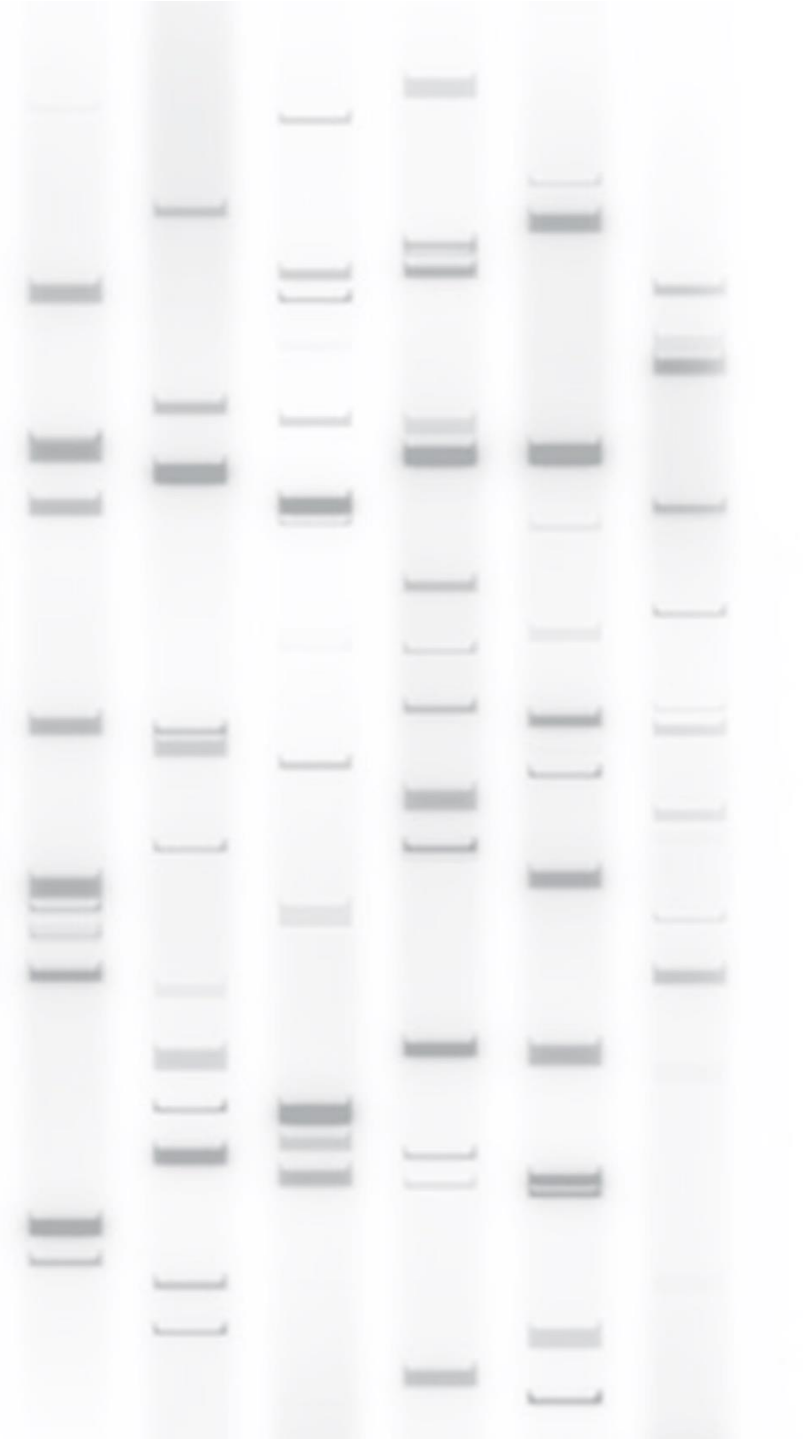
TAYSHA GENE THERAPIES

R&D Day

June 28, 2023 | 9:00 AM CT / 10:00 AM ET



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, 2022. 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

SEAN NOLAN

Board Chairman and Chief Executive Officer

Agenda

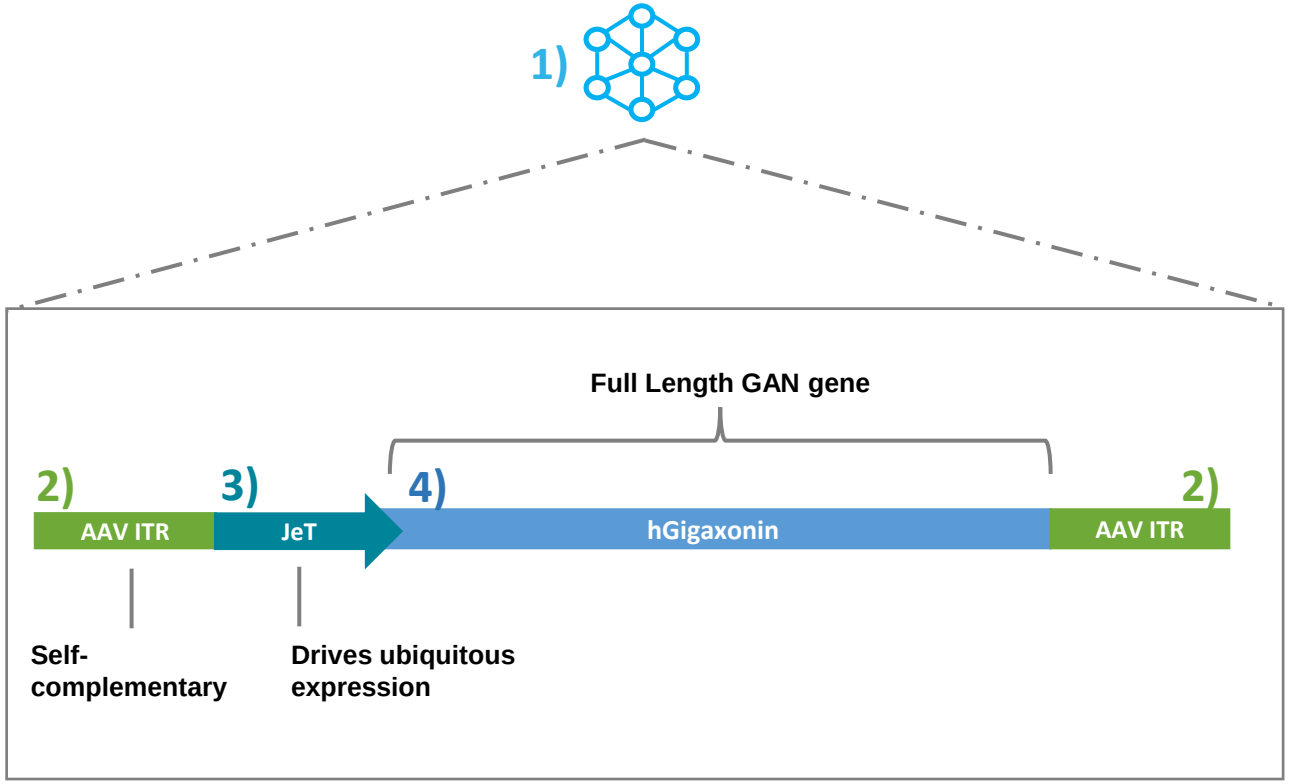
Topic	Presenter
Introduction	Sean Nolan
TSHA-120 Program Overview and History	Sukumar Nagendran, MD
GAN Disease Overview and New Clinical Data Update	Salman Bhai, MD
Regulatory Path Forward for TSHA-120	Sukumar Nagendran, MD
Rett Disease Overview and New Clinical Data Update	Azhar Rana, MD
Q&A and Closing Remarks	Sean Nolan

Program Overview and History: TSHA-120, an Investigational Gene Therapy for GAN

SUKU NAGENDRAN, MD

President and Head of R&D

TSHA-120 construct design aims to address the root cause of giant axonal neuropathy (GAN)



TSHA-120

1) AAV9 viral vector with engineered transgene encoding the human gigaxonin protein
2) Self-complementary inverted terminal repeats (ITR) for rapid activation and stable expression
3) JeT promoter drives ubiquitous expression
4) Designed to deliver a codon optimized, functional copy of the GAN gene with optimal tropism for rapid expression

NIH initiated a natural history (NH) basket study in 2012 that included GAN

Study design	• Clinical and Molecular Manifestations of Neuromuscular and Neurogenetic Disorders of Childhood • Diagnostic and prospective longitudinal natural history study • Data collected over a period of 10 years • n=5650*; of which 53 have a genetic diagnosis of GAN • Aged 3-21 years
Main outcome measures	• Diagnose and characterize patients with neuromuscular and neurogenetic disorders with congenital or pediatric onset and study the natural history and underlying disease mechanism • Identify and develop effective outcome measures for use in future clinical trials

*The full study was a genetic, nerve and muscle disorder basket natural history study

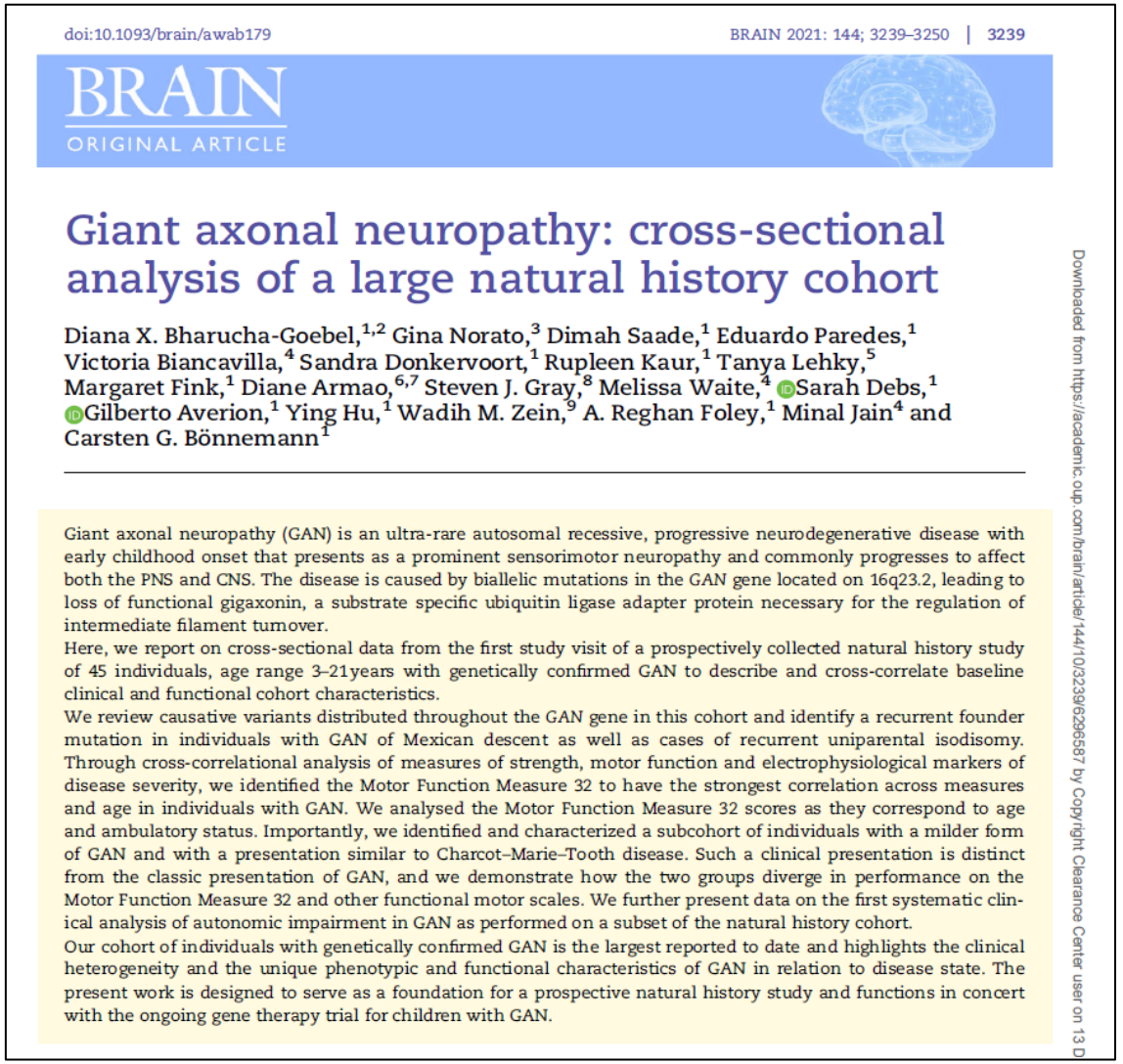
Clinical Trial: NCT01568658

This study presents the largest collection of GAN NH data in world

Natural history data of first 45 GAN patients published in *Brain*

Cross-sectional baseline data from GAN patients in the NH study served as the external control for the Phase 1/2 clinical trial evaluating TSHA-120 for the treatment of GAN

