TAYSHA GENE THERAPIES

Bringing New Cures to Life

CLN1 Disease Investor Day

August 30, 2021 | 9:00 – 11:30 AM CT

Legal disclosure

FORWARD LOOKING STATEMENTS

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “might,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are subject to a number of risks, uncertainties and assumptions. Risks regarding our business are described in detail in our Securities and Exchange Commission filings, including in our Annual Report on Form 10-K for the year ended December 31, 2020. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. All of the market data used in this prospectus involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

Introduction

RA Session II

President, Founder & CEO

Unparalleled gene therapy pipeline focused exclusively on monogenic CNS disorders

PROGRAM		INDICATION	DISCOVERY	PRECLINICAL	PHASE 1/2	Pivotal	GLOBAL COMM. RIGHTS
NEURODEGENERATIVE DISEASES							
TSHA-120	*GRT*	Giant Axonal Neuropathy				Regulatory guidance YE 2021	TAYSHA GENE THERAPIES
TSHA-101	*GRT*	GM2 Gangliosidosis				Currently open CTA	
TSHA-118	*GRT*	CLN1 Disease				Currently open IND	
TSHA-119	*GRT*	GM2 AB Variant					
TSHA-104	*GRT*	SURF1-Associated Leigh Syndrome				IND/CTA submission 2H 2021	
TSHA-112	*miRNA*	APBD					
TSHA-111-LAFORIN	*miRNA*	Lafora Disease					
TSHA-111-MALIN	*miRNA*	Lafora Disease					
TSHA-113	*miRNA*	Tauopathies					
TSHA-115	*miRNA*	GSDs					
Undisclosed	GRT/*shRNA*	Undisclosed					
Undisclosed	GRT	Undisclosed					
NEURODEVELOPMENTAL DISORDERS							
TSHA-102	*Regulated GRT*	Rett Syndrome				IND/CTA submission 2H 2021	TAYSHA GENE THERAPIES
TSHA-106	*shRNA*	Angelman Syndrome					
TSHA-114	*GRT*	Fragile X Syndrome					
TSHA-116	*shRNA*	Prader-Willi Syndrome					
TSHA-117	*Regulated GRT*	FOXG1 Syndrome					
TSHA-107	*GRT*	Autism Spectrum Disorder					
TSHA-108	*GRT*	Inborn Error of Metabolism					
TSHA-109	*GRT*	Inherited Metabolism Disorder					
Undisclosed	GRT	Undisclosed					
Undisclosed	mini-gene	Undisclosed					
GENETIC EPILEPSY							
TSHA-103	*GRT*	SLC6A1 Haploinsufficiency Disorder					TAYSHA GENE THERAPIES
TSHA-105	*GRT*	SLC13A5 Deficiency					
TSHA-110	mini-gene	KCNQ2					
Undisclosed	mini-gene	Undisclosed					

GRT: Gene replacement therapy **miRNA**: microRNA **shRNA**: short hairpin RNA

Investor Mini-Series

TSHA-118 CLN1 Disease Investor Day	**August 2021**
TSHA-102 Rett Syndrome Investor Day	September 2021
TSHA-106 Angelman Syndrome Investor Day	October 2021

Agenda

Topic	Time	Presenter
Introduction	9:00 am CT	RA Session II
Disease Overview and Natural History	9:15 am CT	Angela Schulz, MD, PhD
Disease Burden Patient and Family Perspective	10:10 am CT	Sharon King
Preclinical Pharmacology and Toxicology Data	10:25 am CT	Steven Gray, PhD
Clinical Development Strategy	10:55 am CT	Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM
Closing Remarks	11:15 pm CT	RA Session II

Speaker biographies

Angela Schulz, MD, PhD
Head of NCL Specialty Clinic, University Medical Center Hamburg-Eppendorf
- Specialist in pediatric and adolescent medicine, with expertise in palliative medicine and neuropediatrics
- Research is focused on neurodegenerative brain diseases, and is the PI for clinical study: Natural History and Longitudinal Clinical Assessments in NCLs/Batten Disease, International DEM-CHILD Database

Sharon King
President of Taylor's Tale
- A thought leader who has united public officials, researchers, biotech and industry representatives, and patient advocates to gain real progress in rare disease treatment development
- State-appointed member of the N.C. Advisory Council on Rare Diseases and chair of the N.C. Rare Disease Coalition

Steven Gray, PhD
Associate Professor Department of Pediatrics at UTSW and Chief Scientific Advisor to Taysha
- Expertise in AAV gene therapy vector engineering, optimizing approaches to deliver a gene to the nervous system
- Research focus includes preclinical studies to apply AAV-based platform gene transfer technologies toward the development of treatments for neurological diseases such as Rett Syndrome, Giant Axonal Neuropathy (GAN), Tay-Sachs, Krabbe, AGU, and Batten Disease, and have expanded into human clinical studies to test a gene therapy approach for GAN and CLN7 Batten disease

Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM
Chief Medical Officer and Head of Research and Development at Taysha
- Expertise in international drug development, including preclinical, Phase I-IV trials, regulatory filings, commercial application
- Former CMO of Audentes Therapeutics; led XLMTM AAV8 program from preclinical to initial positive clinical data
- Prior roles include Medical Affairs and Clinical Development at BioMarin, Genzyme Therapeutics, and Eli Lilly and Company
- UK board certified with postgraduate qualifications in Pediatrics, Internal Medicine, Pharmaceutical Development, and Translational Science

Disease Overview and Natural History

Angela Schulz, MD, PhD

Head of NCL Specialty Clinic
University Medical Center Hamburg-Eppendorf

Clinic for Pediatric Degenerative Brain Diseases

Neuronal Ceroid Lipofuscinoses – CLN1 Disease

Angela Schulz, MD PhD

Universitätsklinikum Hamburg-Eppendorf

University Medical Center Hamburg-Eppendorf (UKE)
Clinic for pediatric degenerative brain diseases

Coordination of international DEM-CHILD patient database for all NCLs

In- and outpatient clinic:

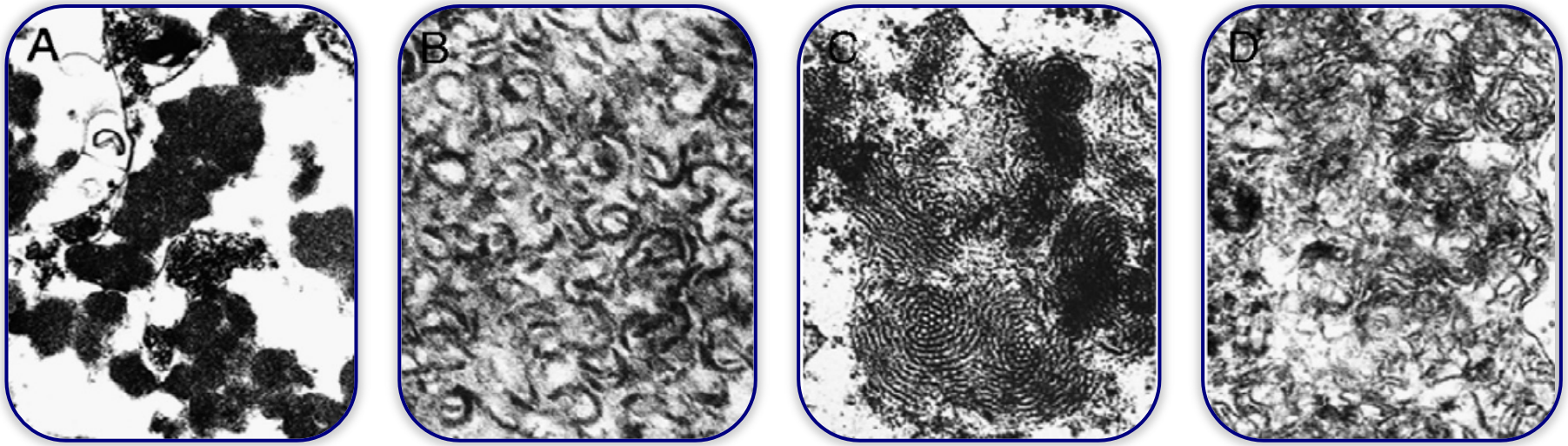
175 patients with Batten disease/year: (national/international)

- 83 patients with CLN2 (of those 52 on ERT)
- 48 patients with CLN3
- 16 patients with CLN1
- 45 patients with CLN5, CLN6, CLN7, CLN8
- Overall data on >250 NCL patients

NCL, Neuronal ceroid lipofuscinosis
ERT – Enzyme replacement therapy

Overview of NCL disorders

Lysosomal storage material in NCL disorders



Granular	Curvilinear	Fingerprint	Other
CLN1	CLN2	CLN3	

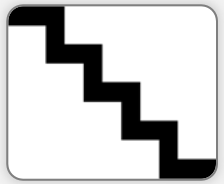
Haltia M. *Biochim Biophys Acta*. 2006;1762:850-856.

Overview of NCL disorders

Growing number of NCL disorders

Today we know **≈13** genetically distinct human NCL disorders
(12 have autosomal recessive inheritance)

Their clinical hallmark is the combination of



Dementia

Visual loss due
to retinopathy

Epilepsy

NCL: The most frequent cause of dementia in young persons

Schulz A, Kohlschütter A. Iranian Journal of Child Neurology. 2013;7:1-8.

Overview of NCL diseases

New classification of NCL disorders

According to **genes** and **clinical type**

Designation of disease

Genetic type	*Mutated gene*	*Clinical type (age of onset)*
• CLN**X**	• CLN**X** disease	• Congenital (at birth) • Infantile (6 to 24 months) • Last infantile (2 to 5 years) • Juvenile (5-7 years) • Adult
Example: CLN2 disease, late infantile		

Williams RE, Mole SE. Neurology. 2012;79:183-191.

Overview of NCL diseases – Genes and clinical onset

Disease		Onset				Protein	*Gene*
Soluble lysosomal enzymes	**CLN1**	Infantile	Late infantile	Juvenile	Adult	Palmitoyl protein thioesterase 1	*CLN1 (PPT1)*
	CLN2	Infantile	Late infantile	Juvenile / Protracted		Tripeptidyl peptidase 1	*CLN2 (TPP1)*
	CLN10	Congenital		Juvenile	Adult	Cathepsin D	*CLN10 (CTSD)*
	CLN13				Adult Kufs B	Cathepsin F	*CLN13 (CTSF)*
Other enzymes	**CLN12**			Juvenile		ATPase	*CLN12 (ATP13A2 §)*
Nonenzyme proteins (function poorly understood)	**CLN3**			Juvenile		Transmembrane protein	*CLN3*
	CLN4				Adult*	Soluble cysteine string protein α	*CLN4 (DNAJC5)*
	CLN5		Late infantile	Juvenile	Adult	Soluble lysosomal protein	*CLN5*
	CLN6		Late infantile		Adult Kufs A	Transmembrane protein	*CLN6*
	CLN7		Late infantile			Transmembrane protein	*CLN7 (MFSD8)*
	CLN8		Late infantile	Juvenile EPMR		Transmembrane protein	*CLN8*
	CLN11				Adult	Progranulin	*CLN11 (GRN*)*
	CLN14	Infantile				Potassium channel protein	*CLN14 (KCTD7⁺)*

Adapted from Schulz A, et al. *Biochimica et biophysica acta*. 2013;1832:1801-1806.

**GRN* mutations als in „Frontotemporal lobar degeneration with TDP43 inclusions" MIM #607485

§ *ATP13A2* mutations also in Kufor-Rakeb syndrome (KRS, Parkinson disease 9) MIM #606693

⁺*KCTD7* mutations also in Progressive Myoclonic Epilepsy Type 3 (EPM3) MIM #611726

CLN1 disease – Introduction

Disease

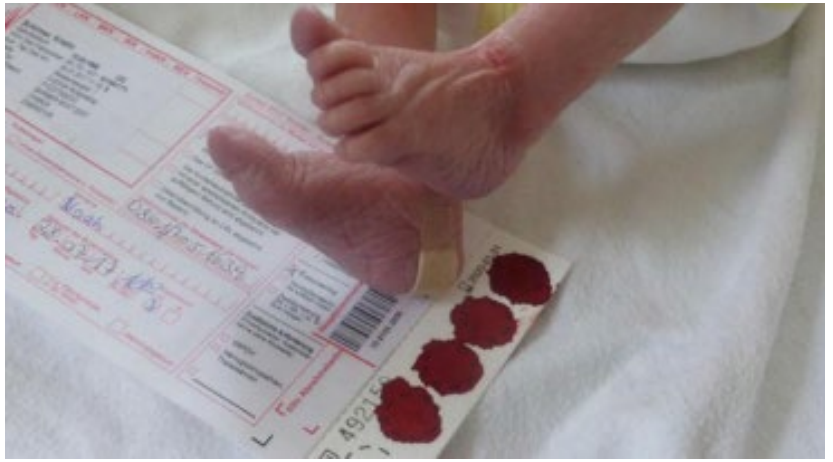
- Deficiency of lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1)
- Caused by mutations in the *CLN1* gene (> 70 pathogenic mutations)
- Autosomal recessive inheritance

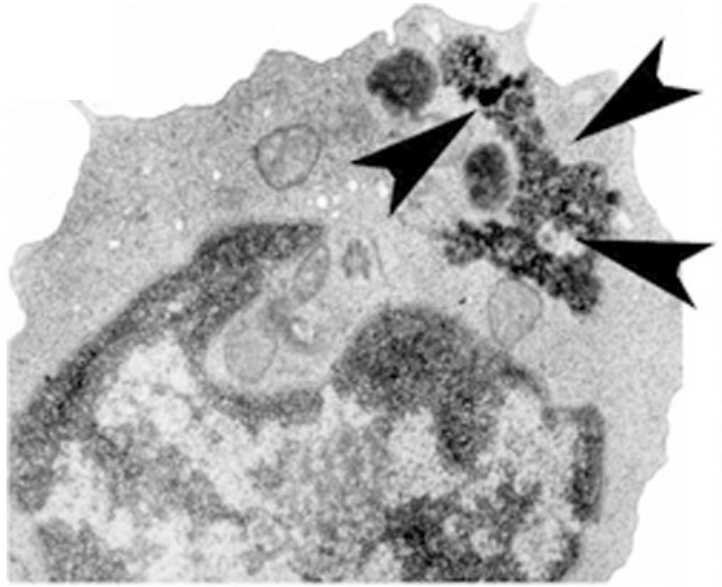
Pathology

- Accumulation of lysosomal storage material leading to (neuronal) cell dysfunction and death

Laboratory diagnosis

- Measurement of PPT1 enzyme activity in dry blood spots, leucocytes, fibroblasts
- Genetic detection of pathogenic mutation of both alleles of *CLN1* gene
- Electronmicroscopic detection of granular deposits in lysosomes in skin biopsy





Compact granular osmiophilic deposits (GROD) in a lymphocyte, infantile NCL

Radke J, Stenzel W, Goebel HH. Human NCL Neuropathology. Biochim Biophys Acta. 2015;1852(10 Pt B):2262-2266

