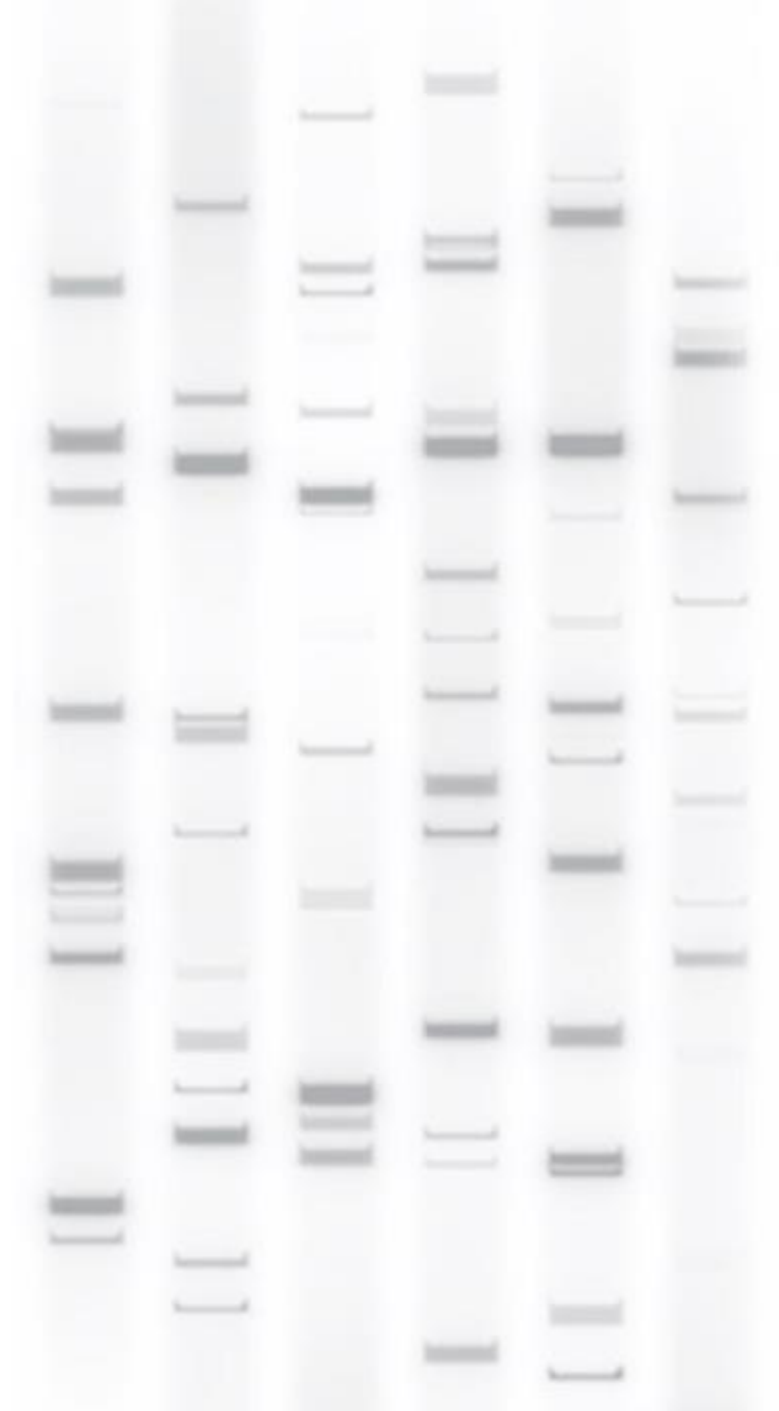




Bringing New Cures to Life

TSHA-120 GAN Program Acquisition – Conference Call
April 12, 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.



Bringing new cures to life

Vision

Driven by a relentless focus on **discovering, developing, and commercializing novel AAV-based gene therapies** for devastating CNS disorders

Strategy

Focus on rapid clinical and commercial development by leveraging a **proven capsid, manufacturing process, and delivery method**

Pipeline

Pipeline **focused on monogenic CNS disorders**: neurodegenerative diseases, neurodevelopmental disorders, and genetic epilepsies



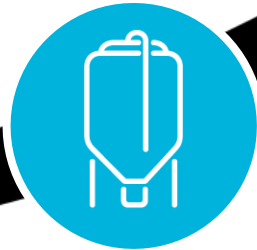
GAN program is a clear validation of the Steven Gray Lab (UTSW) and Taysha scientific approach; provides readthrough to existing pipeline

- 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
- We couple validated gene therapy 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



GAN program immediately transforms Taysha into a sustainable pivotal-stage gene therapy company



Groundbreaking clinical study (1st intrathecally dosed gene therapy study in history)



Validation of the Steven Gray Lab (UTSW) and Taysha's scientific approach, with readthrough to existing pipeline



Clear arrest of disease progression and long-term durability established at therapeutic doses (multiple patients 3+ years post treatment)



Well tolerated with efficacy established at multiple doses in an ongoing clinical trial



Preclinical data suggest treatment with TSHA-120 improved pathology of dorsal root ganglia (DRG) in GAN knockout mouse model



Plan to engage with regulatory agencies in US, EU and Japan on regulatory pathway as soon as possible



Estimated 2,400 prevalent patients in US & EU, representing potentially greater than \$2 billion near-term commercial opportunity



Accelerates build-out of commercial infrastructure to support patient identification, payor engagement and product distribution



Opportunity to achieve human POC for vagus nerve redosing platform with previously treated low dose patients

Animal POC achieved and presented at ASGCT 2020



*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.
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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

GAN program is a value-accretive, bolt-on opportunity that diversifies the portfolio by product stage



Patient Value

- Unmet medical need
- Clinical data demonstrated arrest of disease progression
- Patient access being addressed
- Close collaboration with key patient advocacy groups to ensure awareness



Strategic Value

- Strategic fit
 - Monogenic CNS disease
 - AAV9 vector, HEK293 CMC process
 - Intrathecal delivery
- Fortifies platform
- Enables acceleration of build out of commercial infrastructure
- Significant commercial opportunity



Scientific Value

- Validation of Taysha's platform
- Validation of Dr. Steven Gray's lab (UTSW)
- Potential human POC of redosing platform in previously low dose patients
- Applicability to other programs



Portfolio Value

- Represents >\$2B commercial opportunity
- GAN commercial infrastructure will support existing portfolio
- Near-term value creation
- Diversification of product stage
- Significant NPV

Rights acquired for \$5.5 million upfront, an aggregate of up to \$19.3 million in clinical, regulatory and commercial milestones as well as low, single-digit royalty on net sales

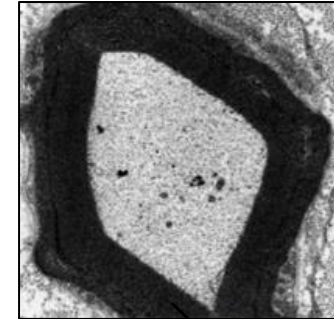


GAN Disease

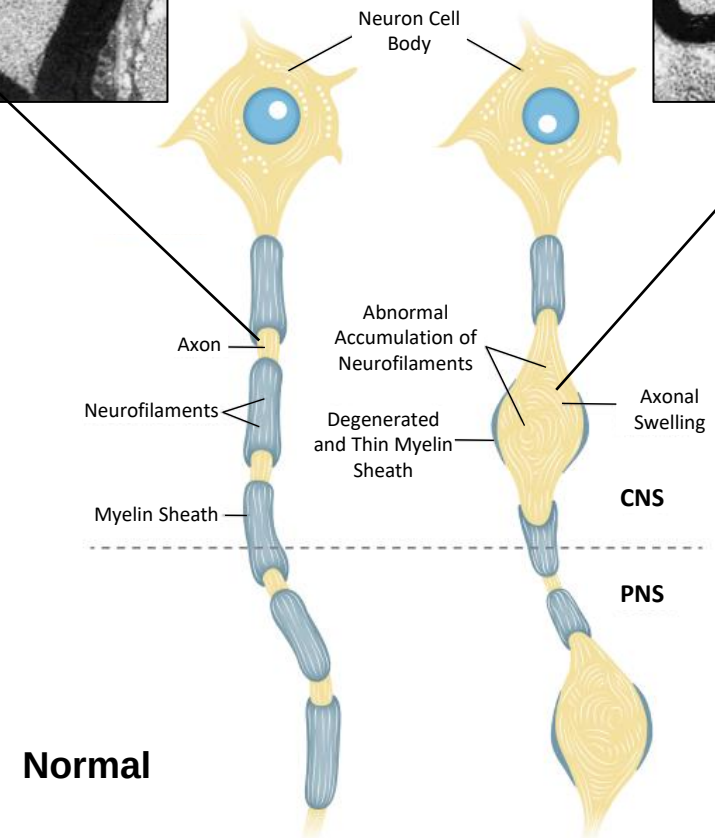
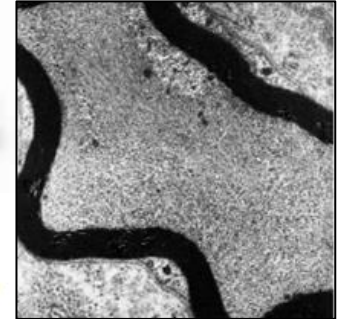
Rationale for targeting the *GAN* gene

- 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)