- 45 subjects (3-21 years) with genetically confirmed GAN
- Mean age of symptom onset for the full cohort is 2.9 years



doi:10.1093/brain/awab179 BRAIN 2021: 144; 3239–3250 | 3239

BRAIN
ORIGINAL ARTICLE

Giant axonal neuropathy: cross-sectional analysis of a large natural history cohort

Diana X. Bharucha-Goebel,[1,2] Gina Norato,[3] Dimah Saade,[1] Eduardo Paredes,[1] Victoria Biancavilla,[4] Sandra Donkervoort,[1] Rupleen Kaur,[1] Tanya Lehky,[5] Margaret Fink,[1] Diane Armao,[6,7] Steven J. Gray,[8] Melissa Waite,[4] Sarah Debs,[1] Gilberto Averion,[1] Ying Hu,[1] Wadih M. Zein,[9] A. Reghan Foley,[1] Minal Jain[4] and Carsten G. Bönnemann[1]

Giant axonal neuropathy (GAN) is an ultra-rare autosomal recessive, progressive neurodegenerative disease with early childhood onset that presents as a prominent sensorimotor neuropathy and commonly progresses to affect both the PNS and CNS. The disease is caused by biallelic mutations in the *GAN* gene located on 16q23.2, leading to loss of functional gigaxonin, a substrate specific ubiquitin ligase adapter protein necessary for the regulation of intermediate filament turnover.

Here, we report on cross-sectional data from the first study visit of a prospectively collected natural history study of 45 individuals, age range 3–21 years with genetically confirmed GAN to describe and cross-correlate baseline clinical and functional cohort characteristics.

We review causative variants distributed throughout the *GAN* gene in this cohort and identify a recurrent founder mutation in individuals with GAN of Mexican descent as well as cases of recurrent uniparental isodisomy. Through cross-correlational analysis of measures of strength, motor function and electrophysiological markers of disease severity, we identified the Motor Function Measure 32 to have the strongest correlation across measures and age in individuals with GAN. We analysed the Motor Function Measure 32 scores as they correspond to age and ambulatory status. Importantly, we identified and characterized a subcohort of individuals with a milder form of GAN and with a presentation similar to Charcot–Marie–Tooth disease. Such a clinical presentation is distinct from the classic presentation of GAN, and we demonstrate how the two groups diverge in performance on the Motor Function Measure 32 and other functional motor scales. We further present data on the first systematic clinical analysis of autonomic impairment in GAN as performed on a subset of the natural history cohort.

Our cohort of individuals with genetically confirmed GAN is the largest reported to date and highlights the clinical heterogeneity and the unique phenotypic and functional characteristics of GAN in relation to disease state. The present work is designed to serve as a foundation for a prospective natural history study and functions in concert with the ongoing gene therapy trial for children with GAN.

Source: Bharucha-Goebel D et al. *Brain* 2021

Phase 1/2 dose-escalating interventional study began enrolling in 2015

Study design	• Open-label, dose-escalation, non-randomized, single-center interventional Phase 1/2 trial • Safety, tolerability and efficacy of TSHA-120 in participants with GAN • Up to 15 years follow up (84.5 months longitudinal follow-up as of 03, May 2023) • n=14 (up to 21 subjects, 14 enrolled)
Dose cohorts	• **Low:** 1.0 x 10^{13} total vg (*n=2*) • **Medium-low:** 3.5 x 10^{13} (*n=4*) • **Medium-high:** 5.3 x 10^{13} total vg (*n=5*) • **High:** 1.0 x 10^{14} total vg (*n=3*)
Key inclusion criteria	• Genetic confirmation of GAN • 3 years of age and older
Route of administration	• Delivered intrathecally
Main outcome measures (*12 months*)	• Safety of the vector • Safety and tolerability of gene transfer in patients with null mutations receiving immunosuppression • Motor function (*e.g., MFM, FARS, NIS, myometry, timed motor functions*) • Electrophysiologic assessment (nerve conduction) of sensory-motor nerves • Neuropathology in peripheral nerve biopsies (*e.g., superficial radial nerve, skin biopsies*) • Examination of cerebrospinal fluid to monitor for inflammatory markers • Assessment of vector shedding

Clinical Trial: NCT02362438

Historical overview of recent interactions with the FDA

December 2022-February 2023	January 2023-Present	Next Steps
Type B End-of-Phase 2 Meeting	**Totality of Data Analysis**	**FDA Interactions**

• Presented FDA with a **subset of available evidence** suggesting favorable benefit/risk profile of TSHA-120
• Significant emphasis placed on MFM32 as primary endpoint
• FDA suggested a double-blind placebo-controlled study given “effort dependent” endpoint and the heterogeneity of disease progression in GAN
• Subsequent feedback from FDA highlighted openness to an alternate study design that's “well controlled” and demonstrates significant impact on clinically meaningful, objective endpoints
	• Taysha obtained **all available data** from 7+ years of the interventional trial and 10+ years of from the natural history study and initiated comprehensive analysis
	• Developed a disease progression model (DPM)* to serve as external control demonstrating a predictable and homogenous disease progression
	• New data analysis reinforces a clinically meaningful treatment effect*:
	  ◦ Functional Measures: MFM32, mFARS, LogMAR
	  ◦ Electrophysiological Measures: SNAP, CMAP
	  ◦ Biological Measures: Nerve biopsies
		• Taysha anticipates formal FDA meeting in Q3 2023
		• In this meeting, Taysha plans to address FDA's previous feedback and present updated analysis to align on path forward

*The DPM models classic GAN only

GAN Disease Overview and New Clinical Data

SALMAN BHAI, MD

Assistant Professor of Neurology at UTSW and Director of the Neuromuscular Center at the Institute for Exercise and Environmental Medicine

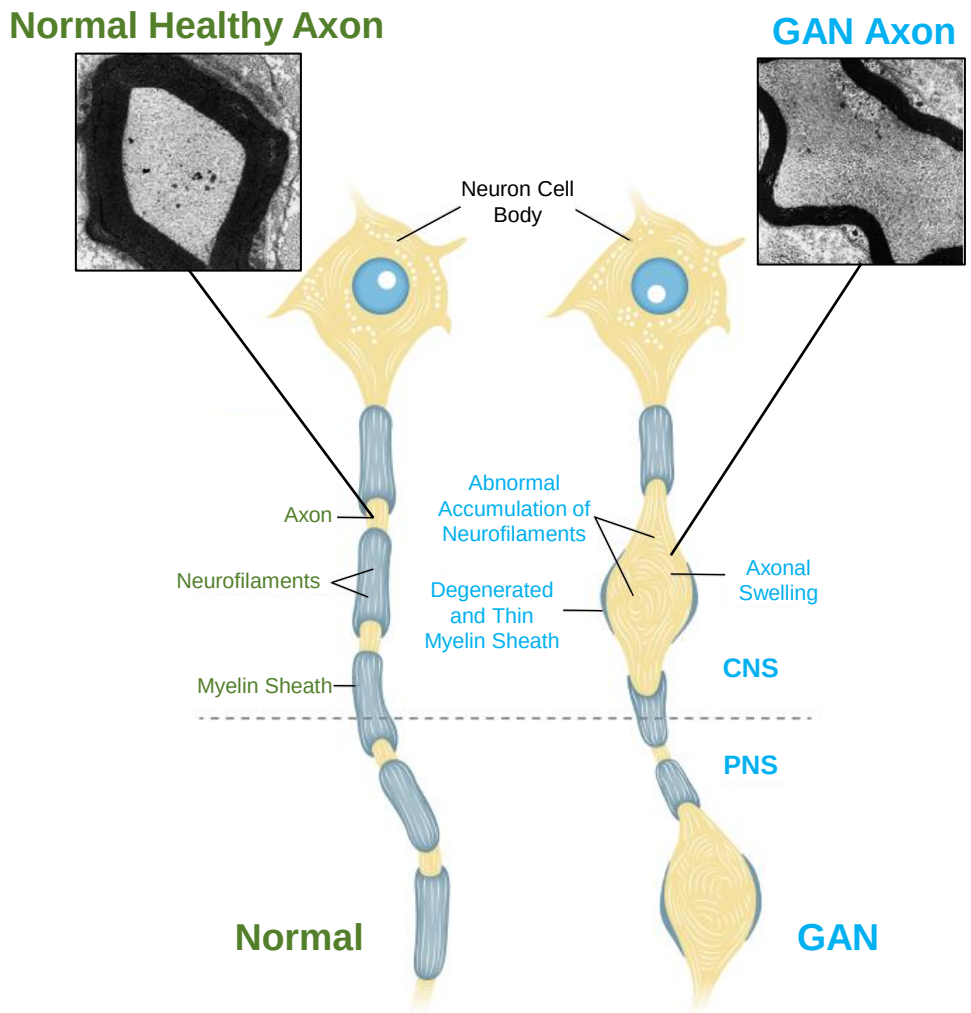
Giant axonal neuropathy (GAN) disease overview

- GAN is an ultra-rare, autosomal recessive, progressive neurodegenerative disease that impacts the central, peripheral and autonomic nervous systems
- Biallelic variants in the GAN gene result in deficiency or complete loss-of-function of gigaxonin and the accumulation of intermediate filaments (IF)
- Accumulation of IF in axons (morphologically "giant" axons) causes neurodegeneration
  - Length-dependent progressive sensory motor axonal neuropathy
  - Progressive cerebellar ataxia

Disease progression:

- Patients with classical phenotype are clinically identified due to delayed developmental milestones between 2 and 3 years of age and tightly curled hair
- A highly predictable decline in balance and distal muscle strength typically leading to loss of ambulation by age 10
- Disease progresses with unsteady gait, limb ataxia, distal muscle weakness in arms and legs, followed by proximal muscle weakness, intellectual disability, and death by the third decade of life, often due to respiratory failure
- Progressive optic nerve atrophy seen early on results in increasing deterioration of visual acuity

No treatments are currently approved; current treatments are palliative only



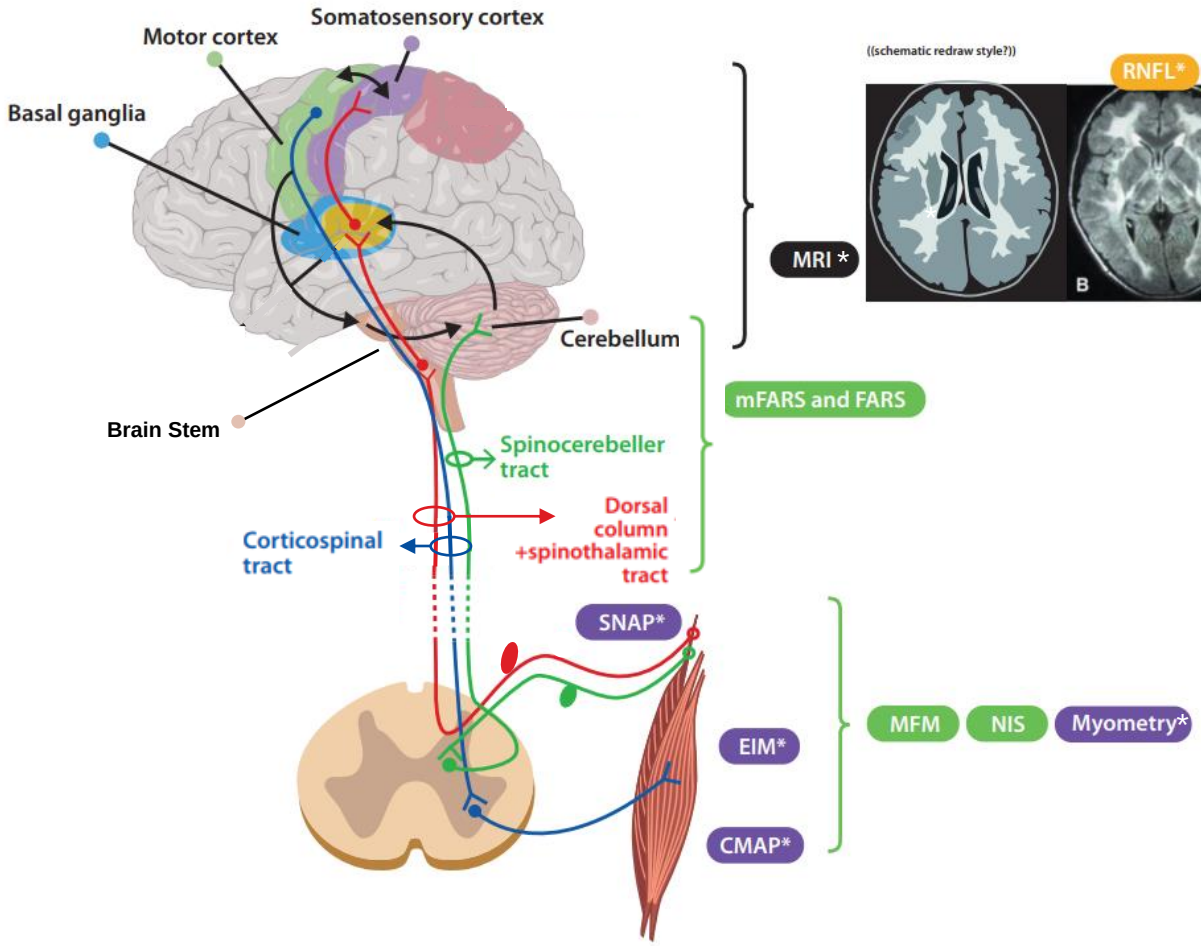
Source: Bharucha-Goebel DX et al. Giant axonal neuropathy: cross-sectional analysis of a large natural history cohort. Brain. 2021;144(10):3239-3250.

Opal P. GAN-Related Neurodegeneration. 2003 Jan 9 [Updated 2021 Oct 14]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1136/

MedlinePlus (2021) Giant Axonal Neuropathy. 2022:01 January 2022. Available from: https://medlineplus.gov/genetics/condition/giant-axonal-neuropathy/

Integrated, multisystem assessment of GAN

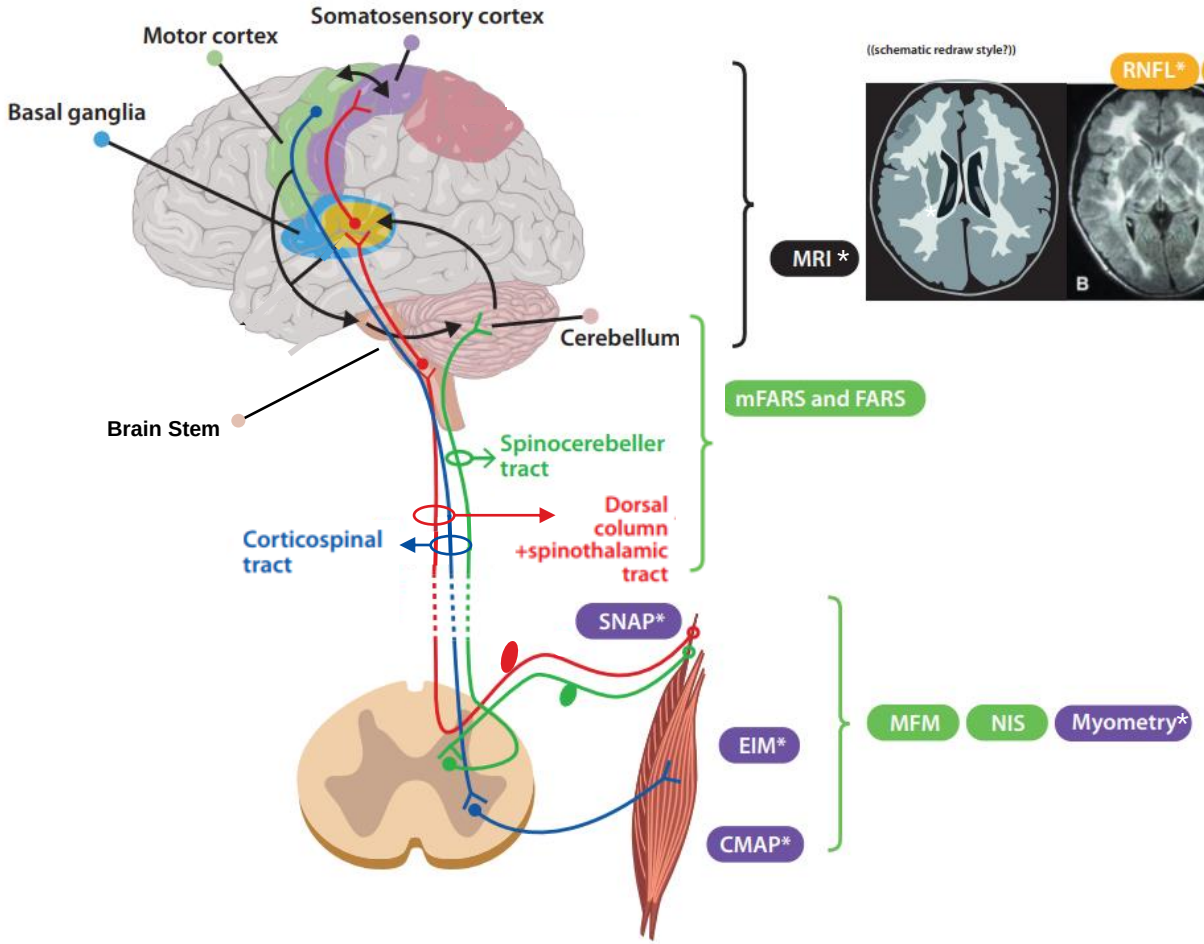
SNAP – Sensory Nerve Action Potential; **CMAP –** Compound Muscle Action Potential; **EIM –** Electrical Impedance Myography; **LogMAR –** Logarithm of the Minimum Angle of Resolution; **FARS**-Friedrich Ataxia Rating Scale; **GCL –** Ganglion cell layer; **mFARS –** modified FARS; **NIS –** Neuropsychological Impairment Scale; **RNFL –** retinal nerve fiber layer

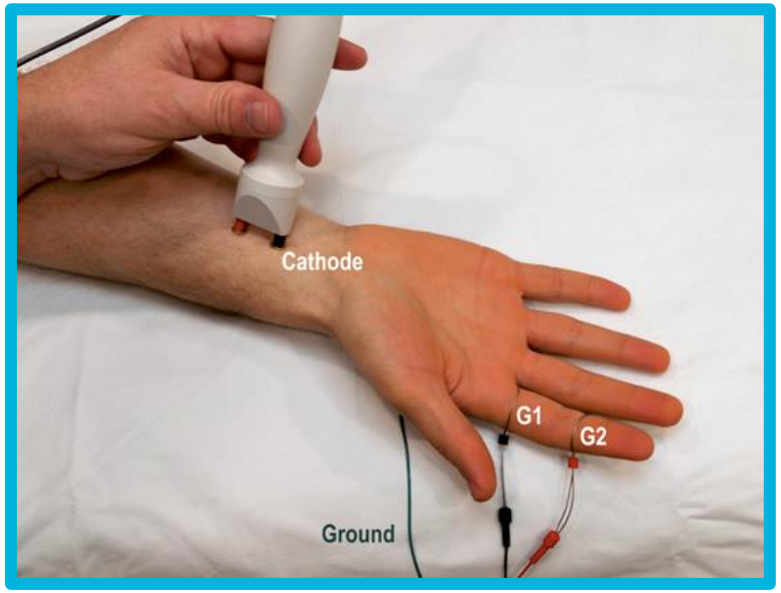


Key
Functional Outcomes
PNS Clinical Data
Ophthalmology
CNS Clinical Data
*Objective Measures

