

CYPRIMUM
THERAPEUTICS

Corporate Presentation
February 2025

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Cyprium Overview

Cyprium Therapeutics is focused on the development of novel therapies for the treatment of Menkes disease, a rare and fatal pediatric condition, and related copper metabolism disorders



AAV-ATP7A

Gene Therapy

- Preclinical; expect to nominate candidate for clinical development in next 12 months
- Granted Orphan Drug Designation from FDA



CUTX-101*

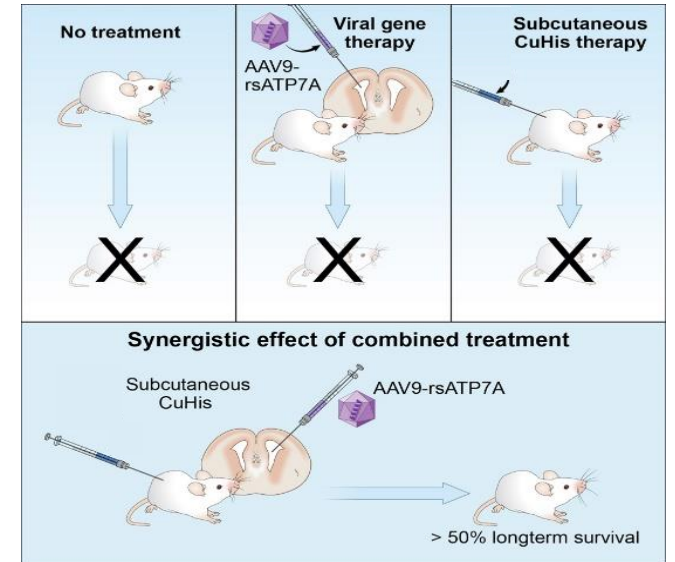
(Copper Histidinate Injection)

- PDUFA target action date of Sept. 30, 2025
- Eligible for Priority Review Voucher worth \$100M+

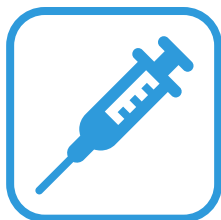
*Cyprium completed Asset Transfer to Sentynl Therapeutics, Inc. in December 2023; Sentynl to complete development of CUTX-101 and responsible for commercialization

AAV-ATP7A Gene Therapy for Menkes Disease

- *Mottled-brindled* mouse model recapitulates the disease phenotype
 - *Atp7a*^{mo-br} phenotype
 - A 6 bp in-frame deletion in exon 11 of *Atp7a*
 - Depigmented coat color and curly whiskers
 - Premature death (~13 days of age)
 - Poor growth; Neurological symptoms
 - Low brain copper; abnormal catecholamine levels
- NICHD developed several constructs for reduced size, codon-optimized AAV-ATP7A gene therapy
- AAV-ATP7A + SC copper histidinate administration led to:
 - Improvements in muscle strength, balance and coordination in preclinical model
 - Improved biochemical phenotype (Cu and catecholamine)
 - Improved survival



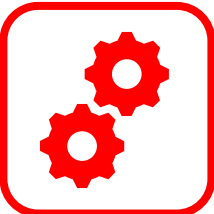



CUTX-101 for Menkes Disease



- **CUTX-101 (Copper Histidinate Injection)** ODD FT RPD BTD OMP
 - NDA accepted and granted priority review by FDA; target PDUFA action date of Sept. 30, 2025
 - Sentyln Therapeutics assumed development from Cyprium in December 2023
 - Sentyln to complete development of CUTX-101 and responsible for commercialization
 - Sentyln also continuing CYP-001 (Intermediate-Size Expanded Access Protocol (NCT04074512)) to provide CUTX-101 for newly diagnosed Menkes disease patients
 - Received \$4.5M milestone; Cyprium remains eligible to receive royalties and up to \$129M in aggregate development and sales milestones
 - Cyprium retains 100% ownership over any FDA Priority Review Voucher (PRV) that may be issued
 - Previously reported positive topline clinical efficacy data showed a nearly 80% reduction in the risk of death (Hazard Ratio = 0.21, $p < 0.0001$)
 - FDA granted Breakthrough Therapy, Orphan Drug, Fast Track, and Rare Pediatric Disease Designations

