Pegtibatinase, an Investigational Enzyme Replacement Therapy for the Treatment of Classical Homocystinuria: Initial Results From the Phase 1/2 COMPOSE Study

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Poster# 55

TRAVERE THERAPEUTICS

Compose

RESULTS

Patient Population

- Data cutoff: 30-Nov-2021
- 19 patients (median age 25 yrs) were enrolled (**Table 1**)
- Majority were male (15/19) and white (17/19)
- 18/19 patients completed the 12-week treatment period and 15/19 patients continued in the study
  - 1 patient discontinued study drug due to an adverse event (AE) (leg fracture unrelated to study drug)
  - No discontinuations due to treatment-related AEs
    - 3 patients withdrew consent for personal reasons after completion of the 12-wk treatment period
- The first patient enrolled remains on treatment since January 2019
- Baseline levels of methionine (met) cycle metabolites are shown in **Table 2**

Table 1. Baseline Patient Demographics

	Placebo (n=5)	Pegtibatinase Cohort 1 (n=3)	Cohort 2 (n=3)	Cohort 3 (n=3)	Cohort 4 (n=2)	Cohort 5 (n=3)	Total (N=19)
Median age, y (range)	27.0 (19-32)	27.0 (25-28)	17.0 (16-26)	27.0 (14-32)	32.5 (14-51)	13.0 (13-21)	25.0 (13-51)
Age at diagnosis, y, n (%)							
<18	3 (60.0)	3 (100.0)	2 (66.7)	1 (33.3)	2 (100.0)	3 (100.0)	14 (73.7)
≥18	2 (40.0)	0	1 (33.3)	2 (66.7)	0	0	5 (26.3)
Gender, n (%)							
Male	4 (80.0)	1 (33.3)	3 (100.0)	2 (66.7)	2 (100.0)	3 (100.0)	15 (78.9)
Female	1 (20.0)	2 (66.7)	0	1 (33.3)	0	0	4 (21.1)
Race, n (%)							
White	5 (100.0)	3 (100.0)	2 (66.7)	2 (66.7)	2 (100.0)	3 (100.0)	17 (89.5)
Black/African American	0	0	0	1 (33.3)	0	0	1 (5.3)
Other	0	0	1 (33.3)	0	0	0	1 (5.3)

Table 2. Mean Met Cycle Metabolite Plasma Levels at Baseline (Day 1 Predose)

	Placebo (n=5)	Pegtibatinase Cohort 1 (n=3)	Cohort 2 (n=3)	Cohort 3 (n=3)	Cohort 4 (n=2)	Cohort 5 (n=3)	Normal Range >12yr
Total homocysteine plasma (μM), n	5	3	3	3	2	3	2-14
Mean (SD)	131.1 (65.7)	151.5 (39.6)	179.5 (129.4)	143.7 (36.5)	182.3 (70.1)	187.0 (16.3)	
Methionine (μM), n	5	3	3	3	2	3	14-41
Mean (SD)	510.1 (263.5)	659.3 (567.4)	525.7 (390.6)	632.2 (597.1)	779.0 (25.3)	729.6 (373.4)	
S-Adenosylmethionine (nM), n	5	3	3	3	2	3	33-95
Mean (SD)	583.1 (323.5)	988.8 (397.6)	414.2 (97.9)	660.1 (137.2)	621.5 (261.3)	669.7 (127.5)	
S-Adenosylhomocysteine (nM), n	5	3	3	3	2	3	13-28
Mean (SD)	367.5 (284.7)	351.3 (160.6)	329.3 (413.3)	464.8 (497.5)	767.8 (176.1)	333.2 (233.1)	

SD, standard deviation. Reference ranges provided by the CLIA lab at the Center of Metabolomics, Institute of Metabolic Disease, Baylor Scott White Research Institute.

Safety

- Pegtibatinase was generally well tolerated at doses up to 1.5 mg/kg twice weekly (BIW) (**Table 3**)
  - Duration of exposure: median 1.9 years; maximum 2.8 years
  - No moderate or severe AEs were reported in the highest dose cohort (Cohort 5; 1.5 mg/kg BIW)
- The most commonly reported treatment-emergent treatment-related AEs in subjects treated with pegtibatinase were injection site reactions (8/14 subjects, including injection site erythema, injection site pain, and injection site pruritus); the second most common AE was urticaria (hives) (3/14 subjects); most AEs were mild and transient in nature with no evidence of dose dependency
- 6 serious adverse events (SAEs) were reported in 3 patients; 5/6 were not treatment-related
  - Only 1 SAE (Cohort 3) was considered likely treatment-related (acute urticaria)
    - Event resolved in 10 days, patient resumed treatment and remains in study with no recurrence
- No treatment-related anaphylaxis or severe immune reactions were reported
- No significant findings in standard clinical laboratory tests or electrocardiogram results were reported
- Immunogenicity assays demonstrated low titers, no dose dependency, and the highest titer was transient

