Reduction in Plasma Phenylalanine Levels in Patients with Phenylketonuria with Live Bacterial Therapeutic SYNB1618

Interim analysis from ongoing Phase 2 study

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PKU: Significant Need Remains for New Treatment Options

US Population[1]

Pediatrics	Adults
~5,000 U.S.	~12,300 U.S.
25% out of Phe control[2]	**65% out of Phe control[2]**

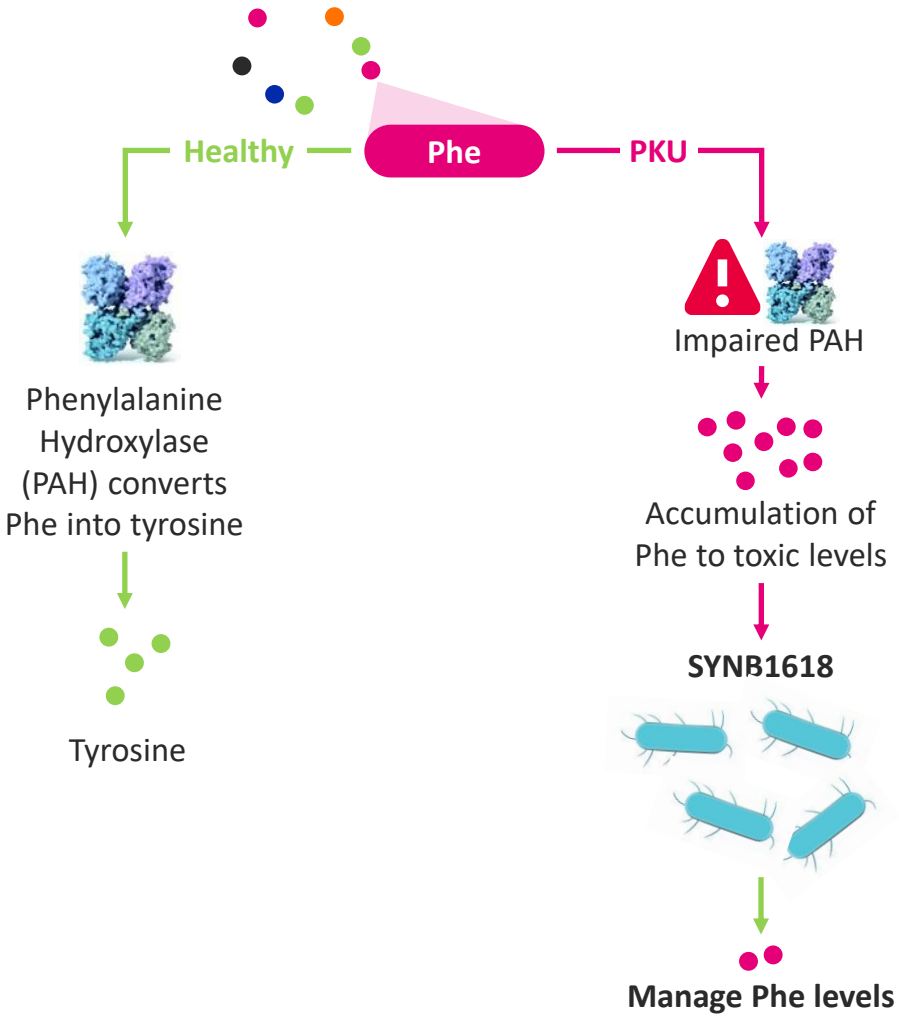
Challenges

- Significant risk for **neurocognitive impairment** if untreated
- Extremely challenging diet with **low compliance**
- **Low response** to current oral therapies: 80% fail to respond[3]
- Most adult patients **out of Phe control** and difficulties in **executive function**
- Substantial need for increased intake of **natural protein**

