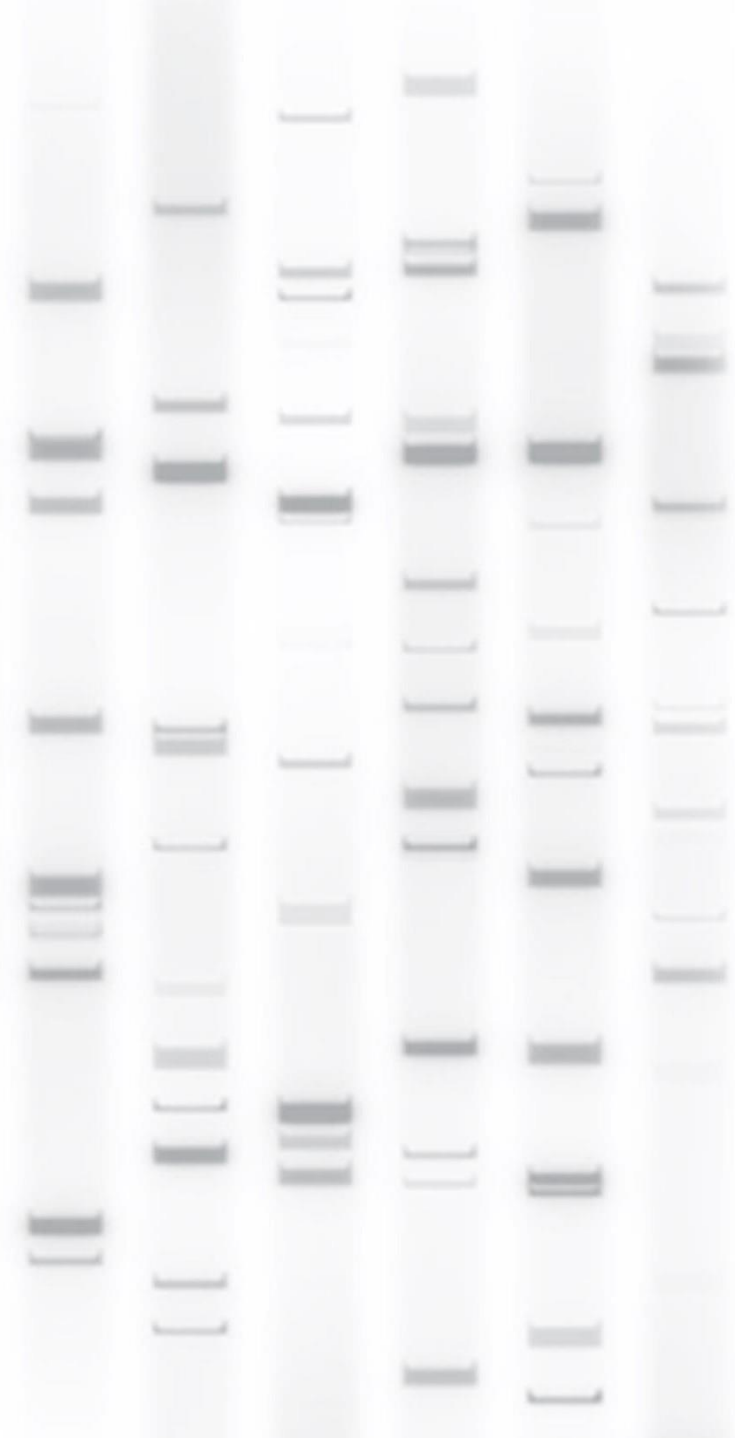
TAYSHA GENE THERAPIES

Bringing New Cures to Life

Oppenheimer Rare & Orphan Disease Summit Presentation
May 2021



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.

Taysha Summary Overview

Multiple product candidates with anticipated near-term catalysts to enhance value	– First in human clinical data for TSHA-101 in GM2 gangliosidosis in 2H 2021 – Additional clinical data for TSHA-120 in GAN in 2H 2021 – Open IND for TSHA-118 in CLN1 disease; initiation of Phase 1/2 trial in 2H 2021 – Submit four IND/CTA filings, including Rett syndrome, in 2021 – Advancement of four product candidates in IND-enabling studies, four in discovery in 2021
Portfolio of 26 CNS gene therapy programs across 3 distinct franchises	– Current pipeline of 26 AAV gene therapy programs – Portfolio addressing over 500,000 patients (US+EU) across monogenic CNS diseases, including neurodegenerative diseases, neurodevelopmental disorders, and genetic epilepsies
UT Southwestern Gene Therapy Program strategic alliance	– Led by Drs. Steven Gray and Berge Minassian; established to accelerate R&D, with integration of translational research, clinical development and GMP manufacturing – Exclusive access to resources, expertise, and novel technology platforms for delivery and dosing of gene therapies
Validated capsid, manufacturing system and route of delivery	– Clinically and commercially proven AAV9 vector platform – Highly scalable suspension HEK293 manufacturing process with excellent yield – Intrathecal delivery enables direct targeting to the CNS with validated biodistribution and safety
Proven management team and investor syndicate	– Deep expertise in the development of gene therapies for rare diseases – Key leadership team members and investors previously led the development and commercialization of Zolgensma®, the first FDA-approved gene therapy for CNS disease

Leadership team uniquely positioned to deliver on corporate mission

Leadership

RA Session II *Founder, President & CEO*	
Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM *Chief Medical Officer and Head of R&D*	
Kamran Alam, CPA, MBA *Chief Financial Officer*	
Fred Porter, PhD *Chief Technical Officer*	
Mishima Gerhart *Chief Regulatory Officer and Head of Quality*	
Sean McAuliffe *Chief Commercial Officer*	
Jim Rouse *Chief Information Officer*	
Emily McGinnis *Chief Patient Officer & Head of Government Affairs*	
Tim Douros, JD *Chief Legal Officer and Corporate Secretary*	
Tracy Porter, M.Ed., SPHR *Chief People Officer*	

Advisors

Steven Gray, PhD *Chief Scientific Advisor*	
Berge Minassian, MD *Chief Medical Advisor*	

Board of Directors

Sean Nolan *Chairman*	
Paul Manning	
Phillip Donenberg	
Sukumar Nagendran, MD	
Laura Sepp-Lorenzino, PhD	
Kathleen Reape, MD	
RA Session II	

Scientific Advisory Board of preeminent international scientific and clinical thought leaders in gene therapy, CNS diseases and drug discovery and development

Scientific Advisory Board

Deborah Bilder, MD	University of Utah Registry of Autism and Developmental Disabilities (URADD); Utah Regional Education; BioMarin Pharmaceutical
Alan Boyd, BCc, MB, ChB, FRSB, FFLM, FRCP, FFPM	Boyd Consultants; Royal Colleges of Physicians; University of Birmingham Medical School; AstraZeneca; Ark Therapeutics Ltd
Wendy K. Chung, MD, PhD	Columbia University; Simons Foundation Autism Research Initiative (SFARI)
David P. Dimmock, MD	Rady Children's Institute for Genomic Medicine; FDA; CDC
Michael W. Lawlor, MD, PhD	The Neuroscience Research Center at the Medical College of Wisconsin; Solid Biosciences
Gerald S. Lipshutz, MD, MS	David Geffen School of Medicine at University of California, Los Angeles; Wellcome Trust, UK; NIH

Diverse pipeline focused exclusively on monogenic disorders of the central nervous system

Neurodegenerative Diseases

Diseases characterized by the progressive degeneration of the structures and function of the CNS and PNS

Neurodevelopmental Disorders

Multi-faceted conditions characterized by impairments in cognition, behavior, and motor function

Genetic Epilepsies

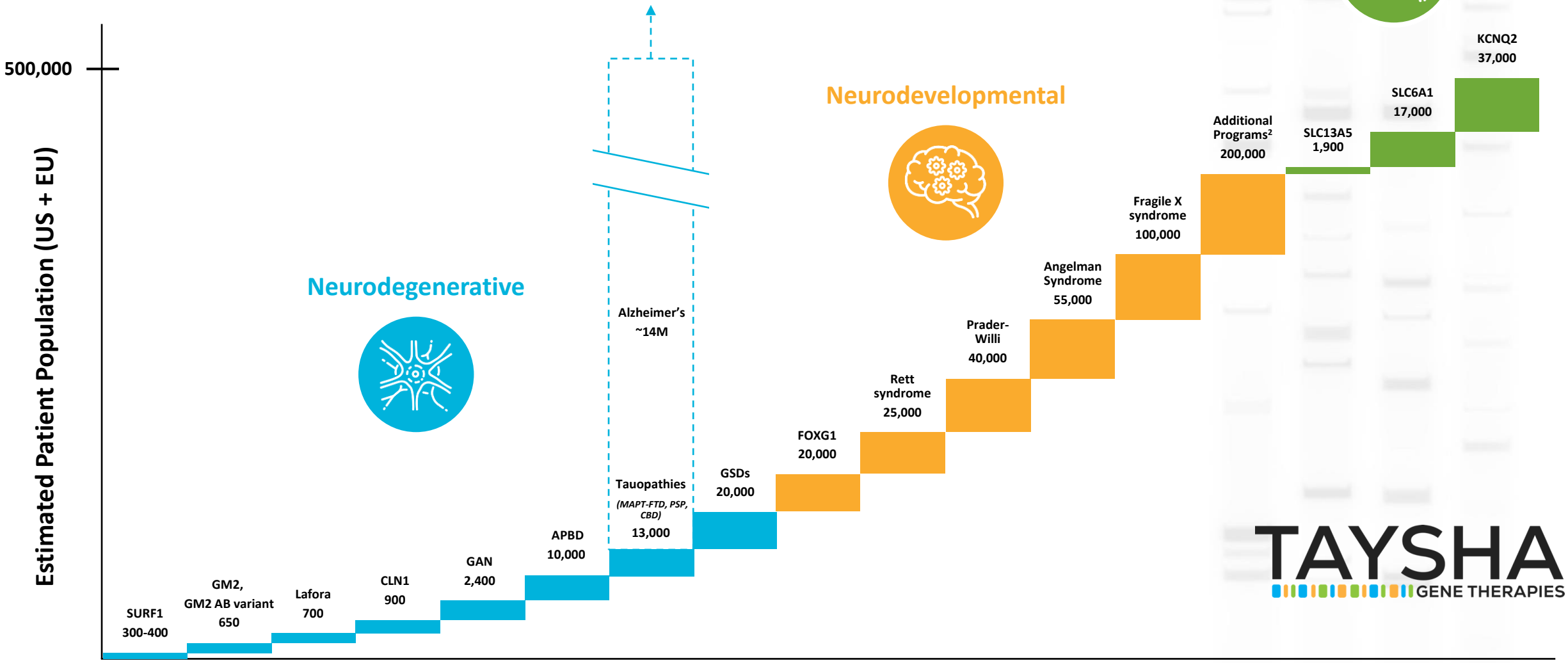
Disorders characterized by recurrent seizures often leading to abnormal development of the brain

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

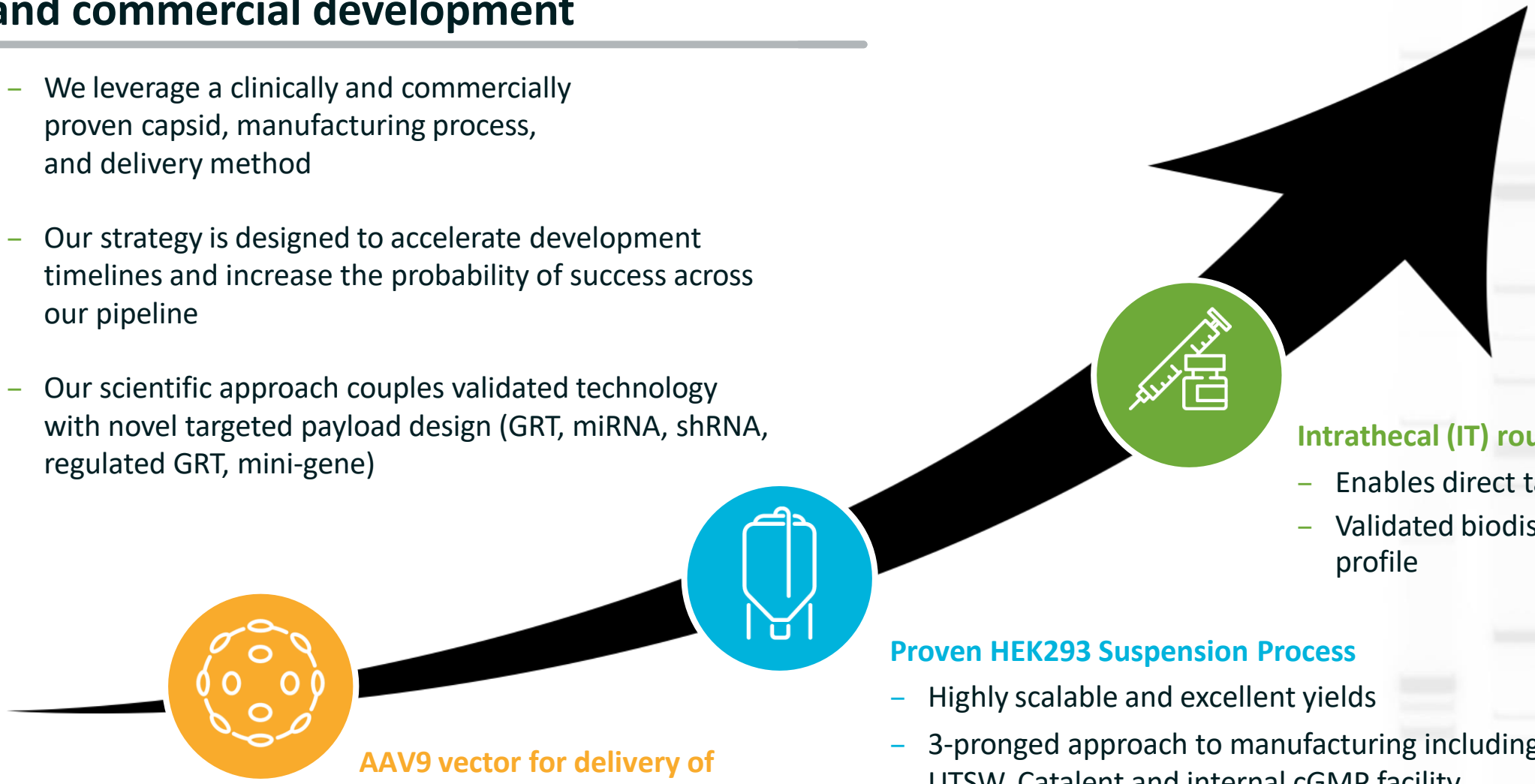
Our three distinct franchises have the potential to address over 500,000+ patients (US+EU)



[1]Tauopathies only include MAPT-FTD, PSP, CBD
[2]Additional programs include TSHA-107, TSHA-108 and TSHA-109

Our strategy is focused on rapid clinical and commercial development

- We leverage a clinically and commercially proven capsid, manufacturing process, and delivery method
- Our strategy is designed to accelerate development timelines and increase the probability of success across our pipeline
- Our scientific approach couples validated technology with novel targeted payload design (GRT, miRNA, shRNA, regulated GRT, mini-gene)



AAV9 vector for delivery of therapeutic transgene

- Demonstrated safety and efficacy across multiple CNS indications

Proven HEK293 Suspension Process

- Highly scalable and excellent yields
- 3-pronged approach to manufacturing including UTSW, Catalent and internal cGMP facility

Intrathecal (IT) route of administration

- Enables direct targeting to CNS
- Validated biodistribution and safety profile

Approach and ability to deliver various payloads

Gene Replacement

- Replace gene of interest to treat diseases or disorders with limited gene expression
- Comprised of a codon-optimized DNA transgene that encodes the wild type gene of interest
- Transgene (or mini-gene) coupled with a promoter selected to ensure expression in the cell or tissue-type of interest

Regulated Gene Replacement

- Regulate expression of a therapeutic transgene
- Built-in regulation system to replace dose-sensitive genes safely and at therapeutic levels
- Uses miRARE, our novel miRNA target panel

Vectorized RNA

- Transgenes designed to express miRNA (small, non-coding sequences of RNA that result in silencing of gene expression)
- Transgenes designed to express short-hairpin RNA (shRNA), which reactivate a silenced gene upon binding to the target of interest

Mini-Gene Payloads

- Many genes are too large to fit in AAV capsids
- Mini-genes designed to overcome limited AAV packaging capacity
- Collaboration with Cleveland Clinic to advance next-generation mini-gene payloads initially for genetic epilepsies and neurodevelopmental disorders

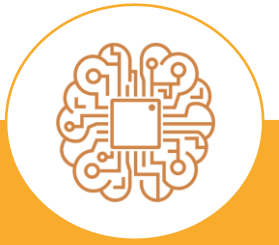
Novel platform technology that powers our research engine

Novel AAV Dosing Platform

- Potential to facilitate redosing via vagus nerve
- Efficient targeting of vagal neurons demonstrated in adult rats, with potential to improve autonomic nervous system symptoms in humans
- Normal vagal nerve fibers and neurons post AAV delivery to the vagus nerve in dogs

miRARE Platform

- Novel miRNA target panel derived from high-throughput miRNA profiling and genome mining
- Designed for safely regulated transgene expression levels in the brain
- Needed in disorders like Rett syndrome where high doses of transgene-expressing vectors may be harmful while low doses may avoid toxicity but be subtherapeutic
- Built-in regulation system harnesses endogenous systems



