Novel Dietary Management Strategies for Classical Homocystinuria (HCU) in HARMONY/ENSEMBLE Phase 3 Studies of Pegtibatinase, an Investigational Enzyme Replacement Therapy

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Poster #33

TRAVERE THERAPEUTICS

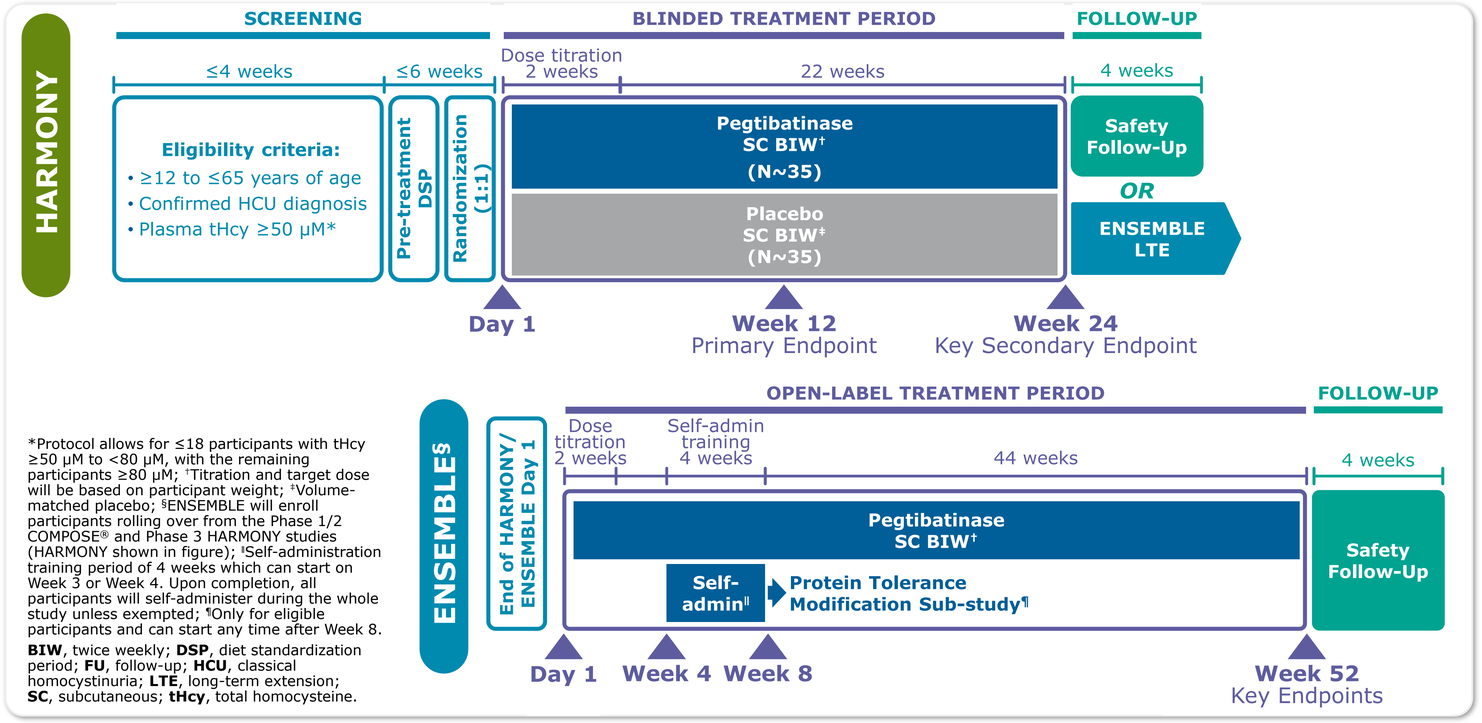
Harmony Ensemble

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]
- As both protein intake and medication play an important role in controlling total Hcy (tHcy) levels, dietary management is a cornerstone of treatment for HCU, especially in patients who are pyridoxine (vitamin B6) unresponsive[2]
- Consequently, these factors must be closely documented and remain as stable as possible when evaluating treatment effects of new therapies
- Pegtibatinase is a novel enzyme replacement therapy currently in development for HCU.[4] To aid efficacy evaluation in clinical trials, new methods to standardize the management and monitoring of daily intact protein intake (DIPI) and HCU-related medications are needed

METHODS

Figure 1. Pegtibatinase Phase 3 Program



*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; §ENSEMBLE will enroll participants rolling over from the Phase 1/2 COMPOSE® and Phase 3 HARMONY studies (HARMONY shown in figure); ‖Self-administration training period of 4 weeks which 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; **DSP**, diet standardization period; **FU**, follow-up; **HCU**, classical homocystinuria; **LTE**, long-term extension; **SC**, subcutaneous; **tHcy**, total homocysteine.

