Pegtibatinase
The HARMONY/ENSEMBLE (Phase 3 Studies): Study Design

Summary

Background

- Pegtibatinase is an injectable, PEGylated, truncated human CBS designed as an ERT for classical homocystinuria (HCU).[1,2] It is an investigational agent not approved by any health authority[3]
- The HARMONY study is a phase 3, randomized, blinded, placebo-controlled clinical trial evaluating the safety and efficacy of SC pegtibatinase in patients with classical HCU[4]
- ENSEMBLE is an open-label extension study to evaluate long-term safety, efficacy, and response to pegtibatinase treatment in patients who have completed the blinded HARMONY treatment period or are active in the Phase 1/2 COMPOSE trial[5]

Background

Pegtibatinase

Pegtibatinase is a genetically engineered, PEGylated, truncated human CBS designed as an ERT for HCU.[1,2] It is an investigational agent not approved by any health authority.[3] Pegtibatinase is administered subcutaneously and metabolizes Hcy to cystathionine in the bloodstream.[1]

Pegtibatinase has shown efficacy in preclinical studies in 3 different mouse models of HCU, demonstrating positive effects in the 4 key organ systems that are also affected in HCU patients: cardiovascular, skeletal, ocular, and CNS.[2,6-8]

Pegtibatinase further demonstrated efficacy in clinical studies. The COMPOSE study was a randomized, double-blind, placebo-controlled trial to examine the safety and efficacy of pegtibatinase in patients aged 12 to 65 years with HCU. Treatment with pegtibatinase 2.5 mg/kg BIW resulted in a 67% relative change from baseline in plasma tHcy levels, and pegtibatinase appeared to be well tolerated at all doses tested.[3]

The HARMONY Study

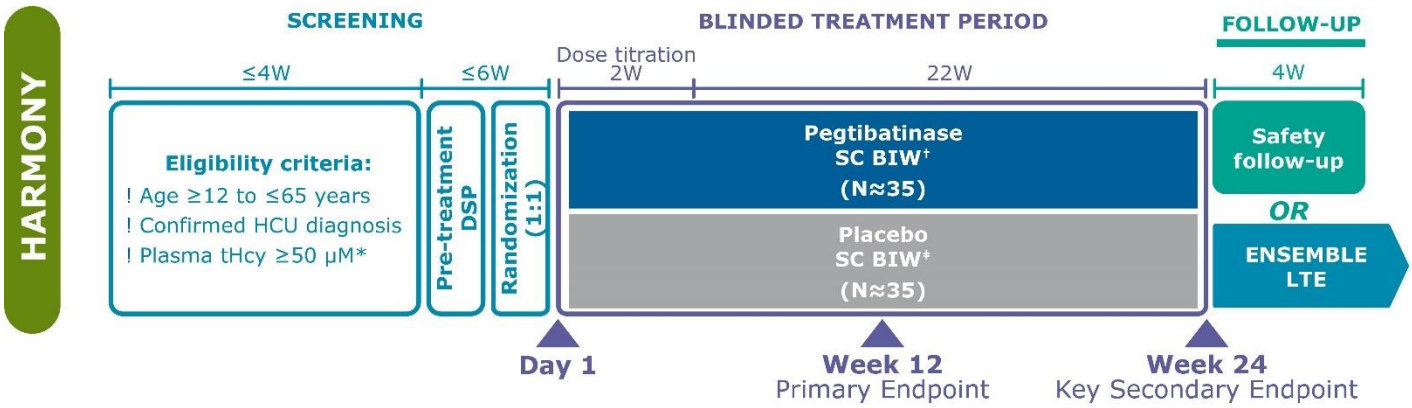
Study Design

The HARMONY study (NCT06247085) is a phase 3, global, randomized, blinded, placebo-controlled study in patients with CBS deficient HCU who continue to have tHcy levels ≥50 µM despite maintaining SOC. Up to 70 study sites are planned in the US, Europe, Gulf countries, Latin America, and Asia Pacific. To be eligible for study participation, patients must be aged ≥12 to ≤65 years and have a diagnosis of HCU based on clinical, biochemical, and/or molecular genetic testing,

with plasma tHcy ≥80 µM at screening. The study protocol allows for enrollment of up to 18 participants with screening plasma tHcy ≥50 to <80 µM. Patients (N≈70) will be randomized 1:1 to receive pegtibatinase or placebo. The planned patient population includes a target of 18 pediatric participants aged 12 to <18 years.[4,5]

