HEMOSHEAR THERAPEUTICS

HST5040 Overview

An Investigational Oral Small Molecule Therapy for MMA and PA

MMA and PA

Methylmalonic acidemia (MMA) and propionic acidemia (PA) are rare intoxication-type inborn errors of metabolism that are characterized by acute metabolic decompensations, acidosis and hyperammonemia leading to severe organ damage, seizures, developmental deficits, and premature death. In the United States, about 1 in 70,000 newborns is diagnosed with MMA, and 1 in 240,000 is diagnosed with PA. There are an estimated 4,000 MMA and PA patients in the US and Europe combined. Despite standard of care involving dietary therapy, carnitine, and in severe cases, organ transplantation, there remains a high unmet medical need in MMA and PA.

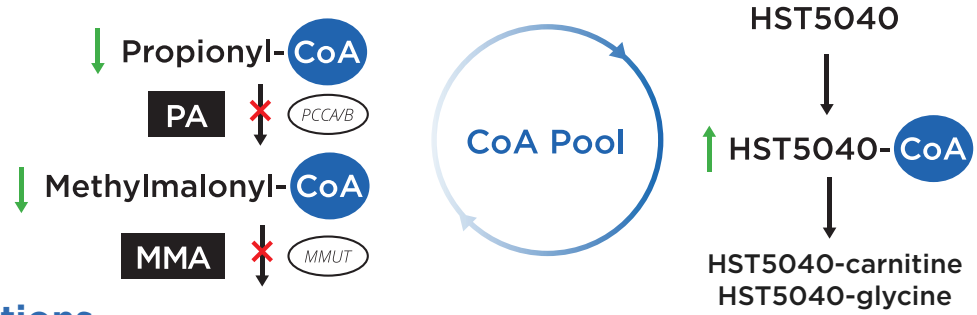
HST5040

HST5040 is an investigational oral small molecule therapy developed by HemoShear Therapeutics, Inc. to reduce the levels of toxins associated with MMA and PA. HST5040 is designed for convenient daily administration at home as a liquid formulation taken either orally or through a gastrostomy tube.

The FDA has granted HST5040 Orphan Drug, Fast Track and Rare Pediatric Disease designations for the treatment of MMA and PA. HemoShear has initiated the HERO (**HE**lp **R**educe **O**rganic Acids) phase 2 clinical study of HST5040 in patients aged 2 and older with MMA or PA.

Mechanism of Action

PA and MMA are caused by deficiencies in sequential enzymes of the propionate pathway, leading to the build-up of toxic levels of propionyl-coenzyme A (P-CoA) in PA and methylmalonyl-coenzyme A (M-CoA) in MMA and other harmful chemicals derived from them. Research in cultured hepatocytes from patients shows that HST5040 reduces P-CoA and/or M-CoA and the other derived toxic chemicals to normal or near normal levels, potentially improving the metabolic state and energy production pathways in the body. HST5040 does this by shunting coenzyme A (CoA) away from P-CoA pathways, resulting in a decrease in P-CoA levels, and consequently, decreased formation of other harmful chemicals. There is limited impact on the free CoA levels because HST5040-CoA is cleared from the cell as HST5040-carnitine and HST5040-glycine conjugates while returning free CoA to the cellular pools.



Publications

Allison J Armstrong, et al. A novel small molecule approach for the treatment of propionic and methylmalonic acidemias. *Molecular Genetics and Metabolism*, 2021 Mar 10 (in press online).

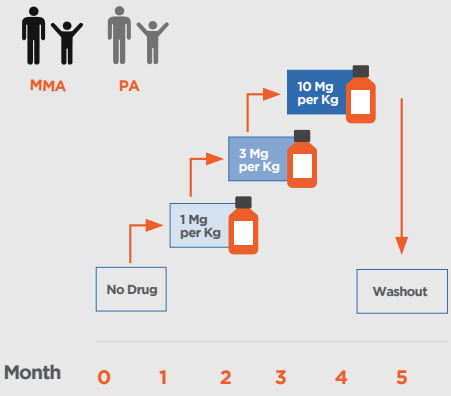
HELP REDUCE ORGANIC ACIDS

HERO STUDY

HemoShear's HERO (**HE**lp **R**educe **O**rganic Acids) phase 2 clinical study of HST5040 is enrolling at least 12 patients aged 2 and older with MMA or PA at select children's hospitals in the United States. The study design includes 3 parts – starting with an open-label dose escalation phase, then progressing to a randomized, double-blind, placebo-controlled crossover period, followed by an open-label long-term extension. More information can be found at clinicaltrials.gov (NCT04732429)