Integrated, multisystem assessment of GAN

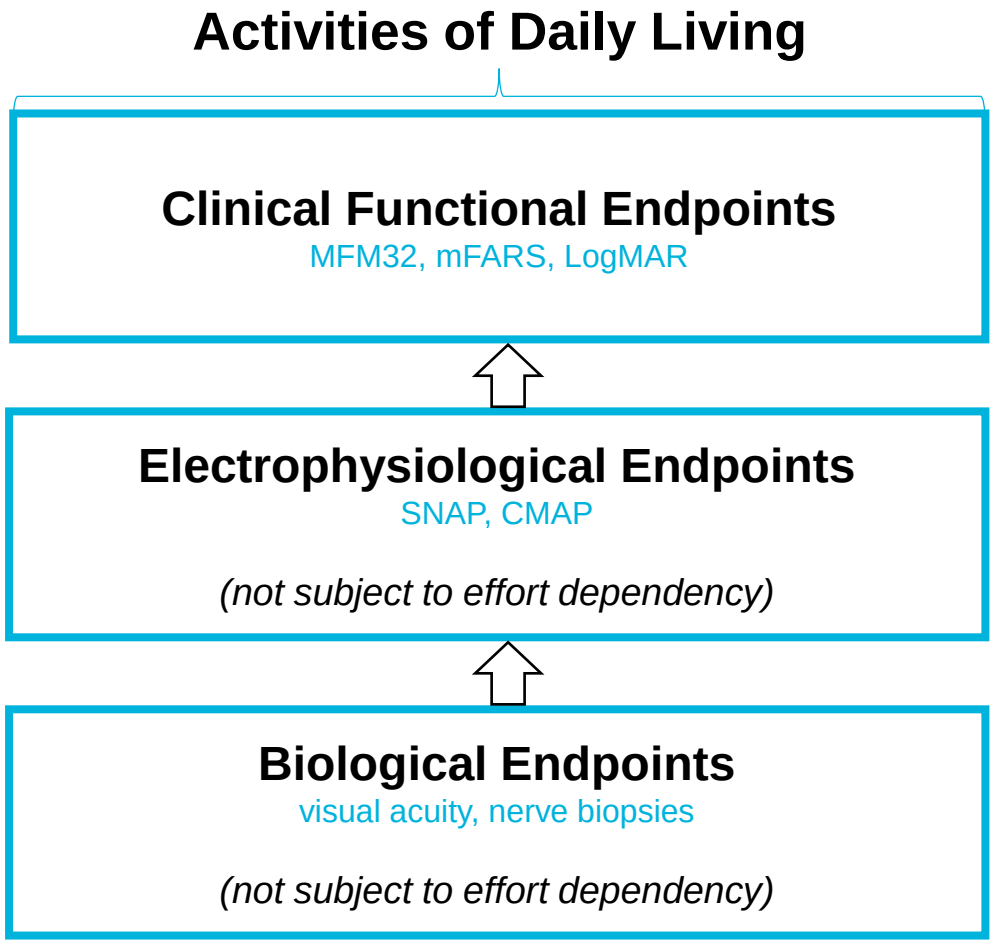
SNAP – Sensory Nerve Action Potential; **CMAP –** Compound Muscle Action Potential; **EIM –** Electrical Impedance Myography; **LogMAR –** Logarithm of the Minimum Angle of Resolution; **FARS**-Friedrich Ataxia Rating Scale; **GCL –** Ganglion cell layer; **mFARS –** modified FARS; **NIS –** Neuropsychological Impairment Scale; **RNFL –** retinal nerve fiber layer





Source: David C. Preston, Barbara Shapiro Electromyography and Neuromuscular Disorders: Clinical Electrophysiologic Correlations. 2. Elsevier. 2005.

New disease progression model (DPM) supports the use of natural history data as external control

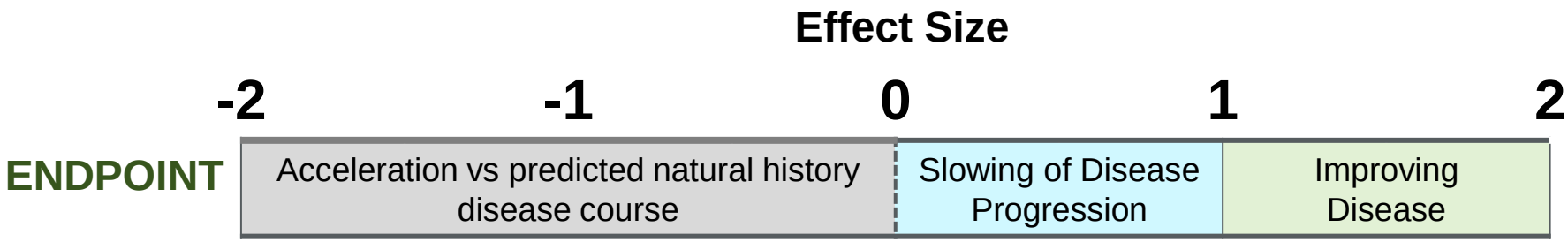


Bayesian DPM establishes a predictable disease course – this enables Taysha to address FDA's concerns in the context of an ultra-rare disease

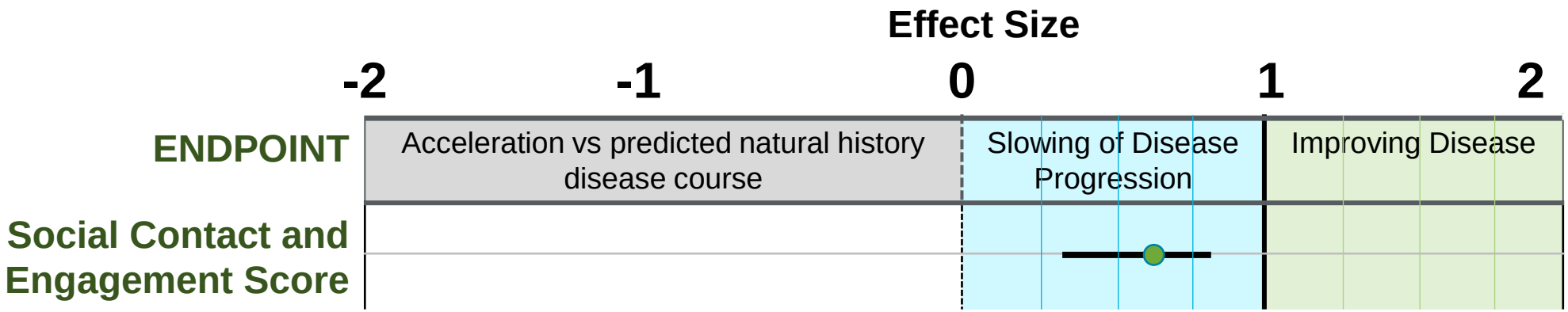
1. Benefits over Patient as Own Control (PAOC): shows homogeneity and monotonicity of disease and can account for limited pre-treatment data
2. DPM confidently estimates a treatment effect across many biological and clinical functional endpoints
3. DPM accepted by regulatory agencies in interventional studies of rare diseases and small patient populations, per FDA's recently published guidance[1]

Source: [1]FDA, U. (2023). Considerations for the design and conduct of externally controlled trials for drug and biological products guidance for industry.
Company data – ongoing analysis, figure is subject to change