Copper is Required in Human Development and Health

	Biological Functions	Copper Containing Proteins
	Brain Development	
	Catecholamine production	Dopamine β -hydroxylase
	Mitochondrial respiration	Cytochrome C oxidase
	Iron and copper transport	Ceruloplasmin
	Peptide amidation	Peptidylglycine α -amidating monooxygenase
	Antioxidant defense	Superoxide dismutase
	Connective tissue formation	Lysyl oxidase
	Pigment formation	Tyrosinase

Source: de Bie, et al, 2007

Menkes Disease is a Rare Pediatric Disease Causing a Disorder of Copper Metabolism

Menkes Disease

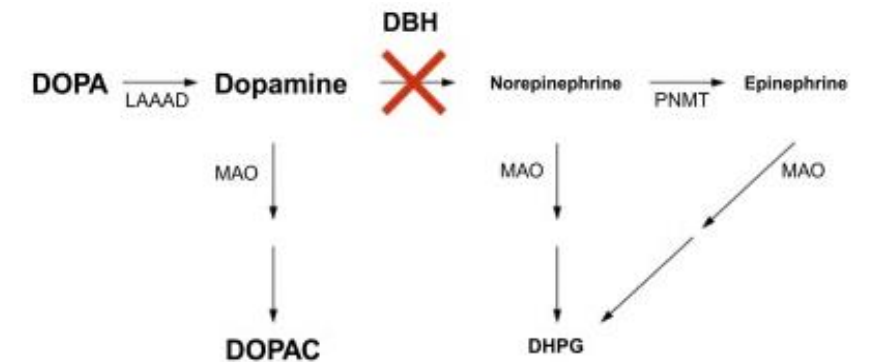
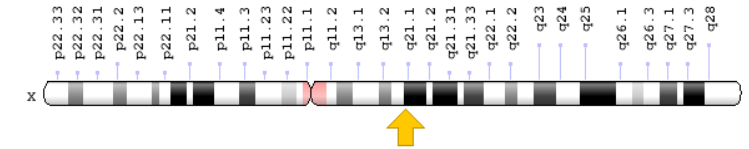
- First described by Dr. John Menkes in 1962
- X-linked recessive disease: affecting mostly boys
- Minimum birth prevalence for Menkes disease believed to be 1 in 34,810 live male births, but could potentially be as high as 1 in 8,664 live male births, higher than previously recognized
- Disorder of copper metabolism caused by mutations in the Copper transporter ATP7A
- **If untreated, premature death in under 2 years**

Distinctive clinical phenotypes

- Sparse, depigmented hair (“kinky hair”)
- Onset of neurologic symptoms: seizures, hypotonia, and developmental delays
- Failure to thrive
- Connective tissue problems

