

CYPRIUM THERAPEUTICS

Corporate Presentation

June 2026

Forward Looking Statements

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Cover Page Image Sources: Kaler SG, NIH

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) – announced the closing of the sale of the PRV for $205M in March 2026

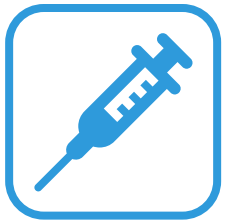
AAV-ATP7A

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® for Menkes Disease (marketed by Sentynl)

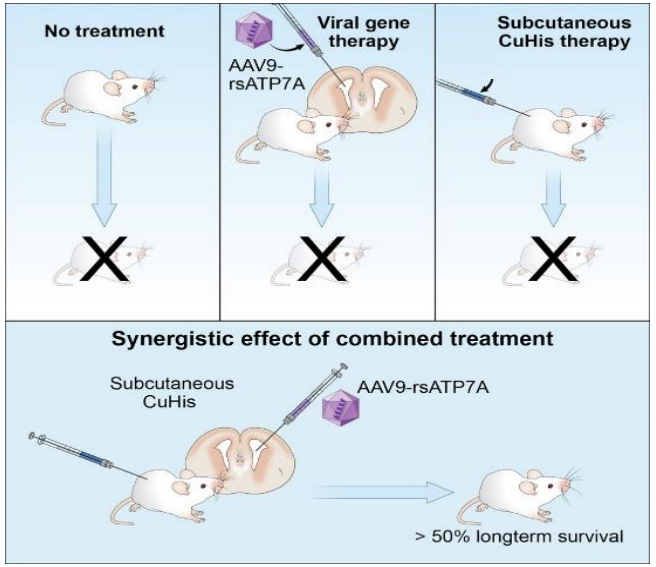


ODD FT RPD BTD OMP

- **ZYCUBO (Copper Histidinate Injection, formerly CUTX-101)**
  - NDA approved January 2026
    - FDA granted Priority Review Voucher (PRV) at approval; Sentynl transferred PRV to Cyprium
    - Cyprium sold the PRV for $205M in March 2026
  - Sentynl Therapeutics assumed development from Cyprium in December 2023
    - Sentynl responsible for commercialization of ZYCUBO
  - Cyprium eligible to receive tiered royalties on net sales and up to ~$128M in aggregate 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$^{mo\text{-}br}$ 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



Source: Stephen G. Kaler, MD; Haddad et al, 2018

Copper is Required in Human Development and Health









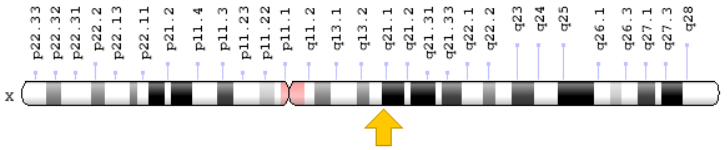
Biological Functions	Copper Containing Proteins
Brain Development	
Catecholamine production	Dopamine β-hydroxylase
Mitochondrial respiration	Cytochrome C oxidase
Iron and copper transport	Ceruloplasmin
Peptide amidation	Peptidylglycine α-amidating monooxygenase
Antioxidant defense	Superoxide dismutase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

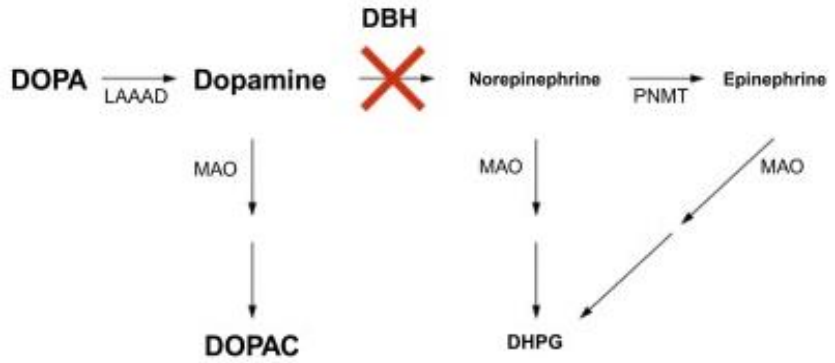
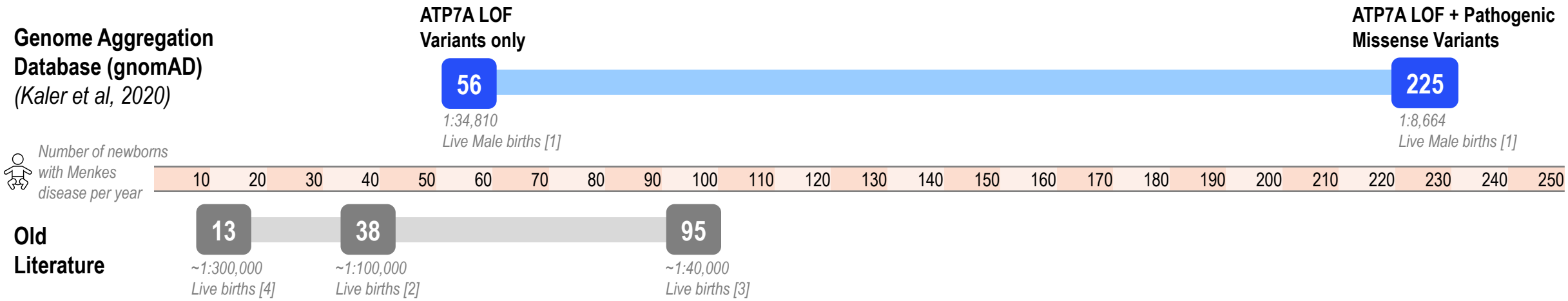


