

**CYPRIMUM**  
THERAPEUTICS

**Corporate Presentation**

May 2025

# Forward Looking Statements

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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\*

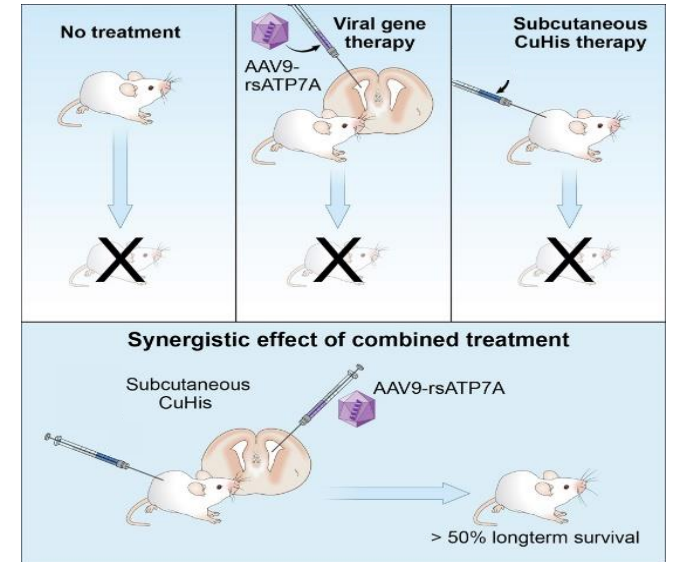
(Copper Histidinate Injection)

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

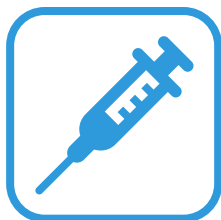
\*Cyprium completed Asset Transfer to Sentyln Therapeutics, Inc. in December 2023; Sentyln to complete development of CUTX-101 and responsible for commercialization

# 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



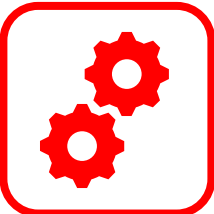



# CUTX-101 for Menkes Disease



- **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
  - Sentynl Therapeutics assumed development from Cyprium in December 2023
    - Sentynl to complete development of CUTX-101 and responsible for commercialization
    - Sentynl 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
	<b>Brain Development</b>	
	Catecholamine production	Dopamine $\beta$ -hydroxylase
	Mitochondrial respiration	Cytochrome C oxidase
	Iron and copper transport	Ceruloplasmin
	Peptide amidation	Peptidylglycine $\alpha$ -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

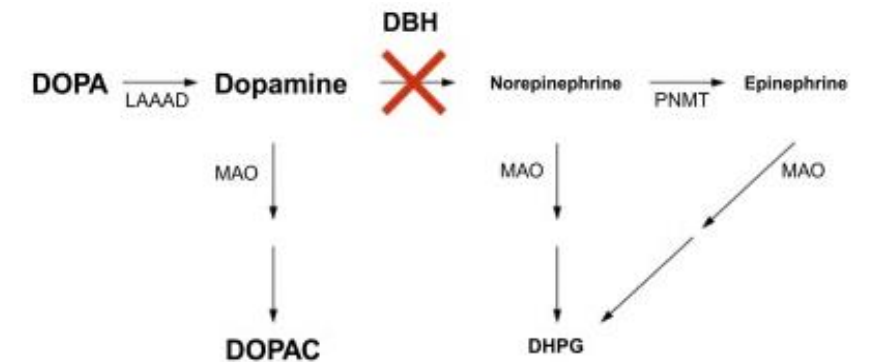
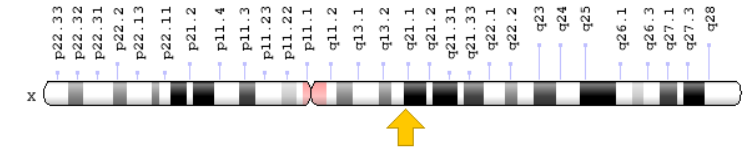
- First described by Dr. John Menkes in 1962
- X-linked recessive disease: affecting mostly boys
- Minimum birth prevalence for Menkes disease believed to be 1 in 34,810 live male births, but could potentially be as high as 1 in 8,664 live male births, higher than previously recognized
- Disorder of 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