CLN1 disease – Clinical phenotypes

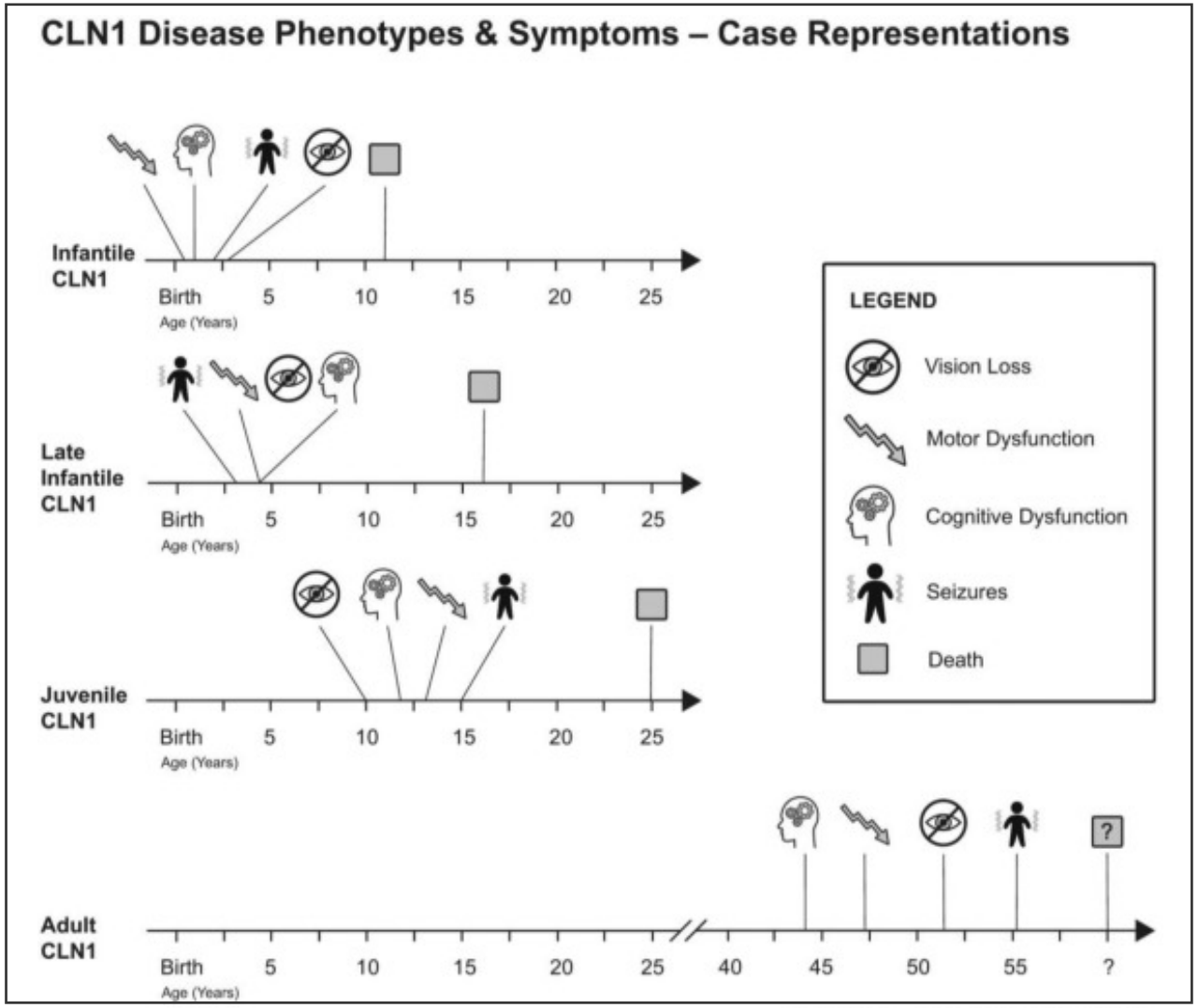
Phenotype	Typical age at symptom onset	Type of first symptom	Rate of progression	Clinical features (order of appearance)
Infantile	6 – 18 months	Psychomotor developmental delay	Rapid	• **Psychomotor delay *(age 12-18 months)*** • **Max motor function: Standing with support** • **Max language function: Single words** • Rapid cognitive and motor decline *(age 18 months)* • Wheelchair bound *(age 24-30 months)* • Muscle hypotonia, ataxia, myoclonus • Epileptic seizures *(age 24-30 months)* • **Vision loss *(age 24 - 36 months)***
Late infantile	>18 months – 4 years	Epilepsy plus psychomotor decline	Rapid	• Seizures *(age 2-4 years)* • Rapid cognitive and motor decline *(age 2 – 4 years)* • Seizures *(age 2-4 years)* • Vision loss *(age 4-6 years)*
Juvenile	>4 years – early adolescence	Vision loss	Slow	• **Normal psychomotor development *until age 8-12 years*** • **Vision loss starting *(age 6-10 years)*** • Cognitive decline *(age 8-12 years)* • Epileptic seizures *(age 10-12 years)* • Motor decline *(age 12-14 years)*
Adult	Late adolescence and older		Protracted	• Cognitive decline • Psychiatric problems, depression • Vision loss • Motor problems: ataxia, parkinsonism

CLN1 disease – Clinical phenotypes

- CLN1 disease phenotypes vary by
  - Age at onset
  - Order of symptom onset
  - Rate of disease progression
  - Life expectancy

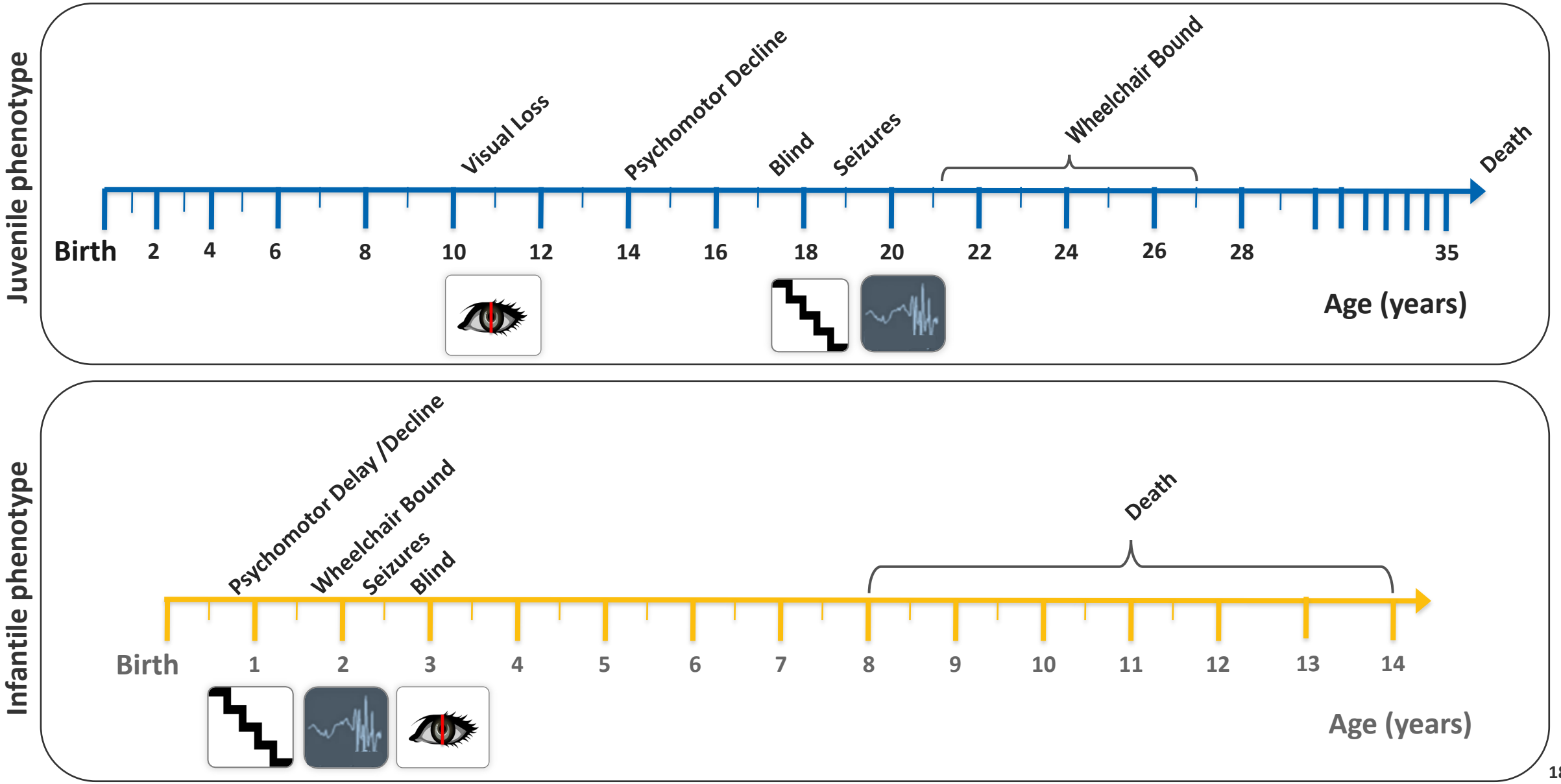
- Infantile and juvenile phenotypes are the most prevalent ones to date

- Strong genotype-phenotype correlations for certain *CLN1* mutations



Augustine EF, Adams HR, de los Reyes E, Drago K, Frazier M, Guelbert N, Laine M, Levin T, Mink JW, Nickel M, Pfeifer D, Schulz A, Simonati A, Topcu M, Turunen JA, Williams R, Wirrell EX, King S. Management of CLN1 disease: International clinical consensus. *Pediatr Neurol* 2021, 120:38-51.

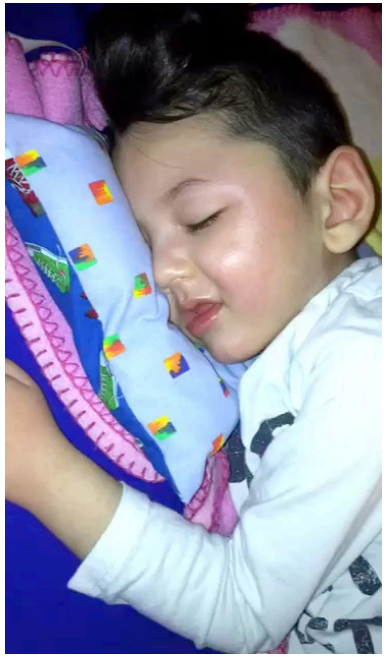
CLN1 disease – Juvenile vs. infantile phenotype



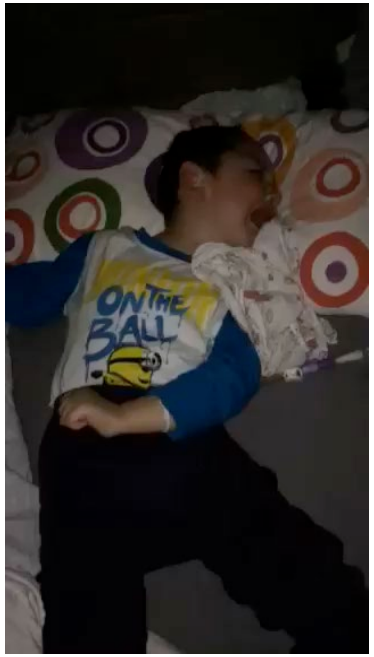
Infantile CLN1 disease

Age 12 months

Age 18 months



Age 2 years



Age 3 years

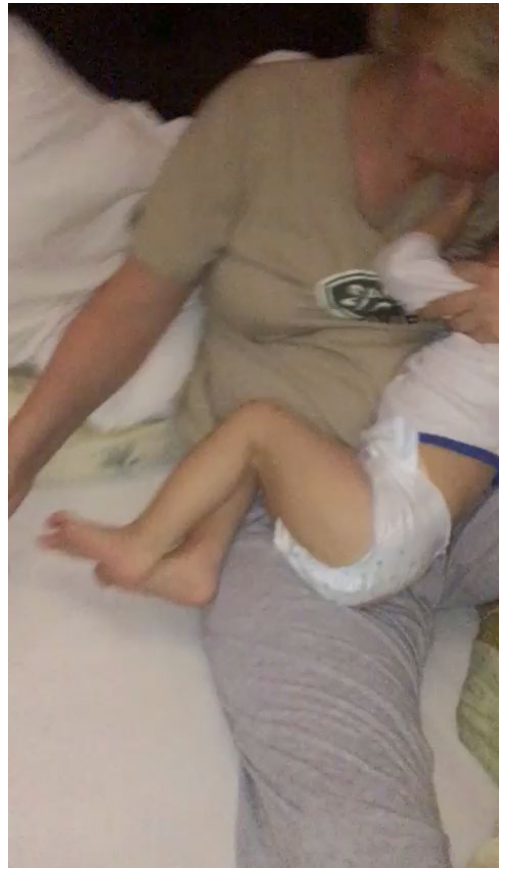
Age 5 years

Age 6 years

Symptoms of agitation / distress in infantile CLN1 disease

- Increasing movements
- Myoclonia
- Agitation
- Spasticity, ophistotonus
- Dystonia
- Crying, screaming, whimpering
- Hypersalivation
- Tachycardia, tachypnoe
- Sweating
- High body temperature

complex clinical picture suggestive of pain!

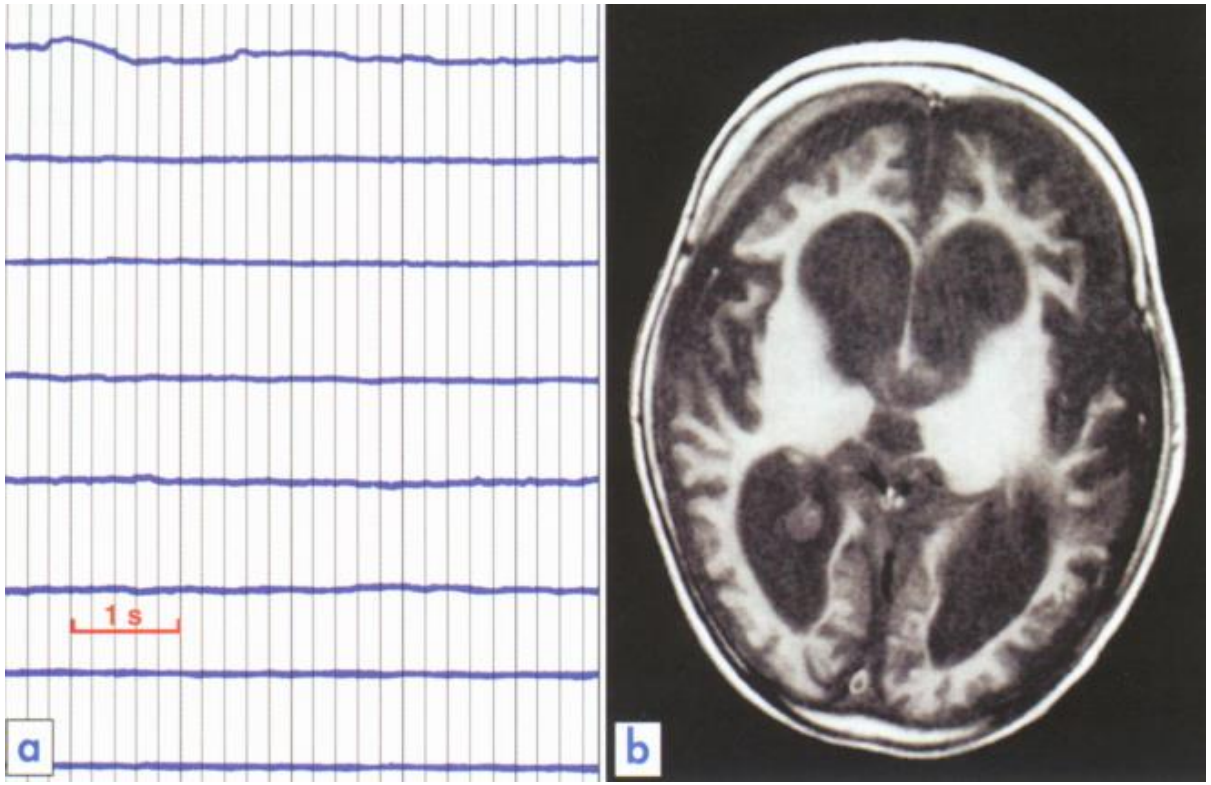


MOST kids with severe rare neurological diseases cannot communicate and suffer from sleep disturbances and restlessness during day

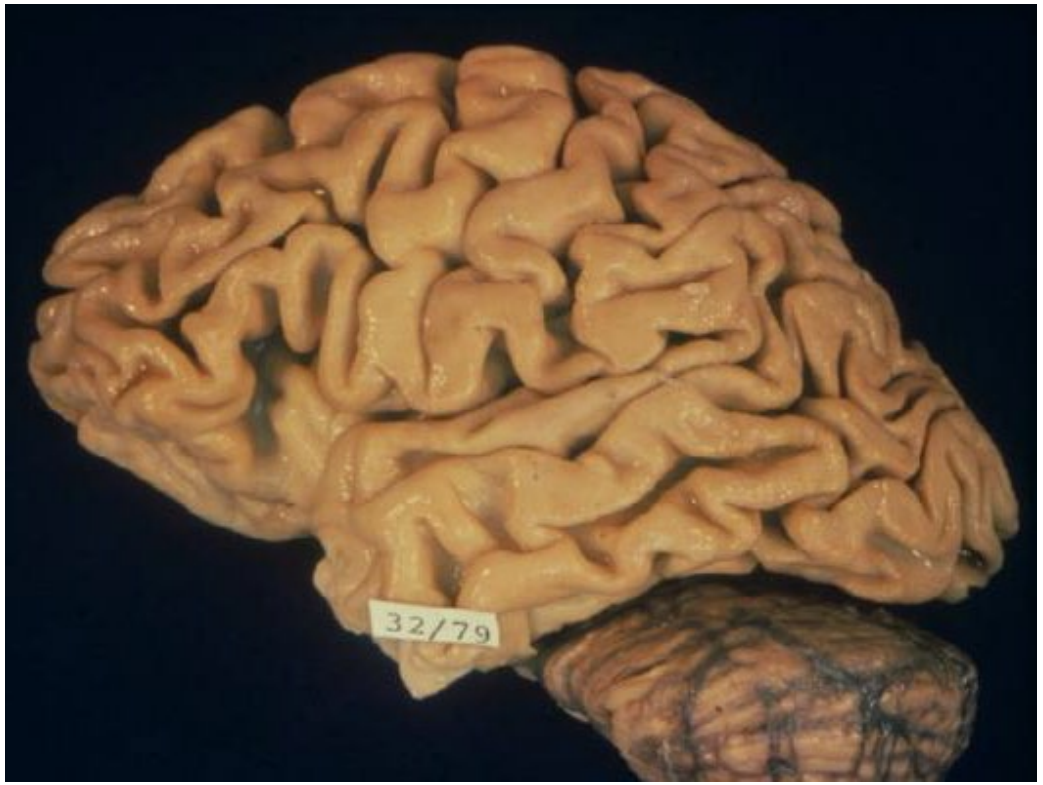
OFTEN these **symptoms are hard to distinguish from pain**