Normal Healthy Axon



GAN Axon



Normal

GAN



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

- 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



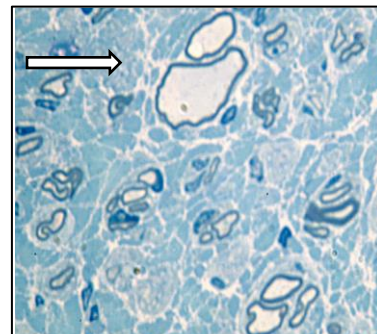
Progressive Scoliosis



Contractures



Giant Axons



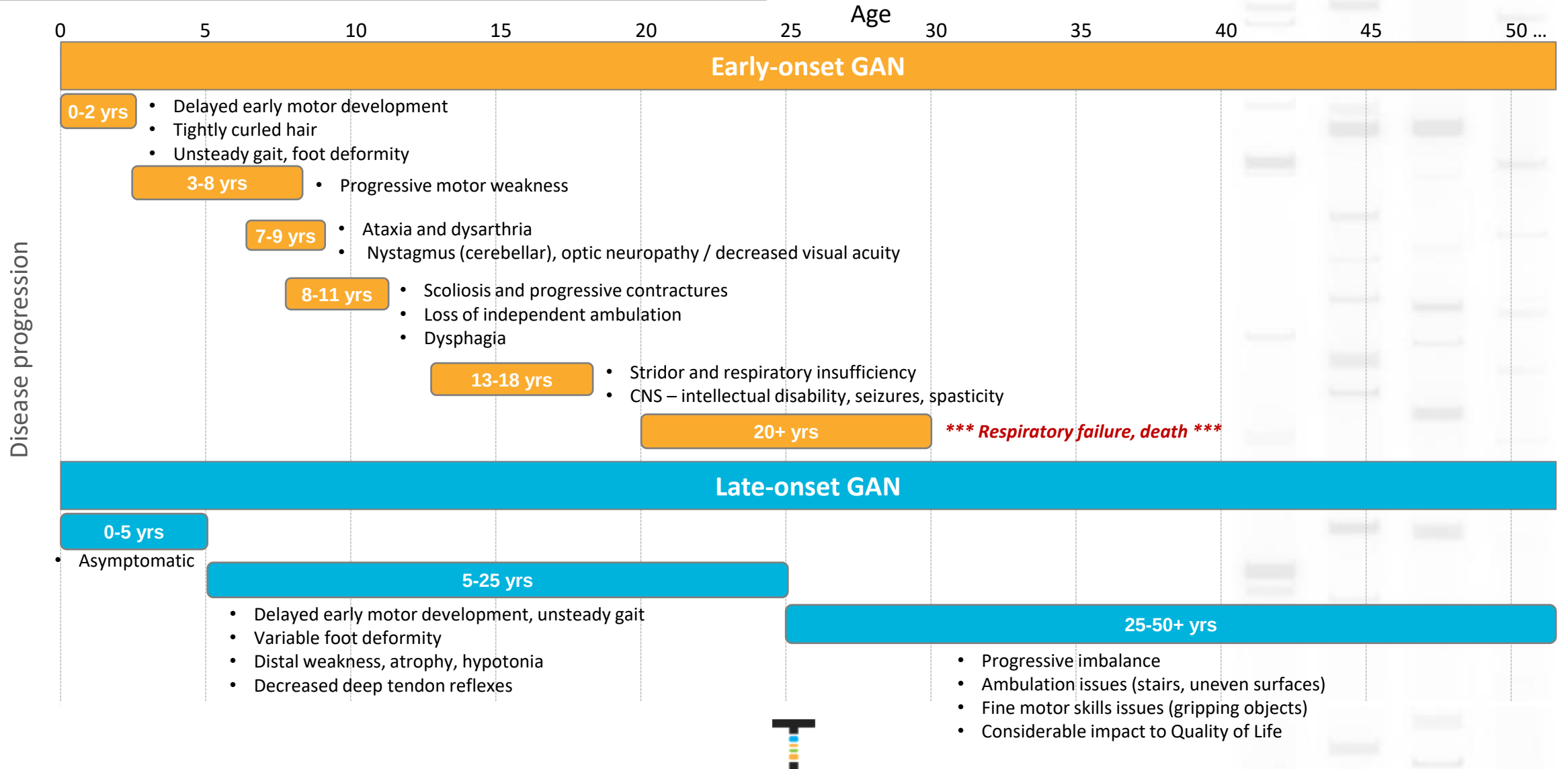
Spinal Cord Atrophy



White Matter Abnormality



GAN natural history and disease progression



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



Earlier diagnosis

- Establish newborn screening
- Partner with and create key centers of excellence
- Engage with patient advocacy groups



Increased awareness

- Educate HCPs on GAN phenotypes (early vs. late onset) with the potential to identify patients earlier in the disease
- Publications to create awareness for GAN phenotypes



Genotyping

- Partner with genetic testing providers (ex. Invitae and GeneDX) to identify patients with GAN mutation
- Screen patients with unknown etiology in CMT clinics worldwide



TSHA-120

Natural History Study

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

Examples of tasks

No.	Domain	Starting Position	Exercise Requested
1	D1	Supine, lower limbs half-flexed, kneecaps at zenith, and feet resting on mat	Raise the pelvis; the lumbar spine, the pelvis and the thighs are aligned and the feet slightly apart
2	D1	Supine	Without upper limb support, sits up
3	D1	Seated on the mat	Stands up without upper limb support
4	D1	Standing	Without upper limb support, sits down on the chair with the feet slightly apart
5	D1	Seated on chair	Stands up without upper limb support and with the feet slightly apart
6	D1	Standing with upper limb supported	Releases the support and maintains a standing position for 5s with the feet slightly apart, the head, trunk, and limbs in the midline position
7	D1	Standing with upper limb supported on equipment	Without upper limb support, raises the foot for 10s
8	D1	Standing	Without support, touches the floor with 1 hand and stands up again
9	D1	Standing without support	Takes 10 steps forward on both heels
10	D1	Standing without support	Takes 10 steps forward on a line
11	D1	Standing without support	Runs for 10m
12	D1	Standing on 1 foot without support	Hops 10 times in place

