



Taysha Gene Therapies Reports First Quarter 2023 Financial Results and Provides Corporate Update

Screening completed and dosing scheduled for first potential subject in the Phase 1/2 REVEAL trial in Rett syndrome; dosing of first adult patient with TSHA-102 expected in Q2 2023; initial available Phase 1/2 clinical data, primarily on safety, expected in Q2 2023

Clinical Trial Application (CTA) submission to United Kingdom (UK) MHRA for TSHA-102 in pediatric patients with Rett syndrome expected in mid-2023; Investigational New Drug (IND) application to United States (U.S.) Food and Drug Administration (FDA) in Rett syndrome anticipated in H2 2023

New preclinical data for TSHA-102 in Rett syndrome to be presented during a poster presentation at the upcoming American Society of Gene and Cell Therapy (ASGCT) 26th Annual Meeting

R&D Day in June 2023 will overview new findings from totality of data evaluation, including comprehensive analyses of functional, biological, and electrophysiological assessments of TSHA-120 in giant axonal neuropathy (GAN), and provide an update on TSHA-102 in Rett syndrome

Formal FDA meeting request submission to discuss regulatory path forward for TSHA-120 in GAN expected in Q2 2023; formal meeting anticipated in Q3 2023

Conference call and live webcast today at 4:30 PM Eastern Time

DALLAS, May 11, 2023 (GLOBE NEWSWIRE) -- Taysha Gene Therapies, Inc. (Nasdaq: TSHA), a clinical-stage gene therapy company focused on developing and commercializing AAV-based gene therapies for the treatment of monogenic diseases of the central nervous system (CNS), today reported financial results for the first quarter ended March 31, 2023, and provided a corporate update.

"We continue to make significant progress with our two lead clinical programs and remain on track to deliver on multiple key milestones, including the generation of first-in-human clinical data for TSHA-102 in adult patients with Rett syndrome, the submission of a CTA to the MHRA to initiate expansion of TSHA-102 in pediatric patients, the submission of an IND application to the FDA for TSHA-102, and obtaining further clarity from the FDA on the regulatory path forward for TSHA-120 in GAN," said Sean P. Nolan, Chairman and Chief Executive Officer of Taysha. "Screening is completed, and dosing is now scheduled for our first potential patient in the adult Rett syndrome study. For GAN, our comprehensive analyses of the totality of data for TSHA-120 continues to be encouraging and includes compelling findings with potential to further support a regulatory path forward."

Sukumar Nagendran, M.D., President, and Head of R&D added, "We plan to seek a formal meeting with the FDA to discuss the totality of findings from the functional, biological, and electrophysiological assessments of TSHA-120 in GAN, anticipated in the third quarter of this year. In the near term, we look forward to hosting an R&D Day in June where we will overview the GAN disease state and share the comprehensive analyses, as well as provide an update on our Rett program. For TSHA-102, new preclinical data supporting the efficacy and safety of TSHA-102 and the miRARE technology in Rett syndrome will be presented as part of a poster presentation at the upcoming ASGCT conference. We believe that the clinical and preclinical data generated to date across our Rett syndrome and GAN programs reinforce our gene therapy approach, and the therapeutic potential to address severe unmet needs in monogenic central nervous system disease."

Recent Corporate Highlights

TSHA-102 in Rett syndrome: a self-complementary intrathecally delivered AAV9 gene transfer therapy in clinical evaluation for Rett syndrome, a rare genetic neurodevelopmental disorder caused by mutations in the X-linked *MECP2* gene. TSHA-102 utilizes a novel miRNA-Responsive Auto-Regulatory Element (miRARE) platform designed to regulate cellular *MECP2* expression. TSHA-102 has received Orphan Drug and Rare Pediatric Disease designations from the FDA and has been granted Orphan Drug designation from the European Commission.

- Phase 1/2 REVEAL trial in adult patients with Rett syndrome
 - Completed screening and scheduled dosing for first potential adult patient with dosing anticipated in Q2 2023
 - Initial available Phase 1/2 clinical data, primarily on safety, expected in Q2 2023, with planned quarterly updates on available clinical data thereafter
 - Continued dosing of adult patients with Rett syndrome in the REVEAL trial in H2 2023
- CTA submission to UK MHRA for TSHA-102 in pediatric patients with Rett syndrome anticipated in mid-2023
- IND application submission to U.S. FDA for Rett syndrome expected in H2 2023
- New preclinical data for TSHA-102 in Rett syndrome to be presented as a poster presentation at the upcoming ASGCT 26th Annual Meeting on Friday, May 19 at 12-2 PM PT; these data and available clinical data from Phase 1/2 REVEAL trial will be presented in upcoming R&D Day in June

TSHA-120 for giant axonal neuropathy (GAN): a self-complimentary intrathecally delivered AAV9 gene therapy in clinical evaluation for GAN, an ultra-rare inherited genetic neurodegenerative disorder with no approved treatments. TSHA-120 has received Orphan Drug and Rare Pediatric Disease designations from the FDA and has been granted Orphan Drug designation from the European Commission.

- Completed CMC module 3 amendment submission detailing commercial process product manufacturing and drug comparability analysis; awaiting FDA feedback
- R&D Day in June 2023 to overview new findings from totality of data evaluation, including comprehensive analyses of functional, biological, and electrophysiological assessments of TSHA-120 in GAN
- Submission of a formal meeting request to the FDA in Q2 2023 to discuss alternative study designs, additional objective measures and regulatory path forward; formal meeting anticipated in Q3 2023

First Quarter 2023 Financial Highlights

Research and Development Expenses: Research and development expenses were \$12.5 million for the three months ended March 31, 2023, compared to \$38.2 million for the three months ending March 31, 2022. The \$25.7 million decrease was due to reduced research and development compensation as a result of lower headcount of \$10.7 million. The decrease was also due to reduced manufacturing and other raw material purchases of \$7.1 million. We also incurred \$6.4 million reduced expense in non-clinical studies related to translational and toxicology studies and \$1.5 million lower expense in other research and development activities.

General and Administrative Expenses: General and administrative expenses were \$8.8 million for the three months ended March 31, 2023, compared to \$11.5 million for the three months ended March 31, 2022. The decrease of \$2.7 million was due to reduced general and administrative compensation as a result of lower headcount and reduced consulting and professional fees.

Net loss: Net loss for the three months ended March 31, 2023 was \$17.6 million or \$0.28 per share, as compared to a net loss of \$50.3 million, or \$1.32 per share, for the three months ended March 31, 2022. The net loss for the three months ended March 31, 2023 was partially offset by revenue of \$4.7 million recognized related to the Astellas Transactions.

Cash and cash equivalents: As of March 31, 2023, Taysha had \$63.4 million in cash and cash equivalents. Taysha continues to expect that its current cash resources will support planned operating expenses and capital requirements into the first quarter of 2024.

Conference Call and Webcast Information

Taysha management will hold a conference call and webcast today at 4:30 pm ET to review its financial and operating results and to provide a corporate update. The dial-in number for the conference call is 855-327-6837 (U.S./Canada) or 631-891-4304 (international). The conference ID for all callers is 10021767. The live webcast and replay may be accessed by visiting Taysha's website at <https://ir.tayshagtx.com/news-events/events-presentations>. An archived version of the webcast will be available on the website for 30 days.

About Taysha Gene Therapies

Taysha Gene Therapies (Nasdaq: TSHA) is on a mission to eradicate monogenic CNS disease. With a singular focus on developing curative medicines, we aim to rapidly translate our treatments from bench to bedside. We have combined our team's proven experience in gene therapy drug development and commercialization with the world-class UT Southwestern Gene Therapy Program. Together, we leverage our fully integrated platform with a goal of dramatically improving patients' lives. More information is available at www.tayshagtx.com.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as "anticipates," "believes," "expects," "intends," "projects," "plans," and "future" or similar expressions are intended to identify forward-looking statements. Forward-looking statements include statements concerning the potential of our product candidates, including our preclinical product candidates, to positively impact quality of life and alter the course of disease in the patients we seek to treat, our research, development and regulatory plans for our product candidates, the potential for these product candidates to receive regulatory approval from the FDA or equivalent foreign regulatory agencies, and whether, if approved, these product candidates will be successfully distributed and marketed, the potential market opportunity for these product candidates, our corporate growth plans, the forecast of our cash runway and the implementation and potential impacts of our strategic pipeline prioritization initiatives. Forward-looking statements are based on management's current expectations and are subject to various risks and uncertainties that could cause actual results to differ materially and adversely from those expressed or implied by such forward-looking statements. Accordingly, these forward-looking statements do not constitute guarantees of future performance, and you are cautioned not to place undue reliance on these forward-looking statements. Risks regarding our business are described in detail in our Securities and Exchange Commission ("SEC") filings, including in our Annual Report on Form 10-K for the full-year ended December 31, 2022, which is available on the SEC's website at www.sec.gov. Additional information will be made available in other filings that we make from time to time with the SEC. Such risks may be amplified by the impacts of the COVID-19 pandemic. These forward-looking statements speak only as of the date hereof, and we disclaim any obligation to update these statements except as may be required by law.

**Taysha Gene Therapies, Inc.
Condensed Consolidated Statements of Operations
(in thousands, except share and per share data)
(Unaudited)**

For the three months ended March 31,	For the three months ended March 31,
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	2023	2022
Revenue:		
Service Revenue	\$ 4,706	\$ -
Operating expenses:		
Research and development	12,514	38,182
General and administrative	8,751	11,469
	<hr/>	<hr/>
Total operating expenses	21,265	49,651
Loss from operations	<hr/>	<hr/>
	(16,559)	(49,651)
Other income (expense):		
Interest Income	319	14
Interest expense	(1,374)	(672)
Other expense	(8)	(8)
	<hr/>	<hr/>
Total other expense	(1,063)	(666)
Net loss	<hr/>	<hr/>
	\$ (17,622)	\$ (50,317)
Net loss per common share, basic and diluted	\$ (0.28)	\$ (1.32)
Weighted average common shares outstanding, basic and diluted	63,260,905	38,174,717

Taysha Gene Therapies, Inc.
Condensed Consolidated Balance Sheet Data
(in thousands, except share and per share data)
(Uaudited)

	December 31, March 31, 2023	2022
ASSETS		
Current assets:		
Cash and cash equivalents		
	\$ 63,425	\$ 87,880
Prepaid expenses and other current liabilities		
	8,933	8,537
Total current assets	<hr/>	<hr/>
	72,358	96,417
Restricted cash		
	2,637	2,637
Property, plant and equipment, net		
	14,642	14,963
Operating lease right-of-use assets		
	10,647	10,943
Other noncurrent assets		
	1,316	1,316
Total assets	<hr/>	<hr/>
	\$ 101,600	\$ 126,276
LIABILITIES, CONVERTIBLE PREFERRED STOCK, AND STOCKHOLDERS' (DEFICIT) EQUITY		
Current liabilities:		
Accounts payable		
	\$ 9,002	\$ 10,946
Accrued expenses and other current liabilities		
	16,602	18,287
Deferred revenue		
	28,851	33,557
Total current liabilities		
	<hr/>	<hr/>
	54,455	62,790
Term loan, net		
	38,161	37,967
Operating lease liability, net of current portion		
	19,928	20,440
Other noncurrent liabilities		
	4,004	4,130
Total liabilities	<hr/>	<hr/>
	116,548	125,327

Preferred stock, \$0.00001 par value per share; 10,000,000 shares authorized and no shares issued and outstanding as of March 31, 2023 and December 31, 2022

Stockholders' (deficit) equity

Common stock, \$0.00001 par value per share; 200,000,000 shares authorized and 63,473,349 and 63,207,507 issued and outstanding as of March 31, 2023 and December 31, 2022, respectively	1	1
Additional paid-in capital	404,114	402,389

Accumulated deficit	(419,063)	(401,441)
Total stockholders' (deficit) equity	(14,948)	949
Total liabilities, convertible preferred stock, and stockholders' (deficit) equity	\$ 101,600	\$ 126,276

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Source: Taysha Gene Therapies, Inc.



Taysha Gene Therapies Reports Initial Clinical Data from First Adult Rett Syndrome Patient Dosed in REVEAL Phase 1/2 Trial and Provides Corporate Update with Second Quarter 2023 Financial Results

Data from first adult patient dosed in REVEAL Phase 1/2 trial showed TSHA-102 was well-tolerated with no treatment-emergent serious adverse events (SAEs) as of six-week assessment and improvement in key efficacy measures, including Clinical Global Impression – Improvement (CGI-I), Clinical Global Impression – Severity (CGI-S) and Rett Syndrome Behavior Questionnaire (RSBQ), four weeks post-treatment

Principal Investigator (PI) observed clinical improvement in multiple domains, including autonomic function (sleep and breathing), vocalization, as well as gross motor skills (gained ability to sit unassisted for three minutes) and fine motor skills (gained ability to hold objects), supported by initial clinical data and video evidence

United States (U.S.) Food and Drug Administration (FDA) cleared the Investigational New Drug (IND) application for TSHA-102 in pediatric patients with Rett syndrome

Clinical Trial Application (CTA) submitted to the United Kingdom (U.K.) Medicines and Healthcare products Regulatory Agency (MHRA) for TSHA-102 in pediatric patients with Rett syndrome

Private placement financing ("PIPE") is expected to result in gross proceeds of approximately \$150 million from new and existing investors and, net proceeds from PIPE, along with existing cash and cash equivalents, extends cash runway into the third quarter of 2025

Conference call and live webcast today at 8:30 AM Eastern Time

DALLAS, Aug. 14, 2023 (GLOBE NEWSWIRE) -- Taysha Gene Therapies, Inc. (Nasdaq: TSHA), a clinical-stage gene therapy company focused on developing and commercializing AAV-based gene therapies for the treatment of monogenic diseases of the central nervous system (CNS), today reported financial results for the second quarter ended June 30, 2023, and provided a corporate update.

