Comparison of Phenylalanine Absorption in Healthy Volunteers and PKU Patients in the Synpheny-1 Study

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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 and SYNB1934 are genetically engineered probiotic bacteria designed to metabolize Phe in the GI tract and lower blood Phe levels (figure 1). The key difference between the strains is that SYNB1934 has a modified PAL variant designed to have higher Phe metabolizing activity.
- To characterize the activity of these bacteria in the GI tract, we developed a method to measure the post-prandial rise of blood Phe levels in both healthy volunteers (HVs) and in patients with PKU.

Methods
Patients
- SYNB1618 and SYNB1934 were tested in multiple-ascending dose cohorts in two HV studies. Data for the 2 x 10¹² live cells dose is shown for each.
- SYNB1618 was studied in PKU patients in a Phase 2 study: Synpheny-1, NCT04534842 (figure 2).
- Synpheny-1 is ongoing with interim analysis data from N=8 PKU patients in Arm 1 with SYNB1618 dosing available.

Results
- Compared to HVs, patients with PKU had a greater increase in peak plasma D5-Phe (approximately 120 μmol/L versus 60 μmol/L).
- Peak plasma D5-Phe returned to fasting levels more slowly in PKU patients compared to HVs (>24 hours for PKU patients and approximately 6 hours for HVs).
- Administration of an engineered strain reduced post meal plasma D5-Phe levels in HVs and PKU patients compared to baseline (Figure 4, Table 2) and led to a corresponding increase in strain-specific biomarkers in plasma (D5-TCA, Figure 5) and urine (D5-HA, data not shown).

Conclusions
- The D5-labeled Phe meal test is a promising method to evaluate the activity of gut restricted therapies in the treatment of PKU.
- Likely due to intact PAH, HVs have lower post-meal excursion of D5-Phe and a lower percent reduction in response to SYNB1618 compared to PKU patients.
- Genetically engineered bacteria SYNB1618 and its optimized version SYNB1934 have demonstrated an ability to metabolize Phe within the GI tract and reduce post-meal plasma Phe levels significantly.
- Increase in strain-specific biomarker D5-TCA demonstrates Phe consumption through the PAL enzyme.
- SYNB1934 appears more active in HVs compared to SYNB1618 and is currently being evaluated in PKU patients in Arm 2 of Synpheny-1.