Diagnosis

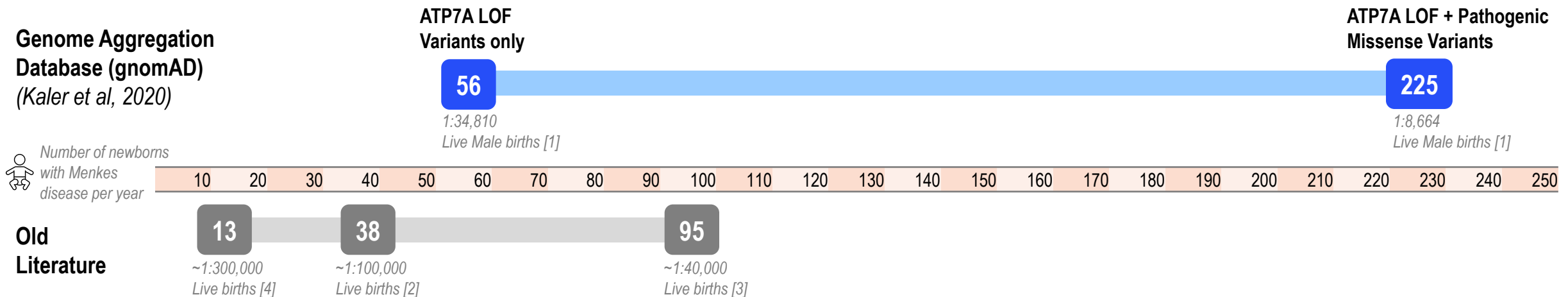
- Low serum copper and ceruloplasmin levels
- Abnormal catecholamine levels
- ATP7A gene sequencing confirmation