Infantile CLN1 disease

Age: 4 years



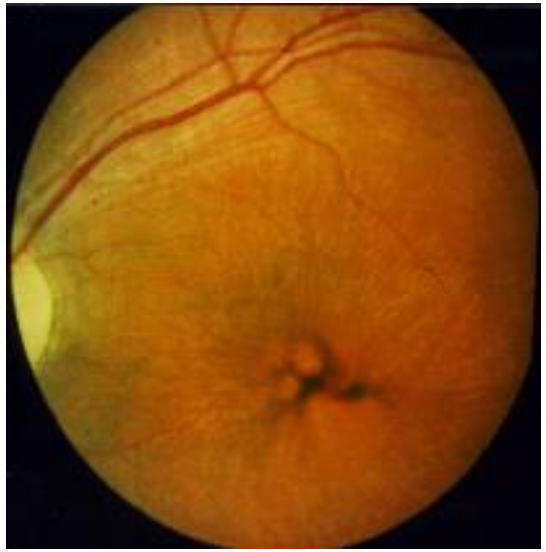
EEG: No activity



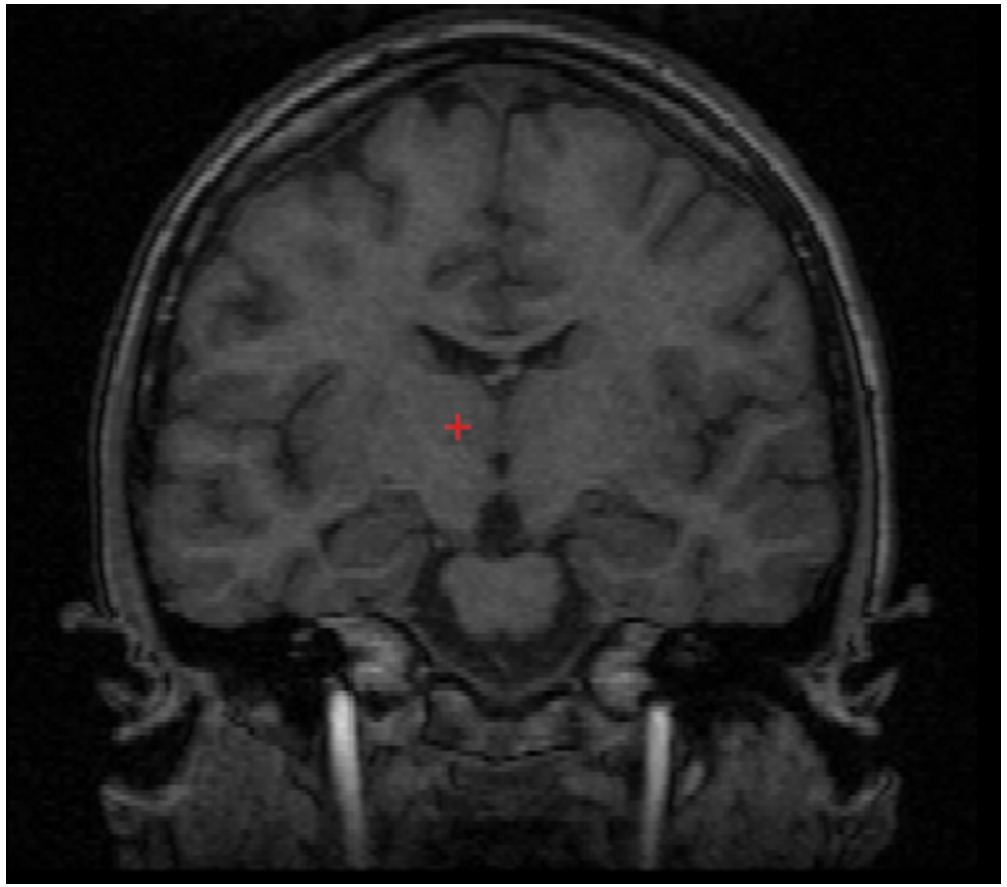
Severe brain atrophy

Juvenile CLN1 disease

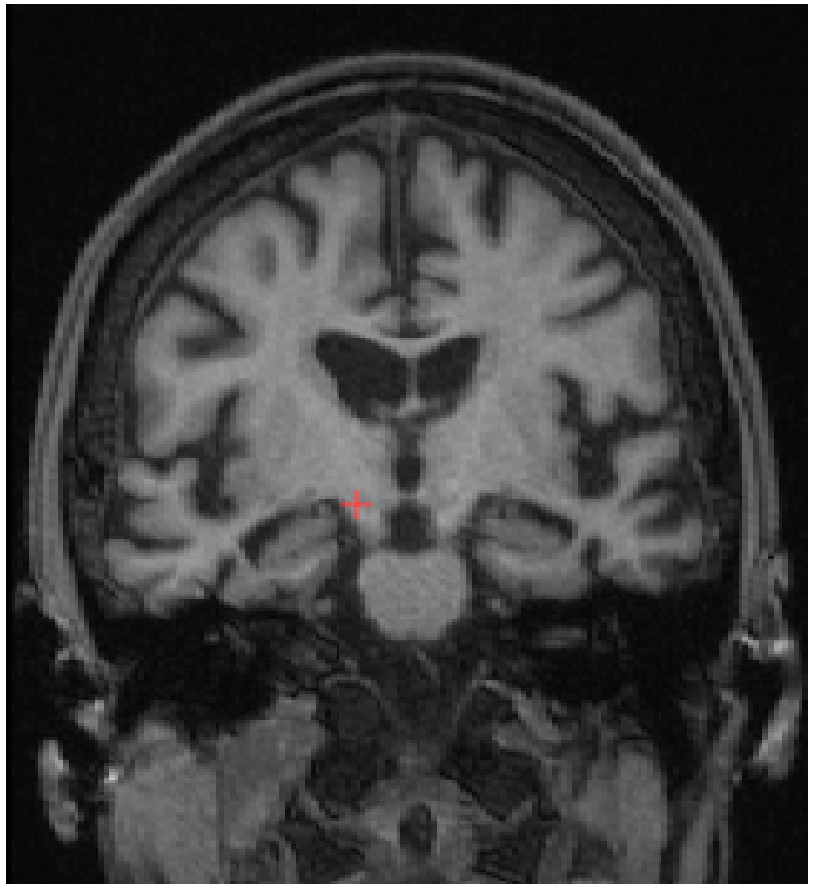
- Normal psychomotor development *until age 8-12 years*
- Vision loss starting “Overlooking” *(age 6-10 years)*
- Cognitive decline *(age 8-12 years)*
- Epileptic seizures *(age 10-12 years)*
- Motor decline *(age 12-14 years) – Parkinson-like movement disorder*



Juvenile CLN1 disease – Progressive brain atrophy



11 years



18 years

Speaker's own patient, images used with permission

Clinical trial design and endpoints – Challenges for CLN1 disease

Limited number of patients

Phenotype variability

Need for reliable clinical outcome measures / clinical biomarkers

Use of natural history control data in clinical trials

DEM-CHILD NCL database consortium

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University Children's Hospital, Ankara

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Rose-Mary Boustany MD PhD
Amrican University of Beirut

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Catherine Caillaud MD PhD
INSERM, Paris

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Maria del Socorro Pérez Poyato MD
Hospital Universitario Marqués de Valdecilla, Santander

19 countries and 26 centers

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Tokyo Medical University

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Universidad Nacional de Cordoba

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University of São Paulo

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Weill Cornell Medical College, New York

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Nationwide Children's Hospital, Columbus

Rebecca Ahrens-Niklas, MD
Children's Hospital of Philadelphia

Kathryn Swobody, MD
Massachussetts General Hospital, Boston

http://www.dem-child.eu/index.php/consortium.html, accessed October 2018

Aims of DEM-CHILD

International collaboration

- To collect precise natural history data of all NCL types
- To improve early diagnosis of NCLs
- To optimize standard of care for patients
- To establish evaluation tools for experimental therapies

…and make these data available to third parties (scientists and industry) in a transparently regulated and time-effective process

http://www.dem-child.eu/index.php/consortium.html, accessed October 2018

Database characteristics

- Online database
- Password protected and SSL encrypted
- In compliance with international and European data safety and protection rules
- Independent data monitoring
- Data safety
  - Audit trail
  - Data storage on two different servers with emergency power supply
  - Backup of entire dataset every 24 hours
  - **Audited and approved by EMA and FDA (for CLN2 natural history data)**

International collaboration – Natural history cohort of 61 CLN1 patients

Country	Patient numbers		
	Infantile	Variant late infantile	Juvenile
Italy	8	9	2
Finland	12	0	0
Germany	13	3	2
USA	6	4	2
Total	**39**	**16**	**6**

Simonati A, Nickel M, Laine M, Augustine E, Adams H, Garavaglia B, Moro F, Pezzini F, Nardocci N, Santorelli F M, **Mink J, Schulz A,** *unpublished (data from 2018)*

Clinical trial design and endpoints – Challenges for CLN1 disease

Limited number of patients

Phenotype variability

Need for reliable clinical outcome measures / clinical biomarkers

Use of natural history control data in clinical trials

Clinical scoring for late infantile and juvenile CLN1 disease

Late Infantile NCL Scale

Functional Category
Motor function
Language
Visual function
Seizures

Steinfeld R, et al. *Am J Med Genet* 2002;112:347-54.

Juvenile NCL Scale

Functional Category
Motor function
Language
Visual function
Intellect
Seizures

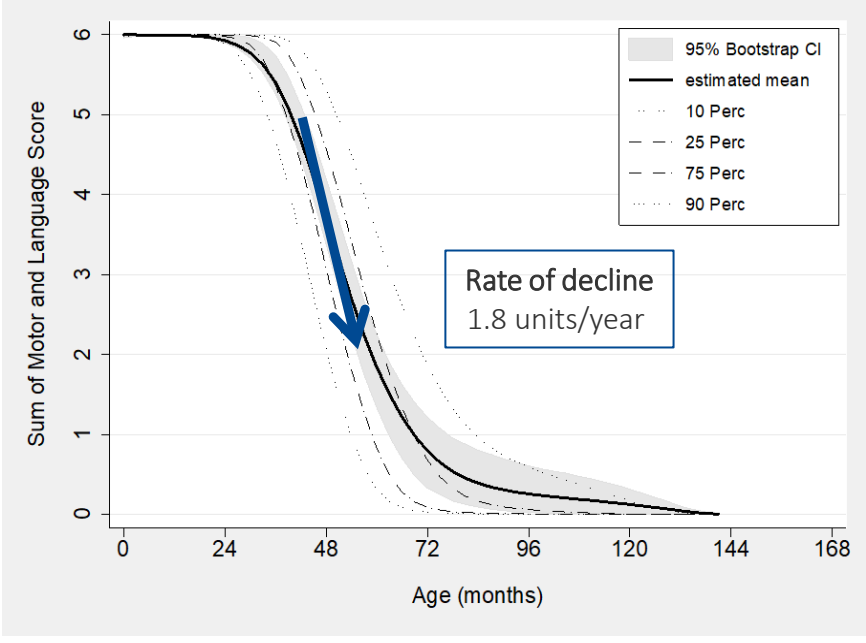
Kohlschütter A, e al. *Acta Paediatr Scand*. 1988;77:867-72.

Each functional category	Scored from 0-3
Normal function	= SCORE 3
Slightly abnormal	= SCORE 2
Severely abnormal	= SCORE 1
No function left	= SCORE 0

Advantages

- Easy to use
- Excellent inter-rater reliability
- Retrospective and prospective use – longitudinal assessment
- Focus on functional relevant outcomes
- **Need adaption / selection of parameters for infantile NCL phenotypes**

Example Hamburg LINCL scale:
Longitudinal assessment of 41 CLN2 patients



Clinical scoring for juvenile CLN1 disease

Unified Batten Disease Rating Scale

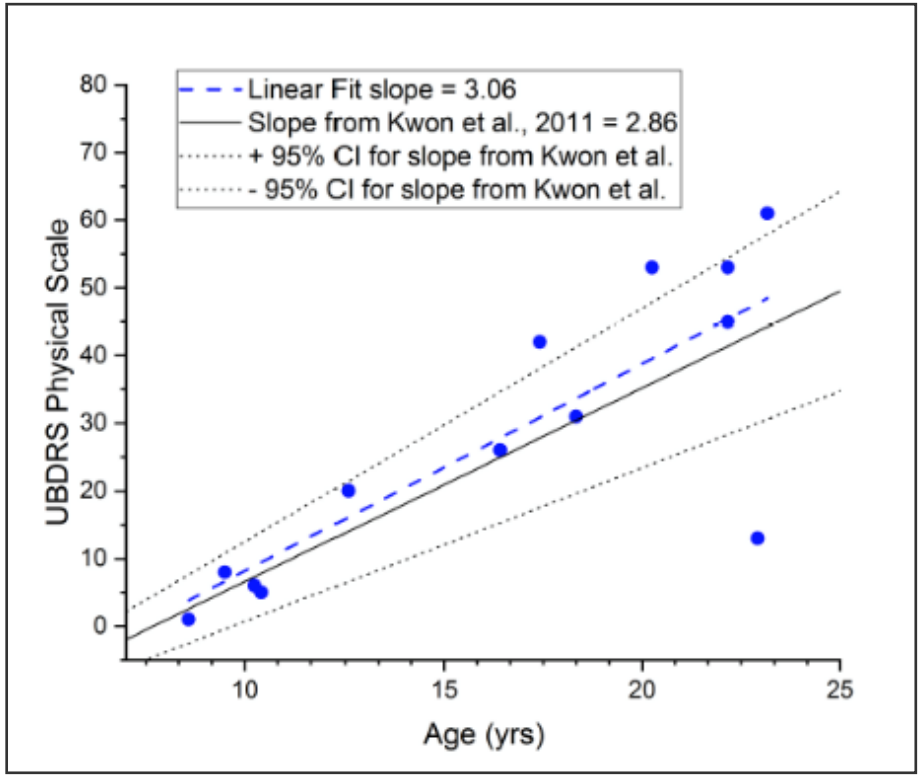
- Developed by J. Mink, Rochester
- **Teaching is important** to ensure good inter-rater reliability
- **Prospective use only**
- **Detailed description** of juvenile NCL phenotypes
- **Needs adaption / selection of parameters for infantile NCL phenotypes**

Hamburg-Rochester Rater Training by J. Mink

ICC Analysis Demonstrated Excellent Inter-Rater Reliability

- **ICC for all 5 raters = 0.92**
- **Agreement between each rater and the trainer was > 0.99**

B	C	D	E
0.99	0.99	0.99	0.99



Hamburg infantile NCL score (Hamburg iNCL score)

Infantile CLN1 Disease

- Most children do not reach milestones to walk without support
- Most children do not reach milestones to talk in short sentences
- All current scoring systems score these milestones and cannot be used

Development of the Hamburg infantile CLN1 score

Supported by

Hamburg infantile NCL score (Hamburg iNCL score)

Infantile NCL Scale

Functional Category
Mobility
Fine motor function
Expressive language

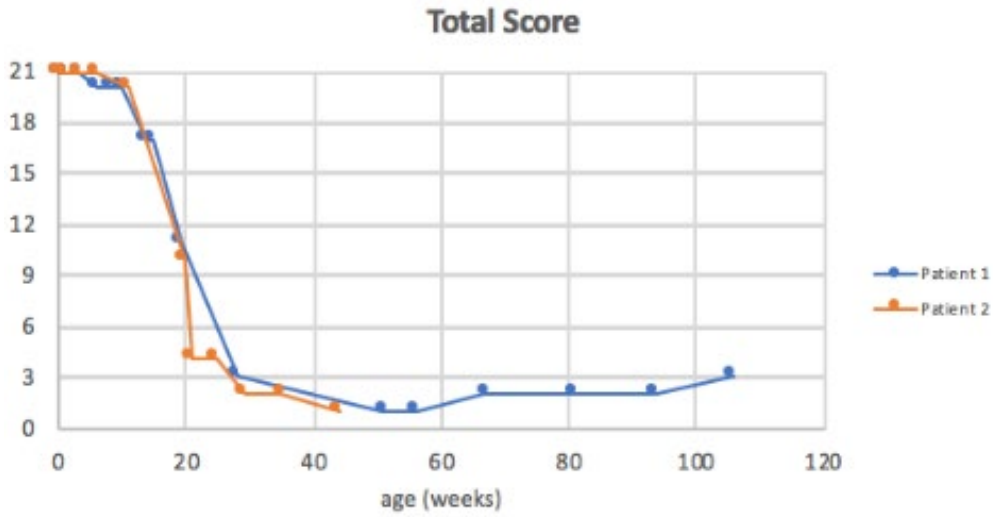
Each functional category	Scored from 0-4
Age appropriate function	= SCORE 4
Developmental delay present	= SCORE 3
First regression of function, active function without help	= SCORE 2
Active function with help	= SCORE 1
No function left	= SCORE 0

