



**CYPRIMUM**  
THERAPEUTICS

**Corporate Presentation**  
February 2024

## ► Forward Looking Statements

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# ► Company Highlights

- **Cyprium Therapeutics** is a rare disease company with a focus on the development and commercialization of novel therapies for Menkes disease, a rare and fatal pediatric disease in copper metabolism.



- **AAV-ATP7A Gene Therapy** ODD





- Preclinical and has been granted Orphan Drug Designation from FDA
- **Expects to nominate candidate for clinical development in 2024**



- **CUTX-101 (Copper Histidinate Injection)** ODD FT RPD BTD OMP

- **Cyprium completed Asset Transfer to Sentynl Therapeutics, Inc. in December 2023**
  - Sentynl to complete development of CUTX-101 and responsible for commercialization
  - Sentynl also continues 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**
- **Rolling NDA submission expected to complete in 2024**
- 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; Image source: freepik.com

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

## Menkes Disease

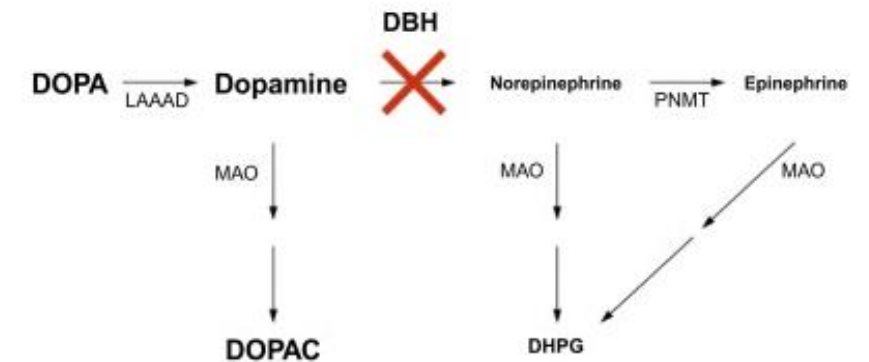
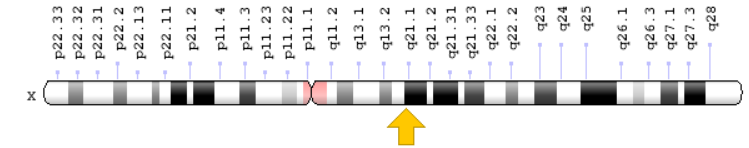
- First described by Dr. John Menkes in 1962
- X-linked recessive disease: affecting mostly boys
- Minimum birth prevalence for Menkes disease believed to be 1 in 34,810 live male births, but could potentially be as high as 1 in 8,664 live male births, higher than previously recognized
- Disorder of copper metabolism caused by mutations in the Copper transporter ATP7A
- **If untreated, premature death ~ 3 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

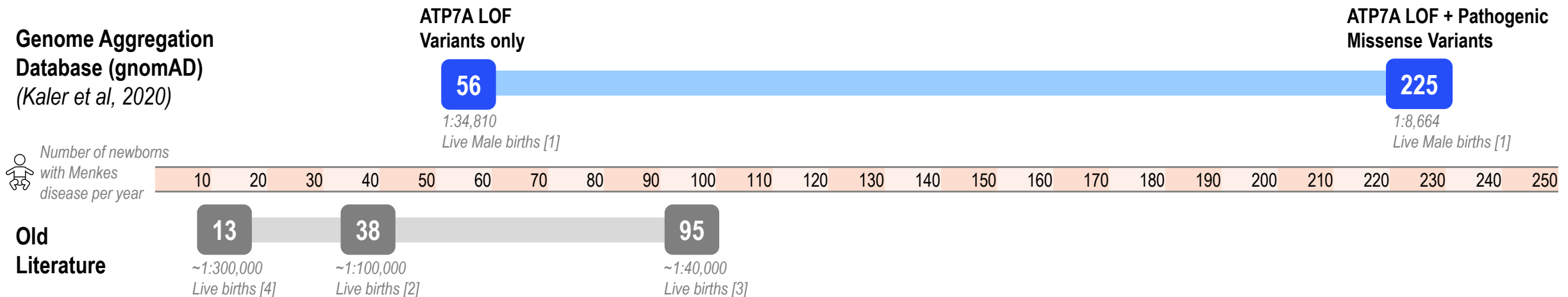
- Low serum copper and ceruloplasmin levels
- Abnormal catecholamine levels
- ATP7A gene sequencing confirmation