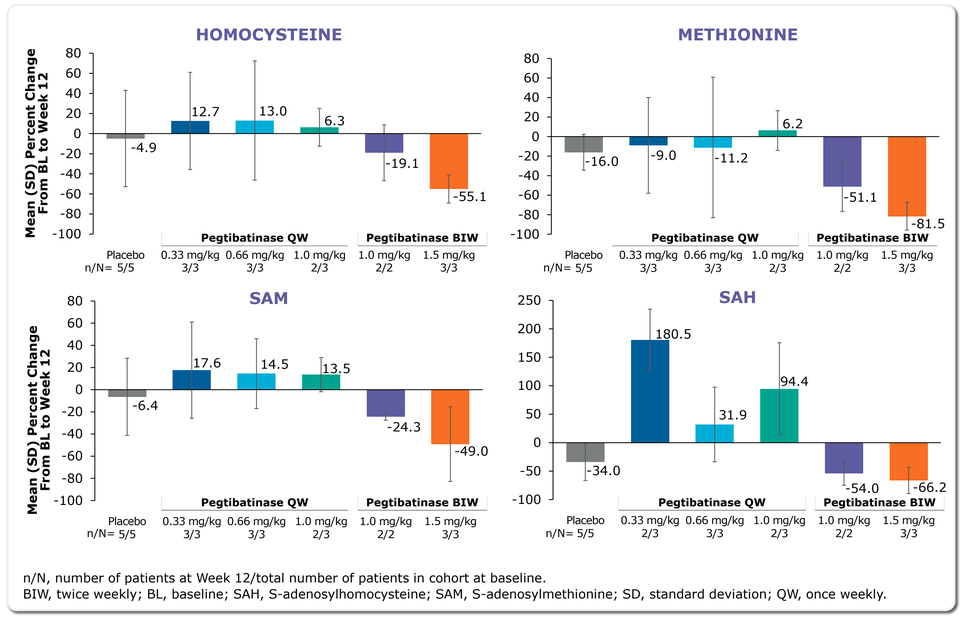
Table 3. Summary of Treatment-Related Treatment-Emergent Adverse Events

	Placebo (n=5)	Pegtibatinase Cohort 1 0.33 mg/kg QW (n=3)	Cohort 2 0.66 mg/kg QW (n=3)	Cohort 3 1.0 mg/kg QW (n=3)	Cohort 4 1.0 mg/kg BIW (n=2)	Cohort 5 1.5 mg/kg BIW (n=3)	Total (N=19)
Treatment-related Treatment-emergent AE, n (%)	2 (40.0)	3 (100.0)	0	2 (66.7)	2 (100.0)	2 (66.7)	11 (57.9)
Injection site reaction	1 (20.0)	1 (33.3)	0	0	1 (50.0)	1 (33.3)	4 (21.1)
Injection site erythema	0	1 (33.3)	0	1 (33.3)	0	1 (33.3)	3 (15.8)
Injection site pain	0	2 (66.7)	0	0	0	1 (33.3)	3 (15.8)
Injection site pruritis	1 (20.0)	1 (33.3)	0	1 (33.3)	0	0	3 (15.8)
Urticaria	0	1 (33.3)	0	1 (33.3)	1 (50.0)	0	3 (15.8)
Arthralgia	0	1 (33.3)	0	1 (33.3)	0	0	2 (10.5)
Injection site rash	0	1 (33.3)	0	0	1 (50.0)	0	2 (10.5)
Eye pain	0	0	0	0	0	1 (33.3)	1 (5.3)
Headache	0	0	0	1 (33.3)	0	0	1 (5.3)
Injection site induration	0	1 (33.3)	0	0	0	0	1 (5.3)
Injection site edema	0	1 (33.3)	0	0	0	0	1 (5.3)
Injection site swelling	0	0	0	0	0	1 (33.3)	1 (5.3)
Injection site urticaria	0	1 (33.3)	0	0	0	0	1 (5.3)
Insomnia	0	1 (33.3)	0	0	0	0	1 (5.3)
Muscle spasms	0	0	0	1 (33.3)	0	0	1 (5.3)
Muscle twitching	0	0	0	1 (33.3)	0	0	1 (5.3)
Pain	0	0	0	1 (33.3)	0	0	1 (5.3)
Pain in extremity	0	0	0	1 (33.3)	0	0	1 (5.3)
Pyrexia	0	0	0	1 (33.3)	0	0	1 (5.3)
Tachycardia	0	1 (33.3)	0	0	0	0	1 (5.3)

