

**CYPRIMUM**  
THERAPEUTICS

**Corporate Presentation**

March 2026

# 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

## ZYCUBO®

(Copper Histidinate Injection)

- NDA approved January 2026
- FDA granted RPD Priority Review Voucher (PRV) – entered into agreement to sell PRV for \$205M

## AAV-ATP7A

Gene Therapy

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

*\*Cyprium completed Asset Transfer to Sentynl Therapeutics, Inc. in December 2023; Sentynl is responsible for the commercialization of ZYCUBO.*

*Please refer to the U.S. Prescribing Information including Instructions for Use (IFU) for ZYCUBO for additional details on the product including safety.*

# ZYCUBO<sup>®</sup> for Menkes Disease (marketed by Sentynt)



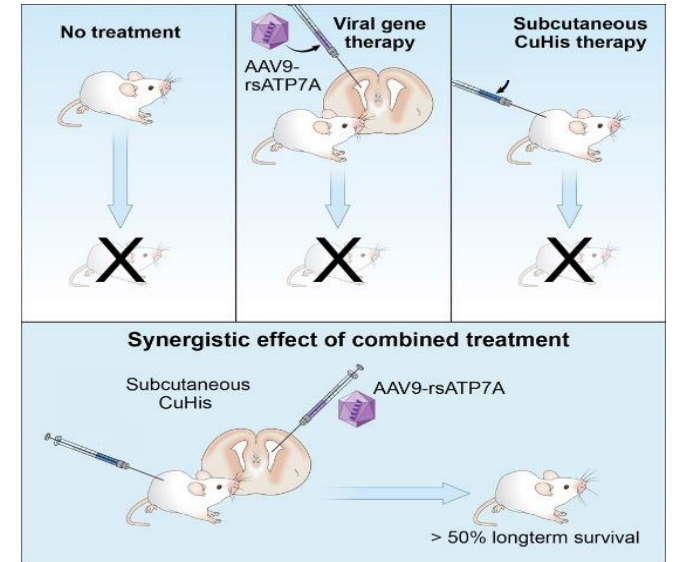
- **ZYCUBO (Copper Histidinate Injection, formerly CUTX-101)**

- NDA approved January 2026
  - FDA granted Priority Review Voucher (PRV) at approval; Sentynt transferred PRV to Cyprium
  - Cyprium entered into an agreement to sell the PRV for \$205M, subject to closing conditions
- Sentynt Therapeutics assumed development from Cyprium in December 2023
  - Sentynt responsible for commercialization of ZYCUBO
- Cyprium eligible to receive tiered royalties on net sales and up to \$129M in aggregate development and sales milestones
- FDA granted Breakthrough Therapy, Orphan Drug, Fast Track, and Rare Pediatric Disease Designations
- European Medicines Agency granted Orphan designation



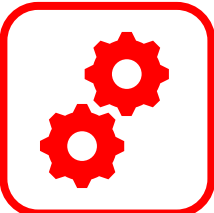



# AAV-ATP7A Gene Therapy for Menkes Disease

- *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 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



# 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

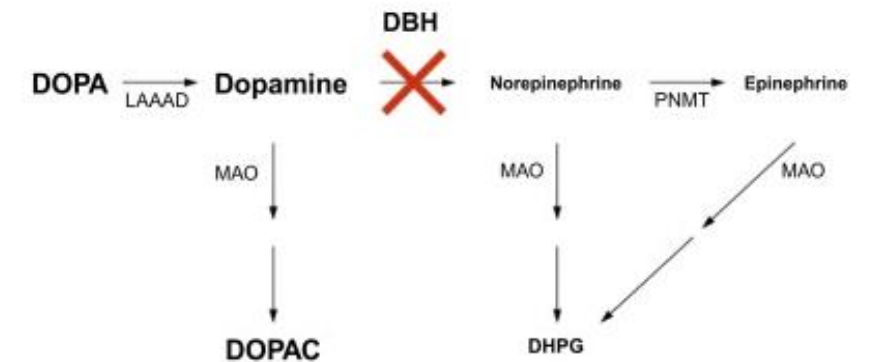
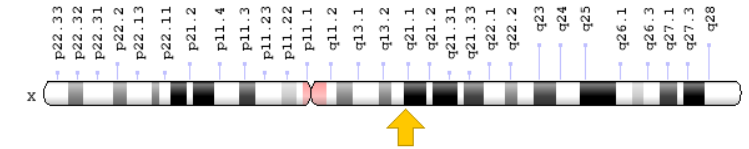
- First described by Dr. John Menkes in 1962
- X-linked recessive disease: affecting mostly boys
- Minimum birth prevalence for Menkes disease believed to be 1 in 34,810 live male births, but could potentially be as high as 1 in 8,664 live male births, higher than previously recognized
- Disorder of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