# ▶ 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 and allow 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

# Potentials of gnomAD and Newborn Screening to Discover More Patients in Rare Pediatric Diseases

- Kaler 2020 study applied the same approach to a different X-linked recessive disorder, Duchenne Muscular Dystrophy (DMD), for which incidence data are better established due to longer lifespan.
- Analysis of gnomAD database entries for the DMD locus indicated 19 unequivocally loss-of-function alleles out of a total of 204,738 sequenced → predicted birth prevalence of DMD equals 1 in 7,246 live male births, in reasonable agreement with population-based estimates (1 in 5,000 newborn males) [1]
- Newborn screening detected a higher than previously estimated prevalence:
  - **Fabry Disease:** 1 in 8,454 in NBS [2] vs 1 in 40,000 to 60,000 males [3]
  - **Pompe Disease:** 1 in 21,979 in NBS [2] vs 1 in 40,000 births [4]

## References:

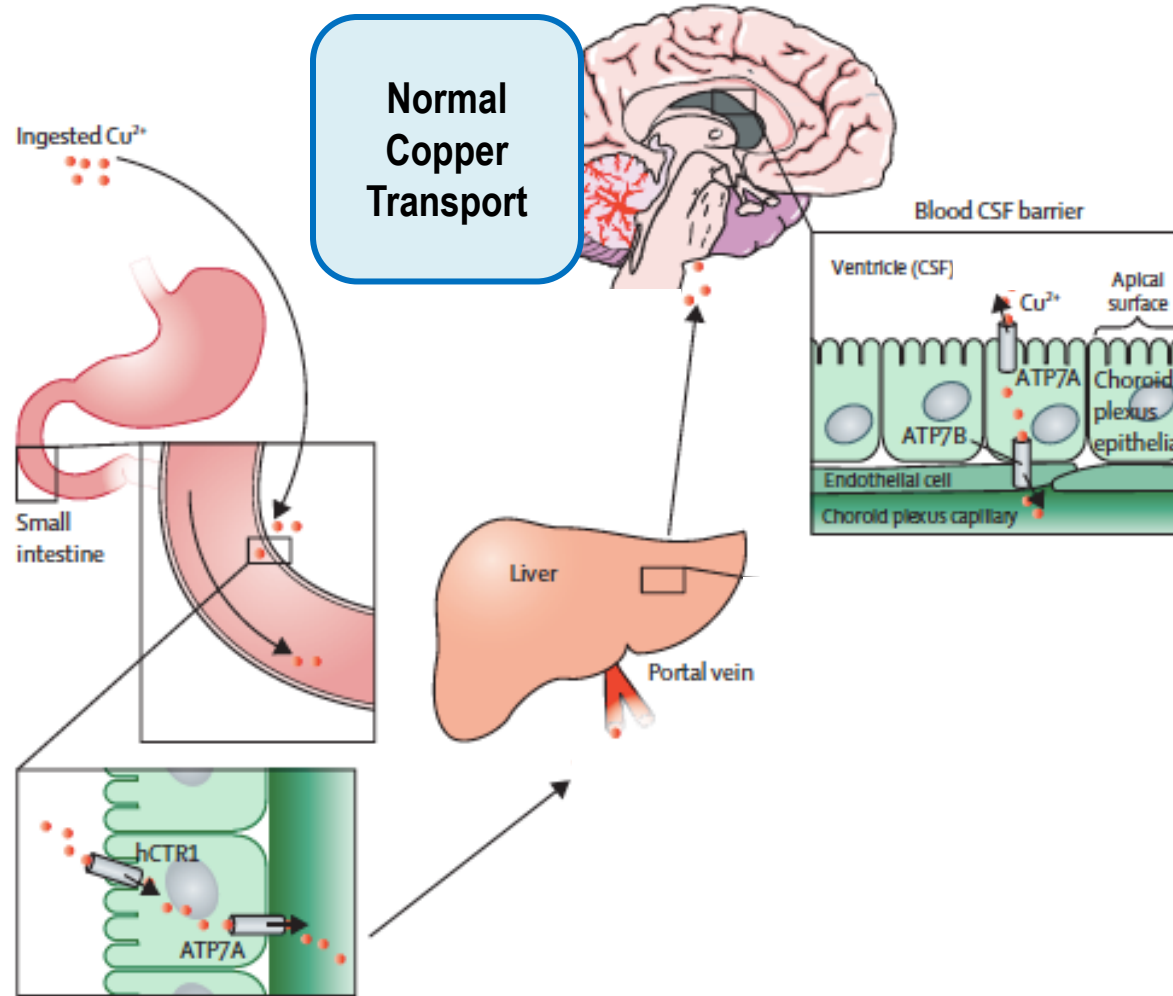
[1] Kaler, et al, 2020

[2] Burton et al, 2017

[3] <https://rarediseases.org/rare-diseases/fabry-disease/>

[4] <https://rarediseases.org/rare-diseases/pompe-disease/>

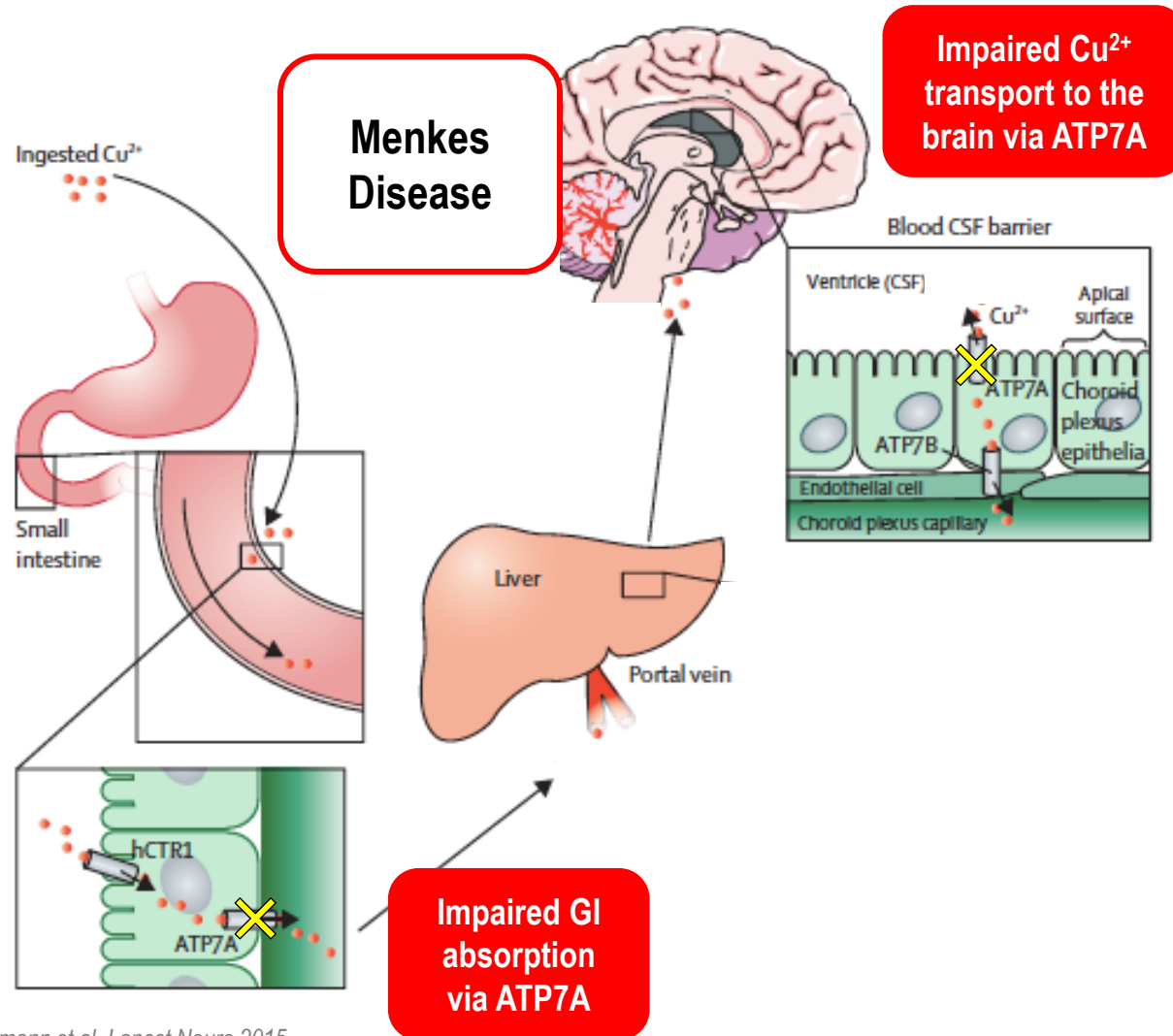
# ▶ ATP7A is Critical for Copper Transport to the Brain & GI



