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Pegtibatinase and Initial Results from the COMPOSE Clinical Trial for Classical HCU

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VP, Clinical Development
Travere Therapeutics

HCU, homocystinuria.

HCU Network America, Organic Acidemia Association, Propionic Acidemia Foundation | 2022 Conference
June 25-26, 2022; Bethesda, Maryland

Disclaimers

Pegtibatinase (TVT-058) is a drug that is currently being studied and it is not approved by any health authority

Pegtibatinase is currently being studied for the first time in humans in the COMPOSE clinical trial for classical HCU

The safety and effectiveness of pegtibatinase are not established

HCU, homocystinuria.

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Travere Therapeutics: Focused on Treatments for Rare Diseases

OUR VALUES:

- *We are patient-inspired*
- *We are courageous*
- *We promote community*
- *We are stronger together*

WE ARE IN RARE FOR LIFE

WHO WE ARE

Travere Therapeutics is a biopharmaceutical company specializing in identifying, developing, and delivering life-changing therapies to people living with rare disease.

Travere acquired Orphan Technologies and the pegtibatinase program (previously OT-58) at the end of 2020.

TEAM

Almost 350 team members worldwide led by President & CEO, Eric Dube, PhD

LOCATIONS

Headquarters:
San Diego, CA, USA

Other offices:
Switzerland, Ireland

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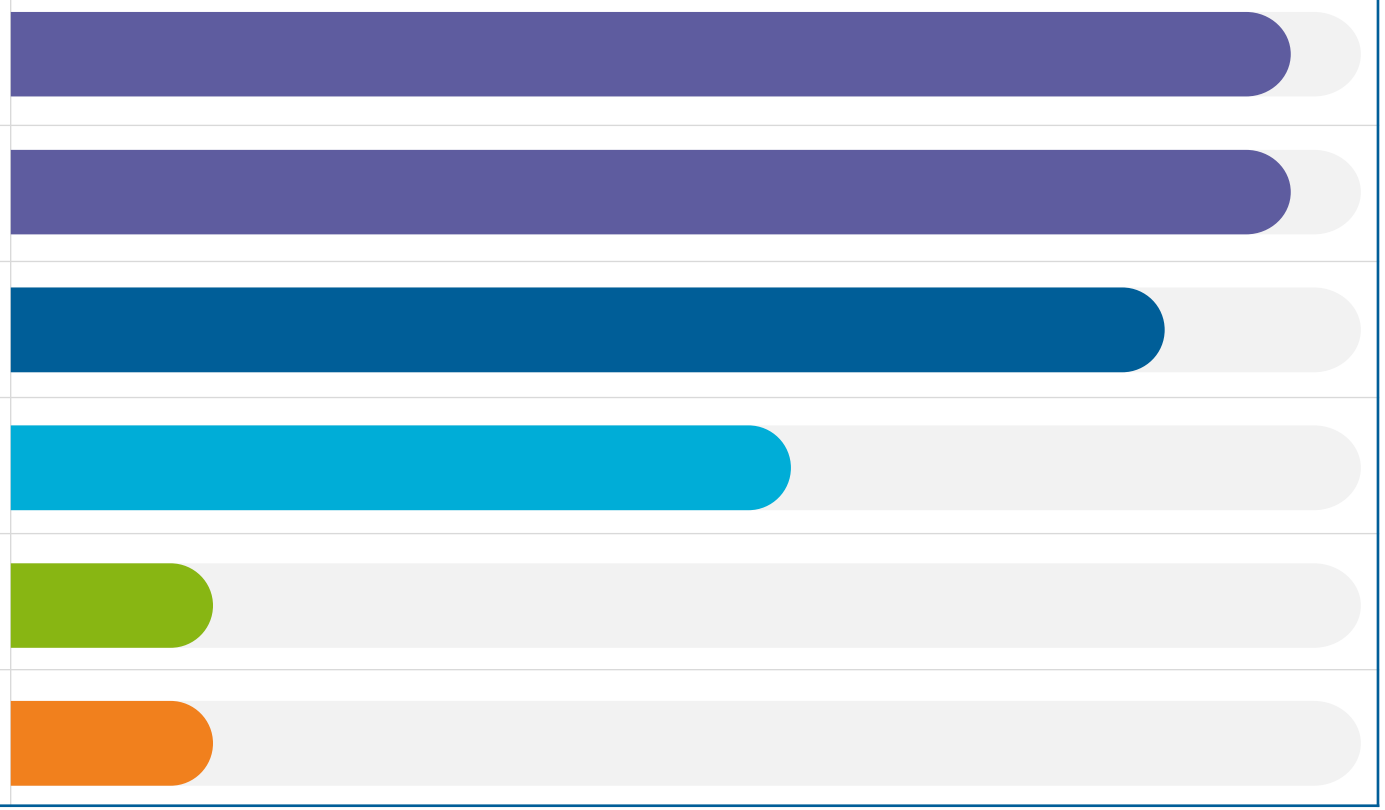
Our Focus Is on Rare Diseases With Unmet Medical Needs

Program	Therapeutic Area	Preclinical	Phase 1	Phase 2	Phase 3
Sparsentan	Focal Segmental Glomerulosclerosis (FSGS)				
Sparsentan	IgA Nephropathy (IgAN)				
Chenodeoxycholic Acid (CDCA)*	Cerebrotendinous Xanthomatosis (CTX)				
Pegtibatinase (TVT-058)**	Classical Homocystinuria (HCU)				
NGLY1 Collaboration	NGLY1 Deficiency				
ALGS Collaboration	Alagille Syndrome (ALGS)				



*CDCA is not approved for use in the treatment of CTX but has received a medical necessity determination in the US by the FDA for CTX. Travere Therapeutics is conducting a Phase 3 clinical trial to examine the safety and efficacy of CDCA (Chenodal®) for the treatment of CTX.
**Pegtibatinase (TVT-058) is currently being studied in a Phase 1/2 clinical trial.
Adapted from: Travere Therapeutics, Inc website. https://travere.com/our-pipeline/. Accessed May 23, 2022.

