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

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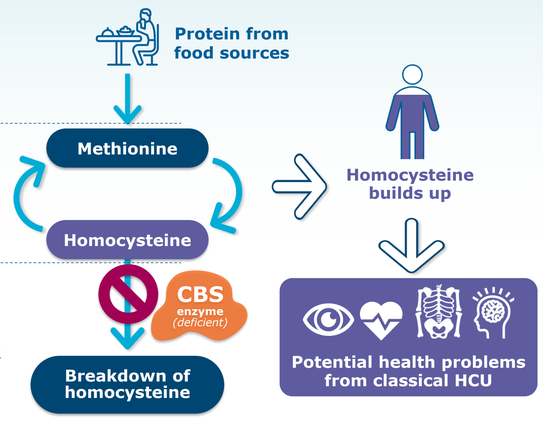
BACKGROUND

HCU is a slowly progressive genetic condition caused by lack of activity of an enzyme called cystathionine β-synthase (CBS)[1,2]

1. Methionine, which comes from protein in food, is an essential building block in the body

2. When methionine is processed, it releases homocysteine

3. The CBS enzyme is deficient in people with classical HCU, which leads to the build up of toxic levels of excess homocysteine



Pegtibatinase as a Potential Treatment for HCU

- Current treatments may include a low-protein diet (typically with metabolic formula), Cystadane® (betaine), and/or vitamin B6[2]
- Even with treatment, many patients ***are not able to keep homocysteine below the recommended 100 µM*** level[2]
- Enzyme replacement therapy is a medical treatment that replaces an enzyme that is missing or deficient in the body
- Pegtibatinase is a modified version of the ***human*** CBS enzyme[3] that is injected under the skin (subcutaneous injection), which is being studied as a potential treatment for HCU

The COMPOSE® Phase 1/2 clinical trial

The COMPOSE® clinical trial previously investigated 24 participants with HCU who were given pegtibatinase for at least 12 weeks. Their average total homocysteine (tHcy) levels between Weeks 6 and 12 were then compared with their levels before treatment started[4]

At the highest dose of 2.5 mg/kg twice a week, pegtibatinase:[4]

- Reduced tHcy levels by 67%, with some participants achieving levels below 50 µM and one participant within normal limits (below 14 µM)
- Was generally well tolerated with most side effects being mild and short-lived
- Did not cause severe allergic or immune reactions

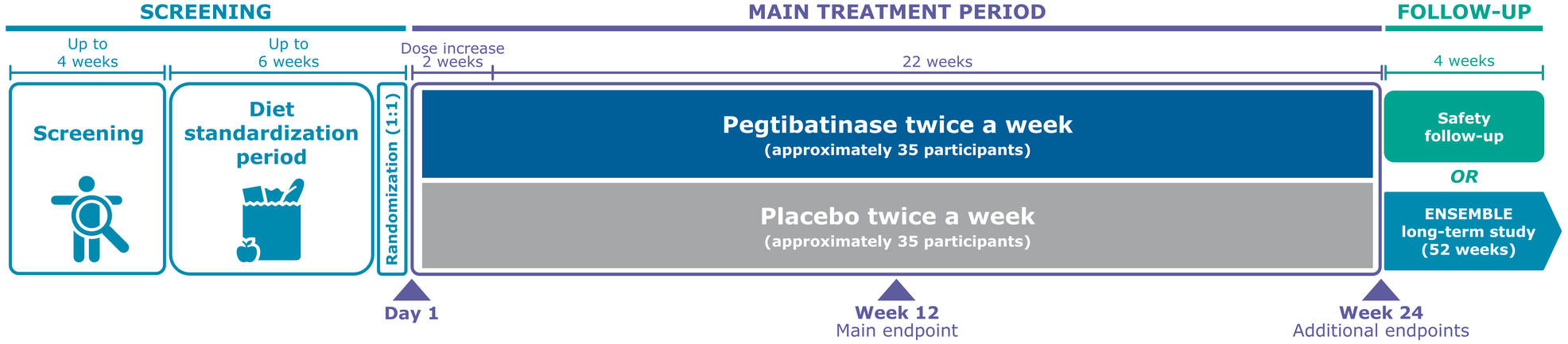
OBJECTIVES OF HARMONY

The global HARMONY trial will investigate how effective and how safe pegtibatinase is in a larger group of participants with HCU

METHODS

STUDY OVERVIEW

- HARMONY is a global Phase 3 study (a big clinical study in which safety and effectiveness data are needed for a drug to be approved) being conducted in multiple regions (USA, Europe, Gulf countries, Asia-Pacific, and Latin America) to investigate pegtibatinase in participants with HCU and high levels of tHcy
- Participants will be randomly assigned to either pegtibatinase or placebo (which does not contain an active drug)
- The study will be blinded, meaning participants, caregivers, and investigators will not know who is receiving pegtibatinase and who is receiving placebo
- Participants will be able to continue any existing treatments (such as metabolic formula, betaine, or vitamin B6) as long as they do not change their doses
- All participants will be trained and monitored to make sure their diet remains stable during the study, as this can influence the levels of tHcy and other molecules being measured