Adapted from: Bandmann et al, Lancet Neuro 2015

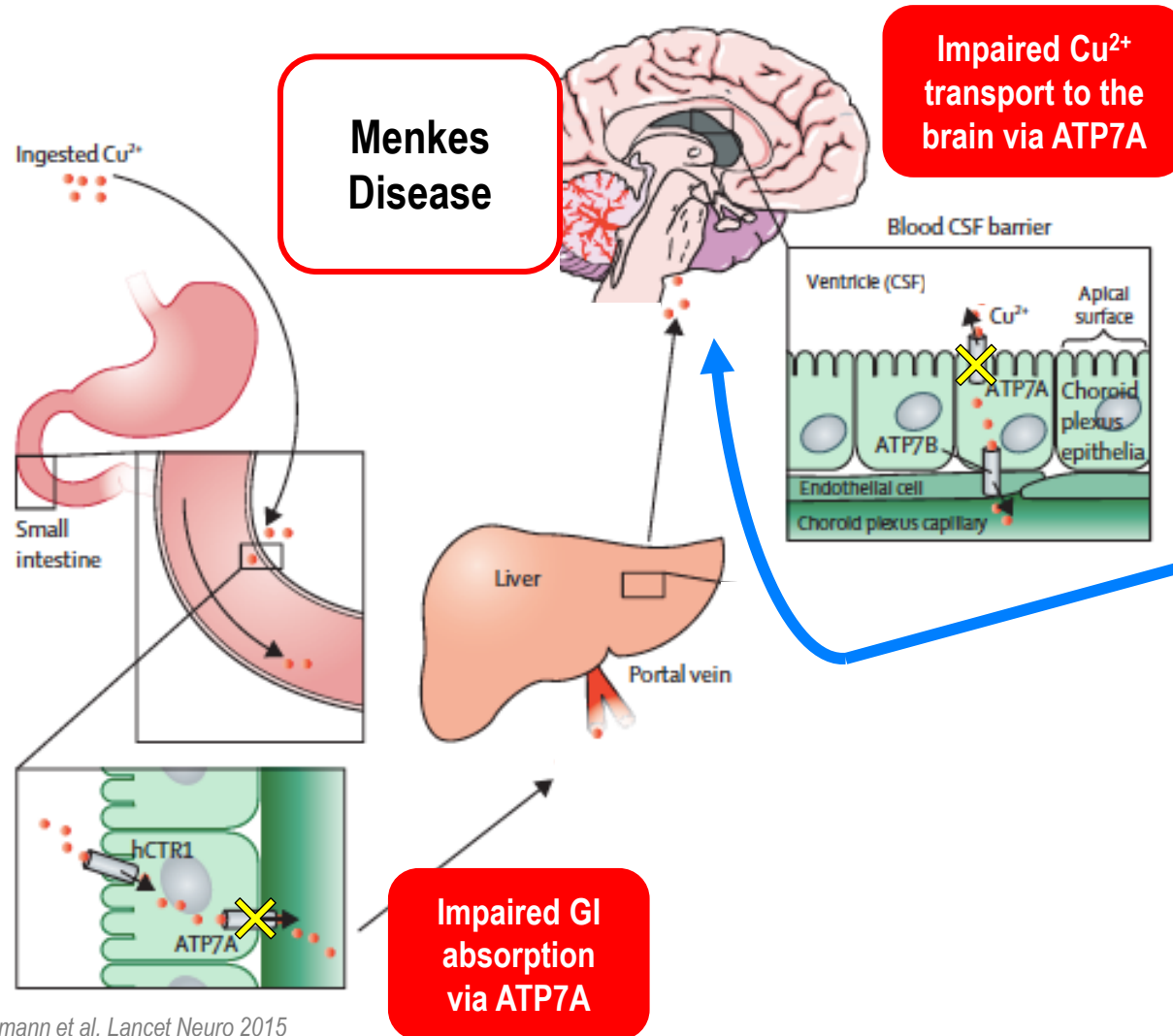


# ▶ Copper Transport is impaired in Menkes Disease



Adapted from: Bandmann et al, Lancet Neuro 2015

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



1

