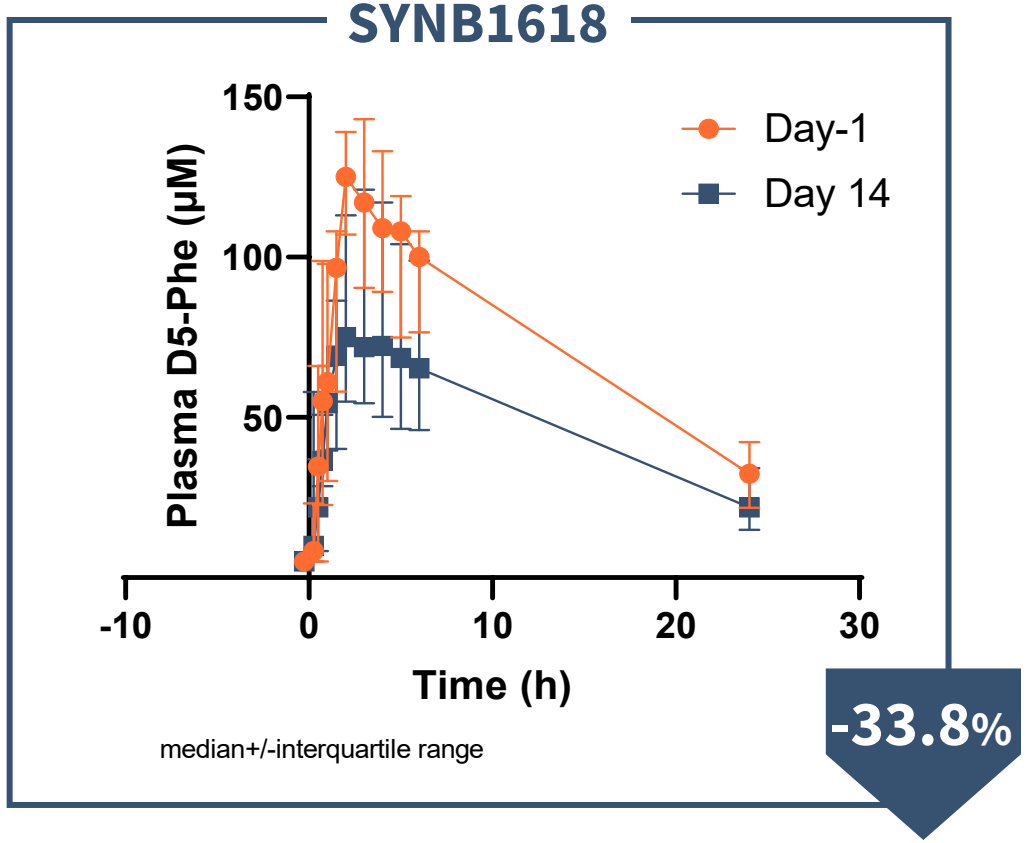
SD = standard deviation.

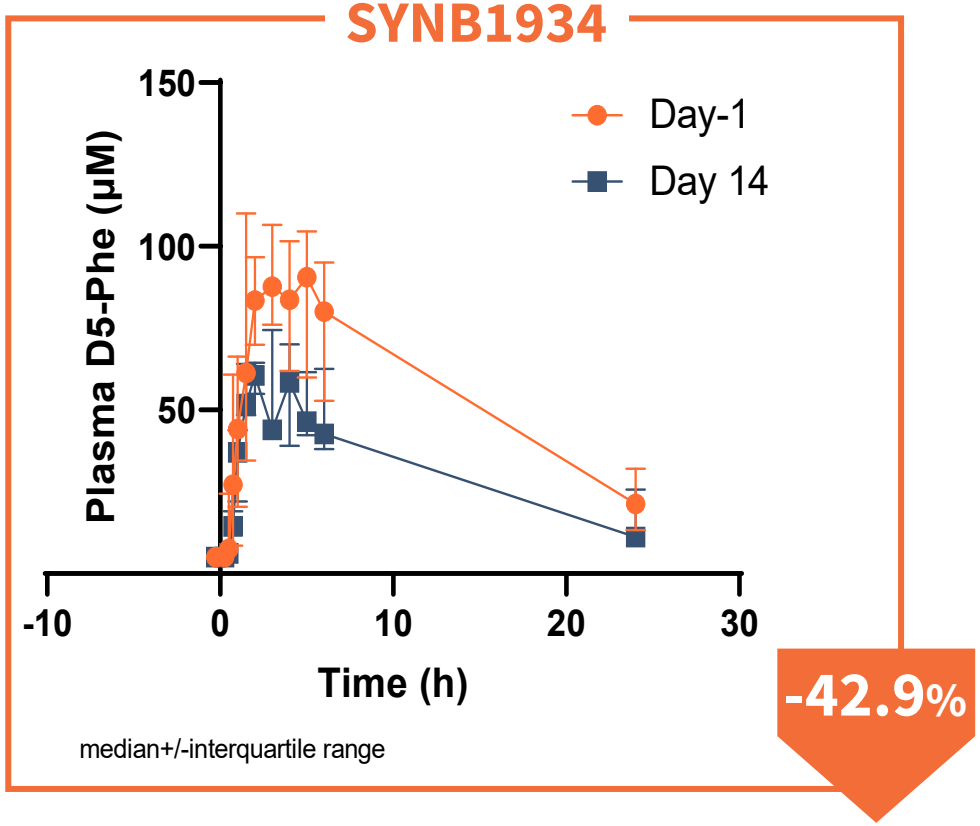
[a] Baseline fasting Phe available for 8/9 patients.