"We are pleased with the progress we have made this quarter in the clinical evaluation of our two lead investigational programs. For TSHA-102 in Rett syndrome, we believe the initial safety profile and significant clinical improvements seen in the first adult patient with severe disease four weeks post-treatment reinforces the transformative potential of our gene therapy to address the root cause of Rett syndrome. Importantly, these early data indicate that the miRNA-Responsive Auto-Regulatory Element (miRARE) technology is mediating *MECP2* expression in the CNS on a cell-by-cell basis, supporting the regulatory control of miRARE. We are highly encouraged by the initial data for TSHA-102 and are focused on continuing to explore its therapeutic potential, with the dosing of the second patient expected in the third quarter. We also received FDA clearance to initiate clinical development of TSHA-102 in pediatric patients in the U.S. and have submitted a CTA to the MHRA for TSHA-102 in pediatric patients with Rett syndrome, which will expand our clinical evaluation to children with earlier stages of disease progression," said Sean P. Nolan, Chairman and Chief Executive Officer of Taysha. "For TSHA-120 in GAN, our new comprehensive data analysis utilizing the Disease Progression Model (DPM) was submitted to the FDA, and we plan to review the potential regulatory pathway for TSHA-120 with the Agency expected in the third quarter."

Mr. Nolan continued, "Our successful completion of a \$150 million PIPE from top-tier investors significantly bolsters our balance sheet and we believe highlights the enthusiasm for our TSHA-102 program and the early clinical readout of the first patient treated in the REVEAL trial. By extending our cash runway into the third quarter of 2025, we can focus on execution as we endeavor to deliver on key value-creating milestones."

Dr. Elsa Rossignol, M.D., FRCP, FAAP, Associate Professor Neuroscience and Pediatrics at CHU Sainte-Justine, affiliated to the Université de Montréal, and Principal Investigator of the REVEAL trial added, "The efficacy response observed following treatment with TSHA-102 in the first adult with an advanced stage of Rett syndrome is promising. Prior to treatment, the patient was in a constant state of hypertonia, had limited body movement, required constant back support, and had lost fine and gross motor function early in childhood. Following treatment, we have observed improvements in breathing patterns, vocalization and motor skills. The patient was able to sit unassisted for the first time in over a decade, and she demonstrated the ability to unclasp her hands and hold an object steadily for the first time since infancy. I believe that the patient achieving these milestones so early in treatment, coupled with the improvements in breathing patterns and quality of sleep that we have observed, are highly encouraging and support the potential of TSHA-102. I am honored to work with the Rett syndrome community and help patients and families suffering from this devastating disease."

Rett syndrome is a rare neurodevelopmental disorder caused by mutations in the X-linked *MECP2* gene. The disorder is characterized by intellectual disabilities, loss of communication, seizures, slowing and/or regression of development, motor and respiratory impairment, and shortened life expectancy. Rett syndrome caused by a pathogenic/likely pathogenic *MECP2* mutation is estimated to affect between 15,000 and 20,000 patients in the U.S., EU and UK.

Recent Corporate Highlights

\$150 million private placement financing strengthens balance sheet and, together with existing cash and cash equivalents, extends cash runway into the third quarter of 2025

- Private placement led by new investor, RA Capital Management, with participation from a large institutional investor, PBM

Capital, RTW Investments, LP, Venrock Healthcare Capital Partners, TCGX, Acuta Capital Partners, Kynam Capital Management, LP, Octagon Capital, Invus, GordonMD® Global Investments LP, and B Group Capital

- Cash runway expected to fund operational plans into the third quarter of 2025
- Net proceeds to primarily fund clinical development of TSHA-102 in Rett syndrome and provide support for program activities for TSHA-120 in GAN, working capital, and other general corporate purposes

Recent Clinical Highlights

TSHA-102 in Rett syndrome: a self-complementary intrathecally delivered AAV9 gene transfer therapy in clinical evaluation for Rett syndrome, a rare genetic neurodevelopmental disorder caused by mutations in the X-linked *MECP2* gene. TSHA-102 utilizes a novel miRARE platform designed to mediate levels of *MECP2* in the CNS on a cell-by-cell basis without risk of overexpression. TSHA-102 has received Orphan Drug and Rare Pediatric Disease designations from the FDA and has been granted Orphan Drug designation from the European Commission.

TSHA-102 is being evaluated in the [REVEAL Phase 1/2 trial](#), a first-in-human, open-label, randomized, dose-escalation and dose-expansion study evaluating the safety and preliminary efficacy of TSHA-102 in adult females with Rett syndrome due to *MECP2* loss-of-function mutation. Primary efficacy endpoints are patient assessments by clinicians using the Clinical Global Impressions Scale – Improvement (CGI-I), Rett Syndrome Hand Function Scale, and Revised Motor Behavior Assessment (R-MBA). Secondary endpoints include patient assessments by clinicians and caregivers using the Clinical Global Impressions Scale – Severity (CGI-S), the Rett Syndrome Behavior Questionnaire (RSBQ) and other clinical assessment scales.

Results from the first adult patient dosed in cohort one (low dose) with TSHA-102 in the REVEAL Phase 1/2 trial:

- Well-tolerated safety profile with no treatment-emergent SAEs as of six-week assessment post-treatment
- The following were demonstrated in key efficacy measures four weeks post-treatment:
 - Clinical Global Impressions – Improvement (CGI-I) scale adapted to Rett syndrome, a clinician-reported assessment of overall improvement using a seven-point scale (one=“very much improved” and seven=“very much worse”), demonstrated a score of two indicating “much improved”
 - Clinical Global Impressions – Severity (CGI-S) scale, a clinician-reported assessment of overall severity of a patient’s illness using a seven-point scale, demonstrated a one-point improvement from the baseline score of six (“severely ill”) to a score of five (“markedly ill”)
 - Rett Syndrome Behavior Questionnaire (RSBQ), a 45-item questionnaire to assess Rett syndrome characteristics, demonstrated a total score improvement of 23 points from the baseline score of 52 to a score of 29
- Seizure diary demonstrated no quantifiable seizure events through week five post-treatment
- No marked changes observed four weeks post-treatment in the Revised Motor Behavior Assessment (R-MBA), a 24-question clinician-reported scale measuring disease behaviors of Rett syndrome
- Initial efficacy data and clinical observations supported by video evidence from PI six-weeks post-treatment indicate clinical improvements in multiple domains, including:
 - Autonomic function with improvements in breathing patterns and sleep quality/duration, including the normalization of night-time behavior
 - Vocalization with increased social interest
 - Gross motor skills with the gained ability to sit unassisted for three minutes
 - Fine motor skills and hand function with the gained ability to hold an object, unclasp her hands and use her fingers to touch a screen
- Further updates on available clinical data expected quarterly
- Dosing of second patient cleared by the Independent Data Monitoring Committee (IDMC) and expected in Q3 2023, with continued dosing of adult patients in second half of 2023
- U.S. FDA cleared the IND application for TSHA-102 in pediatric patients with Rett syndrome
- CTA submitted to U.K. MHRA for TSHA-102 in pediatric patients with Rett syndrome

TSHA-120 for giant axonal neuropathy (GAN): a self-complementary intrathecally delivered AAV9 gene therapy in clinical evaluation for GAN, an ultra-rare inherited genetic neurodegenerative disorder with no approved treatments. TSHA-120 has received Orphan Drug and Rare Pediatric Disease designations from the FDA and has been granted Orphan Drug designation from the European Commission.

- At R&D Day in June 2023, Taysha provided an overview of new comprehensive data analysis and development of disease

progression model (DPM), which the Company believes has the potential to address FDA feedback regarding the heterogeneity of GAN and effort-dependent nature of MFM32 as the primary endpoint in an unblinded study

- New comprehensive data analysis utilizing the DPM submitted as meeting request to the FDA; feedback for a potential regulatory pathway for TSHA-120 expected in Q3 2023
- FDA feedback on CMC module 3 amendment concluded that the analytical data is sufficient to support the comparability of pivotal lot and release for use in clinical studies

Second Quarter 2023 Financial Highlights

Research and Development Expenses: Research and development expenses were \$19.8 million for the three months ended June 30, 2023, compared to \$23.5 million for the three months ending June 30, 2022. The \$3.7 million decrease was due to lower compensation expense as a result of reduced headcount and fewer manufacturing batches and raw material purchases.

General and Administrative Expenses: General and administrative expenses were \$6.0 million for the three months ended June 30, 2023, compared to \$9.9 million for the three months ended June 30, 2022. The decrease of \$3.9 million was due to reduced general and administrative compensation as a result of lower headcount, consulting and professional fees.

Net loss: Net loss for the three months ended June 30, 2023 was \$24.6 million or \$0.38 per share, as compared to a net loss of \$34.1 million, or \$0.85 per share, for the three months ended June 30, 2022.

Cash and cash equivalents: As of June 30, 2023, Taysha had \$45.1 million in cash and cash equivalents. Taysha expects to receive gross proceeds of \$150 million from the Private Placement, which is expected to close August 16, 2023, before deducting placement agent commissions and offering expenses. The net proceeds from the private placement, combined with the current cash and cash equivalents, are expected to fund its operational plans and capital requirements into the third quarter of 2025.

Conference Call and Webcast Information

Taysha management will hold a conference call and webcast today at 8:30 a.m. ET to review its financial and operating results and to provide a corporate update. The dial-in number for the conference call is 877-407-0792 (U.S./Canada) or 201-689-8263 (international). The conference ID for all callers is 13740092. The live webcast can be accessed here: https://viavid.webcasts.com/starthere.jsp?ei=1624983&tp_key=25b742b70a. An archived version of the webcast will be available for 30 days and can be accessed by visiting Taysha's website at <https://ir.tayshagtx.com/news-events/events-presentations>.

About Taysha Gene Therapies

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Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Words such as "anticipates," "believes," "expects," "intends," "projects," "plans," and "future" or similar expressions are intended to identify forward-looking statements. Forward-looking statements include statements concerning the potential of our product candidates, including the reproducibility and durability of any favorable results initially seen in our first patient dosed in the REVEAL trial and including our preclinical product candidates, to positively impact quality of life and alter the course of disease in the patients we seek to treat, our research, development and regulatory plans for our product candidates, the potential for these product candidates to receive regulatory approval from the FDA or equivalent foreign regulatory agencies, and whether, if approved, these product candidates will be successfully distributed and marketed, the potential market opportunity for these product candidates, our corporate growth plans, statements associated with the timing, size and completion of the Private Placement, the forecast of our cash runway and the Company's expectations regarding funding, operating and working capital expenditures. Forward-looking statements are based on management's current expectations and are subject to various risks and uncertainties that could cause actual results to differ materially and adversely from those expressed or implied by such forward-looking statements. Accordingly, these forward-looking statements do not constitute guarantees of future performance, and you are cautioned not to place undue reliance on these forward-looking statements. Risks regarding our business are described in detail in our Securities and Exchange Commission ("SEC") filings, including in our Annual Report on Form 10-K for the full-year ended December 31, 2022, and our Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, both of which are available on the SEC's website at www.sec.gov. Additional information will be made available in other filings that we make from time to time with the SEC. Such risks may be amplified by the impacts of the COVID-19 pandemic. These forward-looking statements speak only as of the date hereof, and we disclaim any obligation to update these statements except as may be required by law.

**Taysha Gene Therapies, Inc.
Condensed Consolidated
Balance Sheet Data**
(in thousands, except share and per share data)
(Unaudited)

December 31,
June 30, 2023
2022

ASSETS

Current assets:			
Cash and cash equivalents	\$ 45,083	\$ 87,880	
Prepaid expenses and other current liabilities	9,032	8,537	
Total current assets	54,115	96,417	

Restricted cash	2,637	2,637
Property, plant and equipment, net	14,139	14,963
Operating lease right-of-use assets	10,348	10,943
Other non-current assets	304	1,316
Total assets	\$ 81,543	\$ 126,276

LIABILITIES AND STOCKHOLDERS' (DEFICIT) EQUITY

Current liabilities:			
Accounts payable	\$ 10,766	\$ 10,946	
Accrued expenses and other current liabilities	19,631	18,287	
Deferred revenue	26,909	33,557	
Total current liabilities	50,641	62,790	
Deferred revenue, net of current portion	6,212		
Term loan, net	38,354	37,967	
Operating lease liability, net of current portion	19,528	20,440	
Other non-current liabilities	3,922	4,130	
Total liabilities	118,657	125,327	

Stockholders' (deficit) equity

Preferred stock, \$0.00001 par value per share; 10,000,000 shares authorized and no shares issued and outstanding as of June 30, 2023 and December 31, 2022

Common stock, \$0.00001 par value per share; 200,000,000 shares authorized and 64,432,637 and 63,207,507 issued and outstanding as of June 30, 2023, and December 31, 2022, respectively	1	1
Additional paid-in capital	406,546	402,389
Accumulated deficit	(443,661)	(401,441)
Total stockholders' (deficit) equity	(37,114)	949
Total liabilities and stockholders' (deficit) equity	\$ 81,543	\$ 126,276

Taysha Gene Therapies, Inc.
Condensed Consolidated Statements of Operations
(in thousands, except share and per share data)
(Unaudited)

	For the three months ended June 30, 2023	For the three months ended June 30, 2022	For the six months ended June 30, 2023	For the six months ended June 30, 2022
Revenue:				
Service Revenue	\$ 2,395	\$ -	\$ 7,101	\$ -
Operating expenses:				
Research and development	19,791	23,506	32,305	61,688
General and administrative	5,988	9,867	14,739	21,336
Total operating expenses	25,779	33,373	47,044	83,024
Loss from operations	(23,384)	(33,373)	(39,943)	(83,024)
Other income (expense):				
Interest Income	223	27	542	41
Interest expense	(1,440)	(743)	(2,814)	(1,415)
Other expense	3	(3)	(5)	(11)
Total other income (expense)	(1,214)	(719)	(2,277)	(1,385)
Net loss	\$ (24,598)	\$ (34,092)	\$ (42,220)	\$ (84,409)
Net loss per common share, basic and diluted	\$ (0.38)	\$ (0.85)	\$ (0.66)	\$ (2.16)
Weighted average common shares outstanding, basic and diluted	64,244,531	40,142,403	63,755,435	39,163,996

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Source: Taysha Gene Therapies, Inc.



