Development of SYNB1934 for the Treatment of Phenylketonuria: Phase 2 Data and Phase 3 Design

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Introduction

Despite the introduction of dietary therapies, there remains an unmet medical need in phenylketonuria (PKU). Phe control by dietary management is difficult and many patients are unable to reach goals, risking cognitive impairment and supporting the need for novel treatment approaches.

Synthetic biotics are a new class of investigational medicines, designed to carry out beneficial activities within patients. Two synthetic strains, SYNB1618 and SYNB1934 were engineered from Escherichia coli Nissle 1917, expressing phenylalanine ammonia lyase (PAL), L-aminino acid deaminase (AAD), and a Phe transporter with auxotrophy to prevent replication in the body.

Phase 2 Synphony-1 Study1

Phase 2 Part 1 was an open-label PKU study to evaluate safety and efficacy of SYNB1618 (arm 1) and SYNB1934 (arm 2) in 18 adult PKU patients. 24-hour Phe was AUC evaluated, d1 to d4 (d1 to d4), and Phe was evaluated in the post-dose phase on days 1, 7, 14, 18. Biomarkers (TCA, HA) evaluated d1, 7, 14; Safety and tolerability. All collected throughout treatment and at day 28.

Patient Disposition

• 28 patients screened
• 20 patients enrolled (13 in arm 1, 9 in arm 2)
• 15 patients completed
• 5 patients discontinued (1 in arm 1, 4 in arm 2)

References:

1. Shockey, L; Sondheimer, N; Grunow, D; Martin, H; Phillips, L; Seidelo, T; Zien, D; Denny, W; Ding, C; Ciroc, S; Humphries, K; McPherson, S; Schoderoff, V; Woodbury, C; Pasciak, K; Kett, C; Brennan, A; Sondheimer, N; Shockey L. Study of efficacy and safety of SYN1618 and SYN1934 in patients with phenylketonuria. Presented at Society for Inherited Metabolic Disorders (SIMD); 2023 March 18-21; Salt Lake City, UT.

Results

Reduction in d5-Phe

Both SYN1618 and SYNB1934 demonstrated on days 10-14 a reduction ≥20% in plasma d5-Phe of patients with PKU. AUC was evaluated, d1 to d4 (d1 to d4), and d7 to d4 (d1 to d14), as well as a change from baseline to d4 (d1 to d6).

Safety and Tolerability Were Comparable Across Both Strains

• No serious adverse events
• TEAEs were all mild to moderate
• GI adverse events were the most common AEs (e.g., nausea, vomiting, abdominal pain, diarrhea) and similar in frequency and severity between the two strains
• Five patients discontinued due to TEAEs (one on SYNB1618 and four on SYNB1934)

Conclusions

• Consistent with HV studies, SYNB1618 and SYNB1934 met the PKU study PKU patients with PKU
• Phe lowering was seen with both SYNB1618 and SYNB1934 in a dose-dependent manner
• There were no serious adverse events or deaths related to SYNB1618 or SYNB1934
• The most commonly observed AEs were mild to moderate gastrointestinal symptoms
• Consistent with preclinical data and head-to-head data in healthy volunteers, SYNB1934 has greater Phe metabolizing activity than SYNB1618
• A Phase 3 Trial has been designed based on the results of SYNB1-1 to further evaluate SYNB1934 safety and efficacy in patients with PKU

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