A Phase 1/2a Oral Placebo-controlled Study of SYNB1618 in Healthy Adult Volunteers and Subjects with Phenylketonuria

Jerry Vockley, M.D., Ph.D.

University of Pittsburgh

Cleveland Family Endowed Chair in Pediatric Research

Children's Hospital of Pittsburgh

Chief of Medical Genetics

Director of the Center for Rare Disease Therapy

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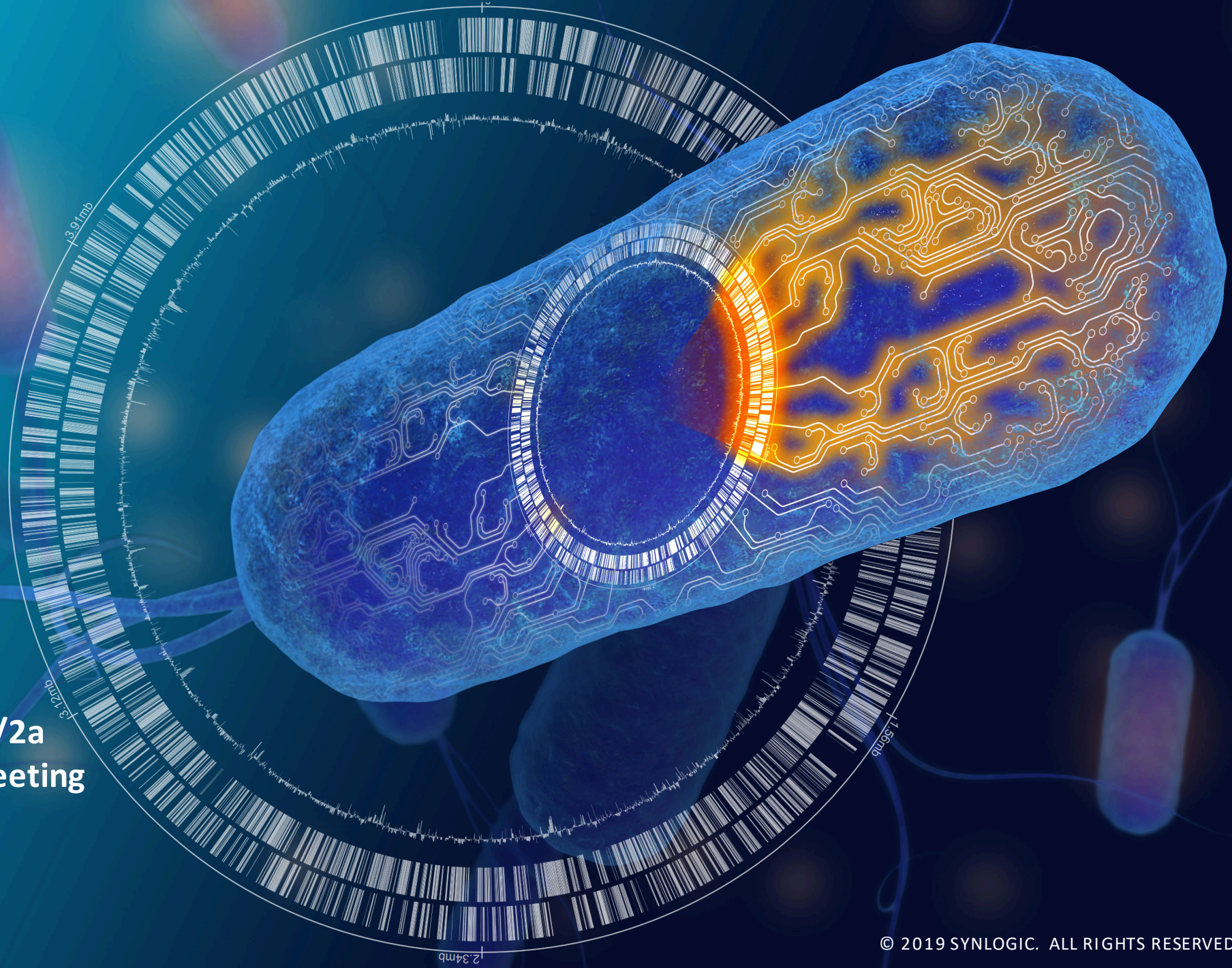
DESIGNED FOR LIFE



SYNB1618-CP-001 Phase 1/2a
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04 September 2019

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Conflicts of Interest

- Research funding
  - NIH
  - Ultragenyx
  - Biomarin
  - Sanofi
  - Shire
  - Aeglea
  - Alexion
  - Glycomine
  - Moderna
  - Mereo
  - Stealth
  - Kaleido
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- Consulting
  - Sena
  - BioLogic
  - PerkinElmer
  - DNARx
  - American Gene Therapies
  - Cobalt Pharma
  - Homology
  - Agios
  - Rand

Phenylketonuria (PKU)

