An Efficient 3-Part Phase 2 Trial Design To Evaluate the Safety, Efficacy, and Pharmacokinetics of HST5040, A Novel Oral Small Molecule, in Patients with Methylmalonic or Propionic Acidemia

(clinicaltrials.gov NCT04732429)

Gerald F Cox¹, Mavis Y. Waller¹, Allison J. Armstrong¹, Mark P. Hayes¹, and Kimberly A Chapman²

¹HemoShear Therapeutics, Charlottesville, VA USA; ²Children’s National Rare Disease Institute, Washington, DC USA

Abstract

HST5040 reduces elevated levels of propionyl-CoA, methylmalonyl-CoA, and their derived metabolites in hepatocytes cultured from the explanted livers of patients with propionic acidemia (PA) or methylmalonic acidemia (MMA) undergoing liver transplant. The mechanism of action is thought to involve the production of HST5040-CoA that diverts coenzyme A (CoA) from toxic CoA metabolites. Previous clinical trials for two unrelated indications based on a different mechanism of action were discontinued due to a lack of efficacy, but importantly demonstrated HST5040 to be well-tolerated at doses higher than predicted necessary for MMA and PA patients.

A three-part Phase 2 clinical trial (“HERO”) to assess the safety, efficacy, and pharmacokinetics of HST5040 in 12 patients with MMA or PA aged 2 and older was initiated in the US in March 2021 (clinicaltrials.gov NCT04732429). Part A is a 5-month, open label, within-patient dose escalation study to identify the optimal dose of HST5040 based on safety and reductions in disease-related biomarkers. Subjects will then enter Part B, which is a randomized, double-blind, placebo-controlled cross-over study involving two 3-month treatment periods separated by a 1-month washout. Part B will assess reductions in biomarkers and early clinical responses with HST5040. Finally, the same subjects will enter Part C, which is an open-label, long-term extension study that may also enroll other potentially responsive subgroups of patients excluded from Part A and B, including those who are post-transplant or have cblA or cblB deficiency.
Background and Supporting Data

HST5040 Was Discovered Using the REVEAL-Tx™ Cell Culture Platform that Mimics the In Vivo Environment of the Liver

HST5040 Has Favorable Attributes as a Small Molecule Drug for MMA and PA

Convenience
• High oral bioavailability
• Liquid formulation for oral or G-tube administration

Safety
• Human safety data in 175 subjects aged ≥12 years for up to 48 weeks in 2 unrelated indications
• Maximum Tolerated Dose = 30 mg/kg/d
• Extensive non-clinical safety package

Systemic Disorder
• Broad tissue distribution
• Evidence of CNS penetration in non-clinical species

Multiple Indications
• Propionic acidemia
  – PCCA
  – PCCB
• Methylmalonic acidemia
  – MMUT - mutase
  – MMAA - Cbl A
  – MMAB - Cbl B

HST5040 Potently Suppresses Disease-Causing Toxins in Hepatocyte Cell Models from MMA and PA Patients

HST5040 is thought to act by diverting CoA away from toxic metabolites without a significant impact to the free CoA pool.
Trial Design

Phase 2 Study of HST5040 Consists of 3 Treatment Periods
Enroll 12 patients with MMA or PA (6 each) at up to 10 US sites

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 open label extension at “optimal” dose

Part B (Cross-Over)

• Randomized, double-blind, placebo-controlled, 2-period 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 continued use of the optimal dose of HST5040 in addition to SoC
• Possible additional cohorts in Part C (post-transplant patients, Cobalamin-A and Cobalamin-B deficiencies)
Trial Design (con’t)

Phase 2 Study Key Entry Criteria

**Inclusion Criteria**

- Confirmed diagnosis of PA (PCCA or PCCB) or MMA (MMUT) with history of metabolic decompensations
- Age ≥2 years
- Inadequate metabolic control in past 4 years, as defined by:
  - Plasma NH₃ >50 μM x2 ≥1 week apart, or
  - Plasma methylmalonic acid >150 μM (MMA only), or
  - ≥ 1 metabolic decompensation
- Plasma 2-methylcitric acid >3x ULN at screening
- Free plasma carnitine ≥10 μM and stable carnitine dose ≥1 wk