Bringing New Cures to Life

CLN1 Disease Investor Day

August 30, 2021 | 9:00 – 11:30 AM CT

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Legal disclosure

FORWARD LOOKING STATEMENTS

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

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

Introduction



RA Session II

President, Founder & CEO

Unparalleled gene therapy pipeline focused exclusively on monogenic CNS disorders

PROGRAM	INDICATION	DISCOVERY	PRECLINICAL	PHASE 1/2	Pivotal	GLOBAL COMM. RIGHTS
NEURODEGENERATIVE DISEASES						
TSHA-120	GRT	Giant Axonal Neuropathy	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>	Regulatory guidance YE 2021	
TSHA-101	GRT	GM2 Gangliosidosis	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>	Currently open CTA	
TSHA-118	GRT	CLN1 Disease	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>	Currently open IND	
TSHA-119	GRT	GM2 AB Variant	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>		
TSHA-104	GRT	SURF1-Associated Leigh Syndrome	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>	IND/CTA submission 2H 2021	
TSHA-112	miRNA	APBD	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>		
TSHA-111-LAFORIN	miRNA	Lafora Disease	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>		
TSHA-111-MALIN	miRNA	Lafora Disease	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>		
TSHA-113	miRNA	Tauopathies	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>		
TSHA-115	miRNA	GSDs	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>		
Undisclosed	GRT/shRNA	Undisclosed	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>		
Undisclosed	GRT	Undisclosed	<div style="width: 100%; background-color: #00AEEF;"></div>	<div style="width: 100%; background-color: #00AEEF;"></div>		
NEURODEVELOPMENTAL DISORDERS						
TSHA-102	Regulated GRT	Rett Syndrome	<div style="width: 100%; background-color: #FFB703;"></div>	<div style="width: 100%; background-color: #FFB703;"></div>	IND/CTA submission 2H 2021	
TSHA-106	shRNA	Angelman Syndrome	<div style="width: 100%; background-color: #FFB703;"></div>	<div style="width: 100%; background-color: #FFB703;"></div>		
TSHA-114	GRT	Fragile X Syndrome	<div style="width: 100%; background-color: #FFB703;"></div>	<div style="width: 100%; background-color: #FFB703;"></div>		
TSHA-116	shRNA	Prader-Willi Syndrome	<div style="width: 100%; background-color: #FFB703;"></div>	<div style="width: 100%; background-color: #FFB703;"></div>		
TSHA-117	Regulated GRT	FOXP1 Syndrome	<div style="width: 100%; background-color: #FFB703;"></div>	<div style="width: 100%; background-color: #FFB703;"></div>		
TSHA-107	GRT	Autism Spectrum Disorder	<div style="width: 100%; background-color: #FFB703;"></div>	<div style="width: 100%; background-color: #FFB703;"></div>		
TSHA-108	GRT	Inborn Error of Metabolism	<div style="width: 100%; background-color: #FFB703;"></div>	<div style="width: 100%; background-color: #FFB703;"></div>		
TSHA-109	GRT	Inherited Metabolism Disorder	<div style="width: 100%; background-color: #FFB703;"></div>	<div style="width: 100%; background-color: #FFB703;"></div>		
Undisclosed	GRT	Undisclosed	<div style="width: 100%; background-color: #FFB703;"></div>	<div style="width: 100%; background-color: #FFB703;"></div>		
Undisclosed	mini-gene	Undisclosed	<div style="width: 100%; background-color: #FFB703;"></div>	<div style="width: 100%; background-color: #FFB703;"></div>		
GENETIC EPILEPSY						
TSHA-103	GRT	SLC6A1 Haploinsufficiency Disorder	<div style="width: 100%; background-color: #6AA84F;"></div>	<div style="width: 100%; background-color: #6AA84F;"></div>		
TSHA-105	GRT	SLC13A5 Deficiency	<div style="width: 100%; background-color: #6AA84F;"></div>	<div style="width: 100%; background-color: #6AA84F;"></div>		
TSHA-110	mini-gene	KCNQ2	<div style="width: 100%; background-color: #6AA84F;"></div>	<div style="width: 100%; background-color: #6AA84F;"></div>		
Undisclosed	mini-gene	Undisclosed	<div style="width: 100%; background-color: #6AA84F;"></div>	<div style="width: 100%; background-color: #6AA84F;"></div>		

TAYSHA
GENE THERAPIES

TAYSHA
GENE THERAPIES

TAYSHA
GENE THERAPIES



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

Investor Mini-Series

TSHA-118 CLN1 Disease Investor Day

August 2021

TSHA-102 Rett Syndrome Investor Day

September 2021

TSHA-106 Angelman Syndrome Investor Day

October 2021

Agenda

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

Speaker biographies



Angela Schulz, MD, PhD

Head of NCL Specialty Clinic, University Medical Center Hamburg-Eppendorf

- Specialist in pediatric and adolescent medicine, with expertise in palliative medicine and neuropediatrics
- Research is focused on neurodegenerative brain diseases, and is the PI for clinical study: Natural History and Longitudinal Clinical Assessments in NCLs/Batten Disease, International DEM-CHILD Database



Sharon King

President of Taylor's Tale

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



Steven Gray, PhD

Associate Professor Department of Pediatrics at UTSW and Chief Scientific Advisor to Taysha

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



Suyash Prasad, MBBS, MSc, MRCP, MRCGPCH, FFPM

Chief Medical Officer and Head of Research and Development at Taysha

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

Disease Overview and Natural History



Angela Schulz, MD, PhD

*Head of NCL Specialty Clinic
University Medical Center Hamburg-Eppendorf*



Neuronal Ceroid Lipofuscinoses – CLN1 Disease

Angela Schulz, MD PhD



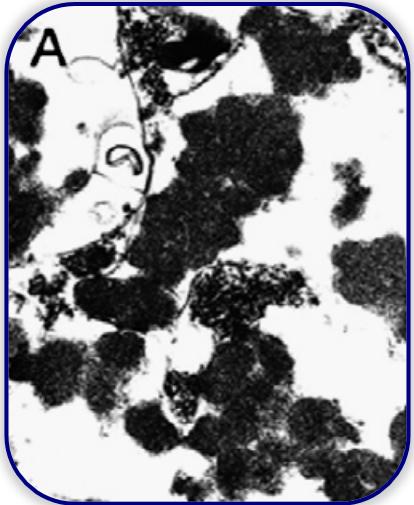
Coordination of international DEM-CHILD
patient database for all NCLs

In- and outpatient clinic:

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

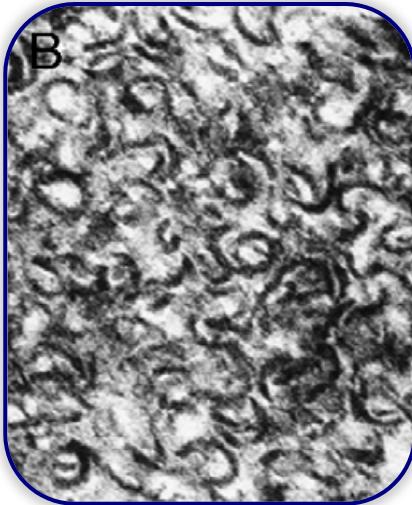
- 83 patients with CLN2 (of those 52 on ERT)
- 48 patients with CLN3
- 16 patients with CLN1
- 45 patients with CLN5, CLN6, CLN7, CLN8
- Overall data on >250 NCL patients

Lysosomal storage material in NCL disorders



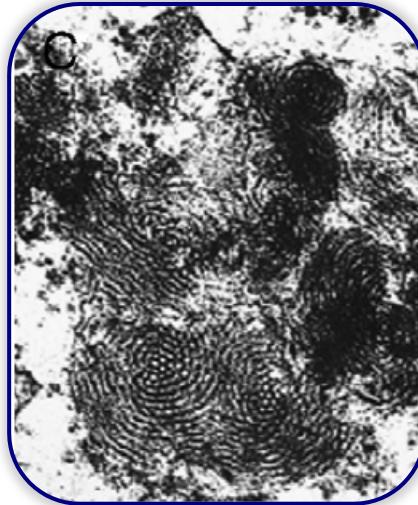
Granular

CLN1



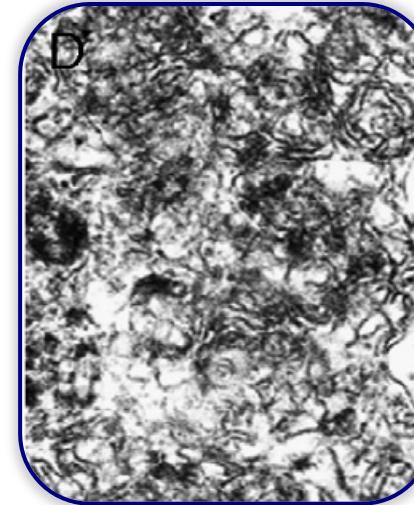
Curvilinear

CLN2



Fingerprint

CLN3

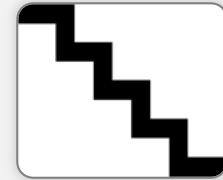


Other

Growing number of NCL disorders

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

Their clinical hallmark is the combination of



Dementia



Visual loss due
to retinopathy



Epilepsy

NCL: The most frequent cause of dementia in young persons

New classification of NCL disorders

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

<i>Designation of disease</i>		
<i>Genetic type</i>	<i>Mutated gene</i>	<i>Clinical type (age of onset)</i>
• CLN1	• CLN1 disease	<ul style="list-style-type: none">• Congenital (at birth)• Infantile (6 to 24 months)• Late infantile (2 to 5 years)• Juvenile (5-7 years)• Adult
<i>Example:</i> CLN2 disease, late infantile		

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

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

*GRN mutations also in „Frontotemporal lobar degeneration with TDP43 inclusions“ MIM #607485

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

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

Disease

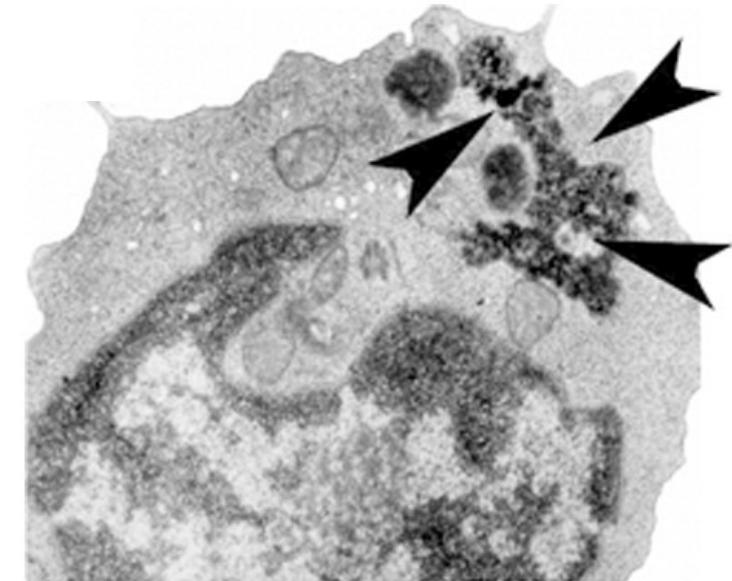
- Deficiency of lysosomal enzyme palmitoyl-protein thioesterase 1 (PPT1)
- Caused by mutations in the *CLN1* gene (> 70 pathogenic mutations)
- Autosomal recessive inheritance