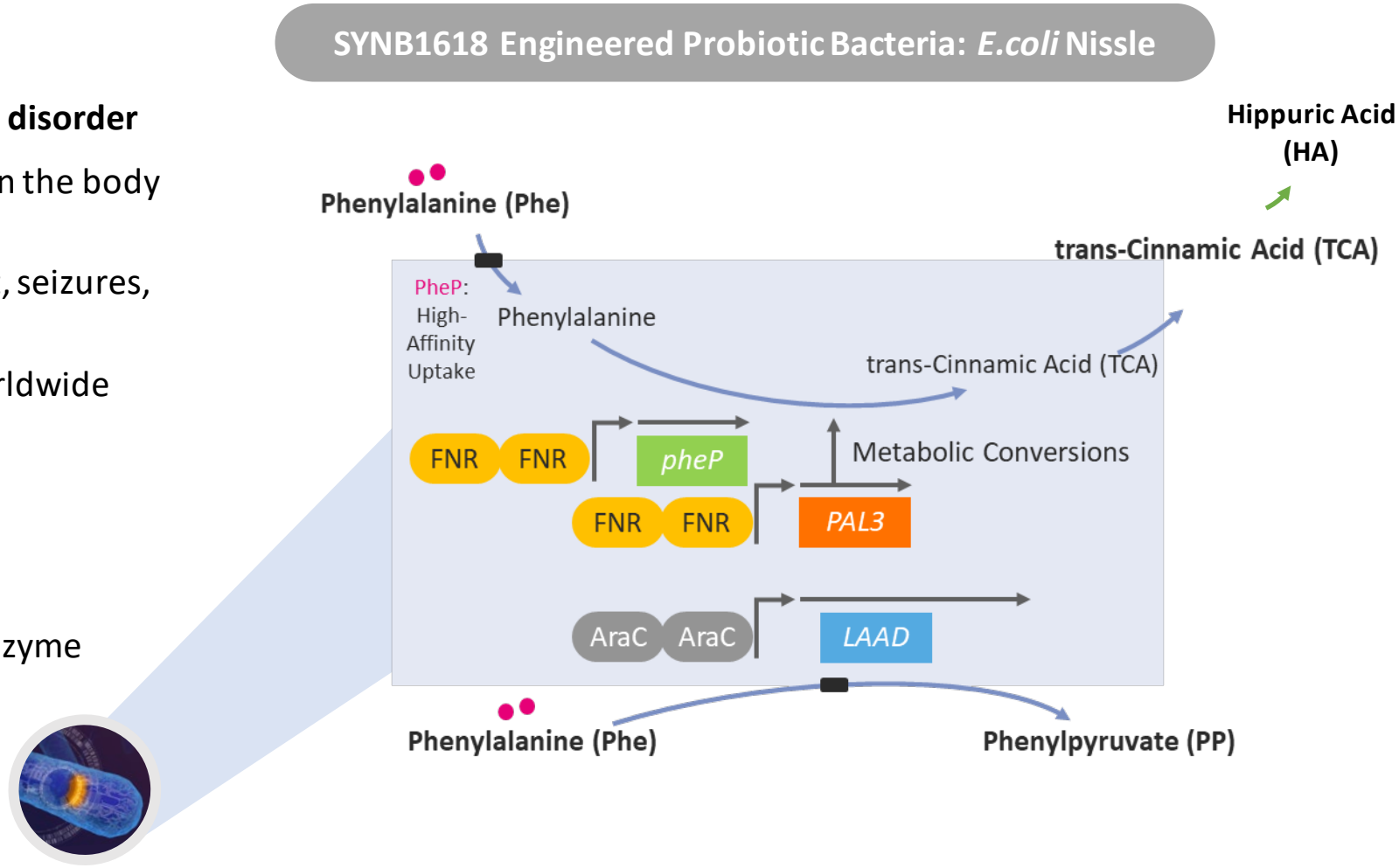
Developing a novel oral therapy using engineered probiotic bacteria

PKU is a rare inherited amino acid metabolism disorder

- Causes accumulation of phenylalanine (Phe) in the body due to deficiency in PAH enzyme
- Untreated PKU leads to cognitive impairment, seizures, behavioral problems, skin rash
- Incidence approximately 1:10,000-20,000 worldwide

Treatment:

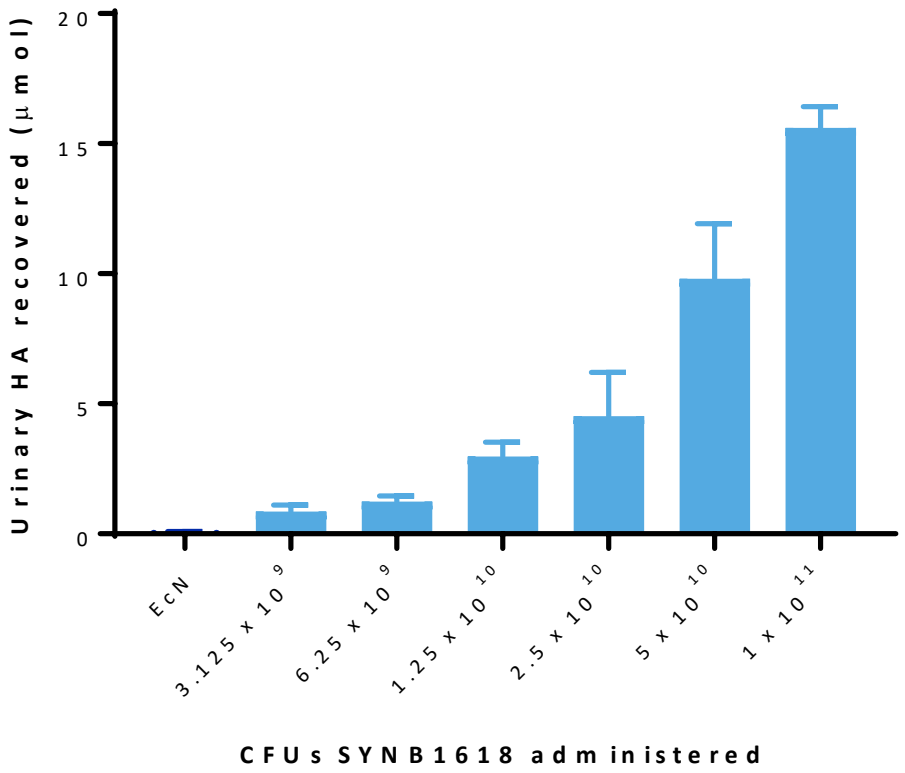
- Low Phe diet with Phe free AA supplements
- Sapropterin dihydrochloride: PAH cofactor
- Pegvaliase: injectable, pegylated, bacterial enzyme (phenylalanine ammonia-lyase or PAL)

