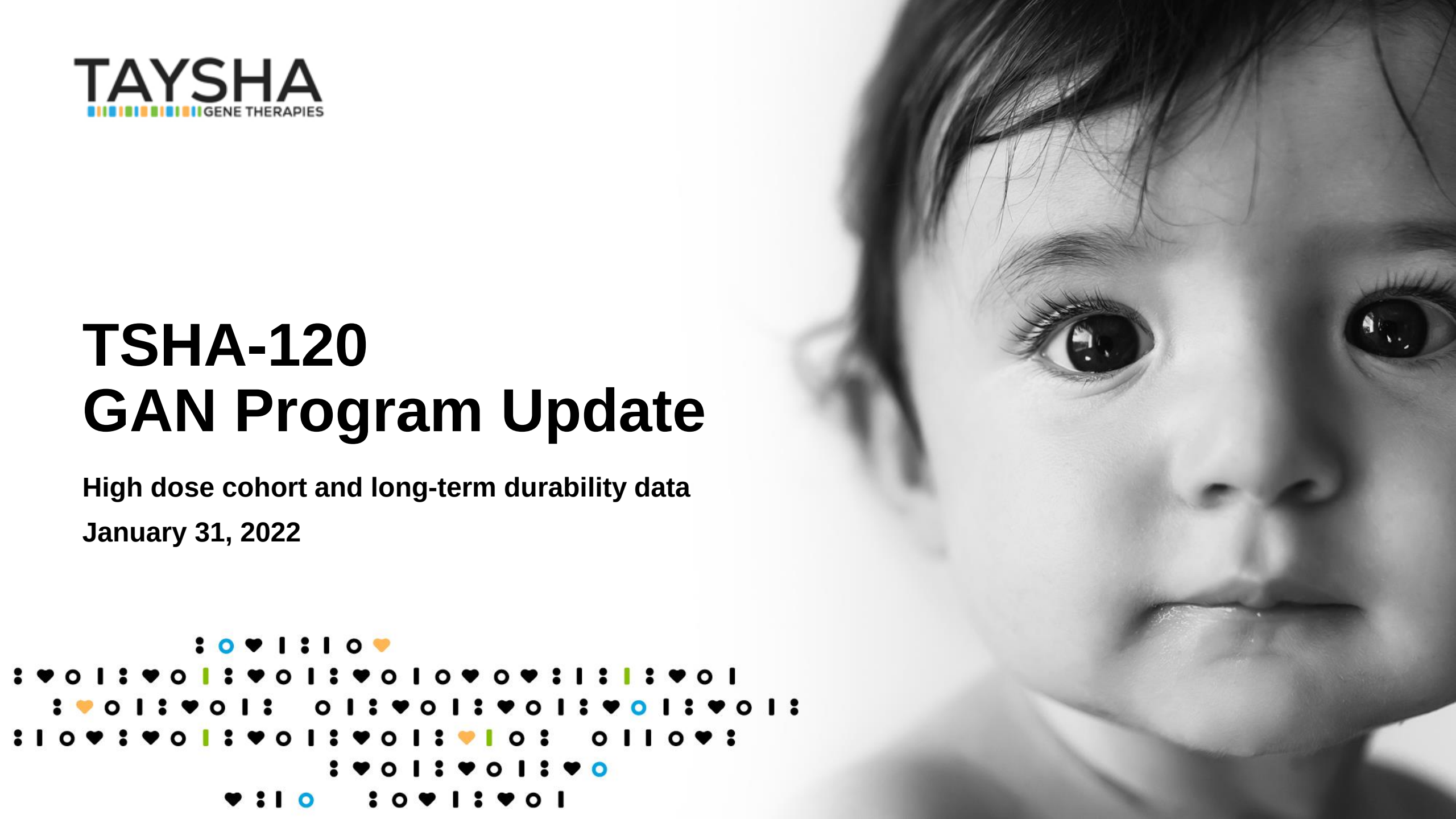
TAYSHA GENE THERAPIES

# TSHA-120
# GAN Program Update

**High dose cohort and long-term durability data**

**January 31, 2022**



# 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, and our Quarterly Report on Form 10-Q for the quarter ended September 30, 2021. 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.

# Clinically meaningful and statistically significant data for TSHA-120 supports pathway to registration

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## Safety

- Long-term data (53 patient-years) across all dose cohorts support TSHA-120's favorable safety and tolerability profile

## Efficacy

- TSHA-120 demonstrated a clinically meaningful and statistically significant slowing or halting of disease progression in the high dose cohort of $3.5x10^{14}$ total vg (n=3) and across all therapeutic dose cohorts (n=12) by Year 1
- Long-term durability data across all therapeutic doses demonstrated a 10-point improvement in the mean change from baseline in MFM32 score for all therapeutic doses by Year 3 compared to the estimated natural history decline of 24 points (n=12)
- Analysis of nerve biopsies confirms active regeneration of nerve fibers following treatment with TSHA-120 (n=6)
- Treatment with TSHA-120 preserved visual acuity and prevented retinal nerve fiber layer (RNFL) thinning (n=12)

## Regulatory

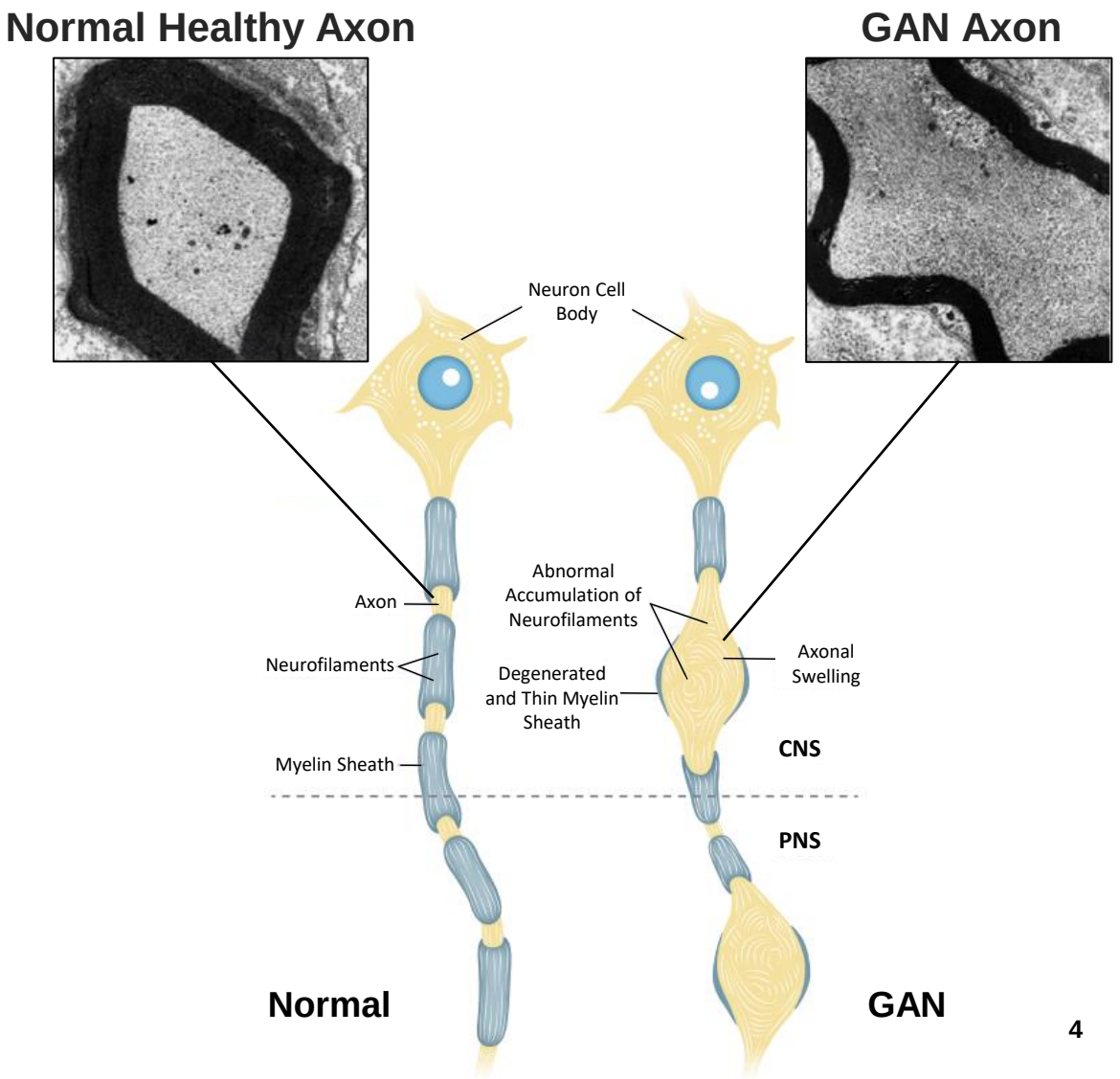
- Totality of data supports plans to engage major regulatory agencies to discuss pathways for registration