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New Treatments Are Needed for Classical HCU

Classical HCU is a slowly progressive genetic disease[1]

- Caused by a deficiency in the enzyme that breaks down homocysteine (a by product of processing methionine, a building block that comes from protein in our diet)
- Causes elevated levels of homocysteine in the body

High levels of homocysteine lead to complications in the eye, skeleton, brain, and blood vessels[1]

Current treatment may include a low protein diet (typically with metabolic formula), Cystadane® (betaine), and/or vitamin B_6[2]

Even with treatment, many patients *are unable to keep their homocysteine levels below 100 µM* as recommended[2]

HCU, homocystinuria.

1. Sacharow SJ, et al. 2004 Jan 15 [Updated 2017 May 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. **2.** Morris AAM, et al. *J Inherit Metab Dis*. 2017;40:49-74.

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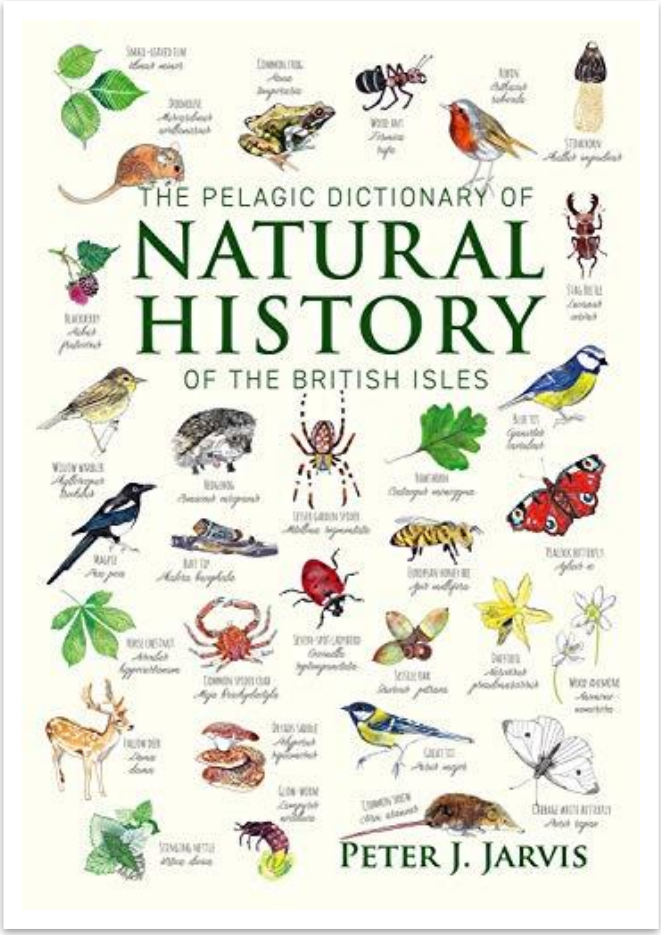
A Natural History Study: What and Why?



- Rare diseases are often not well-studied and poorly understood by the medical community
- A natural history study increases what we know about a disease and provides a "reference point" for testing the impact of new treatments
- Natural history studies provide ways to better understand a disease and design clinical trials

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Travere's Natural History Study Began in 2016

Travere began a natural history study of classical HCU in 2016 to better understand how to develop a new treatment for this disease

Objectives

- Study homocysteine levels over time
- Study the complications of classical HCU over time
- Study what current treatments are being used
- Study the impact of diet

Understanding the current challenges of classical HCU helps provide a "reference point" for testing the potential benefit of pegtibatinase treatment

HCU, homocystinuria.

