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

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Synlogic

DESIGNED FOR LIFE

SYNB1618-CP-001 Phase 1/2a
Presented at the SSIEM Meeting
04 September 2019
Conflicts of Interest

- Research funding
  - NIH
  - Ultragenyx
  - Biomarin
  - Sanofi
  - Shire
  - Aeglea
  - Alexion
  - Glycomine
  - Moderna
  - Mereo
  - Stealth
  - Kaleido
  - Synlogic
  - Carnot

- 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<sup>enu2/enu2</sup> MOUSE*

<table>
<thead>
<tr>
<th>CFUs SYNB1618 administered</th>
<th>Urinary HA recovered (µmol)</th>
<th>Change in serum Phe (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EcN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.125 x 10&lt;sup&gt;9&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.25 x 10&lt;sup&gt;9&lt;/sup&gt;</td>
<td></td>
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</tr>
<tr>
<td>1.25 x 10&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 x 10&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 x 10&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 x 10&lt;sup&gt;11&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*EcN SYNB1618*  
0.0  0.2  0.4  0.6  0.8  1.0  
P = 0.0002

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

<table>
<thead>
<tr>
<th></th>
<th>PKU Single Dose</th>
<th></th>
<th>PKU Multiple Dose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SYNB1618</td>
<td>PBO</td>
<td>SYNB1618</td>
<td>PBO</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td><strong>Age</strong>&lt;br&gt;mean (range)</td>
<td>26.0 (24,27)</td>
<td>20.0 (20, 20)</td>
<td>36.7 (27, 50)</td>
<td>28.5 (22, 41)</td>
</tr>
<tr>
<td><strong>Gender</strong>&lt;br&gt;(% Male)</td>
<td>F 2, M 1 (33.3%)</td>
<td>F 0, M 1 (100%)</td>
<td>F1, M5 (83.3%)</td>
<td>F3, M1 (25%)</td>
</tr>
<tr>
<td><strong>Race</strong>&lt;br&gt;N (%)</td>
<td>White 3 (100%)</td>
<td>White 1 (100%)</td>
<td>White 6 (100%)</td>
<td>White 4 (100%)</td>
</tr>
<tr>
<td><strong>Baseline Phe</strong>&lt;br&gt;Mean (SD) in umol/L</td>
<td>946 (269)</td>
<td>718 (NA)</td>
<td>1354 (436)</td>
<td>937 (643)</td>
</tr>
</tbody>
</table>
Safety Profile of SYNB1618
Generally well-tolerated in HV and PKU

- 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 $2 \times 10^{11}$ CFU. Doses above this level were associated with dose-limiting GI adverse events.
- Based on pharmacodynamic data and tolerability profile, a dose of $7 \times 10^{10}$ CFU was identified for the second part of the study in PKU patients.

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
**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:

**Plasma concentration:**
- Phe/D5-Phe
- TCA/D5-TCA
- HA/D5-HA

**Urinary amount excreted**
- 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**

**TCA AUC single dose dose response**

**MAD 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 $7 \times 10^{10}$ CFU TID leads to similar magnitude of Phe metabolism
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
Acknowledgements

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Clinical Investigators

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• Dr. Cary Harding, Oregon Health & Science University
• Dr. Shawn Searle, PRA Health Sciences Salt Lake City, UT

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