Novel Capsid Identification

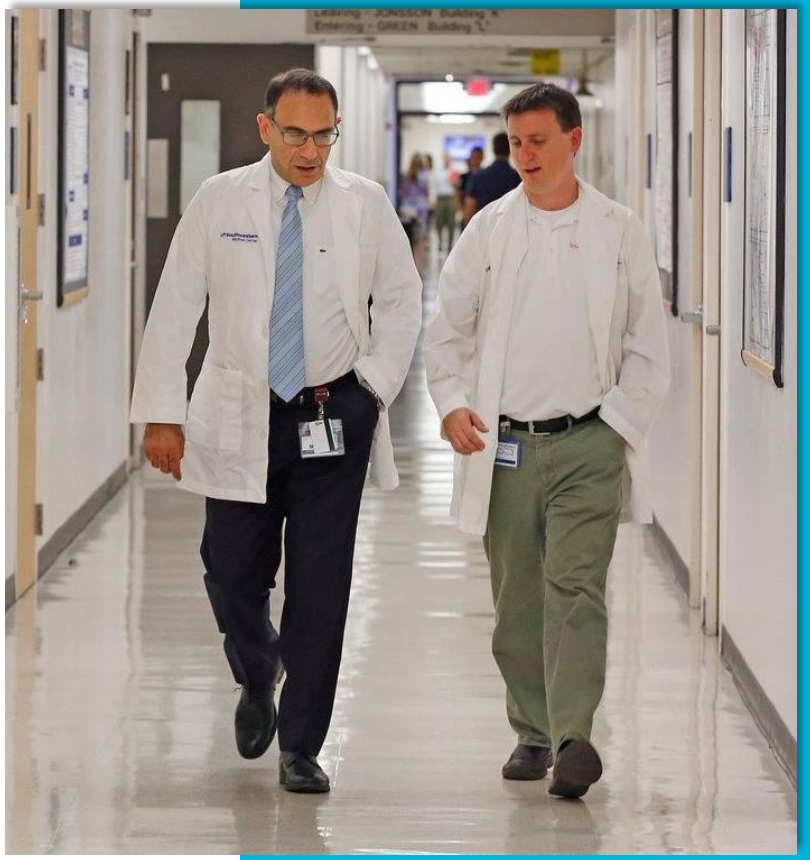
- Improves targeted delivery through use of machine learning, capsid shuffling and directed evolution
- Allows rapid identification of capsids with improved properties in mice and Non- Human Primates (NHPs) to maximize translational relevance
- Potential to drive new product candidates with novel biodistribution and transduction profiles into pipeline

Our strategic partnership with UTSW

UT Southwestern Medical Center

We have access to a world-class team of scientists and cutting-edge technology through an exclusive, worldwide royalty-free license to discover, develop, and commercialize gene therapies led by:

- **Berge Minassian, MD**, Division Chief of Child Neurology
  - Pediatric neurologist with expertise in neurodegenerative diseases, neurodevelopmental disorders, and genetic forms of epilepsy
  - Discovered *MECP2* CNS isoform (Rett syndrome)
- **Steven Gray, PhD**, Director of Viral Vector Core, Associate Professor Dept of Peds
  - AAV-based vector engineering expertise and optimizing CNS delivery of transgenes
  - Administered the first AAV9-based therapy to patients via intrathecal route
- Exclusive access to a flexible, scalable, and well-characterized GMP manufacturing suite that utilizes a suspension HEK293 process
- Exclusive access to next generation platform technologies, including novel redosing platform, transgene regulation (miRARE), and capsid development



Manufacturing strategy allows flexibility and scalability to support broad pipeline

UT Southwestern Medical Center®

- Support the UTSW viral vector core to supply early-phase clinical material
  - Active technical collaboration and knowledge sharing for process information and analytical methods
  - First program is ongoing
- Capabilities
  - 50L tox production
    - 200L available by EOY
  - 500L GMP manufacturing
    - GMP operations began in December 2020
  - In-house support for critical release and stability testing

Catalent®

- Establish collaborations with leading CDMO to provide additional capacity for early-phase and pivotal supply
  - Strategic partnership in place with Catalent Gene Therapies
    - Two programs ongoing
    - Able to leverage process, methods and materials across programs
- Current Capabilities
  - 200/400L tox production
  - 800L GMP manufacturing
  - Full support for release and stability testing

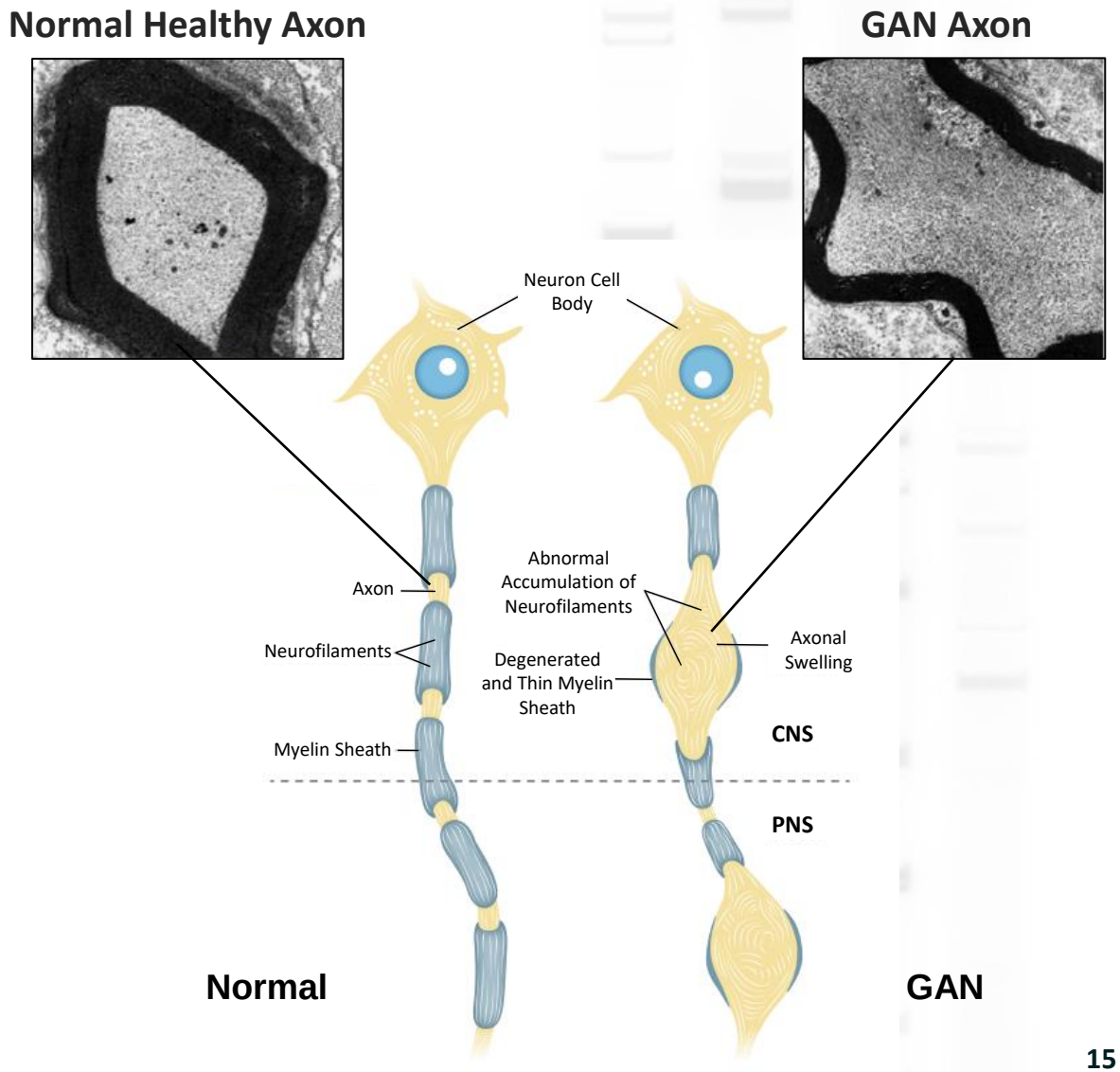
TAYSHA GENE THERAPIES

- Build internal manufacturing facility to support clinical and commercial manufacturing
  - Initial build includes two vector manufacturing trains, one fill/finish suite, QC and technical development labs
  - Building secured in Durham, NC
    - Growing hub for gene therapy manufacturing
- Facility timing
  - Kicked off 1Q 2021
  - Office and development labs operational in 1Q 2022
  - GMP ready in 2023

Neurodegenerative Disease Franchise

Rationale for targeting the *GAN* gene

- Mutations affect production of the protein gigaxonin
  - Leads to accumulation of neurofilaments in giant axons causing signal interruption and neurodegeneration
- Genetic changes in the *GAN* gene have been shown to cause Giant Axonal Neuropathy
- Good candidate for gene transfer approach
  - Small gene that is easy to package into AAV9 capsid
  - High transduction to target organ
  - Low-level expression may restore function
  - A clear model for other disorders with similar mechanism such as GM2 gangliosidosis, CLN1 disease, SURF1-associated Leigh syndrome and amyotrophic lateral sclerosis (ALS)

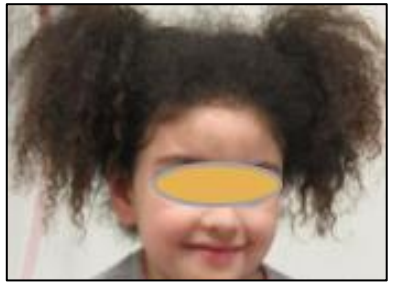


Giant axonal neuropathy (GAN) is a rare inherited genetic disorder that affects both the central and peripheral nervous systems

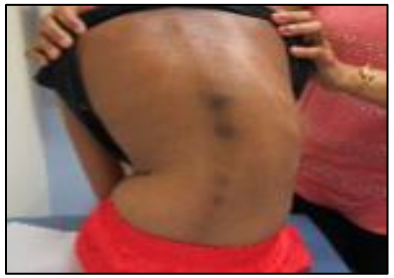
TSHA-120
GAN

- Rare autosomal recessive disease of the central and peripheral nervous systems caused by loss-of-function gigaxonin gene mutations
- Majority of children with GAN show symptoms and features before age 5
  - Dull, tightly curled hair
  - Progressive scoliosis
  - Contractures
  - Giant axons
  - Spinal cord atrophy
  - White matter abnormality
- No approved disease-modifying treatments available
- Symptomatic treatments attempt to maximize physical development and minimize deterioration
- Early- and late-onset phenotypes – shared physiology
  - Late-onset often categorized as Charcot-Marie-Tooth Type 2 (CMT2), with lack of tightly curled hair and CNS symptoms, and relatively slow progression
  - Represents 1% to 6% of all CMT2 diagnosis
  - Late-onset poor quality of life but not life-limiting
- Estimated prevalence of GAN is 2,400 patients (US+EU)

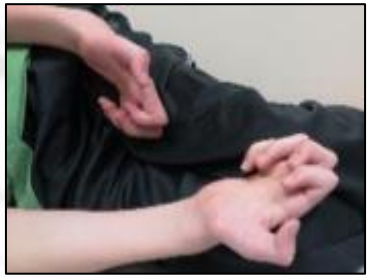
Tightly Curled Hair



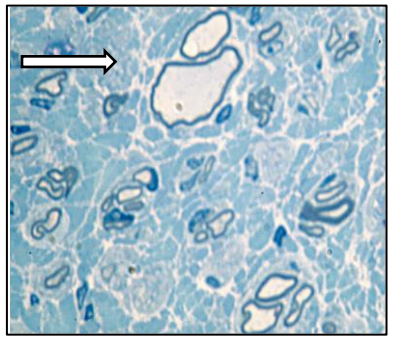
Progressive Scoliosis



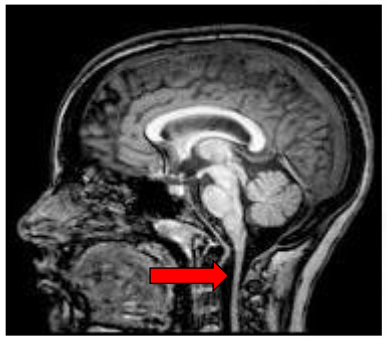
Contractures



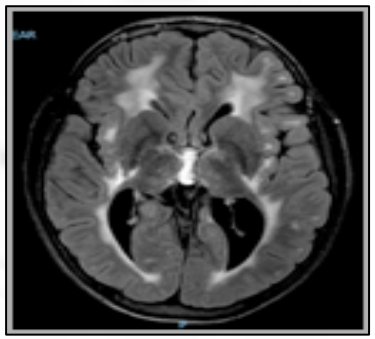
Giant Axons



Spinal Cord Atrophy



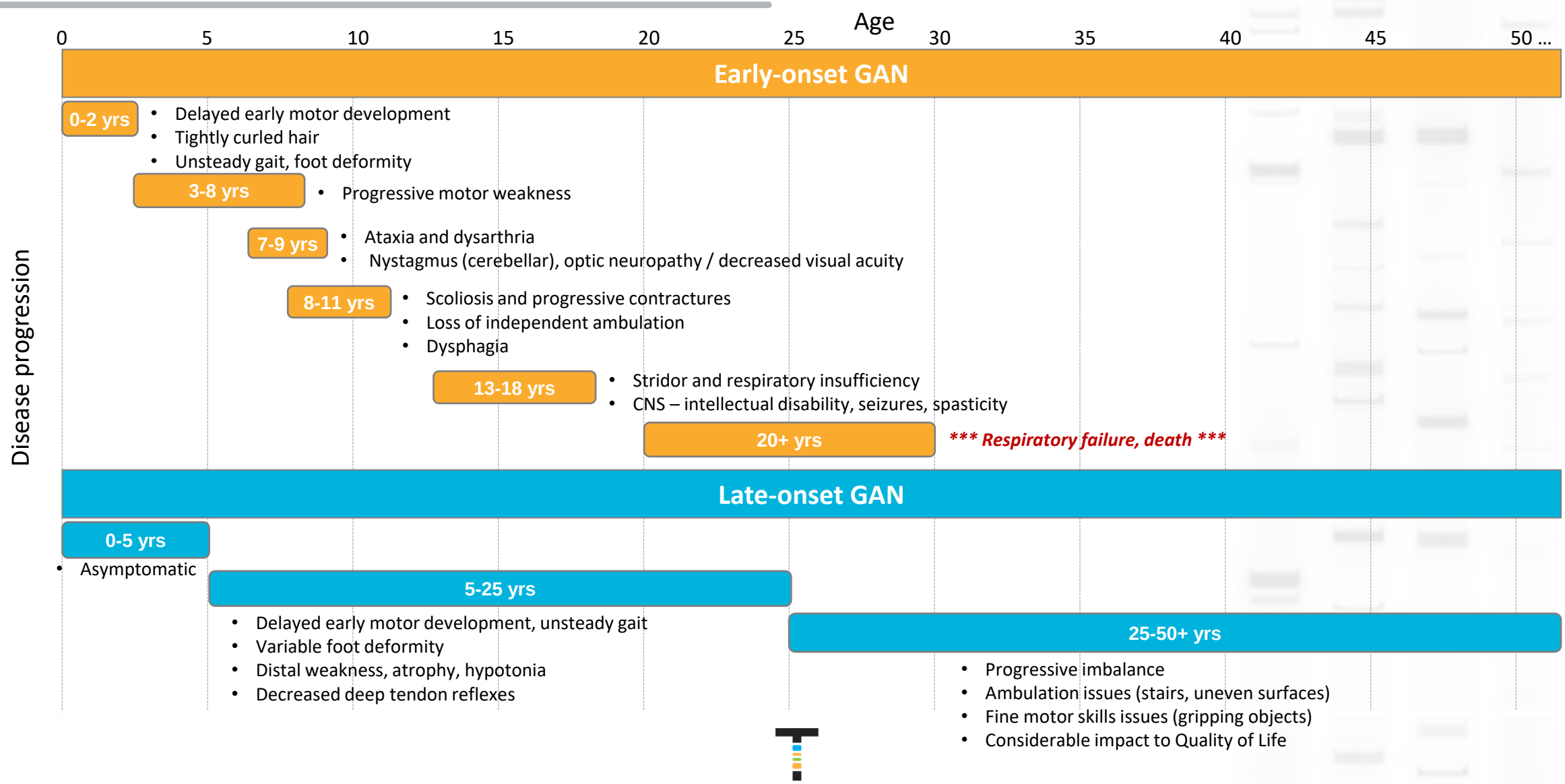
White Matter Abnormality



Murphy SM et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry 2012;83:706–10.
Gess B et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes in a German neuromuscular center population. Neuromuscul Disord 2013;23:647–51.
Antoniadi et al 2014
Bacquet J et al. Molecular diagnosis of inherited peripheral neuropathies by targeted next-generation sequencing: molecular spectrum delineation. BMJ Open. 2018