[b] Baseline Phe intake available for 8/9 patients.

Primary Endpoint

SYNB1618 and SYNB1934 Demonstrated D5-Phe Reduction



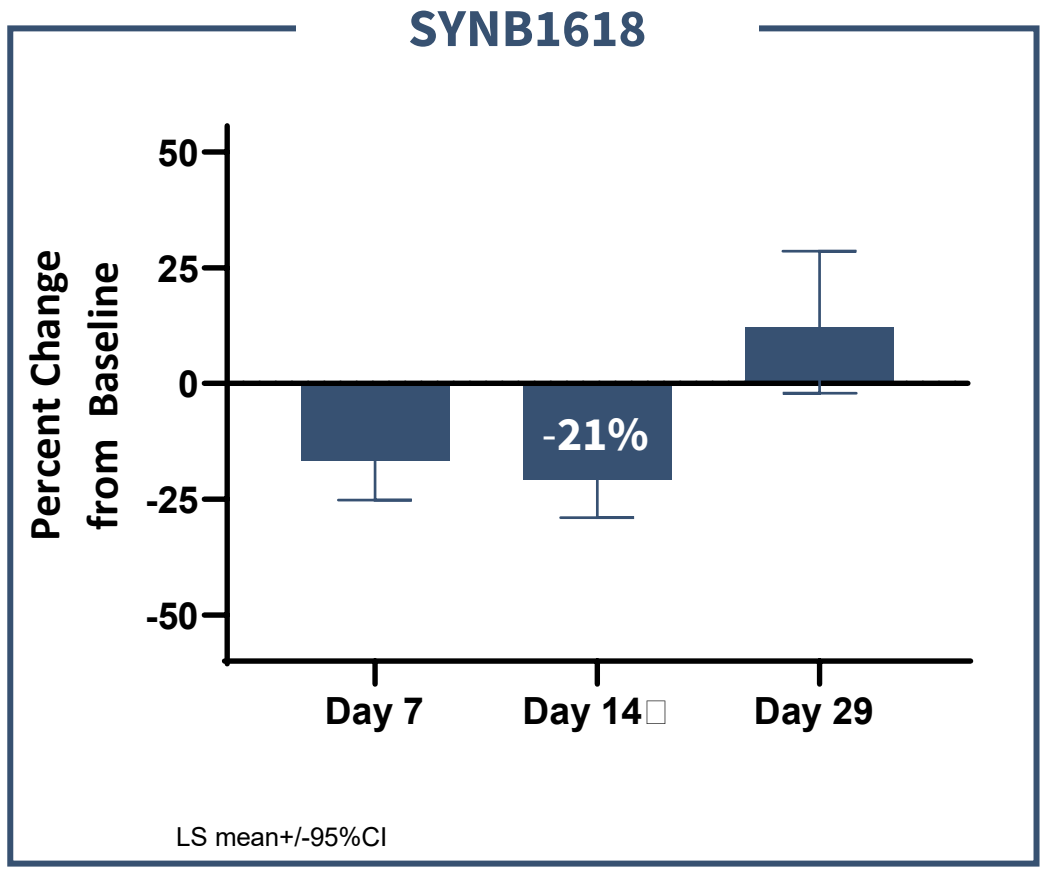


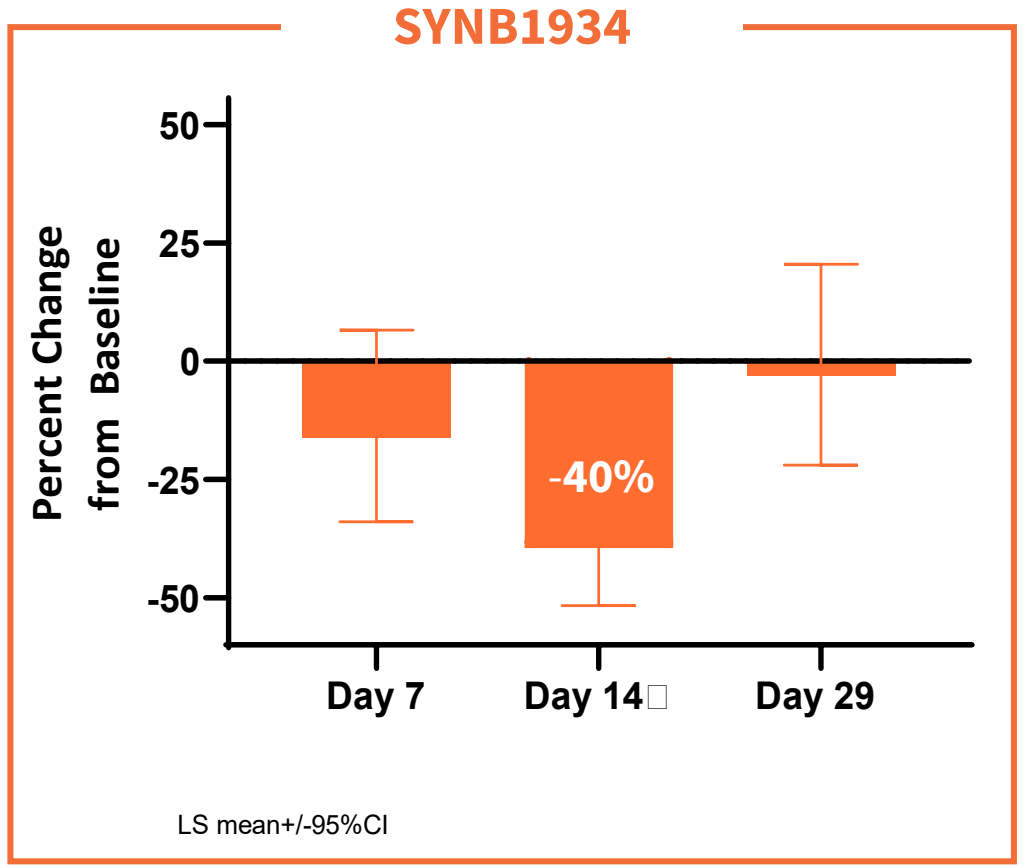
- All participants completing day 14 dosing demonstrated strain-specific Phe metabolism through production of metabolites D5-TCA and D5-HA

