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

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TRAVERE™ THERAPEUTICS

Harmony Ensemble

INTRODUCTION

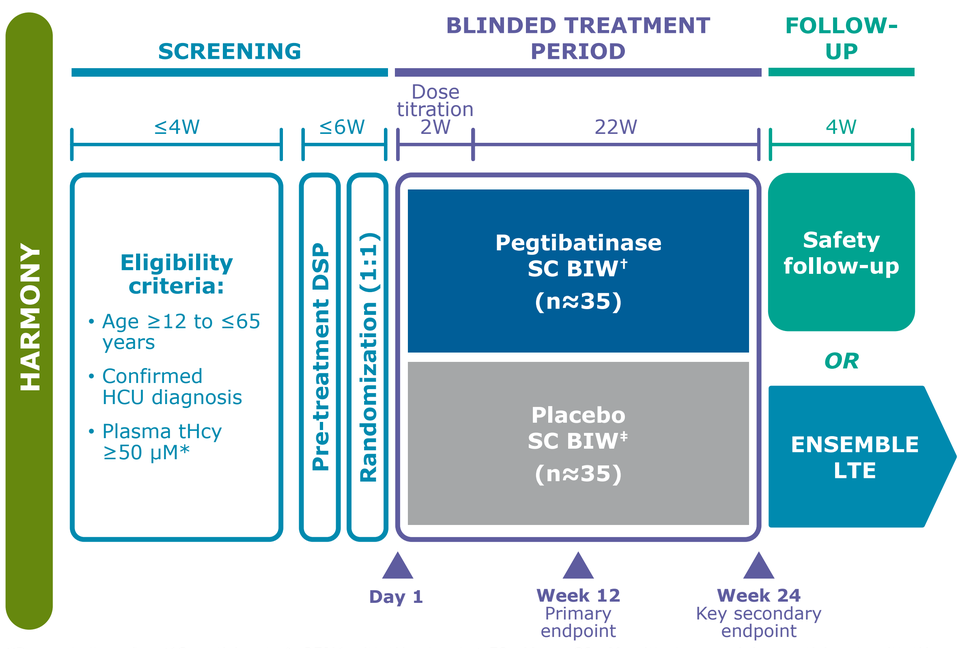
- Classical homocystinuria (HCU) is a rare, monogenic, autosomal-recessive inborn error of metabolism, caused by cystathionine β-synthase (CBS) deficiency and characterized by marked accumulation of homocysteine (Hcy) and methionine (Met) in plasma and tissues,[1–3] leading to risk of severe multisystemic complications of the vasculature, central nervous system, eyes, and skeleton[1,2,4]
- Current standard-of-care (SOC) treatments include protein-restricted diet and supplementation with Met-free metabolic formula, pyridoxine (vitamin B6), and betaine.[2,5] However, these can be suboptimal for reducing plasma total Hcy (tHcy) to clinically relevant target concentrations[2,6]
- Pegtibatinase is a first-in-class, investigational, polyethylene glycol (PEG)ylated, truncated human CBS designed as an enzyme replacement therapy for HCU.[5] The goal of treatment is to replace deficient CBS activity, resulting in a reduction of plasma tHcy levels, which is expected to ameliorate the clinical manifestations of HCU
- In the COMPOSE® Phase 1/2, double-blind, randomized, placebo-controlled, dose-escalation trial of participants with HCU aged ≥12 to ≤65 years (ClinicalTrials.gov Identifier: NCT03406611; N=24):
  - Subcutaneous (SC) 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 who received pegtibatinase 1.5 mg/kg BIW or 2.5 mg/kg SC BIW achieved rapid, sustained reductions in mean plasma tHcy levels below the guideline-recommended 100 µM threshold. Some participants who received 2.5 mg/kg BIW reduced tHcy <50 µM, including one who reduced tHcy <15 µM (considered normal)[7]

Objectives

- The HARMONY and ENSEMBLE Phase 3 studies will evaluate the efficacy and safety of pegtibatinase plus SOC as a potential treatment for patients with HCU