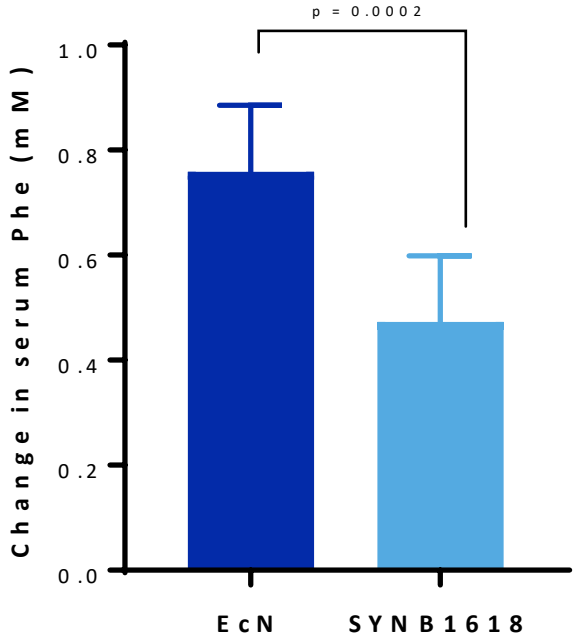


SYNB1618 Preclinical Characterization

Biomarkers Demonstrate Dose-dependent Activity of SYNB1618 in Mouse Model of PKU

IN VIVO EFFICACY IN (PKU) PAH$^{enu2/enu2}$ MOUSE





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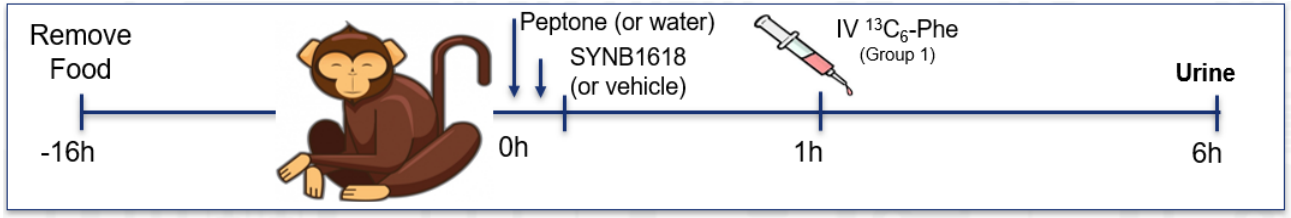
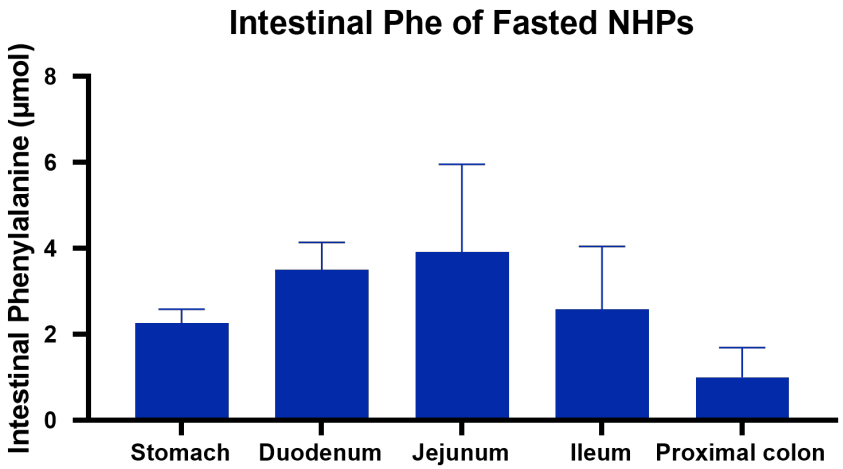
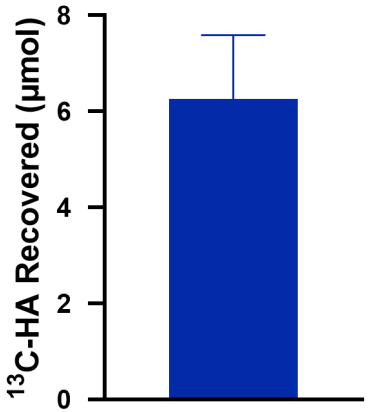
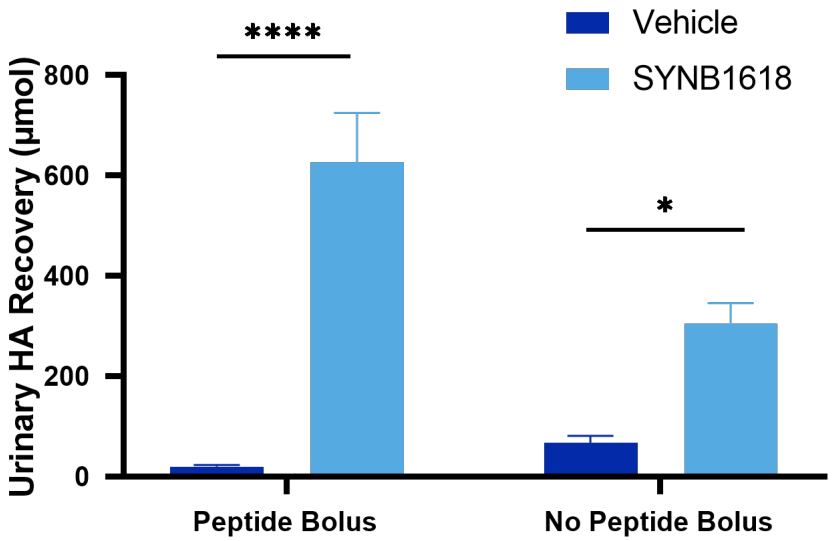
Enterorecirculation of Phe