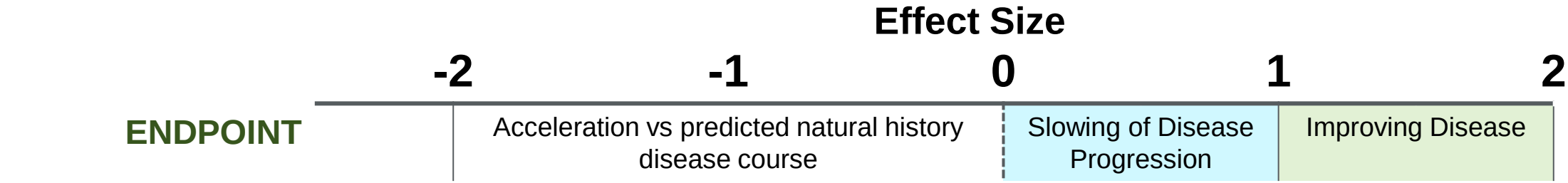
Measuring effect size

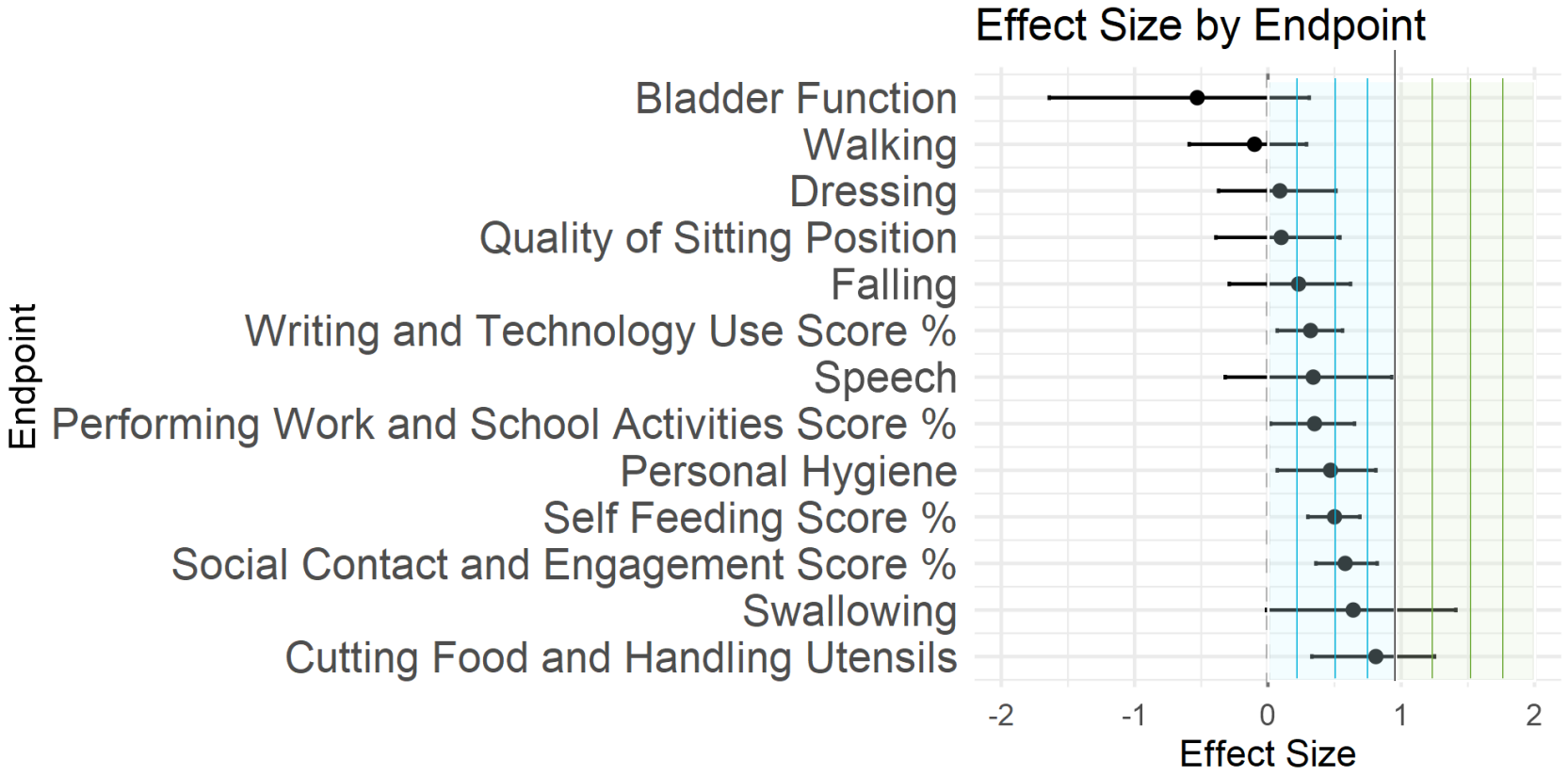


Measuring effect size

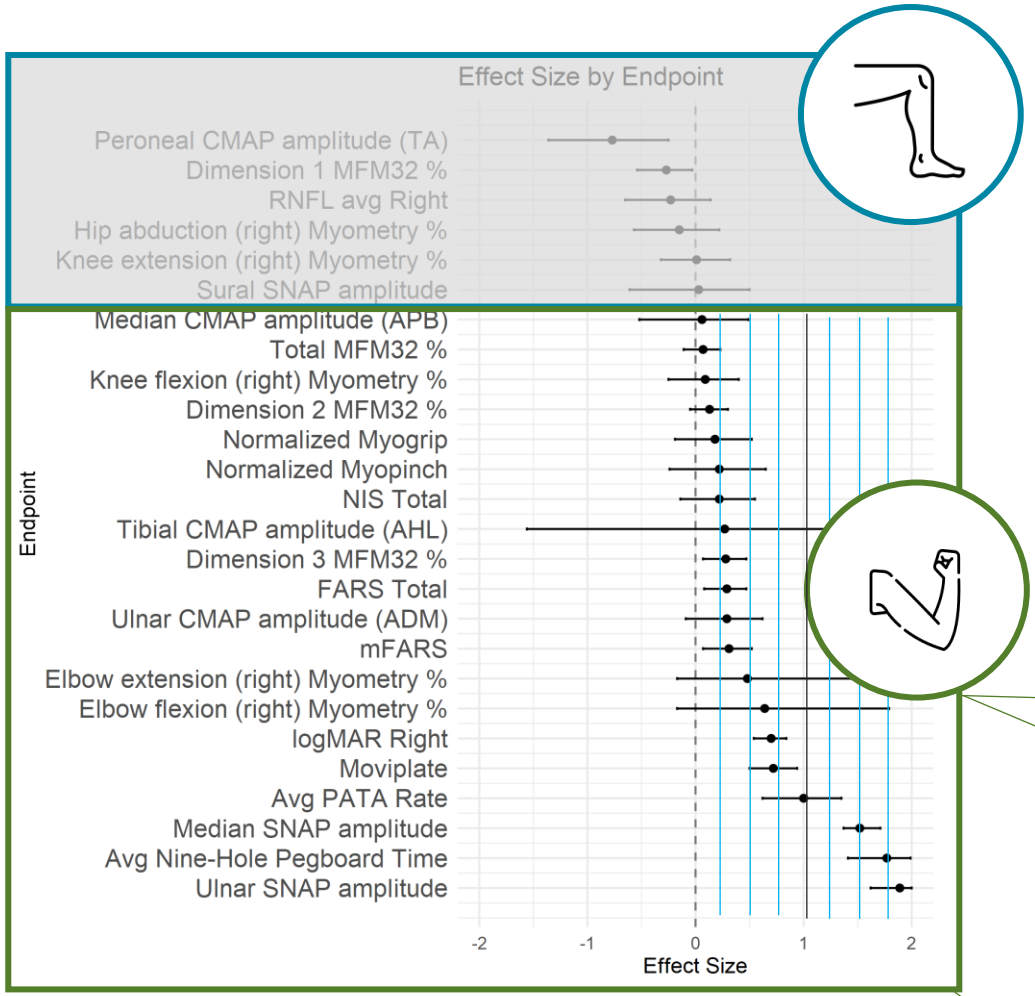


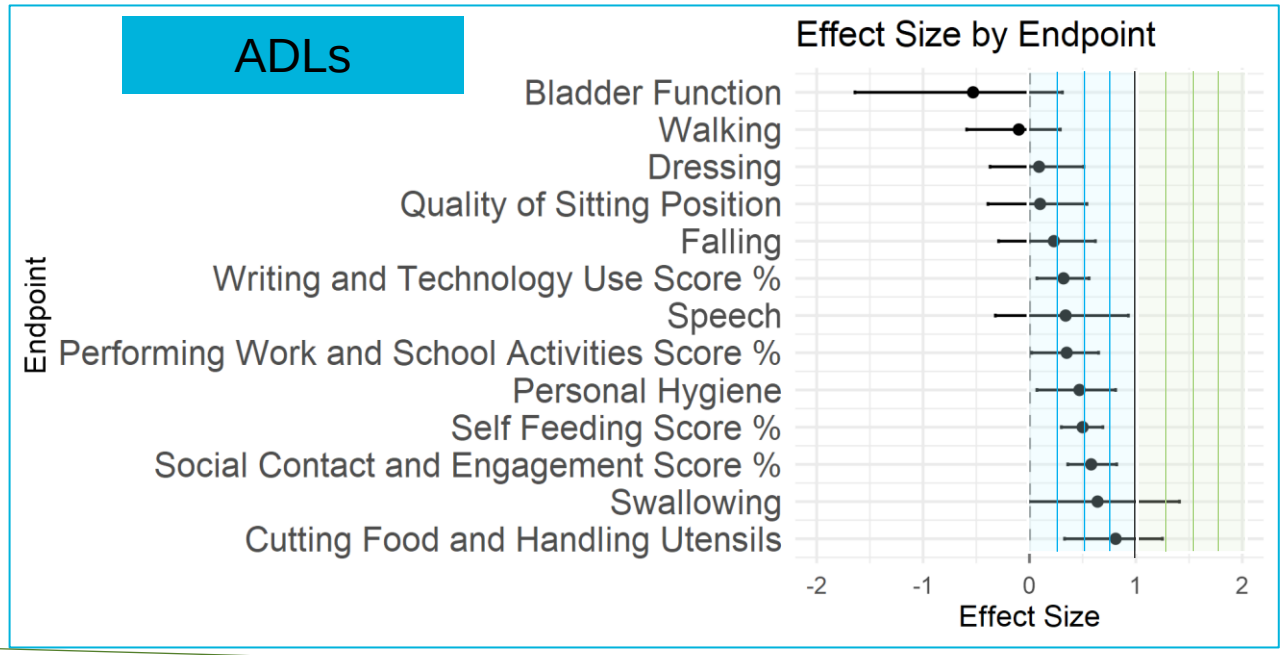
Understanding observed effect size on patients' Activities of Daily Living (ADL)

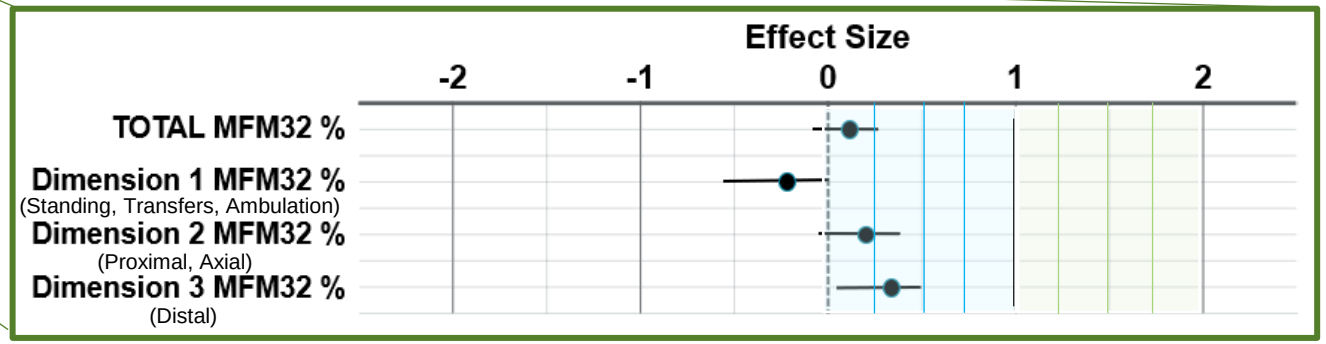




Majority of endpoint measures are consistent with a slowing of the rate of disease progression post-dosing with TSHA-120, compared to DPM

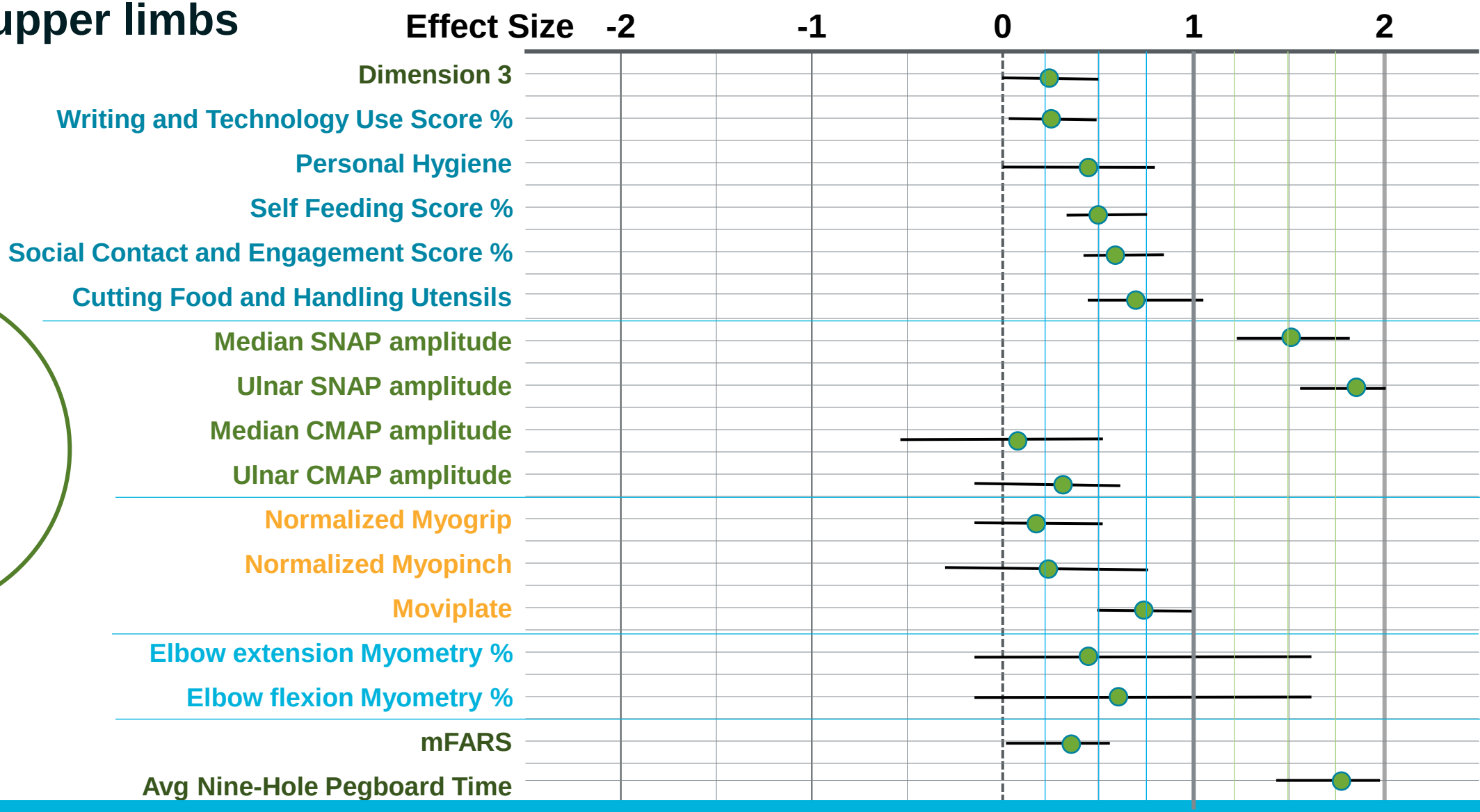






Source: Company data – preliminary data, subject to change

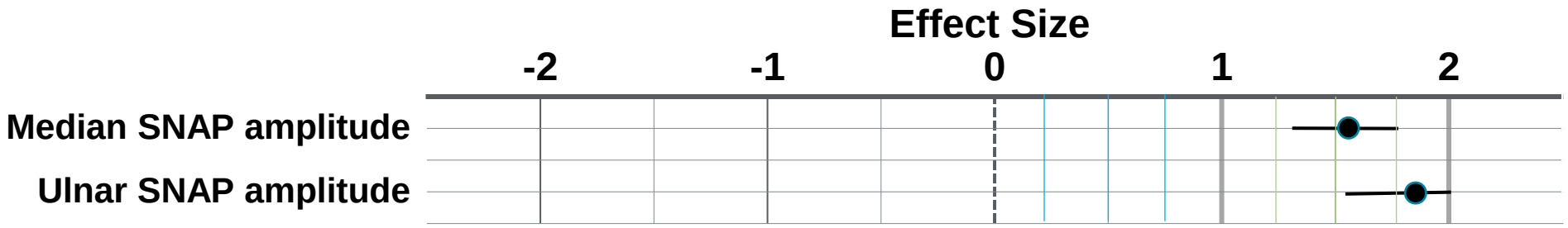
Moderate to robust treatment effects observed in categories related to personal independence and self-care, particularly activities involving the use of the upper limbs