Menkes Disease is Under-estimated and Under-diagnosed

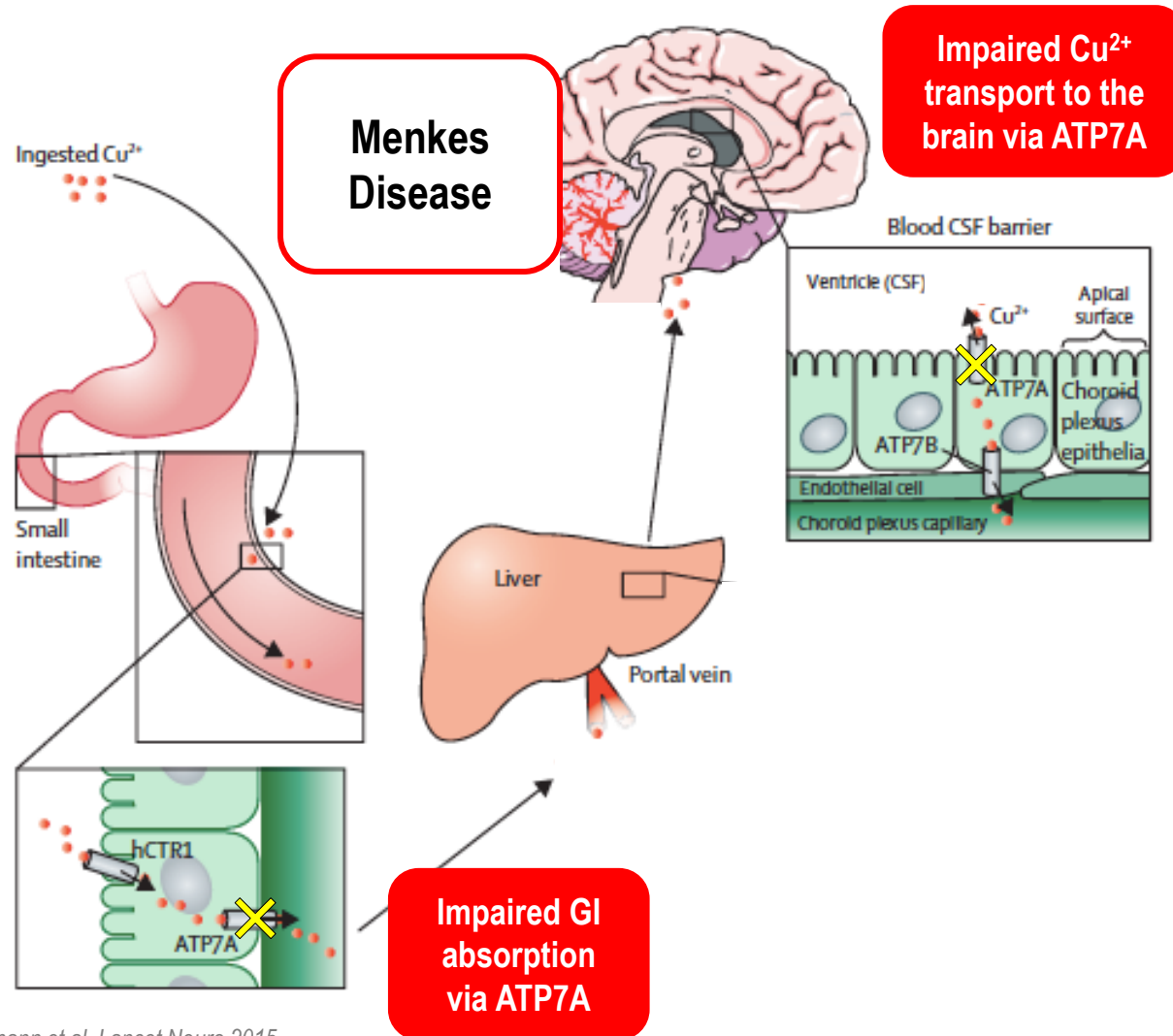
New study estimated birth prevalence of Menkes disease based on the Genome Aggregation Database