RESULTS

HARMONY

HARMONY Study Overview

- HARMONY (N~70) is a global, Phase 3, multicenter, randomized (1:1), blinded, placebo-controlled, parallel-group study to assess efficacy and safety of pegtibatinase versus placebo in participants with HCU aged 12–65 years receiving standard of care (SOC) (**Figure 1**)
  - SOC treatments include pyridoxine, betaine, and Met-free formula
- The ≤38-week trial includes a ≤4-week screening period, ≤6-week diet standardization period (DSP), and 24-week treatment period (including 2 weeks of dose titration), followed by a 4-week safety-follow-up period or enrollment in the ENSEMBLE long-term extension
- Primary efficacy endpoint: change from baseline in plasma tHcy levels averaged over Weeks 6–12 as compared to placebo
- Key secondary endpoints include change from baseline in plasma tHcy levels averaged post-Week 12 (Weeks 16, 20, and 24), safety, tolerability, and immunogenicity

HARMONY Diet Standardization Period (DSP)

- The HARMONY trial has been designed with a pre-treatment diet standardization period (DSP) to ensure all participants are trained to consume a stable diet and medication regimen and are compliant with their dietary management plan prior to randomization with pegtibatinase or placebo
  - These measures were developed based on guidance from literature,[2,5] regulatory authorities,[6] metabolic dietitians, and patients with HCU
  - Study sites will be trained to ensure consistency across centers
  - Participants do not need to be on a protein-restricted diet to participate but must maintain a generally stable diet and HCU medication compliance during the study
- Participants will have several training visits with an experienced metabolic dietitian over 4–6 weeks to ensure stable diet and HCU treatments are maintained throughout the study and provide feedback
- Since HCU has a variable presentation, DIPI allowance and HCU treatment will be individually optimized after the first visit based on participants' dietary preferences and level of metabolic dysfunction, as prescribed by their dietitian in consultation with their study investigator
  - This baseline diet will be used as a reference for future evaluation of dietary protein and supplement intake
  - Monitoring, documentation, and counselling of participants will be standardized prior to beginning the treatment period
- Participants and caregivers will be trained to maintain robust dietary monitoring using the Simplified Ingested Nutrients Guide (SING), a novel HCU-specific tool which combines elements of a food frequency questionnaire with 24-hour recall of dietary intake
  - The goal is to assist diet stabilization, not diet change
  - SING will be customized into local dietary habits
  - A full description of the SING is presented in Poster #16
- To qualify for the blinded treatment period, participants must:
  - Attend all DSP visits,
  - Demonstrate consistent adherence with a stable diet with consistent DIPI and HCU-related treatments based on local dietitian judgement
  - Have tHcy ≥50 µM (most recent sample)
- During the blinded treatment period, participant diet and medication compliance will continue to be monitored regularly by a metabolic dietitian using the SING tool to reinforce a stable DIPI and HCU medication regimen, and aid interpretation of metabolic biomarkers