Pathology

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

Laboratory diagnosis

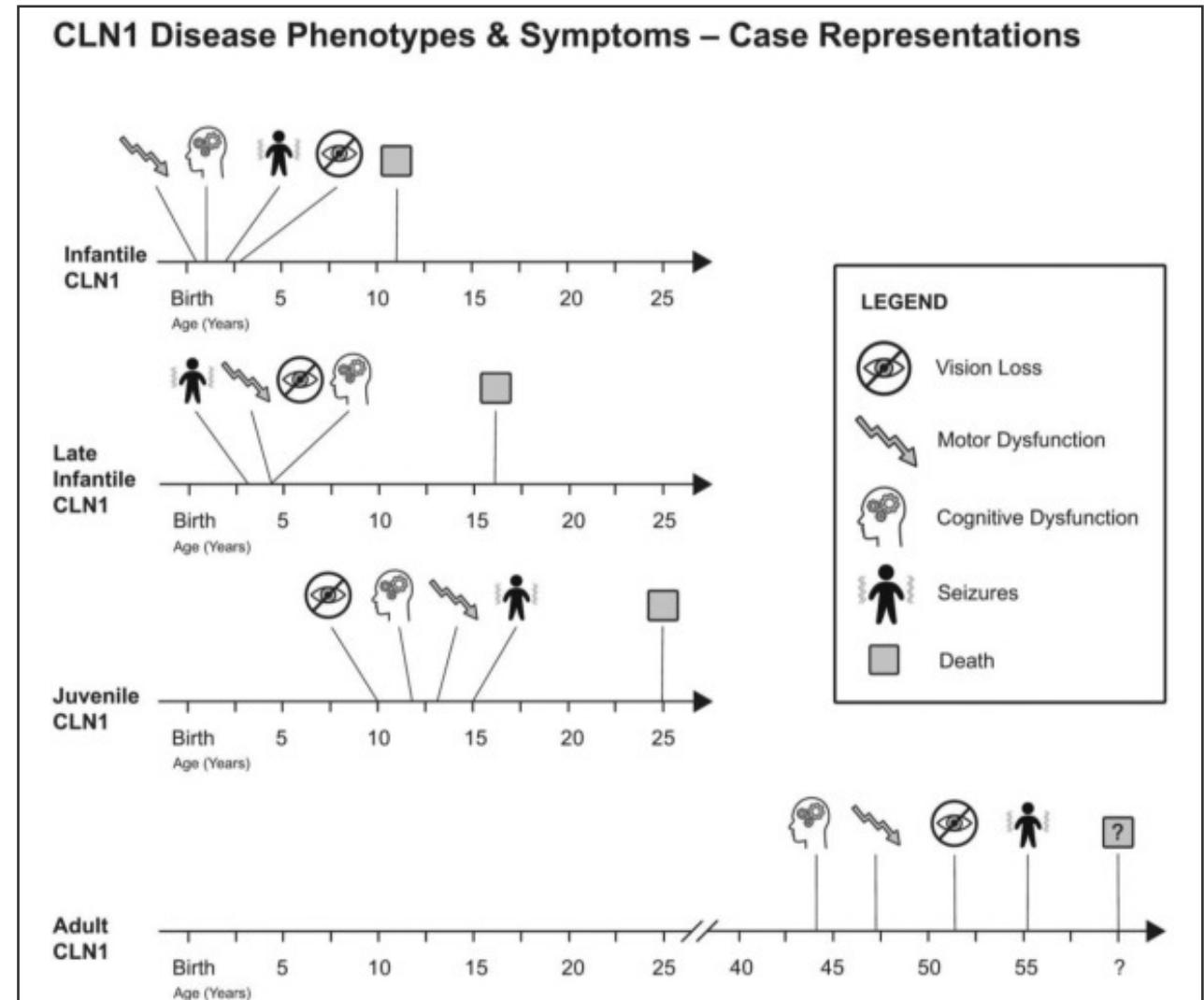
- Measurement of PPT1 enzyme activity in dry blood spots, leucocytes, fibroblasts
- Genetic detection of pathogenic mutation of both alleles of *CLN1* gene
- Electronmicroscopic detection of granular deposits in lysosomes in skin biopsy

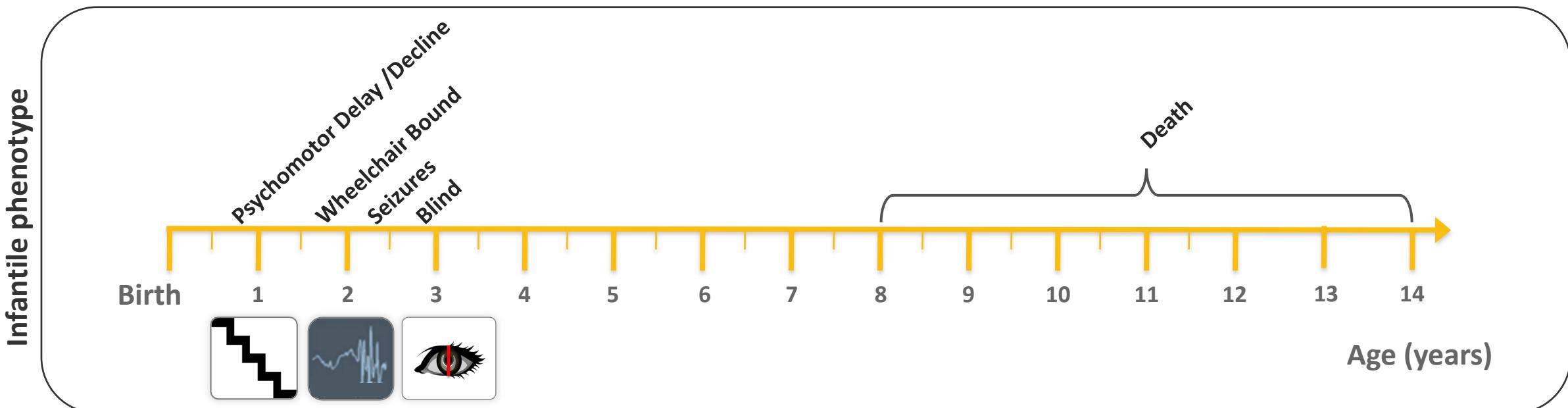
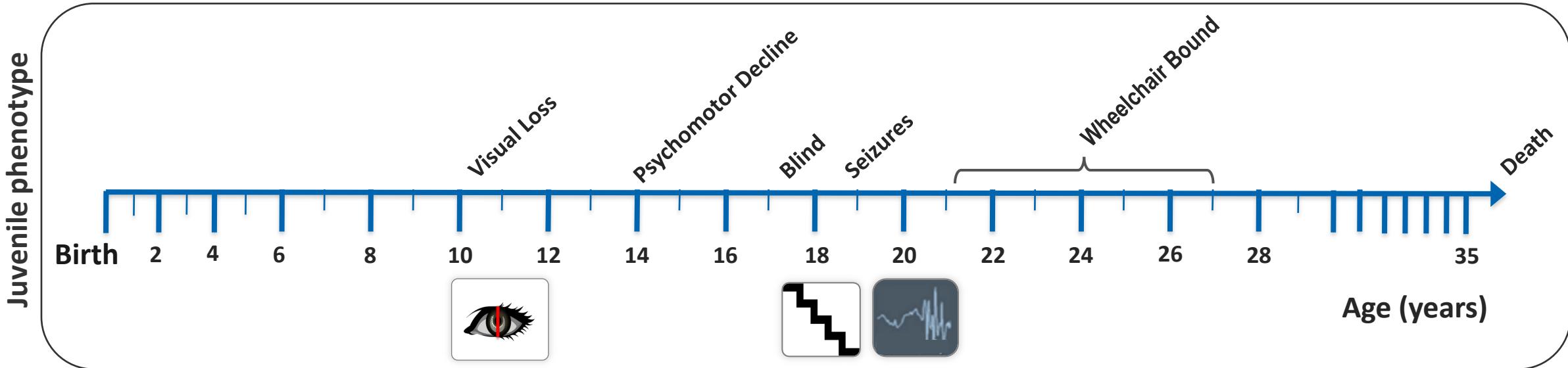


Compact granular osmiophilic deposits (GROD) in a lymphocyte, infantile NCL

Phenotype	Typical age at symptom onset	Type of first symptom	Rate of progression	Clinical features (order of appearance)
Infantile	6 – 18 months	Psychomotor developmental delay	Rapid	<ul style="list-style-type: none"> • Psychomotor delay (<i>age 12-18 months</i>) • Max motor function: Standing with support • Max language function: Single words • Rapid cognitive and motor decline (<i>age 18 months</i>) • Wheelchair bound (<i>age 24-30 months</i>) • Muscle hypotonia, ataxia, myoclonus • Epileptic seizures (<i>age 24-30 months</i>) • Vision loss (<i>age 24 - 36 months</i>)
Late infantile	>18 months – 4 years	Epilepsy plus psychomotor decline	Rapid	<ul style="list-style-type: none"> • Seizures (<i>age 2-4 years</i>) • Rapid cognitive and motor decline (<i>age 2 – 4 years</i>) • Seizures (<i>age 2-4 years</i>) • Vision loss (<i>age 4-6 years</i>)
Juvenile	>4 years – early adolescence	Vision loss	Slow	<ul style="list-style-type: none"> • Normal psychomotor development until <i>age 8-12 years</i> • Vision loss starting (<i>age 6-10 years</i>) • Cognitive decline (<i>age 8-12 years</i>) • Epileptic seizures (<i>age 10-12 years</i>) • Motor decline (<i>age 12-14 years</i>)
Adult	Late adolescence and older		Protracted	<ul style="list-style-type: none"> • Cognitive decline • Psychiatric problems, depression • Vision loss • Motor problems: ataxia, parkinsonism

- CLN1 disease phenotypes vary by
 - Age at onset
 - Order of symptom onset
 - Rate of disease progression
 - Life expectancy
- Infantile and juvenile phenotypes are the most prevalent ones to date
- Strong genotype-phenotype correlations for certain *CLN1* mutations







Age 12 months

Age 18 months

Age 2 years

Age 3 years

Age 5 years

Age 6 years



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



complex clinical picture
suggestive of pain!

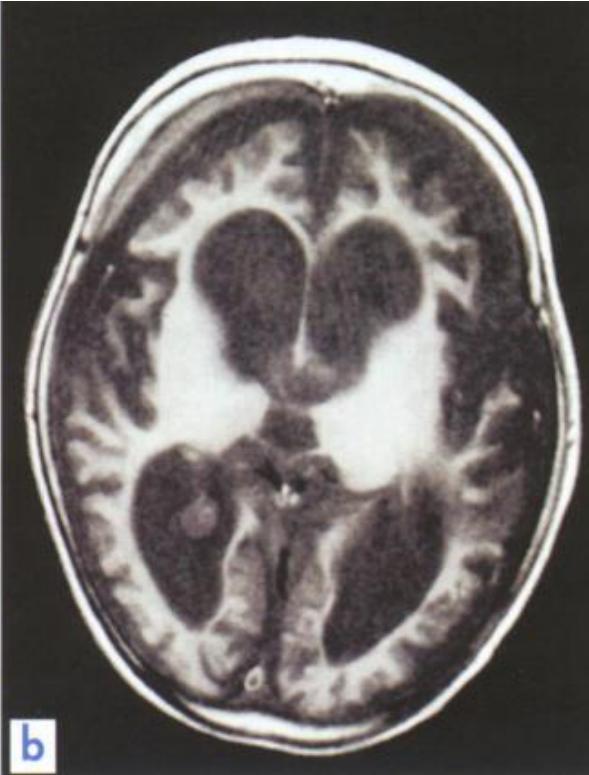
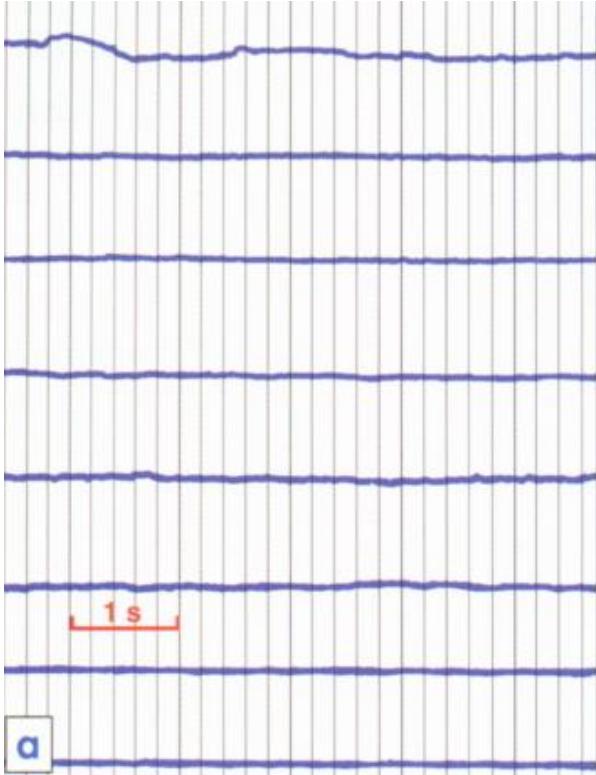


MOST kids with severe rare neurological diseases cannot communicate and suffer from sleep disturbances and restlessness during day