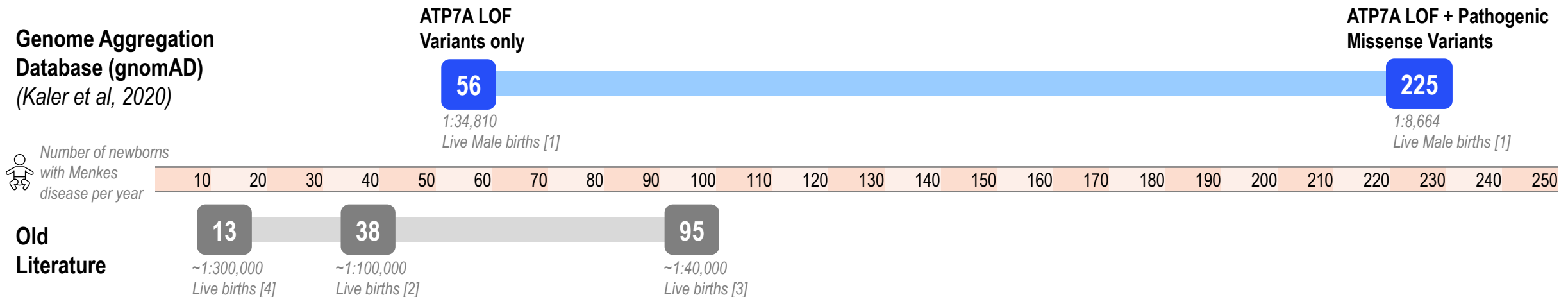




# Menkes Disease is Under-estimated and Under-diagnosed

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

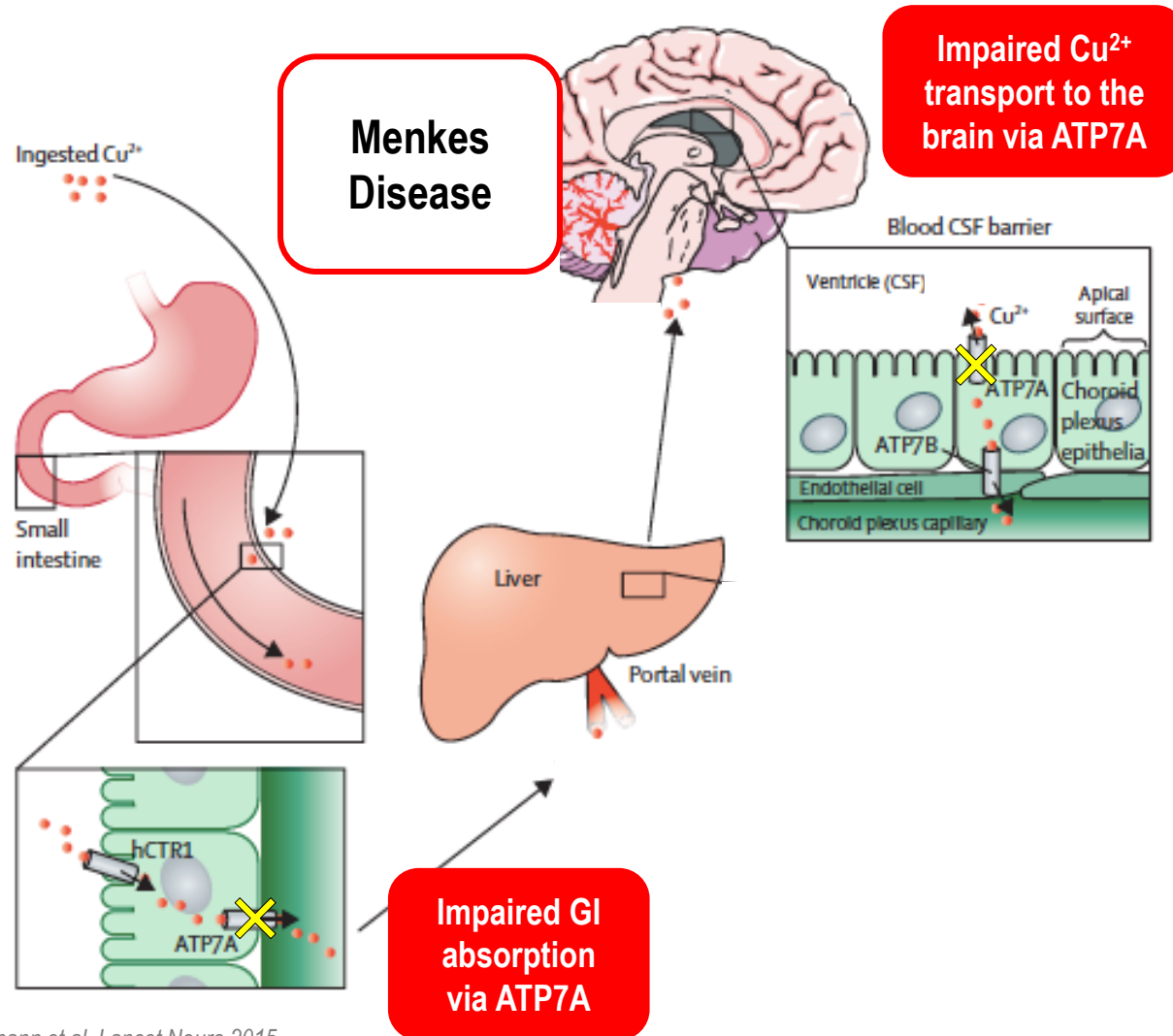
- Accessed Genome Aggregation Database (gnomAD) at MIT/Broad Institute → over 200,000 ATP7A alleles
- Identified 1,106 ATP7A variants
  - 4 Loss-of-Function (LOF) variants → 4 alleles → 1:34,810 live male births → **56 patients per year**
  - 28 potentially pathogenic missense variants (PolyPhen-2) → 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