Resident Phe available in the GI tract provides substrate beyond dietary Phe





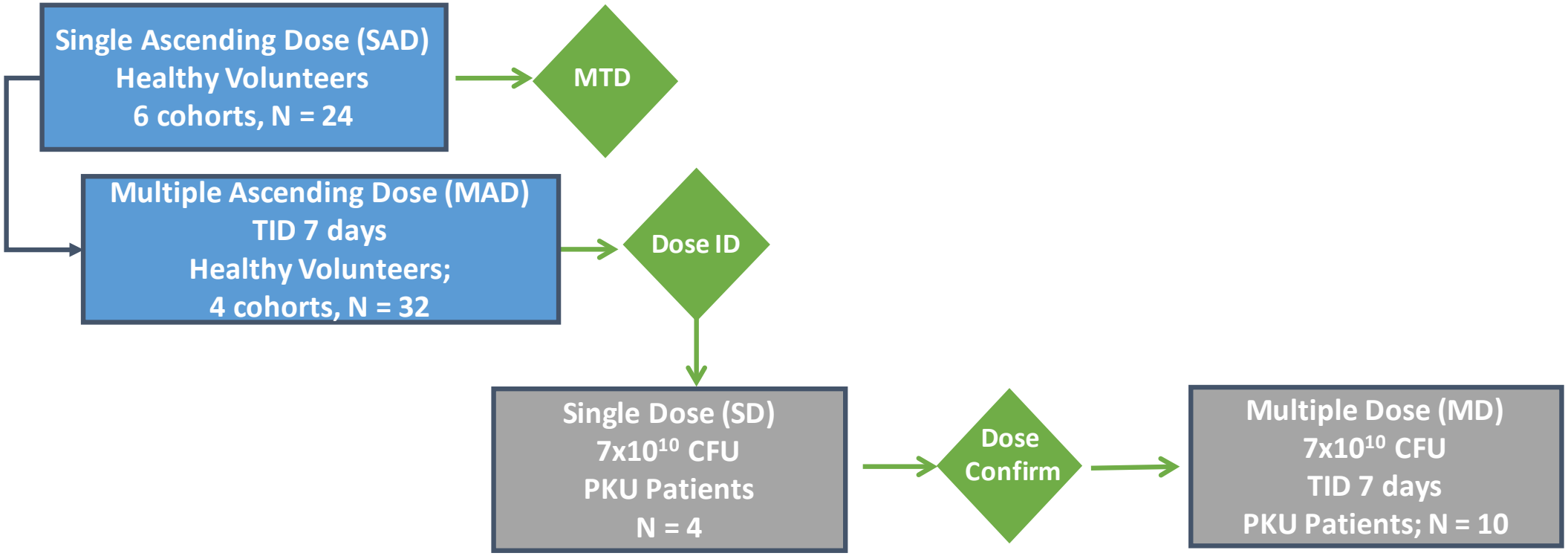




SYNB1618 dosing in the fasted state leads to HA production in NHPs

SYNB1618 First-in-Human Study

Phase 1/2a Randomized, Double-blind Placebo-controlled Study in Healthy Volunteers with PKU Patient Cohort



Study Outcomes

- Designed to show safety and pharmacodynamic effects based on strain-specific biomarkers for further development
- No Phe lowering expected

PKU Study Population

Demographics

	PKU Single Dose		PKU Multiple Dose	
	SYNB1618	PBO	SYNB1618	PBO
N	3	1	6	4
Age mean (range)	26.0 (24,27)	20.0 (20, 20)	36.7 (27, 50)	28.5 (22, 41)
Gender (% Male)	F 2, M 1 (33.3%)	F 0, M 1 (100%)	F1, M5 (83.3%)	F3, M1 (25%)
Race N (%)	White 3 (100%)	White 1 (100%)	White 6 (100%)	White 4 (100%)
Baseline Phe Mean (SD) in umol/L	946 (269)	718 (NA)	1354 (436)	937 (643)