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

Age: 4 years

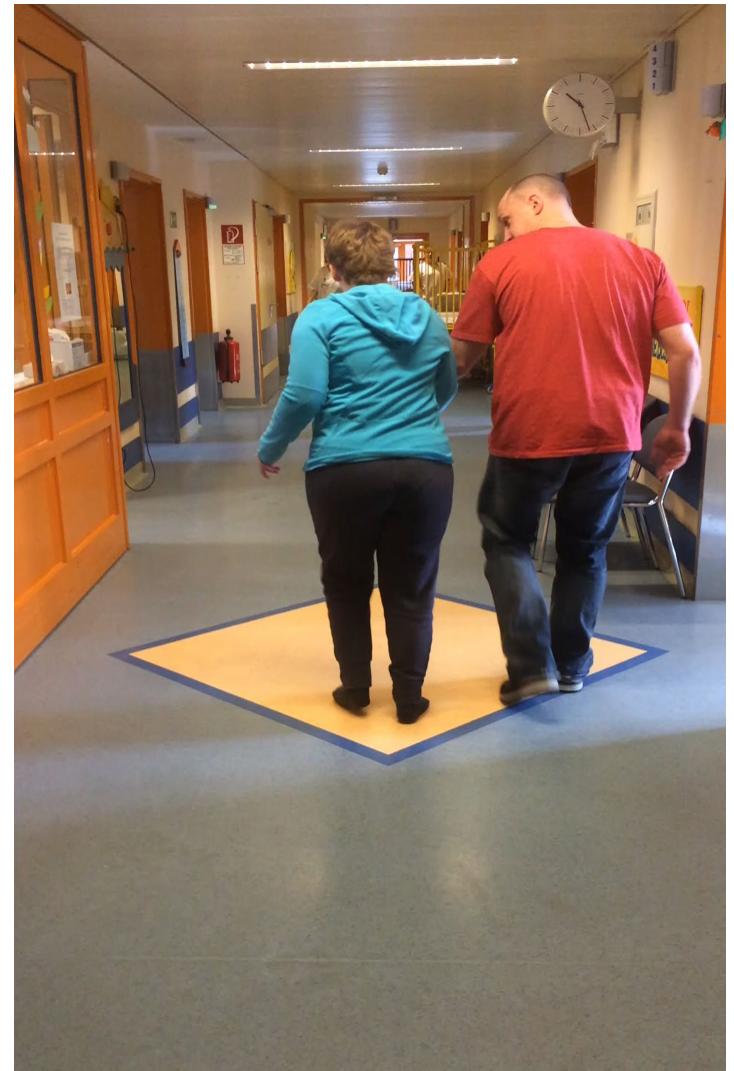


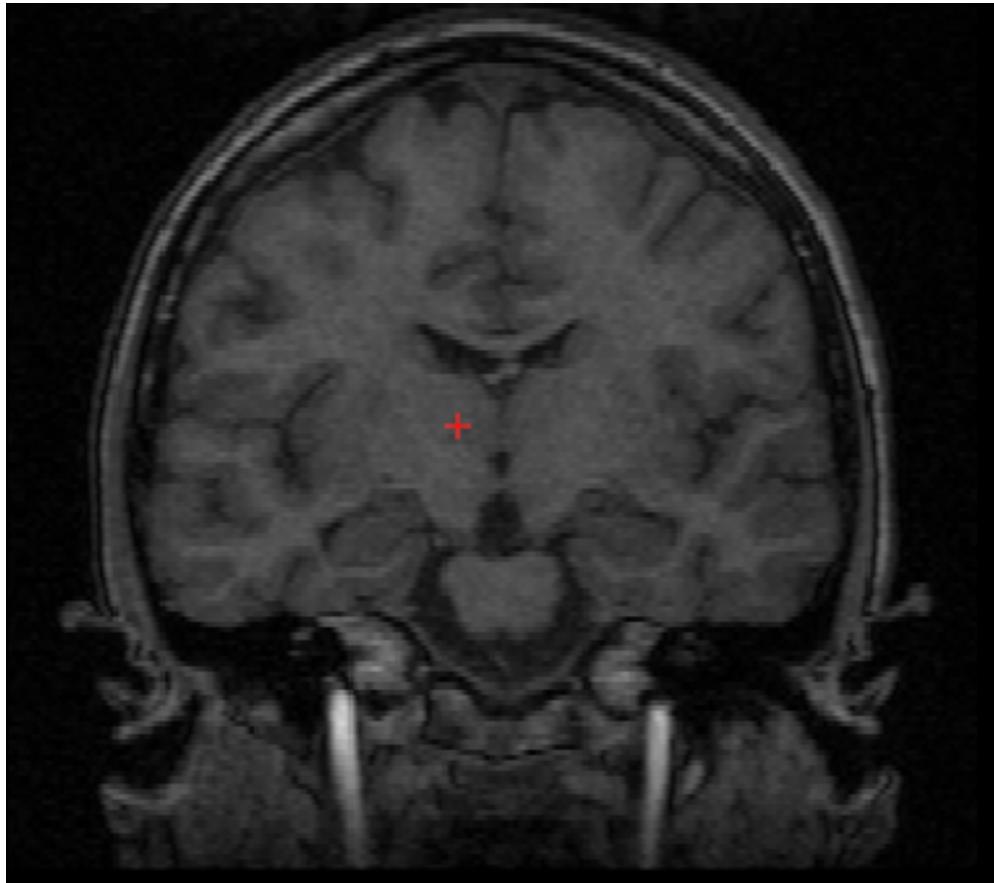
EEG: No activity



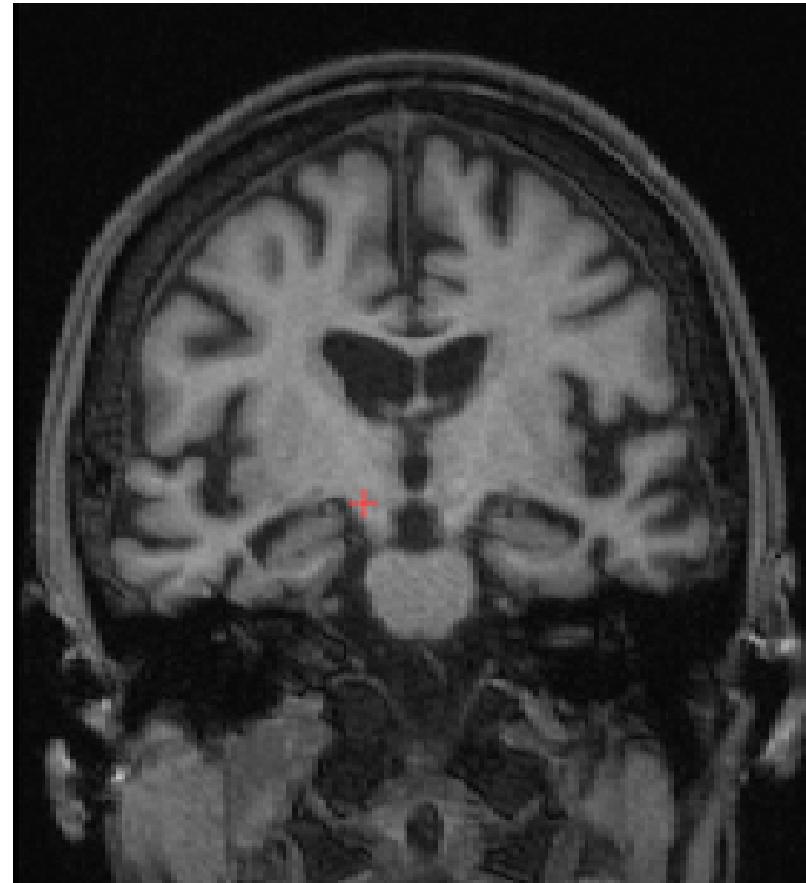
Severe brain atrophy

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





11 years



18 years



Limited number of patients



Phenotype variability



Need for reliable clinical outcome measures / clinical biomarkers



Use of natural history control data in clinical trials

**Norway**

Ingrid Helland, MD
Oslo University Hospital

**Denmark**

Jon R. Ostergaard, MD
Aarhus University Hospital

**Sweden**

Niklas Darin MD PhD
The Queen Silvia Children's Hospital, Gothenburg

**Poland**

Tomas Kmiec MD
Children's Memorial Health Institute, Warsaw

**Netherlands**

Hippe Huidekoper, MD PhD
Erasmus Medical Center, Rotterdam

Claudia van Alfen, MD
Bartiméus Center, Dorn

**Turkey**

Meral Topcu, MD PhD
University Children's Hospital, Ankara

**Serbia**

Ruzica Kravljanc MD
University of Belgrade Medical Faculty, Belgrade

**Lebanon**

Rose-Mary Boustany MD PhD
American University of Beirut

**France**

Catherine Caillaud MD PhD
INSERM, Paris

**Spain**

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Hospital Universitario Marqués de Valdecilla,
Santander

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University of Verona

Nicola Specchio MD
Ospedale Bambino Gesù, Rome

**UK**

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GSTT, London

Paul Gissen MD
Great Ormond Street Hospital

**Finland**

Laura Aberg
Folkhälsan, Helsinki

**India**

Pratibha Singh, MD
PGIMER, Chandigarh

**Japan**

Eto Yoshikatsu, MD PhD
Tokyo Medical University

**Argentina**

Ines Noher de Halac, MD
Universidad Nacional de Córdoba

**Brazil**

Charles Lourenco, MD PhD
University of São Paulo

**USA**

Ron Crystal, MD PhD
Weill Cornell Medical College, New York

**Argentina**

Jonathan Mink, MD PhD
University of Rochester

**Brazil**

Emily de los Reyes, MD
Nationwide Children's Hospital, Columbus

**India**

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

**USA**

Kathryn Swoboda, MD
Massachusetts General Hospital, Boston

19 countries and 26 centers

International collaboration

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

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

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

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



Limited number of patients



Phenotype variability



Need for reliable clinical outcome measures / clinical biomarkers



Use of natural history control data in clinical trials

Late Infantile NCL Scale

Functional Category
Motor function
Language
Visual function
Seizures

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

Juvenile NCL Scale

Functional Category
Motor function
Language
Visual function
Intellect
Seizures

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

Each functional category**Scored from 0-3**

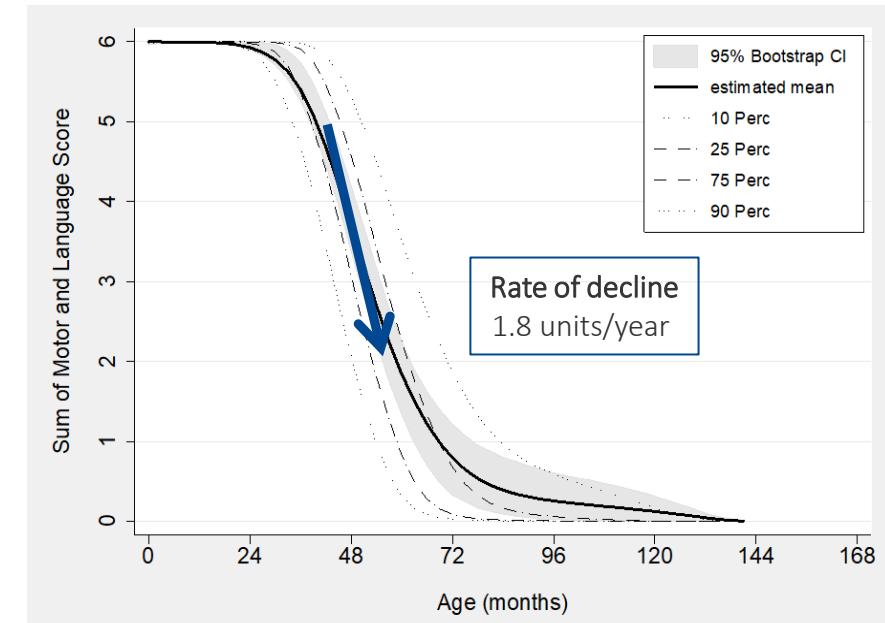
Normal function	= SCORE 3
Slightly abnormal	= SCORE 2
Severely abnormal	= SCORE 1
No function left	= SCORE 0

Advantages

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

Example Hamburg LINCL scale:

Longitudinal assessment of 41 CLN2 patients



Unified Batten Disease Rating Scale

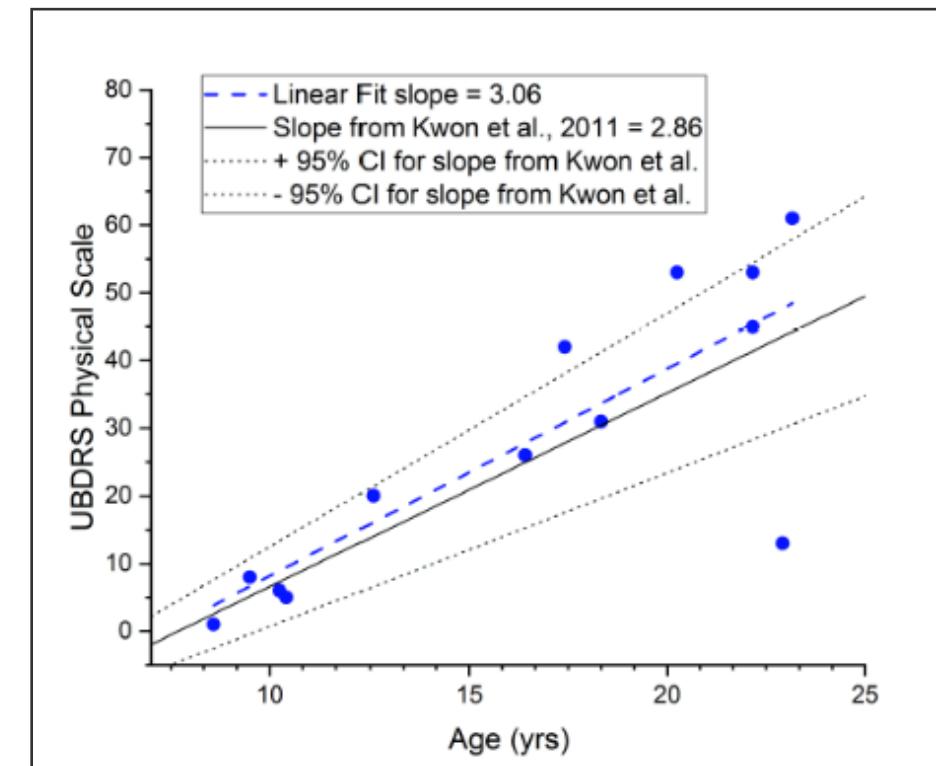
- Developed by J. Mink, Rochester
- **Teaching is important** to ensure good inter-rater reliability
- **Prospective use only**
- **Detailed description** of juvenile NCL phenotypes
- **Needs adaption / selection of parameters for infantile NCL phenotypes**