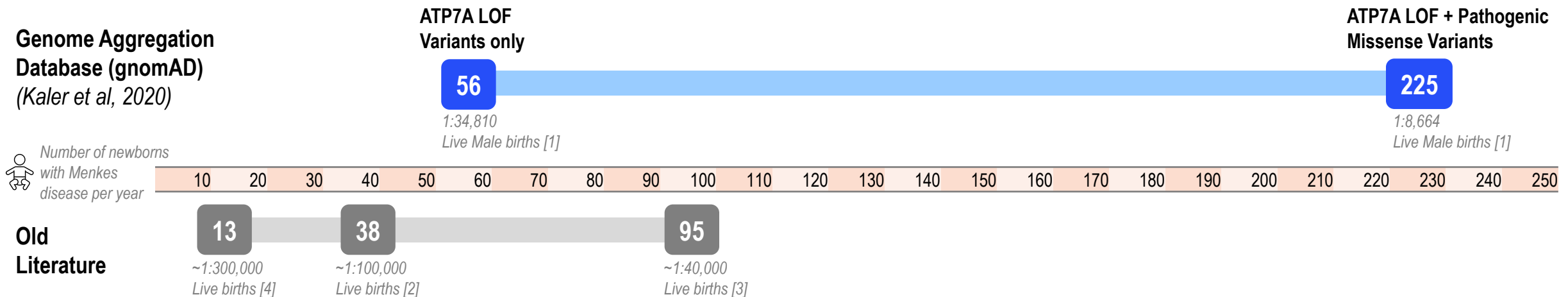
- Low serum copper and ceruloplasmin levels
- Abnormal catecholamine levels
- ATP7A gene sequencing confirmation



# Menkes Disease is Under-estimated and Under-diagnosed

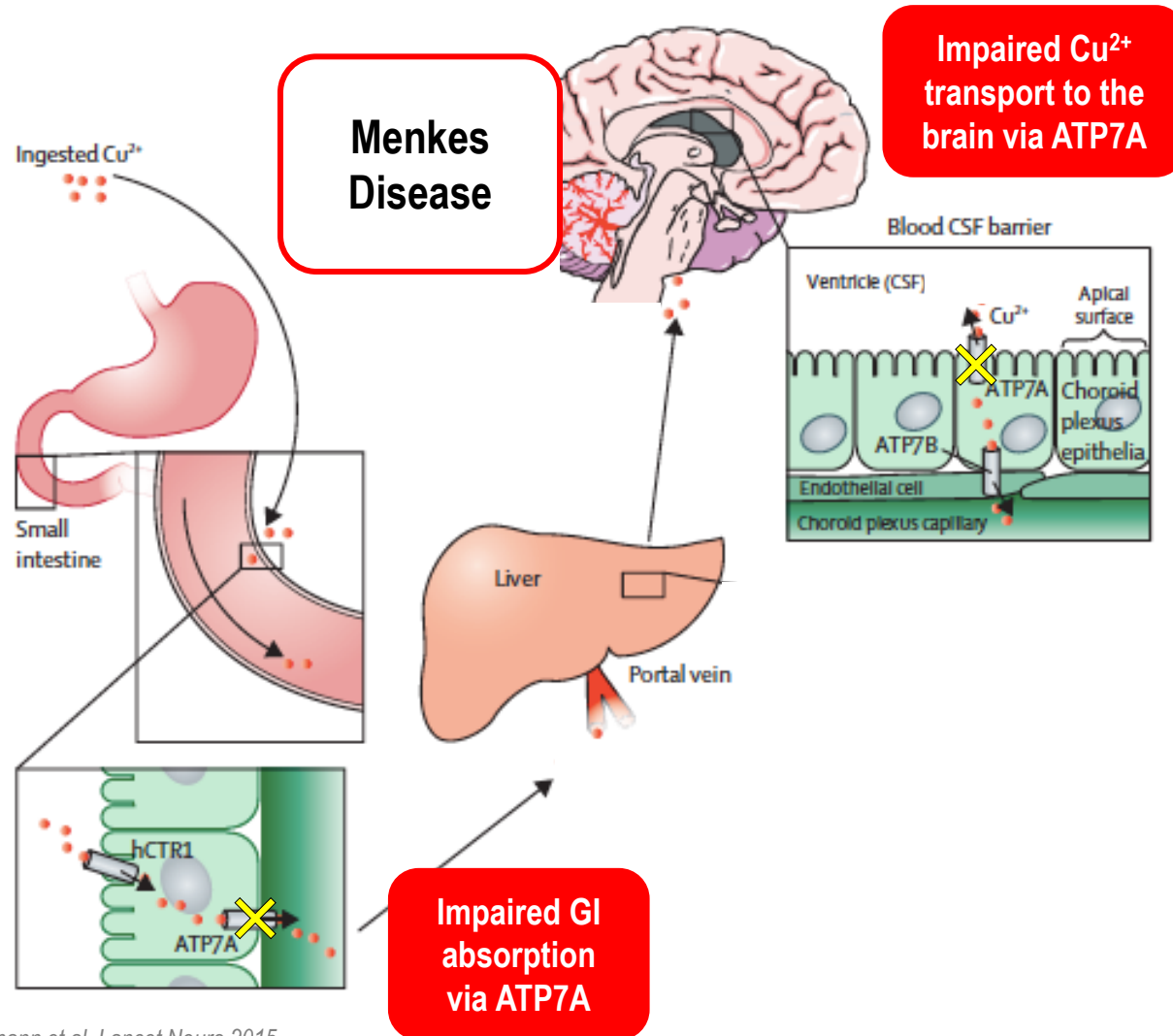
## New study estimated birth prevalence of Menkes disease based on the Genome Aggregation Database