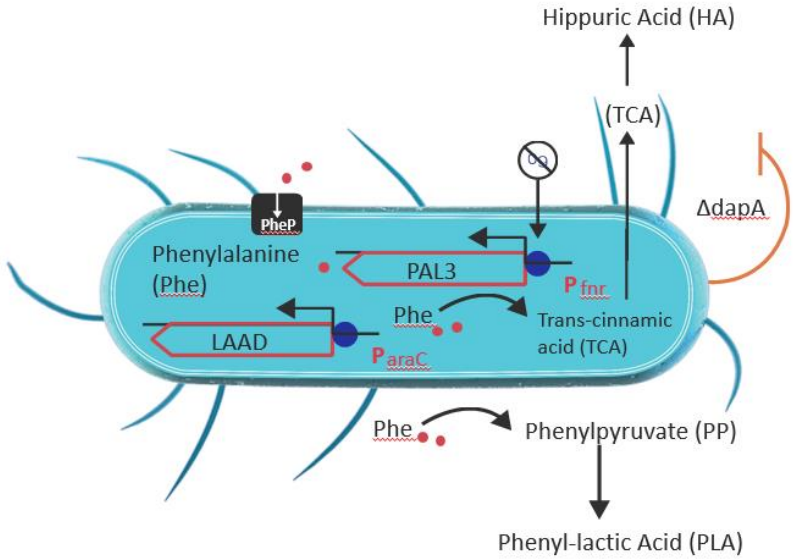
[1] Epi from National PKU Alliance npkua.org
[2] Ndugga-Kabuye MK et al. Characterization of Dietary Protein Intake in PKU Patients. ICIEM 2021, Brown C & Lichter-Konecki U. Molecular Genetics and Metabolism Reports 6 (2016) 8-12
[3] Burton B.K et a. J Inherit Metab Dis (2007) 30:700–707

Mechanism of Action for SYNB1618, a Live Bacterial Biotherapeutic

Phe Metabolism
The Target for PKU Biotherapeutic



Engineered Probiotic Bacteria: *E. coli* Nissle
Components of Synthetic Genetic Circuit



Conversion of Phe into non-toxic metabolites

- PAL3 enzyme converts Phe to *trans*-cinnamic acid
- LAAD enzyme converts Phe to phenylpyruvate

Safety

- Δ dap: Auxotrophy – requires diaminopimelic acid (DAP) to grow

SynPheny-1: Phase 2 Proof-of-Concept Study for SYNB1618

synpheny
LIVING IN HARMONY WITH PKU

Population

Adults with **classic PKU**

Plasma **Phe levels ≥ 600 µmol/L**

Not currently on sapropterin or pegvaliase-pqpz

Stable diet history

Efficacy Endpoints

- Fasting plasma Phe levels after low dose and high dose of SYNB1618
- Labeled plasma D5-Phe AUC, after a meal challenge

Strict diet control

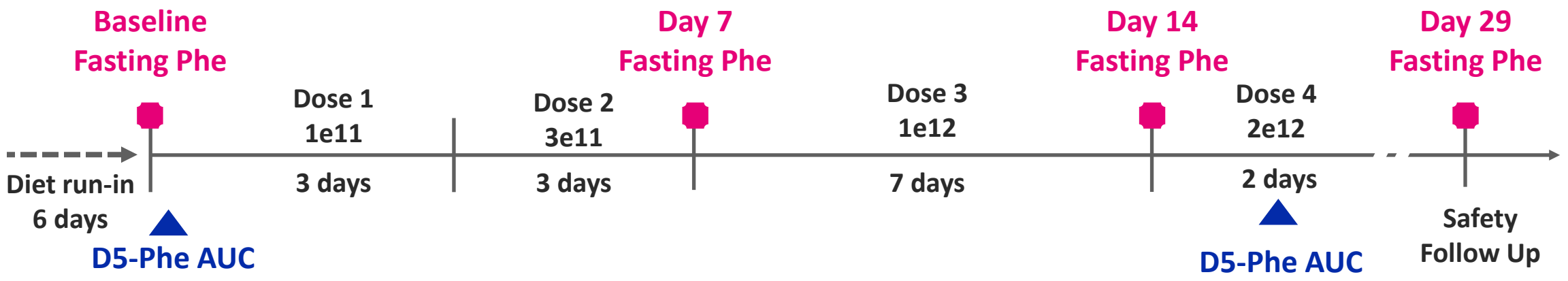
Stable **study diet**

Individualized diet plan to match baseline Phe intake

6-day diet run in prior to baseline to achieve steady state

Continued **diet control for 2 weeks** after last dose

SynPheny-1 for SYNB1618: Phase 2 Study Design



Dosing

- Oral, 3 times/day with meals
- Days 1-3: 1e11 live cells TID
- Days 4-6: 3e11 live cells TID
- Days 7-13: 1e12 live cells TID
- On Days 14 & 15 a single dose of 2e12 live cells

Measurements

- ▲ Plasma D5-Phe $AUC_{0\text{-}24hr}$ at baseline and on Day 14
- ⯃ Fasting Phe at baseline, after low dose (Day 7), after high dose (Day 14), and 2 weeks after cessation of dosing (Day 29)

