Pegtibatinase, an Investigational Enzyme Replacement Therapy, for the Treatment of Classical Homocystinuria (HCU): Design of the HARMONY Phase 3 Study

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Poster #147

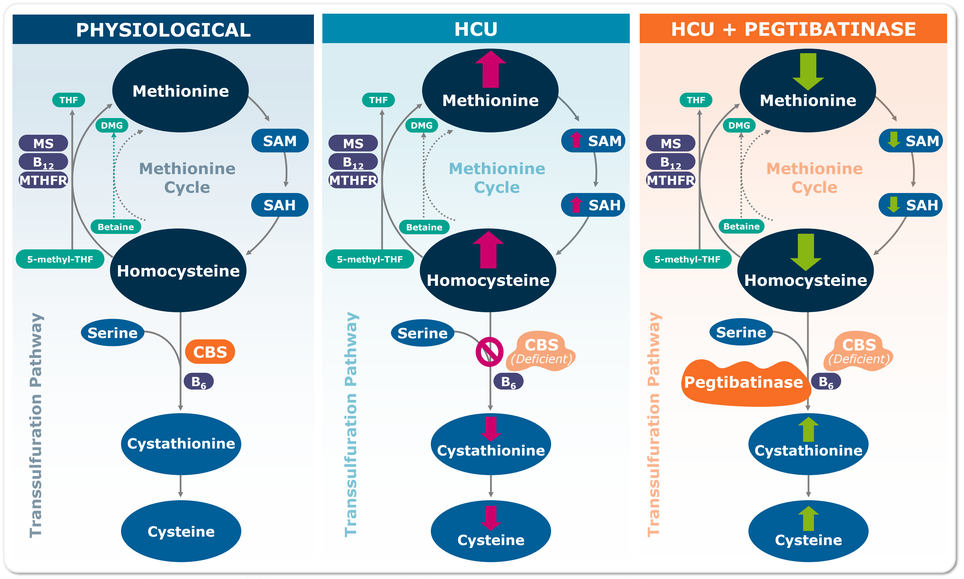
INTRODUCTION

- Classical homocystinuria (HCU) is a rare, monogenic, autosomal recessive inborn error of metabolism, caused by cystathionine β-synthase (CBS) deficiency and characterized by marked accumulation of homocysteine (Hcy) and methionine (Met) in plasma and tissues[1-3] (**Figure 1**)
- HCU is associated with risk of severe multisystemic complications including stroke, cognitive impairment, developmental delays, and ocular and skeletal abnormalities[1,2,4]
- Current standard-of-care (SOC) treatments include a protein-restricted diet and supplementation with Met-free metabolic formula, pyridoxine (vitamin B6), and betaine[2,5]
- However, these interventions can be suboptimal for reducing plasma total Hcy (tHcy) levels to clinically relevant target concentrations, leaving patients at risk of developing HCU-related complications[2,6]
- Pegtibatinase is a first-in-class, investigational, PEGylated, truncated human CBS designed as an enzyme replacement therapy for HCU[5]
- The goal of treatment with pegtibatinase is to replace deficient CBS activity, resulting in a reduction of plasma tHcy levels, which is expected to ameliorate the clinical manifestations of HCU and slow or prevent further deterioration
- In the COMPOSE® Phase 1/2, double-blind, randomized, placebo-controlled, dose-escalation trial (NCT03406611; N=24), pegtibatinase was generally well tolerated at doses up to 2.5 mg/kg twice weekly (BIW) with no anaphylaxis or immune reactions occurring[7]
  - All participants on active treatment of subcutaneous 1.5 mg/kg or 2.5 mg/kg achieved rapid, sustained reductions in mean plasma tHcy levels to below the key clinical threshold of 100 µM in the 12-week efficacy evaluation period; some participants also achieved levels <50 µM and <15 µM (normal)

Objectives

- The HARMONY Phase 3 study will evaluate the efficacy and safety of pegtibatinase plus SOC in reducing plasma tHcy levels in participants with HCU

Figure 1. Methionine Cycle and Transsulfuration Pathway in Healthy Individuals, in HCU, and During Pegtibatinase Treatment



CBS, cystathionine β-synthase; **DMG**, dimethylglycine; **HCU**, classical homocystinuria; **MS**, methionine synthase; **MTHFR**, methylenetetrahydrofolate reductase; **SAH**, S-adenosylhomocysteine; **SAM**, S-adenosylmethionine; **THF**, tetrahydrofolate.

