Latest Results From the COMPOSE® Phase 1/2 Trial for the Treatment of Classical Homocystinuria (HCU) Using Pegtibatinase, a Novel Investigational Enzyme Replacement Therapy

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Poster #139

TRAVERE THERAPEUTICS

Compose

RESULTS

Participant Characteristics

- 23/24 participants completed ≥12 weeks of treatment (data cutoff March 10, 2023)
  - One discontinuation due to unrelated serious adverse event (SAE; leg fracture after accident)
- Eight discontinuations in long-term follow-up due to participant withdrawal or loss to follow-up given long duration of study (4 years) due to COVID-19 delays
- One death in the open-label extension (OLE) period (unrelated to pegtibatinase)
- Overall, participants had a mean age of 24 years, were 75% male, 33% pediatric, and 88% White. Baseline geometric mean and standard deviation values for tHcy and methionine (Met) are shown in **Table 1**

Table 1. Baseline Participant tHcy and Met Values

	Placebo (n=6)	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)	Cohort 6 2.5 mg/kg BIW (n=4)	Total (N=24)
tHcy (µM), n	6	3	3	3	2	3	4	**24**
Mean (SD)* *[Normal: 2–14†]*	124.8 (1.5)	148.2 (1.3)	134.7 (2.8)	140.7 (1.3)	175.4 (1.5)	186.6 (1.1)	96.8 (1.9)‡	135.5 (1.6)
Met (µM), n	6	3	3	3	2	3	4	**24**
Mean (SD)* *[Normal: 14–41†]*	399.8 (2.6)	524.5 (2.2)	444.3 (2.0)	434.2 (3.1)	778.8 (1.0)	669.4 (1.7)	138.0 (3.2)‡	399.8 (2.6)

*Geometric mean (SD). †Reference ranges for participants ≥12 years old provided by the Clinical Laboratory Improvement Amendments lab at the Center of Metabolomics, Institute of Metabolic Disease, Baylor Scott & White Research Institute. ‡Baseline metabolite values for Cohort 6 were lower than Cohorts 1–5 due to relaxation of tHcy eligibility criteria from ≥80 µM to ≥50 µM.
BIW, twice weekly; **Met**, methionine; **QW**, once weekly; **SD**, standard deviation; **tHcy**, total homocysteine.

Table 2. Overall Summary of AEs

	Placebo (n=6)	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)	Cohort 6 2.5 mg/kg BIW (n=4)	Total (N=24)
Number of TEAEs, n	49	160	14	27	11	31	24	316
Any TEAE, n (%)	6 (100.0)	3 (100.0)	3 (100.0)	2 (66.7)	2 (100.0)	3 (100.0)	4 (100.0)	23 (95.8)
Any treatment-related TEAE, n (%)	3 (50.0)	3 (100.0)	0	2 (66.7)	2 (100.0)	2 (66.7)	3 (75.0)	15 (62.5)
Any treatment-emergent SAE, n (%)	0	1 (33.3)	0	2 (66.7)	0	0	0	3 (12.5)
Any treatment-related treatment-emergent SAE, n (%)	0	0	0	1 (33.3)	0	0	0	1 (4.2)
TEAE leading to study drug discontinuation, n (%)	0	0	0	0	0	0	0	0

AE, adverse event; **BIW**, twice weekly; **QW**, once weekly; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event.

Safety

- Pegtibatinase was generally well tolerated at doses up to 2.5 mg/kg BIW with no anaphylaxis or severe immune reactions occurring (**Table 2**)
- Injection-site reactions (ISRs) were the most common treatment-related treatment-emergent adverse events (TEAEs); these were generally mild and self-limiting
  - No participants discontinued due to a treatment-related TEAE
- Only one SAE related to pegtibatinase was reported
  - One Cohort 3 participant developed acute urticaria during the second week of treatment
  - Dosing was interrupted for one dose and subsequently, the participant tolerated re-initiation of treatment with no recurrence of urticaria
- Two Cohort 6 participants reported moderate ISRs associated with urticaria (non-serious), which led to a temporary dose interruption
  - After resolution of each ISR, the participants were able to restart pegtibatinase at a lower dose of 1.5 mg/kg BIW and titrate up to the intended 2.5 mg/kg BIW dose*

*These participants received premedication with histamine 1/2 blockers to mitigate subsequent ISRs.