Safety Profile of SYNB1618

Generally well-tolerated in HV and PKU

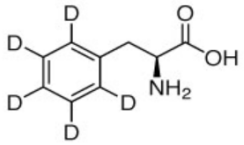
56 healthy volunteers and 14 PKU patients	Adults Age range: 18-62 yrs old (20-50 yrs in PKU)	Received at least one dose of SYNB1618 or placebo

- ✓ There were no treatment-related serious adverse events, no systemic toxicity or infections.
- ✓ Treatment-emergent adverse events were either mild or moderate in severity, and reversible. Most adverse events were GI-related.
- ✓ All subjects cleared the bacteria. There was no evidence of colonization, and no subject required antibiotics.
- ✓ Single dose MTD was defined as $2x10^{11}$ CFU. Doses above this level were associated with dose-limiting GI adverse events.
- ✓ Based on pharmacodynamic data and tolerability profile, a dose of $7x10^{10}$ CFU was identified for the second part of the study in PKU patients.

D5-Phe Tracer Study Design

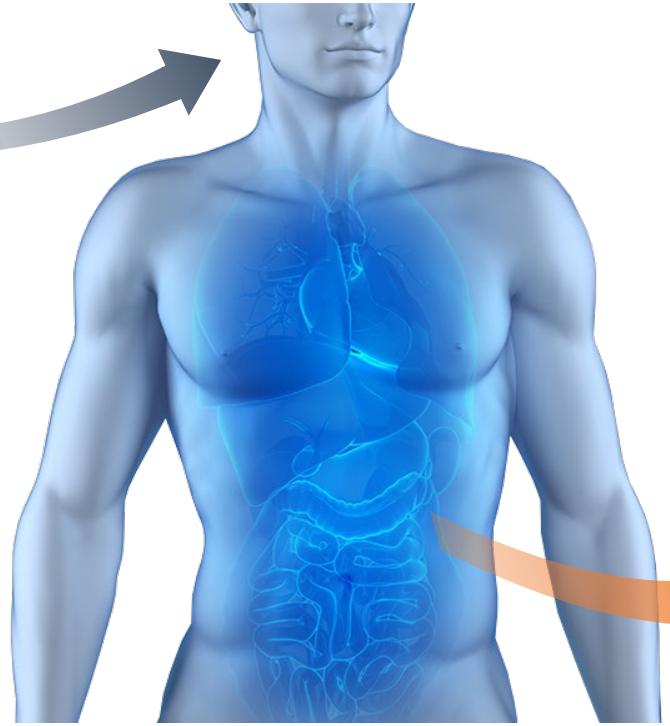
D5-Phe Tracer Enables Tracking of Strain-specific Phe Metabolites TCA and HA

Protein shake / meal (20 g)



D5-Phe (15 mg/kg)

SYNB1618 or placebo



Measure over 6/24hrs:

<u>Plasma concentration:</u>

- Phe/D5-Phe
- TCA/D5-TCA
- HA/D5-HA

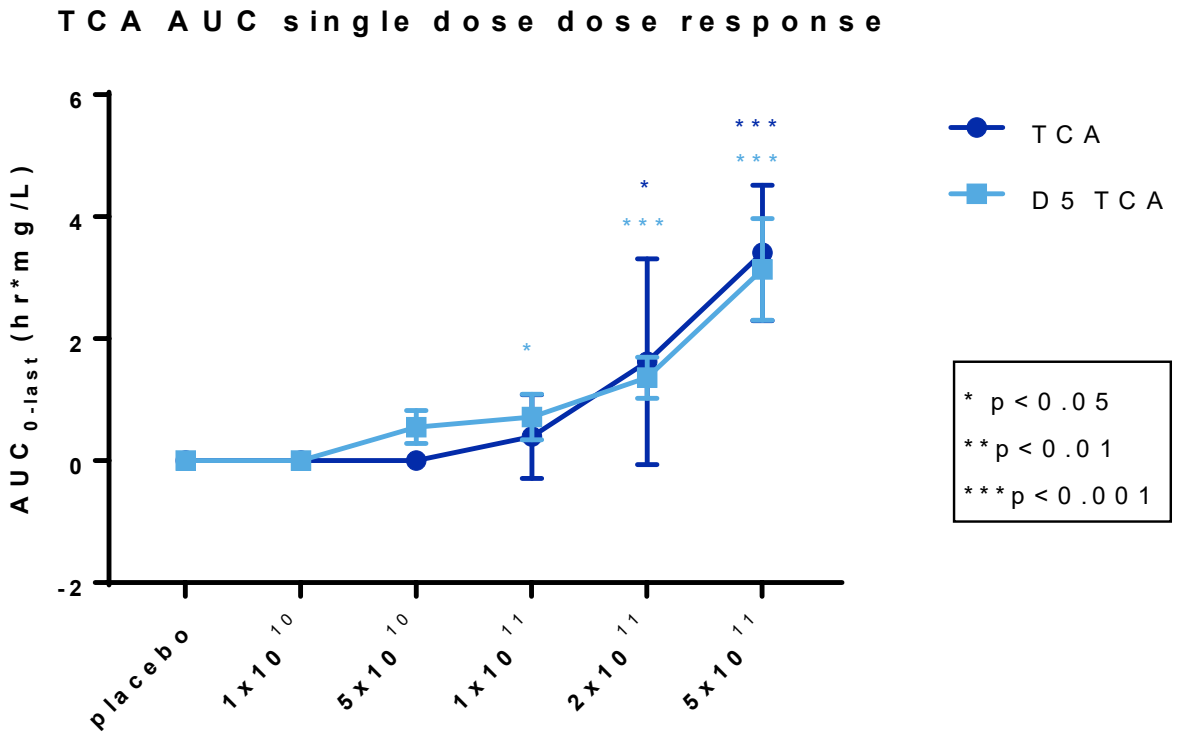
<u>Urinary amount excreted</u>

- HA/D5-HA

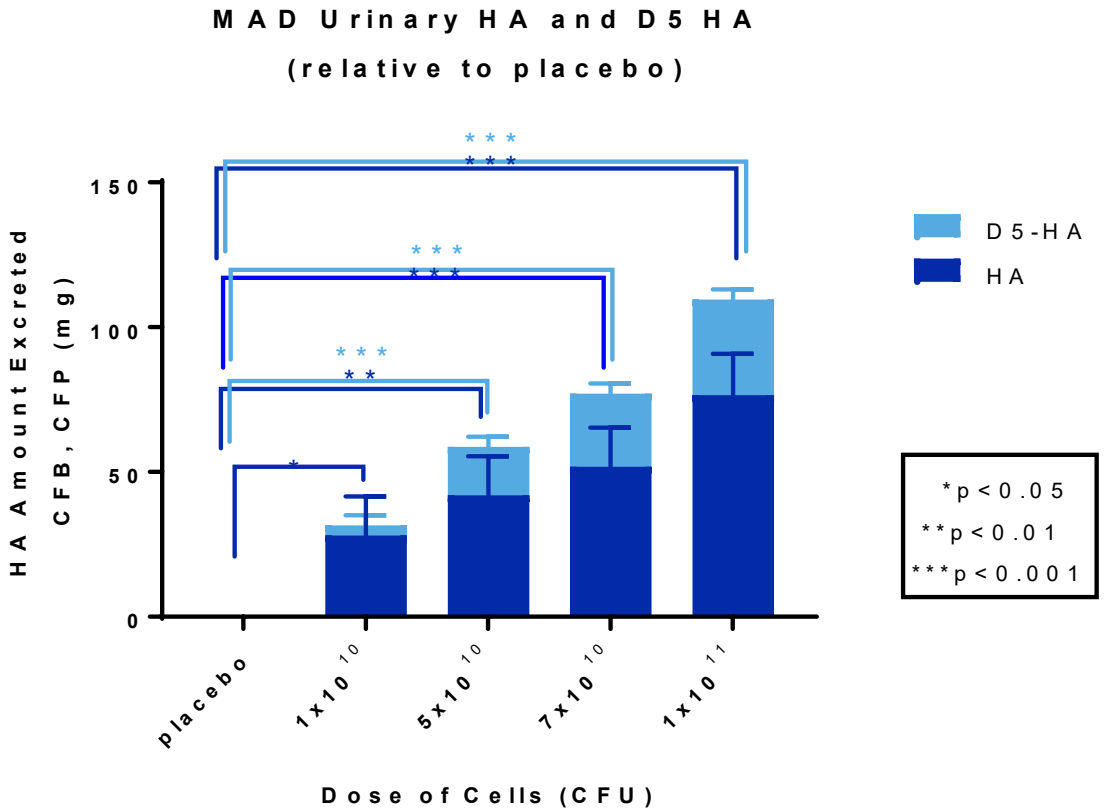
SYNB1618 Performs Engineered Function in Human

Statistically Significant Dose-dependent Activity of SYNB1618 in Healthy Volunteers