ClinicalTrials.gov NCT02998710

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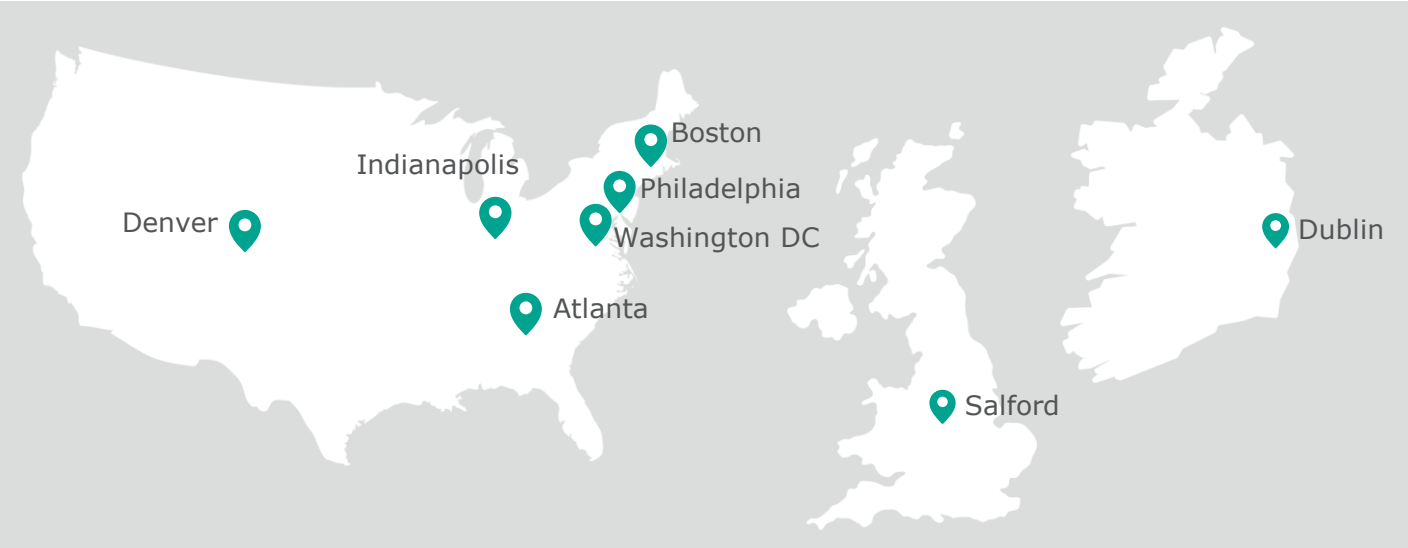
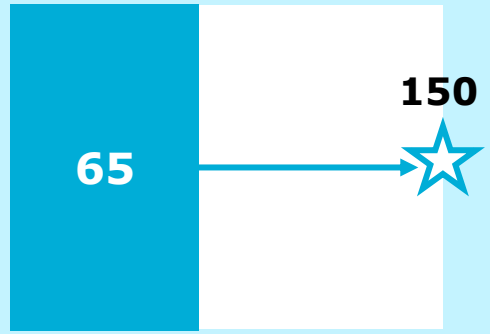
Travere's Natural History Study Is Enrolling

STUDY GOAL: To observe patients with classical HCU over 6 ½ years to understand the course of the disease as it is treated under regular circumstances

Ongoing study at eight clinical sites in the US, UK, and Ireland



65 patients enrolled to date, targeting approximately 150



Note: This is an observational study, no treatments are provided

HCU, homocystinuria.

ClinicalTrials.gov NCT02998710

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Travere's Natural History Study: Who and How?

Key eligibility criteria

- Age 5-65 years old
- Confirmed diagnosis of classical HCU
- Willingness to visit clinic for testing and bloodwork every 6 months
- Willingness to provide diet diaries for 3 days before clinic visits

The study has 5 main parts, all of which are provided free of charge to participants

To learn more about the study:

Go to: ClinicalTrials.gov NCT02998710

Contact: Travere Medical Information
☎ 1-877-659-5518
✉ medinfo@travere.com

HCU, homocystinuria.

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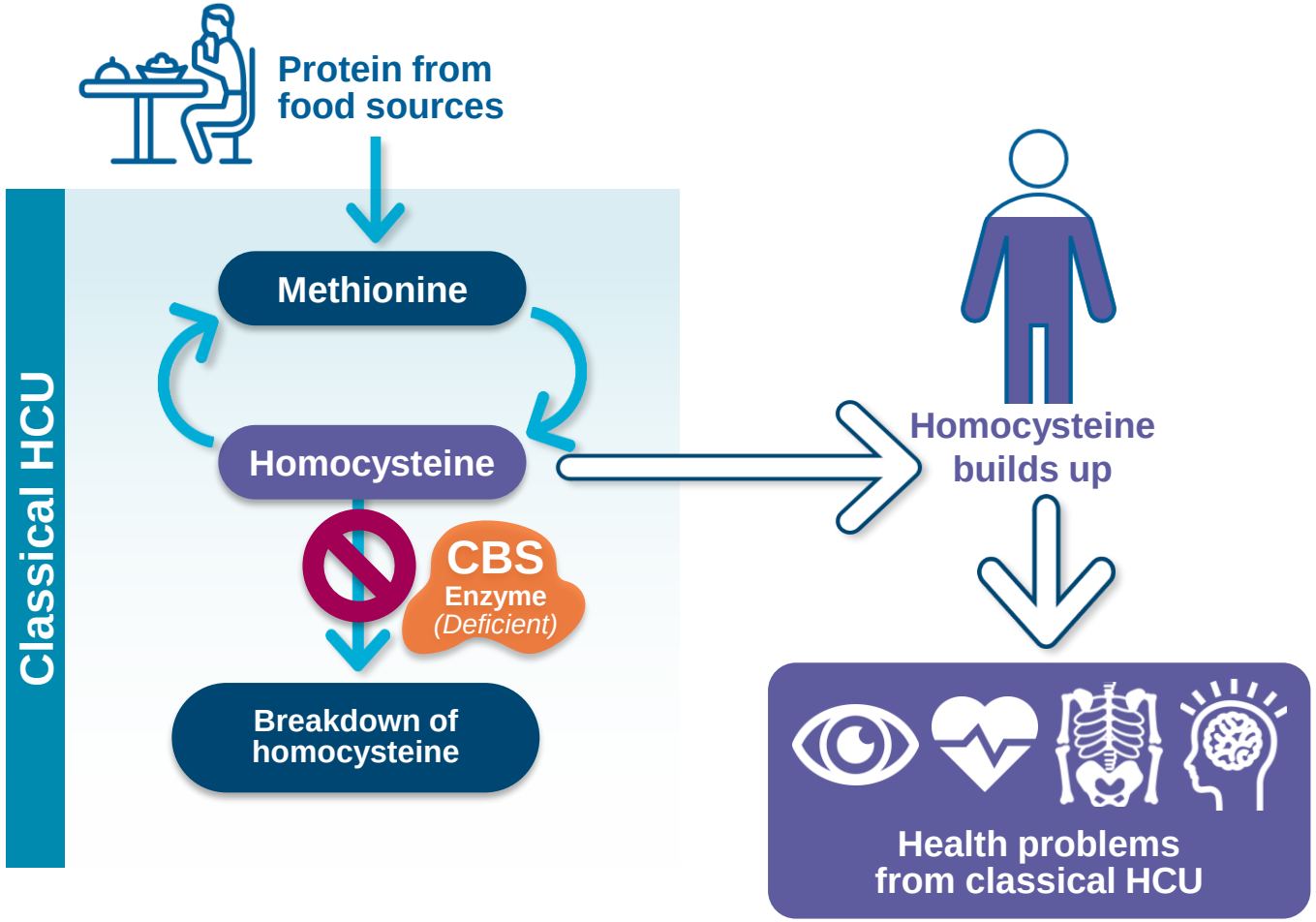
Pegtibatinase: An Enzyme that Breaks Down Homocysteine