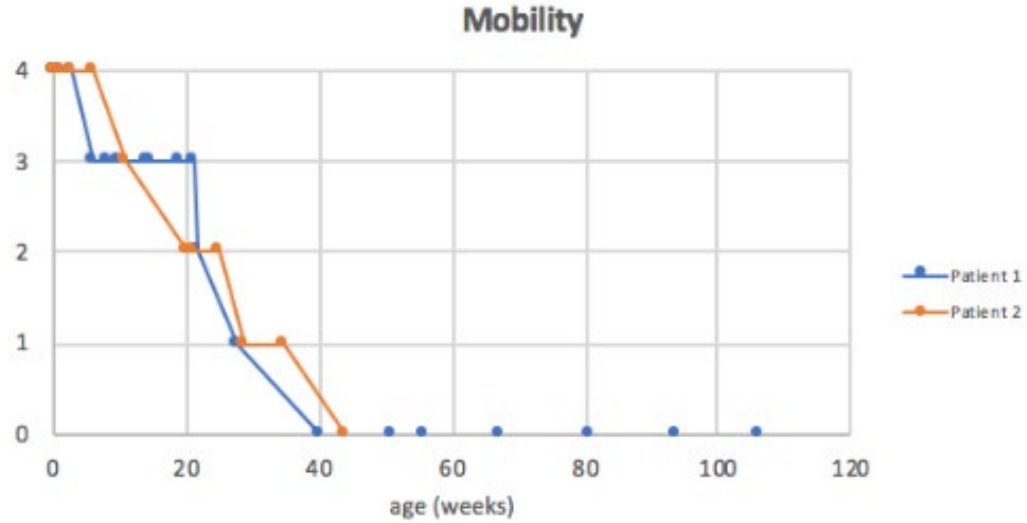
Advantages

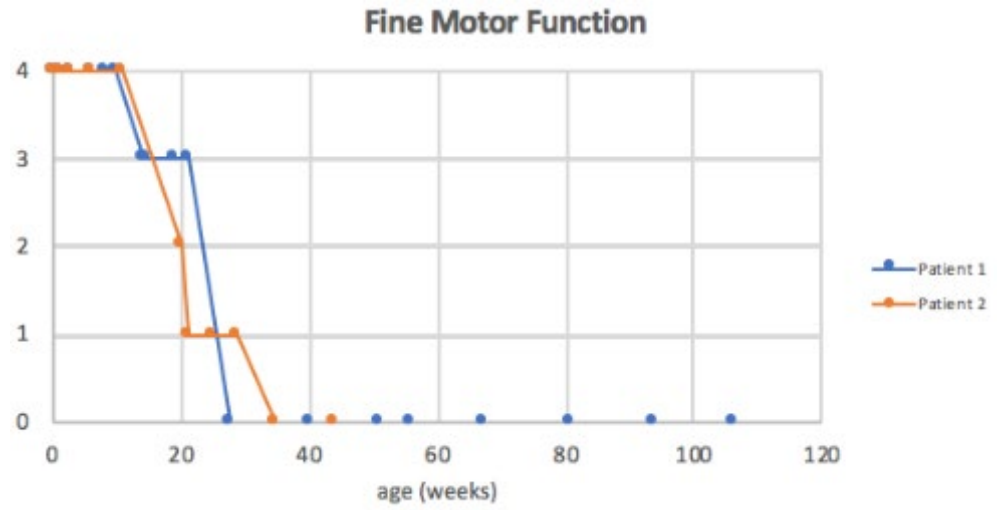
- Easy to use
- Excellent inter-rater reliability
- Retrospective and prospective use
- Focus on functional relevant outcomes

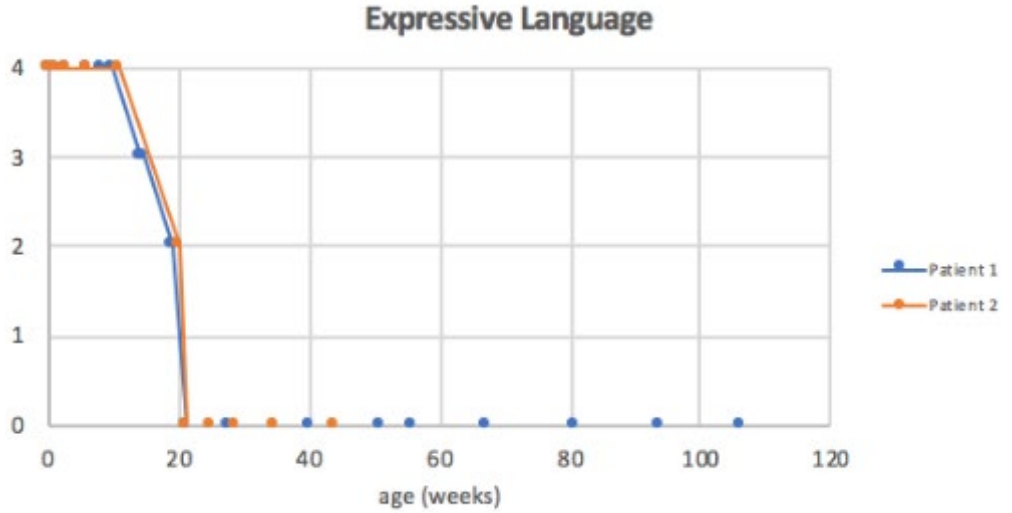
Add-on Categories		
Visual attention	Age appropriate score=1	Pathologic score=0
Agitation / irritabiliy	Age appropriate score=1	Pathologic score=0
Seizures (any type)	Absent score=1	Present score=0
Feeding	Age appropriate score=1	Pathologic score=0
Communication and interaction	Age appropriate score=1	Pathologic score=0

Hamburg infantile NCL score (Hamburg iNCL score)









Clinical trial design and endpoints – Challenges for CLN1 disease

Limited number of patients

Phenotype variability

Need for reliable clinical outcome measures / clinical biomarkers

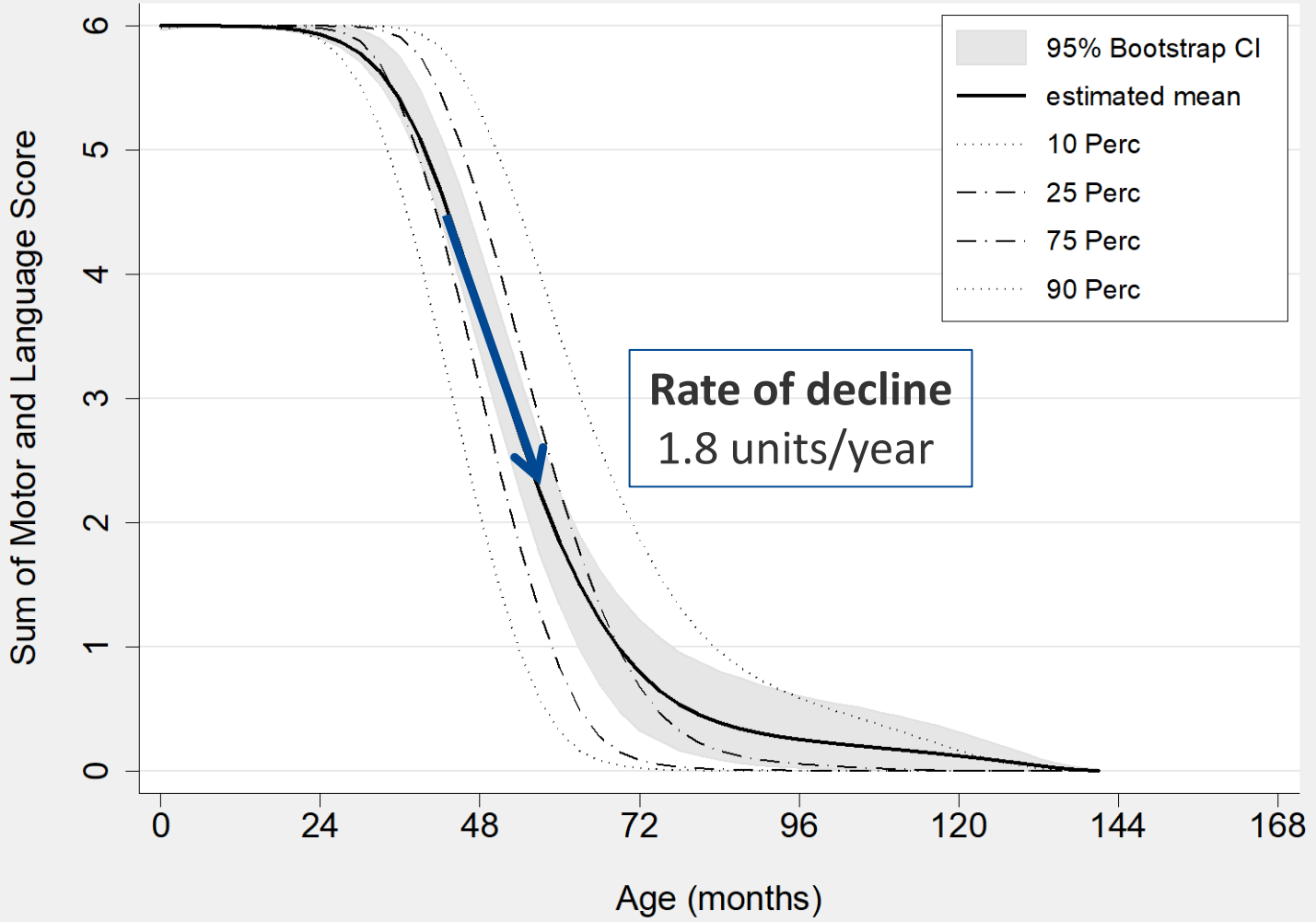
Use of natural history control data in clinical trials – *can it be done?*

Motor & language score – Rate of decline in CLN2 disease

Independent natural history data as primary efficacy outcome measures

Natural history data collection:

- Independent
- Successful audits by FDA and EMA
- International collaboration
- Non-exclusive data transfer

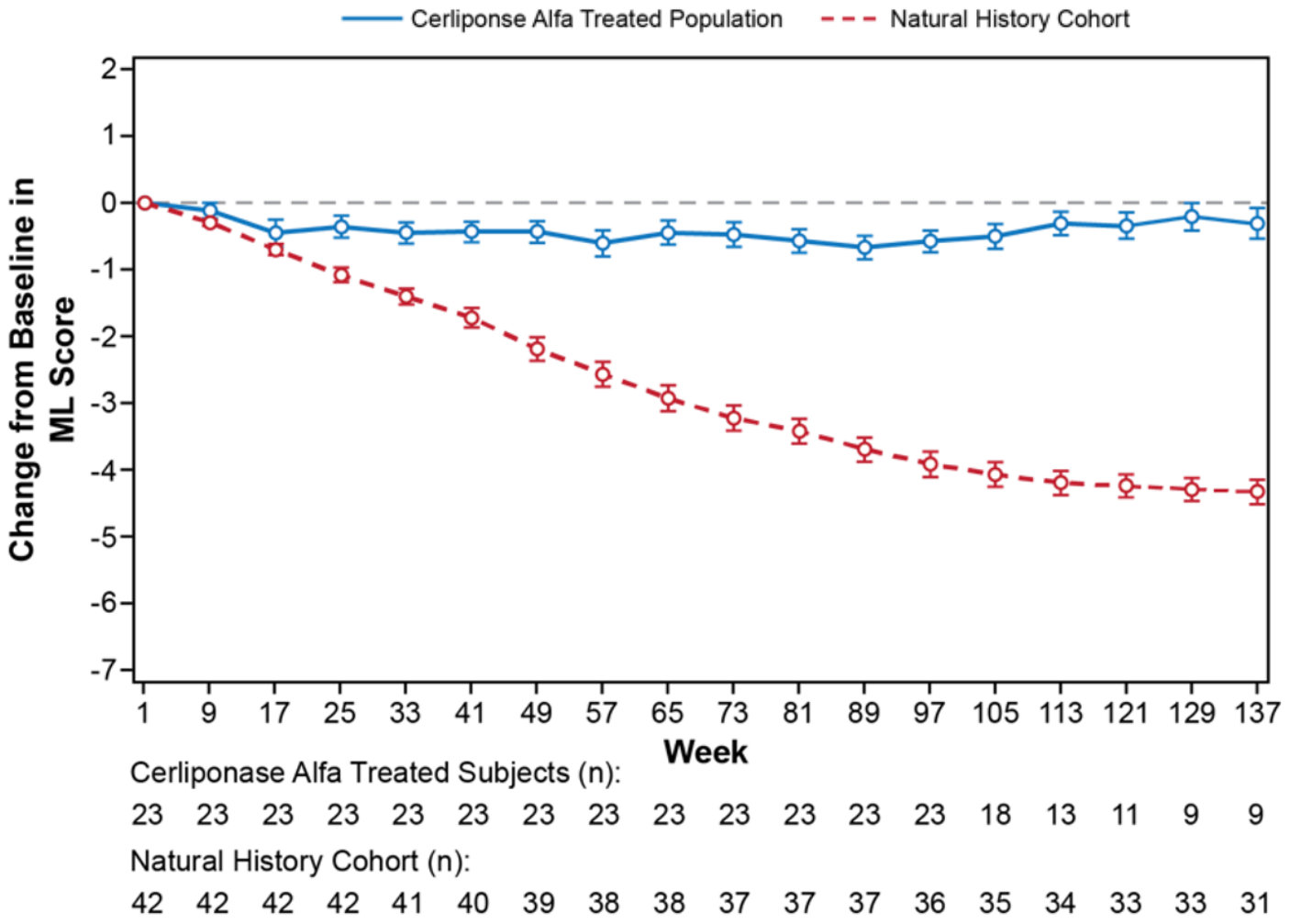


Nickel M et al. *Lancet Child Adolesc Health*. 2018;2:582-590.

Motor & language score (0-6) change from baseline*:

Cerliponase alfa treated CLN2 patients compared to Natural History

- After **48 weeks** of therapy:
  Treatment difference is 1.8 points in favor of treated subjects
- After **96 weeks** of therapy:
  Treatment difference is 3.3 points in favor of treated subjects



*Rate of decline for 201/202 based on change from 300 mg baseline, at last assessment

Schulz A, et al. *N Engl J Med* 2018;378:1896-1907.

Clinical trial design and endpoints – Challenges for CLN1 disease

Limited number of patients

Phenotype variability

Need for reliable clinical outcome measures / clinical biomarkers

Use of natural history control data in clinical trials – we have done it!