Secondary Endpoint

synpheny
LIVING IN HARMONY WITH PKU

Reduction in Mean Fasting Plasma Phe



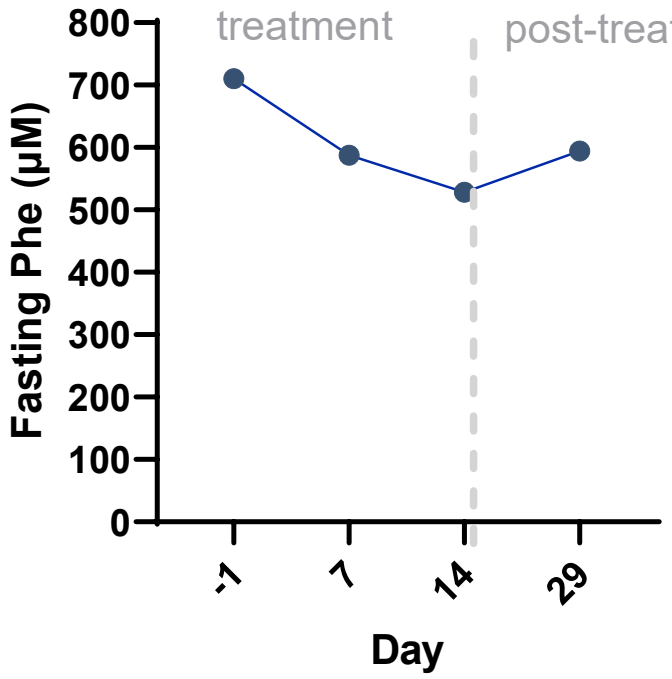


- 60% (n=9) of all participants achieved Phe reduction ≥ 20%
  - Average reduction of -36% in SYNB1618 group and -53% in SYNB1934