## CUTX-101 Copper Histidinate [1]

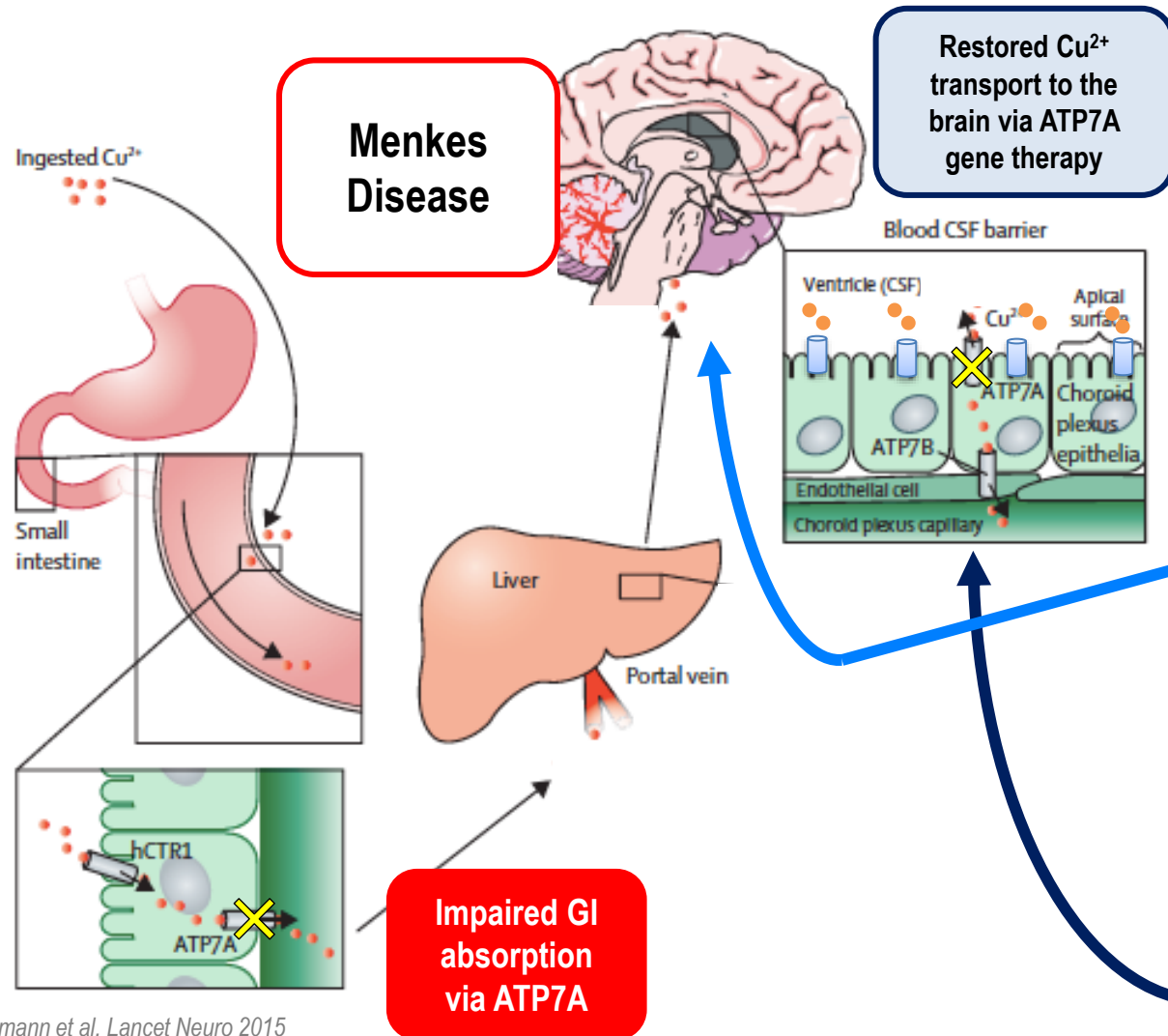
- SC injection to replenish CuHis
- Bypass GI absorption of  $\text{Cu}^{2+}$  (impaired in Menkes patients)
- Better tolerability (pH 7.4)
- May not be sufficient alone in some Menkes patients