Hamburg-Rochester Rater Training by J. Mink

ICC Analysis Demonstrated Excellent Inter-Rater Reliability

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

B	C	D	E
0.99	0.99	0.99	0.99



Infantile CLN1 Disease

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

Development of the Hamburg infantile CLN1 score

Supported by



Infantile NCL Scale

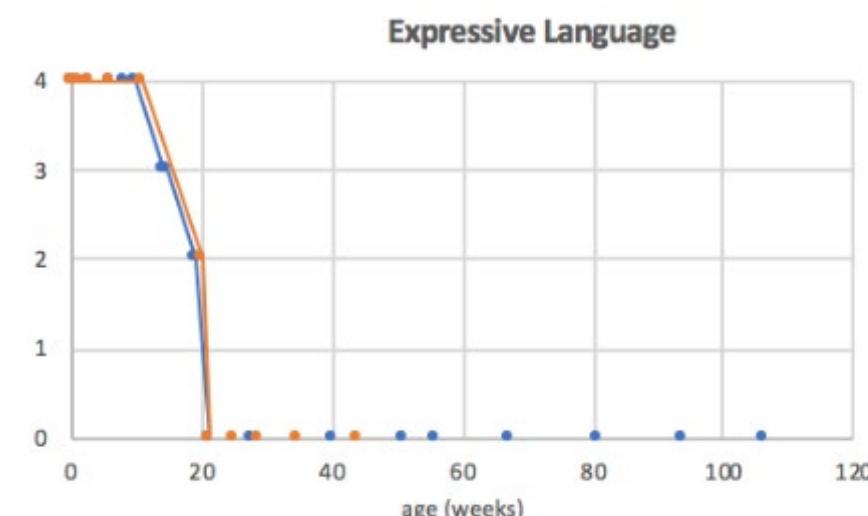
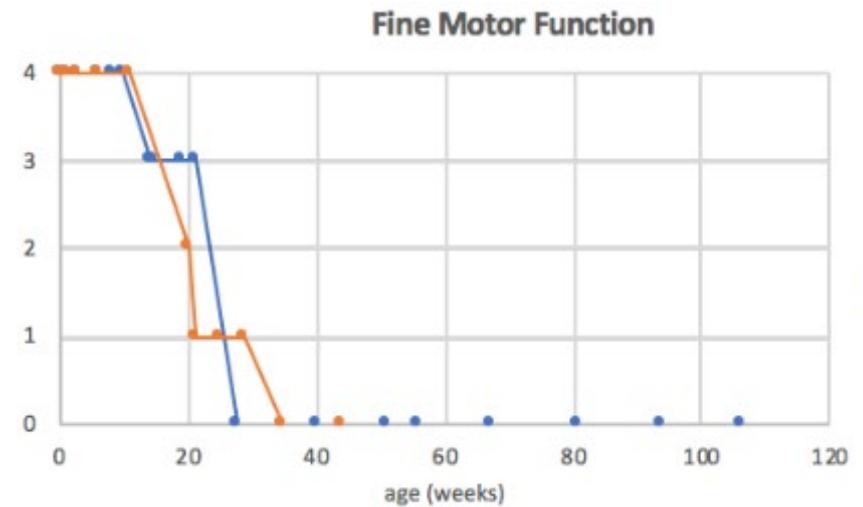
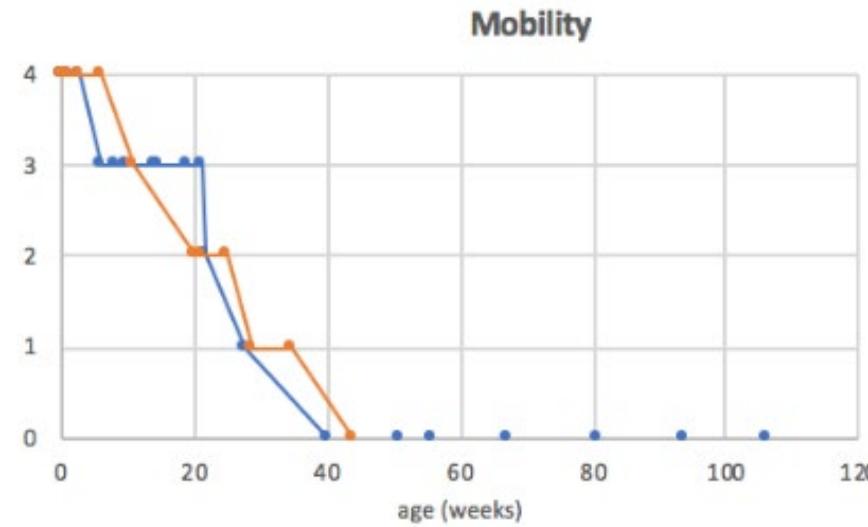
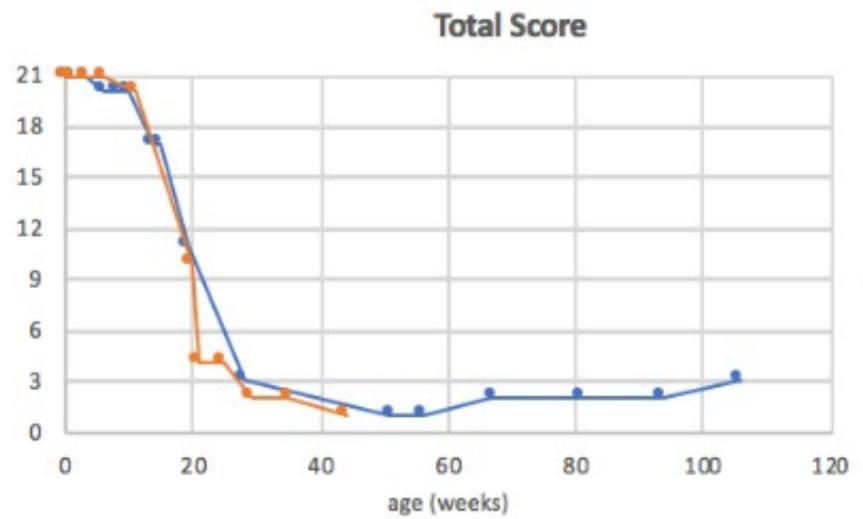
Functional Category
Mobility
Fine motor function
Expressive language

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

Advantages

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

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





Limited number of patients



Phenotype variability



Need for reliable clinical outcome measures / clinical biomarkers

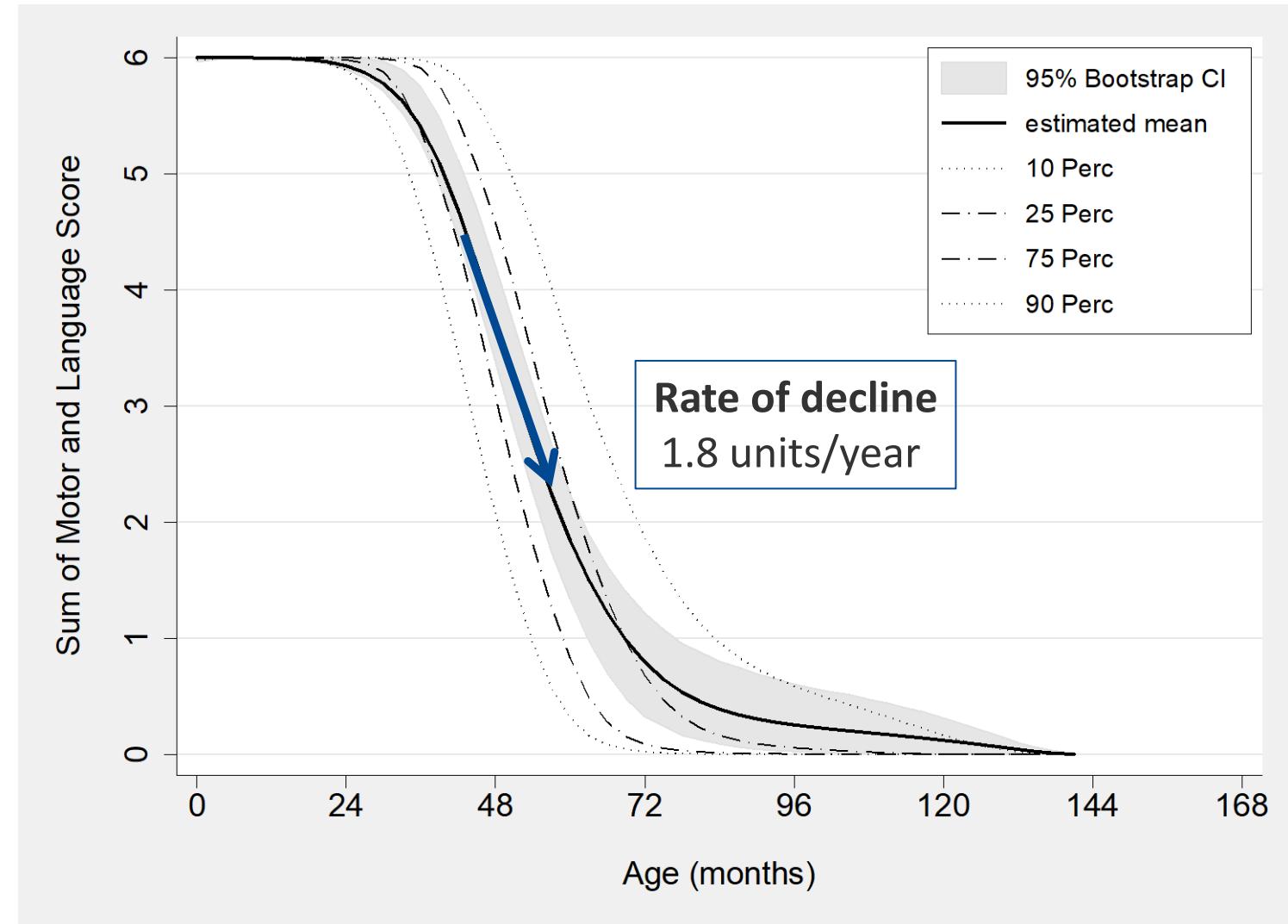


Use of natural history control data in clinical trials – *can it be done?*

Independent natural history data as primary efficacy outcome measures

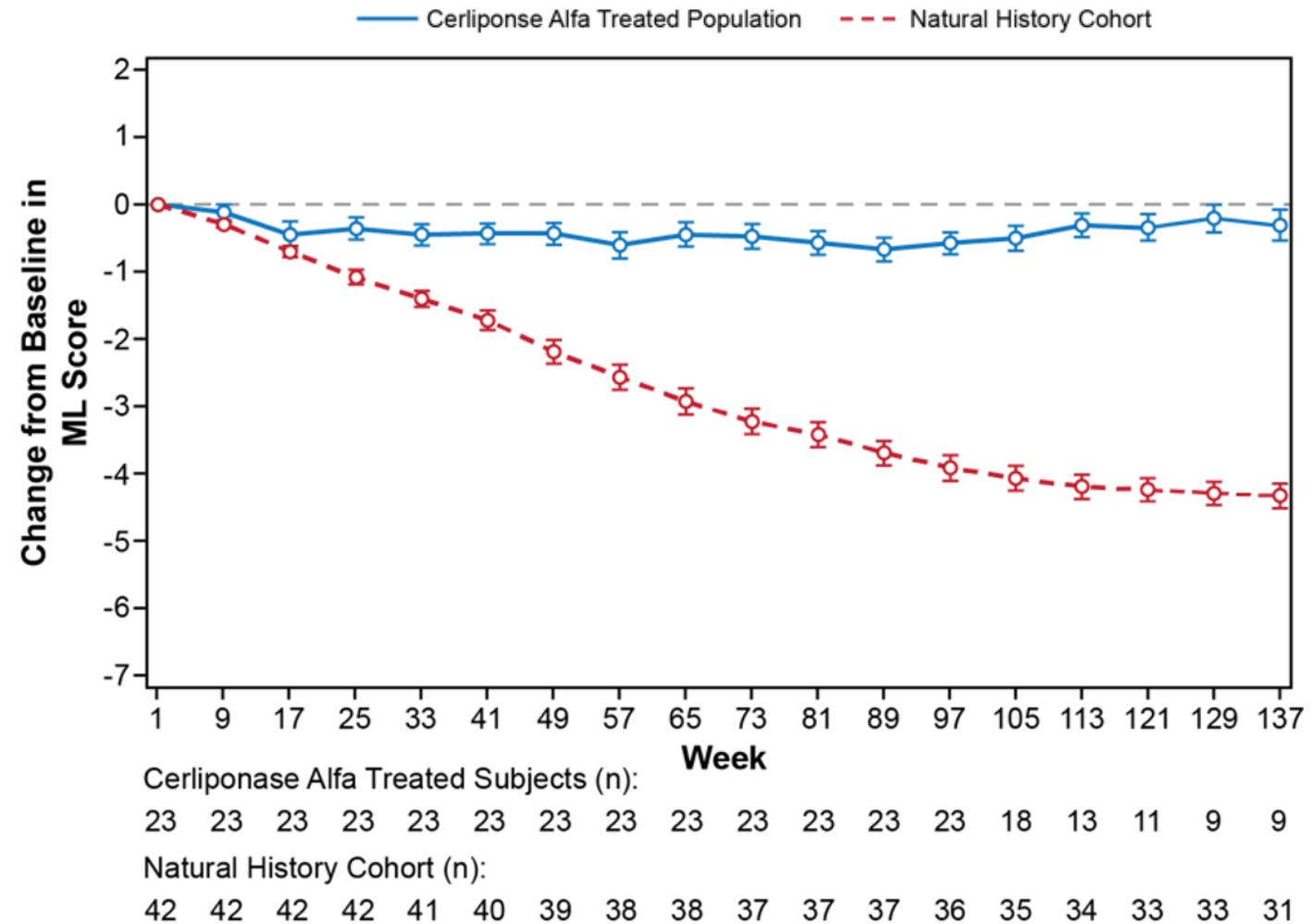
Natural history data collection:

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



Cerliponase alfa treated CLN2 patients compared to Natural History

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



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



Limited number of patients



Phenotype variability

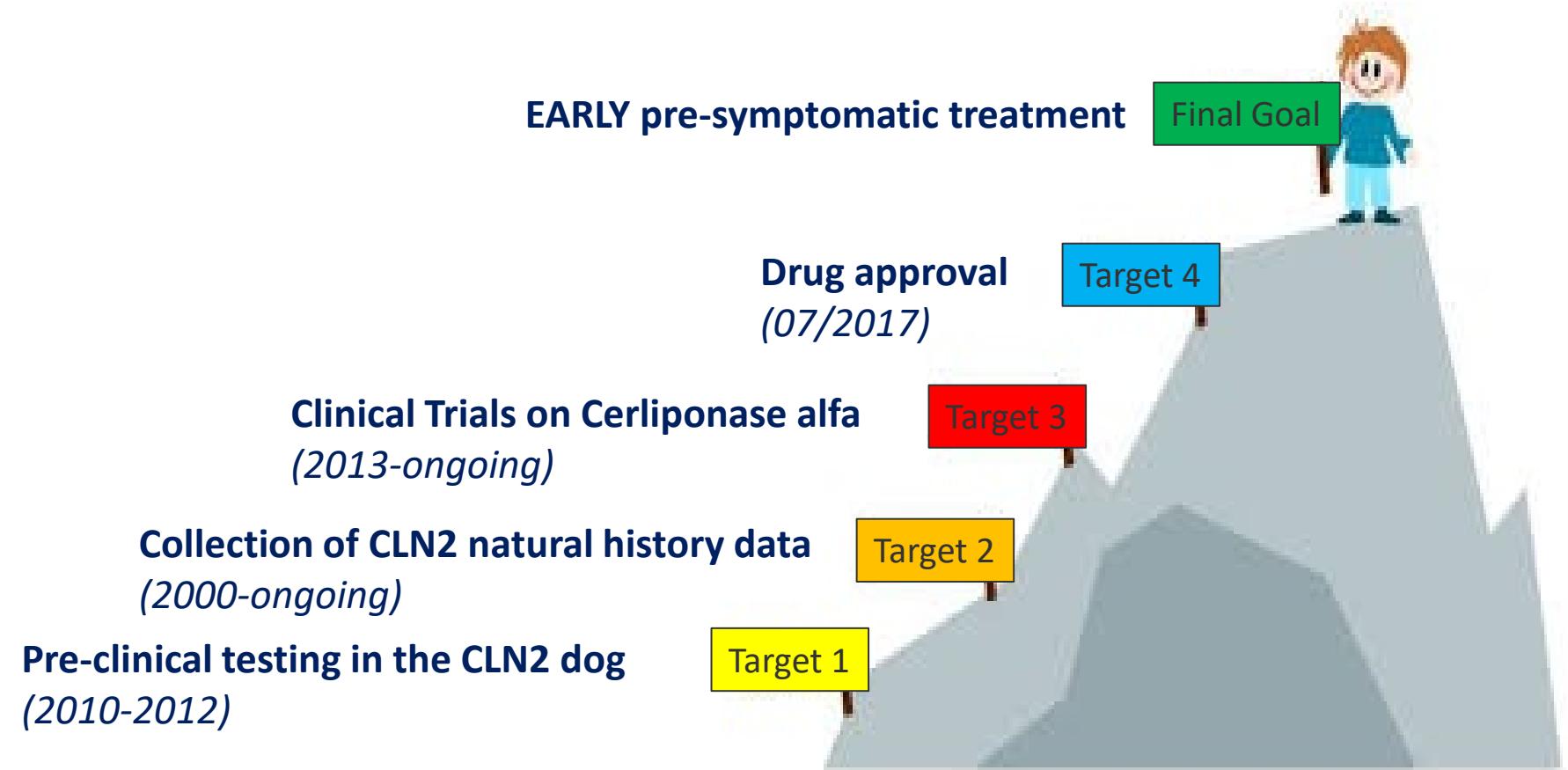


Need for reliable clinical outcome measures / clinical biomarkers

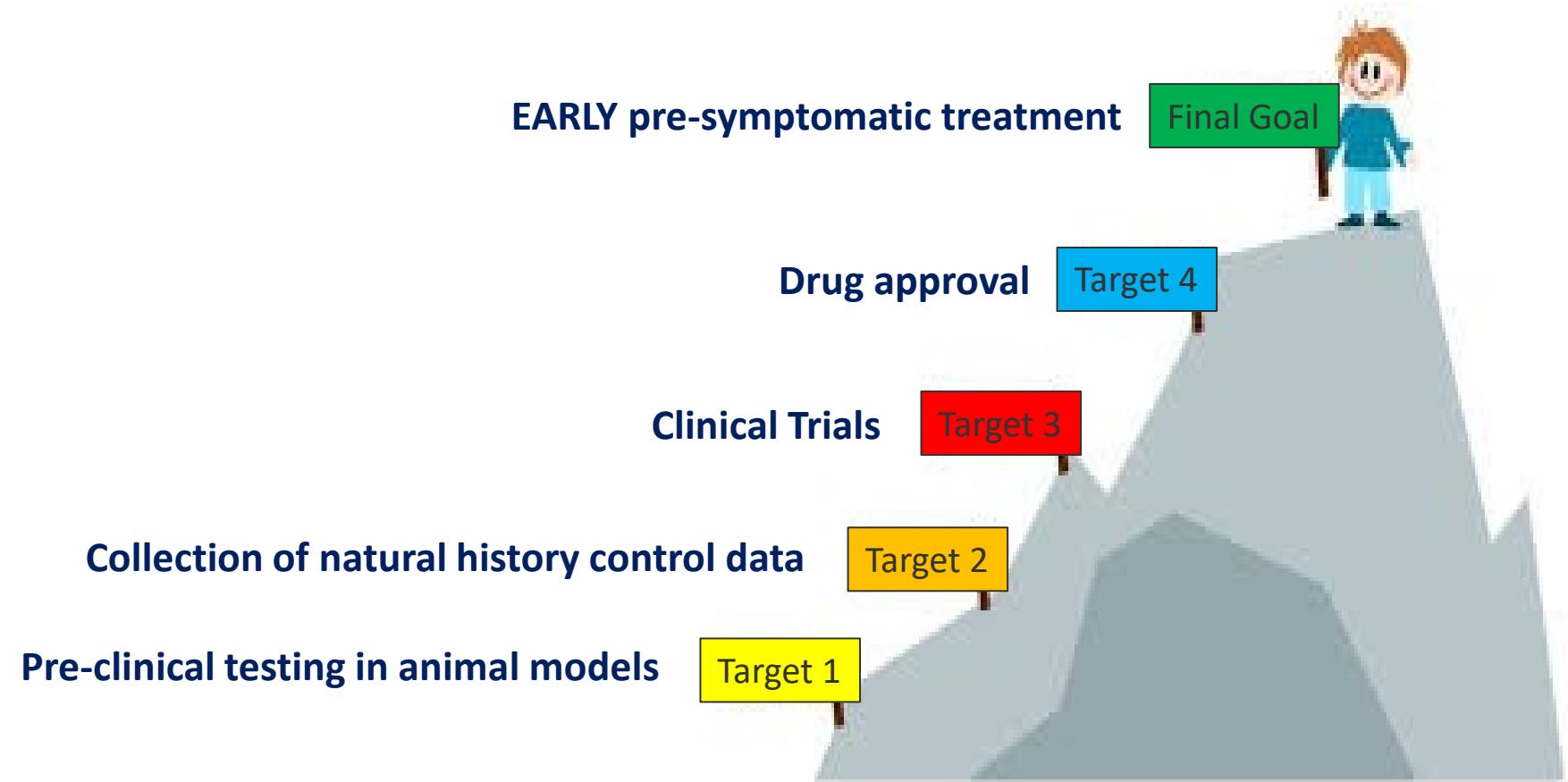


Use of natural history control data in clinical trials – we have done it!

Example from CLN2 Disease



We need to start NOW for CLN1 Disease



Thank you!



Patients & Families

Fundraising



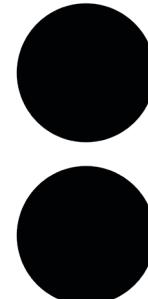
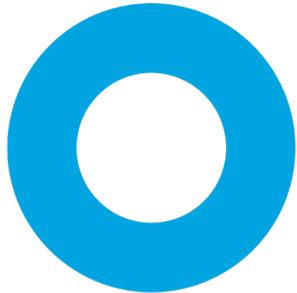
Research Grants



NCL2TREAT



Q & A



Disease Burden – Patient and Family Perspective



Sharon King

President of Taylor's Tale

A life of promise...a legacy for the future



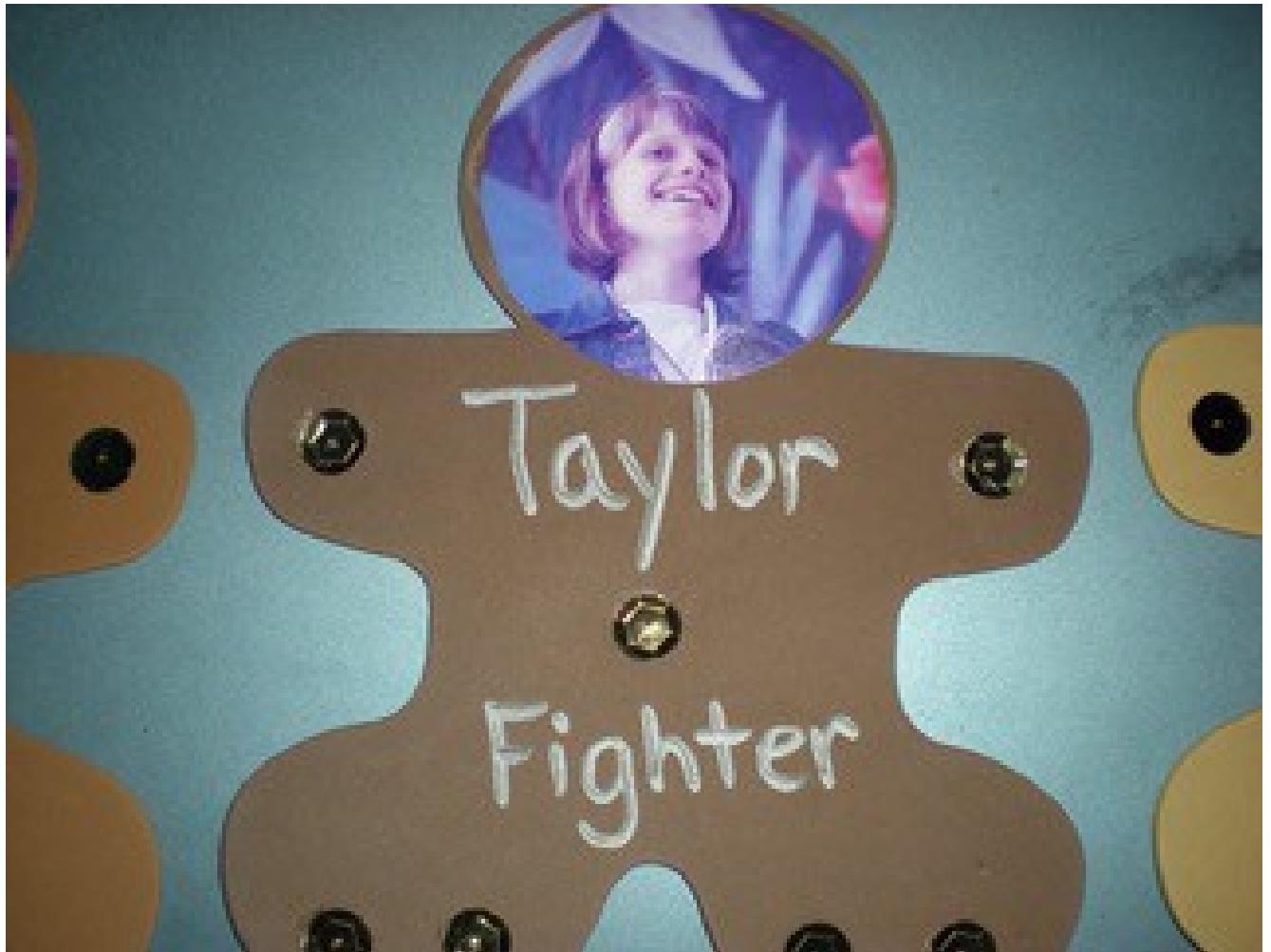
Symptoms leading to diagnosis

- Learning difficulties
- Vision loss

Two children with similar symptoms seeing the same pediatric neurologist...



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



The burden on children and families

- For the child:
 - Isolation
 - Cognitive impairment
 - Loss of vision, speech, and mobility
 - Movement disorder
 - Seizures
 - Ability to swallow
- For the family:
 - Grief, anxiety, and depression
 - Isolation
 - Balancing everyday life and the needs of the child
 - Loss of productivity and the costs associated with chronic illness, often leading to financial difficulties
 - Guilt



Vision, commitment, and dedication to improving outcomes



Sometimes you just have to believe...