- 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) could potentially increase the number of Menkes disease patients identified for early diagnosis and treatment with ZYCUBO



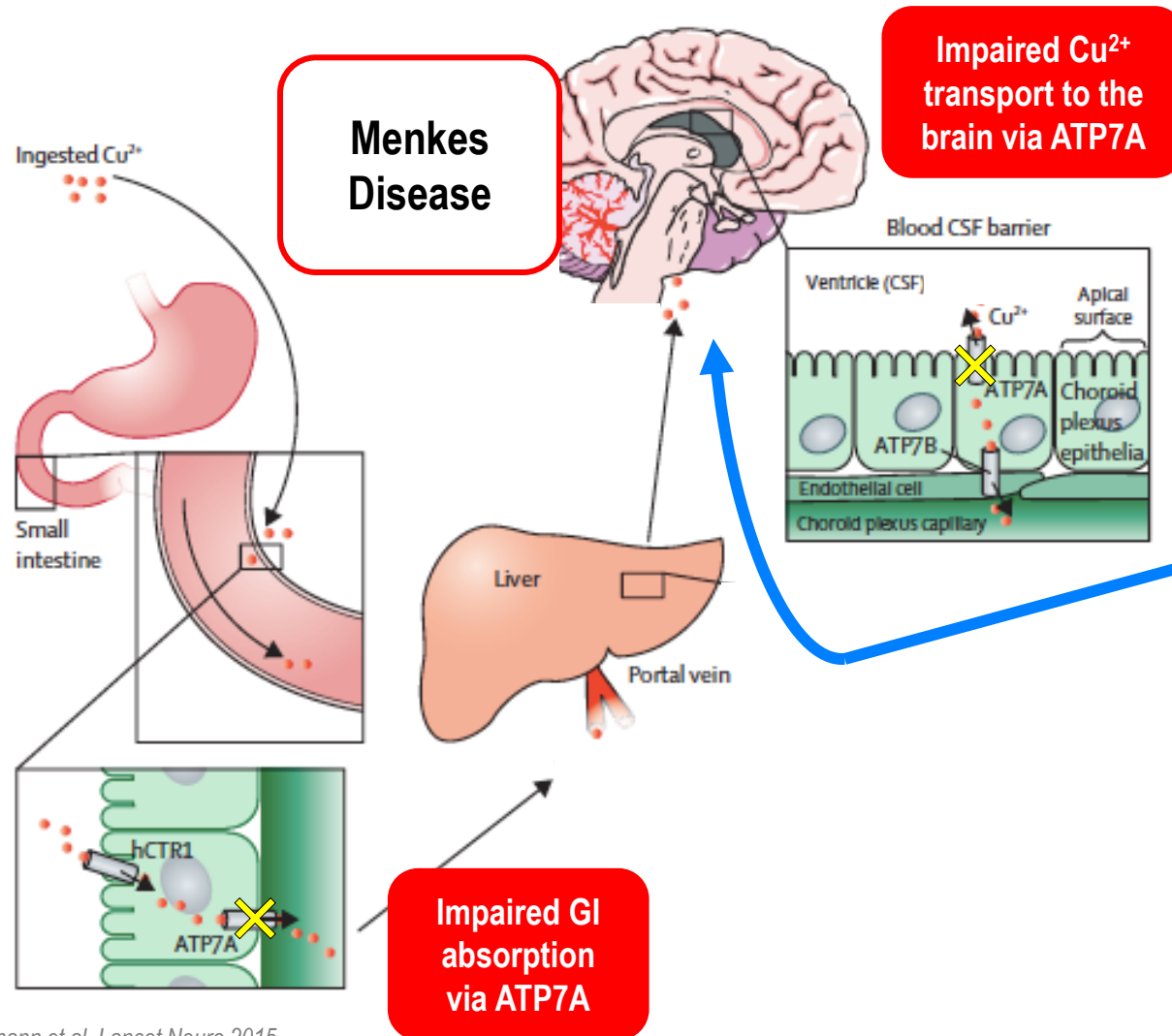
References: [1] Kaler, et al, 2020; [2] Kaler, SG, 1998; [3] Danks DM, 1971; [4] Tonnesen et al 1991