Source: Company data – preliminary data, subject to change

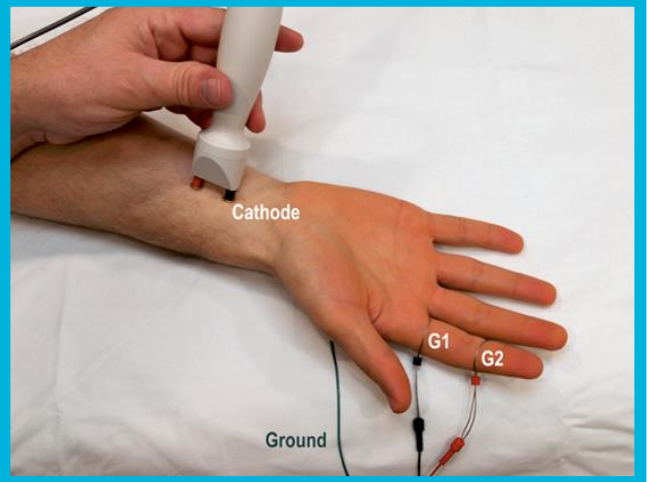
Results suggest direct and real benefit to patients with ancillary reduction of caregiver burden anticipated

Restoration of sensory nerve action potential (SNAP) and increased regenerative clusters on nerve biopsy



5 patients experienced a gain in nerve conduction amplitude post treatment, suggesting neuroregeneration

4 of the 5 patients that had stabilization or improvements in SNAPs had increased regenerative clusters on nerve biopsy

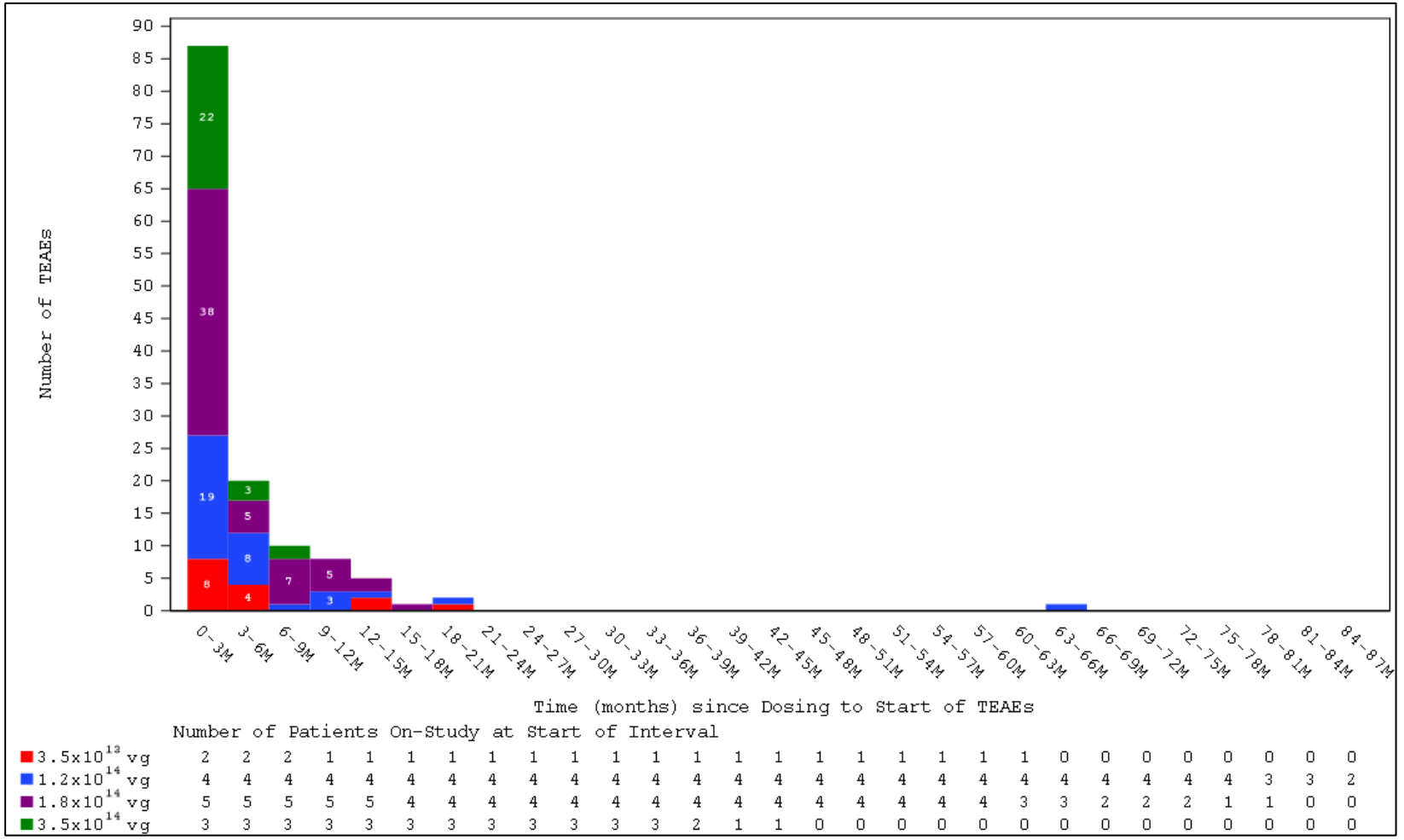


Nerve conduction study of sensory nerves revealed that most interventional study participants were at an advanced state of the disease when first treated with TSHA-120 and had abnormal SNAP responses at baseline

Source: Company data – preliminary data, subject to change
David C. Preston, Barbara Shapiro Electromyography and Neuromuscular Disorders: Clinical Electrophysiologic Correlations. 2. Elsevier. 2005.

Approximately seven years of long-term clinical data support safety and tolerability of TSHA-120, with no significant safety issues

- No dose-limiting toxicity
- Some evidence of asymptomatic cerebrospinal fluid pleocytosis
- Well-tolerated at multiple doses and safely dosed in the presence of neutralizing antibodies
- No signs of significant acute or subacute inflammation, no sudden sensory changes and no drug-related or persisting transaminitis
- All serious adverse events (SAEs) were deemed unrelated or unlikely to be related to TSHA-120 other than one event of Pyrexia(Gr1, resolved within 4 days)



Dose Group: All Patients (data through May 3, 2023)

Preliminary data, subject to change

New data analysis shows an overall impact of treatment on both objective biological and clinically relevant endpoints

GAN is a disorder of the CNS (leukodystrophy) and PNS (CMT)

Combination of weakness and ataxia support clinical relevance of MFM32 and mFARS

Disease Progression Model shows homogeneity of disease progression

The DPM supports the use of NH data as external control

Clinician reported and functional outcomes are supported by objective clinical and biological data unsusceptible to bias

Peripheral nerve regeneration supported by SNAPs and regenerative clusters in a dose-dependent manner

Biological Data + Clinical Data + Clinician Reported and Functional Outcomes

Patients' Activities of Daily Living

We believe in the transformative potential of TSHA-120 to bring meaningful change to patients and families impacted by this ultra-rare disease with no approved treatments.

Regulatory Path Forward for GAN

SUKU NAGENDRAN, MD

President and Head of R&D

Company position: existing data supports approval of TSHA-120 for the treatment of GAN

High unmet need	• GAN is a devastating ultra-rare disease with no approved treatments
Robust dataset	• Robust natural history and interventional study datasets represent a significant percentage of the known patient population
DPM enables external control	• DPM demonstrates monotonicity and homogenous disease progression – supports potential for NH to serve as a suitable external control

Promising new data and analysis	• New analysis demonstrates weakness and ataxia are major sources of disability in GAN
	• Multiple objective and clinically meaningful endpoints identified to demonstrate efficacy
	  • Functional: mFARS, MFM32, LogMAR
	  • *mFARS recently served as basis for approval of Freidrich's ataxia drug*
	  • Electrophysiological: SNAP, CMAP
	  • Biological: visual acuity, nerve biopsies

Established safety	• Approximately 7 years of safety data

Patients need treatment options

The benefit of treatment outweighs the risk in this devastating disease, where there are no approved treatments.

Program Overview and Update: TSHA-102, an Investigational Gene Therapy for Rett Syndrome

AZHAR RANA, MD

Head of Medical Affairs

Rett syndrome is a devastating rare neurological disorder with high unmet medical need

- Rett syndrome is a rare neurological disorder caused by mutations in the X-linked *MECP2* gene
  - *MECP2* regulates the expression of many genes involved in normal brain function and mutations lead to impaired brain development and function
- Disorder causes intellectual disabilities, loss of communication abilities, seizures, slowing and/or regression of development, motor and respiratory impairment and shortened life expectancy
- No approved disease-modifying therapies exist that treat the genetic root cause of the disease
- Estimated prevalence of typical Rett syndrome caused by a *MECP2* mutation is between 15,000 and 20,000 (U.S., EU+UK)
- Rett syndrome occurs worldwide in 1 of every 10,000 female births[1]