## Commercial

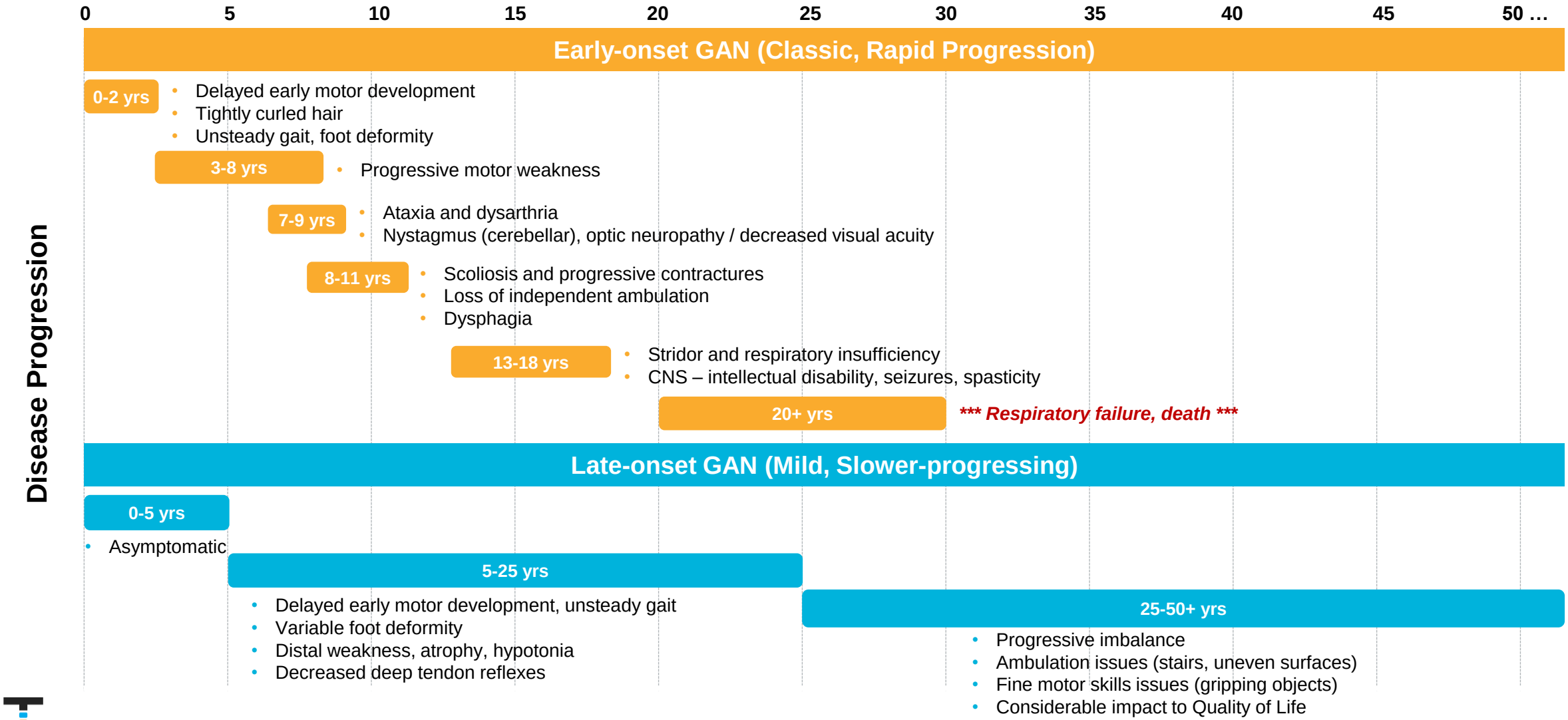
- Estimated 5,000 patients in addressable markets represent significant commercial opportunity

# 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)



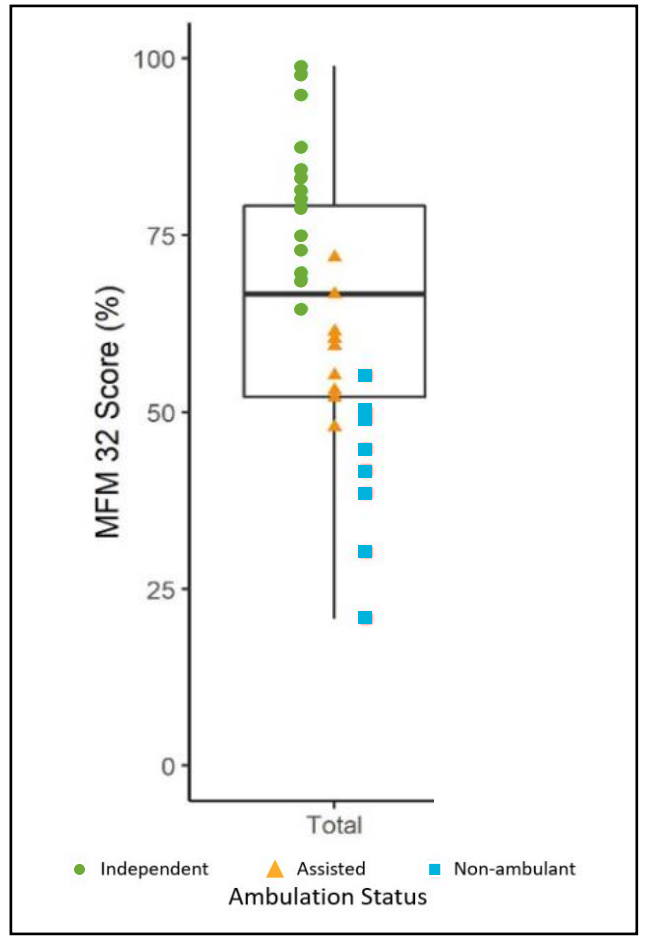
# GAN disease progression



# 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 validated and clinically meaningful in the following indications:
  - DMD
  - SMA
  - LAMA2-related muscular dystrophy
  - Cerebral palsy

**Ambulation Status by MFM32 Total Score**




Note: Plot only includes participants over age 6 in whom the MFM32 was performed (n=37). Eighteen participants were independently ambulant, 10 required assistance to walk, and 9 were non-ambulant.

Source: Bharucha-Goebel 2021

# GAN natural history study data as a robust comparator

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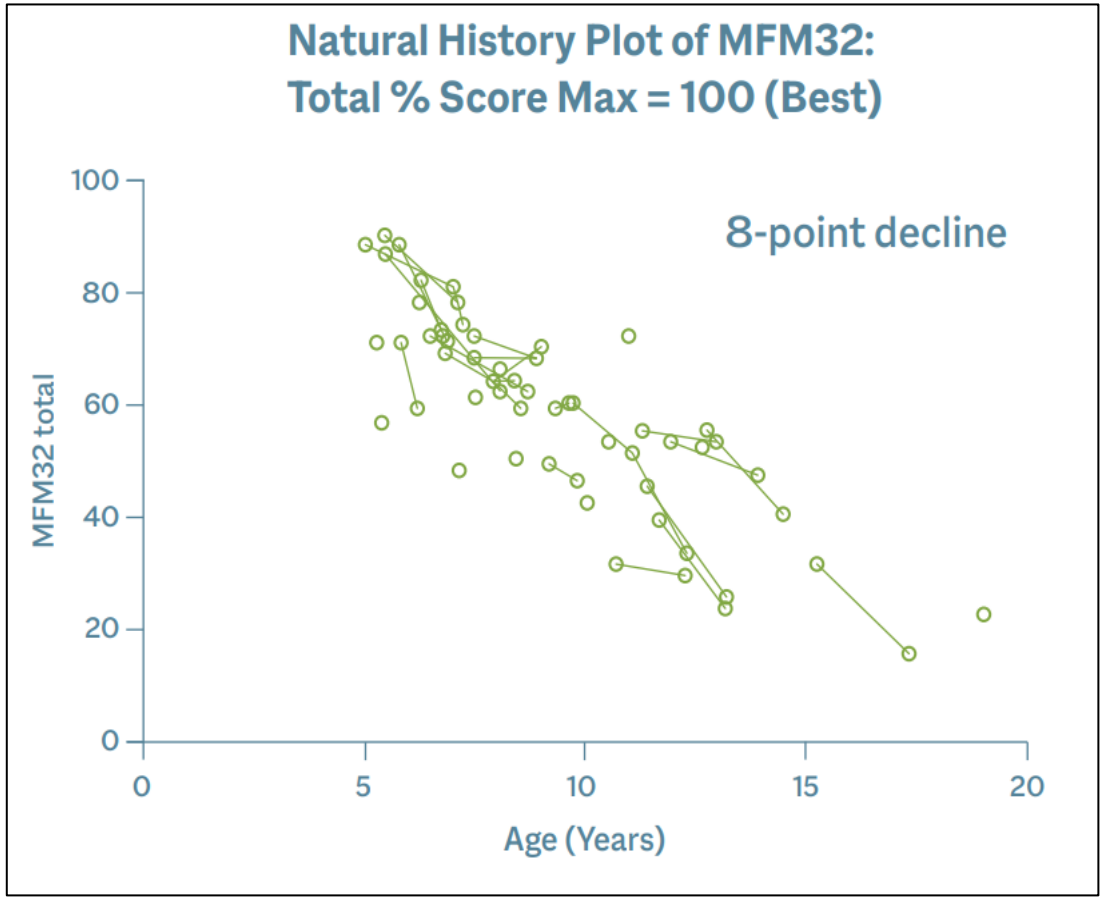
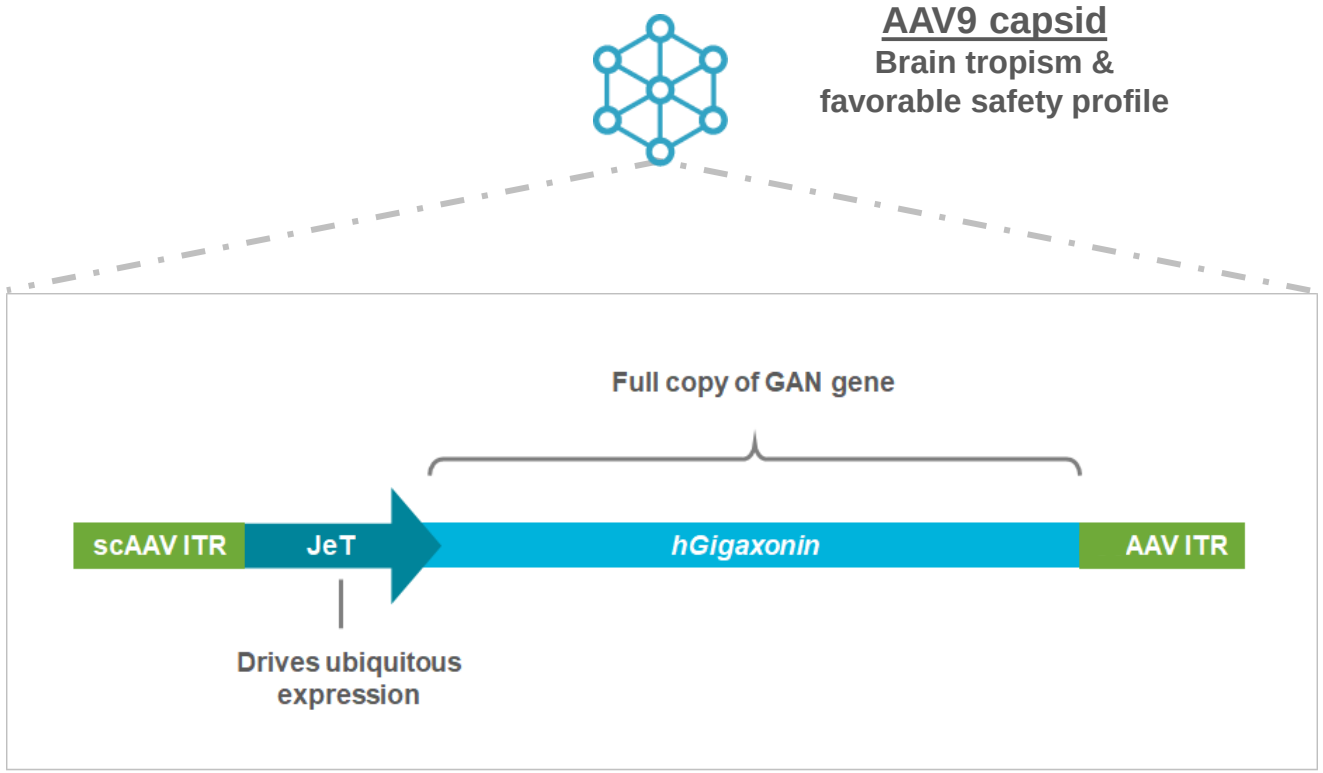
- 45 GAN patients (2013-present) ages 3-21 years
  - Can be accessed for treatment study
  - Will be used as comparator for treatment study
- MFM32 selected as primary endpoint due to least variability and its use in confirmatory trials
- MFM32 score shows uniform decline between patients of all age groups over time