Study duration will be up to 38 weeks, including ≤4 week screening period, ≤6 week DSP, 2 weeks of dose titration, and 22 weeks of active treatment or placebo. A safety follow-up period will be conducted for 4 weeks after last pegtibatinase dose, or eligible patients may continue into the ENSEMBLE LTE study (**Figure 1**).[4,5]

Figure 1. 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.
‖Self-administration training period of 4 weeks that can start on Week 3 or Week 4.

Study Endpoints

The primary study objective is to determine the effect of SC pegtibatinase on plasma tHcy and Met compared to placebo in patients with HCU receiving SOC. The primary efficacy endpoint measures change from baseline in plasma tHcy levels averaged over study Weeks 6 through 12 in patients receiving pegtibatinase vs those receiving placebo. Key secondary endpoints include change from baseline in plasma tHcy levels averaged over Weeks 16, 20, and 24; the proportion of patients achieving tHcy <100 µM averaged over Weeks 6 through 12 among patients with tHcy ≥100 µM at baseline; the proportion of patients achieving tHcy <100 µM after Week 12 among participants with tHcy ≥100 µM at baseline; the proportion of patients with tHcy <50 µM averaged over Weeks 6 through 12; and the proportion of patients with tHcy <50 µM after Week 12. Other secondary endpoints include evaluation of PK of pegtibatinase, safety assessments, and immunogenicity. Evaluation of safety includes incidence of TEAEs, clinical laboratory findings, incidence of hypermethioninemia and hypomethioninemia, proportion of patients requiring dietary protein rescue, and changes from baseline in vital signs, clinical laboratory parameters, and ECG parameters by visit.[4,5,9]

Methods

Diet Standardization Period

Prior to randomization, eligible patients will undergo a pretreatment DSP of up to 6 weeks to minimize variability in protein intake and supplements during study randomization, and to ensure diet and medication compliance throughout the study. Given the variable presentation of HCU, daily protein intake allowance and HCU treatments will be optimized for individual patients based on dietary preferences and level of metabolic dysfunction as determined by a dietitian and confirmed by the investigator. Dietary monitoring will be conducted utilizing the SING HCU-specific tool. To participate in the blinded treatment period, patients must attend all DSP visits, have tHcy ≥50 µM and comply with a stable diet and HCU-related treatment.[4,5]

Blinded Treatment Period

Patients will receive an initial titration dose of SC pegtibatinase BIW for the first 2 weeks of the double-blind treatment period, followed by pegtibatinase target dose BIW for 22 weeks. Patients randomized to placebo will receive volume-matched SC saline BIW. The target dose will be determined by patient weight (**Table 1**). Patient weight will be remeasured at Week 12 to assess for any weight change that causes a need for adjustments in dosing.[4]

Table 1. Study Intervention Administration

Weight Group (kg)	Titration Dose	Titration Dose Volume	Full Target Dose	Full Target Dose Volume
<60	1.5 mg/kg SC BIW	Calculated based on participant's weight	2.5 mg/kg SC BIW	Calculated based on participant's weight
≥60 to <90	100 mg SC BIW	4 mL	200 mg SC BIW	8 mL
≥90 to <120	100 mg SC BIW	4 mL	250 mg SC BIW	10 mL
≥120 to <160	150 mg SC BIW	6 mL	300 mg SC BIW	12 mL

During the 24-week blinded treatment period, patients will have a total of 38 study visits; of these, 17 will be home visits. During this time, dietary protein intake and compliance with HCU treatments will be monitored and recorded by the study site dietician. To determine the PK profile of pegtibatinase, blood samples will be collected from participants at multiple visits throughout the blinded treatment period (**Table 2**).[4]