METHODS

Study Overview

- HARMONY is a prospective, blinded, randomized (1:1), placebo-controlled, multicenter, multinational study in participants with HCU, aged ≥12 to ≤65 years, and tHcy ≥50 µM receiving SOC treatment
- Participants will be stratified by region (USA/Europe or rest of world) and tHcy levels (≥100 µM or <100 µM at pre-treatment Week -3 visit)

Participants

- Overall, a total of ~70 participants aged 12–65 years with a confirmed diagnosis of HCU and receiving SOC treatment will be randomized. Of these 70:
  - ≤18 participants (~25%) with screening plasma tHcy ≥50 to <80 µM will be enrolled. The remaining ~75% will have screening tHcy ≥80 µM
  - The trial will also aim to enroll 18 pediatric participants (~25%) (aged 12–17 years)
- Based on results from the COMPOSE® trial, a sample size of 35 participants in each arm will provide ≥90% power to test that the true change from baseline in plasma tHcy for pegtibatinase vs placebo is >0

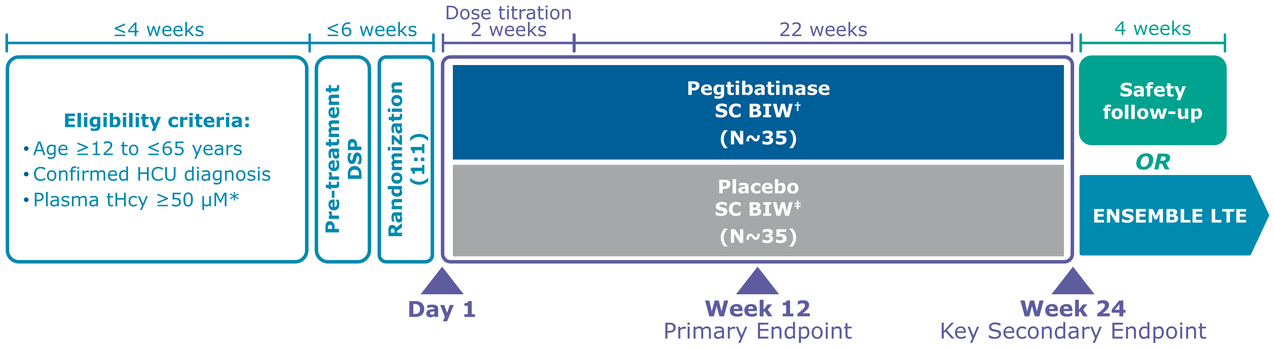
Study Duration

- The total study duration will be ≤38 weeks, incorporating screening (≤4 weeks) and a diet standardization period (DSP; ≤6 weeks) prior to blinded treatment (24 weeks, including a 2-week up-titration period), and post-treatment safety follow-up (4 weeks)
- Participants who complete the study will have the option to subsequently enroll in the ENSEMBLE open-label long-term extension study (**Figure 2**)

Diet Standardization Period (DSP)

- Dietary management of protein intake and HCU medications play an important role in controlling tHcy levels
- Protein intake and HCU medications should remain generally stable for appropriate interpretation of the treatment effect of pegtibatinase
- In HARMONY, a pre-treatment DSP has been incorporated to ensure all participants are trained to maintain a stable diet and HCU medication regimen
  - Enrolled participants will be regularly monitored by a metabolic dietitian throughout the DSP; participants and caregivers will be trained to maintain robust dietary monitoring using the Simplified Ingested Nutrients Guide (SING) tool, which combines a food frequency questionnaire with a 24-hour recall aid
  - Participants do not need to be on a protein-restricted diet to participate
  - Daily protein intake and HCU medications will be individually optimized based on participants' dietary preferences and level of metabolic dysfunction, as prescribed by an experienced metabolic dietitian in consultation with the study investigator
- To qualify for the blinded treatment period, participants must (1) attend all DSP visits, (2) demonstrate that they are following a generally stable diet and demonstrate HCU medication compliance based on dietitian judgment, and (3) continue to have plasma tHcy ≥50 µM

Figure 2. HARMONY Study Design



*Protocol allows for ≤18 participants with tHcy ≥50 µM to <80 µM, with the remaining participants ≥80 µM. †Titration and target dose will be based on participant weight. ‡Volume-matched placebo.
BIW, twice weekly; **DSP**, diet standardization period; **HCU**, classical homocystinuria; **LTE**, long-term extension; **SC**, subcutaneous; **tHcy**, total homocysteine.