# Copper Transport is Impaired in Menkes Disease



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

# Therapeutic Strategy for Menkes Disease: ZYCUBO (Copper Histidinate)



1

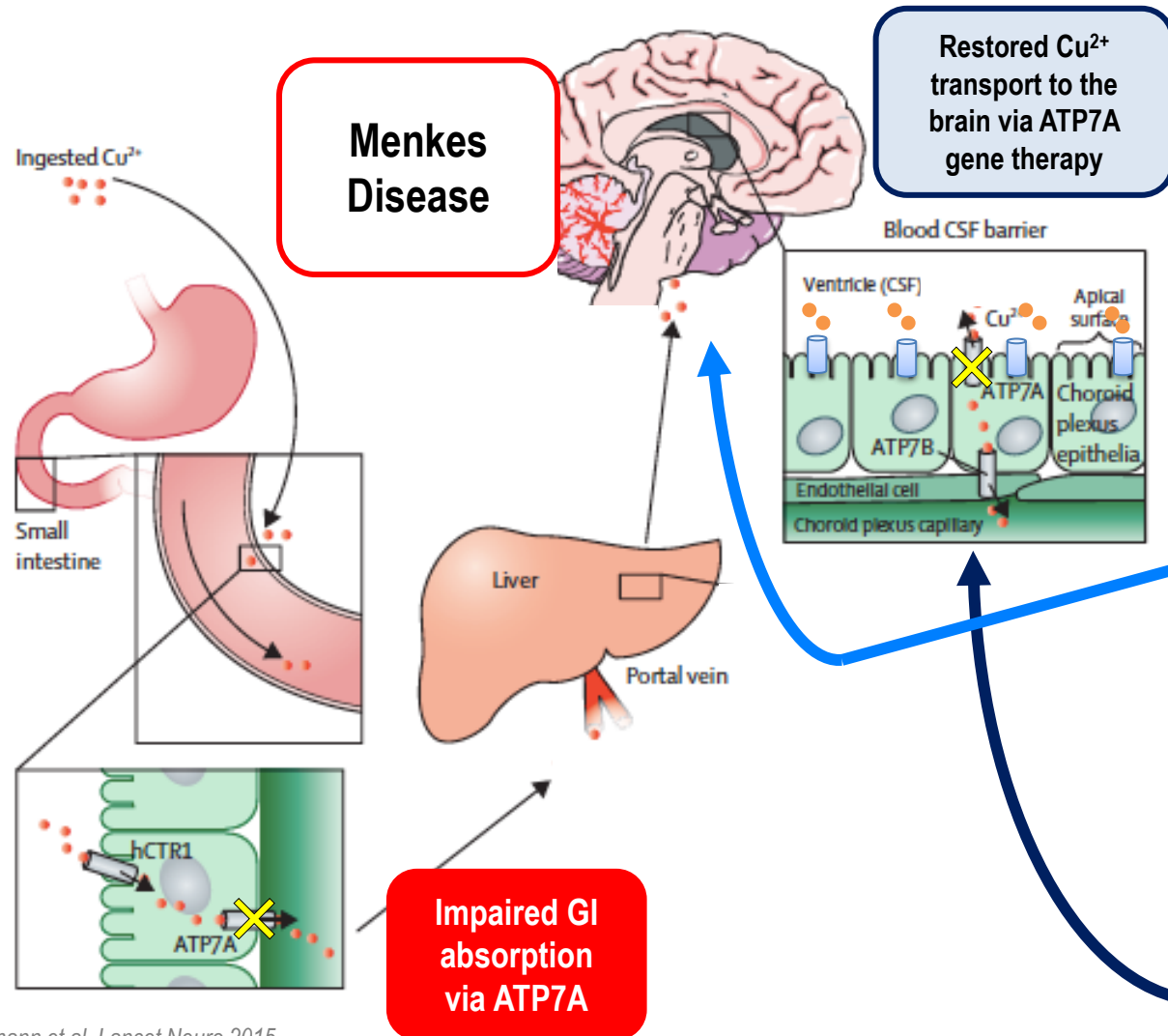
## ZYCUBO (Copper Histidinate (CuHis))