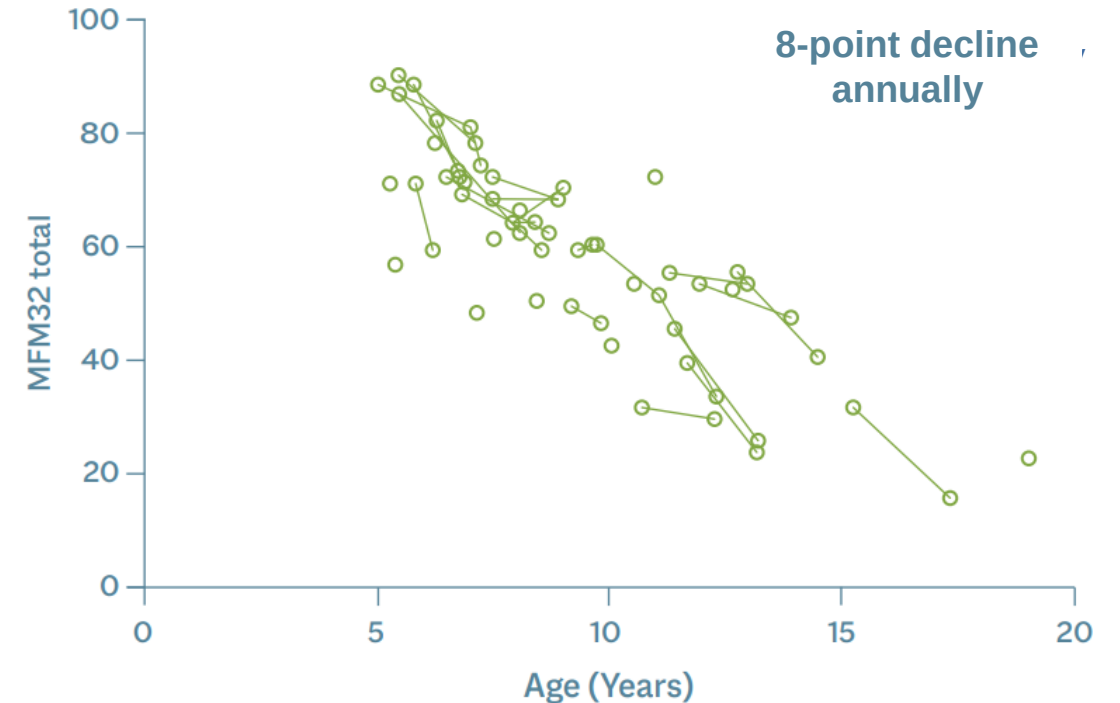


GAN natural history study data as a dependable comparator for future studies

- 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

**Natural History Plot of MFM32:
Total % Score Max = 100 (Best)**

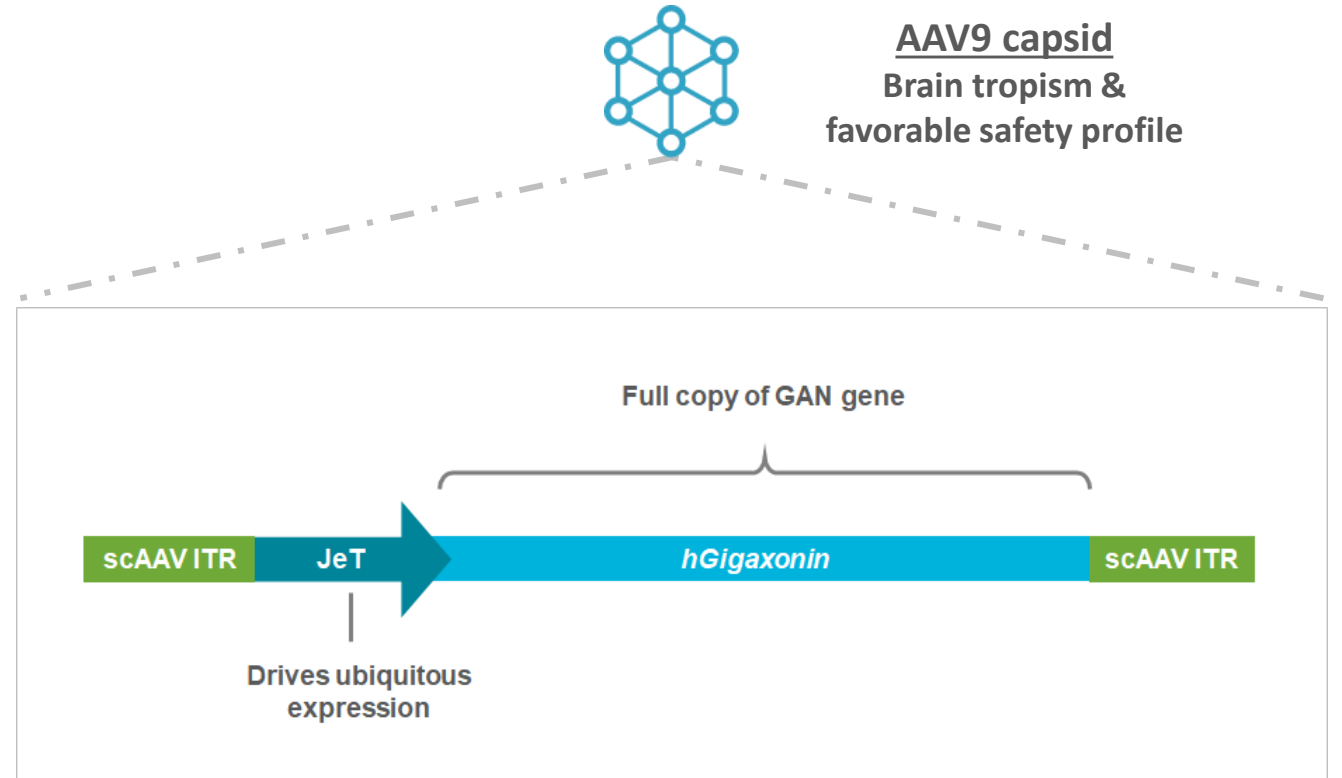


TSHA-120

Overview of Construct and Preclinical Data

TSHA-120 program overview and construct

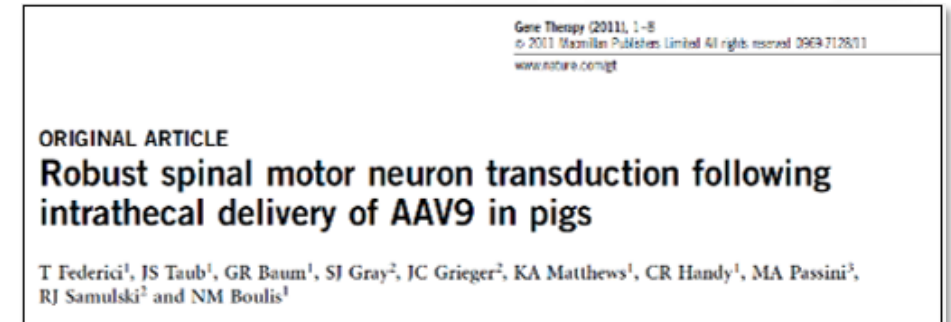
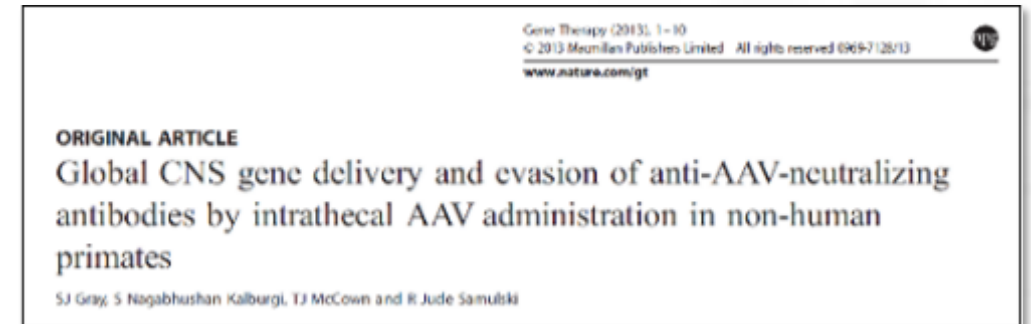
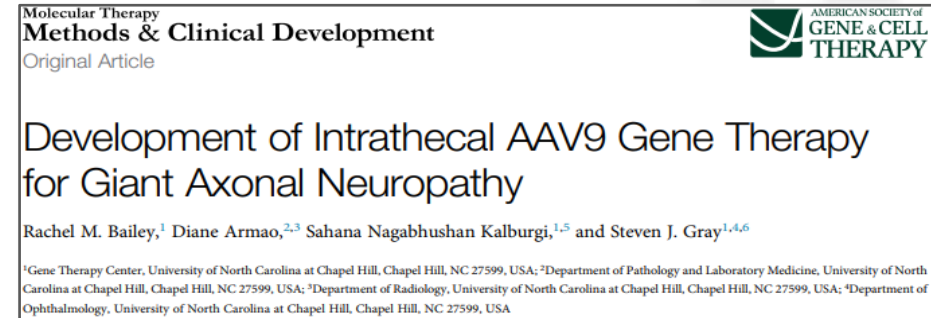
- Construct invented by Dr. Steven Gray (UTSW)
- AAV9 viral vector with engineered transgene encoding the human gigaxonin protein
- Self-complementary AAV capsid (scAAV) for rapid activation and stable expression
- JeT promoter drives ubiquitous expression
- Designed to deliver a functional copy of the 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



Preclinical data supported intrathecal dosing of TSHA-120

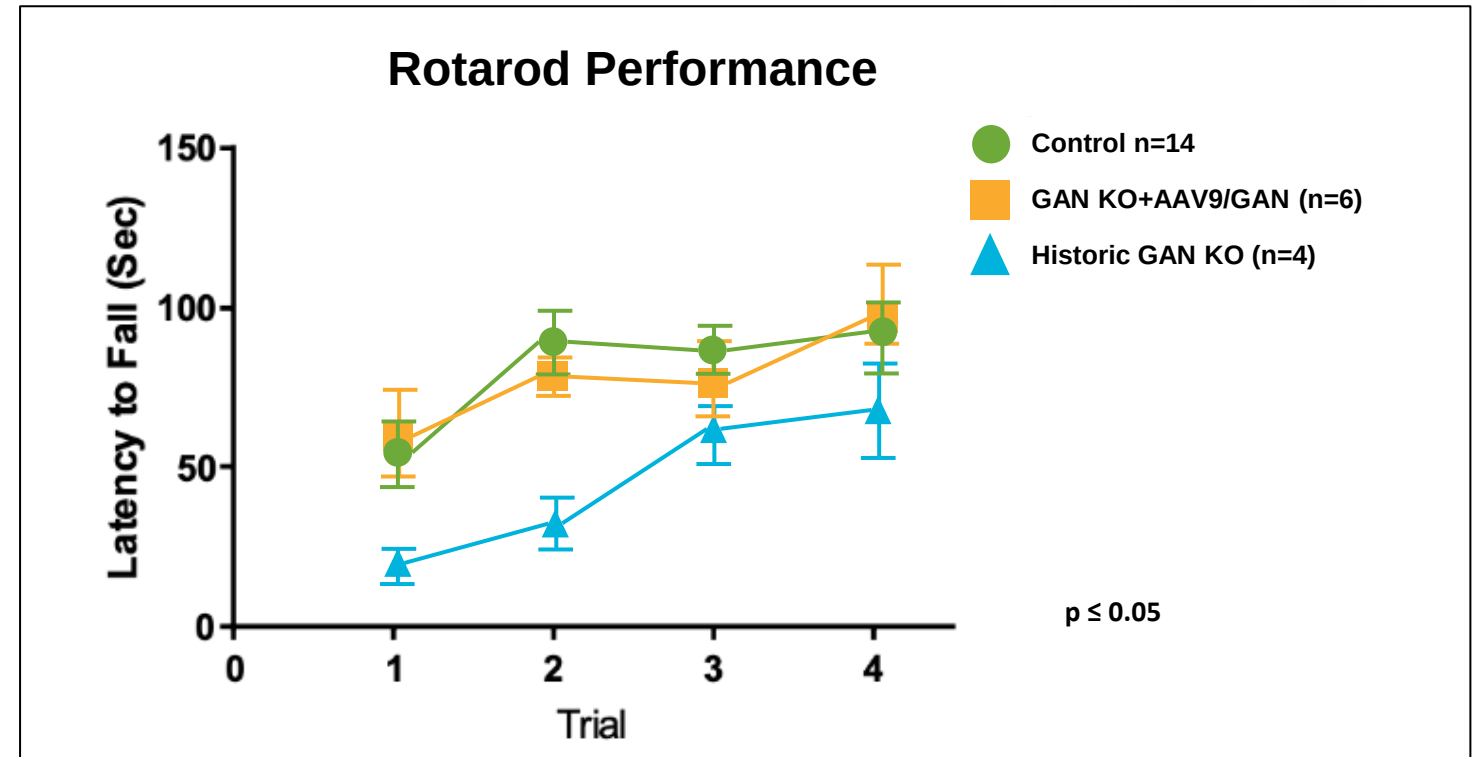
Comprehensive preclinical results demonstrated:

- 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

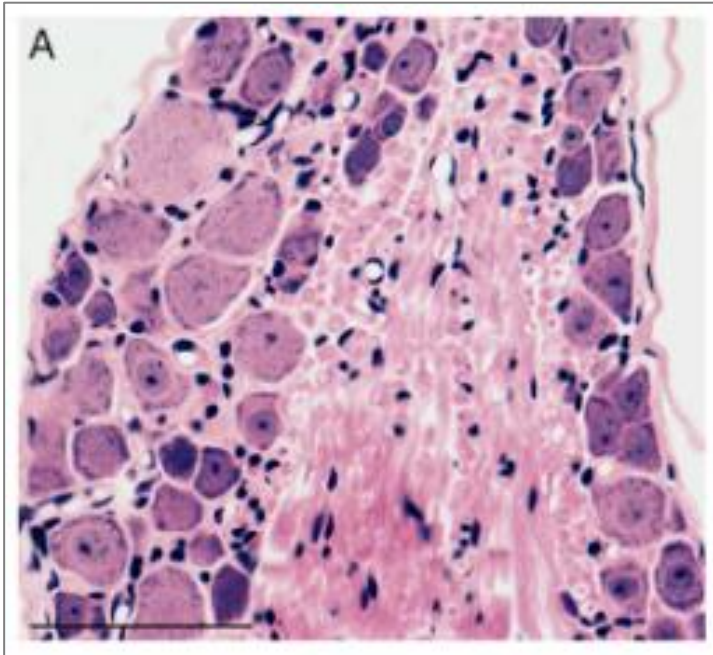


TSHA-120 normalized performance of 18-month-old GAN rodent knockout model

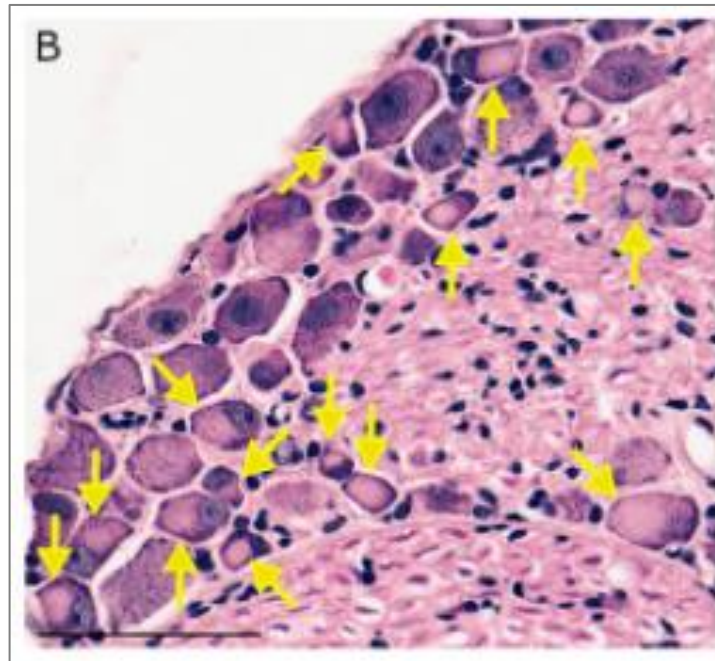
- Untreated GAN rodents performed significantly worse than heterozygous controls
- GAN rodents treated at 16 months old performed significantly better than untreated GAN rodents at 18 months old
- GAN rodents treated at 16 months old performed equivalently to heterozygous controls



