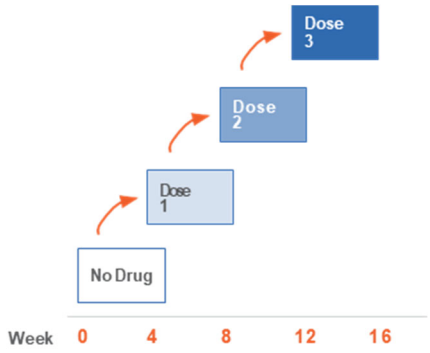
Early Termination of Clinical Study HST20-CL01

Clinical Study HST20-CL01 titled *"A Phase 2 Open-label, Dose Escalation Study of HST5040 in Subjects with Propionic or Methylmalonic Acidemia Followed by a 6-Month, Randomized, Double-blind, Placebo-controlled, 2-period Crossover Study and an Open-label, Long-term Extension Study"* was terminated prior to completion of the study by the Sponsor, HemoShear Therapeutics, Inc. The decision to terminate the study was based on business considerations by the Sponsor. The study was terminated during the dose escalation portion (Part A) and prior to initiation of the cross-over portion of the study (Part B). Data collected prior to termination are presented below; these data are unaudited.

Data from Clinical Study HST20-CL01

Design of Part A

Part A of the study used an intra-subject dose escalation design as shown in the figure below.



Two subjects were enrolled under protocol amendment #2 and received once daily dosing of HST5040 at 1 mg/kg, 3 mg/kg and 10 mg/kg as Doses 1, 2 and 3, respectively. The remaining subjects were enrolled under protocol amendment #3 and received twice daily doses of HST5040; Dose 1 was 3 mg/kg BID, Dose 2 was 9 mg/kg BID and Dose 3 was 15 mg/kg BID.

Blood samples for biomarker assays and safety laboratory assessments were collected every 2 weeks.

Enrollment and Disposition

A total of 26 subjects were enrolled into Part A: 11 subjects with propionic acidemia (PA) and 15 subjects with methylmalonic acidemia (MMA). Six subjects did not receive study drug. The Full Analysis Set is defined as all subjects who received any amount of HST5040 and have at least 1 post-baseline efficacy assessment and includes 18 subjects. The safety set is defined as all subjects who receive at least 1 dose of HST5040 and includes 20 subjects.

At the time of study termination, 8 subjects (40%) in the Safety Set had completed Part A, 7 subjects (35%) were participating in Part A, and 5 subjects (25%) had discontinued the study. The reasons for discontinuation included adverse events in 3 subjects (15%) and withdrawal of consent in 2 subjects (10%).

Demographics

The subject demographics (Safety Set) are presented in the table below:

Demographic Characteristics (Safety Set) N=20	
Characteristic	
Sex [n (%)]	
Female	12 (60.0)
Male	8 (40.0)
Race [n (%)]	
Asian	2 (10.0)
Black or African American	1 (5.0)
White	13 (65.0)
Other	1 (5.0)
Not Reported	1 (5.0)
Multiple Race	2 (10.0)
Ethnicity [n (%)]	
Hispanic or Latino	3 (15.0)
Not Hispanic or Latino	17 (85.0)
Age (years) at Enrollment	
mean (std)	10.0 (4.58)
Weight (kg)	
mean (std)	32.73 (14.35)
Height (m)	
mean (std)	1.28 (0.22)
BMI (kg/m^2)	
mean (std)	18.92 (3.03)

Changes in Important Biomarkers in Subjects Receiving HST5040 Twice Daily

As designed, Part A of clinical study HST5040 was intended to provide data to be utilized in the selection of an optimal dose to be carried forward into the cross-over portion of the study (Part B). However, blood samples were collected and assayed for prespecified biomarkers. The baseline values and percentage change from baseline of some important biomarkers at selected timepoints for those subjects receiving HST5040 twice daily are shown in the table below.

Baseline and Percentage Change from Baseline in Important Biomarkers					
	2-Methylcitric acid	Propionyl-carnitine	Glycine	Methylmalonic acid [a]	Fasting Ammonia
Baseline (nmol/mL) [mean (std)]	19.6 (17.2), N=16	50.70 (34.2), N=16	719.4 (375.4), N=16	576.1 (503.3), N=9	58.9 (23.6), N=14
% change from baseline [mean (std)]					
Week 4	-45.55, n=1	-7.4, n=1	14.0, n=1	-43.9, n=1	No data
Week 8	53.2 (101.9), n=9	39.7 (33.8), n=9	-25.5 (30.7), n=9	5.2 (65.5), n=6	17.1 (41.1), n=7

Week 12	60.5 (87.4), n=7	58.2 (103.2), n=7	-22.3 (34.9), n=6	-6.6 (49.2), n=5	19.7 (31.9), n=6
Week 16	10.1 (71.5), n=6	29.32 (46.7), n=6	-40.0 (27.26), n=6	-11.1 (75.8), n=4	-3.2 (14.8), N=5

[a] includes subjects with methylmalonic acidemia only

Safety Findings

The overall summary of treatment-emergent adverse events by dosing frequency in the Safety Set is provided in the table below.