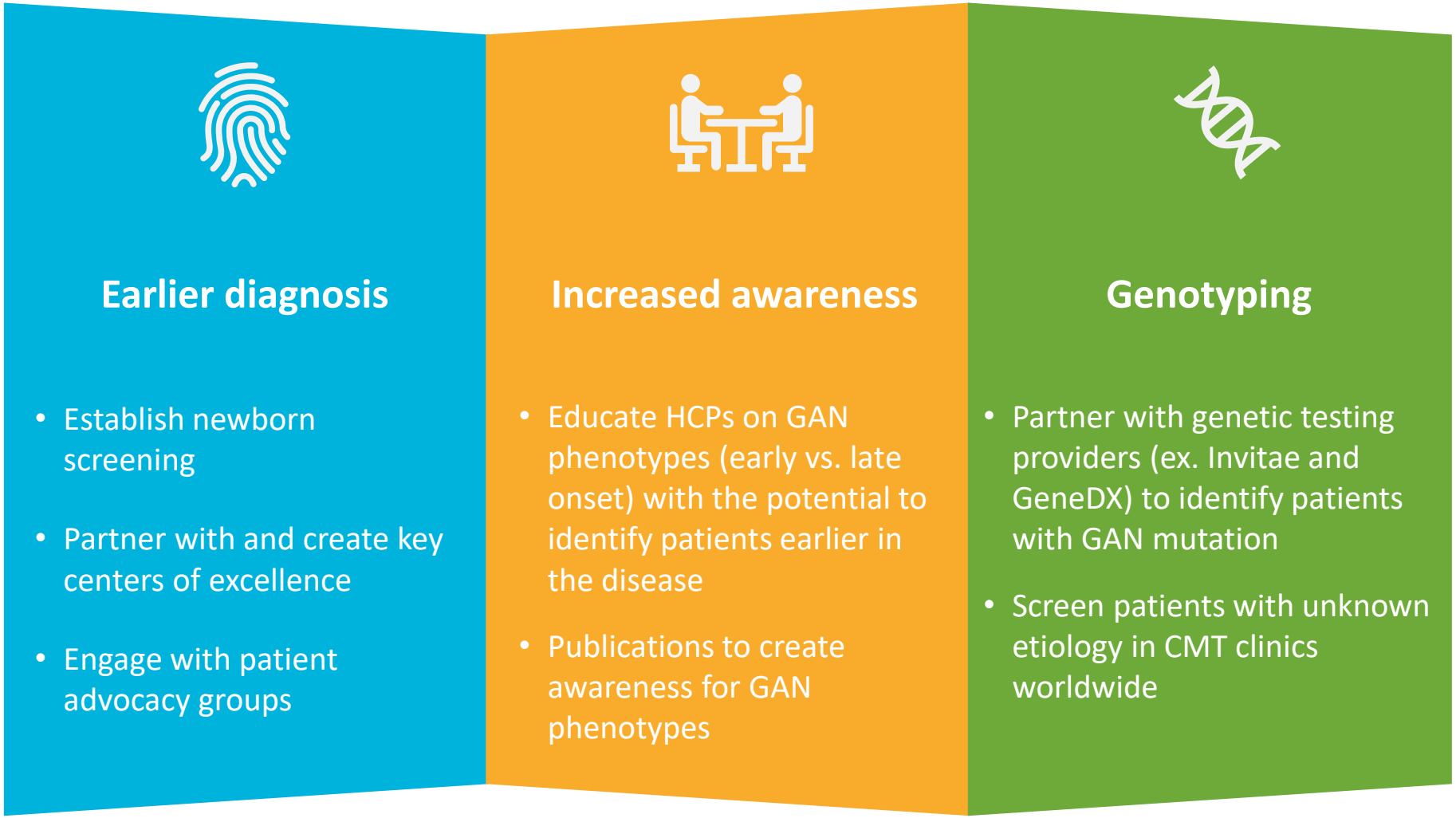
GAN natural history and disease progression

TSHA-120
GAN



Maximizing patient access and identification to address the estimated 2,400 patients in US and EU

TSHA-120
GAN



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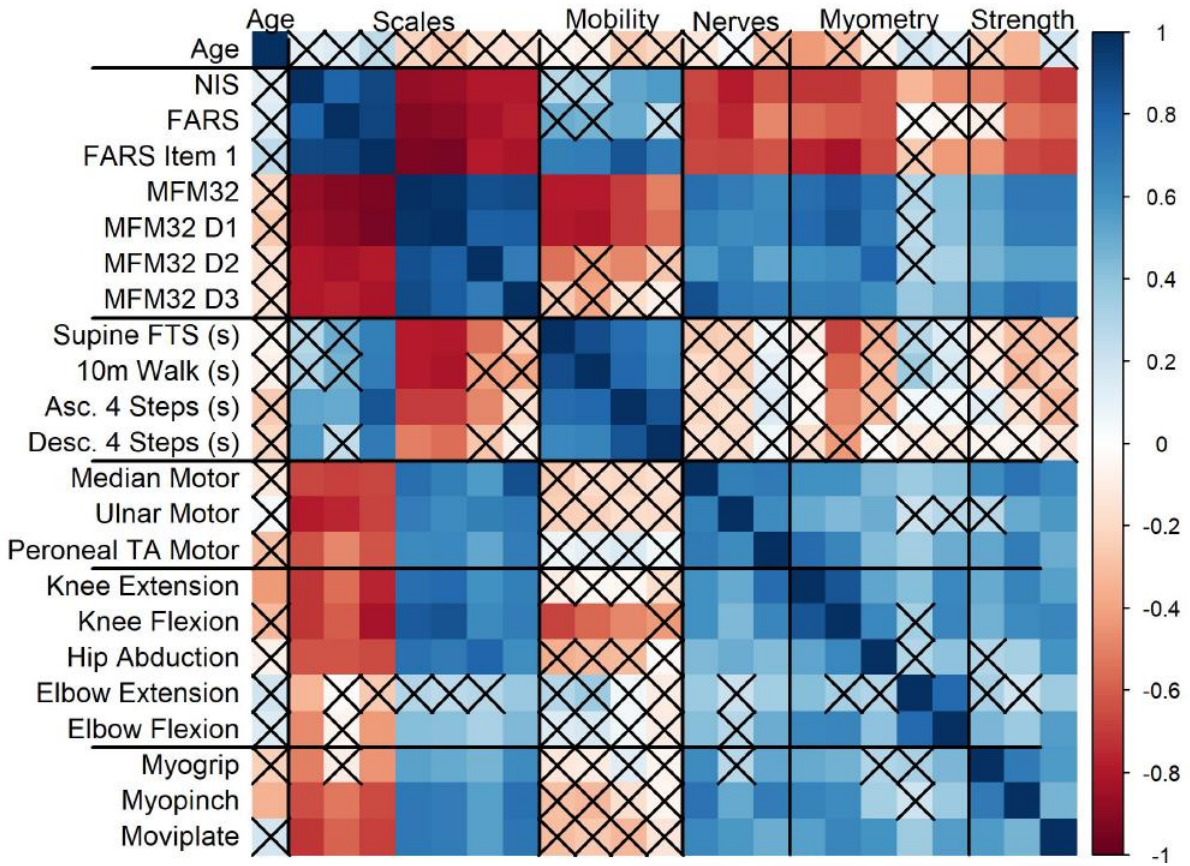
Antoniadi et al 2014
Bacquet J et al. Molecular diagnosis of inherited peripheral neuropathies by targeted next-generation sequencing: molecular spectrum delineation. BMJ Open. 2018

Primary efficacy endpoint is the Motor Function Measure (MFM32) – a validated quantitative scale

- Validated instrument used in multiple regulatory approvals
- A 32-item scale for motor function measurement developed for neuromuscular diseases
- Assesses severity and progression of motor function across a broad spectrum and in 3 functional domains
  - Standing, transfers and ambulation
  - Proximal and axial function
  - Distal function
- 32 items scored between 0 and 3 for a maximum score of 96
  - A higher score means that an individual was able to complete the task
  - Sometimes, the score is converted to a percentage
- A 4-point change is considered clinically meaningful in the following indications:
  - DMD
  - SMA
  - LAMA2-related muscular dystrophy
  - Cerebral palsy

Correlation Matrix Measuring Strength and Frequency of Correlations Across Various Motor and Demographic Assessments

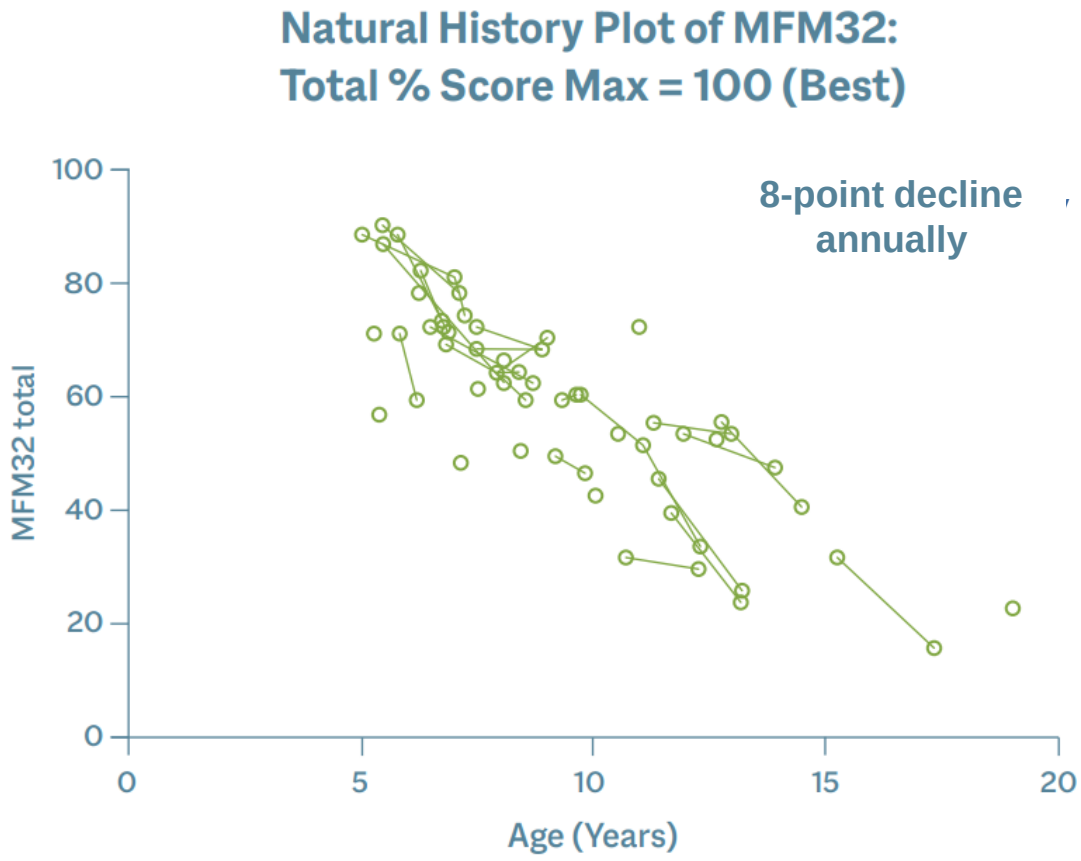


GAN natural history study data as a dependable comparator for future studies

TSHA-120
GAN

- 45 GAN patients (2013-present) ages 3-21 years
  - Can be accessed for treatment study
  - Will be used as comparator for treatment study
- MFM32
  - MFM32 total score shows uniform decline between patients of all age groups over time
  - Average decline is ~8 points per year
  - 4-point change is considered clinically meaningful
- MFM32 selected as primary endpoint due to least variability and its use in confirmatory trials

- **Natural history data: 8-point decline annually in MFM32**
- **4-point change in MFM32 considered clinically meaningful**

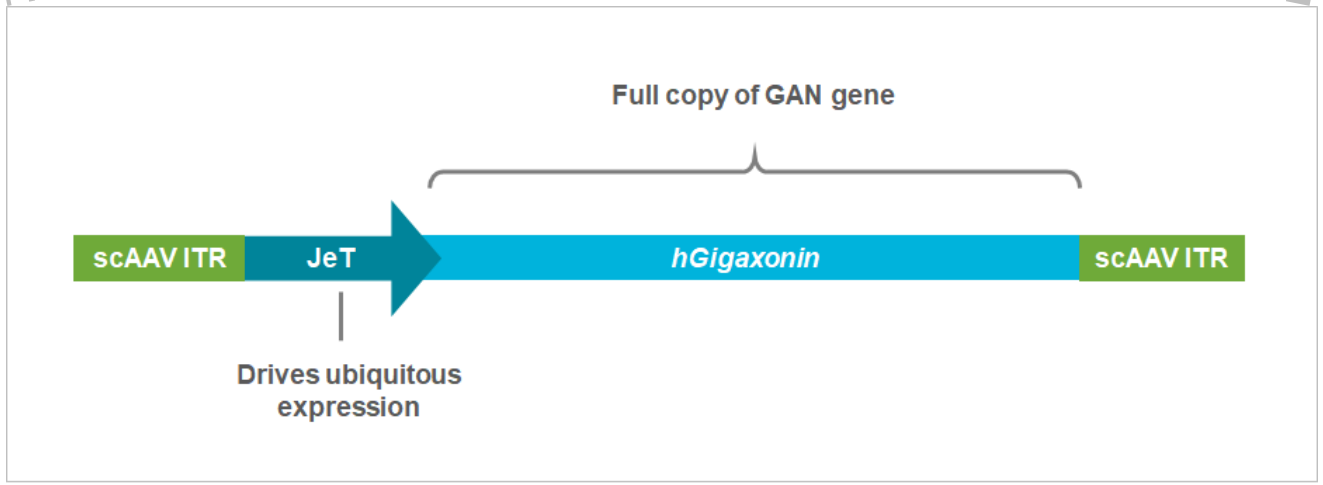


Bönnemann, C. et al; 2020

TSHA-120 program overview and construct

- Construct invented by Dr. Steven Gray (UTSW)
- AAV9 viral vector with engineered transgene encoding the human gigaxonin protein
- Self-complementary AAV capsid (scAAV) for rapid activation and stable expression
- JeT promoter drives ubiquitous expression
- Designed to deliver a functional copy of the GAN gene with optimal tropism and rapid expression
- Received orphan drug and rare pediatric disease designations
- Clinical study ongoing at NIH, led by Carsten Bönnemann, MD

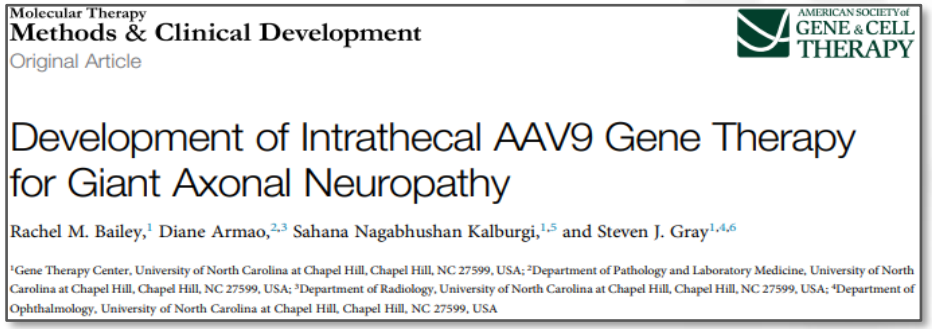
AAV9 capsid
Brain tropism & favorable safety profile



Preclinical data supported intrathecal dosing of TSHA-120

Comprehensive preclinical results demonstrated:

- Function of gigaxonin demonstrated *in vitro* and *in vivo*
- Phenotypic rescue in GAN mice after intrathecal injection, improving motor function and nerve pathology
- No toxicities in mice or non-human primates (NHPs) up to 1 year post injection
- No toxicities observed in rats at a 10-fold overdose up to 6 months post injection
- Improved DRG pathology in GAN knockout (KO) mice
- Preclinical data published in several scientific journals

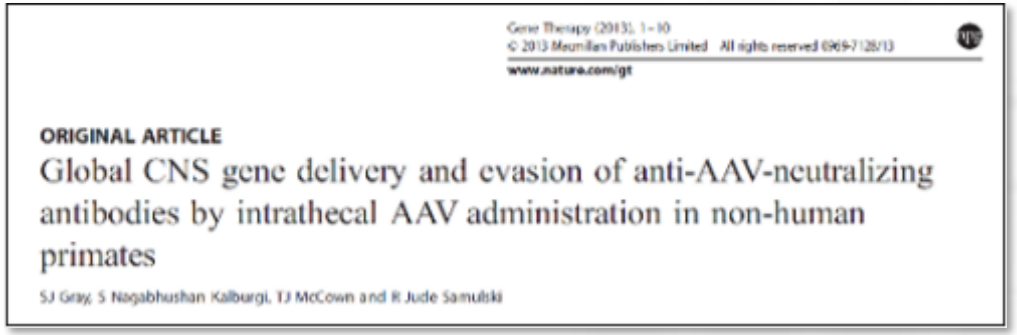

Molecular Therapy
Methods & Clinical Development
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

Development of Intrathecal AAV9 Gene Therapy for Giant Axonal Neuropathy

Rachel M. Bailey,[1] Diane Armao,[2,3] Sahana Nagabhushan Kalburgi,[1,5] and Steven J. Gray[1,4,6]

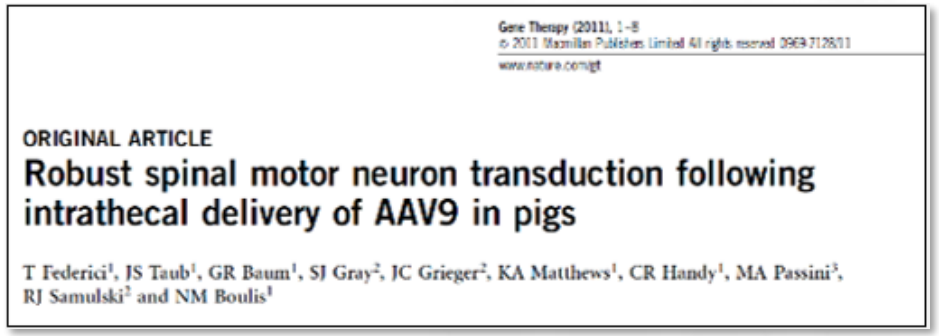
[1]Gene Therapy Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [2]Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [3]Department of Radiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA; [4]Department of Ophthalmology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA


Gene Therapy (2013), 1–10
© 2013 Macmillan Publishers Limited All rights reserved 0969-7128/13
www.nature.com/gt

ORIGINAL ARTICLE

Global CNS gene delivery and evasion of anti-AAV-neutralizing antibodies by intrathecal AAV administration in non-human primates

SJ Gray, S Nagabhushan Kalburgi, TJ McCown and R Jude Samulski


Gene Therapy (2011), 1–8
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www.nature.com/gt

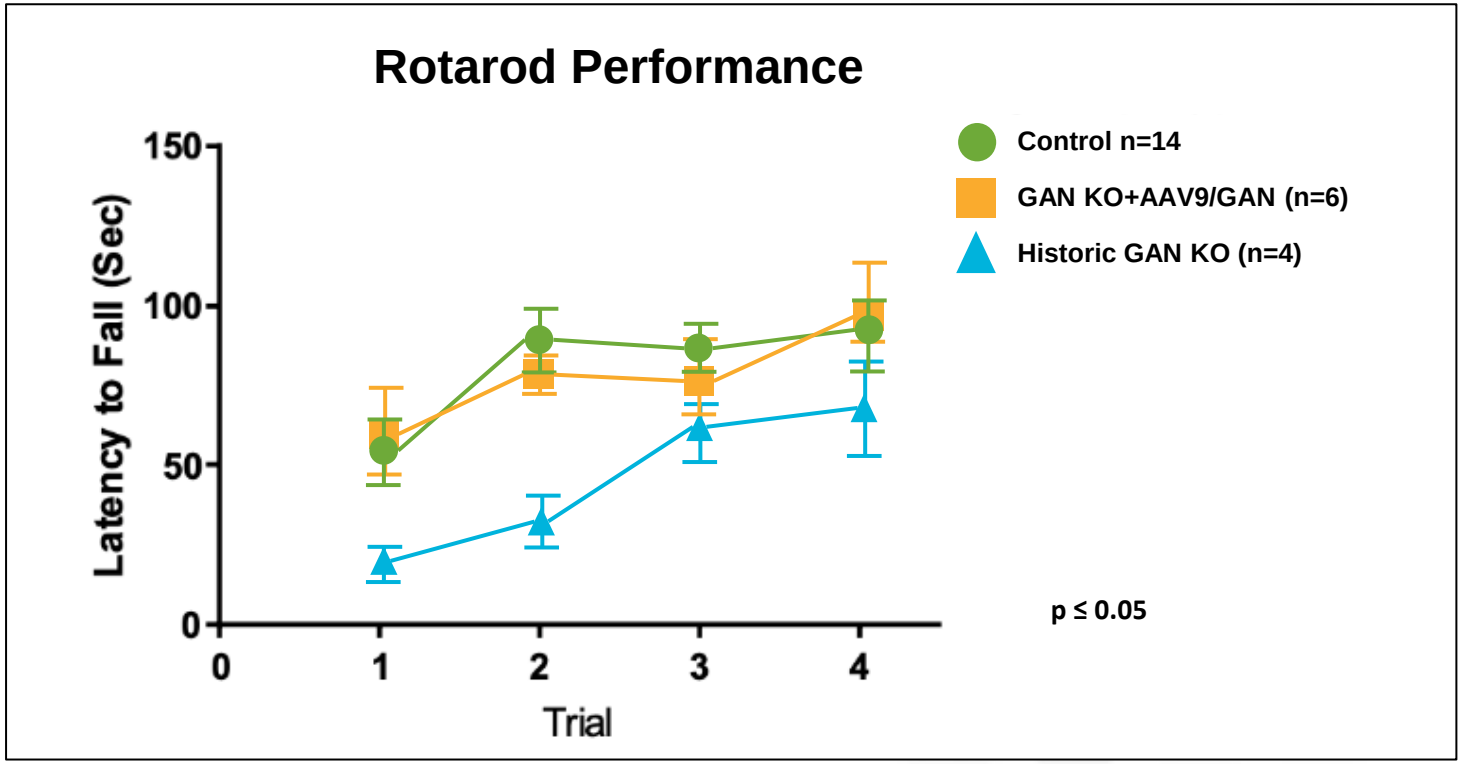
ORIGINAL ARTICLE

Robust spinal motor neuron transduction following intrathecal delivery of AAV9 in pigs

T Federici[1], JS Taub[1], GR Baum[1], SJ Gray[2], JC Grieger[2], KA Matthews[1], CR Handy[1], MA Passini[3], RJ Samulski[2] and NM Boulis[1]

TSHA-120 normalized performance of 18-month-old GAN rodent knockout model

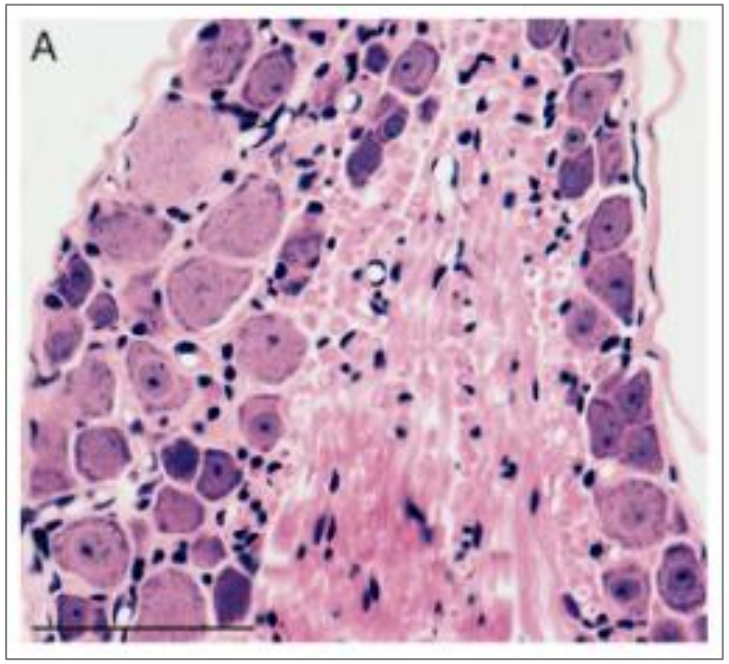
- Untreated GAN rodents performed significantly worse than heterozygous controls
- GAN rodents treated at 16 months old performed significantly better than untreated GAN rodents at 18 months old
- GAN rodents treated at 16 months old performed equivalently to heterozygous controls



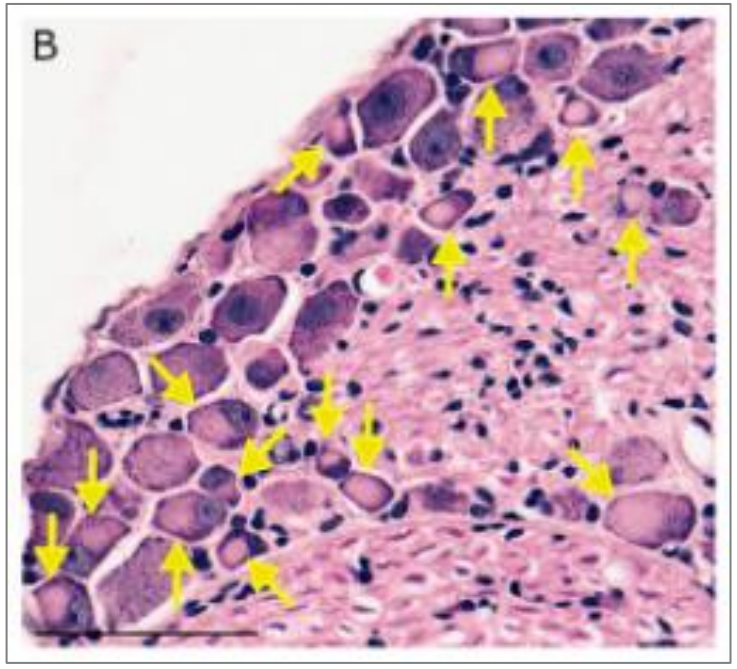
Gray, S.J., unpublished

TSHA-120 improved pathology of the DRG in the GAN KO mice

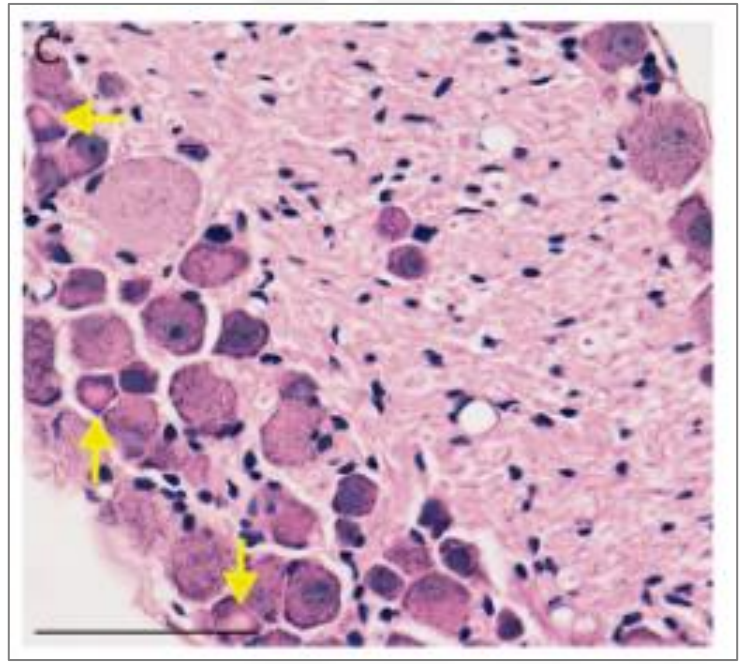
TSHA-120
GAN



Normal control



GAN KO – vehicle injected

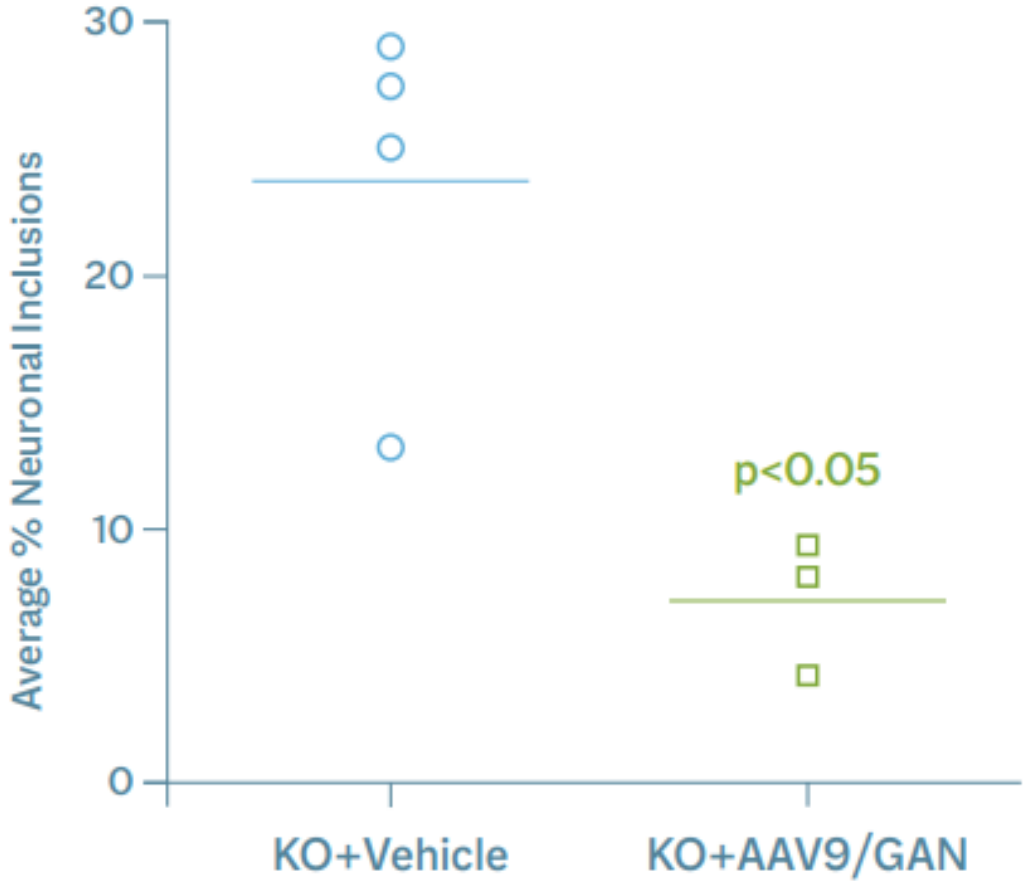


GAN KO – AAV9-GAN

Bailey, R. et al, 2018, MTMCD

TSHA-120 improved pathology of the DRG in the GAN KO mice

Significant reduction in % neuronal inclusions



Bailey, R. et al, 2018, MTMCD

Groundbreaking, historic dose escalation clinical trial – First intrathecally-dosed gene therapy

TSHA-120
GAN

Goals and Targets of Trial

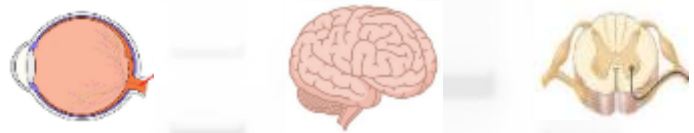
Goals

- **Primary** – Safety: clinical and laboratory assessments
- **Secondary** – Efficacy: pathologic, physiologic, functional and clinical markers

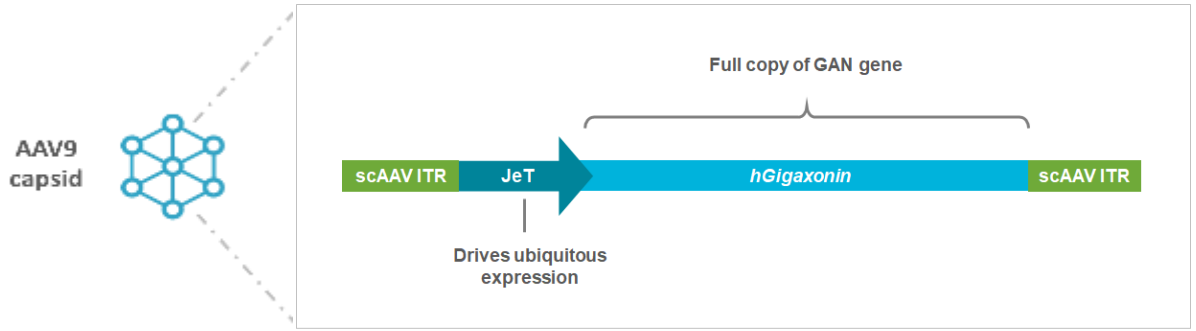
Target Recruitment

- 14 subjects injected
- > 5 years old

Target Areas to Transduce



Product Details and Dose Cohorts



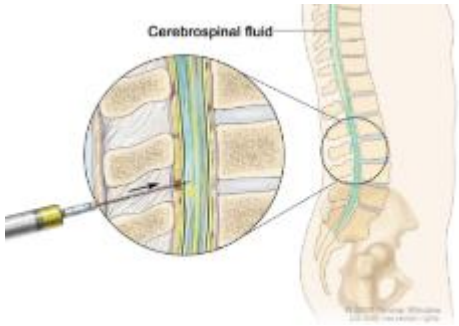
Dose Cohorts*

1x	3.5 x 10^{13} total vg **(N=2)**
3.3x	1.2 x 10^{14} total vg **(N=4)**
5x	1.8 x 10^{14} total vg **(N=5)**
10x	3.5 x 10^{14} total vg **(N=3)**

Route and Method of Administration

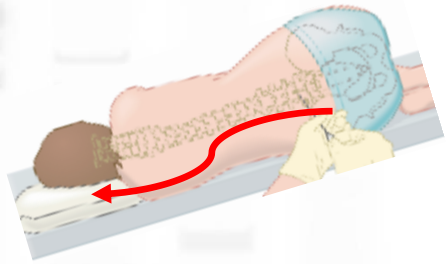
Administration

- Lumbar Intrathecal Infusion (IT)
- Amount and Rate: 10.5 ml; 1 mL/minute
- Immunosuppression regimen of prednisolone and rapamycin