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



# TSHA-120 program overview and construct

- Construct invented in the lab of Dr. Steven Gray, Chief Scientific Advisor for Taysha and inventor of multiple Taysha programs
- 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



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

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## Goals and Targets of Trial

### Goals

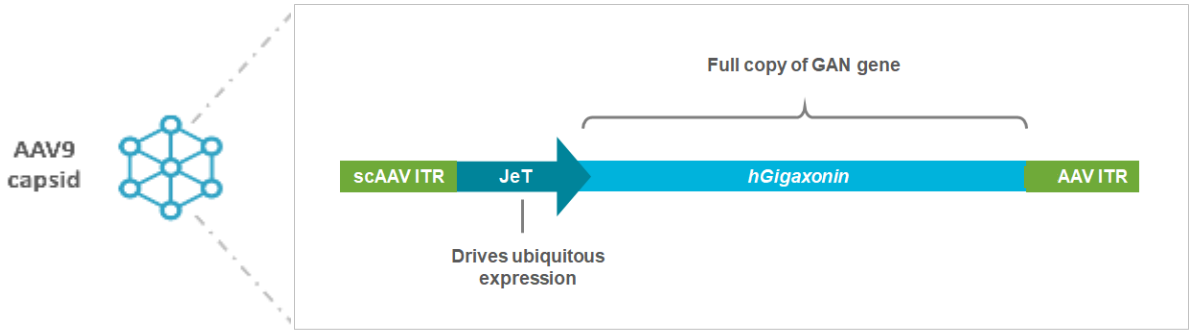
- **Primary** – Safety: clinical and laboratory assessments
- **Secondary** – Efficacy: pathologic, physiologic, functional and clinical markers

### Target Recruitment

- 14 subjects injected
- > 5 years old

### Target Areas to Transduce

## Product Details and Dose Cohorts




### Dose Cohorts*

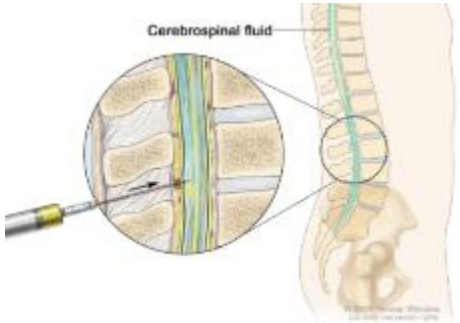
- 1x: 3.5 x $10^{13}$ total vg (n=2)
- 3.3x: 1.2 x $10^{14}$ total vg (n=4)
- 5x: 1.8 x $10^{14}$ total vg (n=5)
- 10x: 3.5 x $10^{14}$ total vg (n=3)

*Doses calculated by qPCR

## Route and Method of Administration

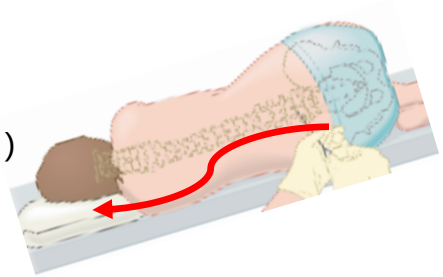
### Administration

- 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°)
- During infusion & 1 hour post infusion



Clinical Trial: NCT02362438

# Treatment with TSHA-120 was well-tolerated with no significant safety issues

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## Safety

- 53-patient years of clinical data support TSHA-120's favorable safety and tolerability profile
- Treatment with TSHA-120 was well-tolerated with no significant safety issues
- No increase in incidence of adverse events with increased dose
- Adverse events related to immunosuppression or study procedures were similar to what is seen with other gene therapies and transient in nature
- No dose-limiting toxicity
- No clinical signs of acute or subacute inflammation (i.e., encephalopathy, persistent headaches, seizures, or vision changes outside of related to underlying disease)
- No sudden sensory changes or evidence by spine MRI of nerve root/DRG inflammation
- No evidence of thrombocytopenia or persisting transaminitis

# TSHA-120 can be safely dosed in the presence of neutralizing antibodies

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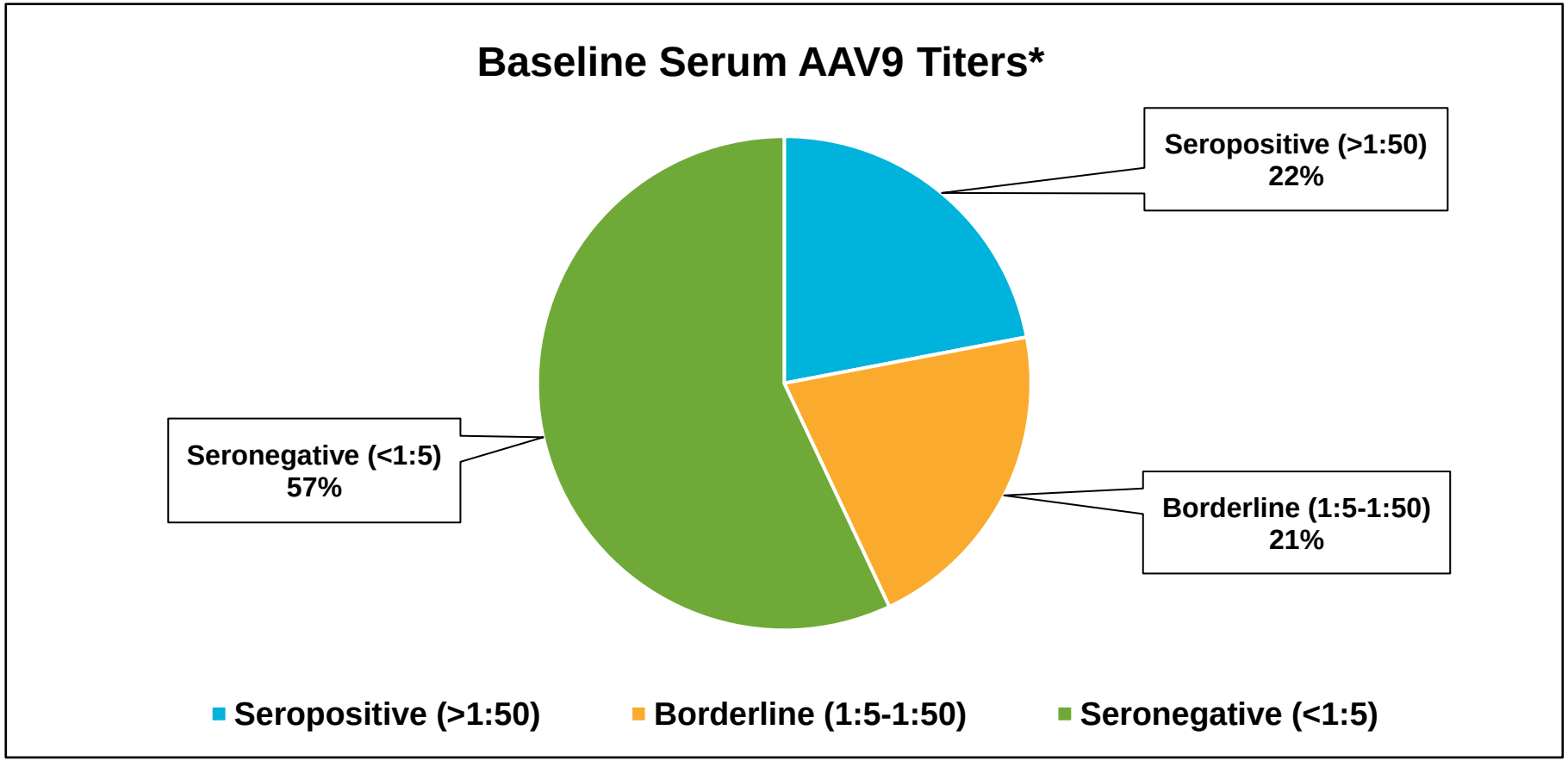
- Combination of route of administration, dosing, and immunosuppression regimen allow for effective dosing in patients with neutralizing antibodies




*All patients with baseline CSF AAV9 Nab titer < 1:5

# Clinically meaningful and statistically significant slowing of disease progression in the high dose cohort of $3.5x10^{14}$ total vg by Year 1 compared to natural history