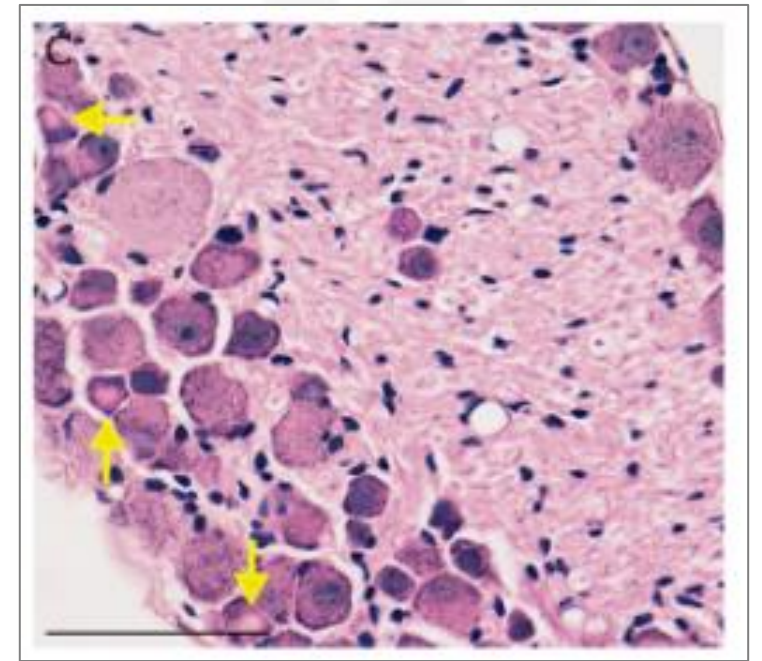
TSHA-120 improved pathology of the DRG in the GAN KO mice



Normal control



GAN KO – vehicle injected

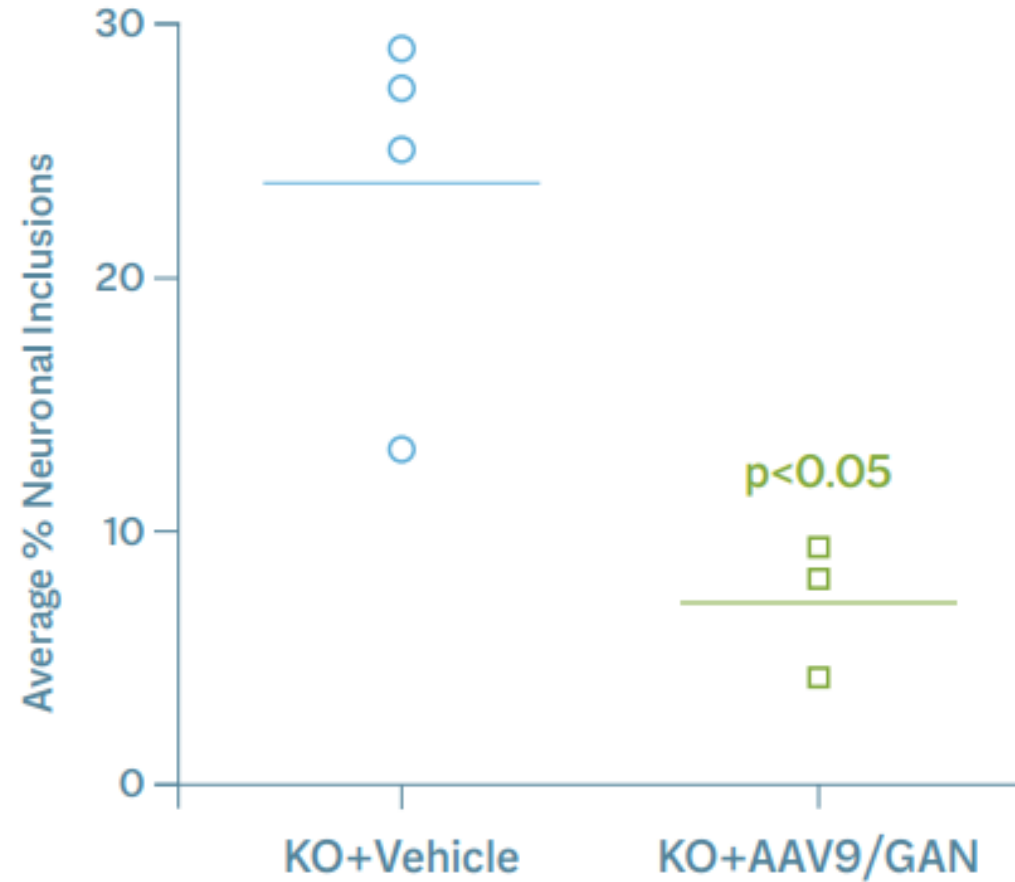


GAN KO – AAV9-GAN



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

Significant reduction in
% neuronal inclusions



TSHA-120

Overview of Human Proof-of-Concept Data

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

Goals and
Targets of Trial

Goals

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

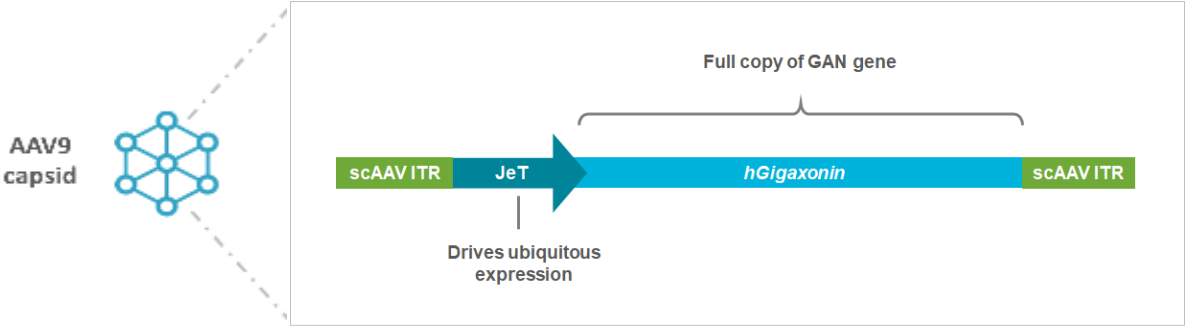
Target Recruitment

- 14 subjects injected
- > 5 years old

Target Areas to Transduce



Product Details
and Dose Cohorts



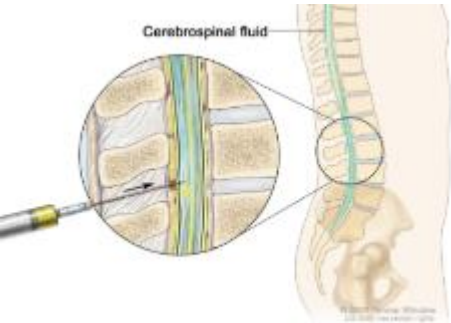
Dose Cohorts*

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

Route and
Method of
Administration

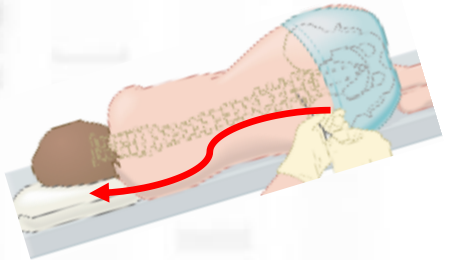
Administration

- 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

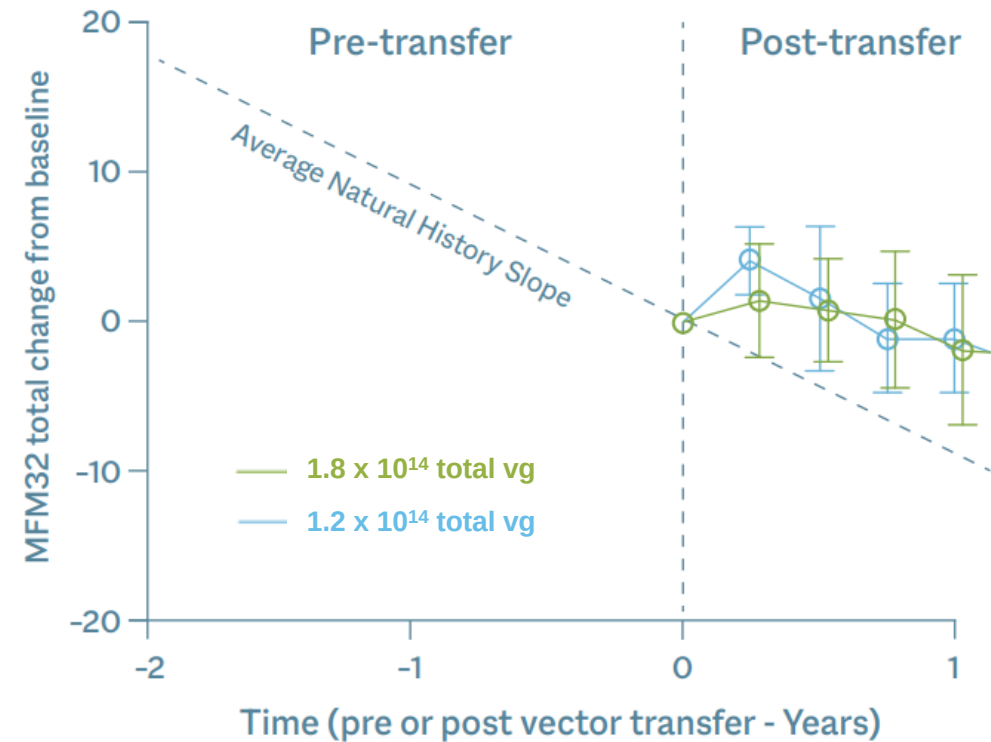


*Doses calculated by qPCR
NOTE: Subsequent slides only show data from
 1.2×10^{14} vg and 1.8×10^{14} vg doses