Efficacy

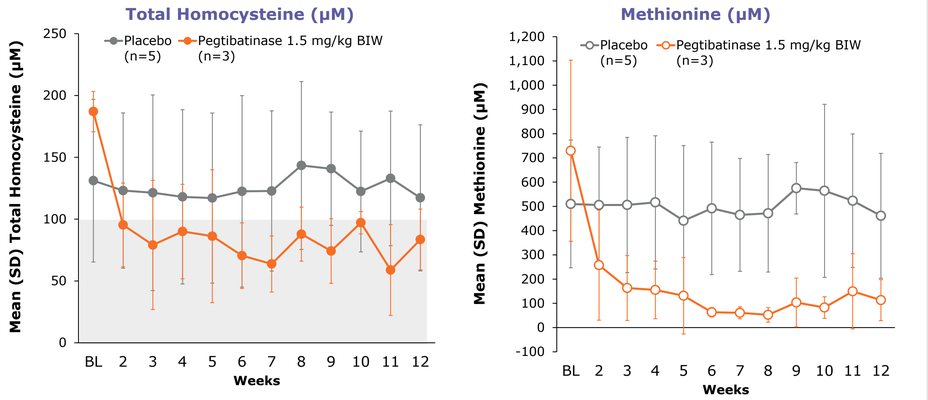
- Dose-dependent decreases were observed in homocysteine with pegtibatinase treatment at Week 12, with a mean decrease of 55% at the 1.5 mg/kg dose BIW compared to -4.9% in placebo (**Figure 4**)
- Dose-dependent decreases were observed in methionine with pegtibatinase treatment at Week 12, with a mean decrease of 82% at the 1.5 mg/kg dose BIW compared to -16% in placebo (**Figure 4**)
- S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) also demonstrated decreases with higher doses of pegtibatinase (**Figure 4**)
- Dose-dependent increases were observed in plasma cystathionine and cysteine levels with pegtibatinase treatment (data not shown)
- Treatment with pegtibatinase at the 1.5 mg/kg dose BIW resulted in rapid and sustained decreases in homocysteine and methionine; mean homocysteine levels were reduced to <100 μM, an important clinical threshold for treatment (**Figure 5**)

Figure 4. Dose-Dependent Changes in Biomarkers With Pegtibatinase Treatment From Baseline to Week 12



n/N, number of patients at Week 12/total number of patients in cohort at baseline.
BIW, twice weekly; BL, baseline; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; SD, standard deviation; QW, once weekly.

Figure 5. Reduction of Total Homocysteine and Methionine Levels With Pegtibatinase Treatment From Baseline to Week 12



Shaded area indicates total homocysteine levels associated with improved long-term clinical outcomes (Morris 2017).
BIW, twice weekly; BL, baseline; SD, standard deviation.

CONCLUSIONS

- Pegtibatinase treatment results in dose-dependent decreases in homocysteine and other methionine-cycle metabolites
- Pegtibatinase rapidly reduced plasma total homocysteine by a mean of 55% in patients treated at the 1.5 mg/kg BIW dose, and the reduction was sustained below the clinical treatment threshold of 100 μM over 12 weeks of treatment
- Pegtibatinase was generally well tolerated at doses up to 1.5 mg/kg BIW and there were no reports of anaphylaxis or severe immune reactions related to study drug
- Results support proof-of-concept for pegtibatinase as a potential novel treatment for classical homocystinuria

DISCLOSURES

HLL: Investigator, Travere Therapeutics; consultant, Travere Therapeutics
JT: Investigator, Travere Therapeutics
CF: Investigator, Travere Therapeutics
ML: Investigator, Travere Therapeutics
JG: Investigator, Travere Therapeutics
MS-M: Consultant, Travere Therapeutics
EMB, LW, JG, YC, FG, SAV: Employees and stockholders, Travere Therapeutics, Inc.