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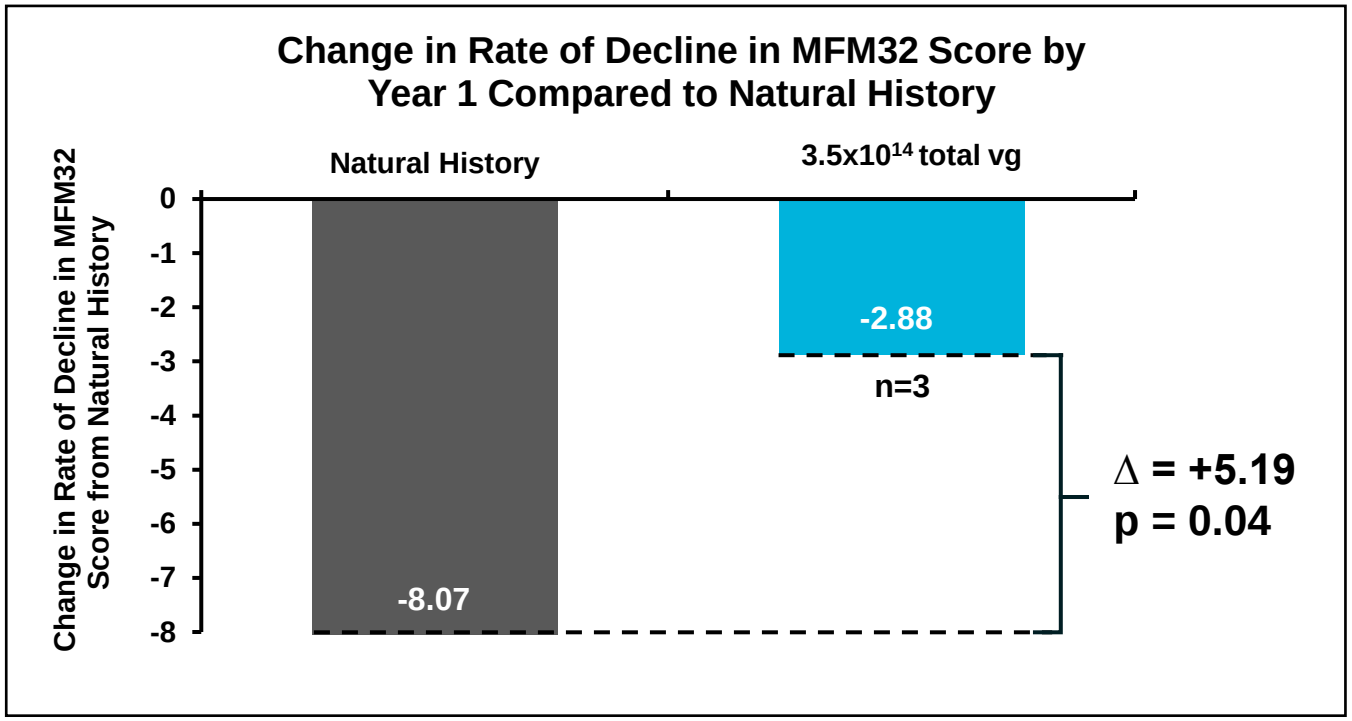
- By 1-year post-gene transfer, a clinically meaningful and statistically significant slowing of disease progression was seen with TSHA-120 at the high dose of $3.5x10^{14}$ total vg (n=3)
- The change in rate of decline in the MFM32 score improved by 5 points in the $3.5x10^{14}$ total vg dose cohort compared to the natural history decline of 8 points by Year 1
- Pre-specified efficacy endpoint is the change in rate of decline in MFM32 score by Year 1 compared to natural history



# Single delayed responding patient at high dose (n=1) achieved complete disease stabilization by Year 2

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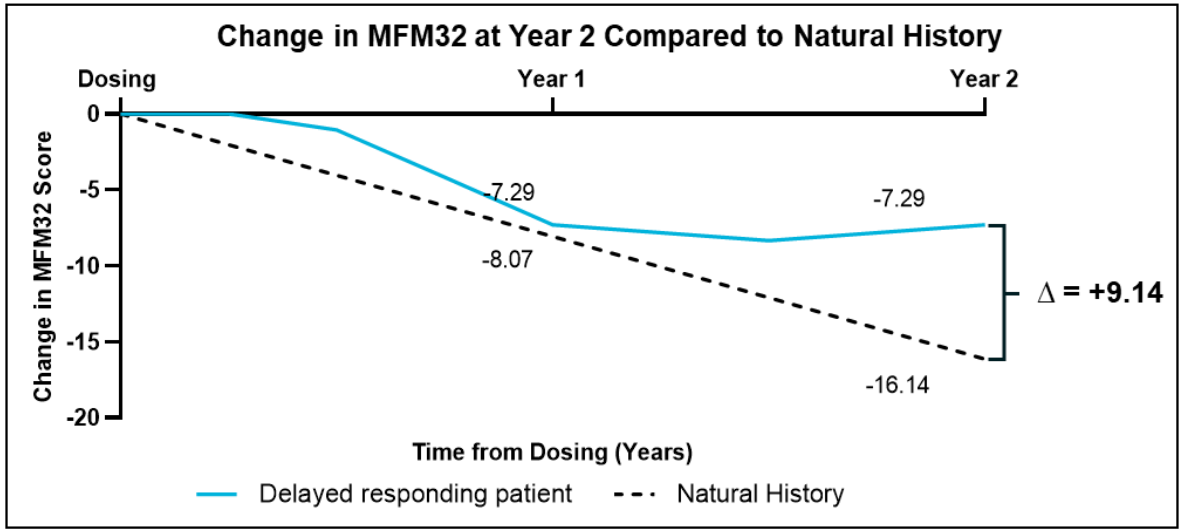
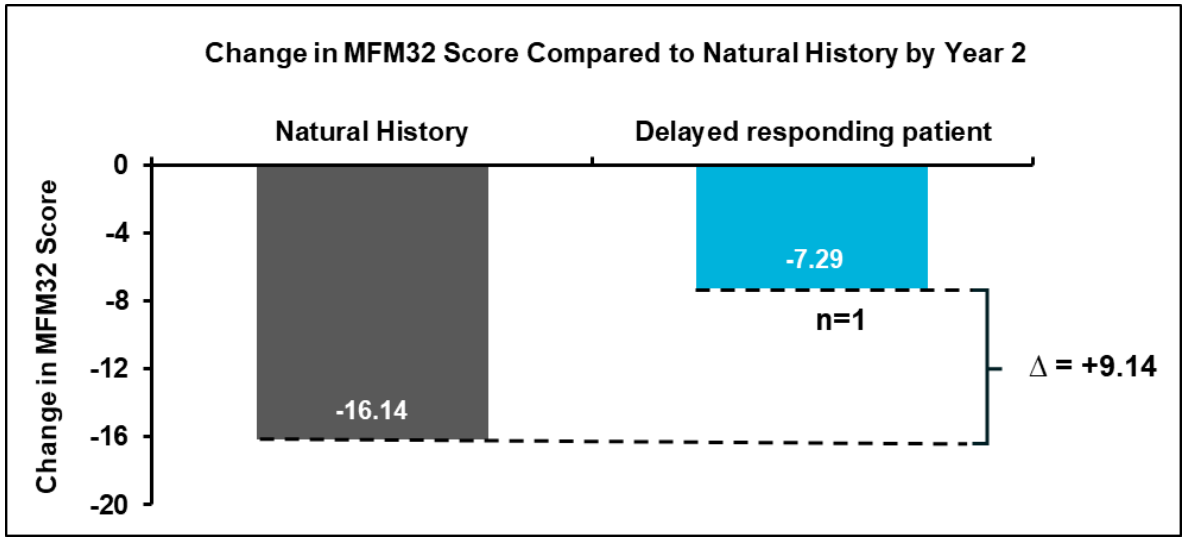
- Delayed responding patient in the $3.5x10^{14}$ total vg cohort at the Year 1 follow-up visit had a 7-point decline in the MFM32 score similar to natural history
- Notably, at the Year 2 time point, the patient's MFM32 score remained unchanged suggesting complete disease stabilization 2 years post-treatment
- Improvement in the patient's MFM32 score was 9 points by Year 2 compared to the estimated natural history decline of 16 points




Annualized estimate of natural history over time assumes same rate of decline as in Year 1

# Analysis of all therapeutic dose cohorts demonstrated a nearly 7-point improvement in MFM32 by Year 1 compared to natural history

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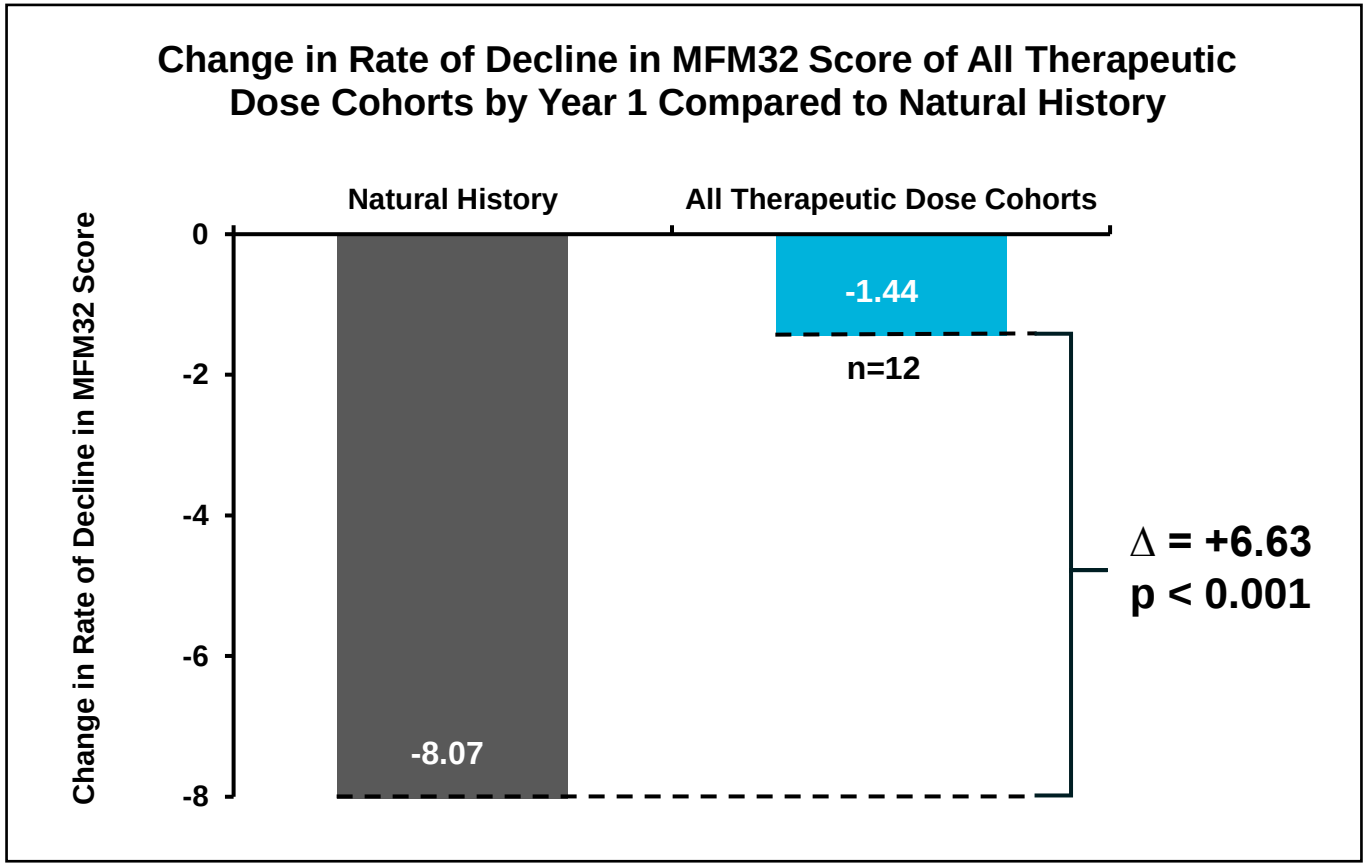
- Additional analysis was performed to include all therapeutic doses, $1.2x10^{14}$ total vg, $1.8x10^{14}$ total vg, $3.5x10^{14}$ total vg dose cohorts (n=12)
- By 1-year post-gene transfer, the change in rate of decline in the MFM32 score for all therapeutic dose cohorts improved by nearly 7 points compared to the natural history decline in the MFM32 score of 8 points
- Data demonstrated a clinically meaningful and statistically significant slowing or halting of disease progression with TSHA-120 ($p<0.001$) by Year 1