METHODS

Figure 1. HARMONY Study Design



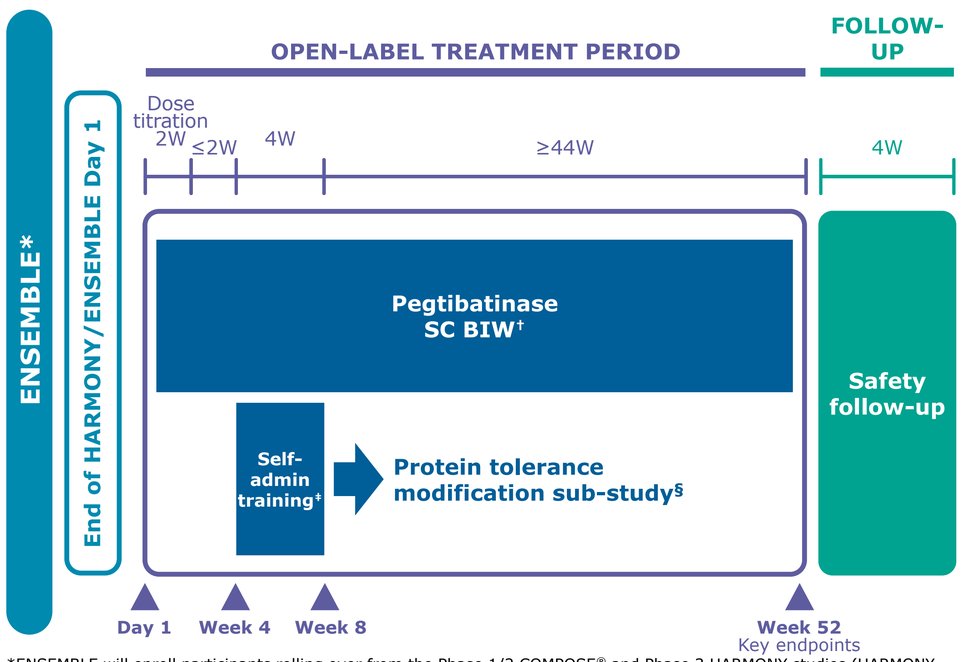
*Protocol allows for ≤18 participants (~25%) with tHcy levels ≥50 µM to <80 µM, with the remaining participants with tHcy levels ≥80 µM (~75%). †Titration and target dose will be based on participant weight. ‡Volume-matched placebo.
BIW, twice weekly; **DSP**, diet standardization period; **HCU**, classical homocystinuria; **LTE**, long-term extension; **SC**, subcutaneous; **tHcy**, total homocysteine; **W**, weeks.

Table 1. Pegtibatinase Dosing in HARMONY*

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

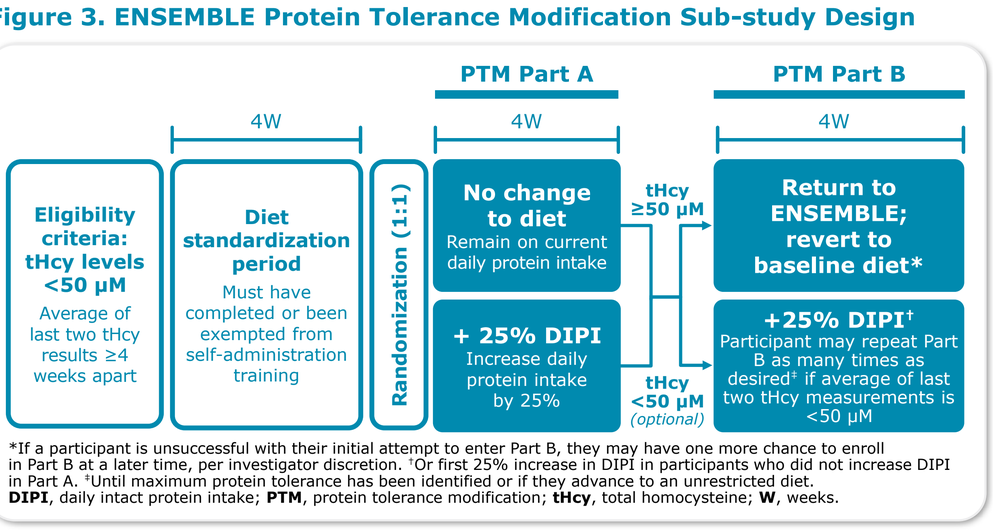
*Based on experiences from COMPOSE®, premedication with histamine 1/2 blockers will also be given to all participants receiving study drug per local SOC to help prevent adverse events such as injection-site reactions and urticaria.
BIW, twice weekly; **SC**, subcutaneous; **SOC**, standard of care.

Figure 2. ENSEMBLE Study Design



*ENSEMBLE will enroll participants rolling over from the Phase 1/2 COMPOSE® and Phase 3 HARMONY studies (HARMONY shown in figure). †Titration and target dose will be based on participant weight as in HARMONY.
‡Self-administration training period of 4 weeks that can start on Week 3 or Week 4. Upon completion, all participants will self-administer during the whole study unless exempted. §Only for eligible participants and can start any time after Week 8.
BIW, twice weekly; **SC**, subcutaneous; **self-admin**, self-administration; **W**, weeks.

Figure 3. ENSEMBLE Protein Tolerance Modification Sub-study Design



*If a participant is unsuccessful with their initial attempt to enter Part B, they may have one more chance to enroll in Part B at a later time, per investigator discretion. †Or first 25% increase in DIPI in participants who did not increase DIPI in Part A. ‡Until maximum protein tolerance has been identified or if they advance to an unrestricted diet.
DIPI, daily intact protein intake; **PTM**, protein tolerance modification; **tHcy**, total homocysteine; **W**, weeks.