Use of natural history control data in clinical trials

Example from CLN2 Disease

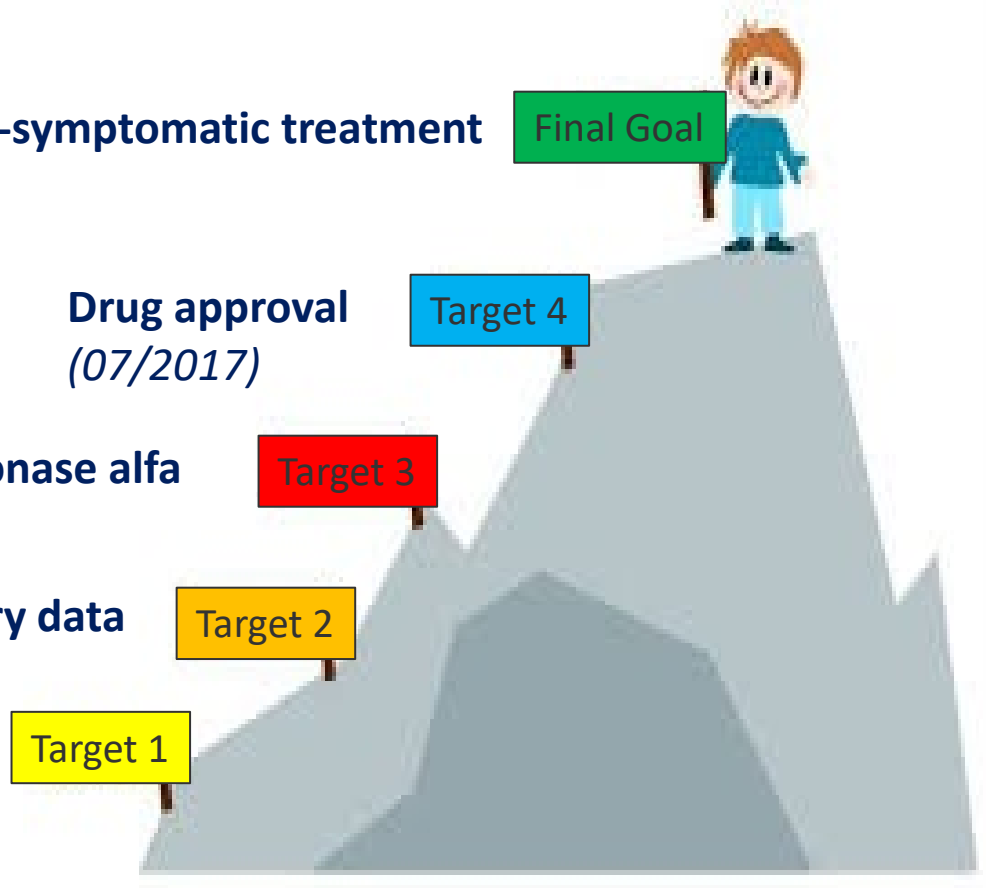
EARLY pre-symptomatic treatment

Drug approval
(07/2017)

Clinical Trials on Cerliponase alfa
(2013-ongoing)

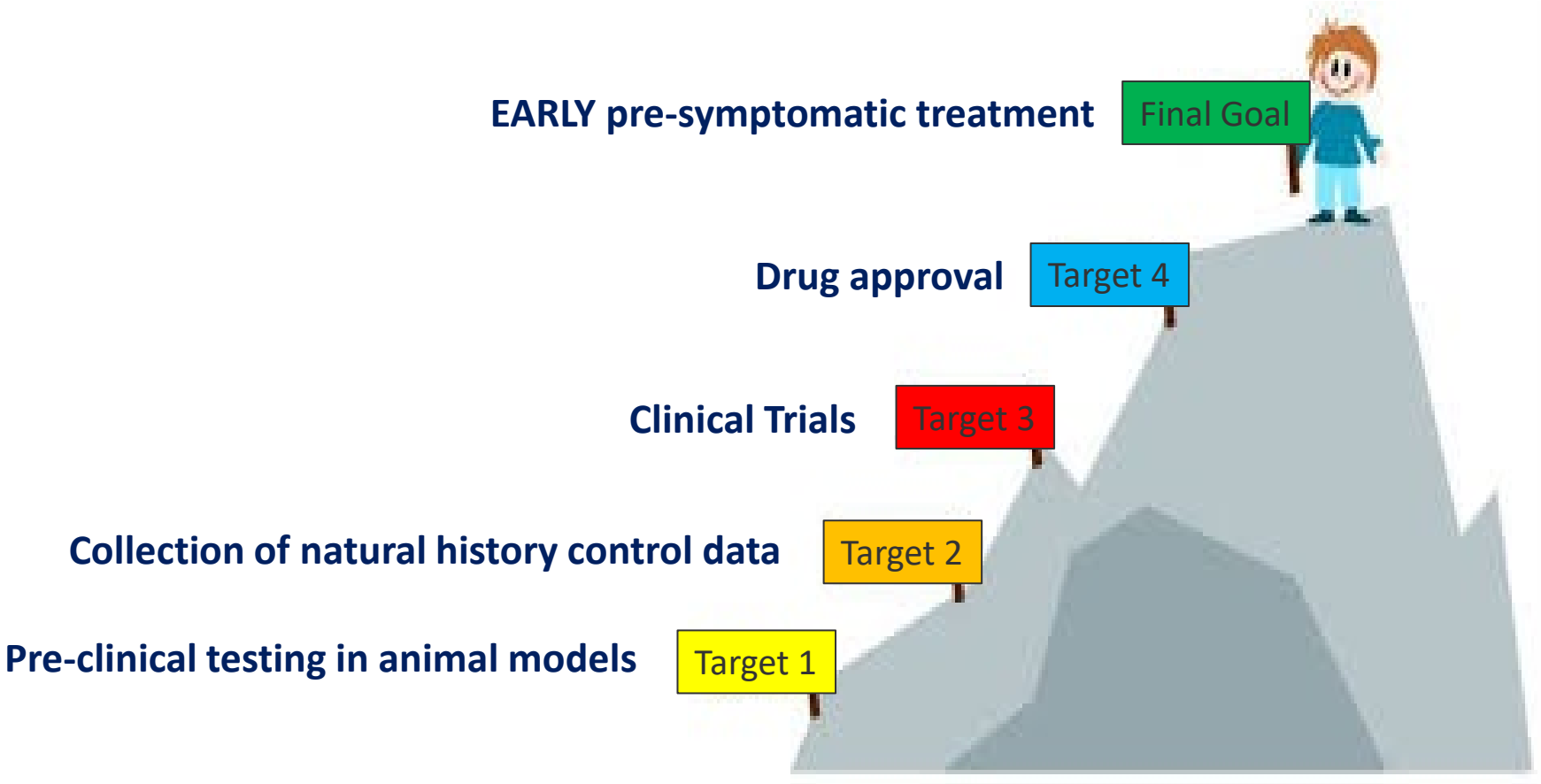
Collection of CLN2 natural history data
(2000-ongoing)

Pre-clinical testing in the CLN2 dog
(2010-2012)



Use of natural history control data in clinical trials

We need to start NOW for CLN1 Disease



Thank you!

Patients & Families

Fundraising

Research Grants

Q & A

Disease Burden – Patient and Family Perspective

Sharon King

President of Taylor's Tale

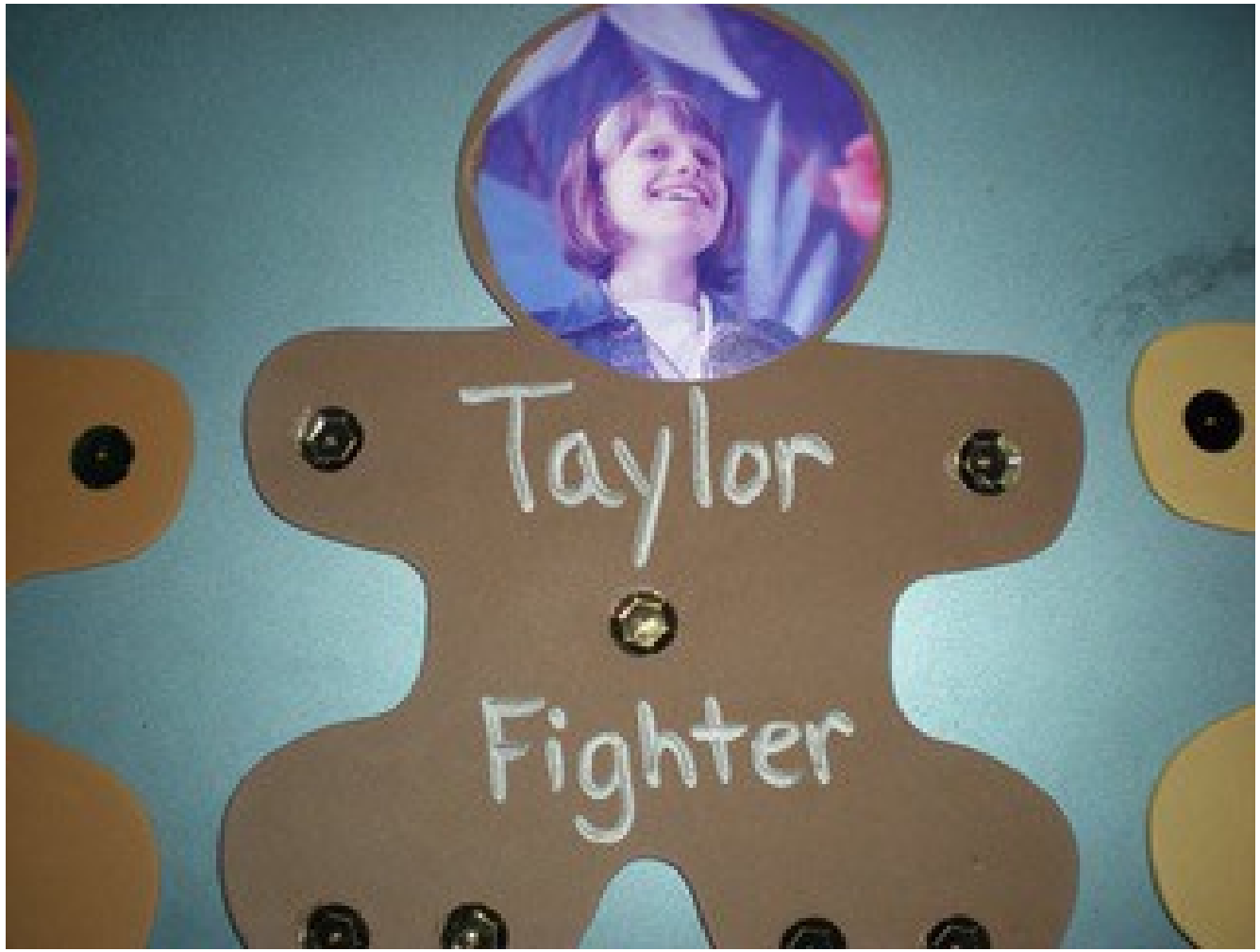
A life of promise…a legacy for the future

Symptoms leading to diagnosis

- Learning difficulties
- Vision loss

Two children with similar symptoms seeing the same pediatric neurologist…

Life changes…in the time it takes to say “CLN1 disease”



The burden on children and families

- For the child:
  - Isolation
  - Cognitive impairment
  - Loss of vision, speech, and mobility
  - Movement disorder
  - Seizures
  - Ability to swallow

- For the family:
  - Grief, anxiety, and depression
  - Isolation
  - Balancing everyday life and the needs of the child
  - Loss of productivity and the costs associated with chronic illness, often leading to financial difficulties
  - Guilt

Vision, commitment, and dedication to improving outcomes

Sometimes you just have to believe…

“I find that having an almost naïve belief that most everything is possible fuels a mindset that can accelerate movement from the impossible to possible."

Bradley W. Davis
Co-Founder, Partners for Parks
Charlotte, NC

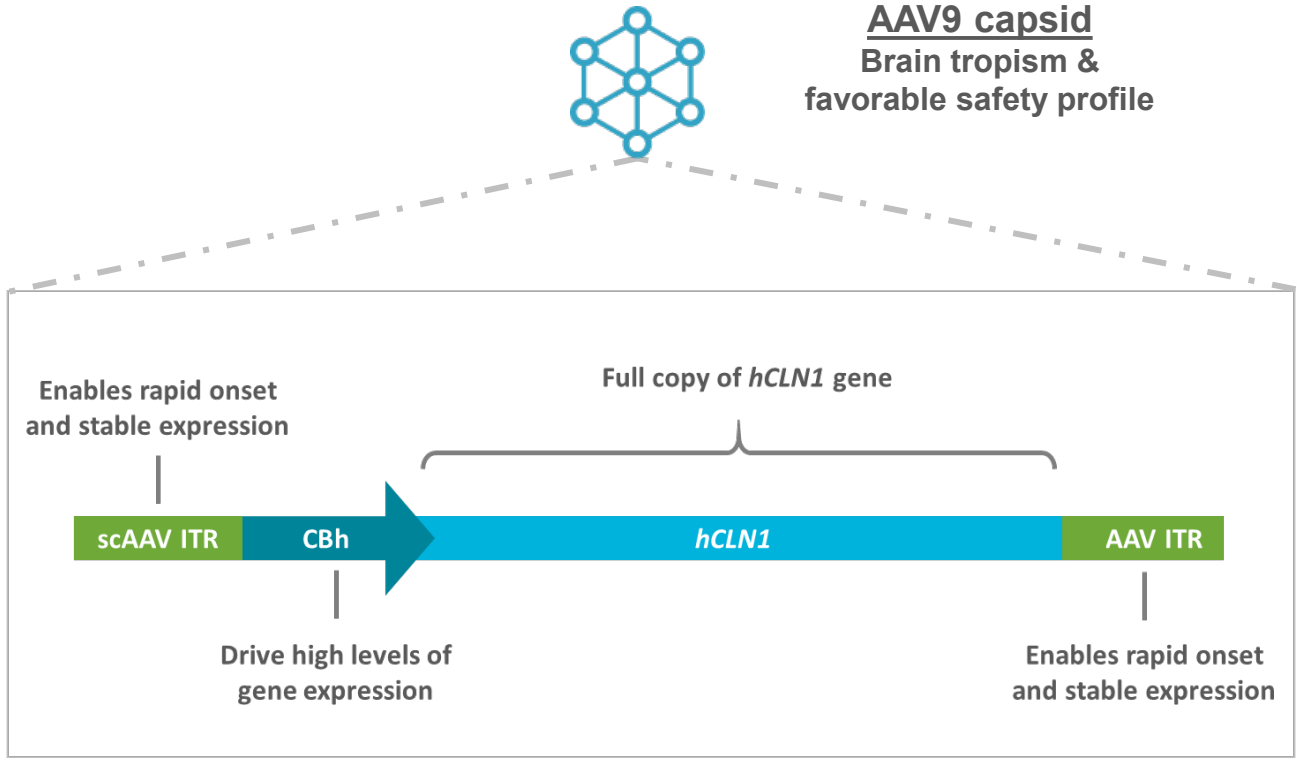
Preclinical Pharmacology and Toxicology Data

Steven Gray, PhD

Associate Professor, Department of Pediatrics at UTSW
Chief Scientific Advisor, Taysha

CLN1 disease is a severe neurodegenerative lysosomal storage disease

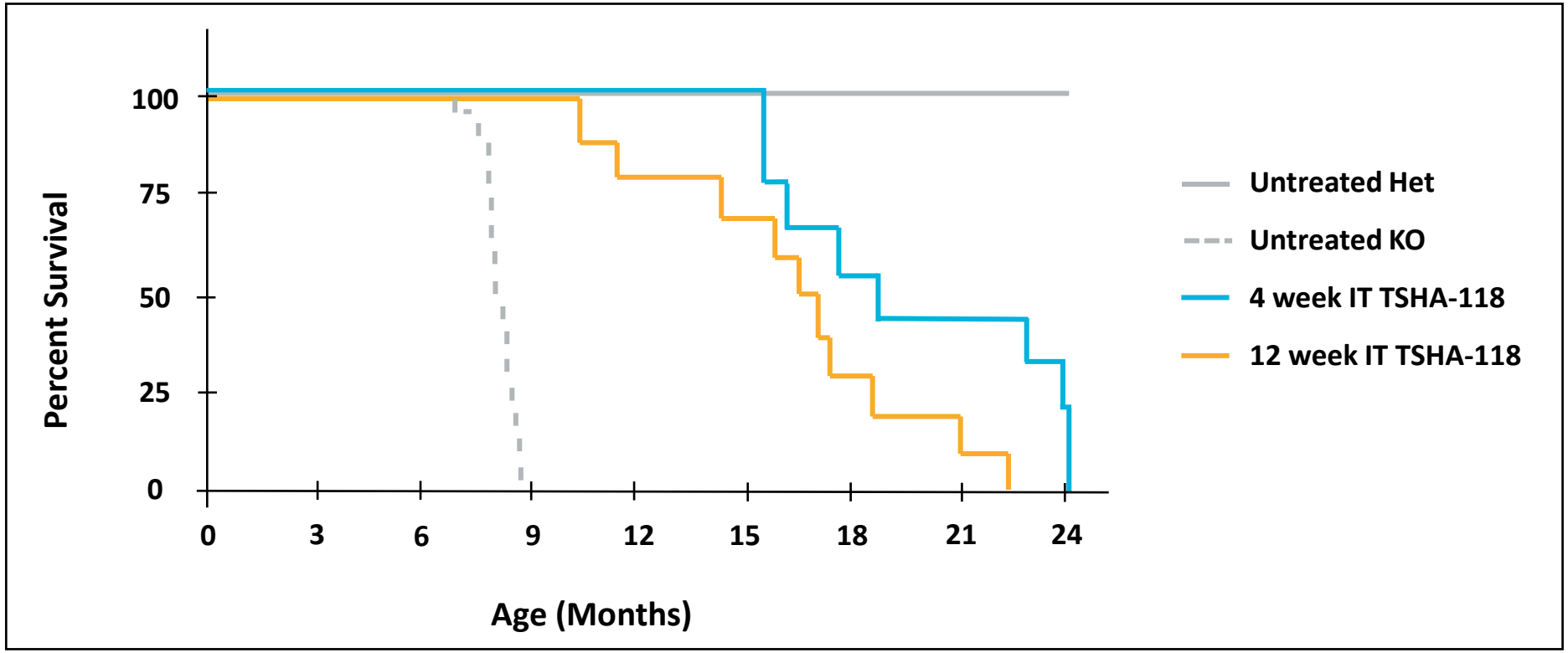
- Severe, progressive, neurodegenerative lysosomal storage disease, with no approved treatment
- Caused by mutations in the *CLN1* gene, encoding the soluble lysosomal enzyme palmitoyl-protein thioesterase-1 (PPT1)
- The absence of PPT1 leads to the accumulation of palmitoylated substrate within the lysosome



