Clinical Characterization of Classical Homocystinuria Due to Cystathionine Beta-Synthase Deficiency: Results From the ACAPPELLA Study

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Poster #B18

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RESULTS

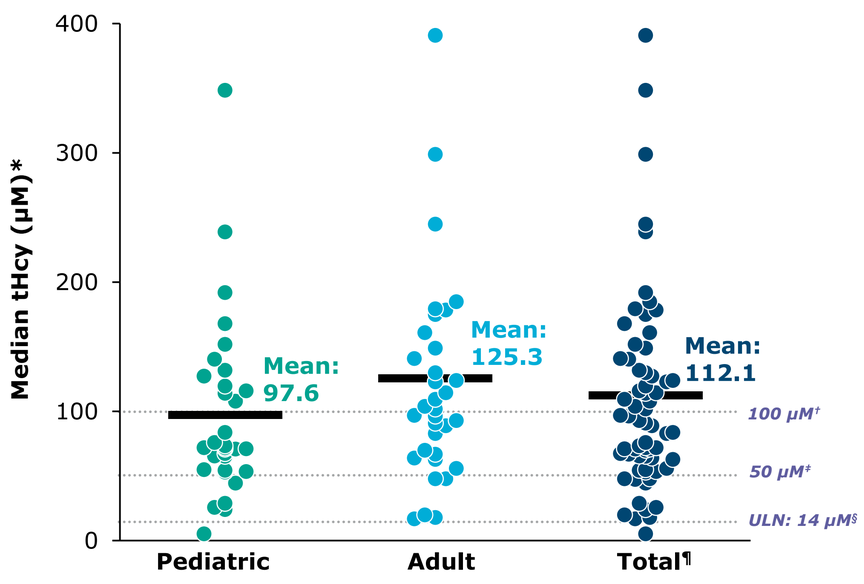
Table 1. Participant Baseline Demographics and Disposition

Category	Pediatric (N=34)	Adult (N=37)	Total (N=71)
Age (years), mean (SD)	10.5 (3.6)	32.5 (9.9)	22.0 (13.4)
Sex, n (%)			
Male	17 (50.0)	17 (45.9)	34 (47.9)
Female	17 (50.0)	19 (51.4)	36 (50.7)
Missing	0	1 (2.7)	1 (1.4)
Race, n (%)			
White	33 (97.1)	33 (89.2)	66 (93.0)
Black or African American	1 (2.9)	2 (5.4)	3 (4.2)
Not provided/missing	0	2 (5.4)	2 (2.8)
Duration of study (years), mean (SD)	2.2 (1.0)	1.9 (1.2)	2.1 (1.1)
Duration categories (years), n (%)			
<1	4 (11.8)	9 (24.3)	13 (18.3)
1 to <3	20 (58.8)	21 (56.8)	41 (57.8)
3 to <6	10 (29.4)	7 (18.9)	17 (23.9)

SD, standard deviation.

- Baseline demographics for the first 71 participants enrolled as of the data cutoff are shown in **Table 1**
- At data cutoff, the mean age of participants was 22 years (range 5–53 years), 48% were pediatric (aged <18 years [27% <12 years]), 48% were male, and 93% were White
- Mean of the median tHcy value for each participant across the first seven study visits (standard deviation [SD]) was 125 (92) µM for adult participants and 98 (68) µM for pediatric participants; overall, the mean of the medians (SD) was 112 (82) µM (**Figure 1**)
- 84% of participants had median tHcy ≥50 µM, including 45% of participants who had median tHcy ≥100 µM