The CBS enzyme is deficient in patients with classical HCU, which leads to the build up of toxic levels of homocysteine[1]

Pegtibatinase is a modified version of the *human* CBS enzyme[2]

Pegtibatinase is administered by injection under the skin (subcutaneous injection)[2]

CBS, cystathionine β-synthase; HCU, homocystinuria.

1. Morris AAM, et al. *J Inherit Metab Dis*. 2017;40:49-74. **2.** Majtan T, et al. *Life Sci*. 2018;200:15-25.

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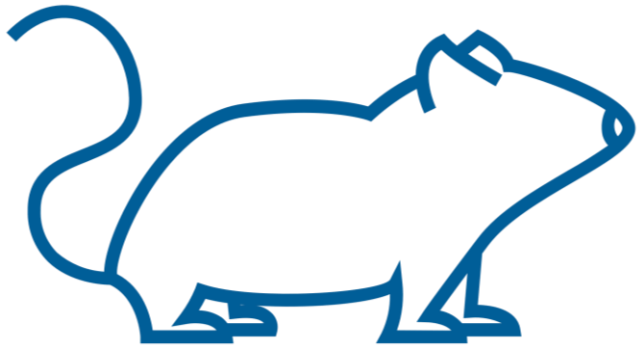
Previous Animal Studies of Pegtibatinase

In studies using mice with classical HCU, pegtibatinase improved HCU-related complications

- Reduced both blood and tissue levels of homocysteine[1]
- Tested extensively for safety



In these early studies, pegtibatinase:

	EYES	→	Improved eye health[1]
	SKELETON	→	Improved bone health[1-4]
	BRAIN	→	Improved learning[3]
	BLOOD VESSELS	→	Improved function[3]

HCU, homocystinuria.

1. Majtan T, et al. *Mol Ther*. 2018;26(3):834-844. **2.** Majtan T, et al. *FASEB J*. 2017;31(12):5495-5506. **3.** Majtan T, et al. *FASEB J*. 2019;33(11):12477-12486. **4.** Majtan T, et al. *Hum Mutat*. 2018;39:210–218.

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COMPOSE Clinical Trial to Study Pegtibatinase in Classical HCU

COMPOSE is a clinical trial (first study in humans) to evaluate the safety and drug effects of pegtibatinase in patients with classical HCU

Objectives

- How safe is pegtibatinase in adults and children with classical HCU aged 12 and over?
- How does pegtibatinase behave in the human body?
- What happens to homocysteine levels after treatment with pegtibatinase?
- What are the effects of pegtibatinase on complications of classical HCU?

HCU, homocystinuria.

ClinicalTrials.gov NCT03406611

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COMPOSE Study Design

Determine patient eligibility for study within 8 weeks of starting main treatment period

Main Treatment Period

- Main treatment period (at least 12 weeks) was "double blind" (doctor and patient were not told if they were receiving pegtibatinase or placebo)
- Each dosing group enrolled up to 4 patients, one group after the other
- For every 3 patients getting pegtibatinase, one patient received placebo ( )
- Doses were given by injection under the skin

Group 1: 0.33 mg/kg once a week

Group 2: 0.66 mg/kg once a week

Group 3: 1.0 mg/kg once a week

Group 4: 1.0 mg/kg twice a week

Group 5: 1.5 mg/kg twice a week

18 of 19 patients completed this 12-week treatment period (one person had to stop the trial for unrelated reasons)

Optional Treatment Period

- Patients who complete the main treatment period have the option to receive pegtibatinase (no placebo) for up to 138 weeks

Levy HL, et al. Poster presented at: SIMD 2022; April 10-13, 2022; Orlando, FL.