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

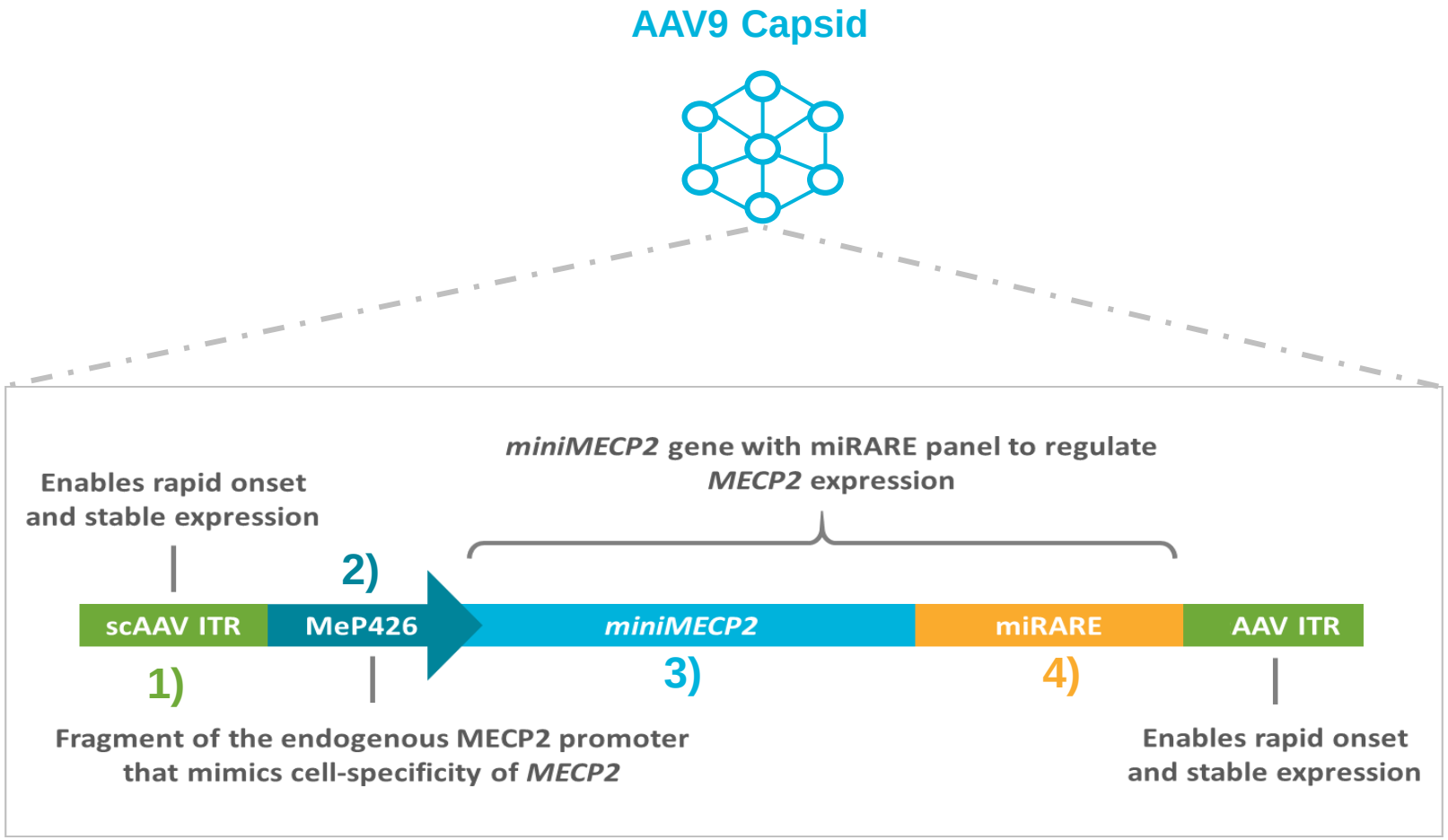
>10 years

Late Motor Deterioration Muscle wasting with age

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

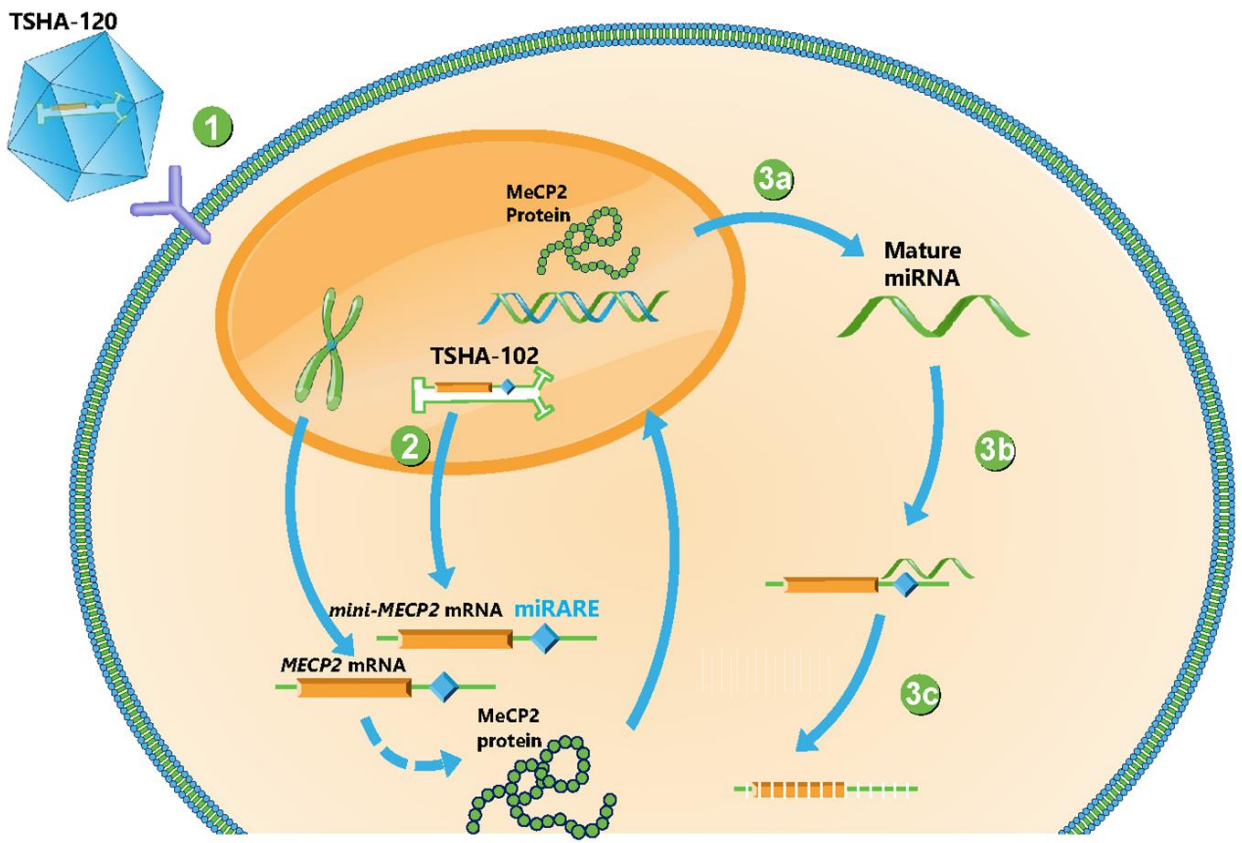
Sources: IRSF; NORD; Amir RE, Van den Veyver IB, Wan M, et al. Rett Syndrome Is Caused by Mutations in X-Linked Mecp2, Encoding Methyl-Cpg-Binding Protein 2. Nat Genet 232:185-188. 1999

TSHA-102 construct designed to regulate cellular *MECP2* expression



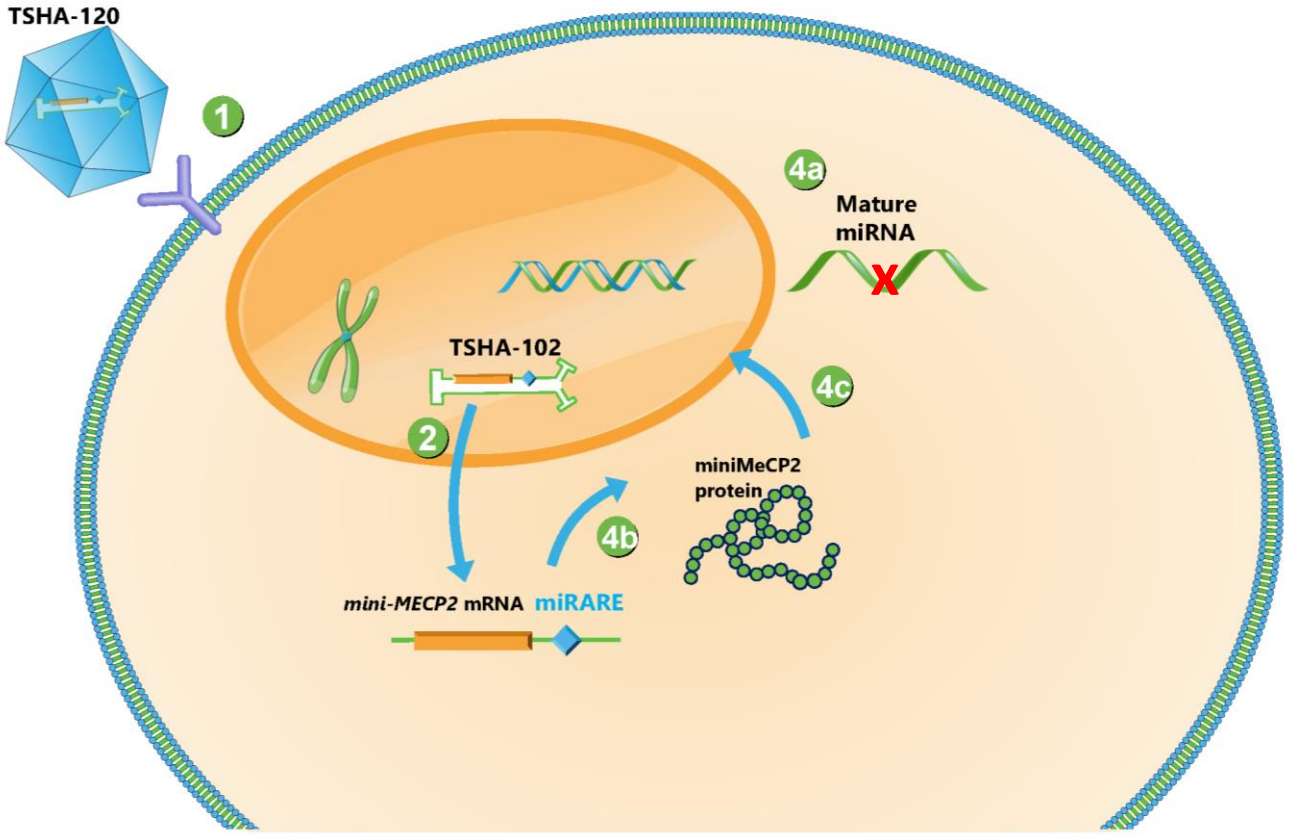
TSHA-102 utilizes a novel miRARE technology to mediate levels of *MECP2* in the CNS on a cell-by-cell basis without risk of overexpression

Healthy, MeCP2-expressing cell



Designed to silence the *miniMECP2* transgene in cells that already express MeCP2

MeCP2-deficient cell



Designed to enable miniMeCP2 protein production in MeCP2-deficient cells

Robust pre-clinical data supports the safety and efficacy for TSHA-102 across animal species

Mice

Pharmacology and tolerability studies

- Conducted in *Mecp2*$^{-/Y}$ knockout (KO) mice and wild-type (WT) mice

Rats

Toxicology and biodistribution studies

- Conducted in Sprague Dawley rats up to ~6 months post-administration
- Three dose levels up to 4x starting clinical dose were evaluated