TSHA-118 preclinical studies to date

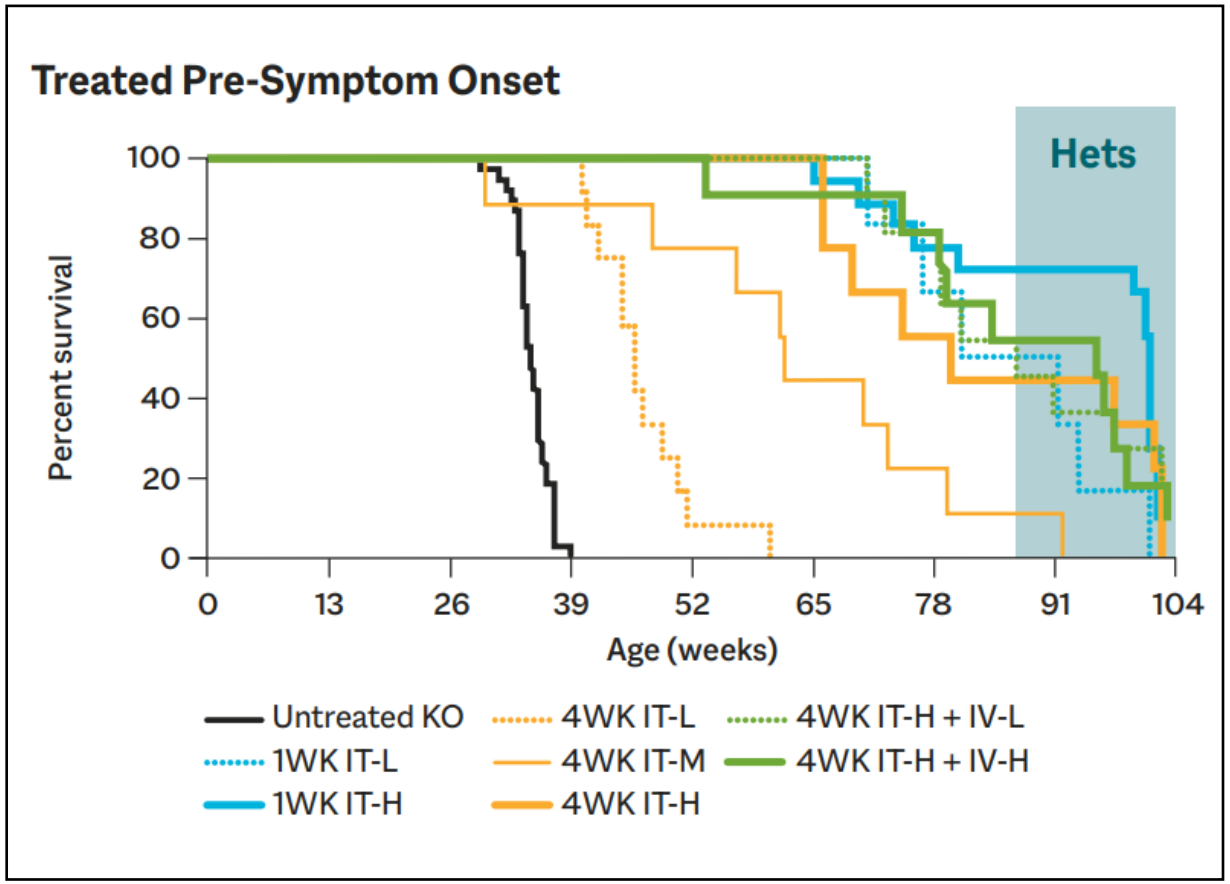
#	Study Scope (ID)	Model System	Age at dosing	Route of Administration & Dose (vg/animal)	Major Findings
1	Proof of Concept; (UNC-2014-001)	PPT1$^{-/-}$ mice	1, 4, 12, 20, 26 weeks	IT: 7.0x10^{10}, 2.2x10^{11}, 7.0x10^{11}	• Elevated levels of active PPT1 in serum • Significant survival benefit and functional improvements • Rescue of behavioral deficits
2	Safety and Efficacy (UNC-2015-001)	PPT1$^{-/-}$ and PPT1$^{+/-}$ mice	P0 – P2	IV: 2.8x10^{11}	• Significant survival benefit: median life-span 21 months in treated mice vs. 8.3 months in untreated mice
3	Efficacy of Combination IT and IV Dosing; (UNC-2016-001)	PPT1$^{-/-}$ mice	20 weeks	IT: 7.0x10^{10}, 7.0x10^{11} IV: 7.0x10^{11} IT: 7.0x10^{10}, 7.0x10^{11} each in combination with IV: 7.0x10^{10}, 2.2x10^{11}, or 7x10^{11}	• Dose-dependent survival benefit and improvements in function • Single routes and lower doses provided some benefit • Maximum benefit with high IT plus high IV dose at this stage of disease (i.e. - 20 week old mice)
4	Efficacy of Combination IT and IV Dosing; (UNC-2017-001)	PPT1$^{-/-}$ mice	4 weeks	IT: 7.0x10^{11} IT: 7.0x10^{11} in combination with IV: 7.0x10^{10} or 7.0x10^{11}	• Testing up to 12 months demonstrated survival or behavioral benefits for the combination treatment similar to IT dose alone, which had a median lifespan of 18.7 months
5	Biodistribution and PPT1 Activity Comparison; (UNC-2017-002)	C57B1/6 mice & Fischer rats	Mouse: 9 wks Rat: 11 wks	IT Mouse: 9.1x10^{11} IT Rat: 3.64x10^{12}	• Maximum dose IT injection of TSHA-118 in wild-type rats and mice resulted in similar levels of vector biodistribution and PPT1 enzyme activity in serum and most tissues of both • Cross-species comparison supports the dosing rationale of 5.0x10^{14} total vg and 1x10^{15} total vg for human trial
6	Toxicology Study in Rat; (MPI-2389-010)	Wistar Hans rats	6 weeks	IT: 2.0x10^{11}, 2.0x10^{12} IV: 5.6x10^{12}, 2.0x10^{13} IT: 2.0x10^{12} in combination with IV: 2.0x10^{13}	• Administration of TSHA-118 was not associated with any mortality, clinical observations, bodyweight, or food consumption changes
Taking these nonclinical studies into consideration, there is support for 5.0x10^{14} total vg and 1.0x10^{15} total vg dosing in human trials					

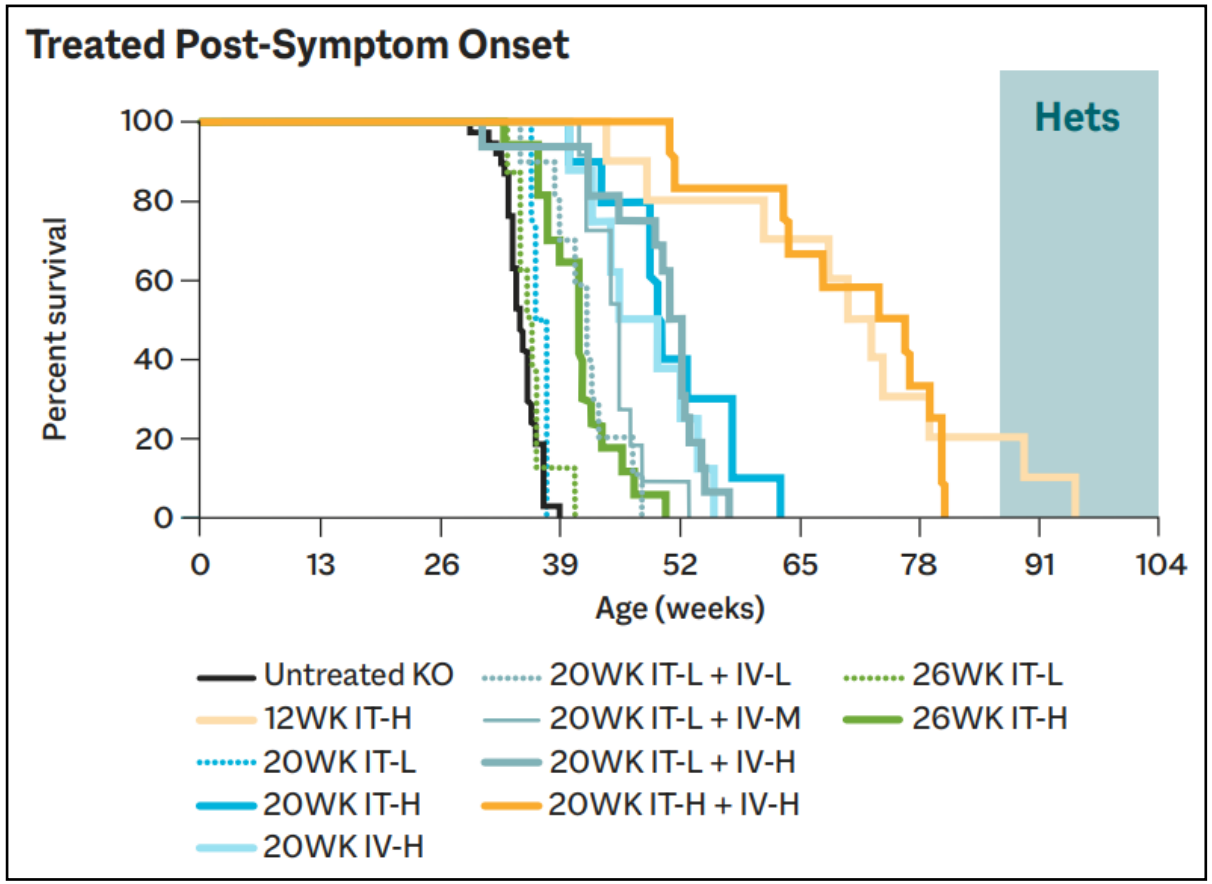
TSHA-118-treated CLN1 KO mice had improved survival rates



IT administration of TSHA-118 significantly extended survival of *PPT1* KO mice for all ages and at all dose levels

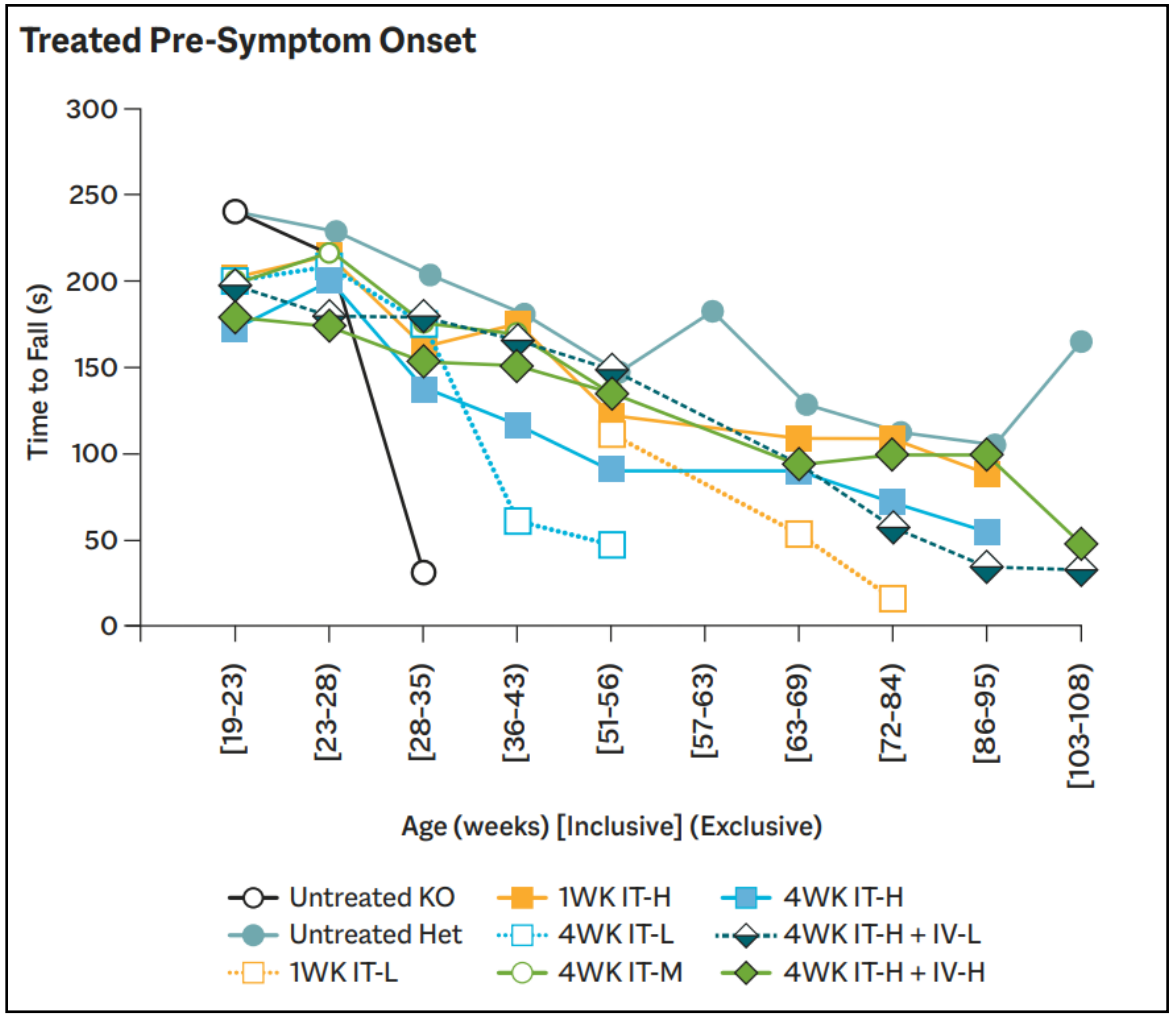
Higher doses of TSHA-118 and earlier intervention mediated stronger rescue of CLN1 KO mice