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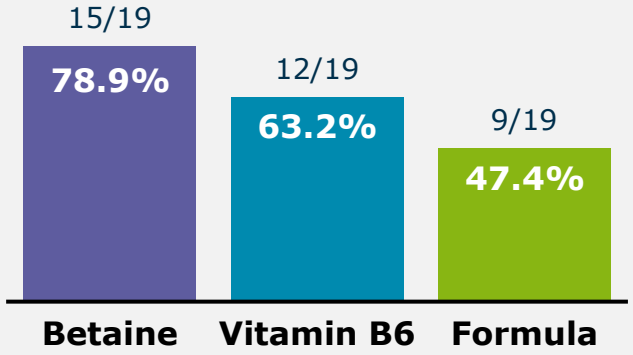
COMPOSE Patients: Who Are They?[1,2]

Number of patients

19 = 15 + 4

- **19** — Total number of patients
- **15** — Diagnosed when younger than 18
- **4** — Diagnosed when older than 18

Treatment before study start



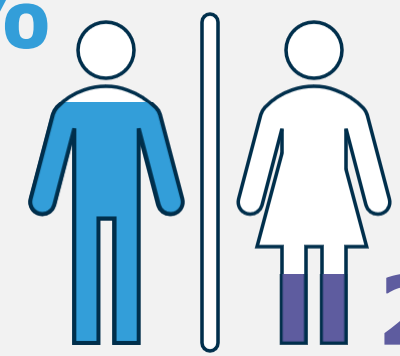
Starting homocysteine levels

131 to 187

Range of average starting total homocysteine levels across dosing groups *(Normal is 2-14)*

Gender

79% Male



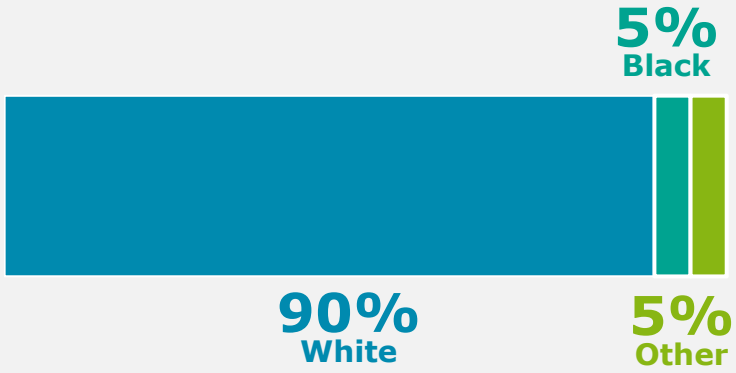
21% Female

Age

24

Average age when study began

Race



1. Levy HL, et al. Poster presented at: SIMD 2022; April 10-13, 2022; Orlando, FL. **2.** Greblikas F. "COMPOSE Phase 1/2 Study: Interim Results." GMDI 2022, May 5-7, 2022, Lake Las Vegas, NV. Invited Presentation.

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COMPOSE Initial Safety Results

Pegtibatinase was generally well-tolerated

Most side effects were mild, did not last long, and did not increase with higher doses

Most common side effects

- Injection site reaction (3 people)
- Injection site redness (3 people)
- Injection site pain (3 people)
- Hives (3 people)
- Injection site itching (2 people)

Serious side effects

- Only 1 serious side effect was reported that was considered likely related to the drug
- It was a case of acute hives which cleared up in 11 days and did not happen again after the patient restarted treatment

Other

- No patient stopped treatment due to a side effect related to the drug
- There were no reports of severe allergic or immune reactions due to the drug
- Other general bloodwork and EKG results were unremarkable

EKG, electrocardiogram.

Levy HL, et al. Poster presented at: SIMD 2022; April 10-13, 2022; Orlando, FL.