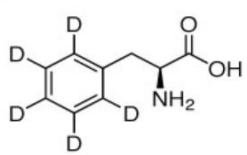
Interim Analysis (n=9) for Synpheny-1: Baseline Characteristics

Category	Characteristics
Age	**31.7** (10.8; 20-50) (mean, SD, range)
Gender	5 Female, 4 Male (55.6% fem)
Baseline Phe level	**969** (435.5) umol/L (mean, SD) **507 -1925** umol/L (range)
Baseline Phe intake	**1889** (2393) mg (mean, SD) **595-8200** mg (range)

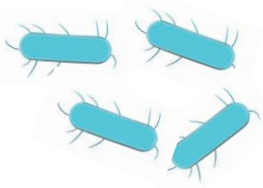
D5-Phe Tracer Tracks Strain-specific Phe Metabolites TCA and HA

Meal challenge

Protein shake / meal (20 g)

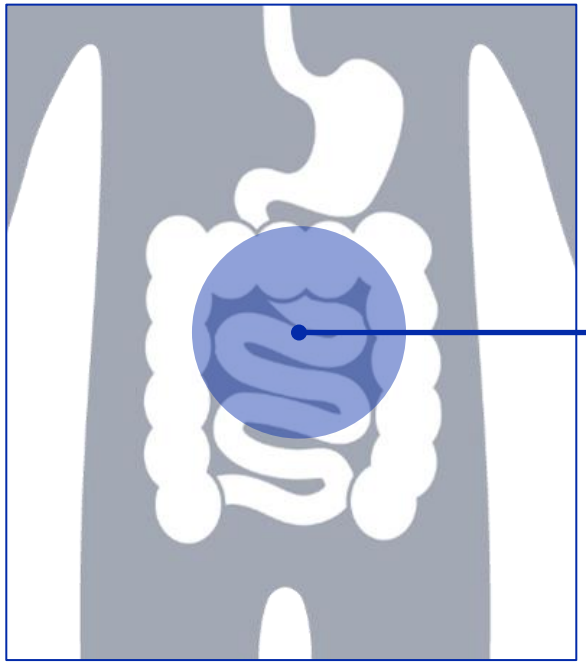


D5-Phe (1 g)



SYNB1618

Measures over 24 hours



Plasma concentration:

Phe/D5-Phe

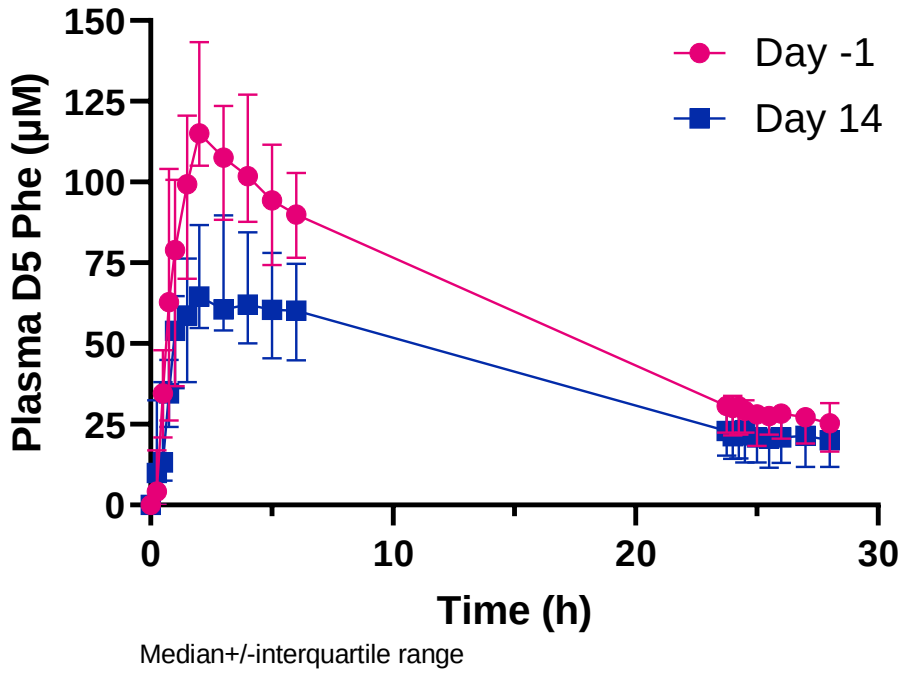
TCA/D5-TCA

Urinary amount excreted:

HA/D5-HA

Interim Analysis: D5-Phe Absorption is Reduced by Treatment

Interim Analysis: D5 Phe Tracer Study (2e12 dose, N = 8)