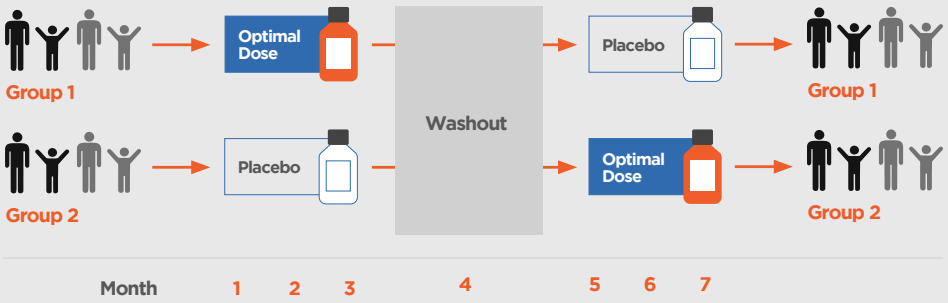
Study Design

Part A (Dose Escalation)



- Open-label, within subject, dose escalation to identify a safe and pharmacologically active (optimal) dose of HST5040 for use in Part B
- One-month washout with no drug followed by an open label extension at optimal dose

Part B (Cross-over)

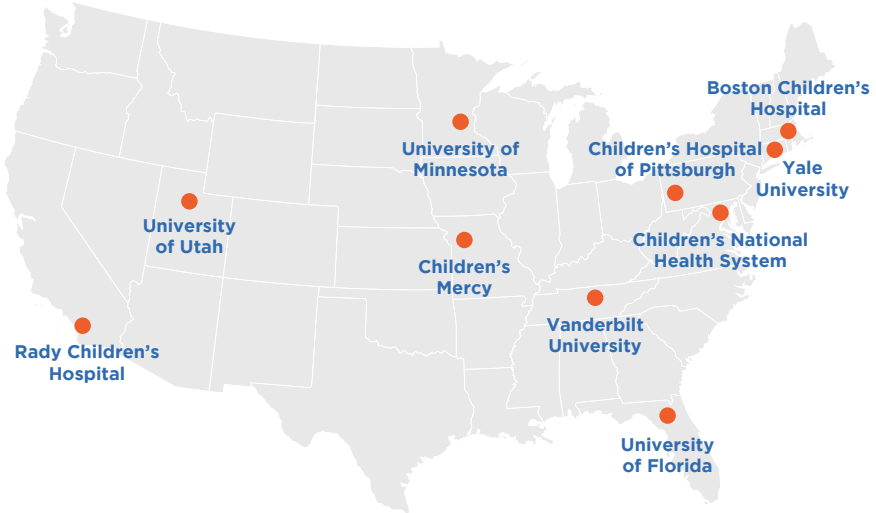


- Randomized, double-blind, placebo-controlled, 2-series crossover to evaluate safety and efficacy of the optimal dose of HST5040 in addition to standard of care (SoC)
- 7 months total: 3 months on drug and 3 months on placebo separated by a 1-month washout with no drug

Part C (Long-term Extension)

- Open-label long-term extension to evaluate sustained safety and efficacy of the optimal dose of HST5040 that provides metabolic stability in addition to SoC
- Possible additional cohorts to Part C (post-transplant patients, Cobalamin-A and Cobalamin-B deficiences)

Study Sites



HemoShear Therapeutics

HemoShear Therapeutics, Inc. is a privately held clinical stage company developing treatments for rare metabolic disorders with significant unmet patient need. For more information visit **HemoShear.com**.