Table 2. Schedule of PK Sampling

Week	W1				W3				W5			W6	W10				W12	W24 EOS/LTE rollover/ET	W28 SFU
Day	1		2	4	15		16	18	29			36	64		65	67			
Visit	5		6	7	8		9	10	11			13	15		16	17	18	21	22
Site Visit	x		x[a]	x[a]	x								x						
Home Visit			x[a]	x[a]			x	x	x			x			x	x			
PK Sampling Timepoint[b]	0h pre-dose	4h post dose	24h post dose	72h post dose	0h pre-dose	4h post dose	24h post dose	72h post dose	0h pre-dose	4h post dose	72h post dose	pre-dose	0h pre-dose	4h post dose	24h post dose	72h post dose	pre-dose	pre-dose[a]	X
Window	-2h	±15 min	±4h	±4h	-2h	±15 min	±4h	±4h	-2h	±15 min	±4h	-2h	-2h	±15 min	±4h	±4h	-2h	-2h	NA

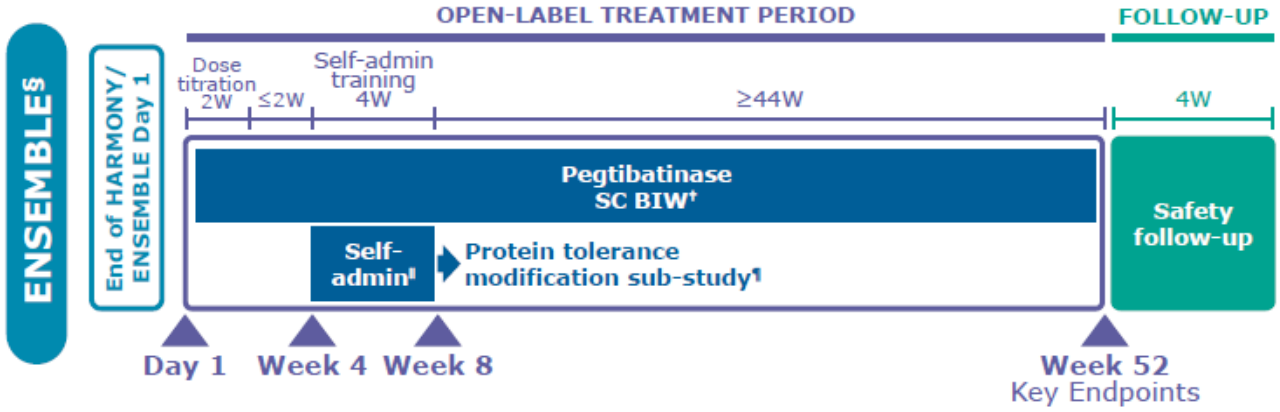
[a]Visit may be conducted at site or as a home visit.
[b]The participant may eat after collection of the pre-dose, fasting sample has been taken. The date, time, and relationship to last meal prior to sample collection must be recorded.
[c]For participants continuing in ENSEMBLE, sample to be collected prior to ENSEMBLE dosing.

ENSEMBLE LTE Study

ENSEMBLE LTE The ENSEMBLE open-label extension study is designed to evaluate long-term safety, efficacy, and response to pegtibatinase treatment in patients who have completed the blinded HARMONY treatment period or are active in the Phase 1/2 COMPOSE trial (NCT03406611).[5] Primary endpoints include assessment of long-term safety and tolerability of pegtibatinase combined with SOC, incidence of TEAEs, incidence of hyper/hypomethioninemia, and dietary protein rescue when needed for hypomethioninemia. Secondary endpoints include effect of pegtibatinase on decreasing plasma tHcy, association between tHcy levels and clinical outcomes, changes in methionine, and PK.[5]

Approximately 90 patients will be enrolled and will participate in the study for 52 weeks. Patients previously randomized to placebo will undergo pegtibatinase dose titration during the first 2 weeks of the trial. Between Weeks 3 and 4, patients will be trained to self-administer pegtibatinase, unless medically exempt. Throughout the study, diet and medication monitoring will be conducted by a metabolic dietician utilizing the SING assessment tool (**Figure 2**).[5]

Figure 2. ENSEMBLE LTE Study Design



§ENSEMBLE will enroll participants rolling over from the Phase 1/2 COMPOSE® and Phase 3 HARMONY studies
¶Only for eligible participants. Those rolling over from HARMONY can enter any time after Week 8 based on the last two unblinded tHcy measurements. Participants rolling over from COMPOSE® may use the last two tHcy measurements from that study and can enter any time from Day 1.
†Titration and target dose will be based on participant weight.
‖Self-administration training period of 4 weeks that can start on Week 3 or Week 4.