- Accessed Genome Aggregation Database (gnomAD) at MIT/Broad Institute → over 200,000 ATP7A alleles
- Identified 1,106 ATP7A variants
 - 4 Loss-of-Function (LOF) variants → 4 alleles → 1:34,810 live male births → **56 patients per year**
 - 28 potentially pathogenic missense variants (PolyPhen-2) → 12 alleles with high confidence (REVEL >0.85)
 - Including both LOF and pathogenic missense variants → 1:8,664 live male births → **225 patients per year**
- Newborn screening (NBS) will likely increase the number of Menkes disease patients identified for early diagnosis and treatment with CUTX-101



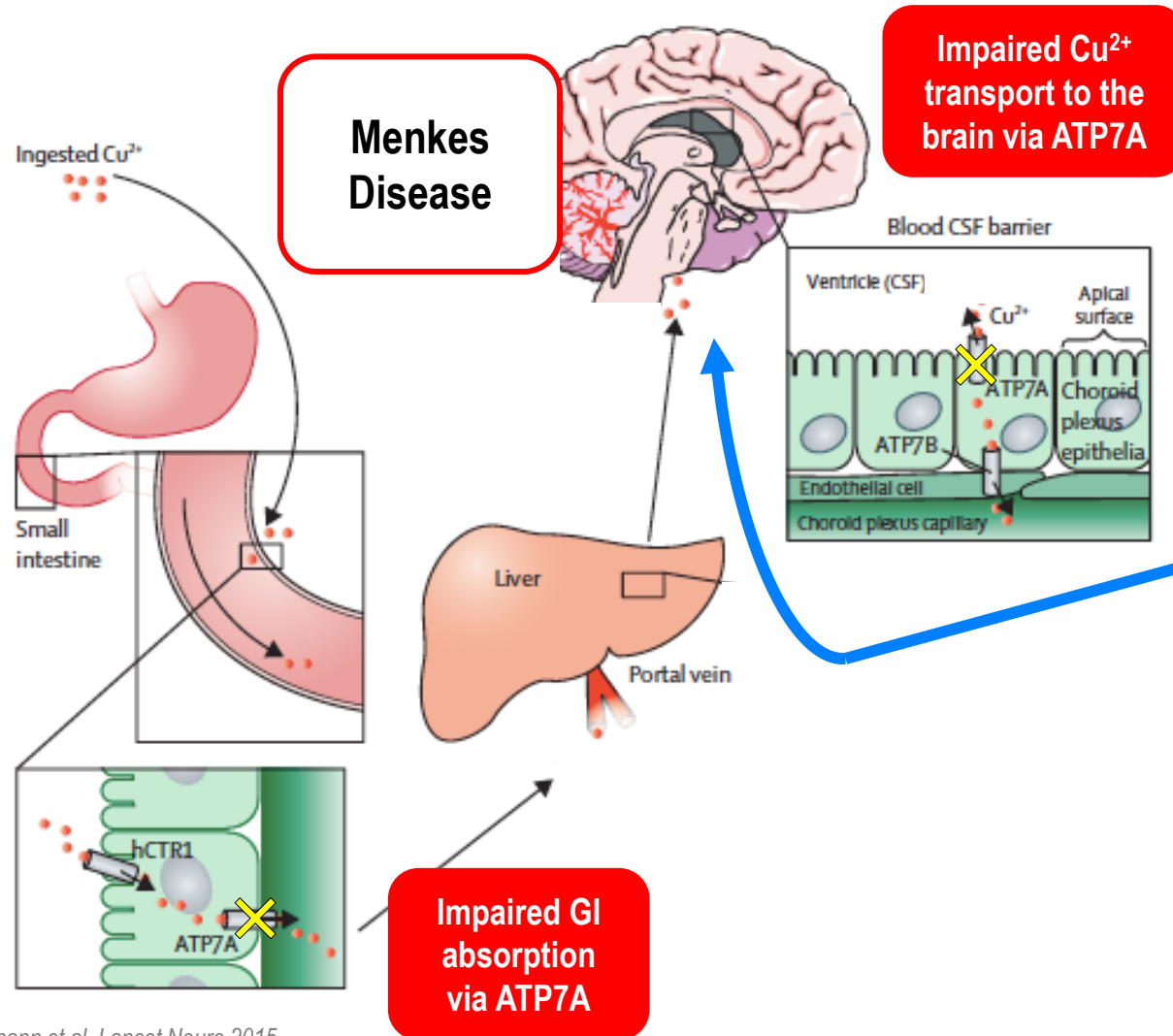
References: [1] Kaler, et al, 2020; [2] Kaler, SG, 1998; [3] Danks DM, 1971; [4] Tonnesen et al 1991