Figure 1. tHcy in Participants With HCU Receiving SOC Treatment by Age Group



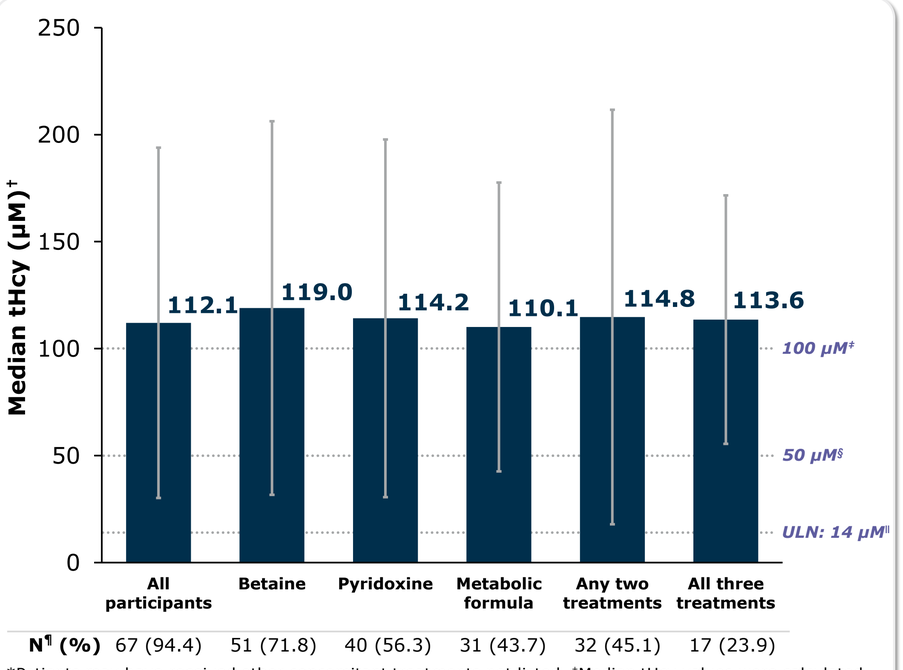
n/N (%) meeting tHcy threshold			
<50 µM	5/32 (15.6)	6/35 (17.1)	11/67 (16.4)
≥50 µM	27/32 (84.4)	29/35 (82.9)	56/67 (83.6)
≥100 µM	12/32 (37.5)	18/35 (51.4)	30/67 (44.8)

*Median tHcy values were calculated for each subject using all available data over the first seven visits. For each subgroup, means were calculated from the median tHcy value of each participant. †Clinical threshold for minimizing HCU complications recommended by E-HOD guidelines.[3] ‡Clinically recommended threshold in pyridoxine-responsive patients (E-HOD).[3] §ULN provided by the Clinical Laboratory Improvement Amendments lab at the Center of Metabolomics, Institute of Metabolic Disease, Baylor Scott White Research Institute. ¶Data unavailable for four participants.

E-HOD, European Network and Registry for Homocystinurias and Methylation Defects; **HCU**, classical homocystinuria; **SOC**, standard of care; **tHcy**, total homocysteine; **ULN**, upper limit of normal.

- SOC treatments for HCU used by participants in the study included betaine (51/71 [72%]), pyridoxine (40/71 [56%]), metabolic formula (31/71 [44%]), or any combination of two (32/71 [45%]) or three (17/71 [24%]) of these. Regardless of treatment, average tHcy for each group remained >100 µM (**Figure 2**).

Figure 2. tHcy in Participants With HCU by SOC Treatment*



N¶ (%)	67 (94.4)	51 (71.8)	40 (56.3)	31 (43.7)	32 (45.1)	17 (23.9)

*Patients may have received other concomitant treatments not listed. †Median tHcy values were calculated for each subject using all available data over the first seven visits. For each subgroup, means were calculated from the median tHcy value of each participant and error bars represent SD. ‡Clinical threshold for minimizing HCU complications recommended by E-HOD guidelines.[3] §Clinically recommended threshold in pyridoxine-responsive patients (E-HOD).[3] ULN provided by the Clinical Laboratory Improvement Amendments lab at the Center of Metabolomics, Institute of Metabolic Disease, Baylor Scott White Research Institute. ¶Data unavailable for four participants.