Plasma TCA AUC



URINARY HA AND D5-HA

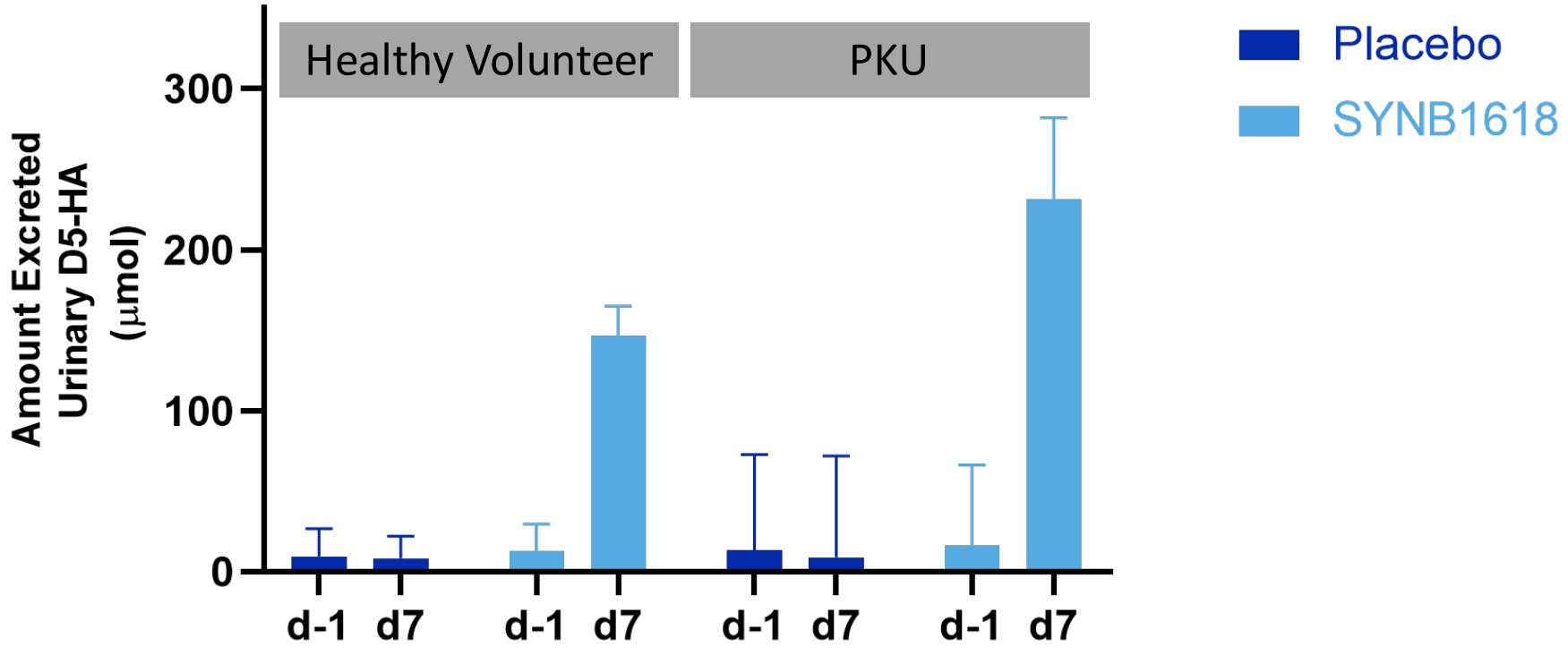


Key: HA: Hippurate, D5-HA: labeled HA, CFB: change from baseline, CFP: change from placebo

SYNB1618 Function is Similar in Healthy Volunteers and PKU

Same dose of $7x10^{10}$ CFU TID leads to similar magnitude of Phe metabolism

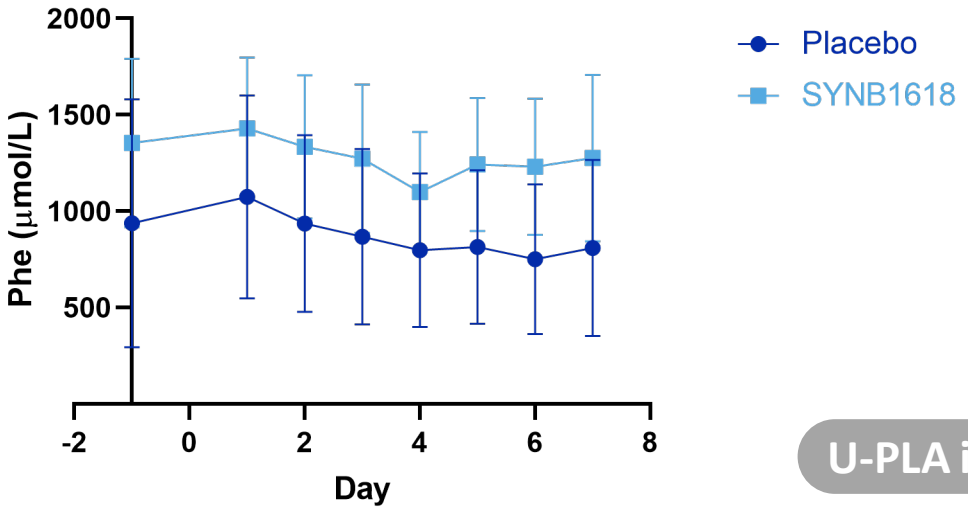
Urinary D5 - HA Amount excreted in healthy volunteers and PKU patients



Evidence of dual functionality of the strain

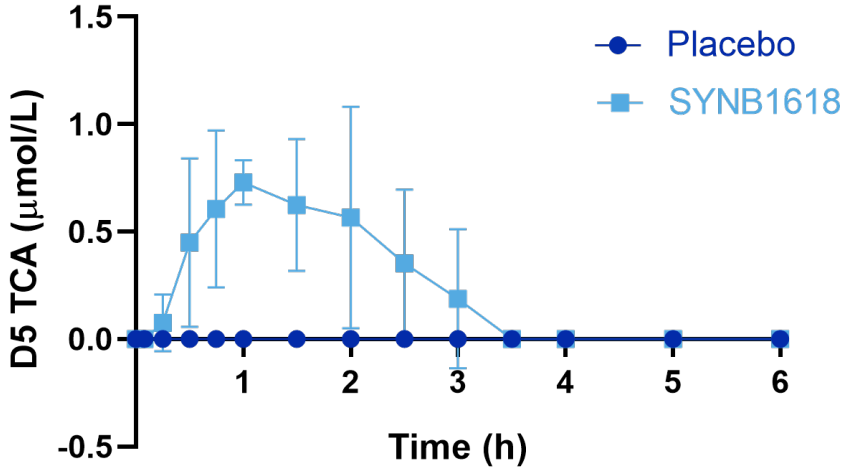
Both PAL and LAAD pathways active *in vivo*