HARMONY

HARMONY Study Overview

- HARMONY (ClinicalTrials.gov Identifier: NCT06247085; N≈70) is a global, Phase 3, multicenter, randomized (1:1), blinded, placebo-controlled, parallel-group study to assess efficacy and safety of weight-based pegtibatinase vs placebo in participants with HCU aged ≥12 to ≤65 years receiving SOC treatment (**Figure 1**, **Table 1**)

HARMONY Endpoints

- **Primary efficacy endpoint:** Change from baseline in plasma tHcy levels averaged over Weeks 6–12 compared with placebo
- **Key secondary endpoints:**
  - Change from baseline in plasma tHcy levels averaged post Week 12 (Weeks 16, 20, and 24) vs placebo
  - Proportion of participants with tHcy levels ≥100 µM at baseline achieving tHcy levels <100 µM averaged over Weeks 6–12 and post Week 12
  - Proportion of participants achieving tHcy levels <50 µM averaged over Weeks 6–12 and post Week 12
  - Safety, tolerability, immunogenicity, and pharmacokinetics

HARMONY Diet Standardization Period (DSP)

- Participants and caregivers will have several training visits with an experienced metabolic dietitian over 4–6 weeks to ensure they are trained to maintain a stable diet (restricted or unrestricted) and medication regimen throughout the study
  - Dietary intact protein intake (DIPI) allowance and treatment will be individually optimized after the first visit based on participant preferences and level of metabolic dysfunction
  - Participants will be trained to use the Simplified Ingested Nutrients Guide (SING), a novel HCU-specific tool that combines elements of a food frequency questionnaire with 24-hour recall of dietary intake and can be customized for local dietary habits
- Participants qualify for the blinded treatment period if they still meet screening criteria, attend all DSP visits, and demonstrate consistent adherence to diet and medications

ENSEMBLE

ENSEMBLE Study Overview

- ENSEMBLE (ClinicalTrials.gov Identifier: NCT06431893; N≈90) is a 56-week, global, multicenter, single-arm, open-label, Phase 3 study to evaluate long-term safety, efficacy, and durability of response to pegtibatinase plus SOC treatment (**Figure 2**)
- Participants who complete the blinded treatment period of HARMONY, as well as those who are active in the Phase 1/2 COMPOSE® trial, are eligible
- All participants will receive ≥4 weeks of training to self-administer pegtibatinase from Week 3 or Week 4 unless medically exempted
- Diet and medication compliance will continue to be monitored by a metabolic dietitian using the SING tool throughout ENSEMBLE

ENSEMBLE Endpoints

- **Primary safety and tolerability endpoints:**
  - Treatment-emergent adverse events
  - Incidence of hypermethioninemia or hypomethioninemia
  - Need for dietary protein rescue
  - Changes in vital signs, clinical laboratory, and electrocardiogram parameters
- **Key secondary endpoints:**
  - Efficacy of pegtibatinase on reducing plasma tHcy and Met
  - Changes in clinical biomarkers/evaluations
  - Immunogenicity
  - Pharmacokinetics

ENSEMBLE Protein Tolerance Modification (PTM) Sub-study

- During ENSEMBLE, an optional PTM sub-study will be conducted for up to 20 eligible participants to assess whether they can tolerate additional dietary protein intake while maintaining acceptable metabolic control (tHcy <50 µM) (**Figure 3**)
- **PTM sub-study endpoints**:
  - Proportion of participants who maintain tHcy <50 µM after 4 weeks on adjusted vs unadjusted diet
  - Change in DIPI
  - Changes in Patient Global Impression of Severity and Clinical Global Impression of Severity at 4 weeks
  - Change in Protein-Restricted Diet Impact; A Novel Outcome Measure (PIANO) at 4 weeks

DISCUSSION

- Following positive Phase 1/2 results in COMPOSE®,[7] the Phase 3 HARMONY trial will aim to confirm the efficacy and safety of pegtibatinase in a larger population of participants with HCU, while ENSEMBLE will evaluate long-term tolerability and response to treatment
  - Enrollment criteria will ensure participants with a broad range of screening plasma tHcy levels and ages will receive study drug
  - Additionally, the studies 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
- Both the Phase 3 HARMONY and ENSEMBLE trials have been designed around achievement of stable diet and HCU medication intake to minimize these potentially confounding factors in the evaluation of pegtibatinase

CONCLUSIONS

✓ The global HARMONY study will follow participants over 24 weeks of double-blind treatment to determine the efficacy and safety of pegtibatinase as a novel, first-in-class enzyme replacement therapy; participants will then be able to continue to receive open-label pegtibatinase for 52 weeks in the ENSEMBLE study

✓ By evaluating participants with HCU over a longer period, HARMONY and ENSEMBLE will also be able to assess the relationship of tHcy with clinical outcomes as well as psychosocial well-being

ABBREVIATIONS

BIW, twice weekly; **CBS**, cystathionine β-synthase; **DIPI**, dietary intact protein intake; **DSP**, diet standardization period; **HCU**, classical homocystinuria; **Hcy**, homocysteine; **LTE**, long-term extension; **Met**, methionine; **PEG**, polyethylene glycol; **PIANO**, Protein-Restricted Diet Impact; A Novel Outcome Measure; **PTM**, protein tolerance modification; **SC**, subcutaneous; **self-admin**, self-administration; **SING**, Simplified Ingested Nutrients Guide; **SOC**, standard of care; **tHcy**, total homocysteine; **W**, weeks.

DISCLOSURES

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

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