Copper Histidinate Treatment for Menkes Disease (Kinky Hair Syndrome)

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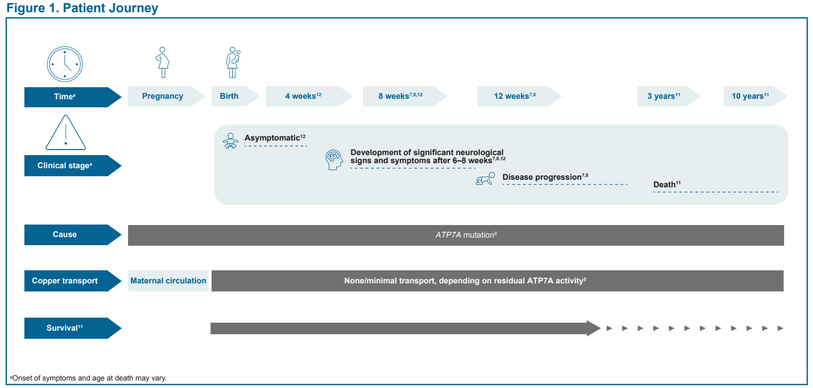
Background

- Copper is an essential trace element required for human development and health
- Menkes disease is an X-linked recessive disorder caused by mutations in the copper transport gene *ATP7A*. Patients with Menkes disease are born with impaired ability to absorb copper from their diet
  - Molecular defects include small deletions or insertions (22% of cases), nonsense mutations (18% of cases), splice junction mutations (18% of cases), large gene deletions (17% of cases), and missense mutations (17% of cases)[1–5]
- A population-scale variant frequency database (gnomAD) genome-based assessment estimated prevalence of Menkes disease at birth as 1 in 34,810 live male births at minimum, and potentially as high as 1 in 8,644[6]
- Pre-symptomatic detection of affected newborns is difficult[7,8]
  - Serum copper levels in affected newborns overlap with low/normal levels in unaffected infants[7]
  - Prematurity, cephalohematomas, hypothermia, hypoglycemia, and jaundice are common but nonspecific features[7,8]
  - Children with Menkes disease would benefit from newborn screening.[8] Newborn screening assays are currently in development
- Affected newborns typically manifest initial clinical signs of the disease approximately 2–4 months after birth[9] (**Figure 1**)
  - Loss of previously obtained developmental milestones, onset of hypotonia, seizures, and failure to thrive are frequent initial manifestations[8]
    - Hair hypopigmentation might suggest a diagnosis,[10] but the twisted, kinky hair shafts (*pili torti*) found on light microscopy at later ages are generally not evident at birth[8]
  - If Menkes disease remains untreated, brain abnormalities, including diffuse atrophy, ventriculomegaly, and tortuosity of cerebral blood vessels, become evident on brain magnetic resonance imaging several months after birth[3,8]
- Without treatment, death by the age of 3 years is the typical outcome in Menkes disease[11]
- Currently, there is no Food and Drug Administration (FDA)-approved therapy for the treatment of Menkes disease
- Here, we describe results from two studies evaluating safety and efficacy with CuHis (CUTX-101) for the treatment of Menkes disease compared with untreated historical controls

Figure 1. Patient Journey



[a]Onset of symptoms and age at death may vary.