Technique to Improve transduction

- Trendelenburg position (15°)
- During infusion & 1 hour post infusion



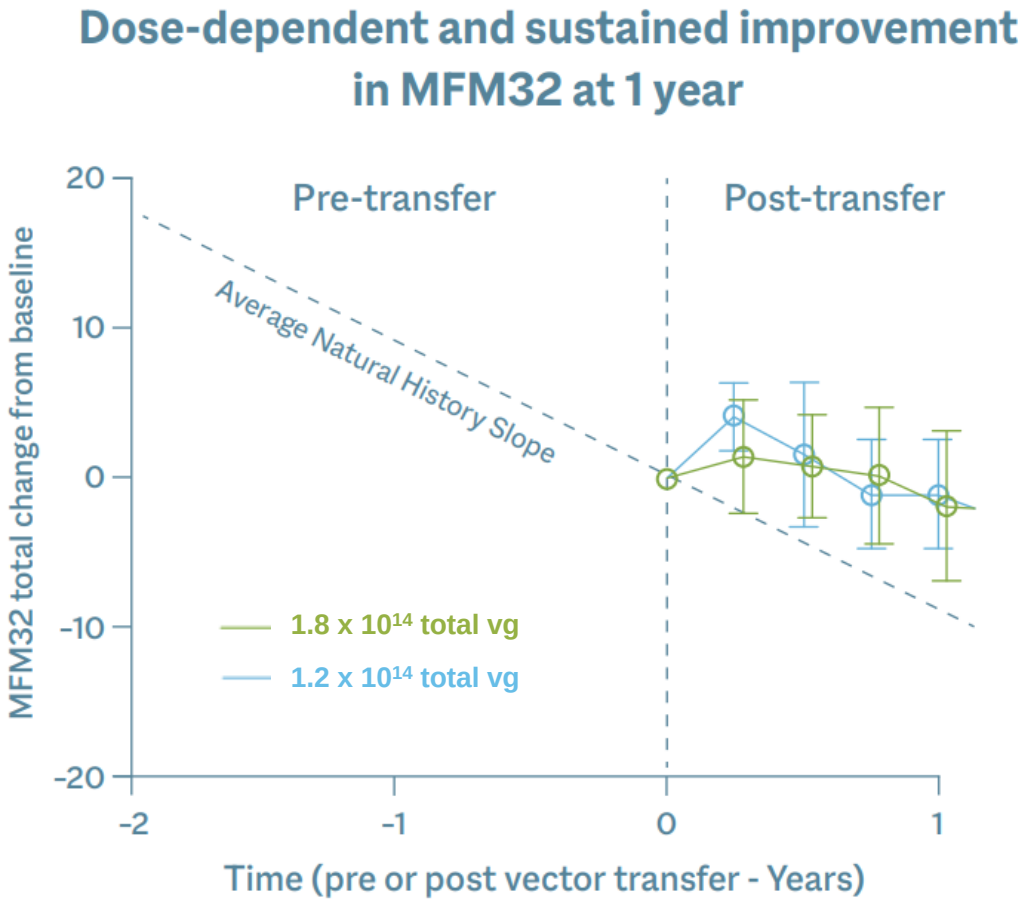
*Doses calculated by qPCR
NOTE: Subsequent slides only show data from 1.2 x 10^{14} vg and 1.8 x 10^{14} vg doses

Clinical Trial: NCT02362438

TSHA-120 achieved sustained improvement in primary efficacy endpoint and was well tolerated at multiple doses

TSHA-120
GAN

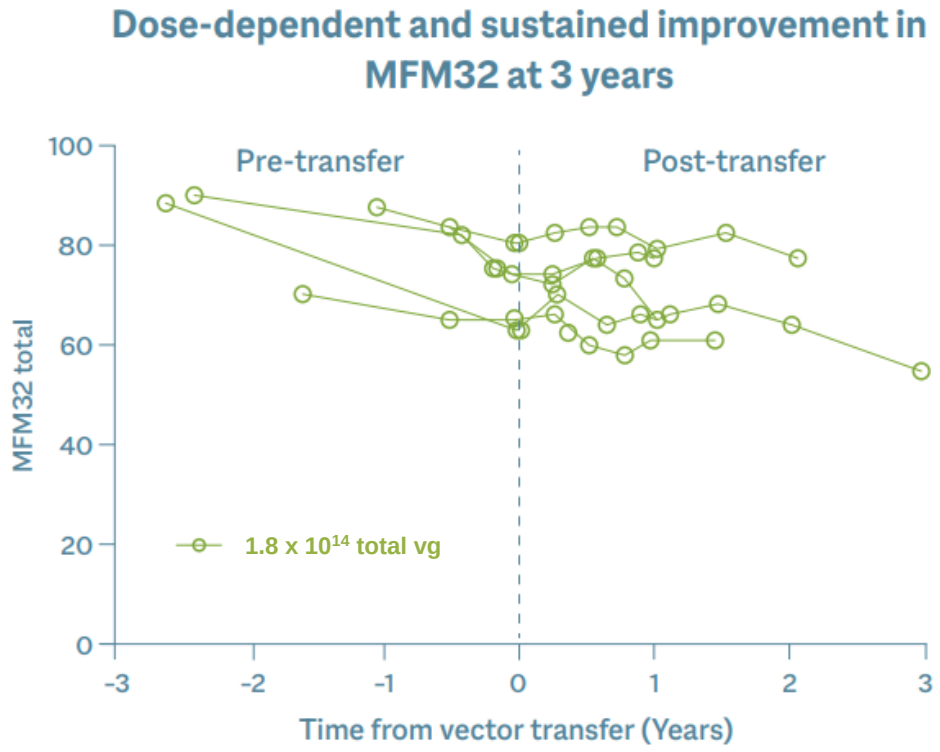
- First successful in-human intrathecal gene transfer
- 14 patients dosed
- Positive efficacy results support a dose-response relationship with TSHA-120
  - $1.8x10^{14}$ total vg dose and $1.2x10^{14}$ total vg cohorts demonstrated statistically significantly slowing of disease progression
  - Data only recently publicly presented
- Treatment with TSHA-120 was well tolerated
  - No signs of significant acute or subacute inflammation
  - No sudden sensory changes
  - No drug-related or persistent elevation of transaminases
- 6 patients beyond 3+ years initial treatment

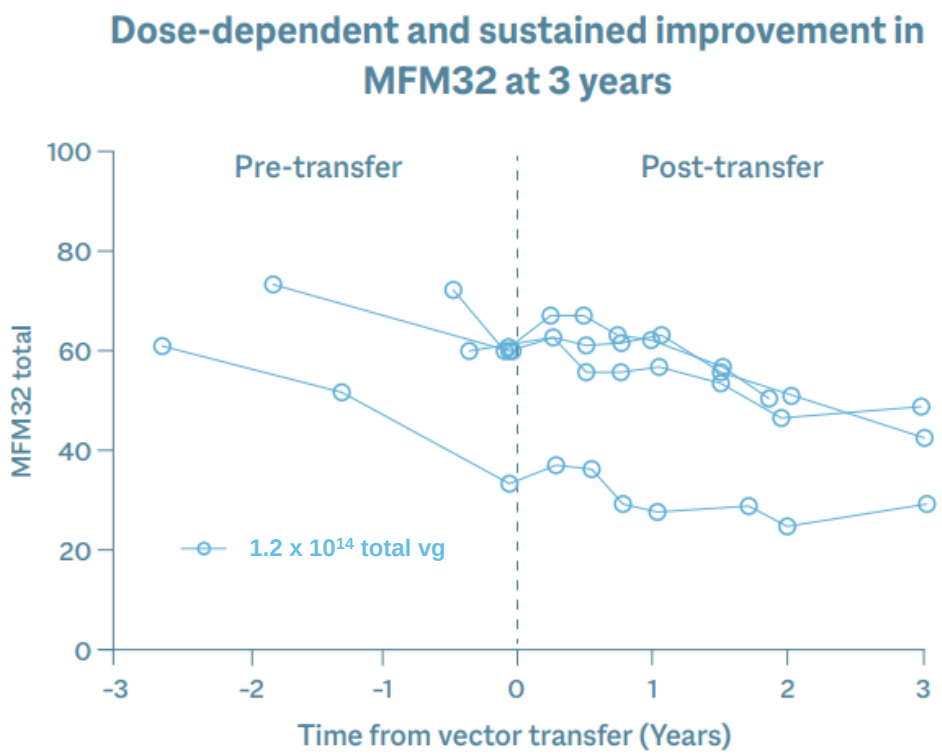


Bönnemann, C. et al; 2020

Treatment with TSHA-120 resulted in a clear arrest of disease progression at therapeutic doses and long-term durability

TSHA-120
GAN





- Arrest of disease progression at therapeutic doses
- TSHA-120 was well tolerated at multiple doses

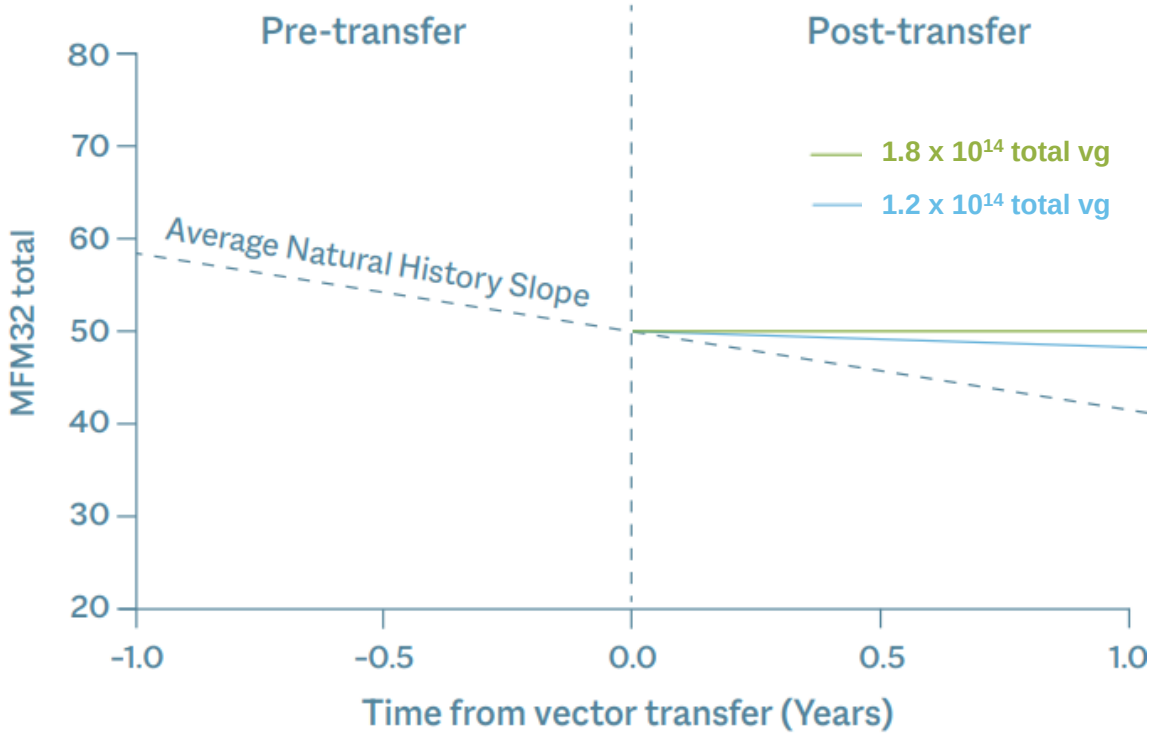
- 6 patients treated for 3+ years supporting long-term durability
- Plan to engage with agencies in US, EU and Japan to discuss regulatory pathway as soon as possible

Bönnemann, C. et al; 2020

Additional analysis using Bayesian methodology confirmed arrest of disease progression

TSHA-120
GAN

- Bayesian analysis
  - Enables direct probability statements about any unknown quantity of interest
  - Enables immediate incorporation of data gathered as the trial progresses
  - Useful and accepted by regulatory agencies when treating rare diseases and small patient populations
  - Can be used as a sensitivity analysis to support the more commonly accepted frequentist approach
  - Can be used as a way of statistically increasing the power of a clinical trial in a small patient population when used to incorporate auxiliary information
- Confirmed documented natural history data of an 8-point decline in the MFM32 total % score per year
  - 4-point decline in the MFM32 is clinically meaningful
- TSHA-120 dose of 1.8x10^{14} total vg resulted in an arrest of disease progression that was statistically significant



	Bayesian Analysis		Frequentist Analysis		
	Mean	Std Dev	Estimate	Std Error	p-Value
Post infusion: 1.8x10^{14} total vg	7.78	1.94	7.78	1.89	<0.001
Post infusion: 1.2x10^{14} total vg	6.09	2.11	6.07	2.05	0.004
Natural history decline	-8.19	0.74	-8.18	0.72	<0.001

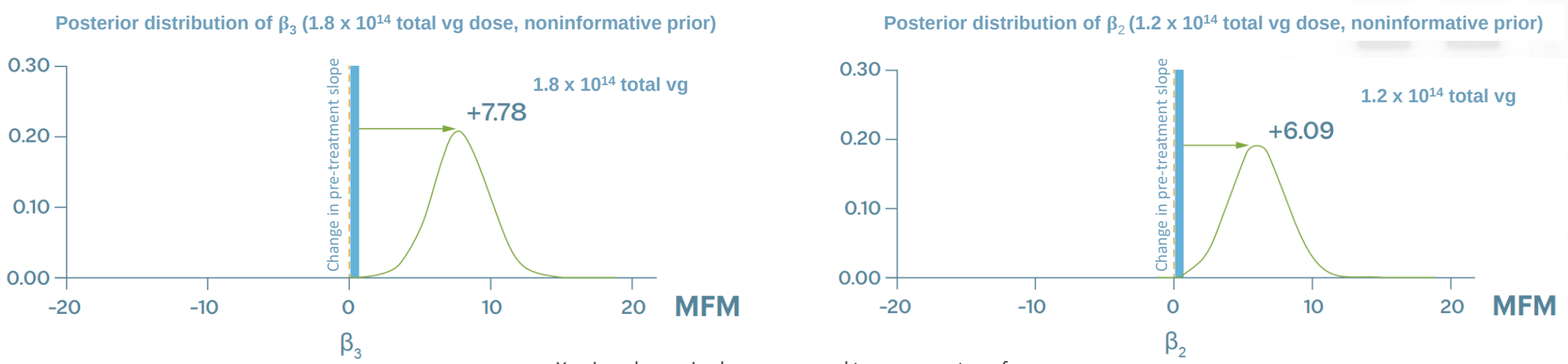
Bönnemann, C. et al; 2020

TSHA-120 halted patient pre-treatment rate of decline at 1.8x10^{14} total vg dose

TSHA-120
GAN

Bayesian Efficacy Analysis

Compared to individual historical data



X-axis = change in slope compared to pre-gene transfer
Blue line = pre-treatment change in slope = 0

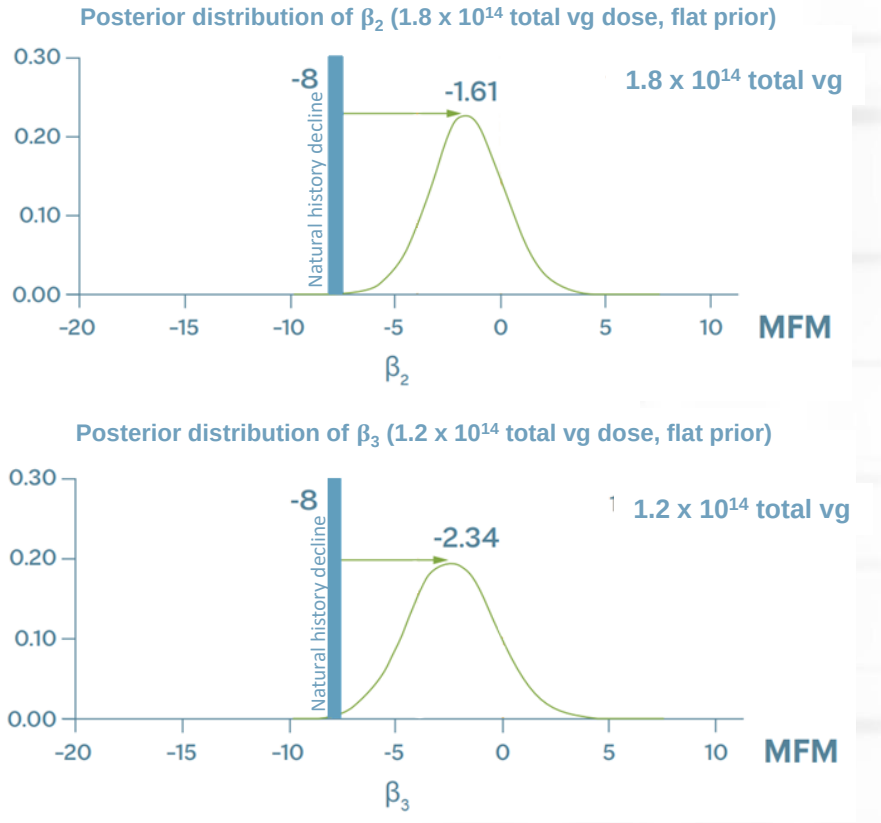
- Graphs depict treated population average annual post-treatment decline for both the 1.8x10^{14} total vg cohort and the 1.2x10^{14} total vg cohort
- 1.8x10^{14} vg halted patient pre-treatment rate of decline, avg annual slope improvement of 7.78 points
- 1.2x10^{14} vg resulted in clinically meaningful slowing of disease progression confirming dose response, avg annual slope improvement of 6.09 points
- Both doses showed superior result compared to natural decline of GAN patients

Bönnemann, C. et al; 2020

Further analyses confirmed nearly 100% probability of clinically meaningful slowing of disease compared to natural history

TSHA-120
GAN

- Further analyses were conducted to assess the probability of clinically meaningful slowing of disease as compared to natural history
- A 4-point decline in the MFM32 is considered clinically meaningful
- Graphs depict treated population annual decline for both the 1.8x10^{14} total vg cohort and the 1.2x10^{14} total vg cohort as compared to natural history
  - 1.8x10^{14} total vg dose confirmed nearly 100% probability of clinically meaningful slowing of disease compared to natural history decline of GAN patients
  - 1.2x10^{14} total vg dose confirmed approximately 85% probability of clinically meaningful slowing of disease and 100% probability of any slowing of disease



X-axis = annual decline in MFM32 total % score
Blue line = natural history decline (-8 points per year)

	Values = % Probability	
Change in disease progression	**1.8x10^{14} total vg**	**1.2x10^{14} total vg**
Any Slowing	99.9	99.8
Clinically meaningful slowing 50% or more	98.3	84.9