Fasting Phe in PKU MAD

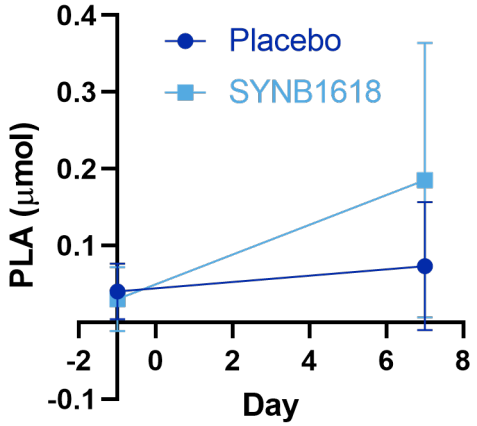


No Phe lowering as expected

P-D5-TCA after a single dose of SYNB1618



U-PLA in Healthy Volunteers

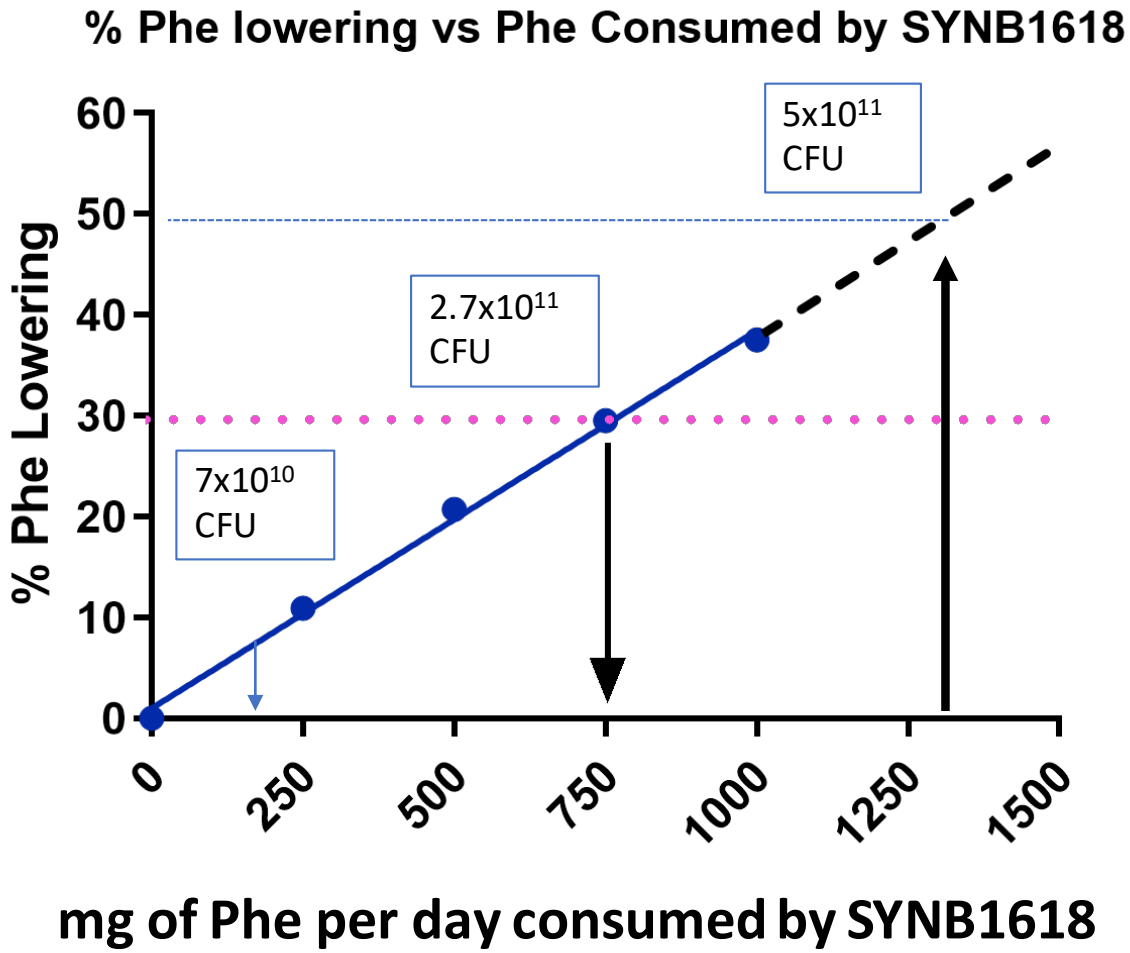


Modeling: Potential For Clinically Meaningful Phe Reduction in PKU Patients

Tool to project effect of SYNB1618 on blood Phe lowering based on biomarkers

- Model based on the known kinetics of Phe metabolism to relate bacterial Phe consumption in the gut to blood Phe lowering.
- Assumes classic PKU (0% PAH), moderately restricted protein intake (50g/day), conservative estimate of only PAL pathway activity without LAAD contribution.

Details on the model: Poster #140



Conclusions

SYNB1618 Phase 1/2a Study

- Preclinical data demonstrate SYNB1618 metabolizes Phe *in vivo*
- HV study confirms strain activity in humans
- SYNB1618 was safe and generally well-tolerated in both healthy volunteers and PKU patients
- A statistically significant, dose-related increase was observed in strain-specific biomarkers showing potential for higher efficacy with further increase in dose
- Multiple day dosing confirms similar strain activity in PKU patients
- Modeling identified a strain dose range with potential for clinically meaningful Phe reduction to be tested in further efficacy studies

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Clinical Investigators

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- Dr. John Phillips, Vanderbilt University Medical Center
- Dr. Cary Harding, Oregon Health & Science University
- Dr. Shawn Searle, PRA Health Sciences Salt Lake City, UT