Image Source: Stephen G. Kaler, MD; NCBI

Menkes Disease is Under-estimated and Under-diagnosed

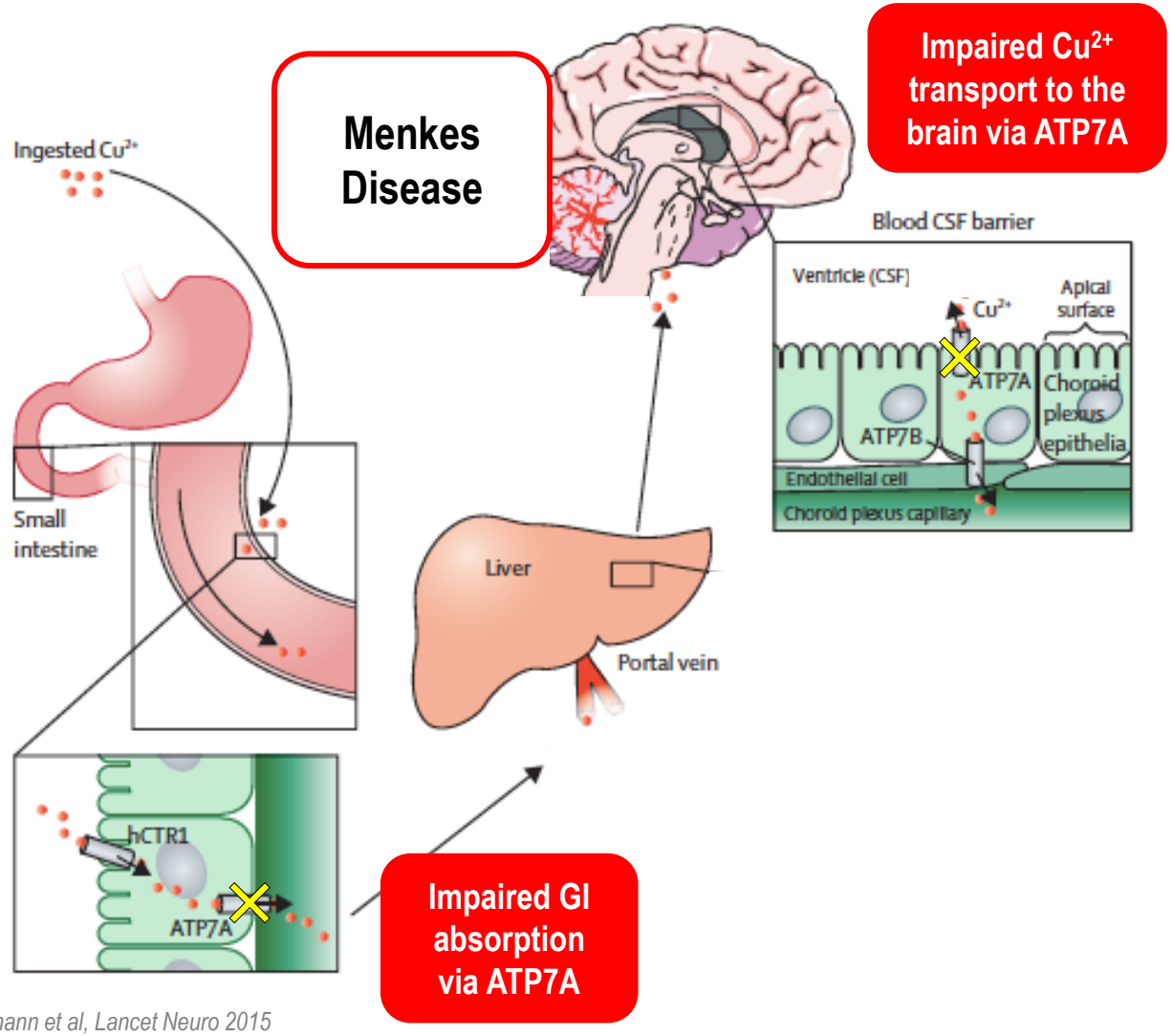
New study estimated birth prevalence of Menkes disease based on the Genome Aggregation Database