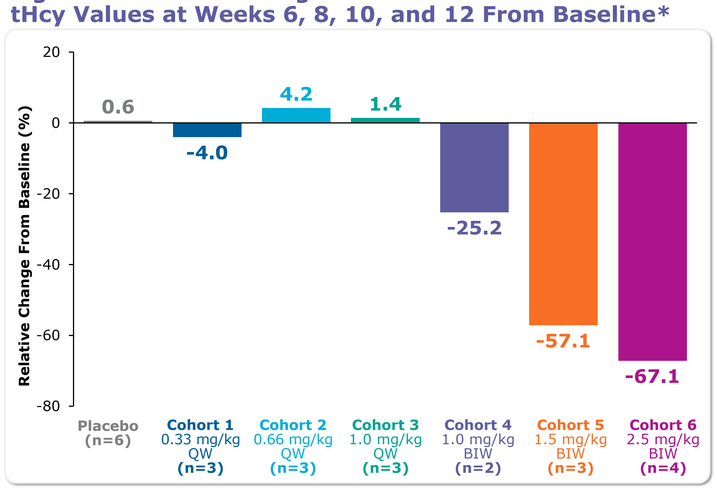
Efficacy

- In Cohorts 5 and 6, post-treatment geometric mean relative reductions of tHcy from baseline of 57% and 67%, respectively, were observed (**Figure 2**)
- Rapid, sustained reductions in tHcy were observed from Week 2 in Cohorts 5 and 6 (**Figure 3**)
- Substantial and sustained reductions in Met were also observed after 2 weeks (**Figure 4**)
- Reductions in S-adenosylmethionine and S-adenosylhomocysteine, and increases in cystathionine and cysteine were also observed at the higher doses
- In Cohort 6, 2/4 participants achieved post-treatment tHcy reductions <50 µM
  - Of these, one participant achieved tHcy below the upper limit of normal (<15 µM) with a decrease in Met below the lower limit of normal not associated with symptomatic AEs. Natural protein was added to their diet during the OLE. Their Met levels have since normalized and titration of protein tolerance begun with frequent tHcy/Met testing
- No reductions in dietary protein intake were observed that could explain the reductions in tHcy/Met (**Figure 5**)

Immunogenicity

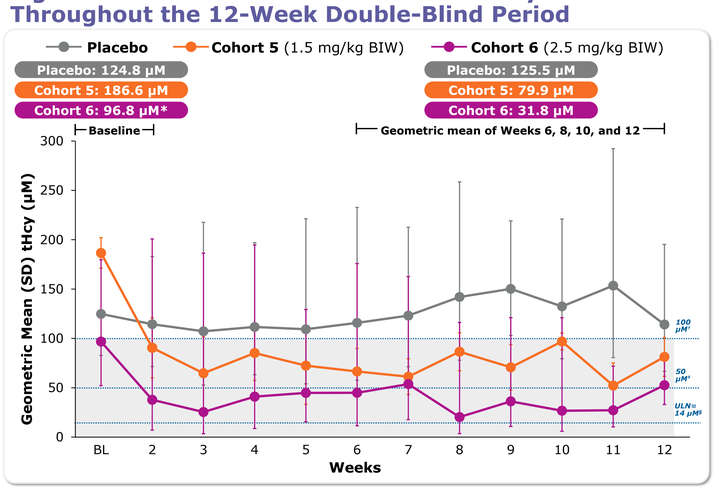
- Immunogenicity (IM) has been monitored for up to 48 months in participants treated with pegtibatinase. Overall, pegtibatinase has not been highly immunogenic, with no signs of IM impacting pharmacokinetics, pharmacodynamics, and safety (no association with AEs or clinical symptoms)
- The overall anti-drug antibody (ADA) incidence ranged from 55% to 80%
- The median ADA titer was mostly lower than 10

Figure 2. Relative Change in Geometric Mean of Available tHcy Values at Weeks 6, 8, 10, and 12 From Baseline*