# Bayesian analysis continues to confirm nearly 100% probability of clinically meaningful slowing of disease compared to natural history

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- Bayesian analysis, updated to include the high-dose cohort, assessed the probability of clinically meaningful slowing of disease progression as compared to natural history
  - Enables direct probability statements about any unknown quantity of interest
  - Useful and accepted by regulatory agencies when treating rare diseases and small patient populations
- For all therapeutic dose cohorts, there is nearly 100% probability of any slowing of disease and a 97% probability of clinically meaningful slowing of 50% or more

| Change in disease progression | Probability of Change in Disease Progression Compared to Natural History Decline in Patients with GAN (Values = % Probability) |
|---|---|
| | Three doses (n=12) |
| **Any Slowing** | 99.9 |
| **Clinically meaningful slowing 50% or more** | 96.7 |

# Durability of effect continues to be observed 3 years post dosing

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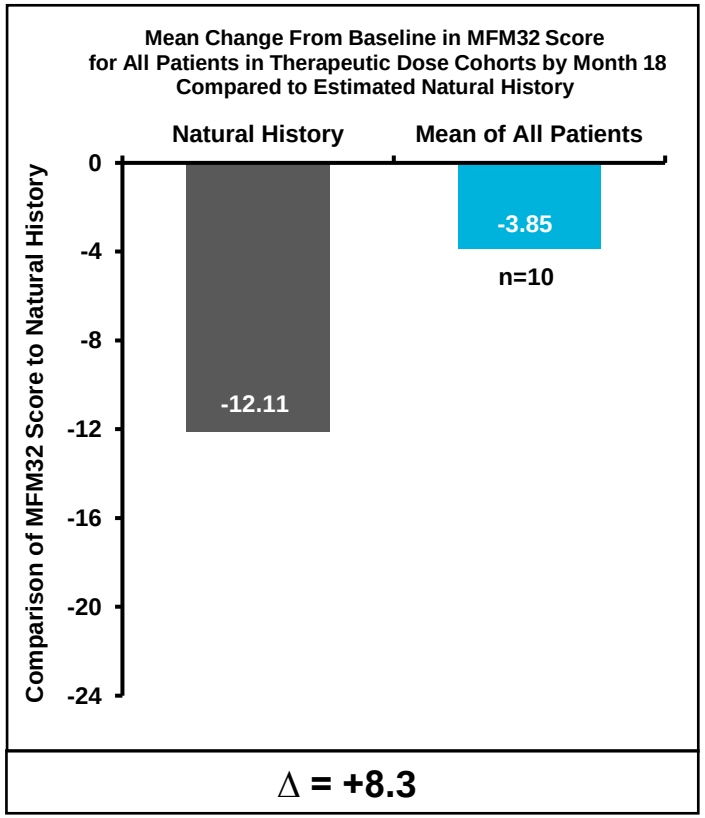


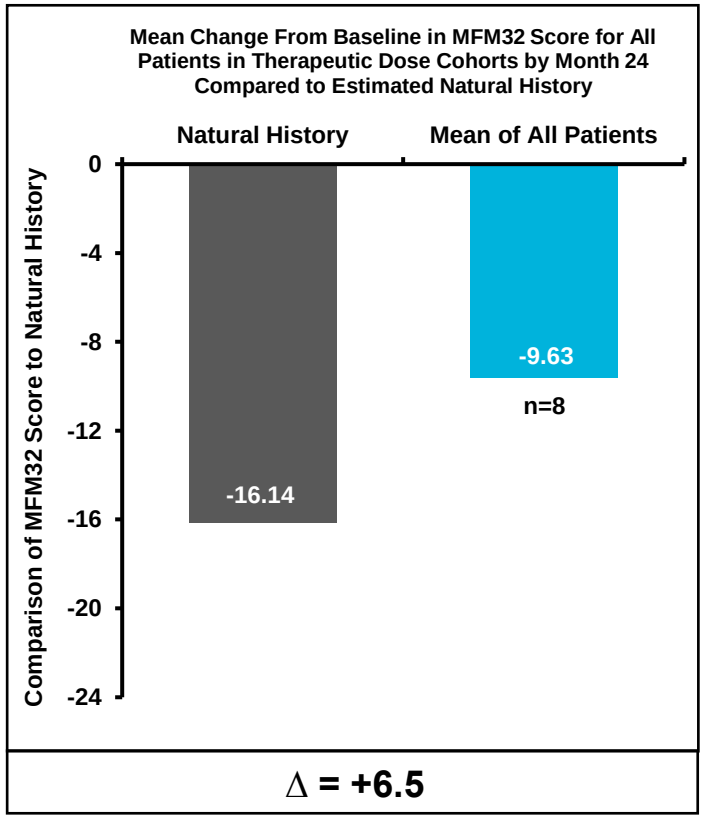


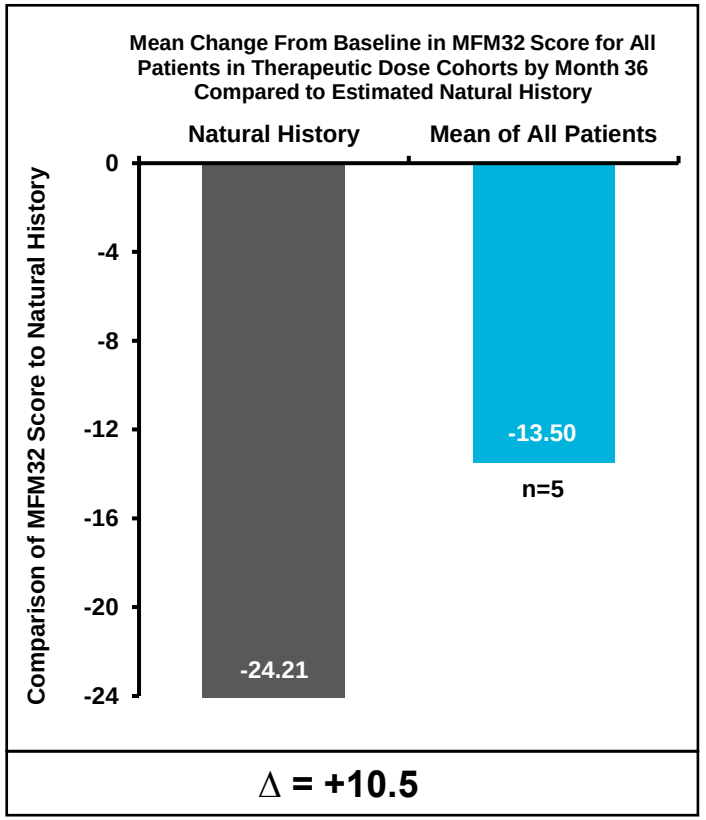


**4-point change is considered clinically meaningful**

Annualized estimate of natural history over time assumes same rate of decline as in Year 1

# TSHA-120 demonstrated clinically meaningful improvement compared to natural history decline in the single patient to reach 5 years post dosing

TSHA-120
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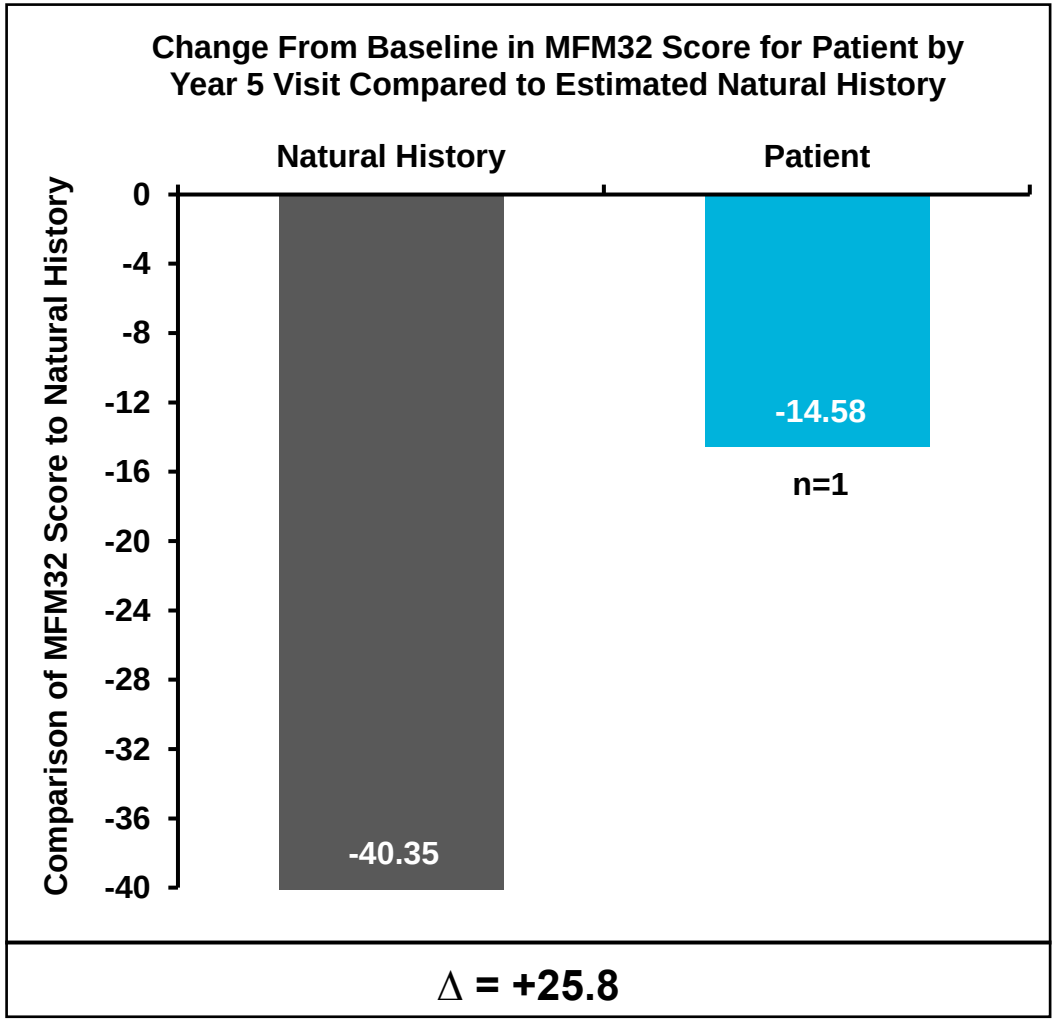
- Additional data for MFM32 change from baseline at Year 5 visit available for one patient
- The change from baseline in MFM32 score improved by nearly 26 points in the $1.2x10^{14}$ total vg dose cohort compared to the estimated natural history decline of 40 points by Year 5