Copper Transport is Impaired in Menkes Disease



Adapted from: Bandmann et al, Lancet Neuro 2015

Therapeutic Strategy for Menkes Disease: CUTX-101 (Copper Histidinate)



1

CUTX-101 Copper Histidinate (CuHis)

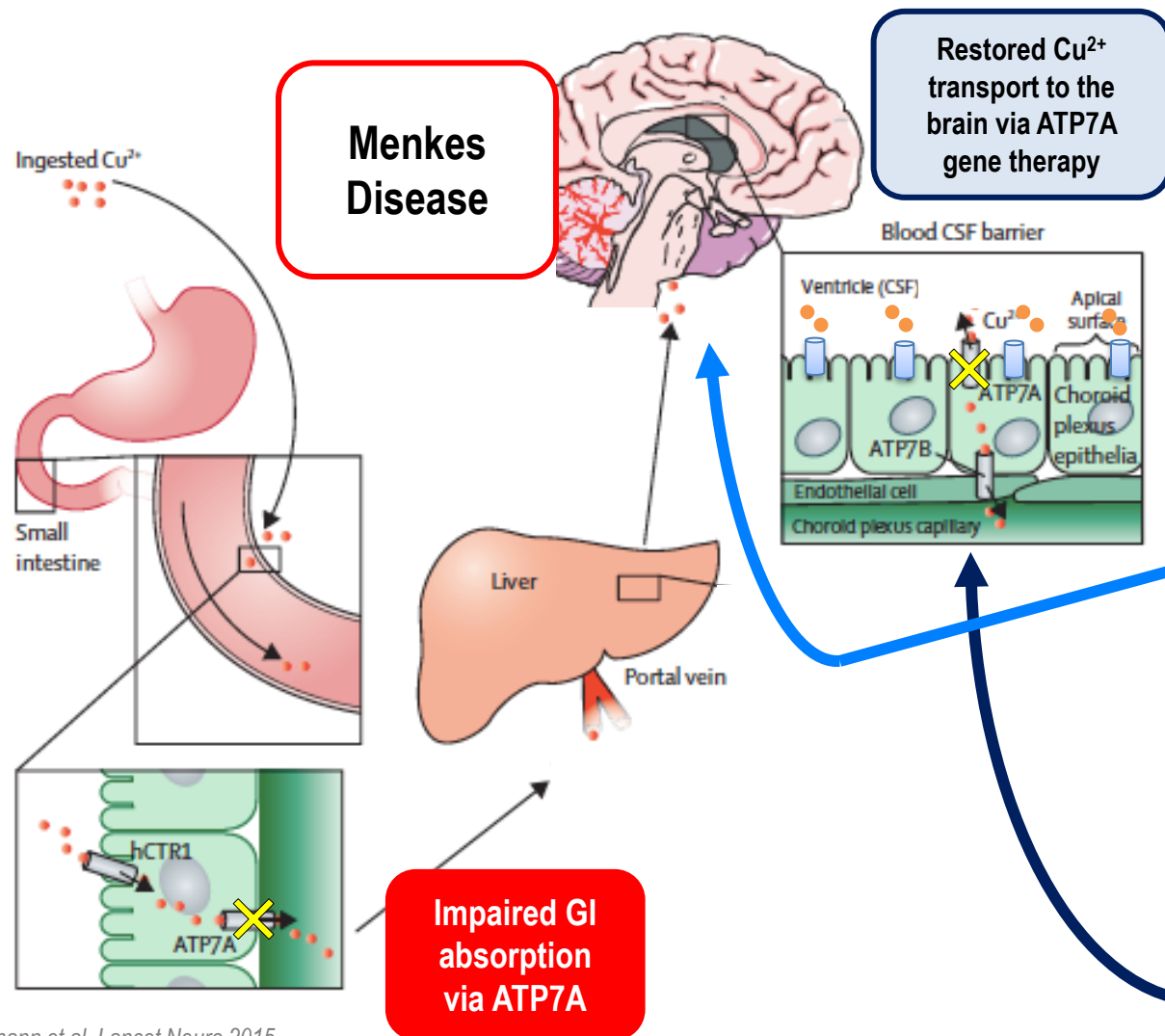
SC injection to replenish CuHis

- Bypass GI absorption of Cu^{2+} (impaired in Menkes patients)
- Better tolerability (pH 7.4)
- May not be sufficient alone in some Menkes patients

◆ NDA accepted and granted priority review by the FDA; target PDUFA action date of September 30, 2025

- ◆ Positive topline clinical efficacy data
- ◆ Expanded Access protocol ongoing

Therapeutic Strategy for Menkes Disease: CUTX-101 (Copper Histidinate) + AAV-ATP7A Gene Therapy



1

CUTX-101 Copper Histidinate

SC injection to replenish CuHis

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2

AAV-ATP7A Gene Therapy

- Codon-optimized reduced-sized ATP7A to be delivered via AAV vector
- May restore Cu^{2+} transport
- Co-administration with CUTX-101 injections