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

◆ Zycubo (formerly CUTX-101) NDA approved January 2026

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



1

## ZYCUBO Copper Histidinate

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

◆ Zycubo (formerly CUTX-101) NDA approved January 2026

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 ZYCUBO injections

Preclinical

Adapted from: Bandmann et al, Lancet Neuro 2015

# ZYCUBO efficacy in Early Treatment Cohort

**Table 3. Primary Efficacy Results: Overall Survival in ZYCUBO Early Treatment and External Control Early Treatment Cohorts with Menkes Disease**

	<b>ZYCUBO-Early Treatment (n=31)</b>	<b>External Control-Early Treatment (n=17)</b>
Number (%) of Patients Alive	16 (52%)	2 (12%)
Median survival time (months) (95% CI)	177.1 (33, NE)	17.6 (11.5, 28.6)
Hazard Ratio (95% CI)	0.22 (0.10, 0.49)	

CI=Confidence Interval; NE=Not estimable

Note: If death dates were unknown, patients were censored at the last known date alive.

- Patients in the ZYCUBO-ET cohort (patients treated with ZYCUBO) had a significant improvement in overall survival compared to patients in the EC-ET cohort, with a **78% reduction in the risk of death**.
- In the ZYCUBO-ET cohort, 15 (48%) patients survived >6 years, including 7 (23%) patients who survived >12 years. In the EC-ET cohort, no patients survived >6 years.

*Early-treatment cohort initiated treatment with ZYCUBO within 4 weeks of birth*

*Source: ZYCUBO Prescribing Information*

*Please refer to the U.S. Prescribing Information including Instructions for Use (IFU) for ZYCUBO for additional details on the product including safety.*

# ZYCUBO efficacy in Late Treatment Cohort

**Table 4. Secondary Efficacy Results: Overall Survival in ZYCUBO Late Treatment and External Control Late Treatment Cohorts with Menkes Disease**

	<b>ZYCUBO Late-Treatment (LT) (n=35)</b>	<b>External Control-Late Treatment (EC-LT) (n=16)</b>
Number of Patients Alive (%)	12 (34%)	2 (12%)
Median survival time (months) (95% CI)	62.4 (29.6, 80.7)	20.7 (12.6, 28.6)
Hazard Ratio (95% CI)	0.27 (0.12, 0.57)	

CI=Confidence Interval

Note: If death dates were unknown, patients were censored at the last known date alive.

- Patients in the ZYCUBO-LT cohort (patients treated with ZYCUBO) had a significant improvement in overall survival compared to patients in the EC-LT cohort, with a **73% reduction in the risk of death**.

*Late-treatment cohort initiated treatment with ZYCUBO after 4 weeks of birth*

*Source: ZYCUBO Prescribing Information*

*Please refer to the U.S. Prescribing Information including Instructions for Use (IFU) for ZYCUBO for additional details on the product including safety.*

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# Thank you!

**Investor Contacts:**

Cyprium Therapeutics, Inc.

Jaclyn Jaffe, Investor Relations

[ir@cypriumtx.com](mailto:ir@cypriumtx.com)