ENSEMBLE

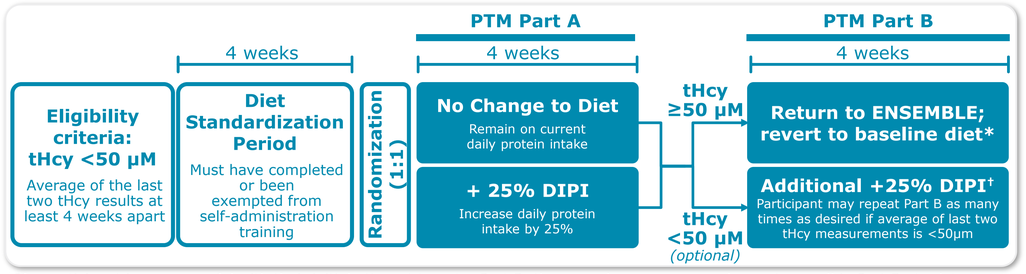
ENSEMBLE Study Overview

- ENSEMBLE (N≤90) is a global, multicenter, single-arm, open-label Phase 3 study to evaluate long-term safety, efficacy, and durability of response to pegtibatinase (**Figure 1**)
- Participants who complete the blinded treatment period of HARMONY, as well as those who are active in the Phase 1/2 COMPOSE® trial (NCT03406611) are eligible to enroll
- Primary endpoints: determine the long-term safety and tolerability of SOC plus pegtibatinase, including incidence of treatment-emergent adverse events, incidence of hyper-/hypomethioninemia, and dietary protein rescue quantity needed for hypomethioninema
- Key secondary endpoints include efficacy of pegtibatinase on reducing plasma tHcy, relationship between tHcy levels and clinical outcomes, long-term changes in Met, immunogenicity, and pharmacokinetics
- All participants will be trained to self-administer pegtibatinase from Week 3 or 4 unless medically exempted
- Diet and medication compliance will be monitored regularly by a metabolic dietitian using the SING tool throughout the ENSEMBLE trial

ENSEMBLE Protein Tolerance Modification (PTM) Sub-Study

- During ENSEMBLE, an optional PTM sub-study will be conducted for eligible participants to assess if they can tolerate additional dietary protein intake while maintaining acceptable metabolic control (tHcy <50 µM) (**Figure 2**)
  - Participants may be eligible if they achieve tHcy <50 µM and have completed or been exempted from self/caregiver administration training
- The PTM sub-study has three sequential parts:
  - **DSP:** To minimize variability in protein intake and supplements during the randomized portion
  - **Part A:** Randomized PTM period to assess effect of increased protein intake on metabolic control and quality of life
    - Participants will be randomized 1:1 to their current diet or a 25% increase in DIPI for 4 weeks
  - **Part B:** Non-randomized PTM period to closely mirror DIPI in clinical practice
    - Participants are eligible if they continue to have tHcy <50 µM in Part A, and will be able to further increase DIPI by 25% for 4 weeks
    - Participants may repeat Part B as many times as necessary until maximum protein tolerance has been identified or if they advance to an unrestricted diet, as long as tHcy stays <50 µM

Figure 2. 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.
DIPI, daily intact protein intake; **tHcy**, total homocysteine.

DISCUSSION

- Although current SOC interventions have some impact on reducing tHcy in patients with HCU, they can be suboptimal for reducing tHcy to clinically relevant target concentrations, leaving patients at risk of HCU-related complications[2,7]
- 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
- The PTM sub-study will also assess the potential for relaxation in dietary protein restrictions in participants receiving SOC treatments plus pegtibatinase, and whether this can offer clinical benefit and quality of life improvements while maintaining tHcy within clinically relevant thresholds

CONCLUSIONS

- ✓ Novel dietary monitoring strategies are being developed for the HARMONY and ENSEMBLE Phase 3 trials to aid evaluation of pegtibatinase efficacy in treatment of HCU
- ✓ A DSP incorporating participant/caregiver dietary training in HARMONY will ensure participant compliance with stable diet and HCU medication intake
- ✓ Diet and medications will be monitored and documented regularly throughout both trials using SING, a combination of a food frequency questionnaire and 24-hour recall
- ✓ Participants in ENSEMBLE may be eligible to increase natural protein intake through the PTM sub-study if they achieve tHcy ≤50 µM
- ✓ These strategies could have further use as clinical tools for dietary management in HCU

ABBREVIATIONS

BIW, twice weekly; **CBS**, cystathionine β-synthase; **DIPI**, dietary intact protein intake; **DSP**, diet standardization period; **FU**, follow-up; **HCU**, classical homocystinuria; **Hcy**, homocysteine; **LTE**, long-term extension; **Met**, methionine; **PTM**, Protein Tolerance Modification; **SC**, subcutaneous; **SING**, Simplified Ingested Nutrients Guide; **SOC**, standard of care; **tHcy**, total Hcy.

DISCLOSURES

JT, TB-O, SvD, 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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