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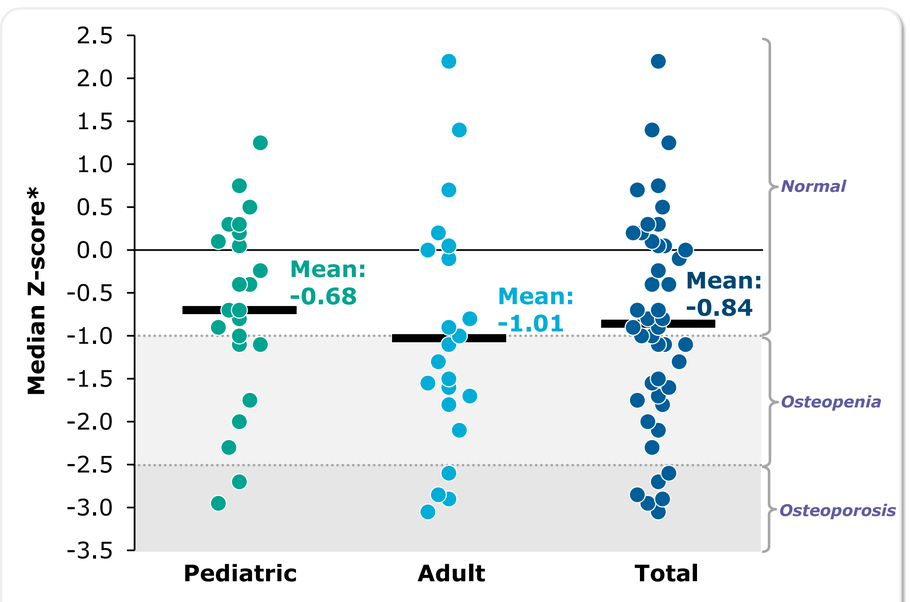
- Dual-energy X-ray absorptiometry (DXA) testing demonstrated clinical deficits in bone mineralization in 47% of participants based on total body Z-score (**Figure 3**)
- 13% of participants had DXA scores consistent with clinically significant osteoporosis

Figure 3. Total Body DXA Z-scores in Participants With HCU by Age Group



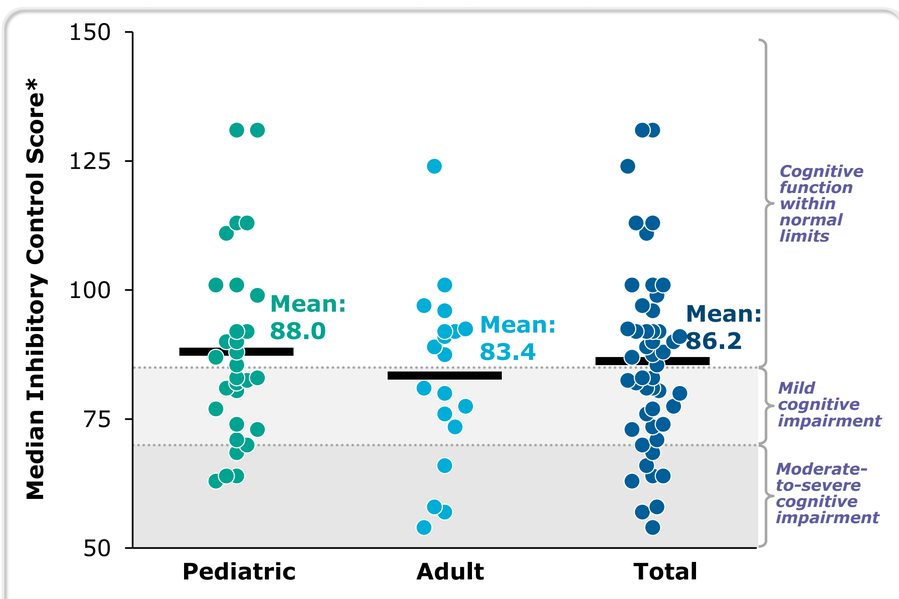
n/N (%) with median values meeting DXA Z-score threshold			
≤-1.0	8/23 (34.8)	13/22 (59.1)	21/45 (46.7)
≤-2.5	2/23 (8.7)	4/22 (18.2)	6/45 (13.3)

*Median scores were calculated for each subject using all available data over the first seven visits. For each subgroup, means were calculated from the median Z-score of each participant. DXA scans were not conducted in all participants.

DXA, dual-energy X-ray absorptiometry; **HCU**, classical homocystinuria.

- Comparable results were observed in DXA assessment of the hip and spine, with 22/51 (43.1%) and 19/50 (38.0%) participants, respectively, meeting the threshold for osteopenia (Z-score ≤-1.0)
- Cognitive function evaluated using the National Institutes of Health Toolbox Cognition Battery showed that:
  - The greatest cognitive deficit in the overall population was in the sub-domain of **inhibitory control** (**Figure 4**); 49% of participants had median scores consistent with clinically significant cognitive impairment (18% moderate to severe)
  - 35% of participants had median **total composite** scores consistent with clinically significant cognitive impairment (19% moderate to severe)
  - 48% of participants had median **cognition fluid composite** scores consistent with clinically significant cognitive impairment; (21% moderate to severe)

Figure 4. NIHTB-CB Inhibitory Control Sub-domain Results in Participants With HCU by Age Group



n/N (%) with median values meeting cognitive score threshold			
≤85	15/30 (50.0)	9/19 (47.4)	24/49 (49.0)
≤70	5/30 (16.7)	4/19 (21.1)	9/49 (18.4)

*Median scores were calculated for each subject using all available data over the first seven visits. For each subgroup, means were calculated from the median Flanker Inhibitory Control score of each participant.