**Exclusion Criteria**

- Plasma Vitamin B5 <LLN
- Clinically significant cardiac disease (LVEF <45%, QTcF >450 msec, or arrhythmia)
- Moderate to severe kidney disease (eGFR <60 ml/min/1.73m²)
- Investigational treatment < 6 months prior
- Exposure to gene therapy for MMA or PA
- Organ transplant (Parts A and B only)

Phase 2 Study Key Assessments

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>Plasma 2-methylcitric acid</td>
</tr>
<tr>
<td><em>Secondary</em></td>
<td>Other disease-related biomarkers</td>
</tr>
<tr>
<td></td>
<td>Ureagenesis (Part B only)</td>
</tr>
<tr>
<td></td>
<td>Acute metabolic decompensations</td>
</tr>
<tr>
<td></td>
<td>Dietary intake</td>
</tr>
<tr>
<td></td>
<td>Neurocognitive function</td>
</tr>
<tr>
<td></td>
<td>Clinician and Caretaker/Patient Global</td>
</tr>
<tr>
<td></td>
<td>Impressions of Change (CGI-C)</td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adverse events</td>
</tr>
<tr>
<td></td>
<td>Physical exams</td>
</tr>
<tr>
<td></td>
<td>Routine clinical labs</td>
</tr>
<tr>
<td></td>
<td>Cardiac function</td>
</tr>
<tr>
<td></td>
<td>Renal function</td>
</tr>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>HST5040 and metabolite concentrations</td>
</tr>
<tr>
<td></td>
<td>(plasma, urine)</td>
</tr>
</tbody>
</table>

Patient Demographics and Disease Characteristics

The first two enrolled patients have PA caused by a homozygous frameshift mutation in the PCCB gene. Pre-treatment metabolite values were averaged over 5 (β-hydroxybutyrate) or 6 (all others) timepoints collected at least 1 week apart. Plasma MCA and C3 levels were markedly elevated (>125 and >30 ×ULN) compared to other metabolite levels (<3 ×ULN). With a reasonable coefficient of variation (25%) and known responsiveness to liver transplant, plasma MCA is likely to be an informative pharmacodynamic biomarker for HST5040.

<table>
<thead>
<tr>
<th>Patient 1001</th>
<th>Patient 1002</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Yr-Sex-Race</td>
<td>5-F-W</td>
<td>3-F-W</td>
</tr>
<tr>
<td>Height-Weight Z Scores</td>
<td>-0.94; 1.04</td>
<td>-0.92; -0.05</td>
</tr>
<tr>
<td><strong>Disease-related biomarkers</strong></td>
<td>Mean ± SD (×ULN)</td>
<td></td>
</tr>
<tr>
<td>Plasma MCA, μM</td>
<td>54 ± 16 (154)</td>
<td>45 ± 9 (129)</td>
</tr>
<tr>
<td>Serum Ammonia, μM</td>
<td>49 ± 19 (1.5)</td>
<td>60 ± 16 (1.8)</td>
</tr>
<tr>
<td>Plasma C3, μM</td>
<td>64 ± 19 (36)</td>
<td>56 ± 19 (32)</td>
</tr>
<tr>
<td>Plasma Glycine, μM</td>
<td>1228 ± 187 (3)</td>
<td>1161 ± 183 (2.8)</td>
</tr>
<tr>
<td>Plasma Glutamine, μM</td>
<td>372 ± 36</td>
<td>400 ± 56</td>
</tr>
<tr>
<td>Serum β-hydroxybutyrate, mM</td>
<td>0.9 ± 0.5 (2.3)</td>
<td>0.7 ± 0.1 (1.8)</td>
</tr>
</tbody>
</table>

MCA: 2-methylcitric acid
### Summary

**HST5040** is a novel oral investigational therapy being developed for MMA and PA.

HST5040 lowers disease-related toxic metabolites in MMA and PA human hepatocyte cell models.

HemoShear has initiated a Phase 2 study (HERO) that plans to enroll 12 patients with MMA and PA.

The sequential within-subject dose escalation and cross-over periods is an efficient design that reduces the number of study subjects.

Pre-treatment data suggests that plasma MCA will likely be an informative pharmacodynamic biomarker for HST5040.

Visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT04732429) for further study details, trial sites, and contact information.

### Study Sites

[Map showing study sites around the United States.]

- Rady Children’s Hospital
- University of Utah
- Children’s Mercy
- University of Minnesota
- Vanderbilt University
- Children’s Hospital of Pittsburgh
- Children’s National Health System
- Boston Children’s Hospital
- Yale University
- University of Florida