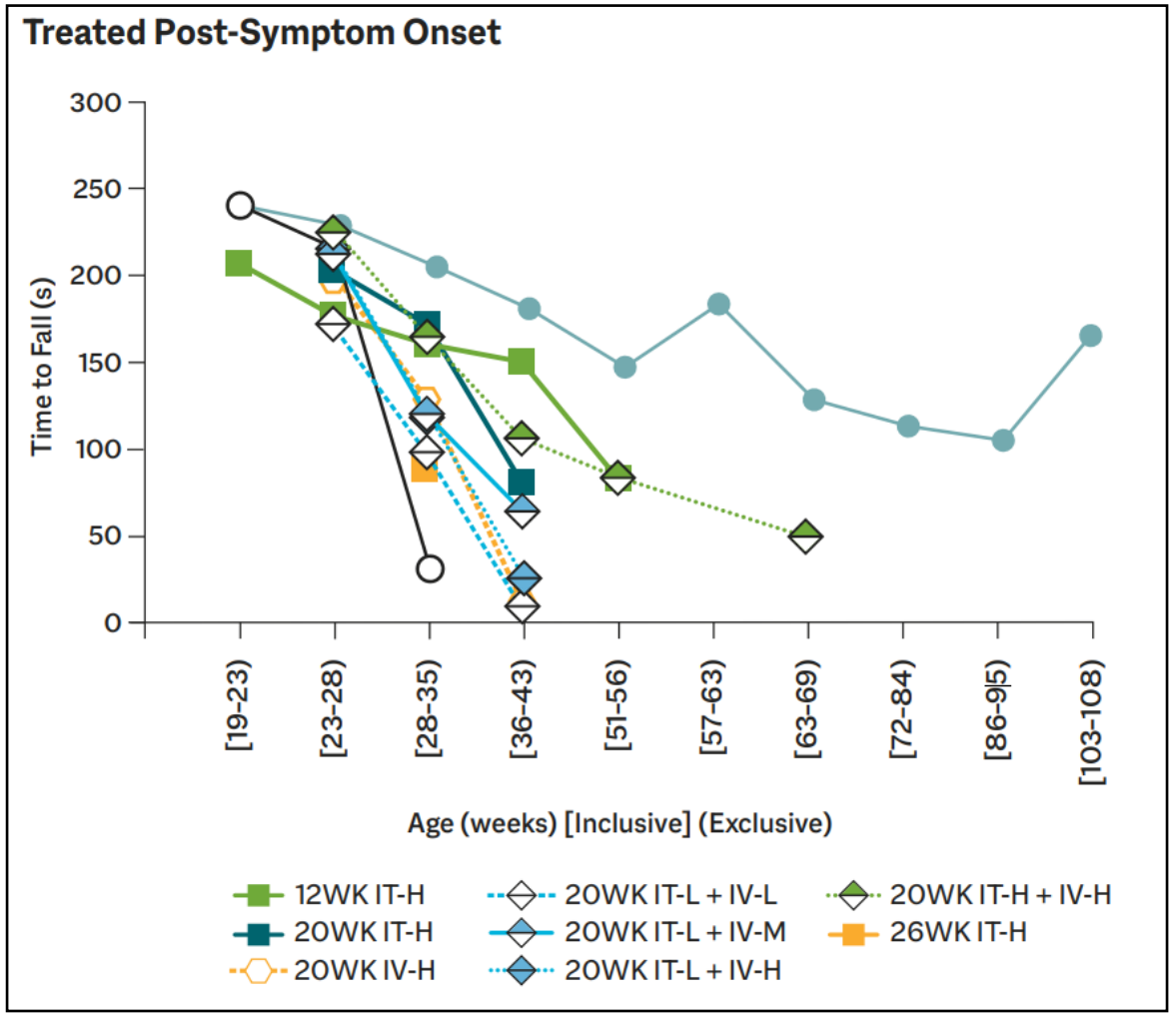




L - $7.0x10^{10}$ vg/mouse M - $2.2x10^{11}$ vg/mouse H - $7.0x10^{11}$ vg/mouse

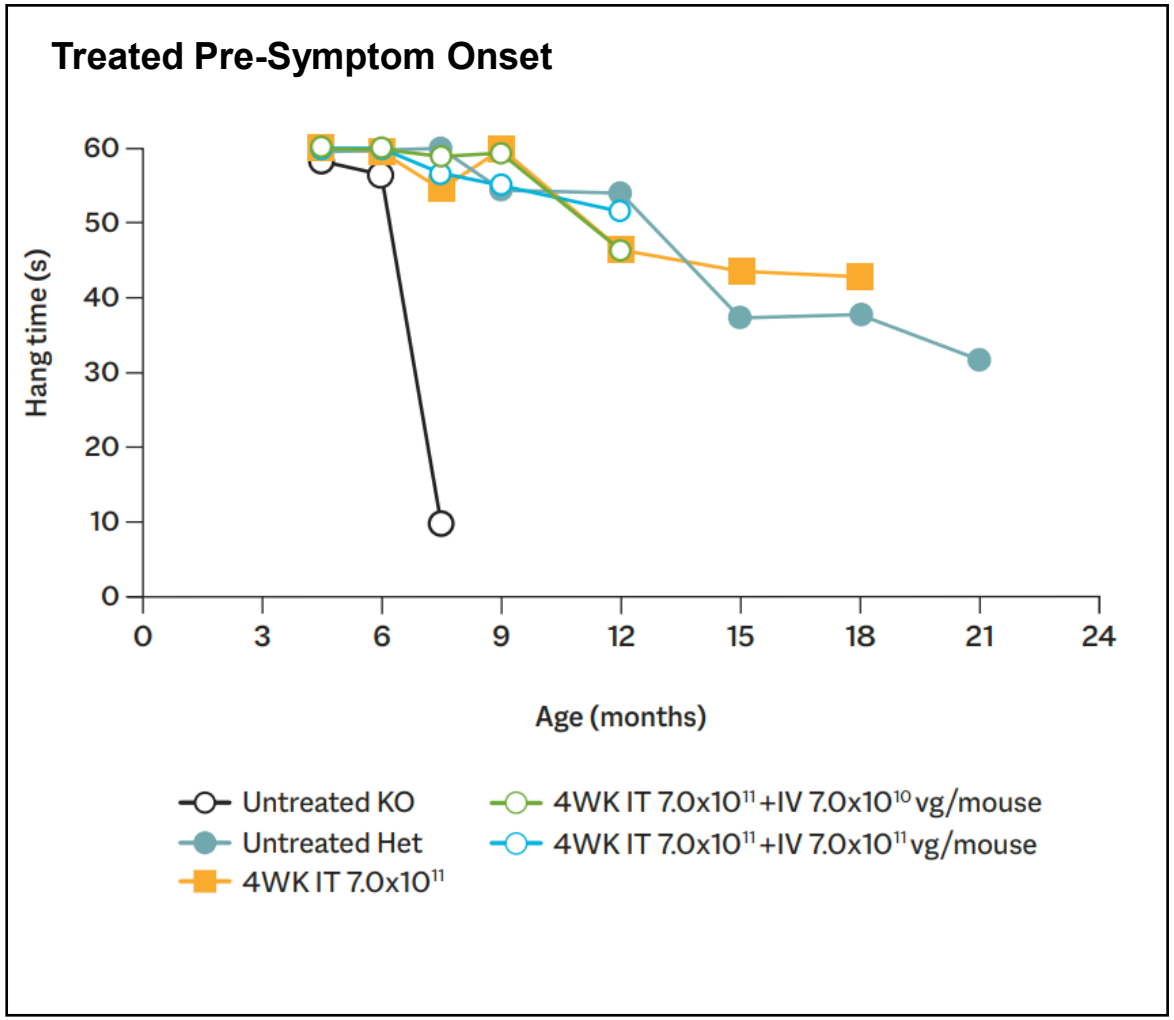
TSHA-118-treated CLN1 KO mice had sustained preservation of motor function as measured by rotarod testing

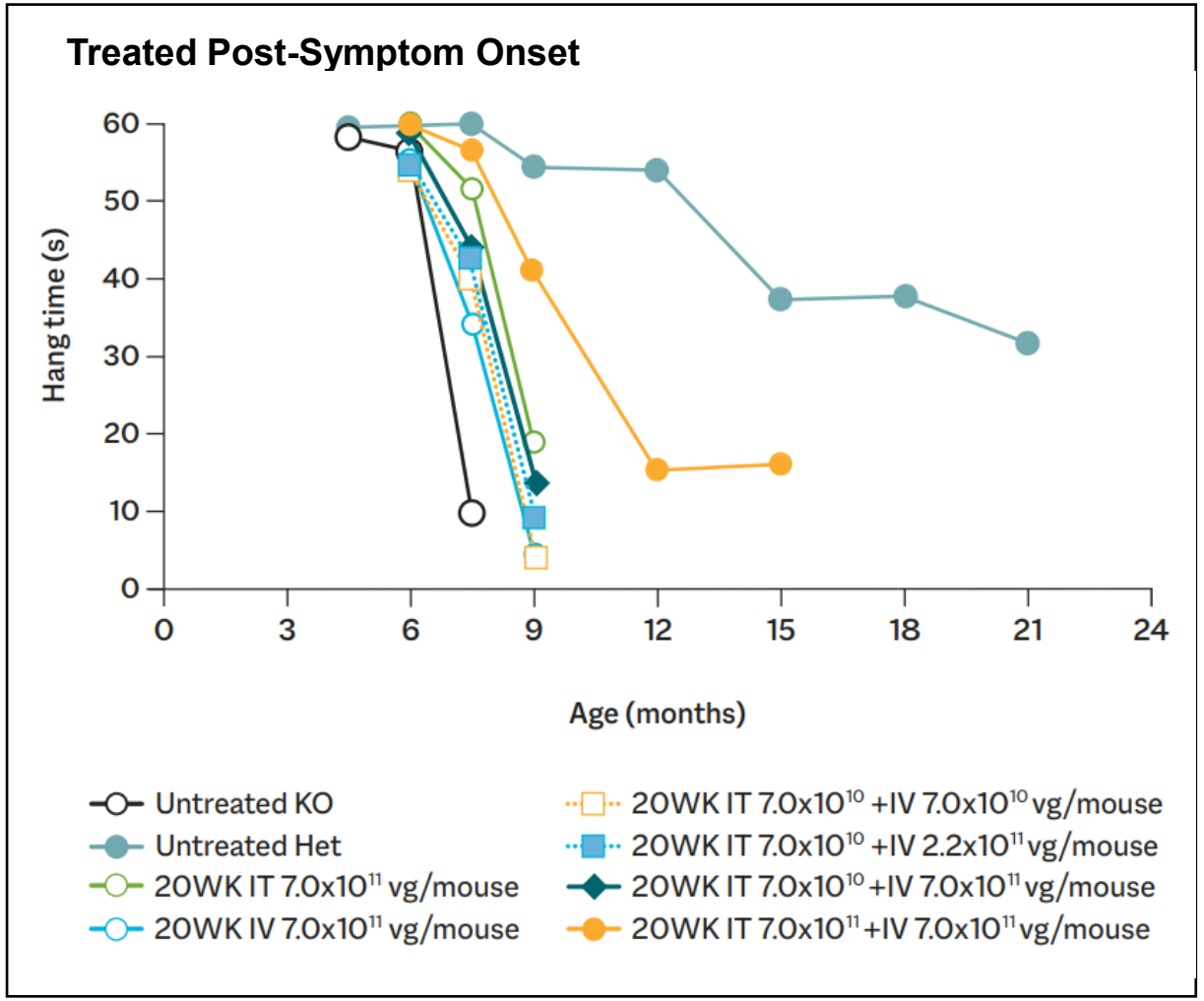




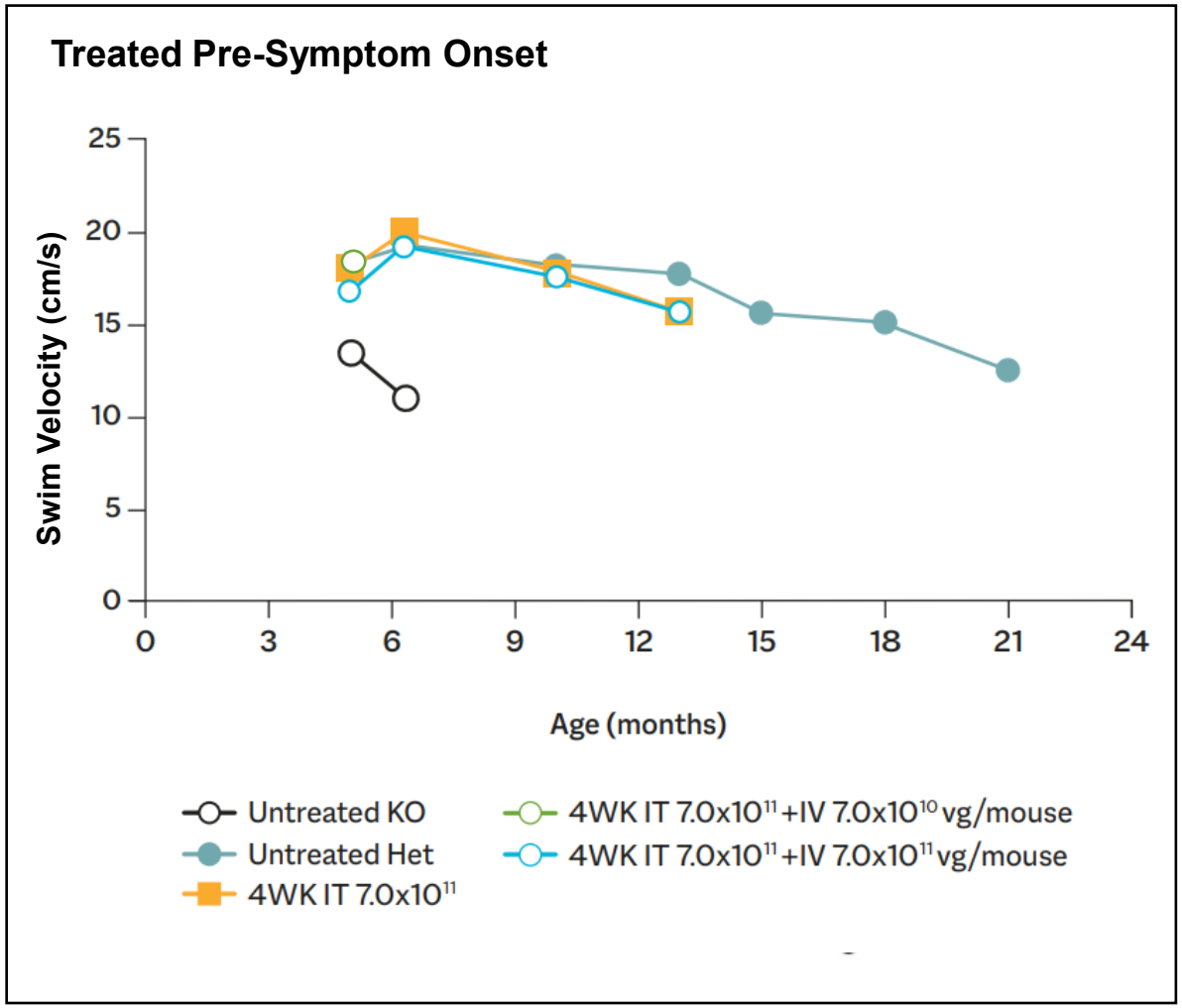
L - $7.0x10^{10}$ vg/mouse M - $2.2x10^{11}$ vg/mouse H - $7.0x10^{11}$ vg/mouse

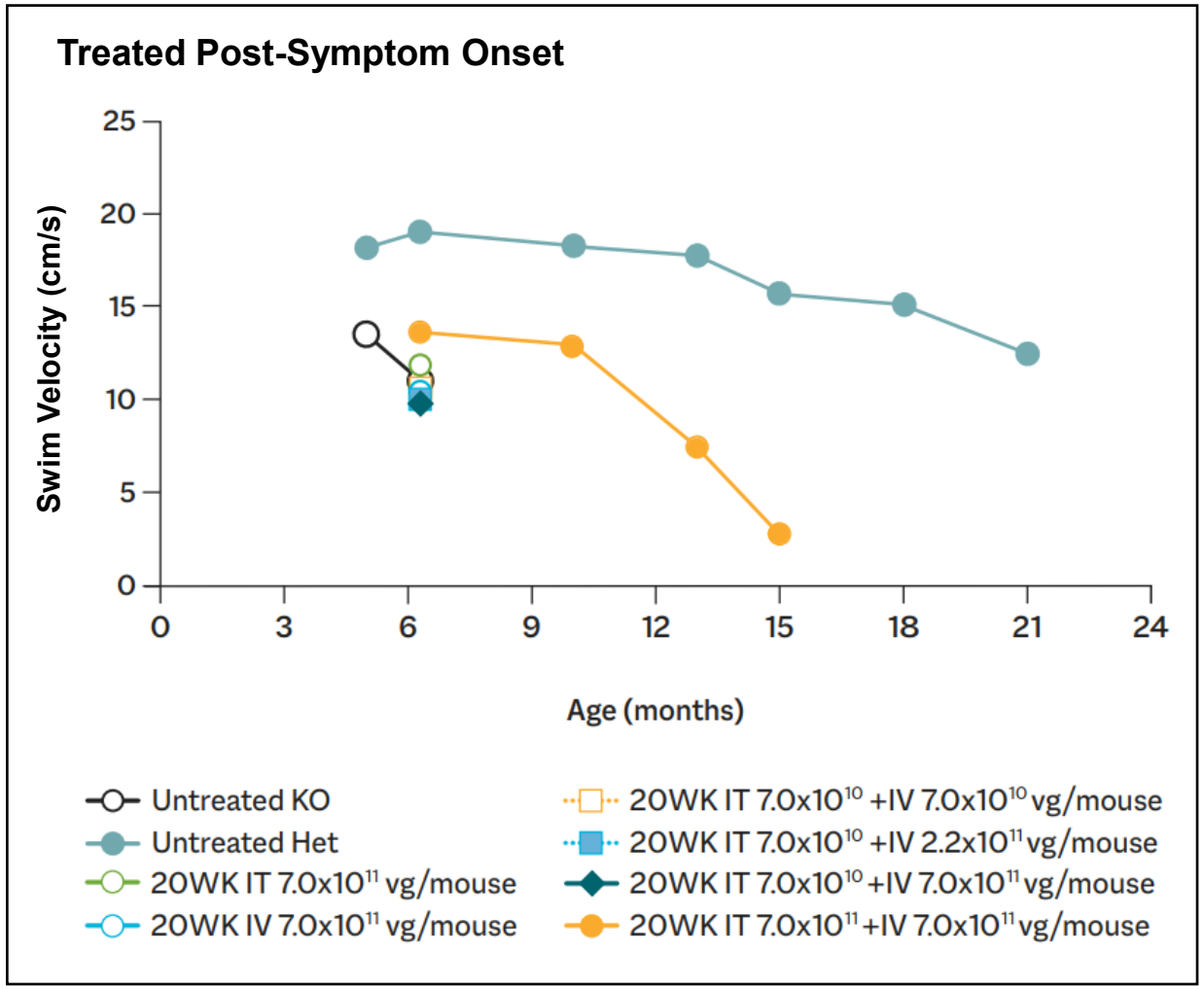
TSHA-118-treated CLN1 KO mice were evaluated for grip strength by measuring hanging time