Preclinical

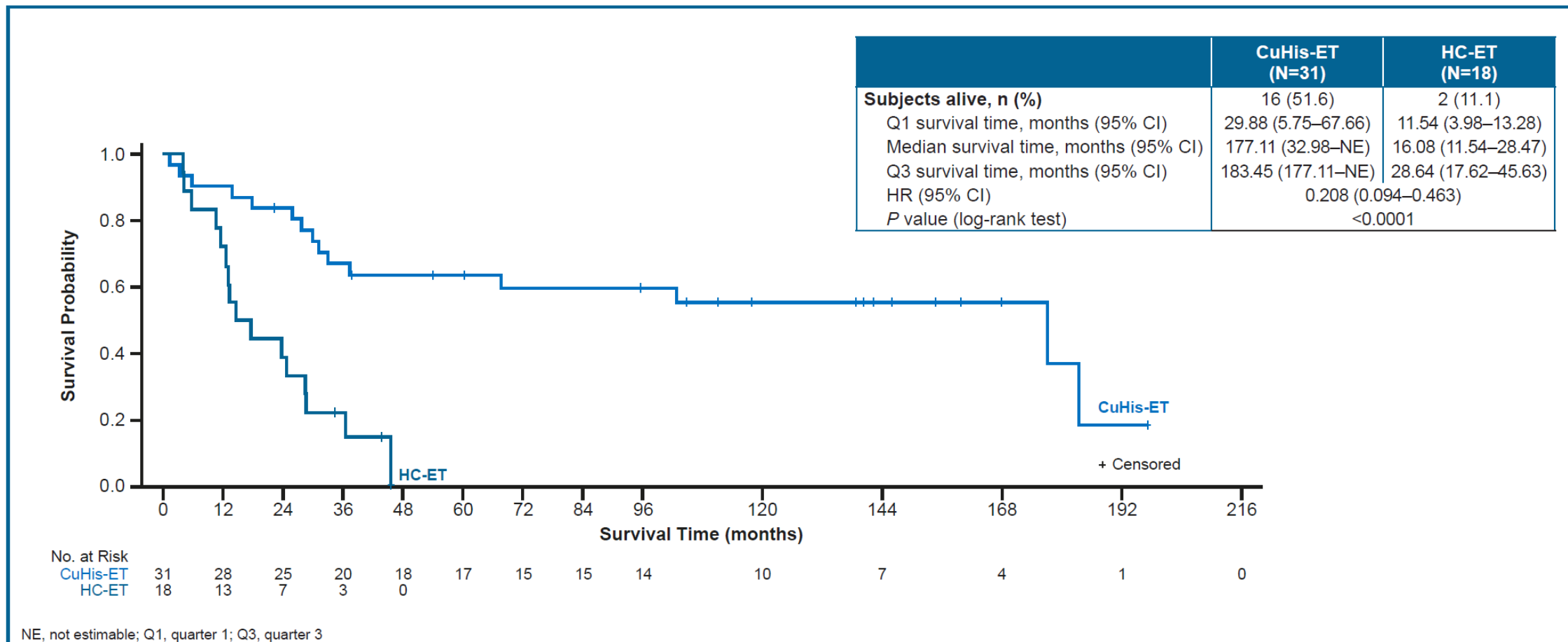
Compelling Top-Line Clinical Efficacy Data for CUTX-101

	Early-Treatment (ET) Cohort		Late-Treatment (LT) Cohort	
	CuHis-ET (n=31)	Historical Control (HC-ET) (n=18)	CuHis-LT (n=35)	Historical Control (HC-LT) (n=17)
Median Overall Survival	14.8 years (177.1 months)	1.3 years (15.9 months)	5.2 years (62.4 months)	1.5 years (17.6 months)
Hazard Ratio (95% CI)	0.208 (0.094, 0.463)		0.253 (0.119, 0.537)	
p-value	<0.0001		<0.0001	
Reduction in Risk of Death	79%		75%	

- CUTX-101 showed significant clinical benefit in both CuHis-ET and CuHis-LT cohorts, with 75-79% reduction in risk of death compared to untreated Historical Control (HC-ET and HC-LT) arms, and increase in Median OS from 1.3 years to 14.8 years in the ET cohort

*Early-treatment cohort: initiated treatment with CUTX-101 within 4 weeks of age
Data presented as a virtual poster at the 2021 American Academy of Pediatrics (AAP) National Conference & Exhibition:
Kaler SG, et al, Copper Histidinate Treatment for Menkes Disease (Kinky Hair Syndrome)*

Kaplan-Meier Overall Survival Curves for Early Treatment Cohorts



- Data presented as a virtual poster at the 2021 American Academy of Pediatrics (AAP) National Conference & Exhibition: Kaler SG, et al, Copper Histidinate Treatment for Menkes Disease (Kinky Hair Syndrome)

Thank you!

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