Methods

- Efficacy analyses are based on data that were integrated from 2 completed pivotal studies conducted as part of the NIH Intramural Research Program
  - Study 90-CH-0149 is a completed, Phase 1/2, open-label, single-center study evaluating CuHis in subjects with Menkes disease (NCT00001262)
  - Study 09-CH-0059 is a completed, Phase 3, open-label, single-arm, single-site study evaluating CuHis in subjects with Menkes disease, occipital horn syndrome, or unexplained copper deficiency (NCT00811785)
  - In both studies, infants up to 12 months of age received 1450 mcg CuHis (250 mcg of elemental copper) in 0.5 mL of reconstituted product administered twice daily (bid) subcutaneously (sc). Children older than 12 months received 1450 mcg CuHis (250 mcg of elemental copper) in 0.5 mL of reconstituted product administered once daily (qd) sc. Subjects received treatment for up to 3 years
  - A cohort of untreated patients with Menkes disease were enrolled as the Historical Control (HC)
- Subjects with Menkes disease born after 1999 with a severe *ATP7A* genotype (deletion/duplication, nonsense, or canonical splice site junction mutation [CSJ]) were identified from the 2 pivotal studies
  - Of these subjects, 4 different patient cohorts, including the HC cohort, were defined for the efficacy analyses (**Figures 2** and **3**)
- Primary and secondary efficacy analyses are based on comparisons of overall survival for CuHis early treatment (CuHis-ET) versus historical control early treatment (HC-ET) and for CuHis late treatment (CuHis-LT) versus historical control late treatment (HC-LT), respectively
  - The treatment effect on overall survival was analyzed using a log-rank statistic via a log-rank model with treatment effects. Using a Cox regression analysis, the estimate of the hazard ratio (HR) and the 95% confidence interval (CI) is presented
- Safety assessments for subjects treated with CuHis included recording of adverse events (AEs; any new clinically relevant finding), signs of significant local skin reactions, collection of blood and urine samples during the outpatient visits, collection of medical history, laboratory tests, physical examination, and recording of all concomitant prescription medications, over the counter medications, and supplements

Results

- In the CuHis-ET cohort, hypoglycemia (12.5%) and infant respiratory distress syndrome (12.5%) were common comorbidities due to prematurity at baseline (**Table 1**)

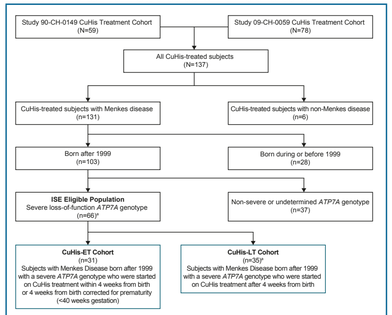
Table 1. Summary of Demographics and Baseline Characteristics

Parameter	CuHis-ET (N=31)	HC-ET (N=18)	CuHis-LT (N=35)	HC-LT (N=17)
Age[a] (months)				
Mean (SD)	0.611 (0.5754)	6.228 (4.7037)	7.979 (6.4773)	6.368 (4.8096)
Median	0.395	4.734	7.068	4.767
Minimum, maximum	0.03–1.87	2.07–22.19	1.22–31.40	2.07–22.19
Age group, n (%)				
<1 year	31 (100.0)	17 (94.4)	31 (88.6)	16 (94.1)
1 to <3 years	0	1 (5.6)	4 (11.4)	1 (5.9)
Sex, n (%)				
Male	31 (100.0)	18 (100.0)	33 (94.3)	17 (100.0)
Female	0	0	2 (5.7)	0
***ATP7A* mutation categories, n (%)**				
Deletion/duplication (severe)	22 (71.0)	10 (55.6)	21 (60.0)	9 (52.9)
Nonsense (severe)	6 (19.4)	5 (27.8)	9 (25.7)	5 (29.4)
Canonical splice junction (severe)	3 (9.7)	3 (16.7)	5 (14.3)	3 (17.6)
Premature to full-term births, n (%)				
Premature	24 (77.4)	15 (83.3)	23 (65.7)	14 (82.4)
Full term	5 (16.1)	3 (16.7)	11 (31.4)	3 (17.6)
Missing	2 (6.5)	0	1 (2.9)	0
Family history of Menkes disease, n (%)				
Yes	27 (87.1)	6 (33.3)	6 (17.1)	6 (35.3)
No	3 (9.7)	1 (5.6)	10 (28.6)	1 (5.9)
Unknown	1 (3.2)	11 (61.1)	19 (54.3)	10 (58.8)
Time to diagnosis of Menkes disease (days)				
Mean (SD)	5.5 (55.22)	190.4 (143.07)	204.3 (184.30)	194.7 (146.29)
Median	1.0	145.0	145.0	146.0
Minimum, maximum	-104 to 227	64–676	11–893	64–676
Significant neurological symptoms, n (%)				
At least 1 significant neurological symptom	2 (6.5)	18 (100.0)	33 (94.3)	17 (100.0)
Seizures	0	18 (100.0)	23 (65.7)	17 (100.0)
Failure to thrive	1 (3.2)	13 (72.2)	11 (31.4)	13 (76.5)
Hypotonia	2 (6.5)	17 (94.4)	26 (74.3)	16 (94.1)

[a]For CuHis-ET and CuHis-LT cohorts, age was based on the date of informed consent and for the HC-ET and HC-LT cohorts, age was based on the date of diagnosis. SD, standard deviation.

