Background

- Phenylketonuria (PKU) is characterized by the inability to metabolize dietary phenylalanine (Phe) resulting in sustained elevation of plasma Phe levels following a protein meal.
- SYNB1618, a live, modified strain of the probiotic bacterium E. coli Nissle was engineered to consume Phe in the gastrointestinal (GI) tract through expression of the enzymes phenylalanine ammonia lyase (PAL) and L-amino acid deaminase (LAAD).
- SYNB1618 metabolizes Phe to harmless compounds trans-cinnamic acid (TCA) which is excreted as hippuric acid (HA) in urine, and phenylpyruvate.
- The potential of SYNB1618 to lower blood Phe level in PKU patients was studied in SynPheny-1. [NCT04534942]

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

Methods

- SynPheny-1 is an open-label study in adult PKU patients with Phe ≥600 micromol/L (Figure 2).
- Patients followed individualized study diets reflecting baseline Phe intake from 7 days prior to dosing to 2 weeks after the last dose.
- The dose of SYNB1618 was gradually increased: 1x10^6 live cells for the first 3 days, 3x10^6 on days 4-6, then 1x10^9 TID on days 7-13.
- A D5-Phe tracer study was conducted at baseline and on Day 14 at the 2x10^12 dose.
- Key outcomes: change from baseline in D5-Phe AUC_0-24h and fasting blood Phe.

Results

- Data from an interim analysis of 9 PKU patients are presented.
- SYNB1618 was generally well-tolerated. The most common AEs were mild to moderate GI symptoms. No SAEs or deaths were observed. 1 patient discontinued the study due to anxiety.
- D5-Phe absorption from the gut was reduced by treatment (Figure 3).
- Plasma Phe was reduced by treatment on Day 7 and Day 14 (Figure 4).
- 4 of 8 patients had at least 20% blood Phe lowering at either Day 7 or Day 14.

Conclusions

- SYNB1618 has demonstrated ability to access Phe from within the GI tract.
- Treatment with SYNB1618 led to a clinically meaningful decrease in blood Phe level.
- An optimized version of SYNB1618, SYNB1934 with improved Phe conversion potential has demonstrated Phe metabolism in healthy volunteers and is currently being evaluated in SynPheny-1.
- Development of live bacterial biotherapeutics as novel modality for treatment of PKU warrants further study in late-stage trials.