**4-point change is considered clinically meaningful**




Annualized estimate of natural history over time assumes same rate of decline as in Year 1

# Mean change from baseline in MFM32 score for therapeutic dose cohorts compared to natural history at patient last visit

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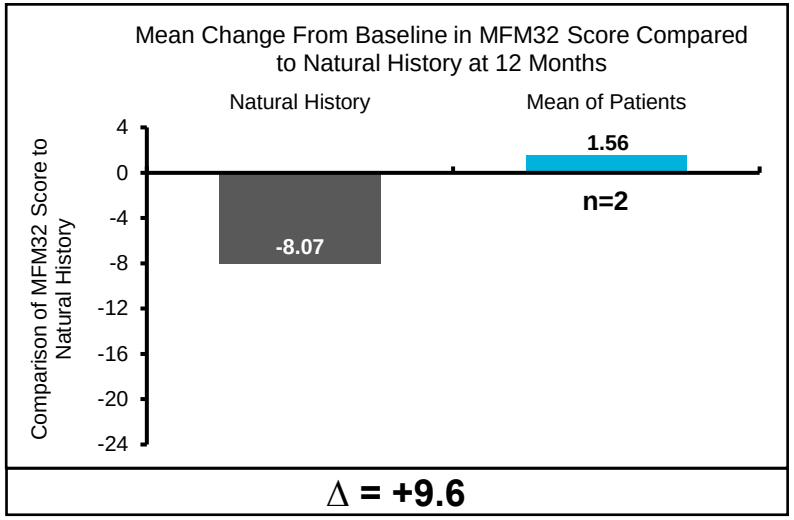
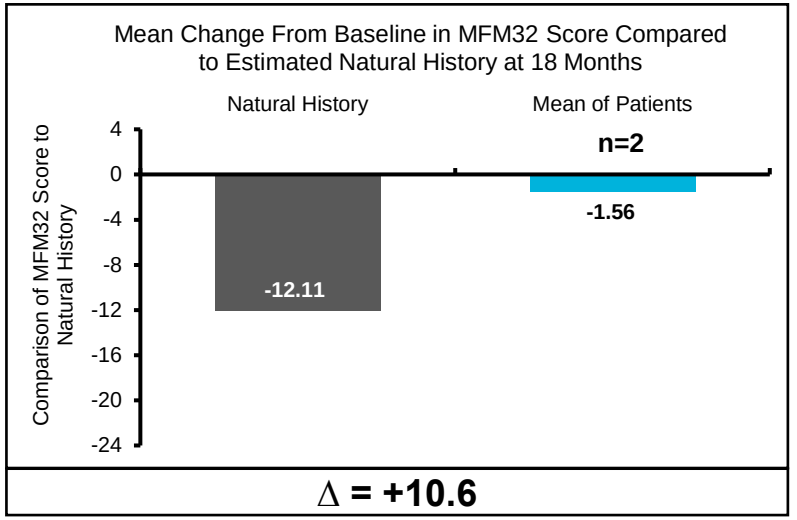
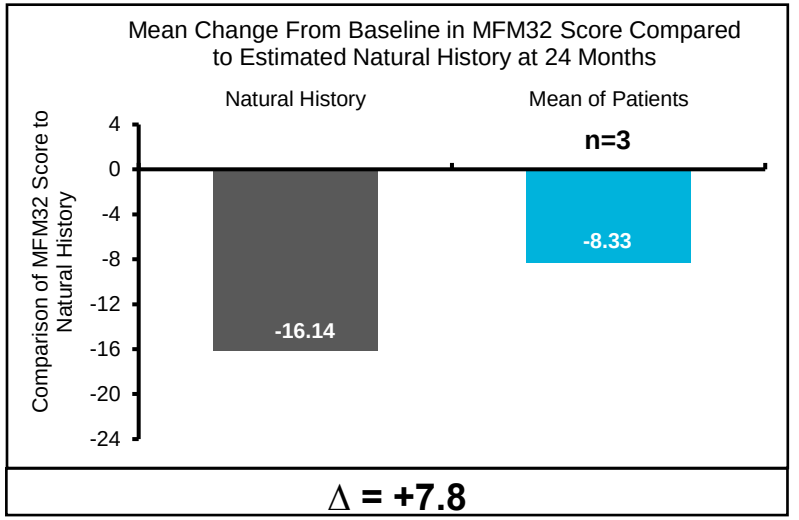


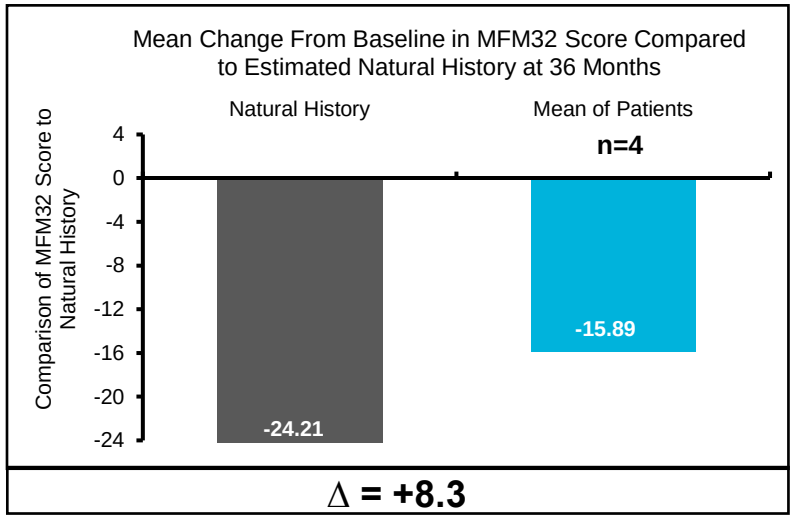

Δ = +9.6



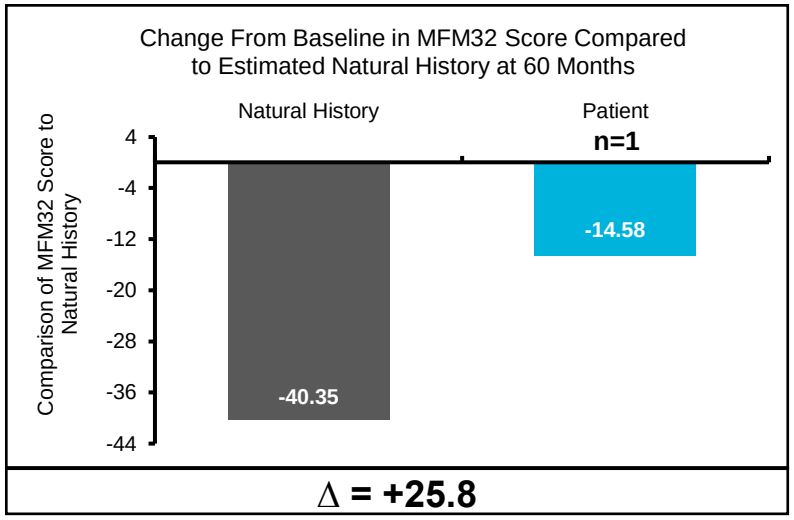

Δ = +10.6




Δ = +7.8




Δ = +8.3




Δ = +25.8

**4-point change is considered clinically meaningful**

# Pathology from nerve biopsies in TSHA-120-treated patients confirmed active regeneration of nerve fibers

TSHA-120
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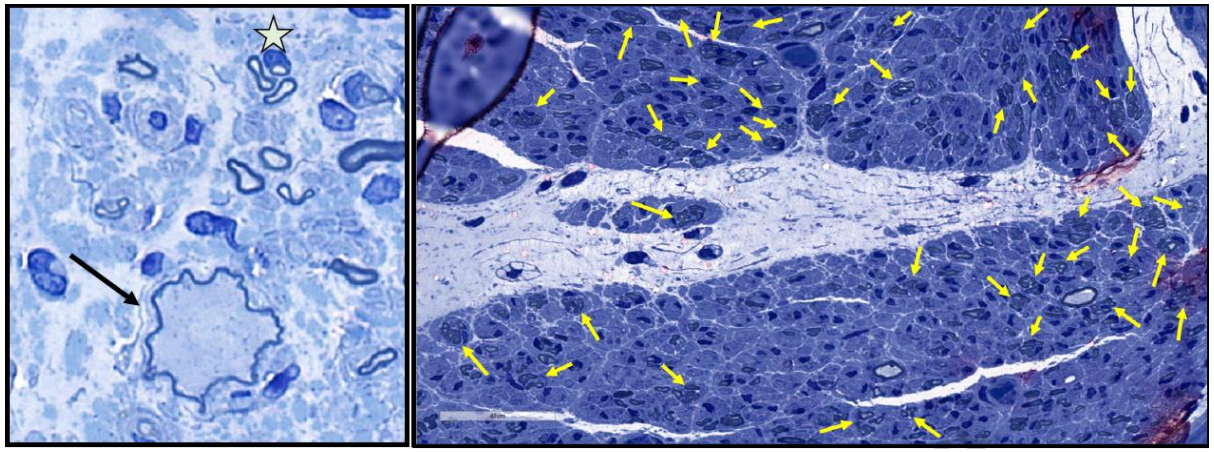
- Peripheral nerve biopsies were obtained at baseline and at 1-year post-gene therapy transfer from the superficial radial sensory nerve
- Analysis of 6 samples have been completed to date. Five samples consistently demonstrated an increase in the number of regenerative clusters (RC) at Year 1 compared to baseline. Remaining patient samples currently being analyzed.
- Data indicated active regeneration of nerve fibers, demonstrating improvement in disease pathology and providing evidence that the peripheral nervous system can respond to treatment