- 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



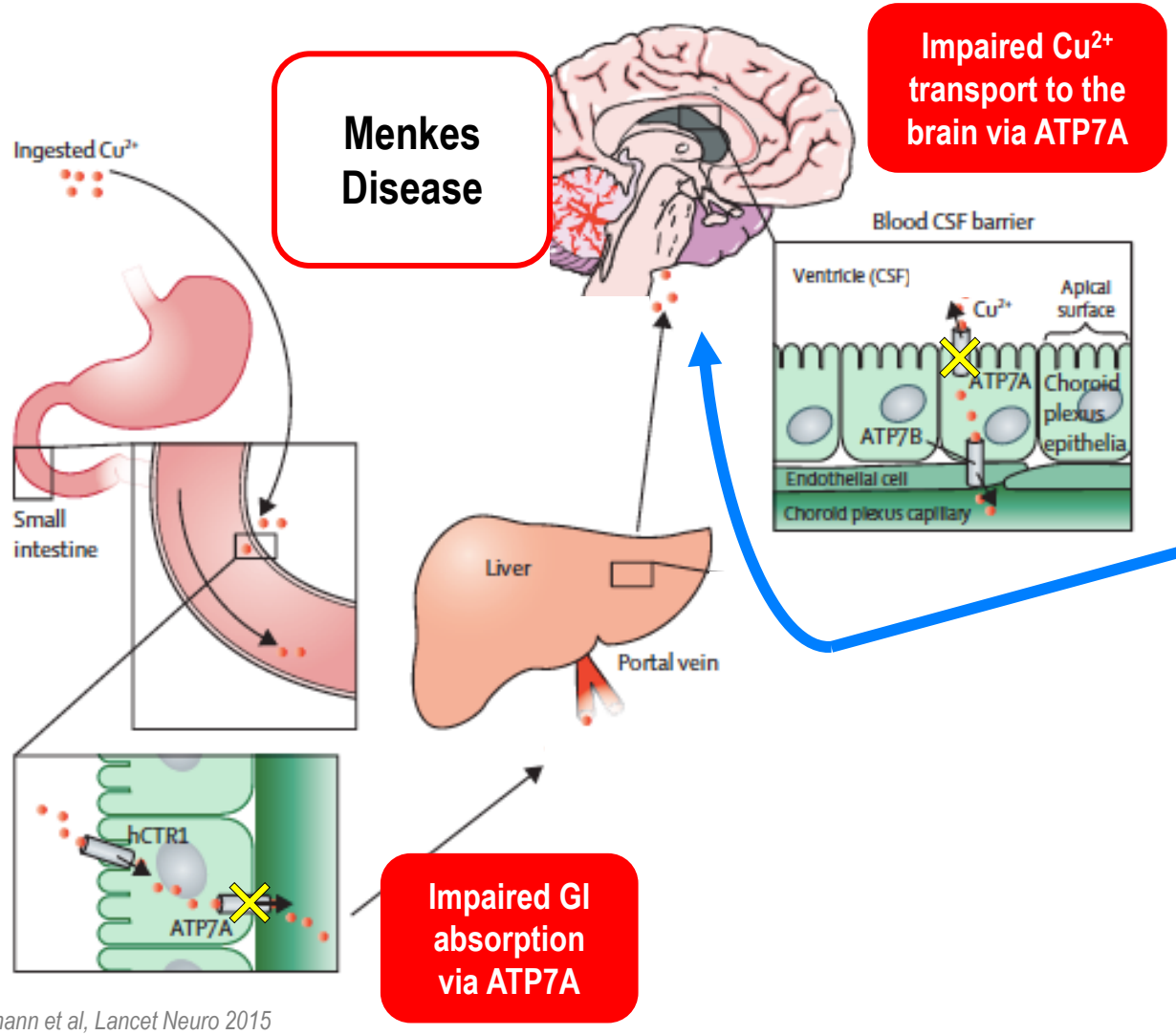
References: [1] Kaler, et al, 2020; [2] Kaler, SG, 1998; [3] Danks DM, 1971; [4] Tonnesen et al 1991