Blinded Treatment Period

- If randomization criteria are met, participants will be randomized 1:1 to receive the titration dose of pegtibatinase for the first 2 weeks of the 24-week treatment period followed by the full target dose of pegtibatinase from Week 3, or volume-matched placebo (**Table 1**)
- Based on experiences from the COMPOSE® trial, premedication with histamine 1/2 blockers will also be given to all participants receiving study drug per local SOC to help prevent adverse events (AEs) such as injection-site reactions and urticaria
- Dietary protein intake and compliance with HCU treatment will continue to be monitored and recorded, and will be supported by dietitians, including ongoing training and feedback
- Participants completing the blinded treatment period will be eligible to roll over to the ENSEMBLE study, which will evaluate long-term safety, efficacy, and durability of response to pegtibatinase

Table 1. Pegtibatinase Dosing During the Blinded Treatment Period

Weight Group	Titration Dose (2 Weeks)	Full Target Dose
<60 kg	1.5 mg/kg SC BIW	2.5 mg/kg SC BIW
≥60 to <90 kg	100 mg SC BIW	200 mg SC BIW
≥90 to <120 kg	100 mg SC BIW	250 mg SC BIW
≥120 to <160 kg	150 mg SC BIW	300 mg SC BIW

BIW, twice weekly; **SC**, subcutaneous.

Endpoints

- Primary efficacy endpoint: change from baseline in plasma tHcy levels averaged over Weeks 6–12 in participants prescribed SOC plus pegtibatinase vs SOC plus placebo
- Key secondary endpoints (hierarchical testing to control for multiple comparisons):
  1. Change from baseline in plasma tHcy averaged post-Week 12 (Weeks 16, 20, and 24) in participants prescribed SOC plus pegtibatinase vs SOC plus placebo
  2. Proportion of participants achieving tHcy <100 µM averaged over Weeks 6–12 in participants with tHcy ≥100 µM at baseline
  3. Proportion of participants achieving tHcy <100 µM averaged post-Week 12 in participants with tHcy ≥100 µM at baseline
  4. Proportion of participants achieving tHcy <50 µM averaged over Weeks 6–12
  5. Proportion of participants achieving tHcy <50 µM averaged post-Week 12
- Safety and tolerability endpoints include incidence of serious AEs, treatment-emergent AEs and their relation to pegtibatinase, and the proportion of participants requiring dietary protein rescue
- Immunogenicity (anti-drug, anti-polyethylene glycol, and neutralizing antibodies) and pharmacokinetics of pegtibatinase will also be evaluated

DISCUSSION

- Following positive Phase 1/2 results in COMPOSE®, the HARMONY trial has been specifically designed to confirm the efficacy and safety of pegtibatinase in a larger population of participants with HCU
  - Enrollment criteria will ensure participants with a broad range of screening plasma tHcy levels and ages will receive study drug
  - Additionally, the study will be conducted in up to 50 study centers, including in the USA, Europe, Gulf countries, Asia Pacific, and Latin America to enable robust evaluation of pegtibatinase treatment in a diverse HCU population

CONCLUSIONS

- ✓ The HARMONY trial will determine the efficacy and safety of pegtibatinase as a novel, first-in-class enzyme replacement therapy in a global cohort of participants with HCU
- ✓ HARMONY has been designed to incorporate measures that ensure participants are trained, monitored, and able to maintain a stable diet and medication regimen, including a pre-treatment DSP
- ✓ Participants completing the HARMONY trial will have the option to enroll in the ENSEMBLE study and receive pegtibatinase as open-label treatment

ABBREVIATIONS

AE, adverse event; **BIW**, twice weekly; **CBS**, cystathionine β-synthase; **DMG**, dimethylglycine; **DSP**, diet standardization period; **HCU**, classical homocystinuria; **Hcy**, homocysteine; **LTE**, long-term extension; **Met**, methionine; **MS**, methionine synthase; **MTHFR**, methylenetetrahydrofolate reductase; **SAH**, S-adenosylhomocysteine; **SAM**, S-adenosylmethionine; **SC**, subcutaneous; **SING**, Simplified Ingested Nutrients Guide; **SOC**, standard of care; **tHcy**, total homocysteine; **THF**, tetrahydrofolate.

DISCLOSURES

JT, TB-O, CF: Investigator, Travere Therapeutics, Inc. **HL:** Investigator and consultant, Travere Therapeutics, Inc. **FM:** Consultant, Travere Therapeutics, Inc. **SM, SS:** Employee and stockholder, Travere Therapeutics, Inc.

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