Overall Summary of Treatment-Emergent Adverse Events (Safety Set)		
Adverse Event Category [n (%) m]	QD dosing N=2	BID Dosing N= 16
Any Treatment-Emergent Adverse events	2 (100) 31	13 (81.3) 76
Any Treatment-Emergent Adverse Events Related to IP	2 (100) 3	12 (75.0) 37
Any Treatment-Emergent Adverse Events with Outcomes of Death	0	0
Any Serious Treatment-Emergent Adverse Events	2 (100) 7	7 (43.8) 12
Any Treatment Related Serious Treatment-Emergent Adverse Events	0	5 (31.3) 6
Any Treatment-Emergent Adverse Events Leading to Discontinuation of IP	0	3 (18.8) 5
Any Severe Treatment-Emergent Adverse Events	2 (100) 6	8 (50.0) 13
Any Disease-Related Treatment-Emergent Adverse Events	2 (100) 10	8 (50.0) 21

n = number of subjects; m = number of events, IP = investigational product, QD = once daily dosing, BID = twice daily dosing

The serious treatment emergent adverse events reported in subjects receiving HST5040 once daily included vomiting in both subjects and anaemia, fatigue, respiratory syncytial virus infection, hypokalemia and tremor in one subject each. Serious adverse events reported in subjects receiving twice daily dose of HST5040 included vomiting in 4 subjects; the remaining serious adverse events were reported in one subject each and included constipation, nausea, CPVID-19 infection, influenza infection, rhinovirus infection, metabolic acidosis, seizure and acute kidney injury.

Adverse events led to discontinuation of investigational product in 3 subjects. Two of these subjects reported vomiting. Nausea, decreased appetite, and seizure were reported by one subject each.

The adverse events reported in the Safety Set and assessed as related to investigational product by the investigator by system organ class and preferred term, dosing frequency, and disease type are shown in the table below.

Treatment-Emergent Adverse Events Related to Investigational Product by System Organ Class and Preferred Term, Dosing Frequency and Disease Type (Safety Set)				
System Organ Class	QD Dosing		BID Dosing	
Preferred Term [n (%) m]	PA N = 2	MMA N = 0	PA N = 6	MMA N = 10
Any Adverse Events related to IP	2 (100) 31		3 (50.0) 5	9 (90.0) 32
Blood and Lymphatic System Disorders	1 (50.0) 1		1 (16.7) 1	2 (20.0) 3
Thrombocytopenia			0	1 (10.0) 1
Anemia	1 (50.0) 1		0	1 (10.0) 1
Gastrointestinal Disorders	0		2 (33.3) 2	6 (60.0) 13
Vomiting	0		2 (33.3) 2	5 (50.0) 7
Abdominal Pain	0		1 (16.7) 1	2 (20.0) 2
Nausea	0		0	5 (50.0) 5
General Disorders and Administration Site Conditions	1 (50.0) 1		0	2 (20.0) 3
Administrative site extravasation	1 (50.0) 1		0	0
Fatigue	1 (50.0) 1		0	2 (20.0) 2
Feeling Cold	0		0	1 (10.0) 1
Hepatobiliary disorders	0		0	1 (10.0) 1
Hyperbilirubinemia	0		0	1 (10.0) 1
Investigations	1 (50.0) 1		1 (16.7) 1	3 (30.0) 7
Gamma-glutamyl Transferase Increased	0		0	1 (10.0) 1
Transaminases Increased	1 (50.0) 1		0	0
Liver Function Test Increased	0		1 (16.7) 1	0
Alanine Aminotransferase Increased	0		0	2 (20.0) 2
Aspartate Aminotransferase Increased	0		0	2 (20.0) 2
Amino Acid Level Decreased	0		0	1 (10.0) 1
Weight Decreased	0		0	1 (10.0) 1
Metabolism and Nutrition Disorders	0		0	5 (50.0) 5
Metabolic Disorder	0		0	2 (20.0) 2
Decreased Appetite	0		0	2 (20.0) 2
Feeding Disorder	0		0	1 (10.0) 1
Nervous System Disorders	0		1 (16.7) 2	2 (20.0) 2
Epilepsy	0		1 (16.7) 1	0
Seizure	0		1 (16.7) 1	0
Headache	0		0	1 (10.0) 1

n = number of subjects; m = number of events, IP = investigational product, QD = once daily dosing, BID = twice daily dosing, PA = propionic acidemia, MMA = methylmalonic acidemia

A manual review of the physical examination findings, electrocardiogram results, echocardiogram results, safety laboratory results, hematology results and urinalysis results did not indicate any significant safety signal.