SYNB1353, A Proposed Therapy for Homocystinuria, Lowers Plasma Methionine and Homocysteine in Healthy Volunteers Exposed to a Methionine Challenge

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Introduction

Classical homocystinuria (HCU) is an inherited disorder caused by pathogenic variants in the cystathionine beta-synthase (CBS) gene (Figure 1) resulting in excessive accumulation of homocysteine (Hcy) and multiorgan clinical manifestations. Early initiation of methionine-restricted diets significantly lowers the risk of developing complications in HCU. Elevated Hcy levels are associated with impairments of the eye, skeletal system, vascular system, and central nervous system. In patients with residual CBS activity (~50% of HCU population), vitamin B6 (pyridoxine) is effective at reducing Hcy levels. For pyridoxine unresponsive patients, betaine involved in remethylation of Hcy to methionine and a low-methionine diet that is very low in natural protein are the current therapeutic options.

SYNB1353: A methionine metabolizing synthetic biotic

SYNB1353 was engineered from the probiotic E. coli Nissle (ECN) to metabolize methionine (Met) via the methionine decarboxylase (MetDC) pathway, preventing its conversion into homocysteine. SYNB1353 converts Met to 3-methylthiopropylamine (3-MTP). To prevent the release of methionine once it enters the cell, the YjeH gene was deleted which is responsible for Met export in ECN.

Study Design

We evaluated SYNB1353 in a double-blinded, placebo-controlled Phase I trial utilizing a multiple ascending dose (MAD) design (Figure 3A). Four cohorts using dose levels, 3x10^11, 6x10^11 and 1x10^12 SYNB1353 live cells, were evaluated for safety, tolerability, and capacity to metabolize methionine in four cohorts of healthy volunteers challenged with 30 mg/kg methionine before and after exposure to SYNB1353. Study demographics are shown in Table 1. Subjects received a methionine challenge on day -1, followed by SYNB1353 using a dose ramp on days 1 to 7 (Figure 3B). The methionine challenge was repeated on day 7 before SYNB1353 dosing. Changes in plasma methionine and total Hcy were assessed over 24h after the methionine challenge.

Results

SYNB1353 was generally well-tolerated in healthy volunteers

Results (continued)

Methionine Load Leads to Increase in Plasma Methionine and Plasma Homocysteine in Healthy Volunteers

Figure 4. Increased plasma methionine and total Hcy following methionine challenge. (A) Plasma methionine and (B) total Hcy levels of all subjects (n=30) from all cohorts over 24h after receiving a 30 mg/kg methionine load challenge. Data represent the mean ± SD. Methionine challenge resulted in an 11-fold increase in plasma methionine (Cmax) and a 2-fold increase in plasma total Hcy (Cmax) compared to baseline values.

Proof-of-Mechanism: SYNB1353 Blocks Methionine Absorption and Lowers Plasma Methionine

Figure 5. SYNB1353 blocks methionine absorption. Percent change from baseline in day 7 (A) plasma methionine AUC(0-24h) and (B) total plasma Hcy AUC(0-24h) for cohorts receiving 1x10^12 live cell of SYNB1353. FORM = formulation. LS mean change, 95% CI *p<0.05

Conclusions

• SYNB1353 was well tolerated in healthy volunteers with GI adverse event rates and severity similar between active and placebo groups
• SYNB1353 has demonstrated methionine metabolism in the GI tract of healthy volunteers, resulting in a lowering of plasma methionine and production of 3MTP-glycine, assessed following a meal challenge to elevate methionine levels
• Previously presented mechanistic modeling data suggests that SYNB1353 may increase protein intake and lower plasma Hcy by up to 58% in HCU patients
• Based on this proof of mechanism in healthy volunteers, SYNB1353 will be advanced to a Phase 2 proof of concept study in patients with HCU

References:

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