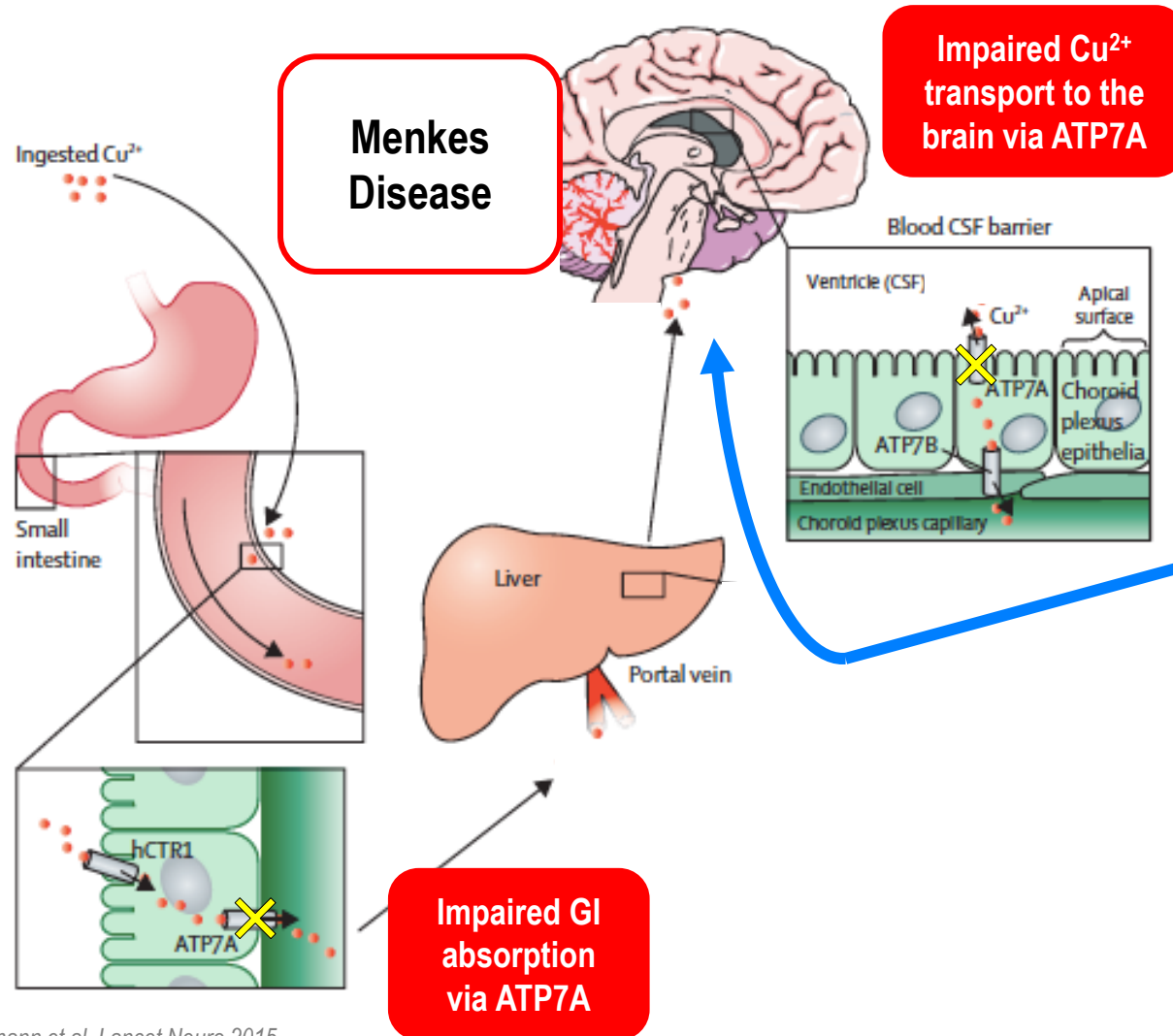


# Copper Transport is Impaired in Menkes Disease



Adapted from: Bandmann et al, *Lancet Neuro* 2015

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



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## CUTX-101 Copper Histidinate (CuHis)