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

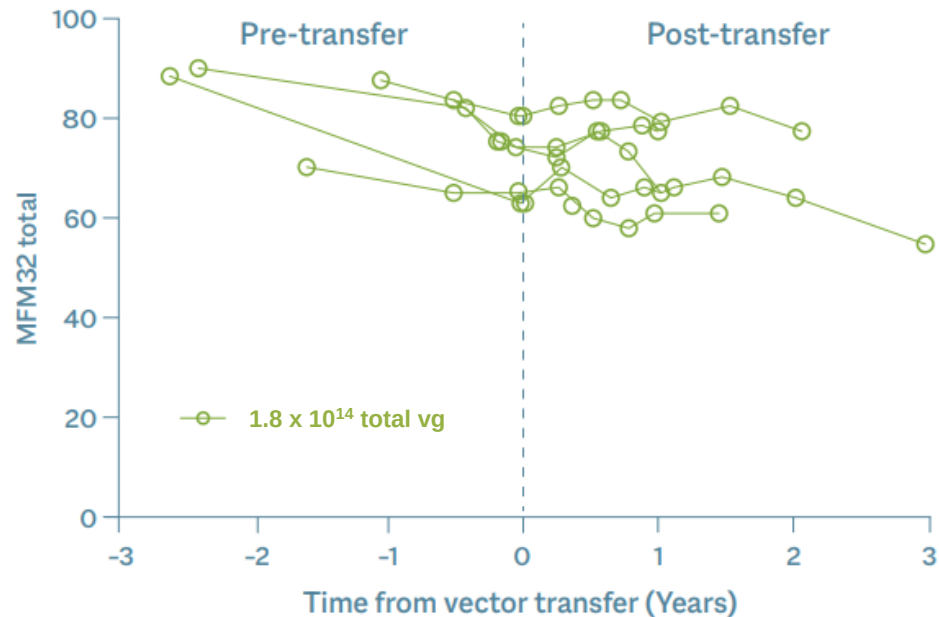
- First successful in-human intrathecal gene transfer
- 14 patients dosed
- Positive efficacy results support a dose-response relationship with TSHA-120
 - 1.8×10^{14} total vg dose and 1.2×10^{14} total vg cohorts demonstrated statistically significantly slowing of disease progression
 - Data only recently 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

Dose-dependent and sustained improvement in MFM32 at 1 year

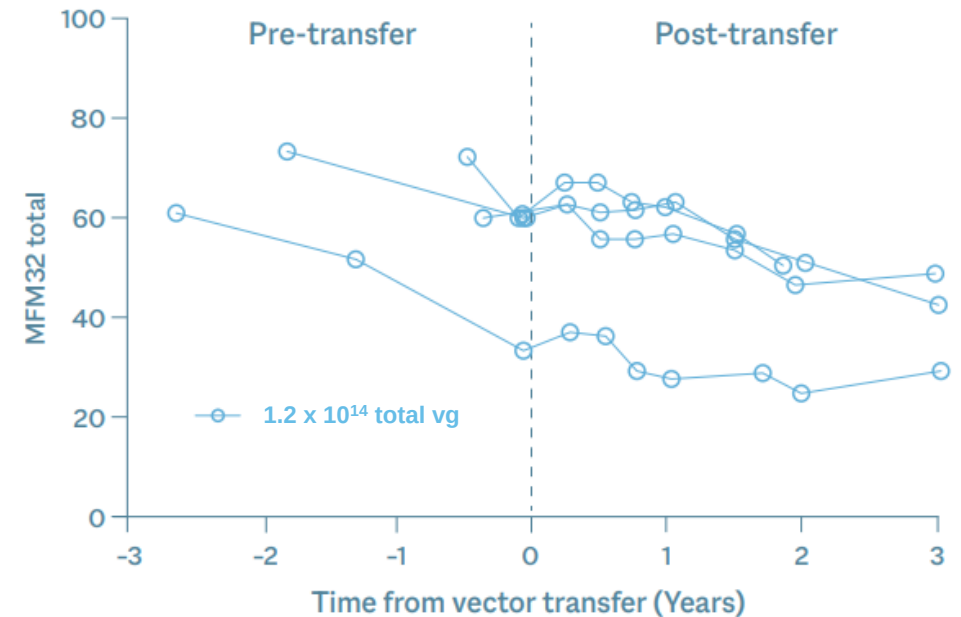


Treatment with TSHA-120 resulted in a clear arrest of disease progression at therapeutic doses and long-term durability

Dose-dependent and sustained improvement in MFM32 at 3 years



Dose-dependent and sustained improvement in MFM32 at 3 years



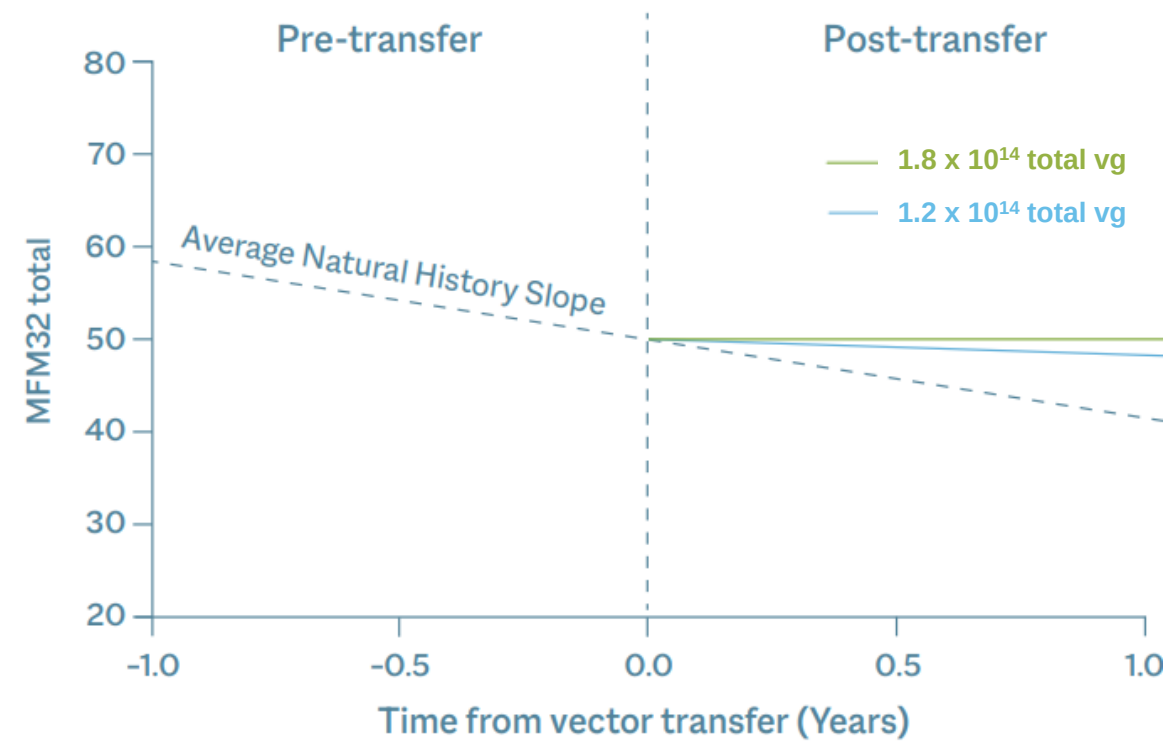
- Arrest of disease progression at therapeutic doses
- TSHA-120 was well tolerated at multiple doses

- 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



Additional analysis using Bayesian methodology confirmed arrest of disease progression

- 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 1.8×10^{14} total vg resulted in an arrest of disease progression that was statistically significant



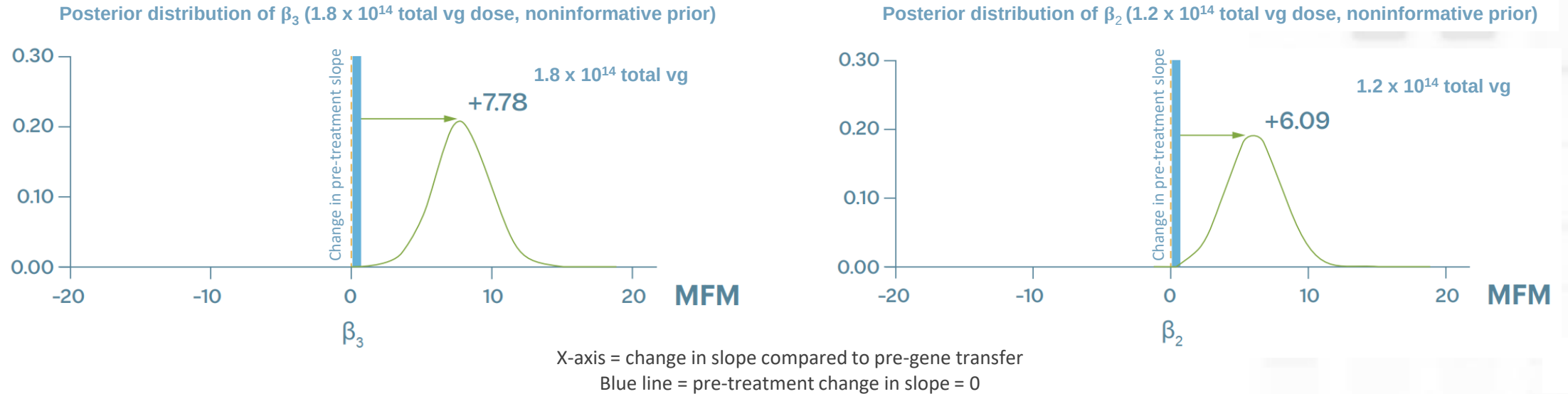
	Bayesian Analysis		Frequentist Analysis		
	Mean	Std Dev	Estimate	Std Error	p-Value
Post infusion: 1.8×10^{14} total vg	7.78	1.94	7.78	1.89	<0.001
Post infusion: 1.2×10^{14} total vg	6.09	2.11	6.07	2.05	0.004
Natural history decline	-8.19	0.74	-8.18	0.72	<0.001