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))

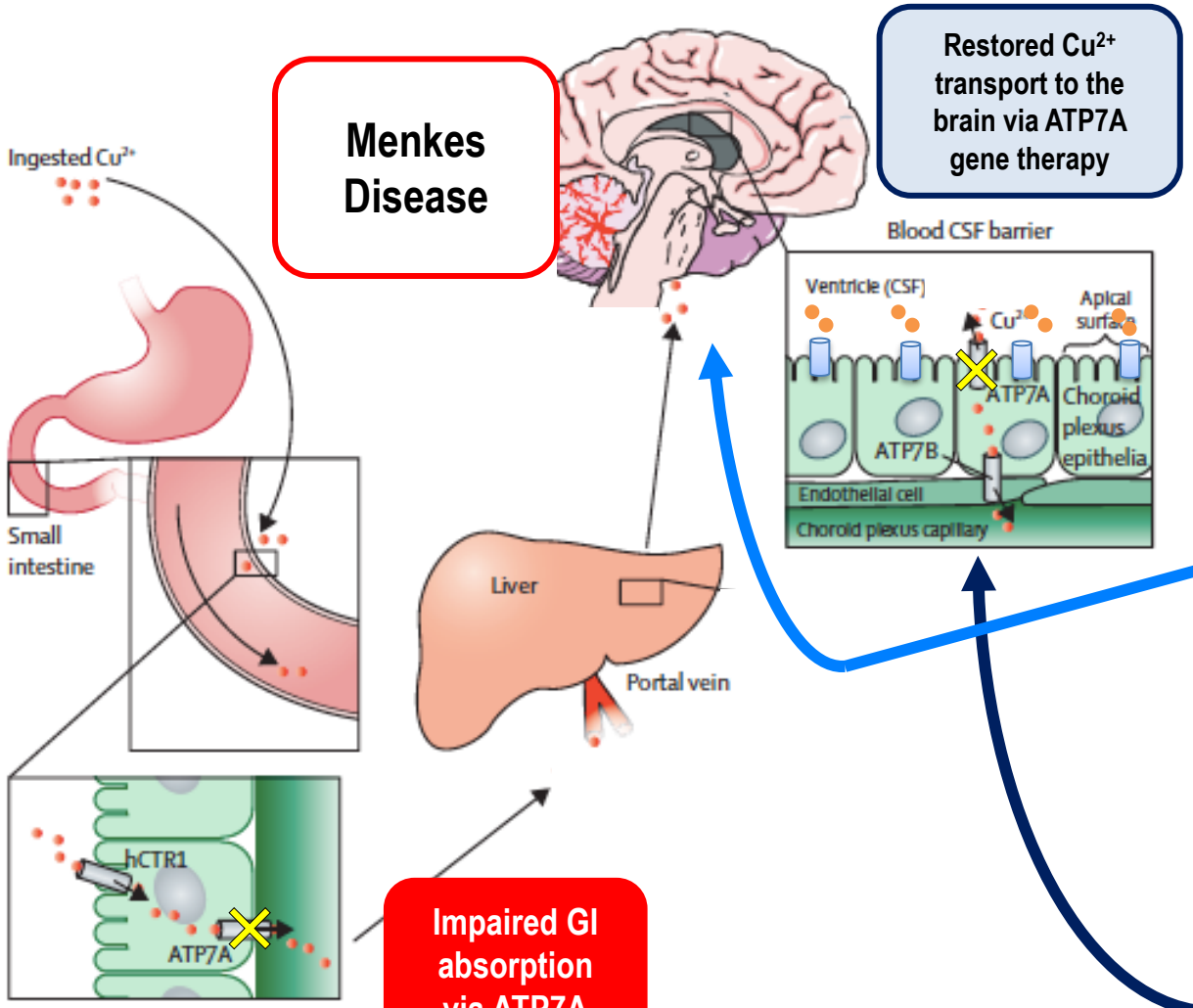
SC injection to replenish CuHis

- Bypass GI absorption of 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

Adapted from: Bandmann et al, Lancet Neuro 2015

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 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 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

	ZYCUBO-Early Treatment (n=31)	External Control-Early Treatment (n=17)
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

	ZYCUBO Late-Treatment (LT) (n=35)	External Control-Late Treatment (EC-LT) (n=16)
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.

Thank you!

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