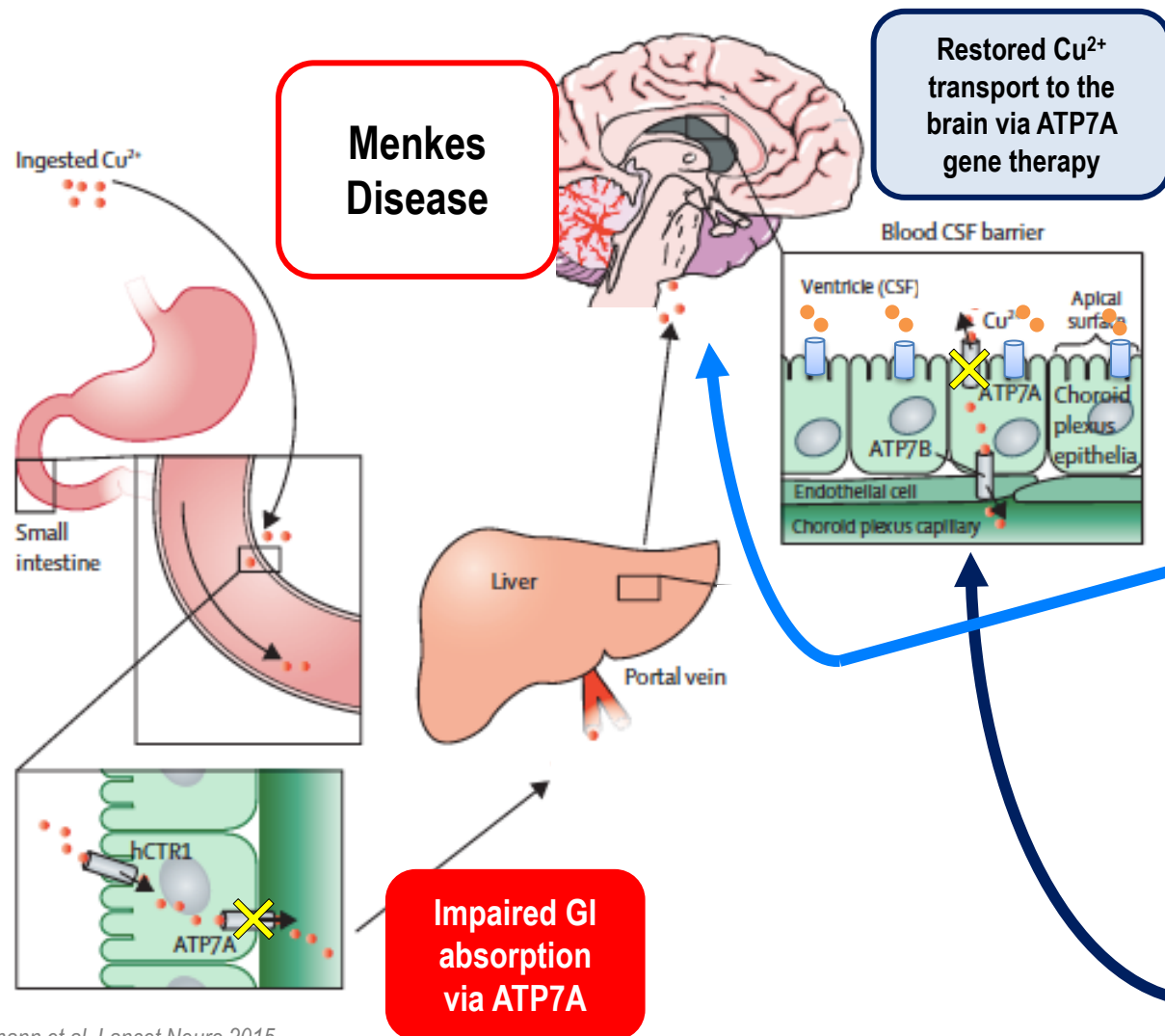
SC injection to replenish CuHis

- Bypass GI absorption of  $\text{Cu}^{2+}$  (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  $\text{Cu}^{2+}$  transport
- Co-administration with CUTX-101 injections