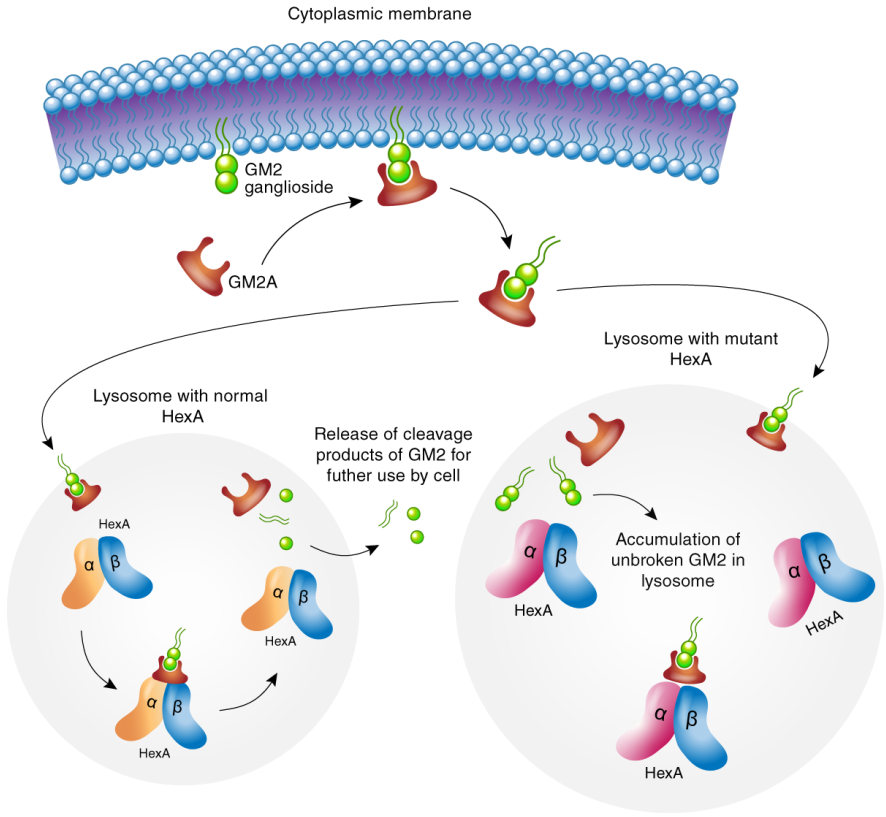
Bönnemann, C. et al; 2020

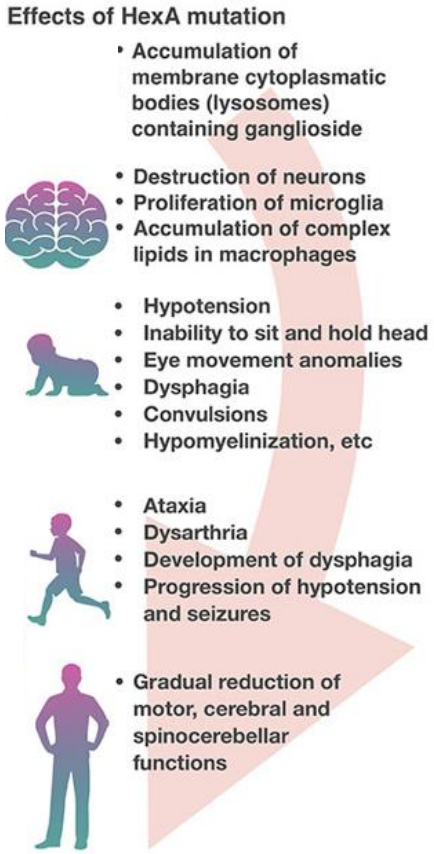
Anticipated next steps for TSHA-120 by the end of 2021

- Complete transfer data from the NIH
- Initiate manufacturing of commercial-grade GMP material
- Request an end-of-Phase meeting; discuss the regulatory pathway for TSHA-120
- Request regulatory guidance from EMA and PMDA
- Initiate new clinical sites in US and EU
- Update on regulatory interactions and current clinical program, including $3.5x10^{14}$ total vg cohort

GM2 gangliosidosis is a severe neurodegenerative disease

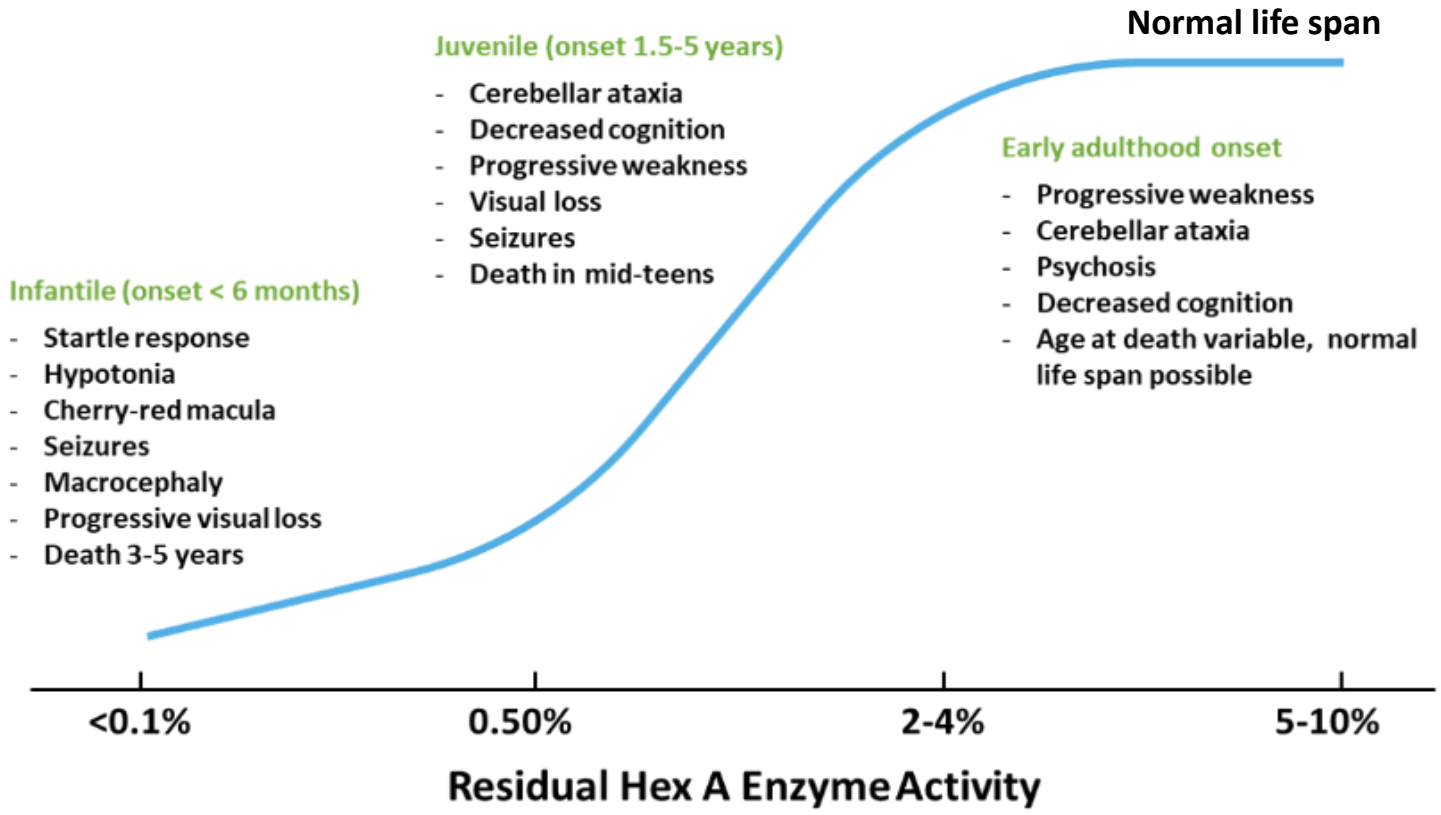
- GM2 gangliosidosis results from a deficiency in the β-hexosaminidase A (Hex A) enzyme
- Hex A is comprised of 2 subunits encoded by the alpha-subunit, *HEXA,* coded for by the *HEXA* gene, and the beta-subunit, *HEXB*, coded for the *HEXB* gene
- Mutations of the *HEXA* gene cause Tay-Sachs disease (TSD) while mutations of the *HEXB* gene cause Sandhoff disease (SD)
- The estimated prevalence is 500 patients (US+EU)
- Preliminary Phase 1/2 safety & biomarker data (Queen's University) expected in 2H 2021
- IND filing and initiation of US Phase 1/2 trial expected in 2H 2021
- Preliminary Phase 1/2 clinical data (Queen's University) expected by the end of 2021





Residual Hex A activity determines the severity of GM2

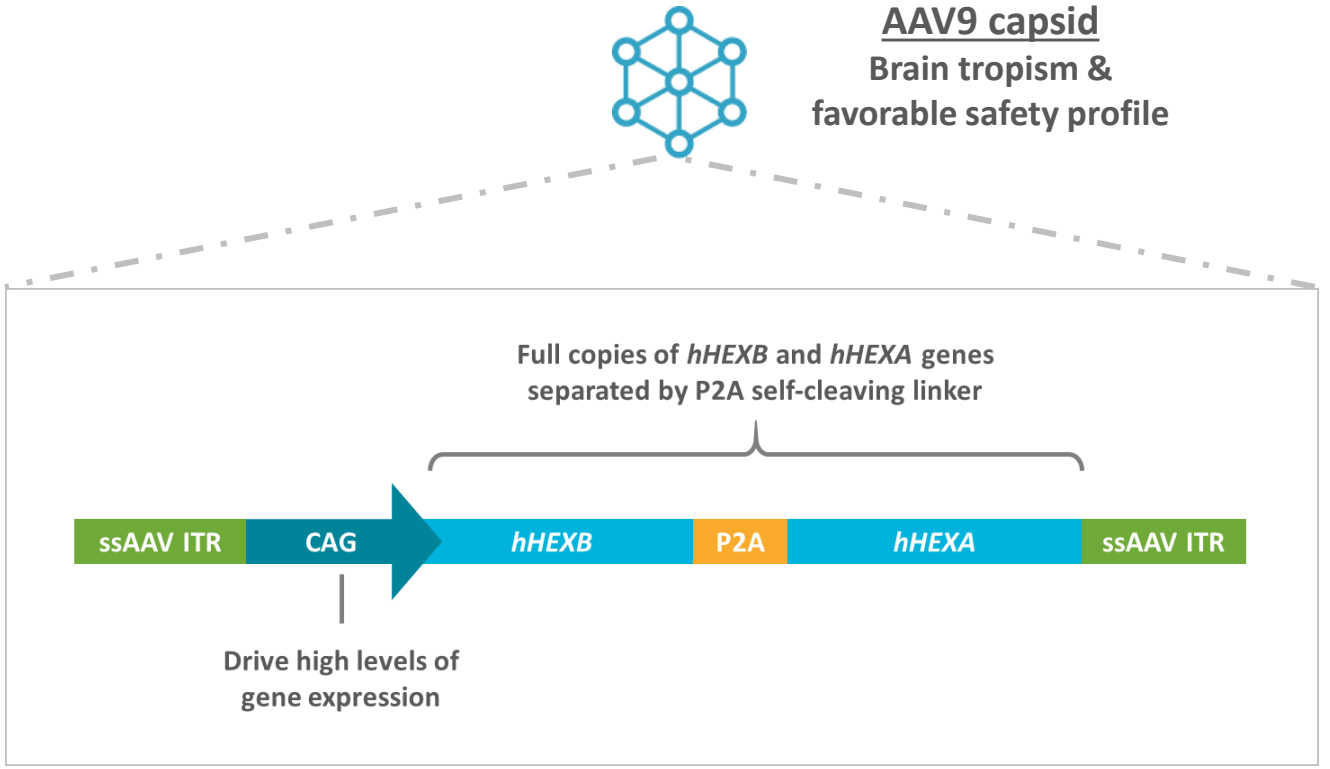
- Small increases in Hex A activity may lead to significant improvements in clinical outcomes and quality of life
- Infantile onset is the most severe form of GM2
- Infantile forms may die within the first 4 years of life, and juvenile onset patients rarely survive beyond mid-teens



Novel bicistronic vector design allows consistent expression of *HEXA* and *HEXB* genes

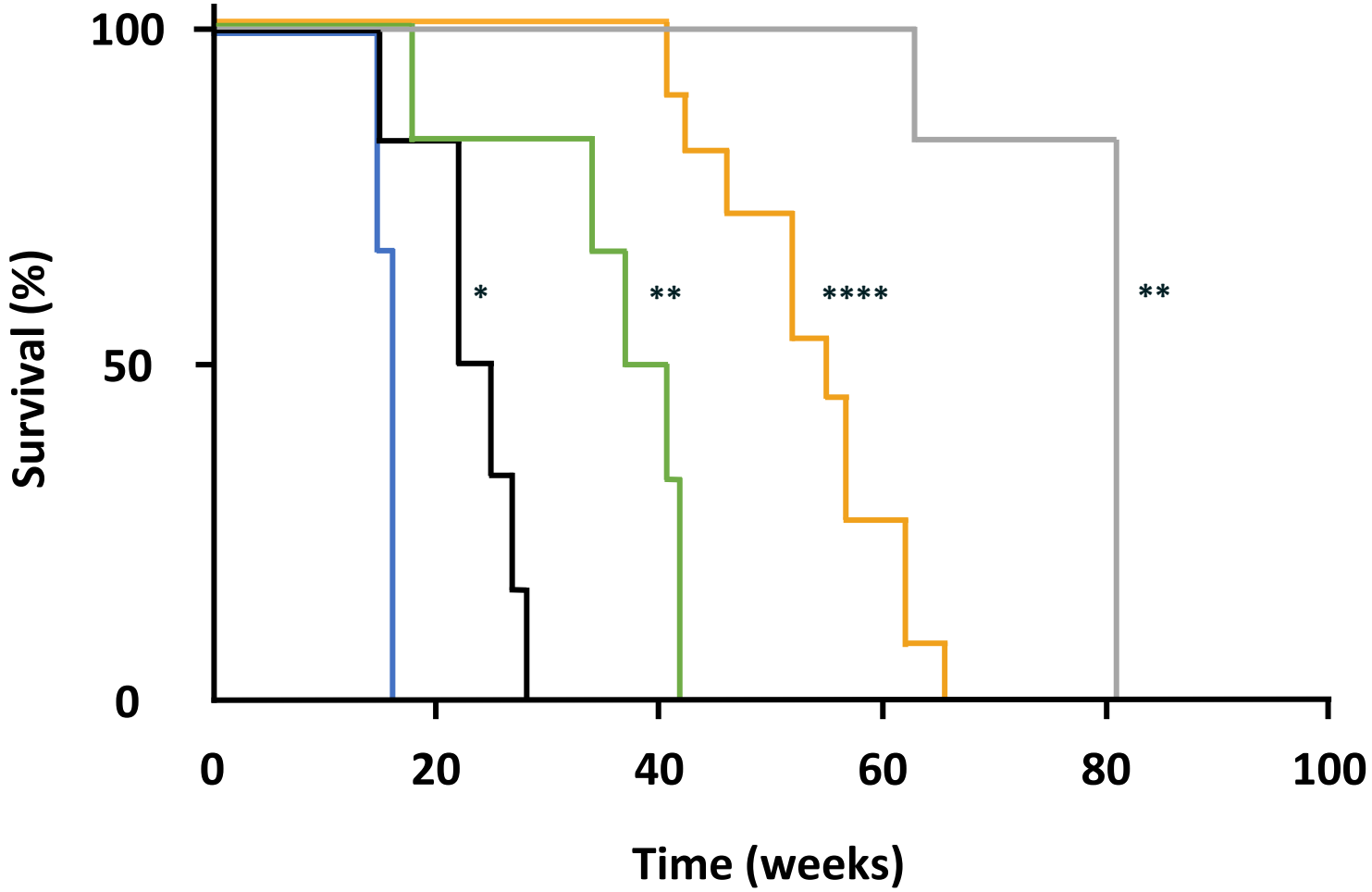
TSHA-101
GM2 gangliosidosis

- *HEXA* and *HEXB* genes are required to produce the subunits of the beta-hexosaminidase A enzyme
- The novel bicistronic vector design enables 1:1 expression of the alpha-subunit, *HEXA,* and the beta-subunit, *HEXB,* under the control of a single promoter with a P2A-self-cleaving linker
- SD mice received vehicle or varying doses of TSHA-101 after 6 weeks:
  - High dose ($2.5x10^{11}$ vg/mouse)
  - Medium dose ($1.25x10^{11}$ vg/mouse)
  - Low dose ($0.625x10^{11}$ vg/mouse)
  - Vehicle controls



Significant, dose-dependent improvement in survival observed in mice treated with TSHA-101