TSHA-120 halted patient pre-treatment rate of decline at 1.8×10^{14} total vg dose

Bayesian Efficacy Analysis

Compared to individual historical data



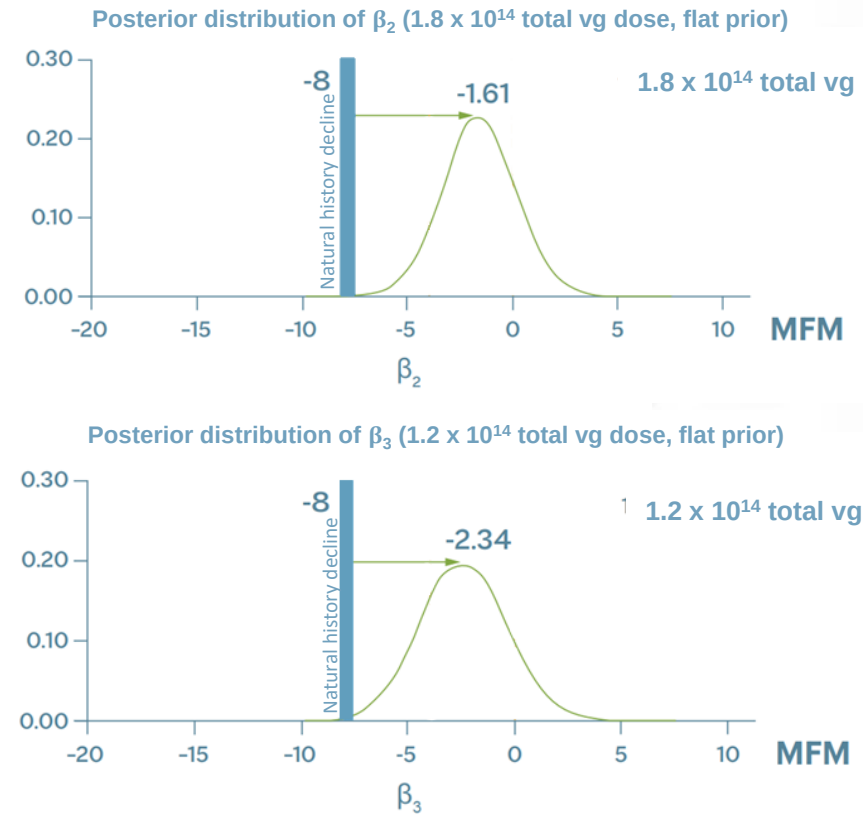
- Graphs depict treated population average annual post-treatment decline for both the 1.8×10^{14} total vg cohort and the 1.2×10^{14} total vg cohort
- 1.8×10^{14} vg halted patient pre-treatment rate of decline, avg annual slope improvement of 7.78 points
- 1.2×10^{14} vg resulted in clinically meaningful 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



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

- 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 1.8×10^{14} total vg cohort and the 1.2×10^{14} total vg cohort as compared to natural history
 - 1.8×10^{14} total vg dose confirmed nearly 100% probability of clinically meaningful slowing of disease compared to natural history decline of GAN patients
 - 1.2×10^{14} total vg dose confirmed approximately 85% probability of clinically meaningful slowing of disease and 100% probability of any slowing of disease

Bayesian Efficacy Analysis Compared to natural history data



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

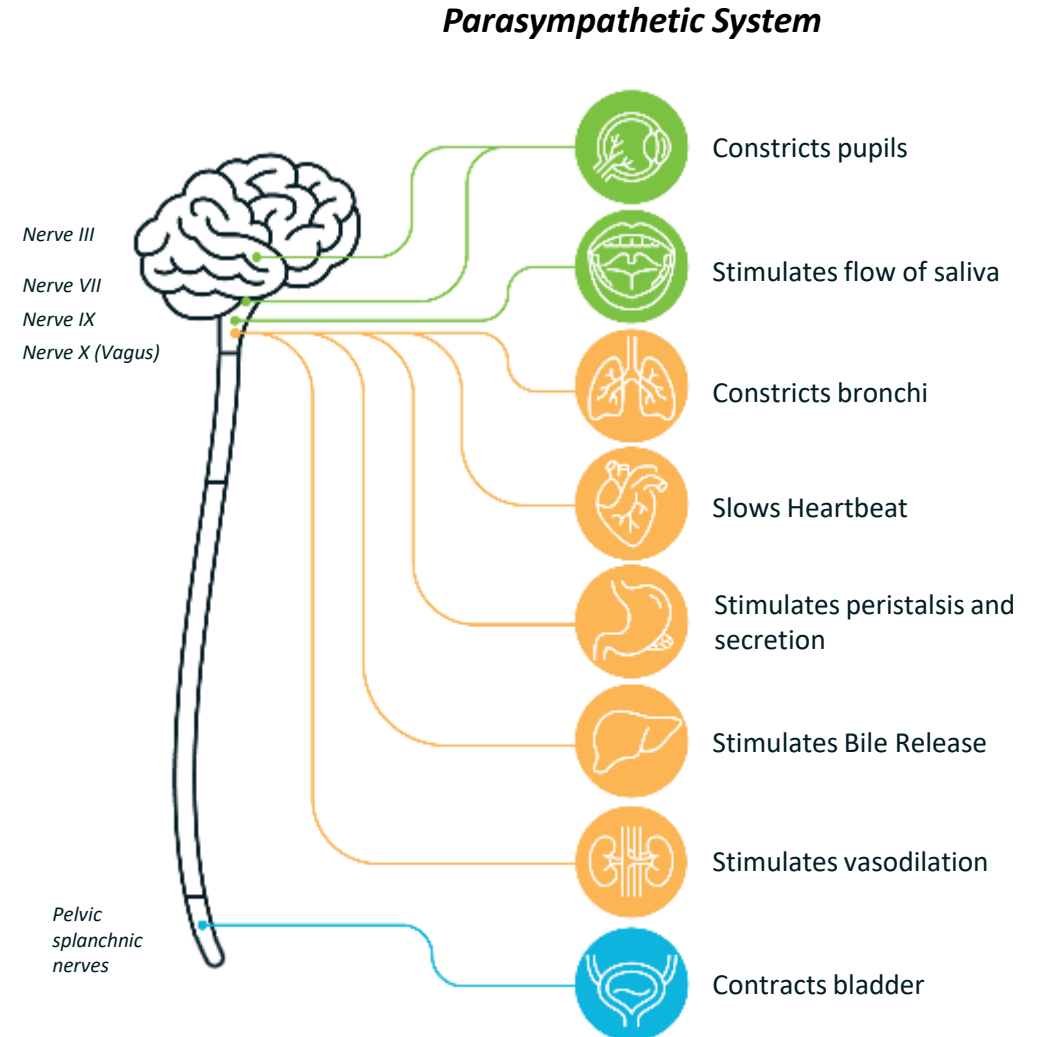
	Values = % Probability	
Change in disease progression	1.8x10 ¹⁴ total vg	1.2x10 ¹⁴ total vg
Any Slowing	99.9	99.8
Clinically meaningful slowing 50% or more	98.3	84.9



Vagus Nerve Redosing

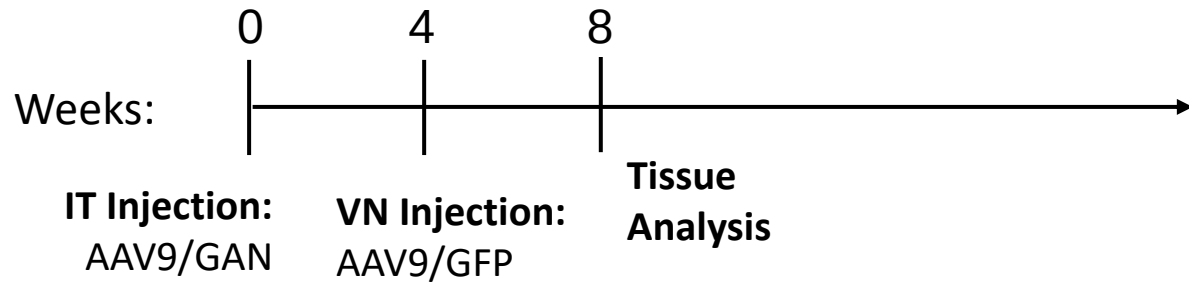
Opportunity to achieve human POC for vagus nerve redosing

- The vagus nerve represents the main component of the autonomic nervous system
- Direct delivery to the vagus nerve may provide broad coverage of the autonomic nervous system and enable redosing by subverting the humoral immune response
- Proof-of-concept established in rodent and canine models; oral presentation of data at ASGCT 2020
- Plan to execute confirmatory preclinical studies in canines
- Platform may be utilized to facilitate redosing of previously treated patients in the GAN AAV9 clinical trial as well as other indications

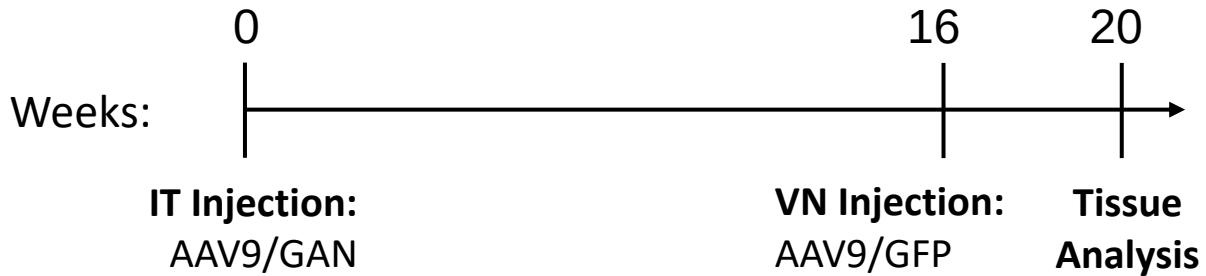


Robust expression of GFP in the vagus nerve and associated nodose ganglia in rats support redosing via vagus nerve injection