Preclinical

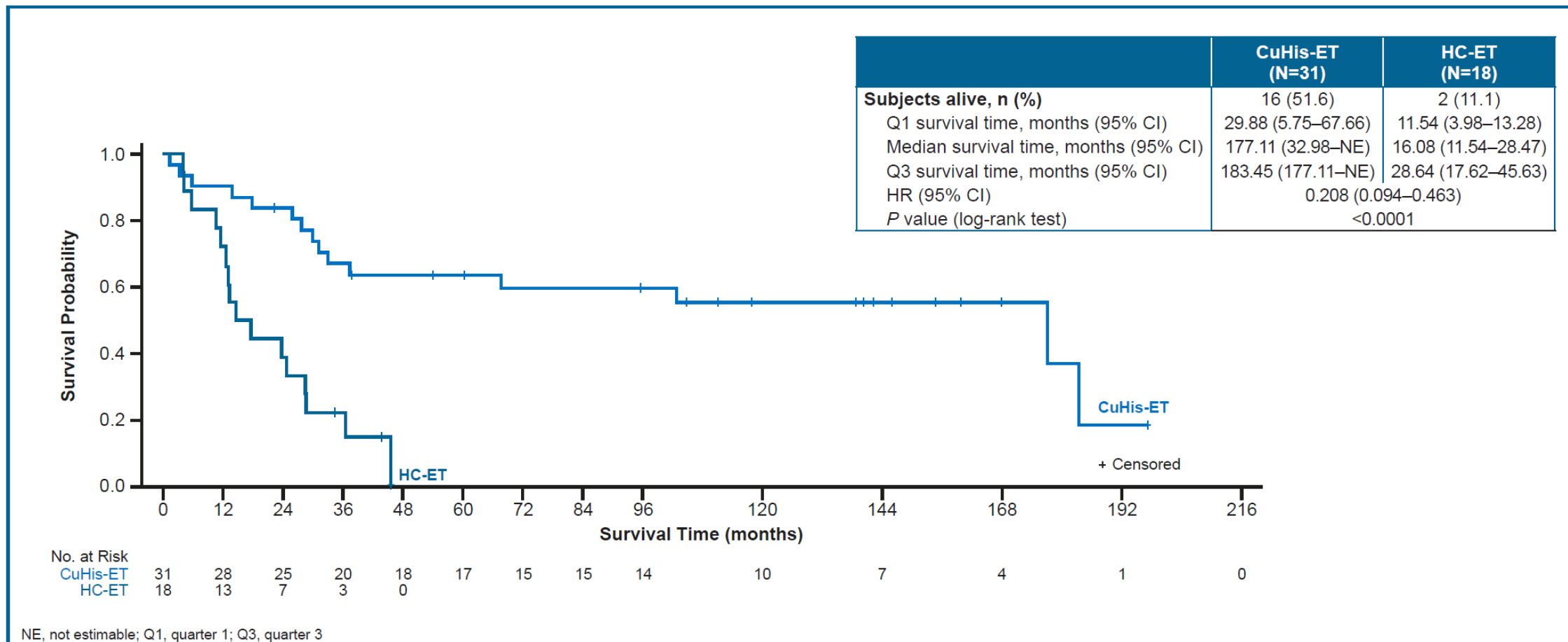
# Compelling Top-Line Clinical Efficacy Data for CUTX-101

	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)
<b>Median Overall Survival</b>	<b>14.8 years</b> <b>(177.1 months)</b>	1.3 years (15.9 months)	<b>5.2 years</b> <b>(62.4 months)</b>	1.5 years (17.6 months)
<b>Hazard Ratio (95% CI)</b>	<b>0.208</b> <b>(0.094, 0.463)</b>		<b>0.253</b> <b>(0.119, 0.537)</b>	
<b>p-value</b>	<b>&lt;0.0001</b>		<b>&lt;0.0001</b>	
<b>Reduction in Risk of Death</b>	<b>79%</b>		<b>75%</b>	

- 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)

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# Thank you!

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