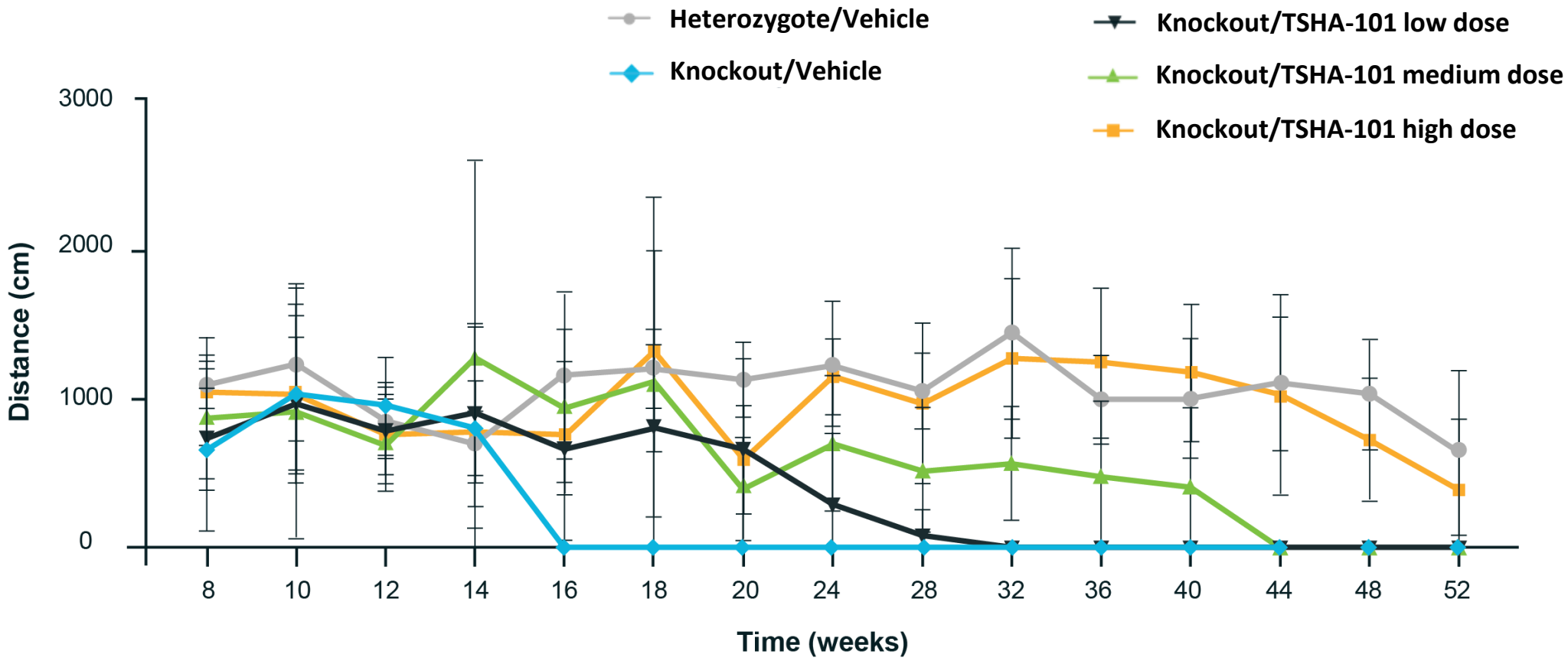
TSHA-101
GM2 gangliosidosis



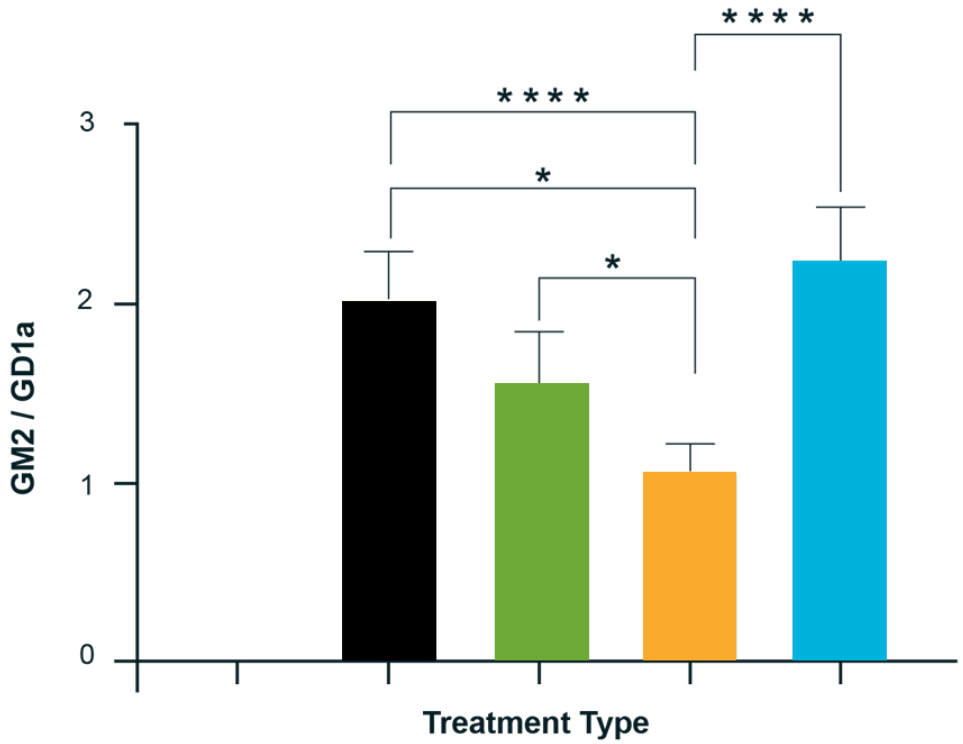
Heterozygote/Vehicle (n=6)
Knockout/TSHA-101 low dose(n=6)
Knockout/TSHA-101 medium dose (n=6)
Knockout/TSHA-101 high dose (n=11)
Knockout/Vehicle (n=6)

* p-value=0.0141
** p-value=0.0012
**** p-value<0.0001

Dose-dependent improvements observed in rotarod assessments in mice treated with TSHA-101



GM2 accumulation was significantly reduced in the mid-section of the brain following treatment with TSHA-101 after 16 weeks



Heterozygote/Vehicle (n=6)

Knockout/TSHA-101 low dose (n=6)

Knockout/TSHA-101 medium dose (n=6)

Knockout/TSHA-101 high dose (n=11)

Knockout/Vehicle (n=6)

**** p-value<0.0001

* p-value = 0.0179, 0.0295

Phase 1/2 adaptive trial for TSHA-101 in GM2 gangliosidosis

Study design and duration	• Open-label, single center, Phase 1/2 trial • Patients evaluated for one year, followed by longer-term extension
Patient cohort (n=4)	• Age younger than 1 year • Pathogenic confirmation of mutation in *HEXA* or *HEXB* gene • Patients not on ventilator support
Intervention	• Single total dose of $5x10^{14}$ vg of TSHA-101 (AAV9/*HEXB*-P2A-*HEXA)* • Delivered intrathecally
Key clinical assessments	• Safety and tolerability • Gross motor and fine motor milestones • Bayley score, CHOP-INTEND • Bulbar function/vocalization • Respiratory function • Seizure frequency/medications • Ophthalmological assessments • QOL and caretaker burden assessments
Key biomarker assessments	• Hex A enzyme in CSF and serum • GM2 accumulation in CSF • MRI changes

Neurodevelopmental Disorder Franchise

Rett syndrome is one of the most common genetic causes of intellectual disabilities in women

TSHA-102
Rett Syndrome

- Rett Syndrome is caused by mutations in the X-linked *MECP2* gene
- *MeCP2* regulates the expression of many genes involved in normal brain function
- A brief period of normal development is followed by a devastating loss of speech and purposeful hand use along with the emergence breathing abnormalities
- Disease reversibility described in animal models as demonstrated by Sir Adrian Bird[1]
- The estimated prevalence of Rett syndrome is 25,000 patients in the US and EU
- IND/CTA filing expected in 2H 2021
- Initiation of Phase 1/2 trial expected by the end of 2021

STAGE I

6-18 months (typical)
≤6 months (early)

Developmental Arrest Symptom Onset

Infants are generally described as having normal development until approximately 6 to 18 months of age

STAGE II

1-4 years

Rapid Deterioration Symptom progression-regression

Hallmark Rett symptoms appear: Hand wringing or squeeze, clapping, rubbing, washing, or hand to mouth movements

STAGE III

4-10 years

Pseudo stationary Symptoms stabilize/improve

After a period of rapid deterioration neurological symptoms stabilize, with some even showing slight improvements

STAGE IV

>10 years

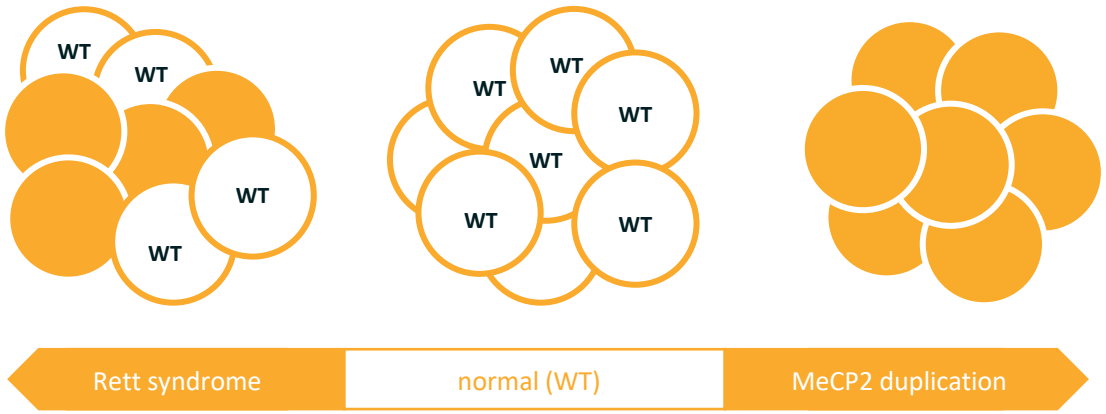
Late Motor Deterioration Muscle wasting with age

85-90% of affected people may **experience growth failure** and **muscle wasting** that worsens with age

1. Guy J et al. Science 2007

Rett syndrome (RTT) is an X-linked neurodevelopmental disorder

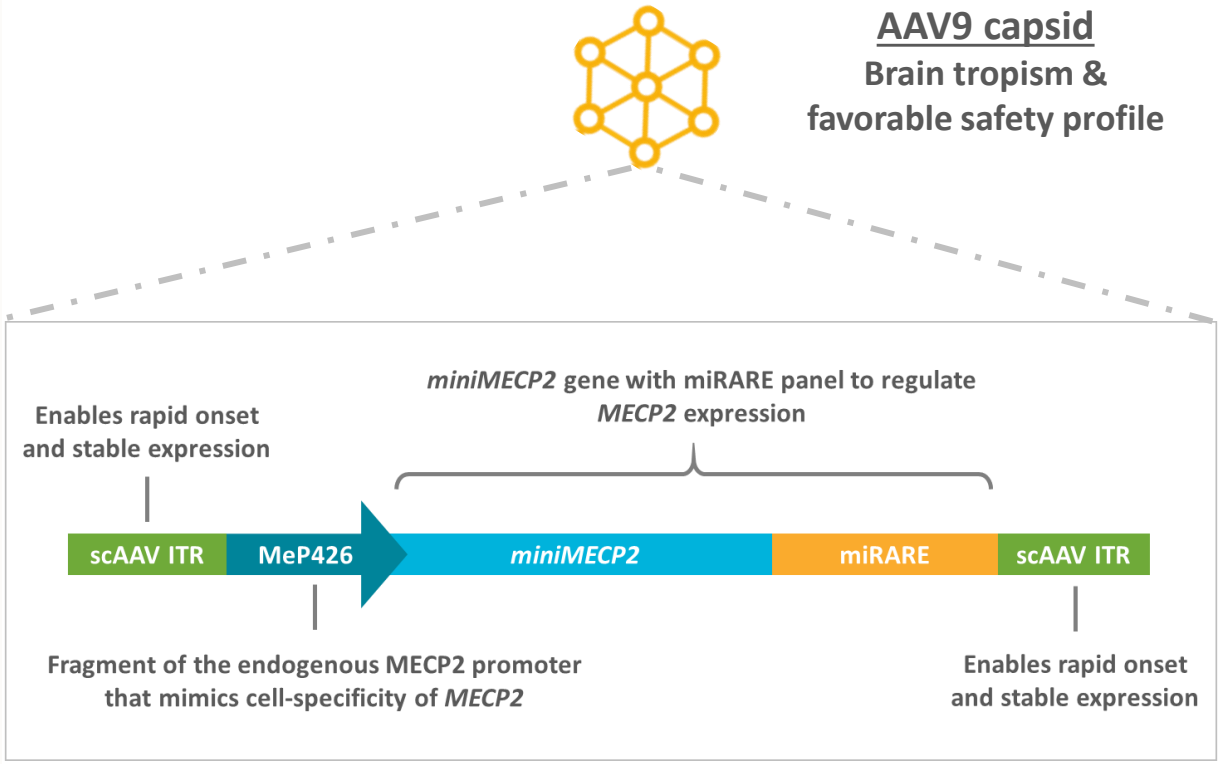
- Characterized by mutations in methyl CpG-binding protein 2 (*MECP2*), a protein that is essential for neuronal and synaptic function in the brain.
- Female heterozygous RTT patients are mosaic carriers of normal and mutated *MECP2*
- RTT falls along a spectrum of *MECP2* activity and toxicity from gene therapies is linked to unregulated expression of *MECP2*
- *MECP2* expression must be regulated to correct the deficiency, while avoiding toxicity associated with overexpression



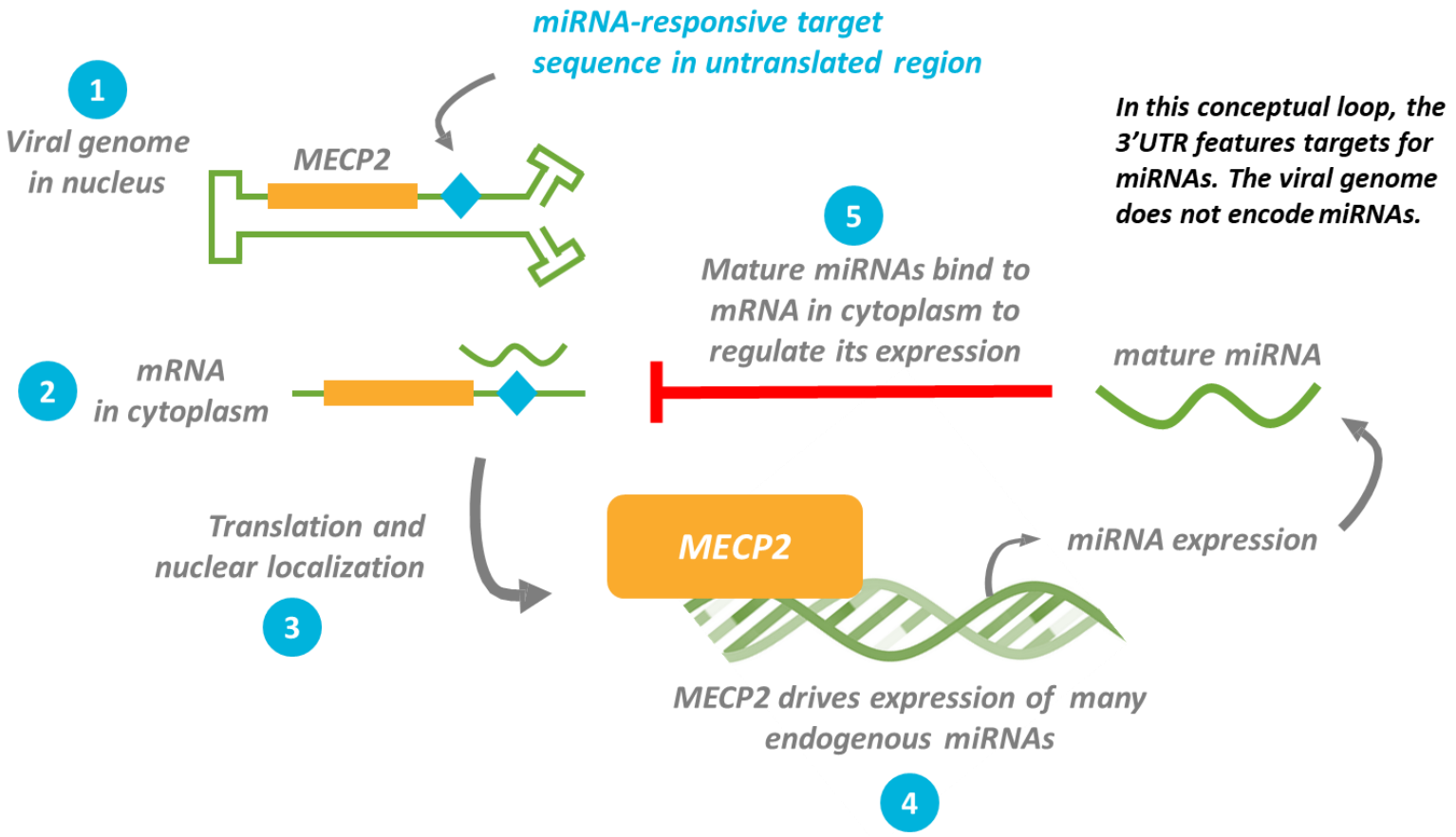
Development of a gene therapy for Rett syndrome requires regulated expression of *MECP2*

TSHA-102
Rett Syndrome

- AAV9/*MECP2* caused dose-dependent side effects after intraCSF administration in WT and KO mice
- We have developed a novel miRNA-responsive target sequence (miRARE) that regulates the expression of the *MECP2* transgene
- Our approach provides a superior therapeutic profile to that of competitor unregulated *MECP2* gene replacement



miRARE is a targeting panel for endogenous miRNAs which regulate MECP2 expression