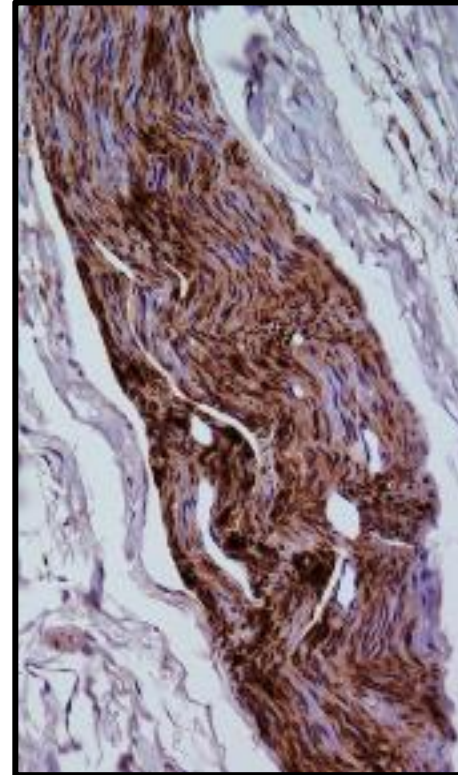
Study 1



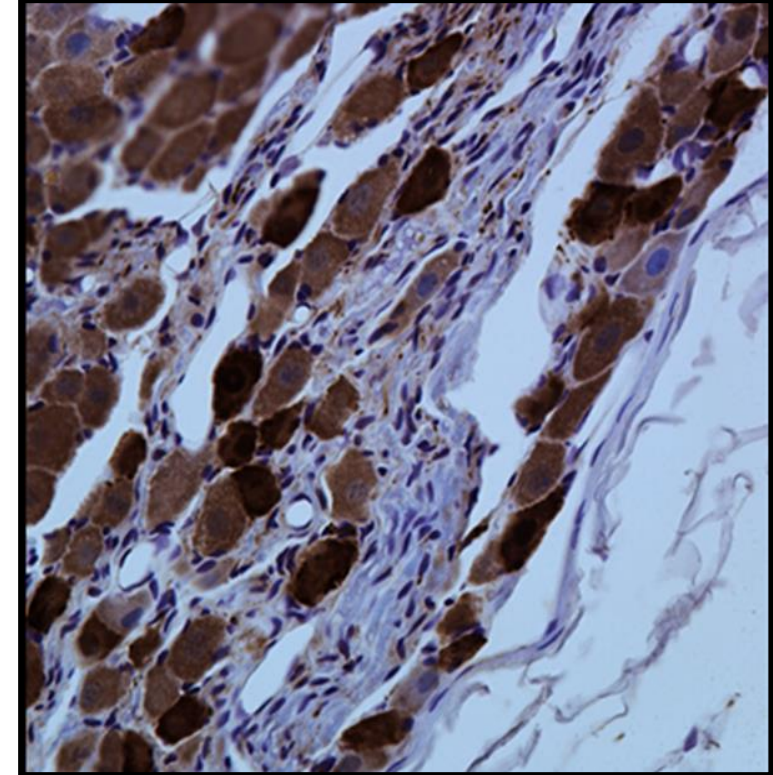
Study 2



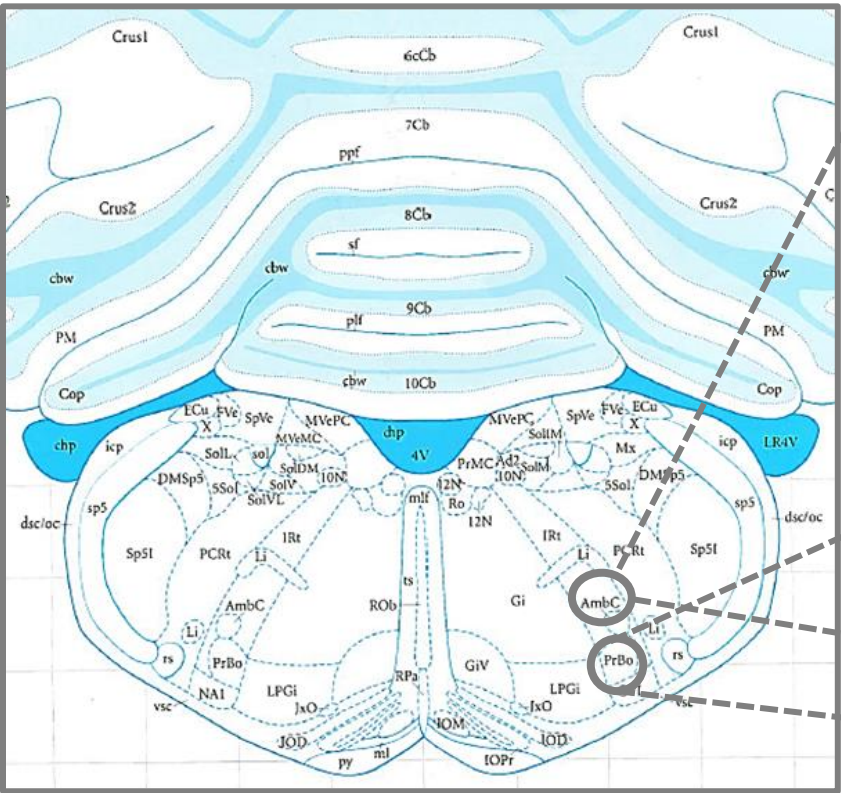
Vagus Nerve



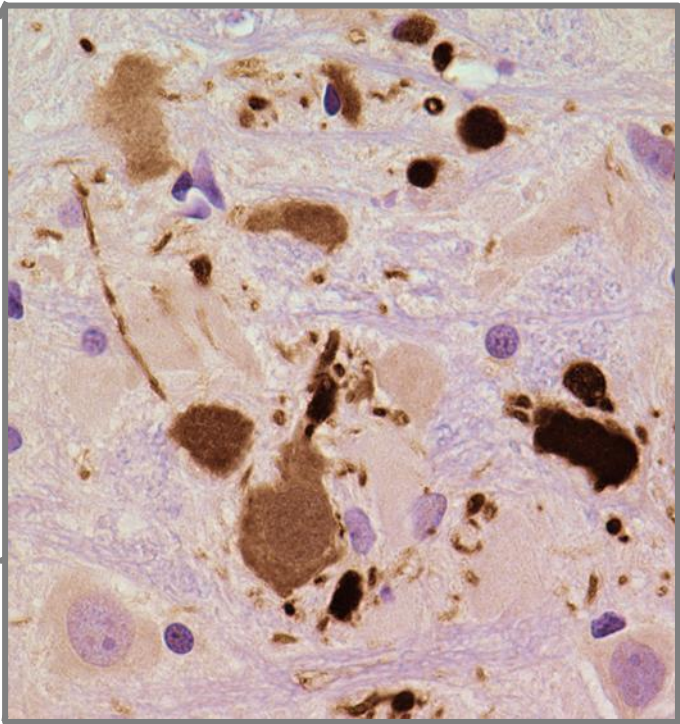
Nodose Ganglia



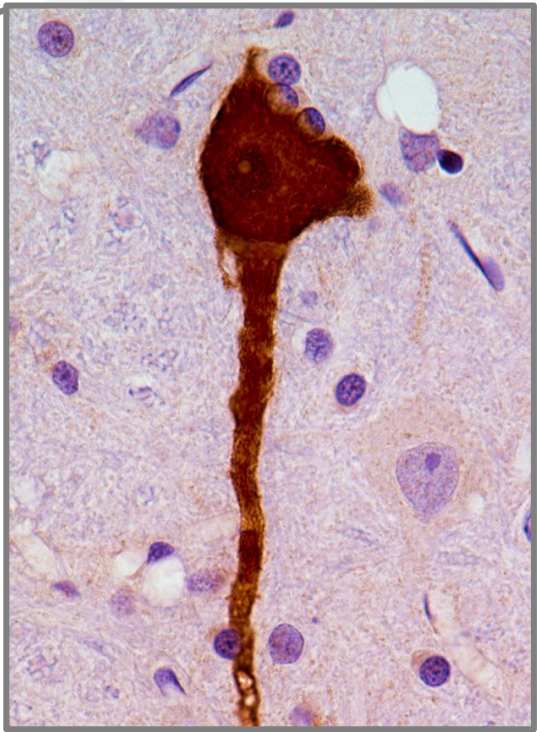
Successful transduction of relevant brain neurons following redosing via vagus nerve injection