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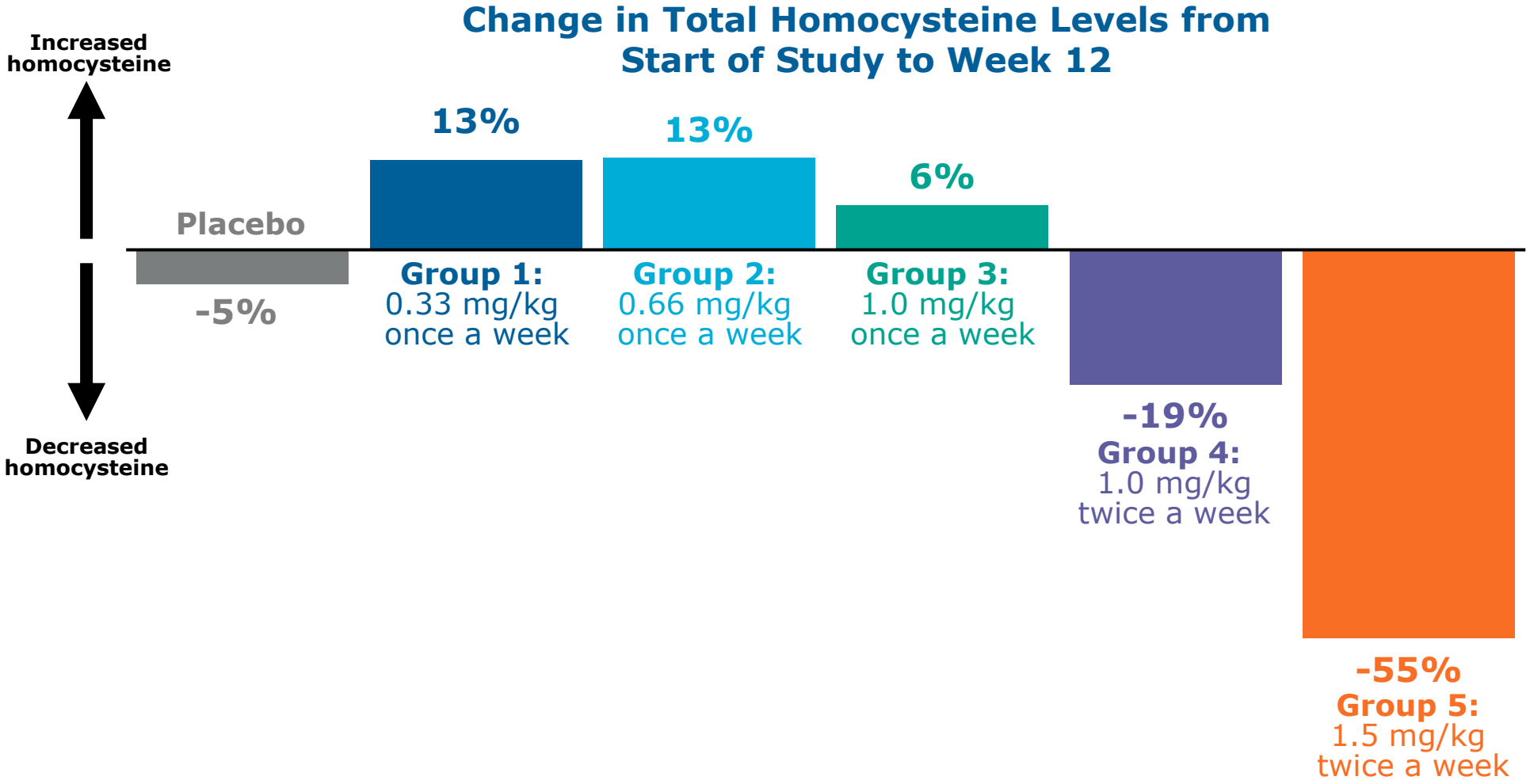
How Pegtibatinase Affected Homocysteine Levels



Patients who received the highest dose of pegtibatinase had the largest decrease in total homocysteine levels, with an average reduction of 55% after 12 weeks

Levy HL, et al. Poster presented at: SIMD 2022; April 10-13, 2022; Orlando, FL.