- Meal challenge at Day -1 and Day 14 at high dose 2e12
- Phe load as D5-labeled and protein-bound unlabeled Phe

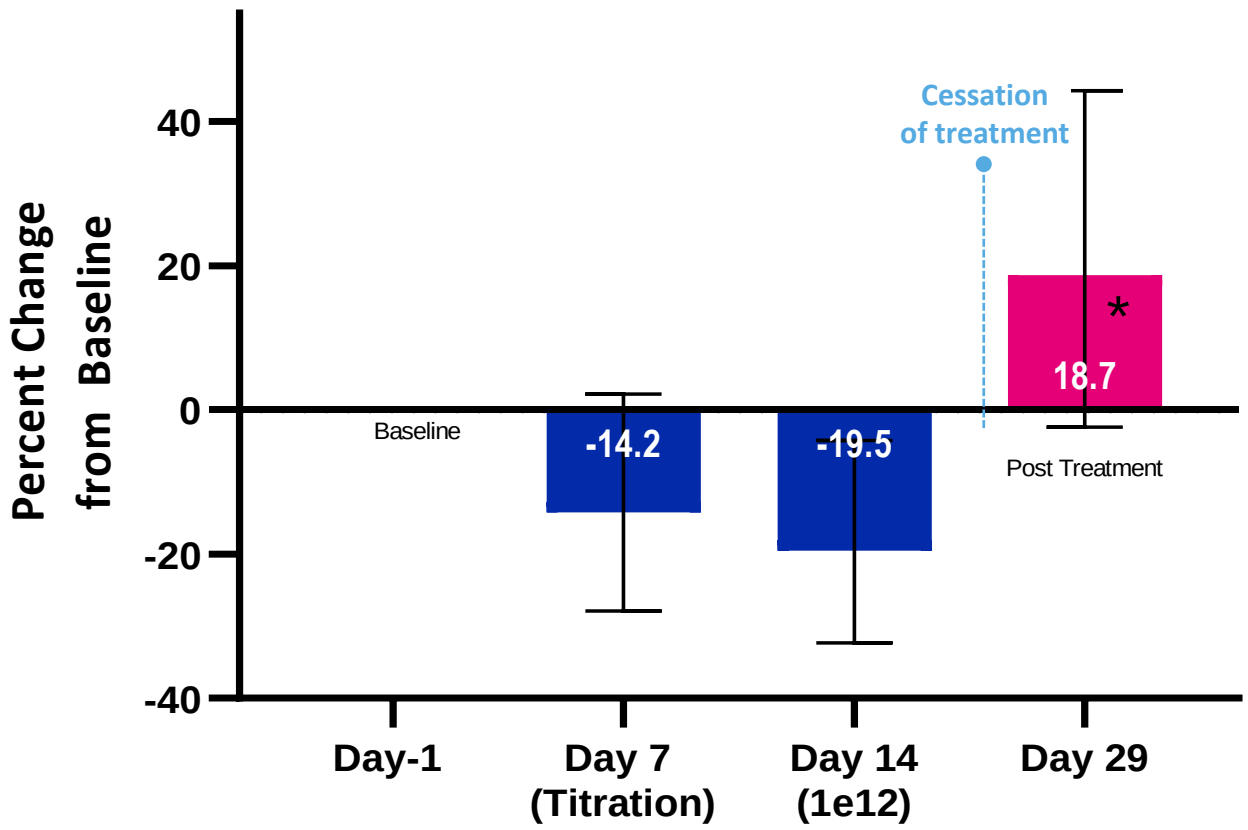
- Mean (upper CI, Lower CI) reduction in D5-Plasma Phe AUC of -39.99% (2.7% - 64.95%)*
- 4 of 8 patients experienced >40% D5-Phe lowering after meal challenge
- Corresponding plasma D5-TCA and urinary D5-HA biomarker signal confirms strain activity
- Similar reductions in labeled and unlabeled Phe levels post meal