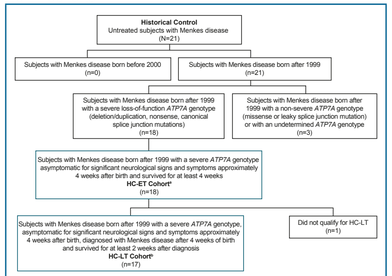
- The primary efficacy endpoint of overall survival was met. The analysis demonstrated statistically significant improvement in overall survival in subjects with Menkes disease who received ET with CuHis (CuHis-ET) compared with untreated subjects (HC-ET) (**Figure 4**)
- The secondary efficacy endpoint of overall survival was met. The analysis demonstrated statistically significant improvement in overall survival in subjects with Menkes disease who received LT with CuHis (CuHis-LT) compared with untreated subjects (HC-LT) (**Figure 5**)
- Sensitivity analyses demonstrated that CuHis treatment is associated with an increase in survival time regardless of severe *ATP7A* mutation type or prematurity
- The safety of CuHis was evaluated in subjects with Menkes disease who received at least 1 dose of CuHis: 31 subjects in the CuHis-ET cohort and 35 subjects in the CuHis-LT cohort (**Table 2**)
- The median (range) duration of exposure was 28.5 (1.1–36.0) months
- Treatment emergent adverse events (TEAEs) were reported in 61 subjects (92.4%)
  - None were considered related to study treatment
  - Serious TEAEs were reported in 50 subjects (75.8%), and TEAEs that led to death and discontinuation of study treatment were reported in 19 subjects (28.8%); none were considered related to study treatment

Figure 2. Disposition of Subjects Treated With CuHis for the ET and LT Cohorts From Studies 90-CH-0149 and 09-CH-0059



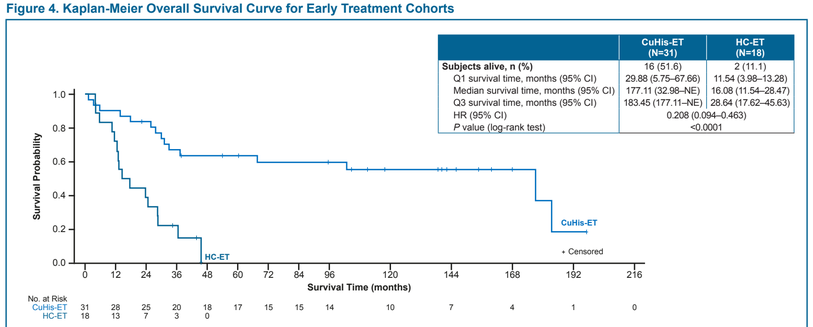
[a]One subject was enrolled in both NIH studies and is only counted once. ISE, integrated summary of efficacy.

Figure 3. Disposition of Untreated Subjects for the HC-ET and HC-LT Cohorts



[a]For the untreated subjects in the Historical Control Cohort, clinical information and survival status were collected by the principal investigator (SGK) and Cyprium based on medical records, interviews with parents/caregivers, obituary records, and communications with treating physicians. [b]One subject did not qualify for the HC-LT Cohort. This subject was diagnosed with Menkes disease at approximately 4 months of age and survived for less than 2 weeks after diagnosis.