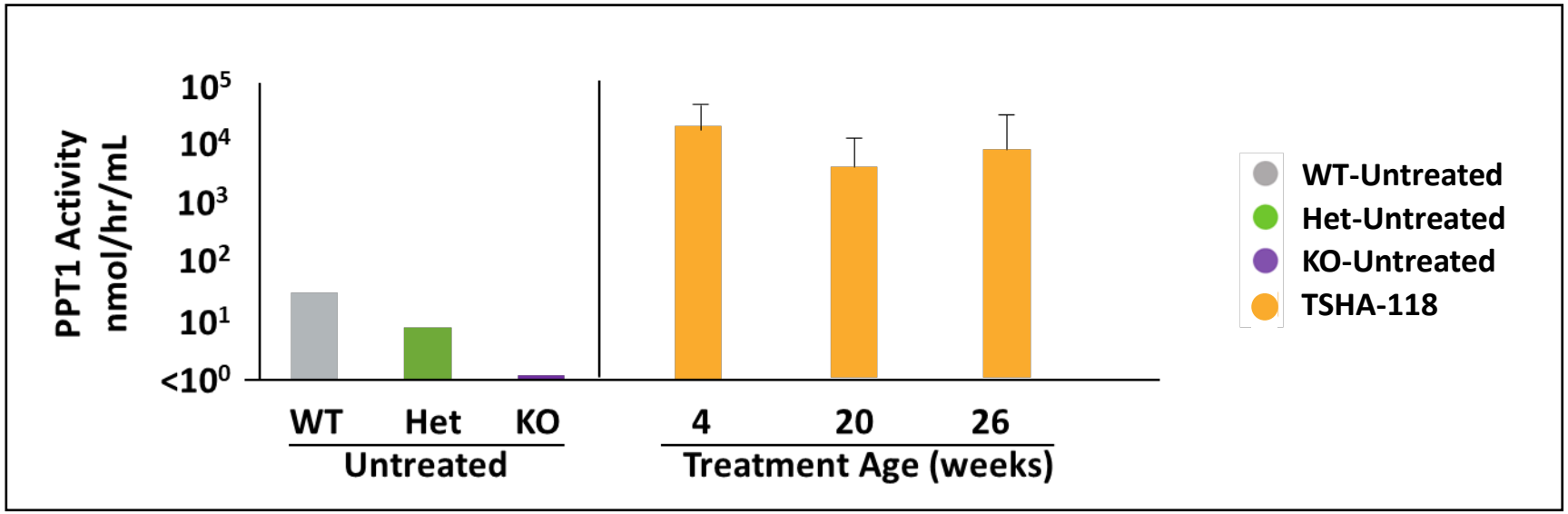


TSHA-118-treated CLN1 KO mice were evaluated on swimming speed as measured by morris water maze testing





TSHA-118-treated CLN1 mice had increased and sustained plasma PPT1 activity



- Supraphysiological levels of active PPT1 were observed in all TSHA-118 treated mice and persisted through the study endpoint
- Persistence of effect after animal sacrificed up to 8.5 months post-treatment

Summary of 6-month toxicology safety study

- Study to assess the potential toxicity and tissue biodistribution of TSHA-118 following IT and / or IV administration in wild-type Wistar Hans rats (108 male and 108 female) at 6 weeks of age
- There was a wide therapeutic window with which to dose (vg/animal); IV low dose of $5.6x10^{12}$, IV high dose of $2.0x10^{13}$, IT low dose of $2.0x10^{11}$, IT high dose of $2.0x10^{12}$, and combination IV and IT high dose
- The viral vector was widely distributed and detected in all tissue samples at Day 8 and Week 12
- Transduction of brain, spinal cord, and other organs was evident
- No toxicology findings at high dose in organs or tissues
- **Administration of TSHA-118 was not associated with any mortality, clinical observations, body weight, or food consumption changes that were considered adverse out to 6 months post-injection**
- **Administration of TSHA-118 resulted in supraphysiologic PPT1 enzyme activity in serum, liver, heart, brain, and spinal cord, which persisted over time**

Q & A

Clinical Development Strategy

Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM

Chief Medical Officer and Head of R&D

TSHA-118 program update

- Advisory board March 2021
- Conducted CLN1 patient focus groups in the early part of the year
- Overall positive regulatory feedback with multiple key regulatory agencies
- Completed cGMP drug product fill
- Study design and patient feedback abstracts accepted by International Congress on Neuronal Ceroid Lipofuscinosis
- Interventional protocol nearing completion

Advisory board overview

Scientific advisory board of preeminent international scientific and clinical thought leaders in Battens disease, gene therapy, CNS diseases, and metabolic medicine

Feedback from global, rare disease expert KOLs during program advisory boards is used to inform clinical study design and plan regulatory interaction

Advisors provided insightful recommendations on the current clinical study design, preclinical results, and utility of the CLN1 natural history data

Recommendations for patient identification and selection, inclusion / exclusion criteria, and outcome assessments (including UBDRS and other disease scales) were obtained

Key takeaways from Advisory board

- Diagnosis is typically confirmed with genetic testing
  - Early CLN1 diagnosis may be challenging due to common nonspecific initial symptoms
- Showing positive PPT1 activity in the CNS would provide assurance of possible disease correction
  - **An increase from 0.1% to 5% would be positive, adult-onset patients range from 5% to 8%**
- Different outcome measure may be needed for different age cohorts; disease onset and rate of progression varies among infantile, late-infantile and juvenile patients
  - Slow attainment of skills followed by regression is typically seen in infantile patients
  - Vision loss is a common initial symptom in infantile, late-infantile, and juvenile patients
  - Seizures and behavioral issues may occur prior to vision deterioration in some juvenile and late-infantile patient
- IT administration will have systemic leakage and may reflect a dual route of administration approach with transduction in several non-CNS regions (e.g., liver and heart)
- When infantile patients start to experience signs and symptoms, it is likely that some degree of neuronal loss is already occurring
  - Low dose early treatment may be more effective than late high-dose treatment
- Select outcome measures specific to the patient and produce clinically meaningful change for patients and families (important to FDA, EMA and all regulatory agencies in general)
- KOL advisors were enthusiastic and optimistic about Taysha's CLN1 gene therapy program

We work closely with patients and families to inform our clinical development plan

CURIOSITY

Understand the patient experience, including most challenging symptoms and QOL impacts

Identify patient-centric endpoints and meaningful outcomes

Uncover educational gaps for families about gene therapy and clinical trials

COLLABORATION

Develop clinical trial protocols based on patient and family insights

Partner with community to raise awareness and recruit clinical trials

Co-create the optimal clinical trial support to enhance experience and aid retention

Patient / caregiver input into TSHA-118 clinical study design

We routinely engage with caregivers of loved ones with rare diseases to learn about their experiences, needs, and priorities as well as to inform clinical study design

12 CLN1 disease caregivers participated; 5 with infantile CLN1 disease, 2 with late infantile CLN1 disease, 4 with juvenile CLN1 disease, with the assistance of patient advocacy groups (Batten Disease Support and Research Association and Batten Disease Family Association)

Caregivers shared perspectives on CLN1 disease symptoms and therapeutic priorities via an in-depth survey, a discussion forum, and focus group

Most challenging symptoms of CLN1 disease

Caregivers of loved ones with CLN1 disease were recruited from the US, Canada, and UK

	Infantile CLN1 disease	Late Infantile CLN1 disease	Juvenile CLN1 disease
CLN1 disease symptoms by phenotype and disease progression	• Communication issues/ inability to speak • Seizures • Inability to sit • Inability to stand or walk • Myoclonic jerks • Irritability • Scoliosis • Chest infections • Decline in mental development/dementia	• Communication issues / inability to speak • Seizures • Inability to sit • Inability to stand or walk	• Communication issues / inability to speak • Vision loss • Cognitive impairment / dementia • Muscle stiffness • Hallucinations • Restlessness / sleep issues

Source: Patient Focus Groups

Voices from the front line - Impact of CLN1 disease

When caregivers were asked "Which symptoms have / had the greatest impact on your / your loved one's quality of life," they replied:

Cognitive decline, mood, communication, and speech

"I miss seeing my girl playing with toys, and I miss the days when she could look me in the eye and attempt to communicate. I want to hear her laugh again."

"It is painful to watch her struggle to remember her words and articulate her ideas. She tries so hard but gets frustrated. I can see the light bulb dimming and it's very difficult to watch."

"I would give anything to hear his voice again, and it would be such a comfort if he could tell me what he's thinking and feeling."

Seizures

"It seems to be the most disabling for her and the whole family. It keeps everyone's anxiety high."

Motor decline

"No child should be left unable to play and explore. I miss the days of scooping a mouthful of dirt and grass out of his mouth or prying his dirty little fingers apart before he could eat more!"

"We have to move her into different positions and try to keep her comfortable. We end up holding her a lot, which limits the things we can get done during the day. She will cry and need to be repositioned during the middle of the night."

Vision

"I wish he could see what we see and experience. Blindness caused a lot of depression and anxiety for him."

Source: Patient Focus Groups

Phase 1/2 adaptive trial for TSHA-118 in CLN1

Goals and Targets of Trial

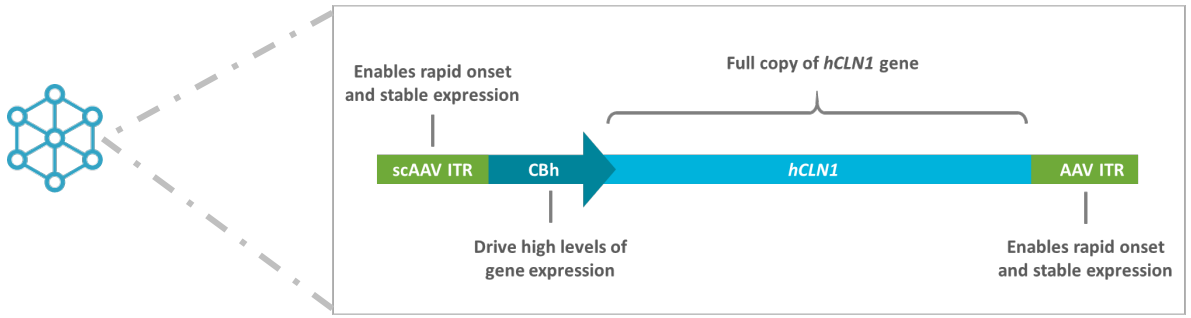
Goals

- **Key biomarker endpoint** – PPT1 enzyme activity in CSF and serum
- **Key efficacy endpoints** – Pathologic, physiologic, functional and clinical markers, UDBRS, Hamburg scale, developmental milestones, seizure activity, visual acuity

Target Recruitment

- Approximately 12-15 subjects with confirmed CLN1 diagnosis
- Infants, late infantile, and juvenile cohorts to be included in study

Product Details and Dose Cohorts



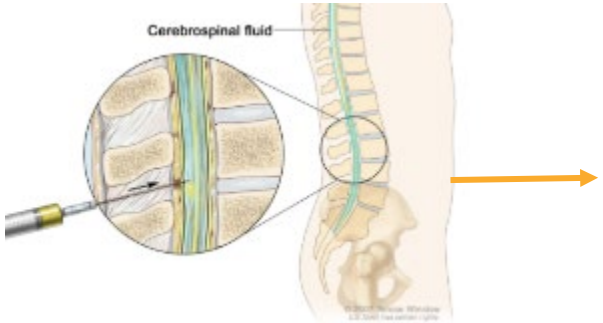
Dose Cohorts

- 5×10^{14} vg (IT)
- 1.0×10^{15} vg (IT)
- Dose expansion

Route and Method of Administration

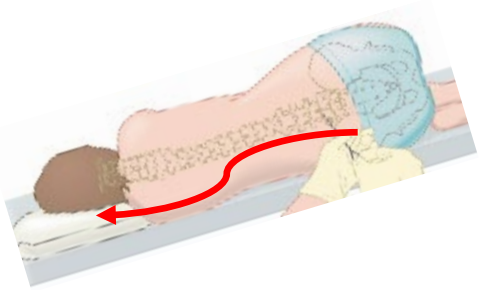
Administration

- Lumbar Intrathecal Infusion (IT)
- Amount and rate: 1 mL/min for total of 10-12 mL
- Immunosuppression regimen of prednisolone and sirolimus



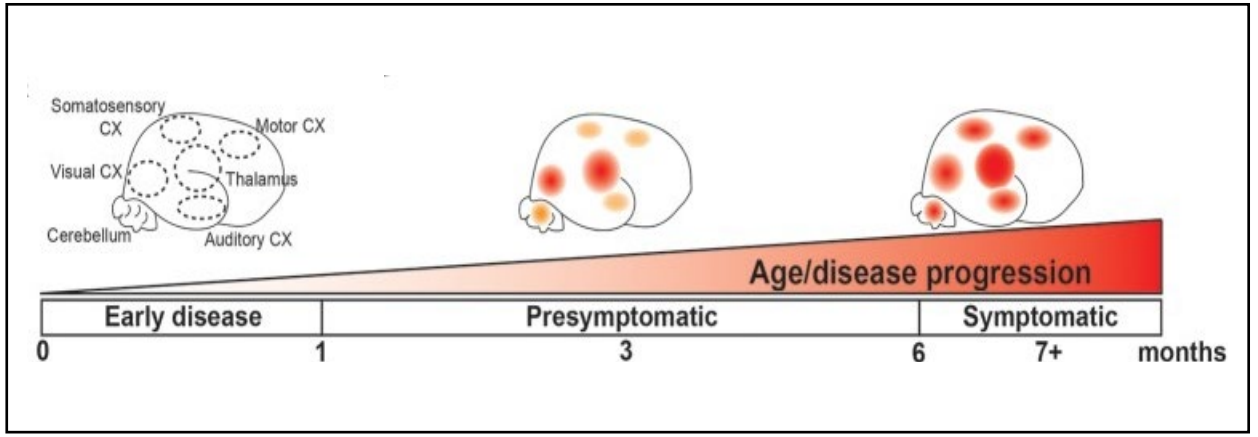
Technique to Improve Transduction

- Trendelenburg position (15-30^{o})
- During infusion & 1 hour post infusion



Importance of PPT1 as a biomarker for CLN1 disease

- Disease pathology due to bi-allelic loss-of-function mutations in the *PPT1* gene, which encodes the enzyme palmitoyl-protein thioesterase-1 (PPT1), a small glycoprotein involved in the catabolism of lipid-modified proteins in the lysosome
- In all forms of CLN1 disease, absence of PPT1 enzyme leads to accumulation of palmitoylated substrate in cells (visible on electron microscopy)
- This accumulation leads to cell dysfunction, cell death and neurodegeneration
- TSHA-118 is designed to replace the faulty gene in affected cells and restore functionality of the protein
- Advisors noted an increase from 0.1% to 5% would be positive, adult-onset patients range from 5% to 8%



Introduction of a functional *PPT1* gene offers the potential of a minimally invasive and effective therapeutic approach, which targets the root cause of the disease, the loss of PPT1 enzyme

Koster KP, Yoshii A. Depalmitoylation by Palmitoyl-Protein Thioesterase 1 in Neuronal Health and Degeneration. *Front Synaptic Neurosci*. 2019;11:25. Published 2019 Aug 29. doi:10.3389/fnsyn.2019.00025

Overview of key efficacy endpoints

Biomarker: PPT1 enzyme activity in CSF and serum	• PPT1 is the underlying pathological deficit and replacement should enable removal of accumulated substrate
Unified Batten Disease Rating Scale (UBDRS) for global disease burden	• Designed to assess motor, seizures, behavioral, and functional capability in children with NCL • Seizure type, frequency, and duration will also be assessed by UBDRS • Precedent with other forms of Battens disease
Hamburg Scale for motor, visual, language, and seizure scores	• An established tool to capture function, rate of decline, and / or regression specific for NCLs • Seizure scores will also be assessed by the Hamburg Scale • Precedent with other forms of Batten disease
Bayley-III	• Cognitive Scale assesses attention to familiar and unfamiliar objects, looking for a fallen object, and pretend play • Language Scale focuses on recognition of objects and people, following directions, and naming objects and pictures • Motor Scale assesses gross and fine motor skills such as grasping, sitting, stacking blocks, and climbing stairs
Clinical Global Impression-Improvement (CGI-I) Scale	• A clinician-rated assessment tool used to establish global improvement or change in comparison to baseline following care, treatment, or intervention

Overview of secondary and exploratory endpoints

Disease-Specific/Global Assessments
- CHOP INTEND: motor function
- Seizure type, frequency, and duration assessed by seizure diary
- Vineland-III to assess adaptive behaviors
- Intellectual capacity assessed by WPPSI-IV or WISC-V

Ophthalmological Assessments
- ERG, OCT, and preferential looking test
- Visual acuity

Imaging and neurophysiology
- Brain MRI including volumetric changes (% gray matter volume, % ventricular volume, and total brain volume)
- Standard awake 60-minutes electroencephalogram (EEG)

Biomarkers
- Reduction in accumulation of palmitoylated substrate

Communication Assessments
- Observer Reported Communication Assessment (ORCA)

Quality of Life/Other Assessment
- PedsQL™ Generic Core Scales
- Pittsburgh Sleep Quality Index (PSQI)
- Parenting Stress Index, 4th Edition (PSI-4)
- Patient Global Impression (PGI) Form

Anticipated next steps for TSHA-118 by the end of 2021

Ongoing collection of natural history data

Initiate Phase 1/2 clinical study and dose first patient in 2H 2021

Patient finding activity in collaboration with UTSW, Rochester, Hamburg, and other potential sites and patient organizations

Site activation activities in the US and outside the US ongoing

Q & A

Closing Remarks

RA Session II

President, Founder & CEO

Focused on achieving anticipated near-term milestones in 2021 and building long-term value

GAN clinical program update, including 3.5 x 10^{14} total vg cohort
GM2 gangliosidosis preliminary biomarker data in 2H 2021
CLN1 program to dose first patient in 2021 under open IND

4 open IND/CTAs expected by the end of 2021, including Rett syndrome

Initiated construction of internal cGMP facility in 1H 2021

5 additional programs currently in IND-enabling studies
TSHA-102 Rett syndrome Investor Day September 2021
TSHA-106 Angelman Investor Day October 2021
Numerous value generating catalysts over the next 18 months

TAYSHA GENE THERAPIES

Thank you