Screening: Participants

Confirmed HCU diagnosis

Approximately **70** participants

Age **12–65** Years old

including **18** aged 12-17 years (pediatric participants)

50–79 µM ~1 in 4 participants tHcy **≥80 µM** ~3 in 4 participants

Screening: Diet Standardization Period

- In HARMONY, there will be a 6-week pre-treatment diet standardization period
  - **Participants are not required to change their protein intake**
  - Diet, formula, and medications must be consistent throughout the study so that the impact of the study drugs (pegtibatinase and placebo) can be accurately measured
  - This period has been added because protein from diet and HCU medications can influence tHcy and other molecules that will be measured in HARMONY

Regular monitoring and visits with an expert dietitian

Training for participants and caregivers using the Simplified Ingested Nutrients Guide (SING) to maintain a consistent diet

Participants should maintain a consistent diet and medication regimen throughout the study

- To qualify for the treatment period, participants must:
  1. **Attend all visits**
  2. **Demonstrate consistent and stable diet and HCU medication**
  3. **Have tHcy levels consistently above 50 µM***

*~25% of enrolled participants will have tHcy 50–80 µM, ~75% will have tHcy >80 µM.

Main Treatment Period

Participants who successfully meet the diet standardization period criteria will be placed into two groups at random to receive pegtibatinase or placebo twice a week as an injection under the skin

A low dose of pegtibatinase will initially be given, which will be increased over the following 2 weeks to a target dose depending on participant weight

Participant weight	Starting dose	Full target dose
<60 kg	1.5 mg/kg twice a week	2.5 mg/kg twice a week
≥60 to <90 kg	100 mg twice a week	200 mg twice a week
≥90 to <120 kg	100 mg twice a week	250 mg twice a week
≥120 to <160 kg	150 mg twice a week	300 mg twice a week

To reduce the risk of side effects related to the injection, participants will also receive antihistamine medication

Diet and HCU medications will continue to be monitored; dietitians will continue to give training and feedback

Efficacy Endpoints:
Change from start of treatment for pegtibatinase versus placebo

Primary efficacy endpoint: Change in tHcy at Weeks 6-12

Additional efficacy endpoint: Change in tHcy at Weeks 16-24

Other efficacy endpoints measured at Weeks 6-12 and Weeks 16-24
- Proportion of participants with tHcy levels ≥100 µM at start of treatment who have tHcy levels <100 µM
- Proportion of participants with tHcy levels <50 µM

Other Endpoints:
In all participants who receive at least one dose of pegtibatinase or placebo

Safety
Side effects that occur during treatment, serious side effects, side effects related to pegtibatinase, and proportion of participants requiring increases in dietary protein

Immune reaction markers

Participants who complete the main treatment period will have the opportunity to enroll in the global, **open-label (all participants will receive pegtibatinase)** ENSEMBLE study, which will evaluate long-term safety, efficacy, and durability of effect in approximately 90 participants over 52 weeks. The trial:
- Includes training for patients and caregivers to learn how to self-administer pegtibatinase
- Features a sub-study where participants who have tHcy levels <50 µM have the opportunity to increase natural protein in their diet in a controlled way to determine if tHcy remains low

CONCLUSIONS

COMPOSE® was a small initial trial that showed pegtibatinase was generally well tolerated and effective in reducing homocysteine; the global HARMONY trial will investigate the efficacy and safety of pegtibatinase in approximately 70 participants with HCU

Entry requirements will ensure a broad range of participants, with different ages and tHcy levels included (minimum tHcy >50 µM)

HARMONY includes measures to ensure participants are trained, monitored, and able to maintain a stable diet and medication regimen throughout the study

Participants completing HARMONY may enroll in the ENSEMBLE long-term open-label study (everyone receives pegtibatinase). A sub-study in ENSEMBLE will evaluate whether participants with tHcy <50 µM can increase natural protein in their diet and still maintain metabolic control

ABBREVIATIONS

CBS, cystathionine β-synthase; **HCU**, classical homocystinuria; **SING**, Simplified Ingested Nutrients Guide; **tHcy**, total homocysteine.

DISCLOSURES

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

ACKNOWLEDGMENTS

This study was supported by Travere Therapeutics, Inc. (San Diego, CA). Medical writing assistance was provided by Simon Lott of LiNK Health Group and was funded by Travere Therapeutics, Inc.
We thank Sergio Slawka for his valuable contributions to the HARMONY study.
We also thank Heather Hartley-Thorne of Sephirus Communications, Inc. for her valuable contributions to data visualization.

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08/2024 MA-PE-24-0059

Presented at the HCU Network America Conference; June 29-30, 2024; Aurora, CO, USA