**Regenerative Clusters in the Superficial Radial Sensory Nerve of a Participant Treated with TSHA-120**



**Baseline** **1-year post-gene therapy transfer**

- Left: The arrow identifies a “giant” degenerating axon and the star identifies regenerating clusters
- Right: Arrows indicate regenerating clusters

# Treatment with TSHA-120 stabilized visual acuity compared to pretreatment decline

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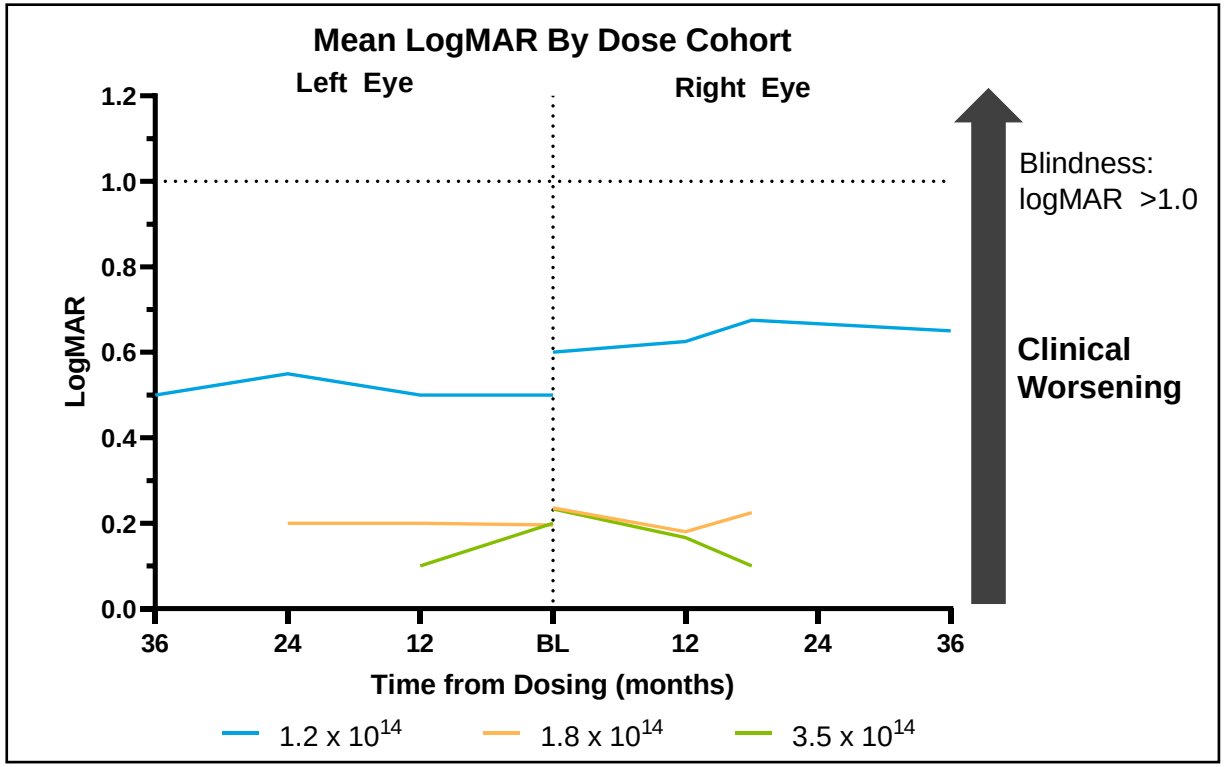
- Logarithm of the Minimum Angle of Resolution (LogMAR) was utilized to measure visual acuity
- Based on natural history, individuals with GAN experienced a decrease in visual acuity and therefore an increase in their LogMAR score
- Treatment with TSHA-120 demonstrated stabilization of visual acuity, which should significantly benefit patients and families from a quality-of-life perspective



# TSHA-120 stabilized retinal nerve fiber layer thickness (RNFL) preventing further progression of axonal loss

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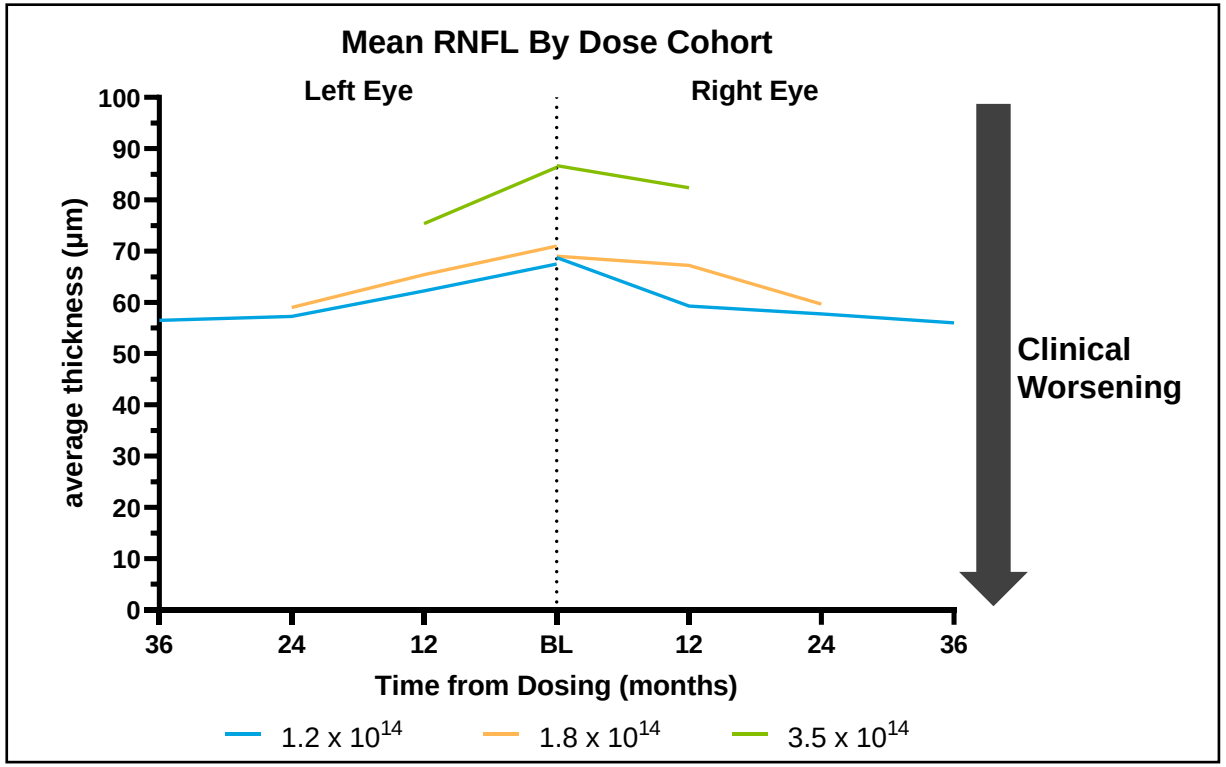
- RNFL thickness is an objective biomarker of visual system involvement and overall nervous system degeneration in GAN
- Based on natural history, individuals with GAN experience progression of axonal loss resulting in eventual loss of visual acuity
- Treatment with TSHA-120 resulted in stabilization of RNFL thickness and prevented further progression of axonal loss as measured by optical coherence tomography



# GAN program currently meets the vast majority of registration requirements from FDA and EMA guidance

TSHA-120
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| Human Gene Therapy for Neurodegenerative Disease Draft Guidance for Industry – Jan 2021 | | GAN Program |
|---|---|---|
| **Safety** | • Extended safety data monitoring of at least 1-2 years<br>• Monitoring for systemic immune reactions via immunoassays<br>• Collection and monitoring of all adverse events, including clinical and laboratory parameters | ✓ |
| **Endpoints** | • Efficacy outcomes must be compared to a control<br>• Cohort size will depend on variability between subjects<br>• Close interpretation of functional rating scales: age, language, culture | ✓ |
| **Natural history** | • Natural history studies to compare data: must align genetic mutation, age, age of onset, clinical course of disease, scales being used<br>• Match natural history patients as close as possible for control | ✓ |
| **Preclinical** | • Identification of dose range and recommendations for dosing regimen<br>• Establishment of feasibility and reasonable safety of the proposed clinical route of administration<br>• Identification of potential toxicities to guide clinical monitoring | ✓ |
| **CMC** | • Lots manufactured using final manufacturing process. Process validation complete<br>• Commercial release specifications set. Product release and potency assays validated<br>• Delivery device compatibility testing complete | In progress |

# Current dataset supports pathway for registration

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

**Potential to file for conditional approval based on current dataset per EMA guidance documents**

FDA

| | | |
|---|---|---|
| 1 | Immediate file for approval based on current data set and comparability | If agency is in alignment with the current dataset and agrees with analytical comparability of commercial grade material |
| 2 | Dose few more patients for clinical comparability of commercial material | Possible need to demonstrate comparability of clinical effect between clinical and commercial-grade material<br><br>Similar approval pathway for Zolgensma in SMA |
| 3 | Perform a new pivotal trial | Unlikely given recently published guidance document on gene therapies for neurodegenerative diseases and the extensive long-term safety and efficacy dataset available |