Preclinical data for TSHA-102 in Rett syndrome recently published in *Brain*

ACCEPTED MANUSCRIPT

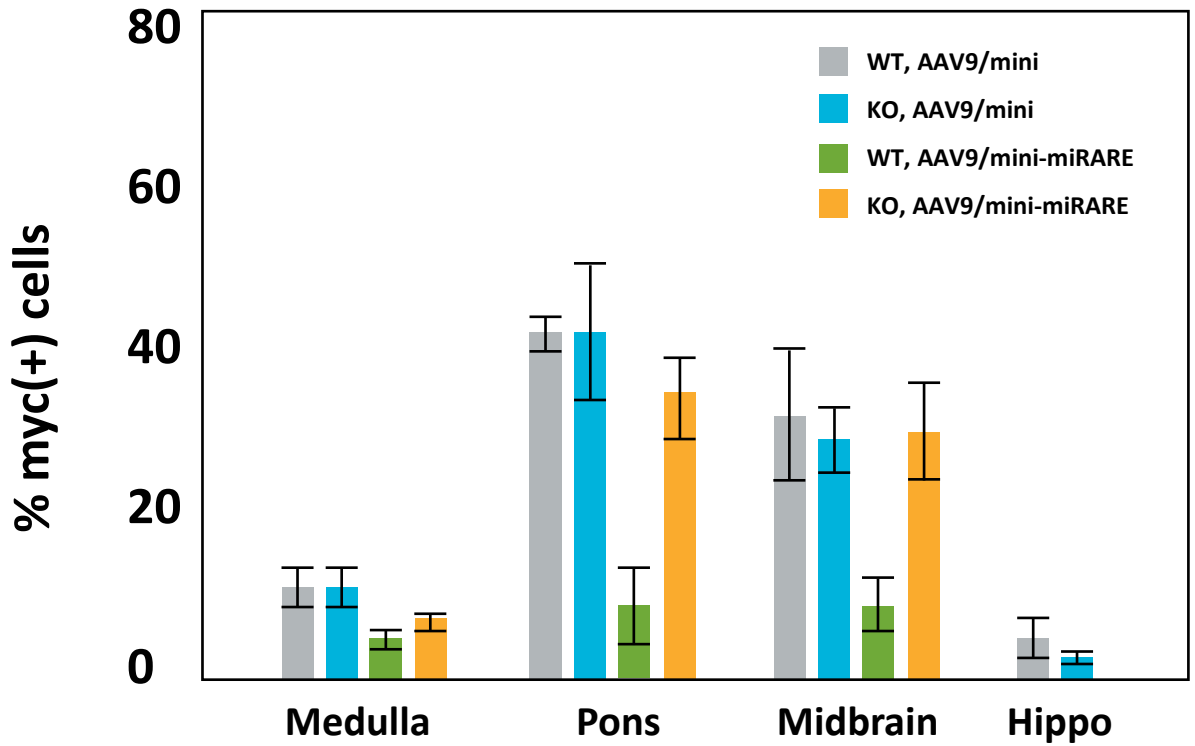
Engineered microRNA-based regulatory element permits safe high-dose mini*MECP2* gene therapy in Rett mice

Sarah E Sinnett, Emily Boyle, Christopher Lyons, Steven J Gray

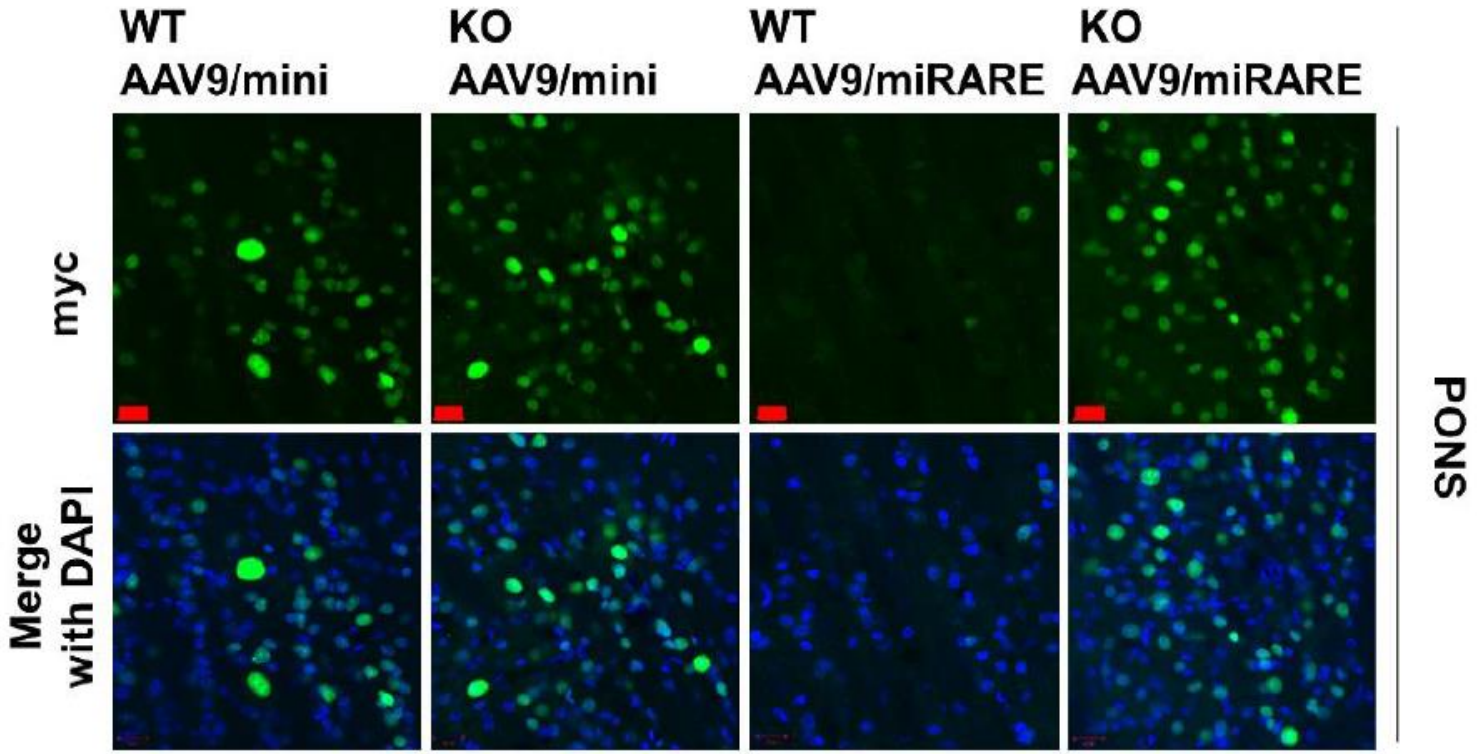
Abstract

MECP2 gene transfer has been shown to extend the survival of *Mecp2*$^{-/y}$ knockout (KO) mice modeling Rett syndrome (RTT), an X-linked neurodevelopmental disorder. However, controlling deleterious overexpression of MeCP2 remains the critical unmet obstacle towards a safe and effective gene therapy approach for RTT. A recently developed truncated mini*MECP2* gene has also been shown to be therapeutic after AAV9-mediated gene transfer in KO neonates. We show that AAV9/mini*MECP2* has a similar dose-dependent

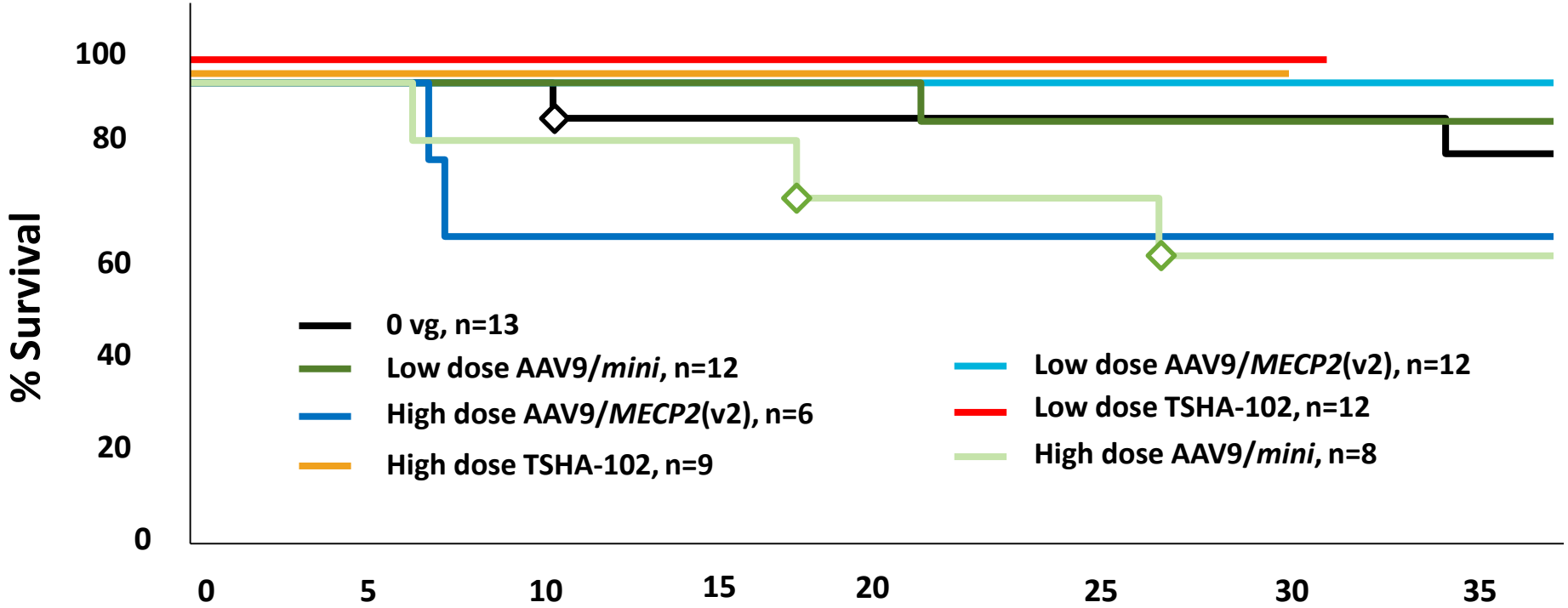
miRARE regulates genotype-dependent MECP2 expression across different brain regions in wild type and knockout Rett mouse models



Significantly fewer cells demonstrated expression in the pons and midbrain in TSHA-102-treated wild type mice compared to knockout mice



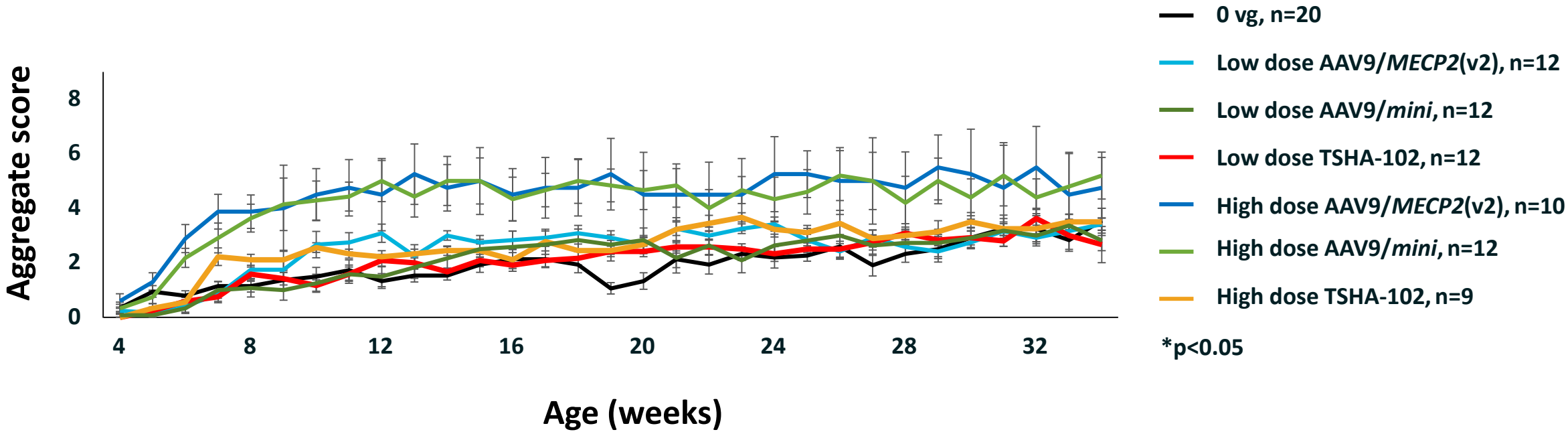
Safety: Intrathecal TSHA-102 was not associated with early death in WT mice



Mice were dosed P28-35

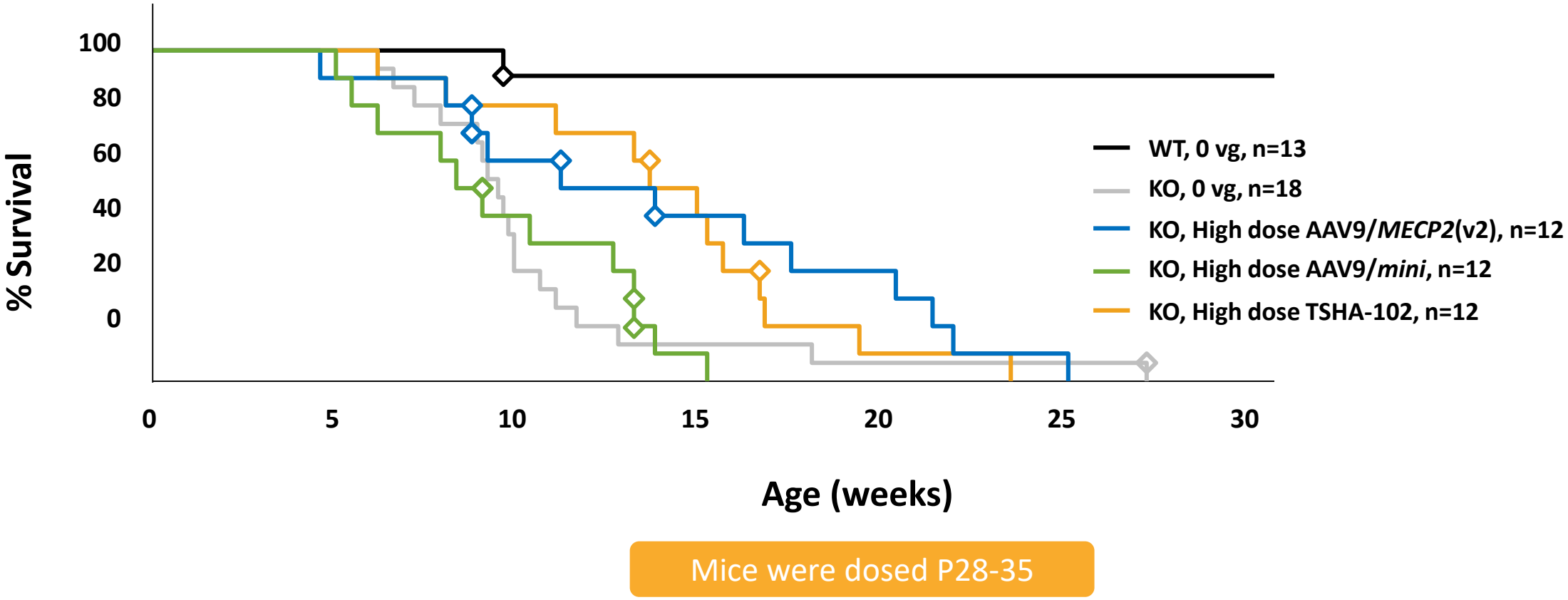
Diamond = vet-requested euthanasia for prolapse or bullying-related injury

Safety: TSHA-102 did not cause adverse behavioral side effects in WT mice



Mice were dosed P28-35

Efficacy: TSHA-102 outperformed unregulated AAV9/mini in MECP2 KO mouse survival study



Mice were dosed P28-35

Diamond = vet-requested euthanasia, primarily for lesions. Lesions have been observed with varying frequencies among saline-treated KO mice, virus-treated WT and KO mice, as well as untreated RTT weanlings.

IND/CTA filing for TSHA-102 in Rett syndrome expected in 2H 2021

TSHA-102
Rett Syndrome

Study design and duration	• Open-label, dose-ranging, randomized, multi-center Phase 1/2 trial • Safety and preliminary efficacy • Each cohort randomized 3:1 (one patient is a delayed treatment control)
Key inclusion/exclusion criteria	• Adults with pathogenic confirmation of mutation in *MECP2*
Intervention	• First cohort (n=4): single dose of $5x10^{14}$ total vg of TSHA-102 (AAV9/*MECP2*-miRARE) • Second cohort (n=4): single dose of $1x10^{15}$ total vg of TSHA-102 (AAV9/*MECP2*-miRARE) • Delivered intrathecally
Key clinical assessments	**Rett-Specific/Global Assessments** • Motor Behavior Assessment Scale (MBA) • Rett Syndrome Hand Apraxia Scale (RHAS) • Rett Syndrome Behavior Questionnaire (RSBQ) • Functional Mobility Scale in Rett Syndrome (FMS) • Clinical Global Impression **Behavior/Mood Assessments** • Anxiety, Depression, and Mood Scale (ADAMS) • Aberrant Behavior Checklist (ABC) **Seizure Assessments** • EEG and neurophysiology • Seizure diary **Respiratory Assessments** • Respiratory Disturbance Index (RDI) • Sleep apnea, sleep study **Communication Assessments** • Observer Reported Communication Assessment (ORCA) **Quality of Life/Other Assessment** • SF-36 – Quality of life assessment from principal caregiver • RTT-CBI – Caregiver burden inventory **Wearables** • Hexoskin: cardiac, respiratory, sleep & activity

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

6 additional programs currently in IND-enabling studies
2-day R&D Day (June 28-29, 2021)
Numerous value generating catalysts over the next 18 months