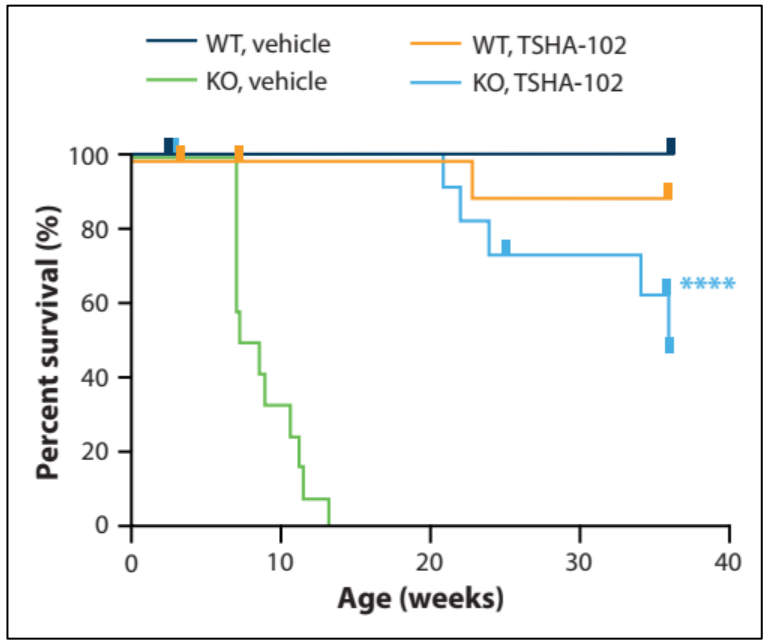
Non-Human Primates

Toxicology and biodistribution studies

- Conducted in cynomolgus monkeys up to 6 months post-administration
- Three dose levels up to 4x starting clinical dose were evaluated

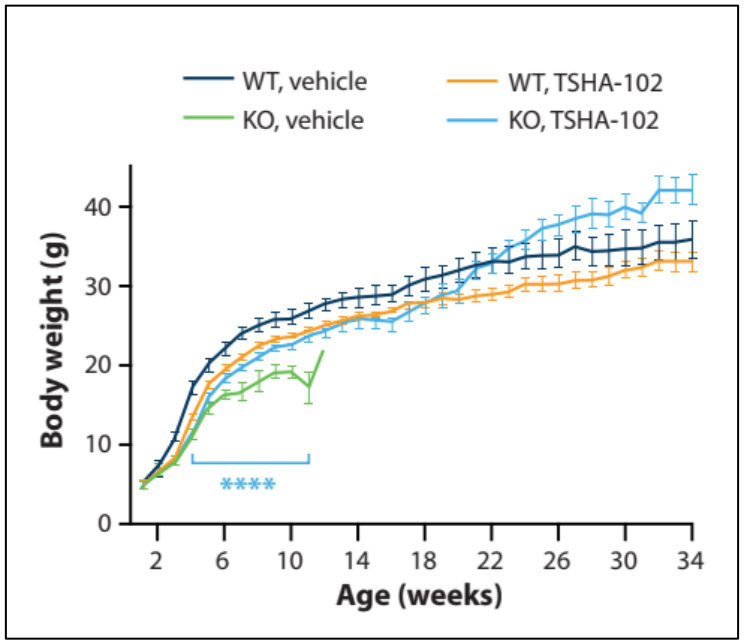
TSHA-102 improved survival, weight and behavior in neonatal *Mecp2*$^{-/Y}$ knockout mice with no impact on wild-type mice

Neonatal mouse efficacy study – 45 pups treated with TSHA-102 ($8.8x10^{10}$ vg) or vehicle via ICV at P2



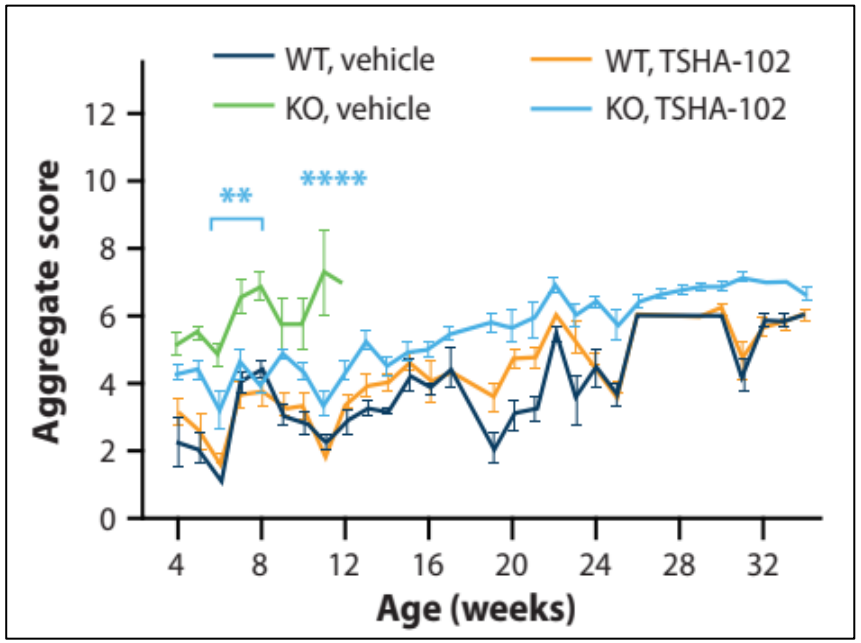
TSHA-102 extended survival of KO mice, no reduction on WT

- 47% KO mice survived the 36-week study vs a median survival of 8.1 weeks with vehicle-treated KO mice
- Significant ($p<0.0001$)>4-fold lifespan extension



Normalization of body weight following TSHA-102 in KO mice, no impact on WT

- TSHA-102 restored normal and faster-than-normal growth in KO mice ($p<0.05$ vs vehicle-treated KO mice)



Early sustained improvement in Rett-like phenotypes in KO mice following TSHA-102, no impact on WT

- Average age of onset for severe clasping from approximately 7 to 21 weeks in KO mice
- Severely abnormal gait from approximately 8 to 20 weeks in KO mice

Source: Okposo K, Haque E, Sadhu C, Prasad S, Newman M, Lawlor MW, Steven J. Gray SJ, Sinnett SE. A Human-Ready Regulated AAV9/mini*MECP2*-miRARE Gene Therapy (TSHA-102) Improves Survival, Weight, and Behavior after Intracerebroventricular (ICV) Dosing in the Neonatal Knockout Rett (RTT) Mouse Model. 26th Annual Meeting, American Society of Gene and Cell Therapy. Los Angeles, California. May 19, 2023. Poster 1365.

Neonatal data reinforce the ‘Goldilocks’ potential of the miRARE technology to enable the optimal amount of MeCP2

Regulated *MECP2* expression in deficient CNS cells	Supported by significant improvements in survival, overall neurobehavioral function and growth in *Mecp2*$^{-/Y}$ knockout mice
Avoided toxic overexpression in cells already expressing MeCP2	Supported by no deleterious impact on survival, neurobehavioral functions and overall health in wild-type mice

miRARE technology may address the risks associated with both under and overexpression of MeCP2 resulting from the mosaic pattern of *MECP2* silencing in females with Rett syndrome

Source: Okposo K, Haque E, Sadhu C, Prasad S, Newman M, Lawlor MW, Steven J. Gray SJ, Sinnett SE. A Human-Ready Regulated AAV9/mini*MECP2*-miRARE Gene Therapy (TSHA-102) Improves Survival, Weight, and Behavior after Intracerebroventricular (ICV) Dosing in the Neonatal Knockout Rett (RTT) Mouse Model. 26th Annual Meeting, American Society of Gene and Cell Therapy. Los Angeles, California. May 19, 2023. Poster 1365.

TSHA-102 REVEAL Phase 1/2 trial in adults with Rett syndrome

Study design	• Open-label, dose-escalation, randomized, multi-center Phase 1/2 trial (the REVEAL study) • Safety and preliminary efficacy
Study location	**Canada (CHU Sainte-Justine)**
Key inclusion criteria	• Adult females with pathogenic confirmation of *MECP2* mutation
Intervention	• **Cohort one**: $5x10^{14}$ total vector genomes (vg) • **Cohort two**: $1x10^{15}$ total vector genomes (vg)
Route of Administration	• Intrathecal route of administration

NCT05606614

The first adult patient was dosed with TSHA-102 at CHU Sainte-Justine, in Montreal, Canada, under Dr. Rossignol, principal investigator.

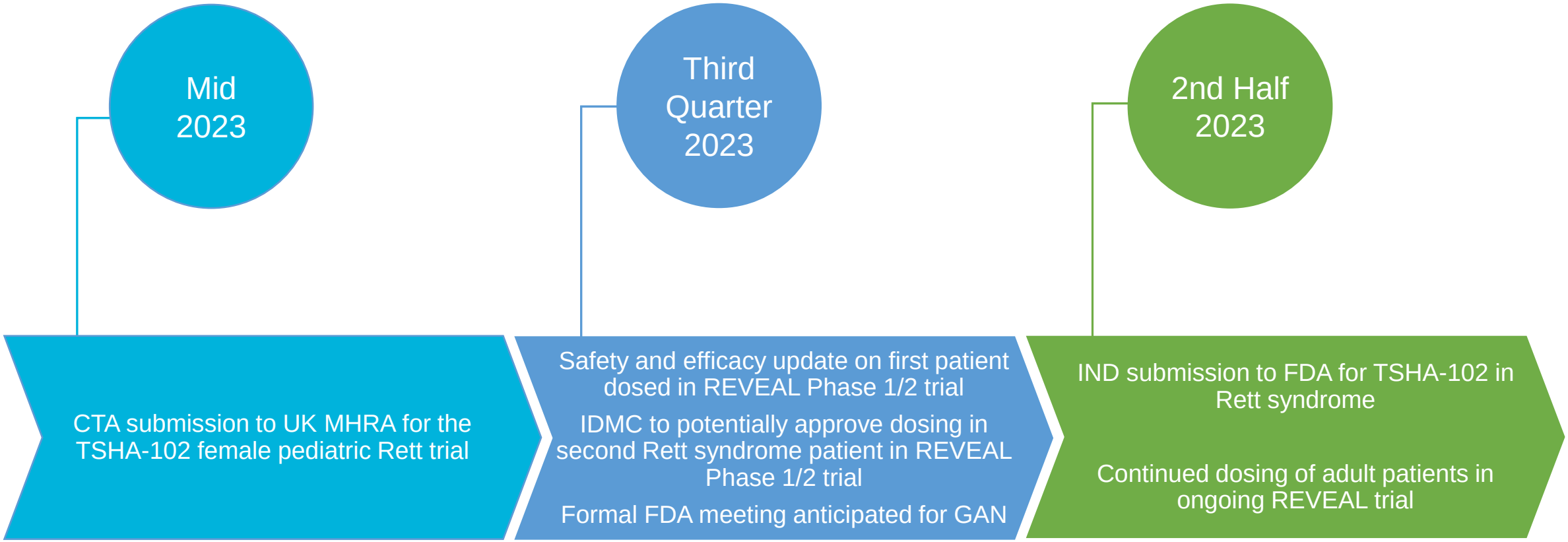
IDMC will review available clinical data from the first patient at approximately 6 weeks post-dosing.

Closing Remarks

SEAN NOLAN

Board Chairman and Chief Executive Officer

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



TAYSHA GENE THERAPIES

Q&A