# TSHA-120 in GAN represents a significant commercial opportunity

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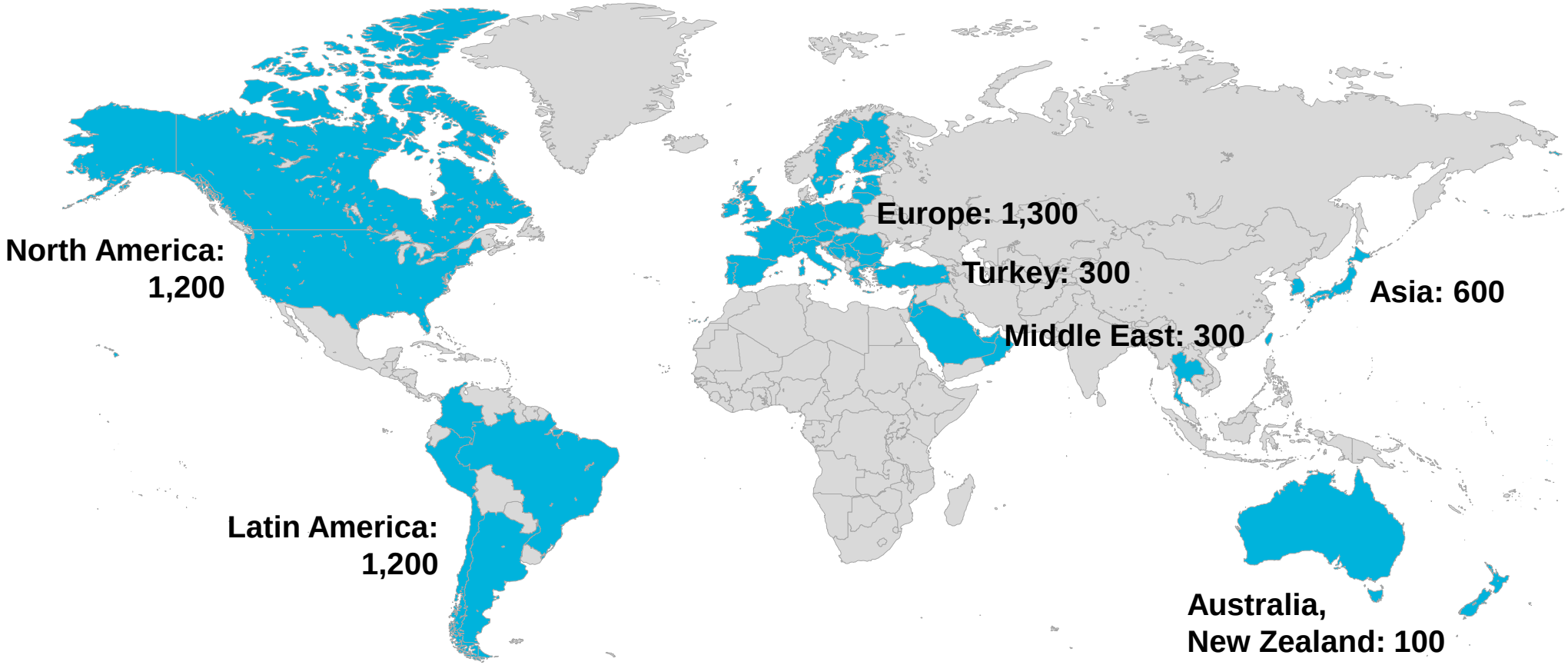
## Estimated 5,000 addressable patients globally



# Seasoned commercial team with extensive global gene therapy product launch experience



| Commercial Leadership | |
|---|---|
| **Sean McAuliffe**<br>*Chief Commercial Officer* | avexis · NOVARTIS · Baxalta |
| **Michael Cibulsky**<br>*VP of Marketing, Sales and HUB Services* | avexis · NOVARTIS · Lundbeck |
| **Brad Martin**<br>*VP of Market Access* | avexis · SAREPTA THERAPEUTICS · Lundbeck |
| **Donna DiStefano**<br>*Senior Director, Business Insights and Analytics* | Verana Health · imshealth · IQVIA |
| **Tionna Wilson**<br>*Director, Institutional Access and Reimbursement* | avexis · NOVARTIS · Shire Human Genetic Therapies |

# Launch readiness plan: Maximizing patient identification, site readiness and market access

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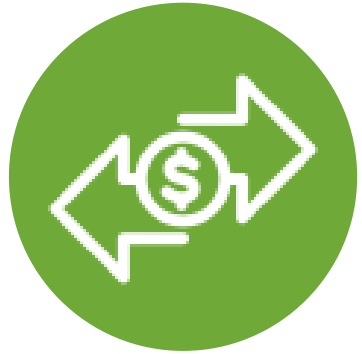
## Education

- KOL development and patient identification initiatives
- Health care professional and patient-focused disease state awareness initiatives
- Explore all access pathways in ex-US markets

## Genotyping

- Partnerships with genetic testing providers to identify patients with GAN mutations
- Identification of patients with unknown etiology in CMT clinics and other institutions treating axonal neuropathies worldwide
- Earlier diagnosis through newborn screening, partnerships with centers of excellence and advocacy groups



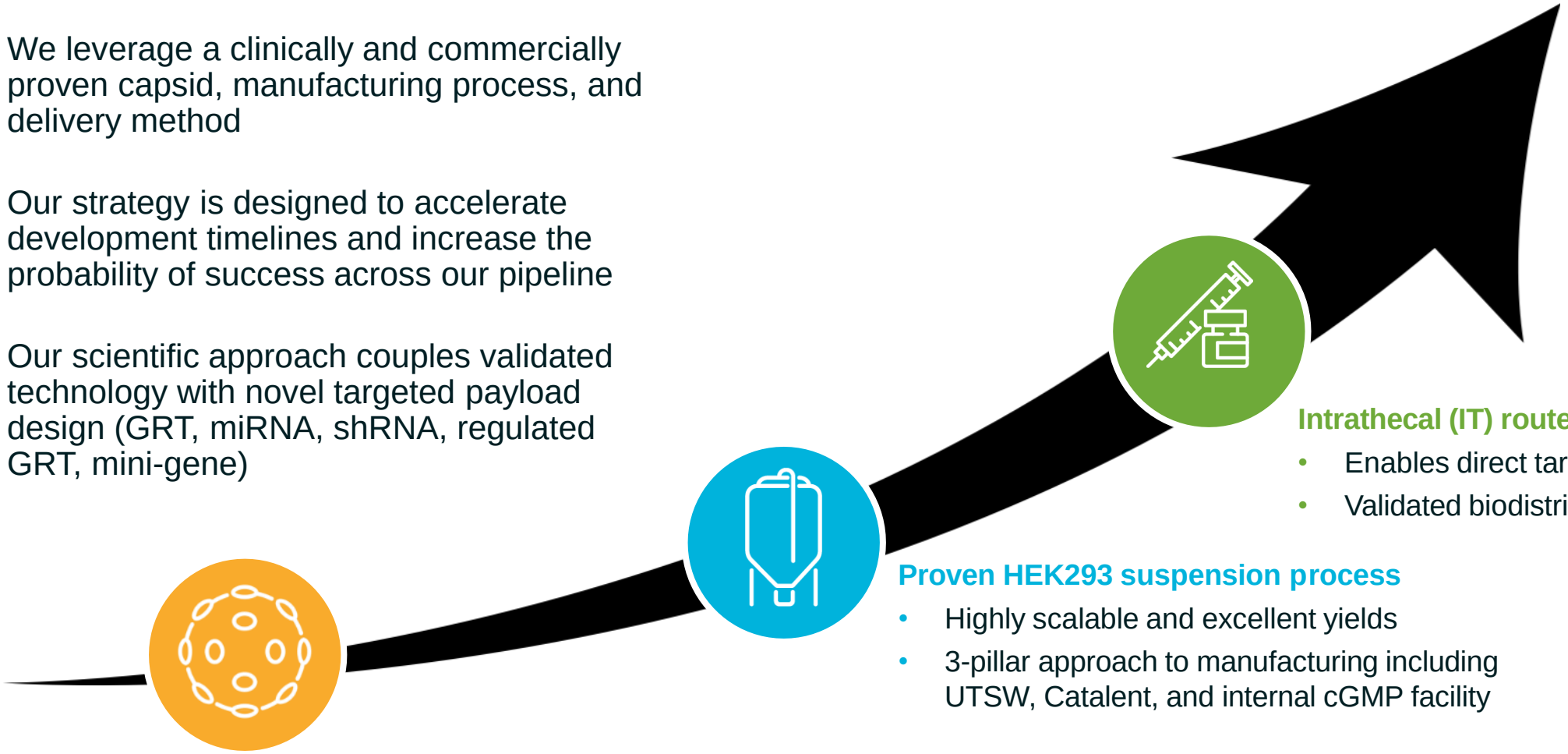
## Payer and Reimbursement

- Early engagement with US and ex-US payers to educate on GAN one-time dose gene therapies
- Implement comprehensive value-based strategy to ensure timely and sustainable access for TSHA-120
- Access strategy will be supported by global HEOR plan to ensure real world evidence and burden of illness support value proposition

# Our strategy is focused on rapid clinical and commercial development

TSHA-120
GAN

- 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)



**Intrathecal (IT) route of administration**

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

**Proven HEK293 suspension process**

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

**AAV9 vector for delivery of therapeutic transgene**

- Demonstrated safety and efficacy across multiple CNS indications

# Manufacturing strategy for TSHA-120 significantly de-risks registration pathway

TSHA-120
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- Viralgen (AskBio) produced initial clinical material
- Product manufactured at Viralgen is comparable to clinical lots (testing in progress) ensuring consistency in efficacy and safety for commercial material
- Collaboration to manufacture drug product for the TSHA-120 program
  - Commercial manufacturing infrastructure to support all future manufacturing for the program
  - Platform process and methods well suited to produce comparable product to previous TSHA-120 vector lots
  - Working closely to ensure successful regulatory discussions to enable product licensure

# Clinically meaningful and statistically significant data for TSHA-120 supports pathway to registration

TSHA-120
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## Safety

- Long-term data (53 patient-years) across all dose cohorts support TSHA-120's favorable safety and tolerability profile

## Efficacy

- TSHA-120 demonstrated a clinically meaningful and statistically significant slowing or halting of disease progression in the high dose cohort of $3.5x10^{14}$ total vg (n=3) and across all therapeutic dose cohorts (n=12) by Year 1
- Long-term durability data across all therapeutic doses demonstrated a 10-point improvement in the mean change from baseline in MFM32 score for all therapeutic doses by Year 3 compared to the estimated natural history decline of 24 points (n=12)
- Analysis of nerve biopsies confirms active regeneration of nerve fibers following treatment with TSHA-120 (n=6)
- Treatment with TSHA-120 preserved visual acuity and prevented retinal nerve fiber layer (RNFL) thinning (n=12)

## Regulatory

- Totality of data supports plans to engage major regulatory agencies to discuss pathways for registration

## Commercial

- Estimated 5,000 patients in addressable markets represent significant commercial opportunity

# Current status and next steps

- Finalized plan for commercial grade material and initiated development of comparability protocol to support BLA / MAA submission; engineering run currently underway
- Manufacture of commercial validation lot to be completed by Q3 2022
- Discussions with regulatory agencies focused on registration pathway for TSHA-120
- Institutional readiness activities, patient identification and maximizing patient access
- Several publications expected by NIH in collaboration with Taysha

# Thank you to our patients, caregivers, advocacy groups, and collaborators

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Patients & Caregivers

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HEREDITARY NEUROPATHY FOUNDATION

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