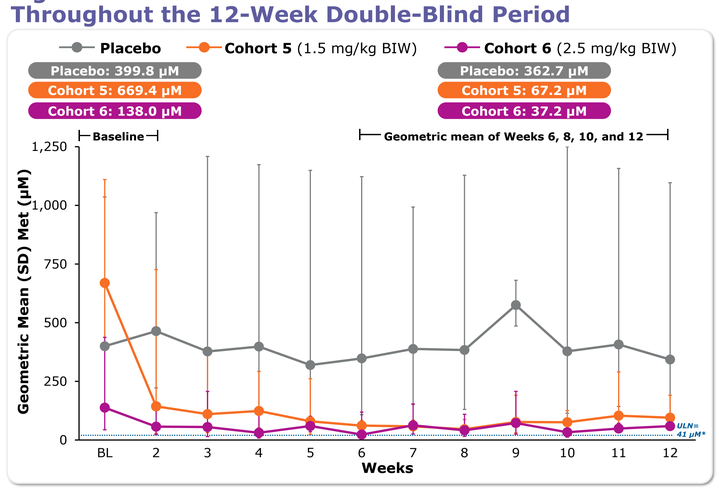
*Regardless of actual dose administered (eg, in cases of dose interruption).
BIW, twice weekly; **QW**, once weekly; **tHcy**, total homocysteine.

Figure 3. Geometric Mean of Available tHcy Values Throughout the 12-Week Double-Blind Period



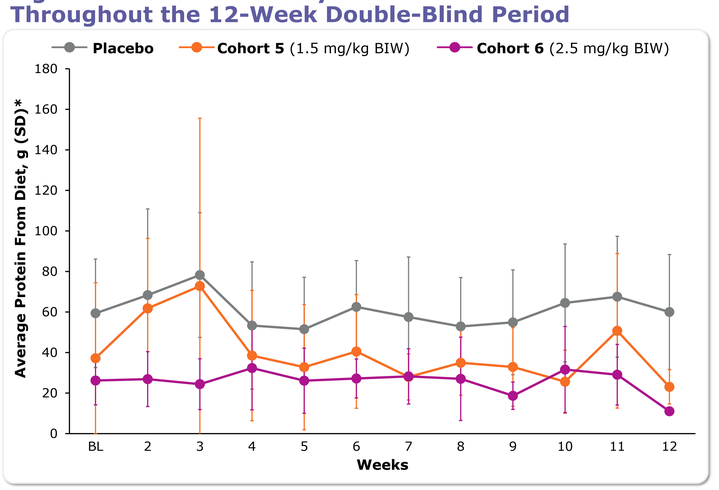
*Baseline metabolite values for Cohort 6 were lower than Cohorts 1–5 due to relaxation of tHcy eligibility criteria from ≥80 µM to ≥50 µM. †Clinical threshold for minimizing HCU complications recommended by E-HOD guidelines.[1] ‡Clinically recommended threshold in pyridoxine-responsive patients (E-HOD).[1] §ULN provided by the Clinical Laboratory Improvement Amendments lab at the Center of Metabolomics, Institute of Metabolic Disease, Baylor Scott & White Research Institute.
BIW, twice weekly; **BL**, baseline; **E-HOD**, European Network and Registry for Homocystinurias and Methylation Defects; **HCU**, classical homocystinuria; **SD**, standard deviation; **tHcy**, total homocysteine; **ULN**, upper limit of normal.

Figure 4. Geometric Mean of Available Met Values Throughout the 12-Week Double-Blind Period



*ULN provided by the Clinical Laboratory Improvement Amendments lab at the Center of Metabolomics, Institute of Metabolic Disease, Baylor Scott & White Research Institute.
BIW, twice weekly; **BL**, baseline; **Met**, methionine; **SD**, standard deviation; **ULN**, upper limit of normal.

Figure 5. Mean Total Daily Intact Protein Intake Throughout the 12-Week Double-Blind Period



*A diet diary was recorded for 72 hours prior to study visits and reviewed by a metabolic dietitian. Dietary protein intake was calculated from diet diaries and change from baseline was analyzed longitudinally.
BIW, twice weekly; **BL**, baseline; **g**, grams; **SD**, standard deviation.

CONCLUSIONS

- Pegtibatinase was generally well tolerated at doses up to 2.5 mg/kg BIW with no anaphylaxis or severe immune reactions occurring
- Participants in Cohorts 5 and 6 achieved mean post-treatment tHcy levels below the key thresholds of 100 µM and 50 µM, and for one participant, tHcy levels normalized
- Reductions in Met and changes in other Met-cycle metabolites aligned with tHcy reductions
- Dietary protein intake was generally stable throughout the double-blind period
- Immunogenicity testing revealed generally low levels of antibodies indicating that pegtibatinase is not highly immunogenic

ABBREVIATIONS

ADA, anti-drug antibody; **AE**, adverse event; **BIW**, twice weekly; **BL**, baseline; **COVID-19**, coronavirus disease 2019; **E-HOD**, European Network and Registry for Homocystinurias and Methylation Defects; **g**, grams; **HCU**, classical homocystinuria; **IM**, immunogenicity; **ISR**, injection-site reaction; **Hcy**, homocysteine; **Met**, methionine; **OLE**, open-label extension; **QW**, once weekly; **SAE**, serious adverse event; **SC**, subcutaneous; **SD**, standard deviation; **TEAE**, treatment-emergent adverse event; **tHcy**, total Hcy; **ULN**, upper limit of normal.