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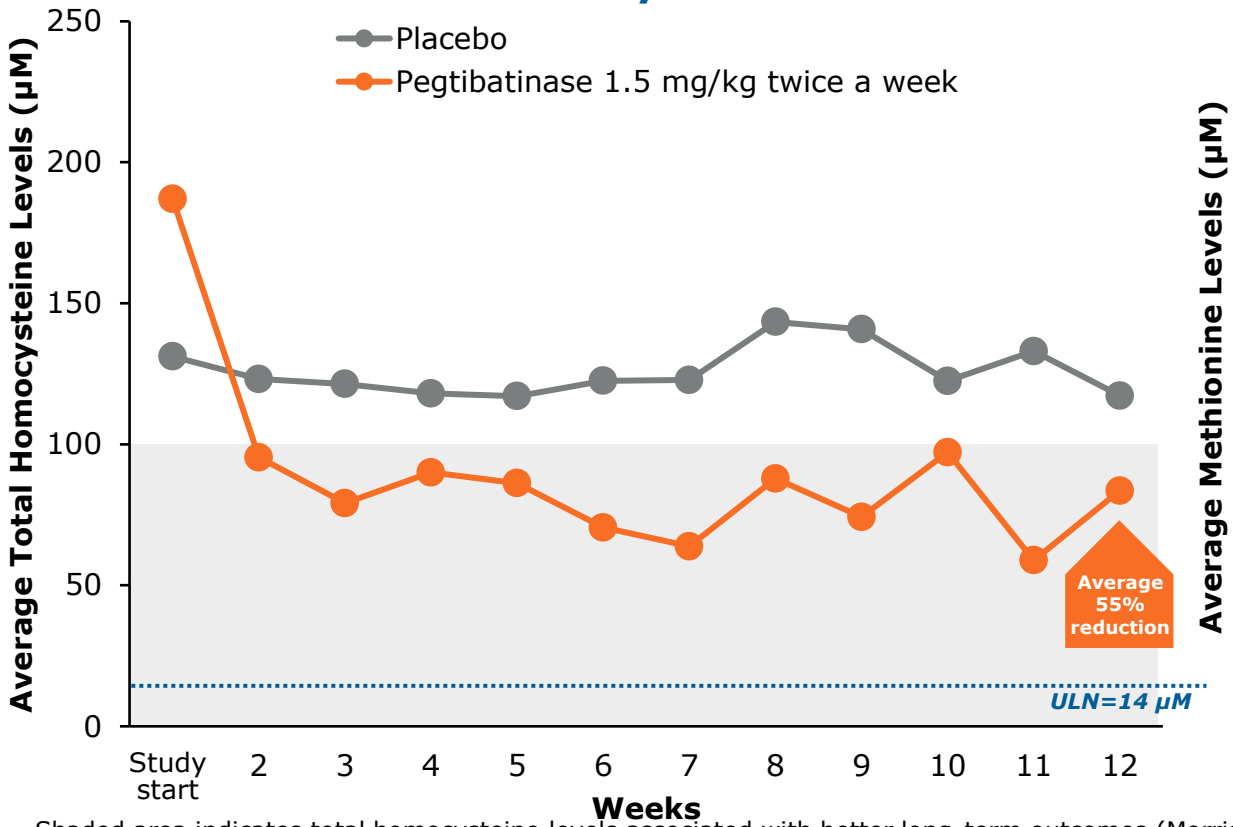
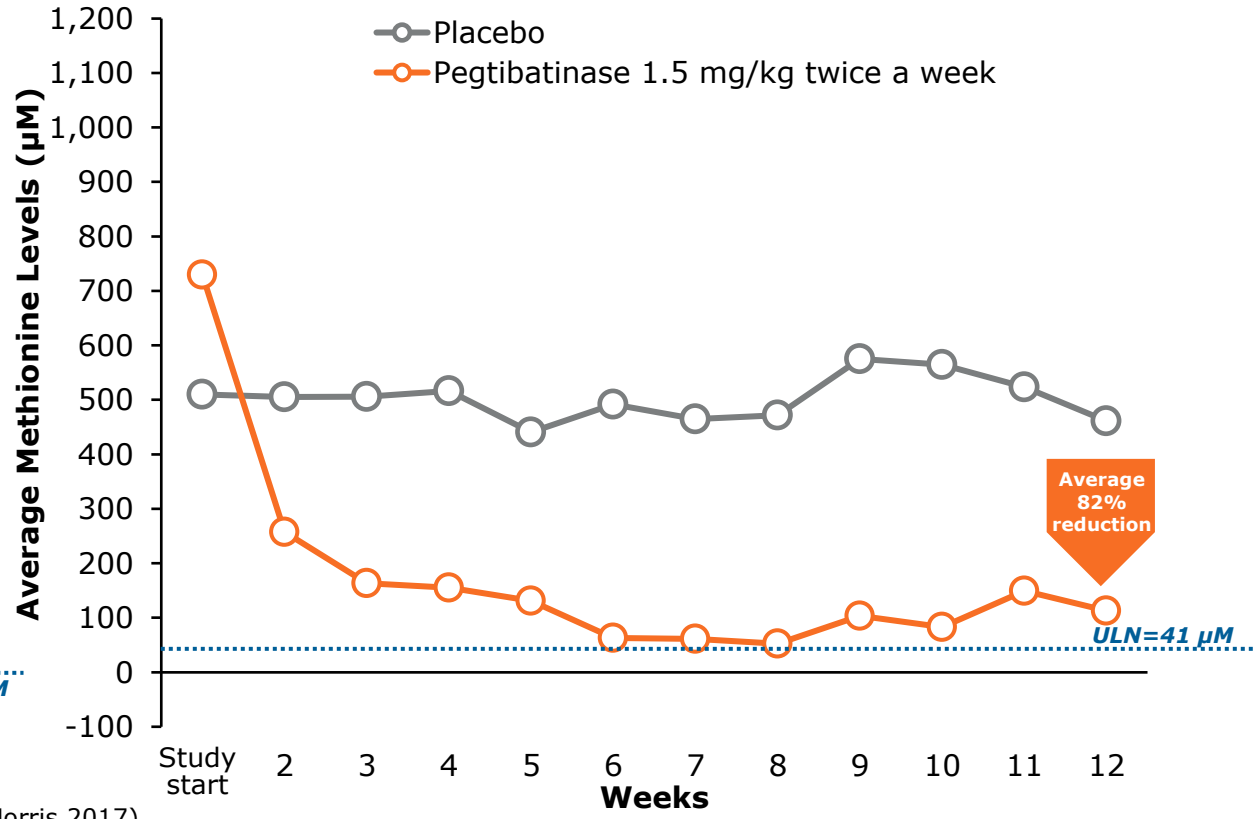
How Pegtibatinase Affected Homocysteine and Methionine Levels Over the 12 Weeks of Double-blind Treatment of the Study

Patients who received the highest dose of pegtibatinase rapidly reduced total homocysteine and methionine levels; average homocysteine levels were reduced below 100 µM as recommended

Total Homocysteine Levels



Methionine Levels



Shaded area indicates total homocysteine levels associated with better long-term outcomes (Morris 2017).
ULN, upper limit of normal.

Levy HL, et al. Poster presented at: SIMD 2022; April 10-13, 2022; Orlando, FL.