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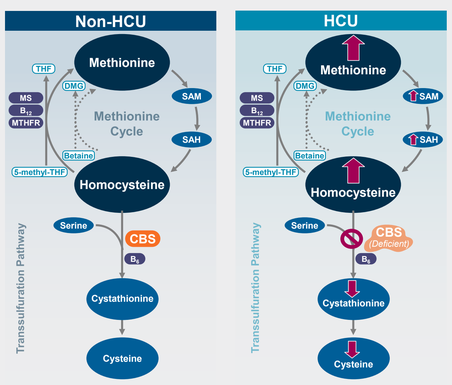
BACKGROUND

- Cystathionine beta synthase (CBS) is a critical enzyme that converts homocysteine to cystathionine via the transsulfuration pathway[1] (**Figure 1 – Non-HCU**)
- CBS-deficient homocystinuria (HCU), also known as classical HCU, is a rare autosomal recessive metabolic disorder caused by pathogenic variants in the *CBS* gene[1-3]
- Deficiency in CBS leads to toxic accumulation of homocysteine (**Figure 1 - HCU**) resulting in clinical manifestations of HCU affecting the cardiovascular, skeletal, neurologic, and ocular organ systems[1,2]
- Recent HCU management guidelines recommend maintaining plasma levels of total homocysteine <100 μM to reduce clinical complications[2]
- With current standard of care (methionine-restricted diet, vitamin B6, and betaine), many patients do not adequately reduce their homocysteine levels and still present with clinical signs and symptoms of disease[4-6]
- Pegtibatinase, a first-in-class, investigational, pegylated, modified recombinant truncated human enzyme (CBS), is being evaluated as a potential treatment for HCU[4,5]

Figure 1. Methionine Cycle and Transsulfuration Pathway: Non-HCU and HCU

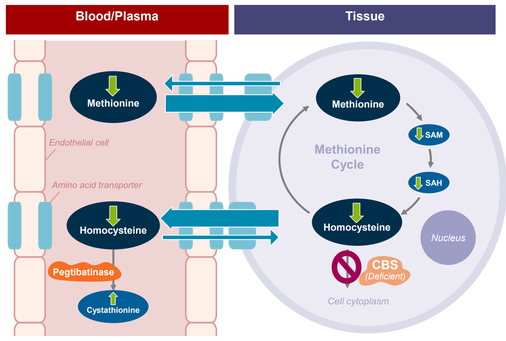


CBS, cystathionine β-synthase; DMG, dimethylglycine; HCU, homocystinuria; MS, methionine synthase; MTHFR, methylenetetrahydrofolate reductase; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; THF, tetrahydrofolate.

HYPOTHESIS

- We hypothesize that pegtibatinase functions as a "metabolic sink" and can reduce both plasma and tissue levels of homocysteine and methionine (**Figure 2**)

Figure 2. Proposed Concept for Pegtibatinase Mechanism of Action: The Metabolic Sink Hypothesis

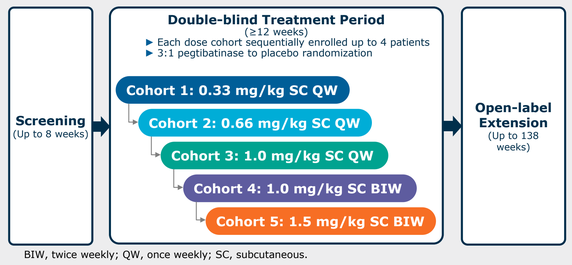


CBS, cystathionine β-synthase; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine.

METHODS

- COMPOSE (NCT03406611) is a double-blind, randomized, placebo-controlled, phase 1/2 pegtibatinase dose-escalation study in treatment-naïve patients with HCU (**Figure 3**)
- Objectives of COMPOSE are to assess safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of pegtibatinase administered subcutaneously either once or twice weekly

Figure 3. Study Design



BIW, twice weekly; QW, once weekly; SC, subcutaneous.

Key Inclusion Criteria

- Diagnosis of HCU confirmed by genetic test and plasma tHcy ≥80 μM
- Age ≥12 and ≤65 years
- Willing to maintain a stable diet and therapy for the treatment period

Key Exclusion Criteria

- Known hypersensitivity to any components of pegtibatinase or polyethylene glycol (PEG)
- Use or planned use of any injectable drugs containing PEG, other than pegtibatinase or COVID vaccines, within 3 months
- Use of any investigational product or investigational medical device within 30 days
- History of organ transplantation or use of chronic immunosuppressive therapy
- Pregnancy or breast-feeding

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