- ◆ Positive topline clinical efficacy data
- ◆ Rolling NDA Submission ongoing
- ◆ Expanded Access protocol ongoing

Adapted from: Bandmann et al, Lancet Neuro 2015

[1] Cyprrium completed Asset Transfer to Sentyln Therapeutics in December 2023

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



1

## CUTX-101 Copper Histidinate [1]

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2

## AAV-ATP7A Gene Therapy

- Codon-optimized reduced-sized ATP7A to be delivered via AAV vector (Preclinical)
- May restore  $\text{Cu}^{2+}$  transport
- Will need CUTX-101 injections

Preclinical

Adapted from: Bandmann et al, Lancet Neuro 2015

[1] Cyprrium completed Asset Transfer to Sentyln Therapeutics in December 2023

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

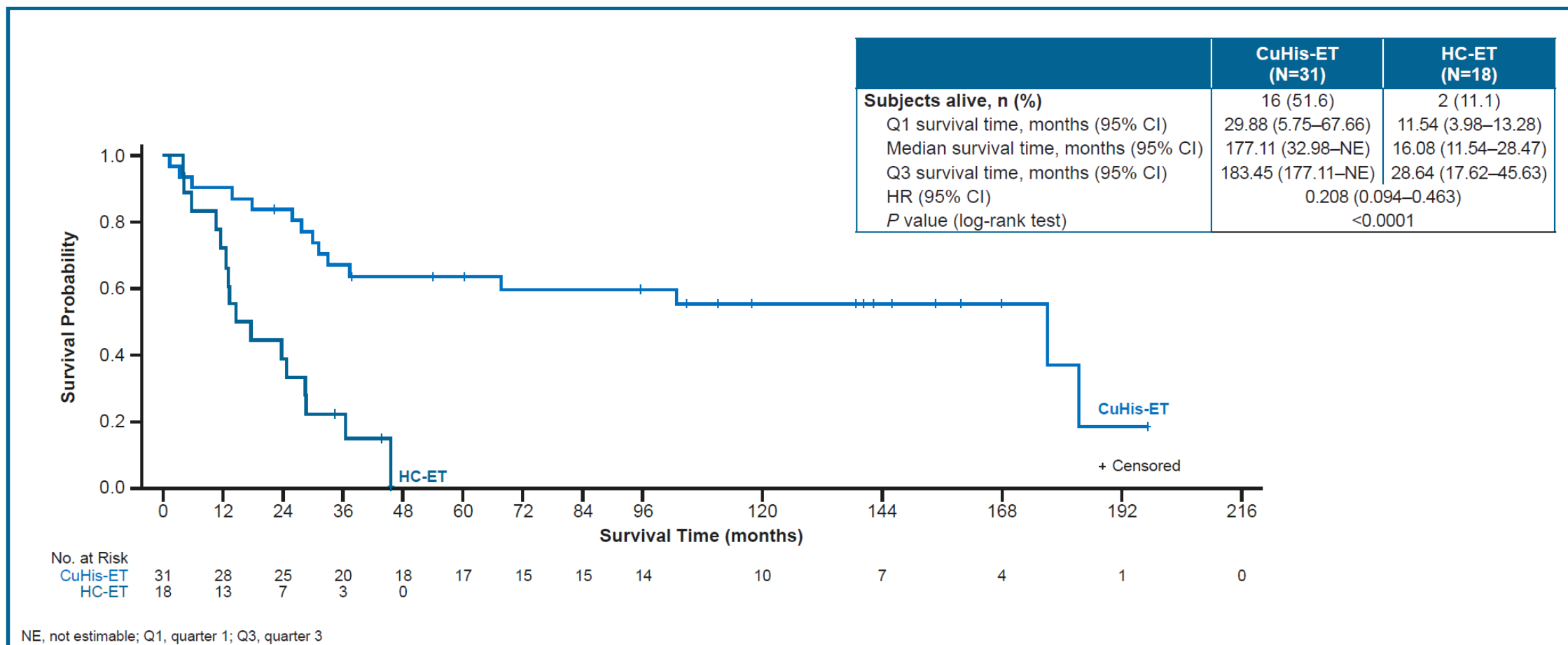
	Early-Treatment (ET) Cohort		Late-Treatment (LT) Cohort	
	CuHis-ET (n=31)	Historical Control (HC-ET) (n=18)	CuHis-LT (n=35)	Historical Control (HC-LT) (n=17)