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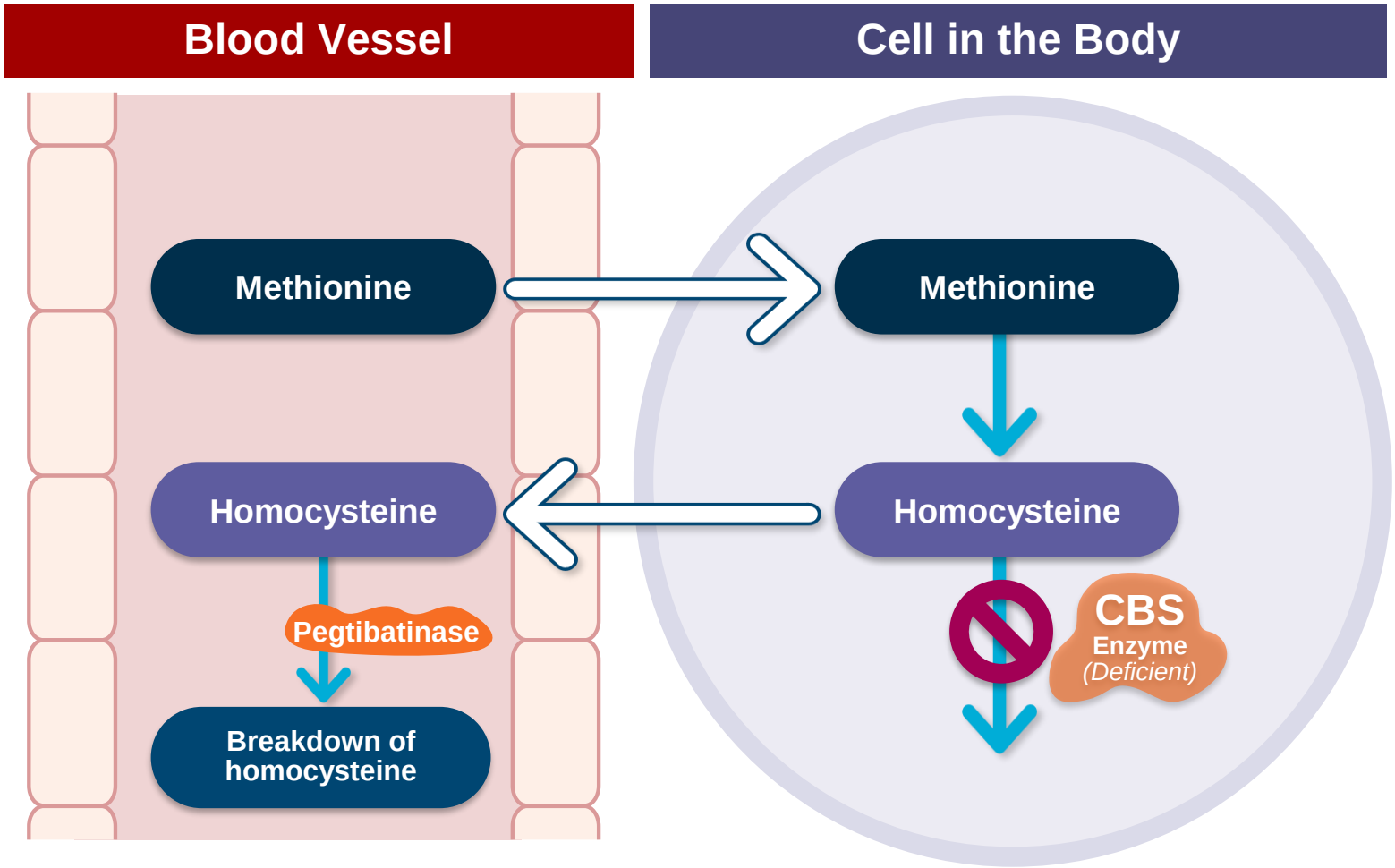
How Does Pegtibatinase Work?
The Metabolic Sink Hypothesis



CBS, cystathionine β-synthase.

Levy HL, et al. Poster presented at: SIMD 2022; April 10-13, 2022; Orlando, FL.

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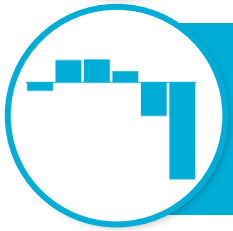
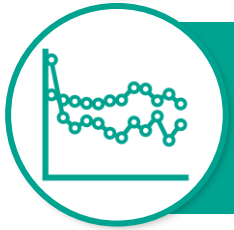
COMPOSE Initial Results Conclusions

Pegtibatinase was generally well tolerated at all doses tested and there were no reports of severe allergic or immune reactions due to study drug; no patients stopped treatment due to side effects



Patient groups on higher doses of pegtibatinase showed rapid reduction in total homocysteine levels; patients treated with the highest dose had an average reduction of 55% at 12 weeks



Patients treated with the highest dose of pegtibatinase twice weekly had a sustained reduction of homocysteine over 12 weeks and maintained their average homocysteine level below 100 µM as recommended

These results suggest that pegtibatinase may have the potential to be a new treatment for classical HCU

HCU, homocystinuria.

Levy HL, et al. Poster presented at: SIMD 2022; April 10-13, 2022; Orlando, FL.

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Future Steps for Pegtibatinase Development

COMPOSE is enrolling one more group of patients to study a higher dose and new preparation of pegtibatinase

Compose

Work is being done to plan a Phase 3 study and reach agreement with the FDA and other regulatory authorities

Travere is working with doctors, patients, and other interested parties to better understand classical HCU and the potential role of pegtibatinase treatment

HCU, homocystinuria.

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Questions?

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