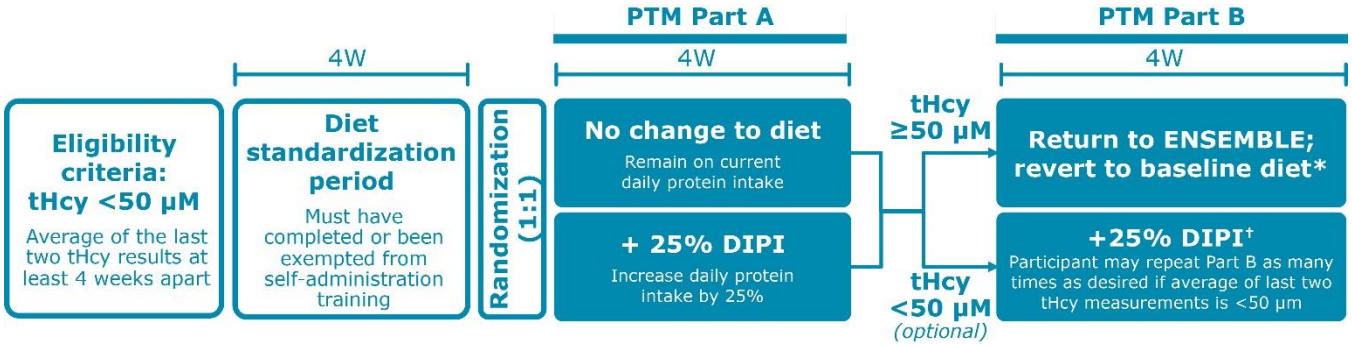
ENSEMBLE PTM Sub-study

Patients enrolled in ENSEMBLE have the option to participate in a PTM sub-study. Eligible patients must achieve tHCY <50 µM and have completed or been exempt from self/caregiver administration training. The PTM sub-study will evaluate if patients can tolerate increased dietary intake and maintain metabolic control, defined as tHcy <50 µM.[5]

The PTM sub-study will be conducted in 3 parts (**Figure 3**)[5]:

- DSP: This is to decrease variability in protein intake and supplements during the sub-study
- Part A: Patients are randomized to their current diet or a 25% increase in DIPI. PART A continues for 4 weeks and evaluates effects of increased protein on metabolic control and QOL
- Part B: Study segment is non-randomized and will represent DIPI in clinical practice
    - Patients who maintained tHcy <50 µM throughout Part A can increase DIPI for 4 more weeks
        - Patients who did not alter their diet in Part A can increase DIPI by 25%
        - Patients who increased DIPI by 25% in Part A can further increase 25%
    - Part B can be repeated until patient reaches maximum protein tolerance or unrestricted diet and tHcy is maintained at <50 µM

Figure 3. ENSEMBLE PTM 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.

Abbreviations

BIW, twice weekly; CBS, cystathionine-β-synthase; CNS, central nervous system; D, day; DIPI, daily intact protein intake; DSP, diet standardization period; ECG, electrocardiogram; EOS, end of study; ERT, enzyme replacement therapy; ET, early termination; h, hour; HCU, classical homocystinuria; Hcy, homocysteine; KO, knockout; LTE, long-term extension; Met, methionine; PEG, polyethylene glycol; PK, pharmacokinetics; PTM, protein tolerance modification; QOL, quality of life; SC, subcutaneous; self-admin, self-administration; SFU, safety follow-up; SING, Simplified Ingested Nutrients Guide; SOC, standard of care; TEAE, treatment-emergent adverse event; tHcy, total homocysteine; US, United States; W, week.

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