Medulla



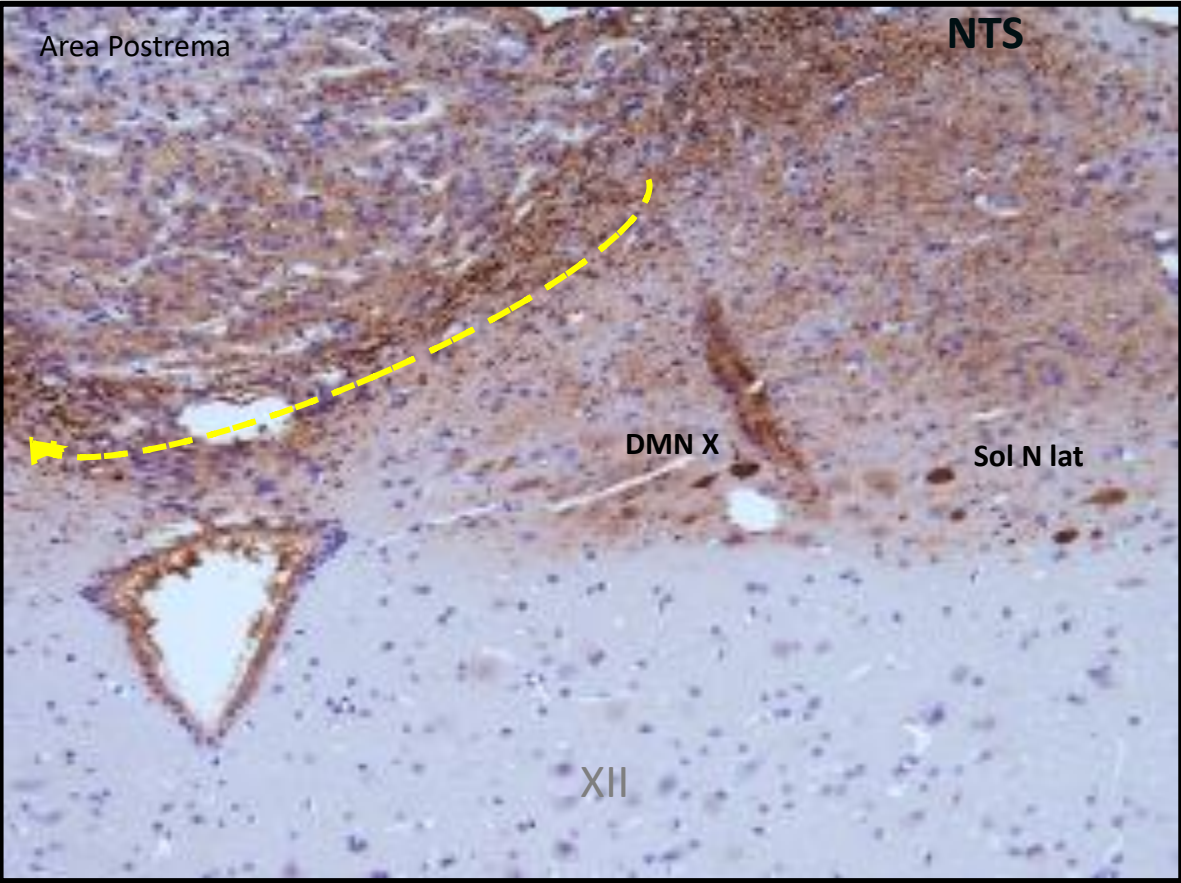
Nucleus Ambiguus



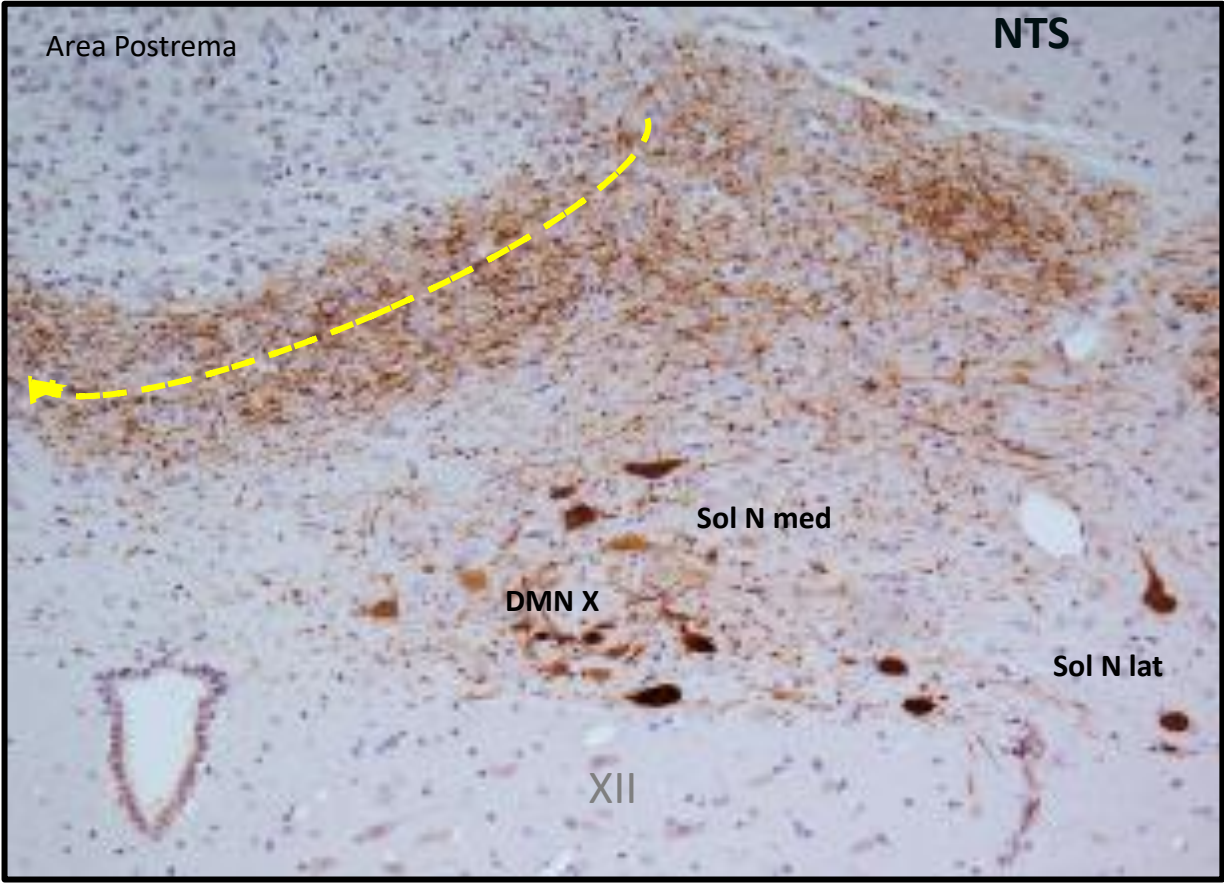
Pre-Botzinger Complex



Vagus nerve injection permits AAV9 redosing confirmed in brain slices of AAV9-immunized rats



Naive



AAV9 Pre-immunized



Closing Remarks

GAN program immediately transforms Taysha into a sustainable pivotal-stage gene therapy company



Groundbreaking clinical study (1st intrathecally dosed gene therapy study in history)



Validation of the Steven Gray Lab (UTSW) and Taysha's scientific approach, with readthrough to existing pipeline



Clear arrest of disease progression and long-term durability established at therapeutic doses (multiple patients 3+ years post treatment)



Well tolerated with efficacy established at multiple doses in an ongoing clinical trial



Preclinical data suggest treatment with TSHA-120 improved pathology of dorsal root ganglia (DRG) in GAN knockout mouse model



Plan to engage with regulatory agencies in US, EU and Japan on regulatory pathway as soon as possible



Estimated 2,400 prevalent patients in US & EU, representing potentially greater than \$2 billion near-term commercial opportunity



Accelerates build-out of commercial infrastructure to support patient identification, payor engagement and product distribution



Opportunity to achieve human POC for vagus nerve redosing platform with previously treated low dose patients

Animal POC achieved and presented at ASGCT 2020



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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

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



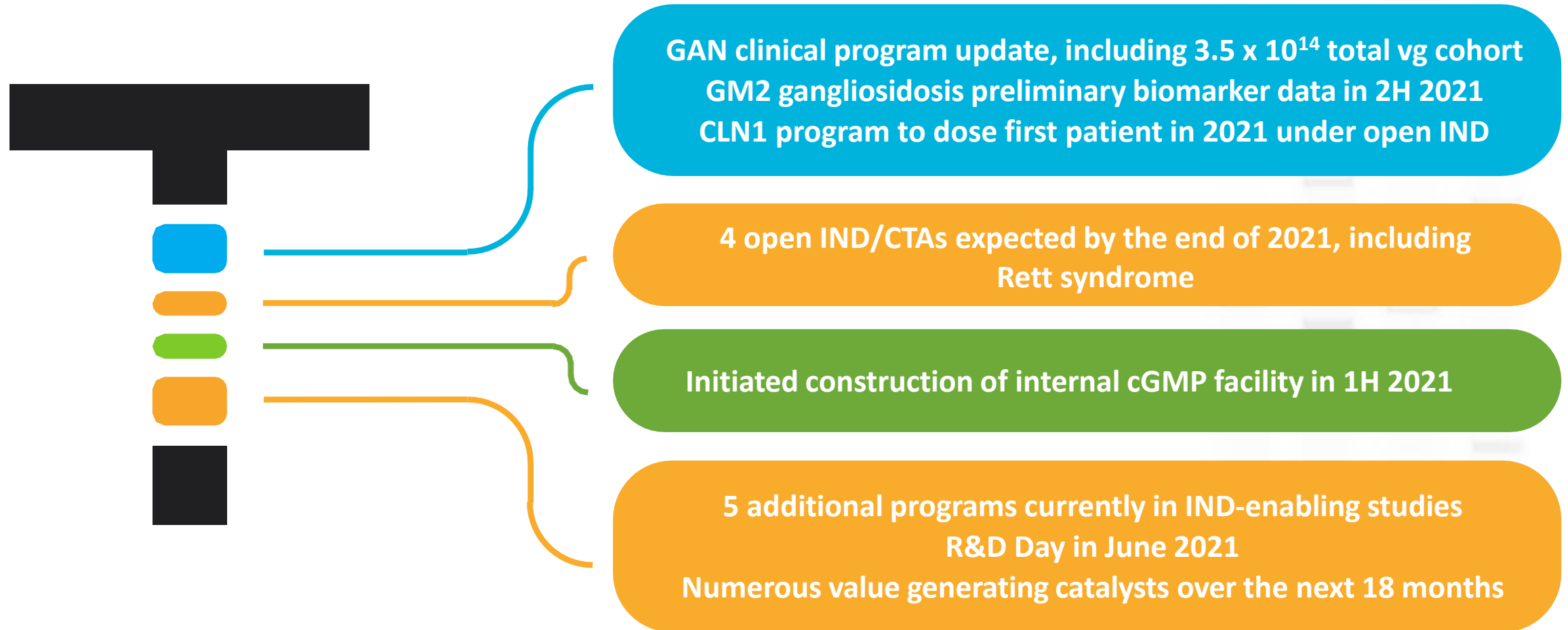
Initiate new clinical sites in US and EU



Update on regulatory interactions and current clinical program, including 3.5×10^{14} total vg cohort



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



Special Thanks



UTSouthwestern
Medical Center



National Institute of
Neurological Disorders
and Stroke

Q&A