Clear evidence of strain Phe metabolism from GI Tract

*Percent change from baseline +/- 95% confidence interval

Interim Analysis: Mean "All-Comers" Results for Phe Reductions

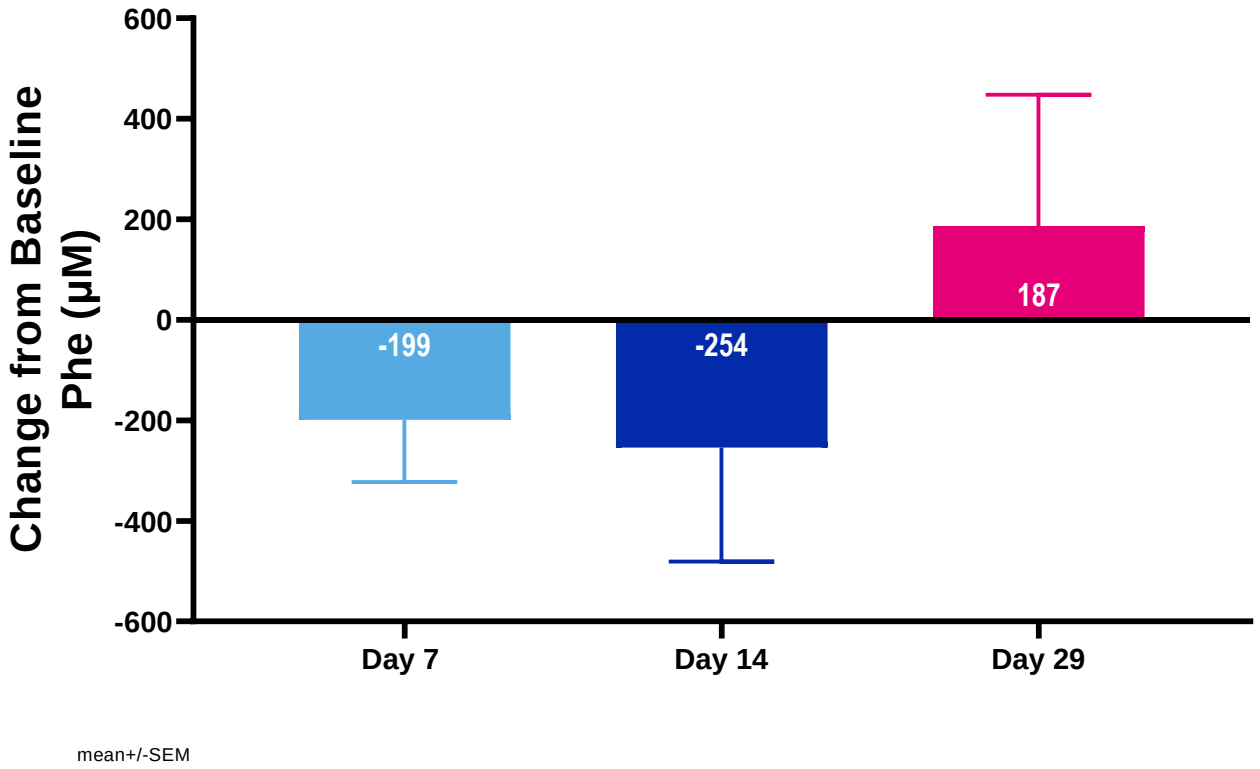
% Mean Change in Plasma Phe (1e12 dose N=8)



- Rapid **reduction of fasting Plasma Phe** at 3e11 dose
- **Mean "all-comers" fasting plasma Phe lowering** at 1e12 dose met **20%**
- Elevation of plasma Phe **upon cessation of treatment**

Interim Analysis: Phe Reduction for >20% Responders

Change in Plasma Phe From Baseline (N = 4)



mean+/-SEM

- Response defined as **>20% reduction in Phe** at either day 7 or day 14
- **Four subjects** met this responder criterion in interim analysis
- **254 µM mean reduction in Phe** in responder population (N = 4)

Safety and tolerability summary from interim analysis

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LIVING IN HARMONY WITH PKU

Tolerability summary

No SAEs or systemic safety issues identified

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

Mild to Moderate GI AEs

1 discontinued (anxiety due to PKU)

Efficacy response and tolerability suggest **individualized dosing and titration** may be available to meet patient needs.

This will be **evaluated in future studies**.

Conclusions from the Interim Analysis of Synpheny-1, Phase 2 for SYNB1618

- SYNB1618 has **demonstrated ability to access Phe** from within the GI tract
- **40% reduction in D5-Phe** absorption after a meal challenge
- **20% reduction in fasting plasma Phe** across interim analysis population
- **254 µM mean reduction** in fasting plasma Phe among responders (>20% reduction)
- SYNB1618 was generally well tolerated, with **profile consistent with Phase 1 study**
- An optimized version of SYNB1618, **SYNB1934 with improved Phe conversion potential** has demonstrated Phe metabolism in healthy volunteers and will be evaluated in SynPheny-1 (abstract #569)

Development of live bacterial biotherapeutics as **novel modality for treatment of PKU** warrants further study in late-stage trials

Thank you to study patients and investigators!

synlogic