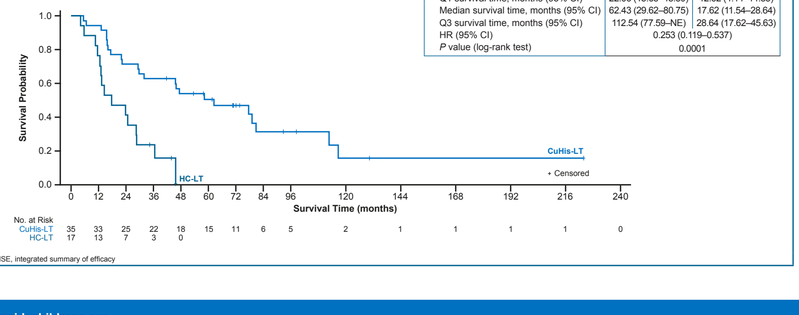
Figure 4. Kaplan-Meier Overall Survival Curve for Early Treatment Cohorts



	CuHis-ET (N=31)	HC-ET (N=18)
Subjects alive, n (%)	16 (51.6)	2 (11.1)
Q1 survival time, months (95% CI)	29.88 (5.75–67.66)	11.54 (3.98–13.28)
Median survival time, months (95% CI)	177.11 (32.98–NE)	16.08 (11.54–28.47)
Q3 survival time, months (95% CI)	183.45 (177.11–NE)	28.64 (17.62–45.63)
HR (95% CI)	0.208 (0.094–0.463)	
P value (log-rank test)	<0.0001	

NE, not estimable; Q1, quarter 1; Q3, quarter 3

Figure 5. Kaplan-Meier Overall Survival Curve for Late Treatment Cohorts (ISE Eligible Population)



	CuHis-LT (N=35)	HC-LT (N=17)
Subjects alive, n (%)	12 (34.3)	2 (11.8)
Q1 survival time, months (95% CI)	22.06 (15.65–45.50)	12.62 (4.14–14.53)
Median survival time, months (95% CI)	62.43 (29.62–80.75)	17.62 (11.54–28.64)
Q3 survival time, months (95% CI)	112.54 (77.59–NE)	28.64 (17.62–45.63)
HR (95% CI)	0.253 (0.119–0.537)	
P value (log-rank test)	0.0001	

ISE, integrated summary of efficacy

Table 2. Summary of TEAEs by System Organ Class and Preferred Term (at Least 10% of Subjects in Any Group; ISS Eligible Population)

System Organ Class Parameter	CuHis-ET and CuHis-LT (N=66) n (%)
Infections	
Pneumonia	20 (30.3)
Upper respiratory tract infection	7 (10.6)
Urinary tract infection	9 (13.6)
Nervous system	
Seizure	14 (21.2)
Gastrointestinal	
Vomiting	7 (10.6)
Renal and urinary	
Bladder diverticulum	8 (12.1)
Metabolism and nutrition	
Dehydration	12 (18.2)
Failure to thrive	11 (16.7)
Investigations	
Diastolic blood pressure decreased	8 (12.1)
Respiratory, thoracic and mediastinal	
Respiratory distress	10 (15.2)
Injury, poisoning and procedural complications	
Rib fracture	7 (10.6)
Musculoskeletal and connective tissue	
Osteopenia	8 (12.1)
Vascular	
Jugular vein distension	8 (12.1)

Conclusions

- CUTX-101 was safe and well tolerated
- In pre-specified primary and secondary efficacy analyses, overall survival was significantly improved in subjects with Menkes disease treated with CUTX-101 compared with untreated subjects
- Clinical benefit with CuHis-ET was greater than CuHis-LT, underscoring the importance of early identification, including newborn screening, and prompt initiation of treatment
- An expanded access program for newly diagnosed patients with Menkes disease is ongoing

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Disclosures

- SGK is first named inventor on PCT/62/244594 and WO2017070472A1 entitled "Codon-optimized reduced size ATP7A cDNA and uses for copper transport disorders" filed by NIH. In 2017, SGK received research funding under a Collaborative Research and Development Award (CRADA) between NIH and Cyprium Therapeutics, Inc., New York, NY. SM, MC, RN, and LSY are employed by Cyprium Therapeutics, Inc

Acknowledgments

- The patients and families who made the study possible
- The study was supported by Cyprium Therapeutics, Inc
- All authors contributed to and approved the presentation; editorial assistance was provided by Spark Medica Inc, funded by Sentynl Therapeutics, Inc

Presented at the American Academy of Pediatrics National Conference & Exhibition, October 8–12, 2021.

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