<b>Median Overall Survival</b>	<b>14.8 years</b> <b>(177.1 months)</b>	1.3 years (15.9 months)	<b>5.2 years</b> <b>(62.4 months)</b>	1.5 years (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
- Newborn screening will be key to allow early diagnosis of Menkes disease and treatment with CUTX-101

*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)*

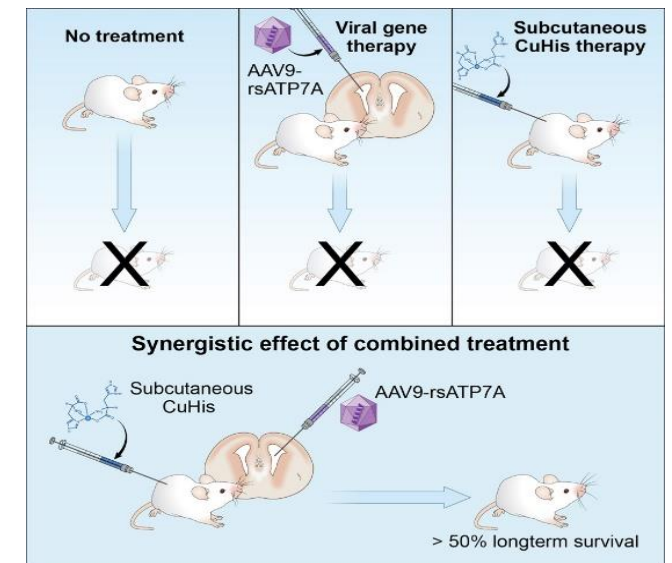
# Kaplan-Meier Overall Survival Curves for Early Treatment Cohorts



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

# ▶ AAV-ATP7A Gene Therapy for Menkes Disease

- *Mottled – brindled* mouse model recapitulates the disease phenotype
  - *Atp7a*<sup>mo-br</sup> 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 has developed several constructs for reduced size, codon-optimized AAV-ATP7A gene therapy
- AAV-ATP7A + SC CuHis administration led to:
  - Improvements in muscle strength, balance and coordination in preclinical model
  - Improved biochemical phenotype (Cu and catecholamine)
  - Improved survival



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# Thank you!

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