HCU, classical homocystinuria; **NIHTB-CB**, National Institutes of Health Toolbox Cognition Battery.

CONCLUSIONS

- ✓ Many participants with HCU who were receiving current SOC had tHcy levels above clinically recommended thresholds
- ✓ Despite being prescribed treatment with betaine, pyridoxine, metabolic formula, or any combination, many participants had suboptimal metabolic control of tHcy
- ✓ Many participants with HCU had clinically significant deficits in bone mineral density and cognitive function
- ✓ There is an urgent need for new therapies that allow for better control of tHcy and improve clinical outcomes in HCU

DISCLOSURES

CF: Investigator for Travere Therapeutics, Inc. **KC:** Investigator for and consultant to Travere Therapeutics, Inc. **ML:** Investigator for and consultant to Travere Therapeutics, Inc. **HLe:** Investigator for and consultant to Travere Therapeutics, Inc. **HLi:** Investigator for and consultant to Travere Therapeutics, Inc. **JT:** Investigator for Travere Therapeutics, Inc. **YC:** Employee and stockholder of Travere Therapeutics, Inc. **SAV:** Employee and stockholder of Travere Therapeutics, Inc. **EC:** Investigator for and consultant to Travere Therapeutics, Inc. **RS:** Investigator for Travere Therapeutics, Inc.

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INTRODUCTION

- Classical homocystinuria (HCU) is a rare genetic metabolic disorder caused by a deficiency of the enzyme cystathionine beta-synthase, resulting in accumulation of homocysteine (Hcy) and methionine (Met) in plasma and tissues, alongside other metabolic anomalies[1,2]
- Patients with Hcy levels >100 µM are at risk of various severe multisystemic complications,[3] which can affect the vasculature (thromboembolism, stroke), central nervous system (seizures, cognitive impairment), eyes (myopia, ectopia lentis), and skeleton (osteoporosis, scoliosis)[1]
- Current standard-of-care (SOC) treatments include a protein-restricted diet and supplementation with Met-free metabolic formula, pyridoxine (vitamin B6), and betaine[1,3]
- However, these interventions can be suboptimal for reducing total Hcy (tHcy) to clinically relevant target concentrations, leaving patients at risk of HCU-related complications
- Prescribed diet restrictions must be followed closely and continuously in order to keep tHcy levels lowered, representing a challenging lifelong commitment for patients[3,4]

Objectives

- This ongoing study aims to characterize the clinical course of HCU in pediatric and adult patients under current SOC management.[5] Multiple biochemical and clinical assessments are being investigated with the aim of gaining insights into HCU disease progression.

METHODS

- ACAPPELLA (NCT02998710) is a prospective, longitudinal, multicenter, multinational, natural history study, which has planned to enroll up to 150 patients with HCU aged 1–65 years at 10 sites across the USA, UK, Canada, and Ireland[5]
- The protocol has been developed to assess participants over 78 months old at 6-month intervals for a total of 14 visits to monitor the natural history and outcomes of HCU
- Average duration of participation was ~2 years at the data cutoff: March 8, 2023

DISCUSSION

- ACAPPELLA is a large and comprehensive prospective natural history study of HCU
- The interim results demonstrate that suboptimal metabolic control of tHcy was observed even when participants managed at large academic institutions were prescribed one or multiple SOC treatments
- Clinically significant deficits were observed in bone mineralization and cognitive function in many adult and pediatric participants

Limitations

- Although this heterogeneous study population provides a valuable snapshot into the natural history of HCU and current management in the real world, the observational nature of this cohort means that treatment was not controlled
- HCU slowly progresses over years to decades whereas the average duration of participation in this study so far was 2 years, which may not capture some chronic features of the disease
- Timing of diagnosis (eg, newborn screening vs. late diagnosis), pyridoxine responsiveness, length of time on treatments, and regional differences were not considered in this analysis
- Participant adherence to specific prescribed treatments is unknown

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