Participants (n=2) Chronically Taking Sapropterin Achieved Additional Phe Reduction

SYNB1618

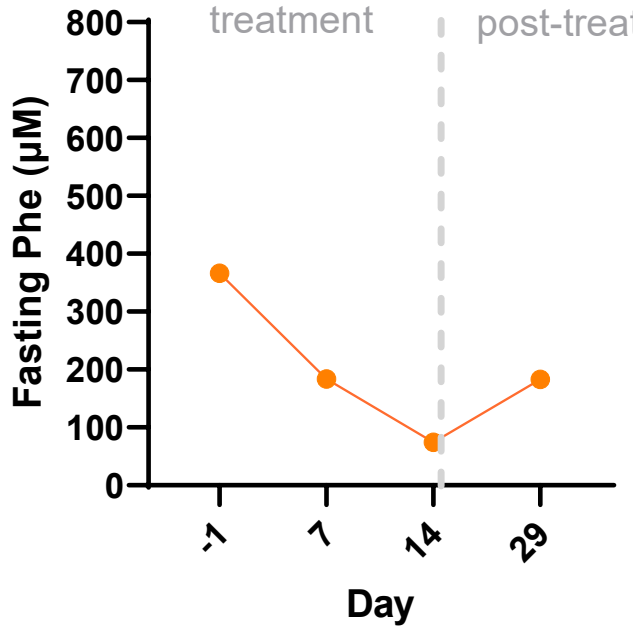
Screening Phe= 870 µM
Phe intake=705 mg



-26%

SYNB1934

Screening Phe=707 µM
Phe intake=1778 mg



-80%

Synpheny-1 Safety and Tolerability

- Across the PKU program, AEs have been mild or moderate, and predominantly GI-related
- GI-related side effects vary by individual, and are consistent with those described in the dosing of probiotics
- Safety and tolerability findings are comparable across both strains

Adverse Events	SYNB1618 (n=11) n (%)	SYNB1934 (n=9) n (%)
Subjects with SAEs	0	0
Subjects with 0 TEAE	0	2
Subjects with at least 1 TEAE (%)	11 (100)	7 (78)
Mild	3 (27)	3 (33)
Moderate	8 (73)	4 (44)
Severe	0	0
TEAE-related discontinuations*	1 (9)	3 (33)

GI Adverse Events	SYNB1618 (n=11) n (%)	SYNB1934 (n=9) n (%)
Nausea	8 (73)	4 (44)
Vomiting	5 (46)	2 (22)
Abdominal pain	3 (27)	2 (22)
Diarrhea	3 (27)	2 (22)
Flatulence	3 (27)	2 (22)
Abdominal distension	2 (18)	1 (11)
Gastrointestinal sounds abnormal	2 (18)	0
Abdominal discomfort	1 (9)	1 (11)
Constipation	1 (9)	0
Dyspepsia	1 (9)	1 (11)

* SYNB1618: 1 discontinuation due to anxiety and GI AEs. SYNB1934: 1 participant discontinued at Day -1 due to mis-dosing and GI AEs; 3 participants discontinued in treatment, 1 possible allergic reaction and 2 with GI AEs .

Conclusions

- Consistent with HV studies, SYNB1618 and SYNB1934 metabolize Phe in the GI tract in patients with PKU
- There were no serious adverse events or deaths related to SYNB1618 or SYNB1934
  - Most commonly observed AEs were gastrointestinal
- Consistent with preclinical data and head-to-head data in healthy volunteers, SYNB1934 has greater Phe metabolizing activity than SYNB1618
- Phe lowering was seen with both SYNB1618 and SYNB1934 in a dose dependent manner
- SYNB1934 may be effective in combination with sapropterin in patients who continue to have elevated Phe levels

Questions/Acknowledgements

- Participating patients
- Medical staff at participating sites
  - Mount Sinai
  - Washington University
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  - UTHealth
  - Vanderbilt
  - ICON
  - University of Colorado
  - University of Florida
  - University of Pittsburgh
- NPKUA
- CanPKU
- The Synlogic team