DISCLOSURES

JGa, JT, WES, DK, CF: Investigator, Travere Therapeutics, Inc. **ML, HL**: Investigator and consultant, Travere Therapeutics, Inc. **JGü, SM, SAV, LW**: Employee and stockholder, Travere Therapeutics, Inc.

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REFERENCE

1. Morris AA, et al. *J Inherit Metab Dis*. 2017;40(1):49-74.

Some data first presented at the Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium 2023; August 29–September 1, 2023; Jerusalem, Israel

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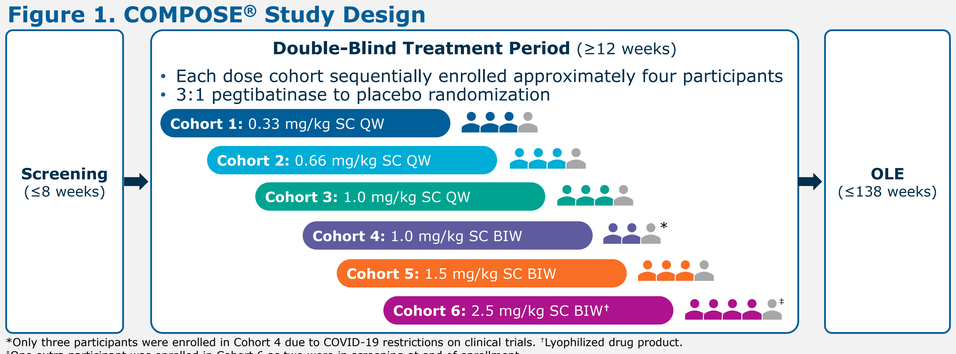
INTRODUCTION

- COMPOSE® (NCT03406611) is a first-in-human, double-blind, randomized, placebo-controlled, Phase 1/2 dose-escalation trial of pegtibatinase in participants with HCU
- The objectives are to assess safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of pegtibatinase administered subcutaneously either once weekly (QW) or twice weekly (BIW)

METHODS

- Six sequential dose cohorts were enrolled (**Figure 1**)

Figure 1. COMPOSE® Study Design



*Only three participants were enrolled in Cohort 4 due to COVID-19 restrictions on clinical trials. †Lyophilized drug product.
‡One extra participant was enrolled in Cohort 6 as two were in screening at end of enrollment.
BIW, twice weekly; **COVID-19**, coronavirus disease 2019; **OLE**, open-label extension; , placebo participant; **QW**, once weekly; **SC**, subcutaneous.

Key Eligibility Criteria

- Diagnosis of HCU confirmed by cystathionine β-synthase gene analysis and plasma total homocysteine (tHcy):
  - Cohorts 1–5: ≥80 µM
  - Cohort 6:* ≥50 µM
- Age ≥12 and ≤65 years
- Willing to maintain a stable diet and therapy for the treatment period
- No use or planned use of any injectable drugs containing polyethylene glycol, other than pegtibatinase or coronavirus disease 2019 (COVID-19) vaccines, within 3 months
- No history of organ transplantation or chronic immunosuppressive therapy
- Not pregnant or breastfeeding

*In Cohort 6, the eligibility criteria changed from tHcy ≥80 µM to tHcy ≥50 µM to determine the effect of pegtibatinase in a broader HCU population.

DISCUSSION

- A 67% post-treatment relative reduction from baseline of plasma tHcy levels was achieved at the highest dose of pegtibatinase; reductions were evident from Week 2 and sustained throughout the 12-week study period
- All participants in Cohorts 5 and 6 achieved mean post-treatment tHcy levels below the key clinical threshold of 100 µM; some Cohort 6 participants were able to reduce tHcy below 50 µM and 15 µM (considered normal)
- Met reductions aligned with tHcy reductions; one participant achieved Met levels below the lower limit of normal and was able to add natural protein to their diet

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