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

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

Preclinical Pharmacology and Toxicology Data

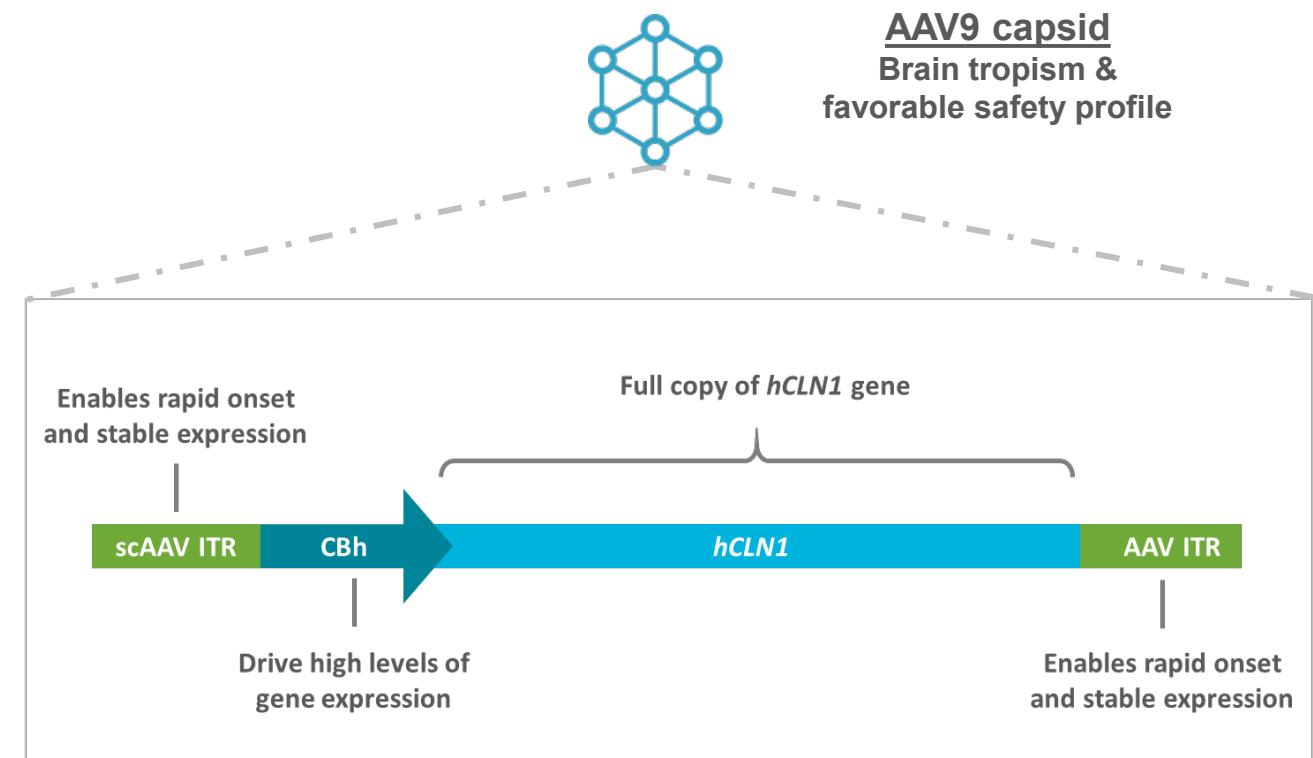


Steven Gray, PhD

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

CLN1 disease is a severe neurodegenerative lysosomal storage disease

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

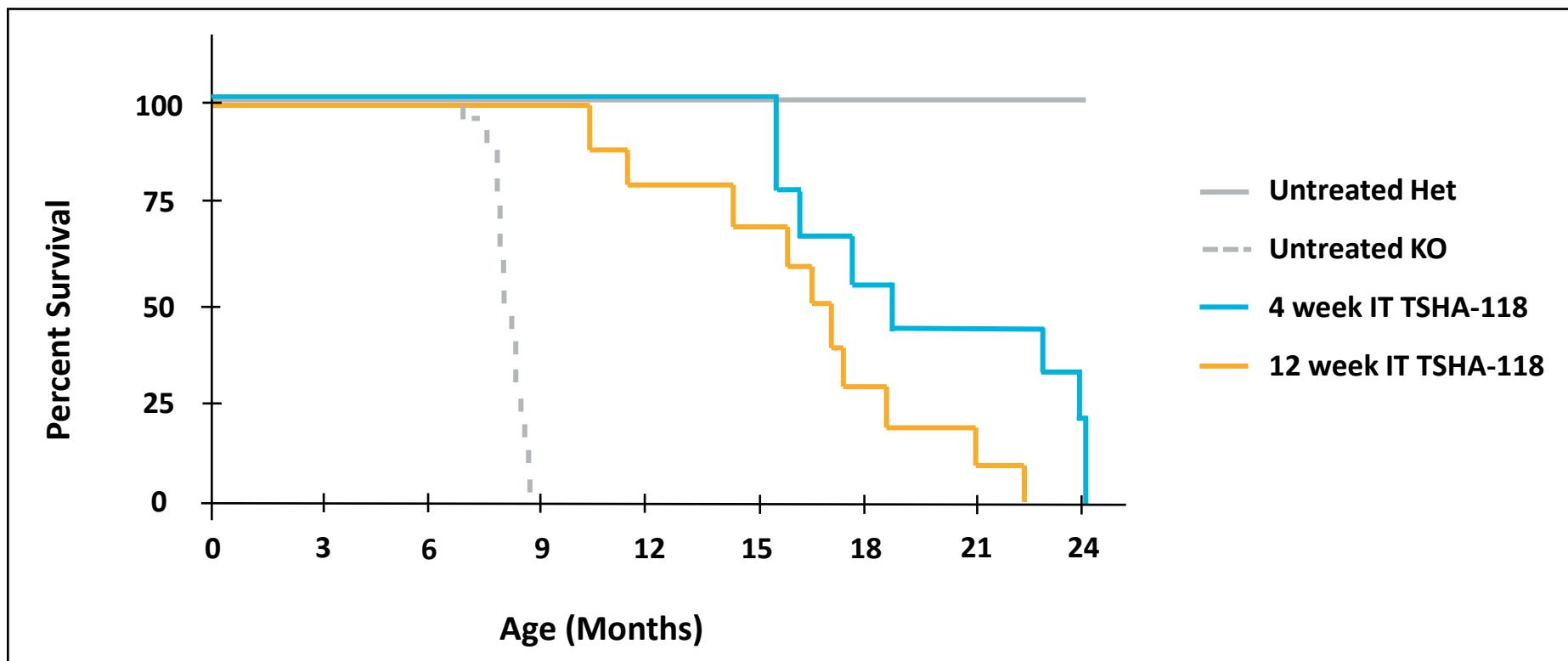


TSHA-118 preclinical studies to date

#	Study Scope (ID)	Model System	Age at dosing	Route of Administration & Dose (vg/animal)	Major Findings
1	Proof of Concept; (UNC-2014-001)	PPT1 ^{-/-} mice	1, 4, 12, 20, 26 weeks	IT: 7.0×10^{10} , 2.2×10^{11} , 7.0×10^{11}	<ul style="list-style-type: none"> Elevated levels of active PPT1 in serum Significant survival benefit and functional improvements Rescue of behavioral deficits
2	Safety and Efficacy (UNC-2015-001)	PPT1 ^{-/-} and PPT1 ^{+/-} mice	P0 – P2	IV: 2.8×10^{11}	<ul style="list-style-type: none"> Significant survival benefit: median life-span 21 months in treated mice vs. 8.3 months in untreated mice
3	Efficacy of Combination IT and IV Dosing; (UNC-2016-001)	PPT1 ^{-/-} mice	20 weeks	IT: 7.0×10^{10} , 7.0×10^{11} IV: 7.0×10^{11} IT: 7.0×10^{10} , 7.0×10^{11} each in combination with IV: 7.0×10^{10} , 2.2×10^{11} , or 7×10^{11}	<ul style="list-style-type: none"> Dose-dependent survival benefit and improvements in function Single routes and lower doses provided some benefit Maximum benefit with high IT plus high IV dose at this stage of disease (i.e. - 20 week old mice)
4	Efficacy of Combination IT and IV Dosing; (UNC-2017-001)	PPT1 ^{-/-} mice	4 weeks	IT: 7.0×10^{11} IT: 7.0×10^{11} in combination with IV: 7.0×10^{10} or 7.0×10^{11}	<ul style="list-style-type: none"> Testing up to 12 months demonstrated survival or behavioral benefits for the combination treatment similar to IT dose alone, which had a median lifespan of 18.7 months
5	Biodistribution and PPT1 Activity Comparison; (UNC-2017-002)	C57B1/6 mice & Fischer rats	Mouse: 9 wks Rat: 11 wks	IT Mouse: 9.1×10^{11} IT Rat: 3.64×10^{12}	<ul style="list-style-type: none"> Maximum dose IT injection of TSHA-118 in wild-type rats and mice resulted in similar levels of vector biodistribution and PPT1 enzyme activity in serum and most tissues of both Cross-species comparison supports the dosing rationale of 5.0×10^{14} total vg and 1×10^{15} total vg for human trial
6	Toxicology Study in Rat; (MPI-2389-010)	Wistar Hans rats	6 weeks	IT: 2.0×10^{11} , 2.0×10^{12} IV: 5.6×10^{12} , 2.0×10^{13} IT: 2.0×10^{12} in combination with IV: 2.0×10^{13}	<ul style="list-style-type: none"> Administration of TSHA-118 was not associated with any mortality, clinical observations, bodyweight, or food consumption changes

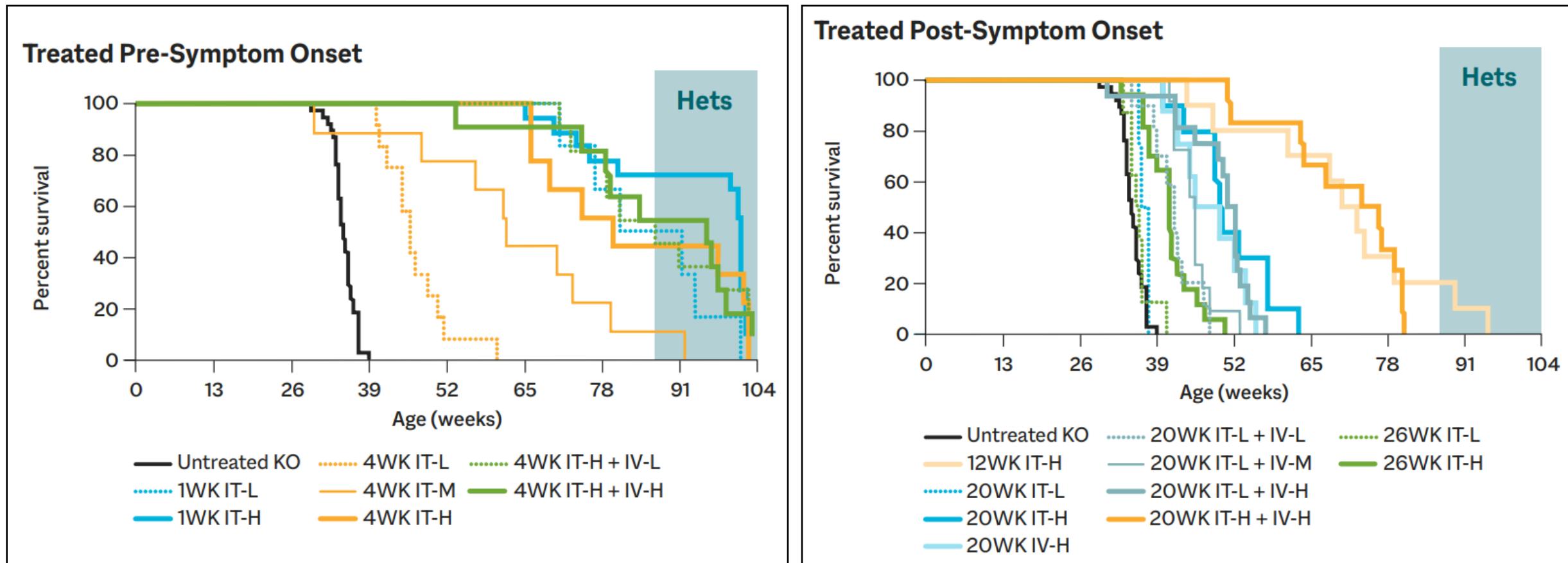
Taking these nonclinical studies into consideration, there is support for 5.0×10^{14} total vg and 1.0×10^{15} total vg dosing in human trials

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



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

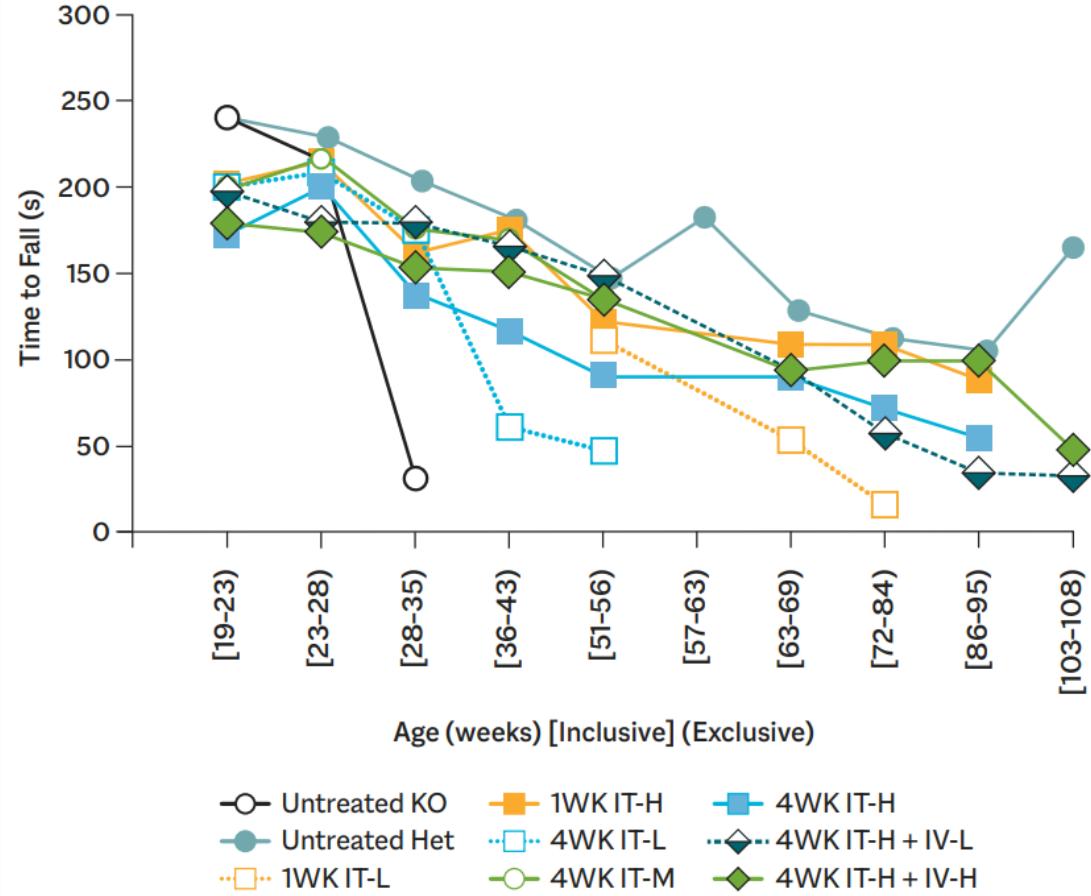
Higher doses of TSHA-118 and earlier intervention mediated stronger rescue of CLN1 KO mice



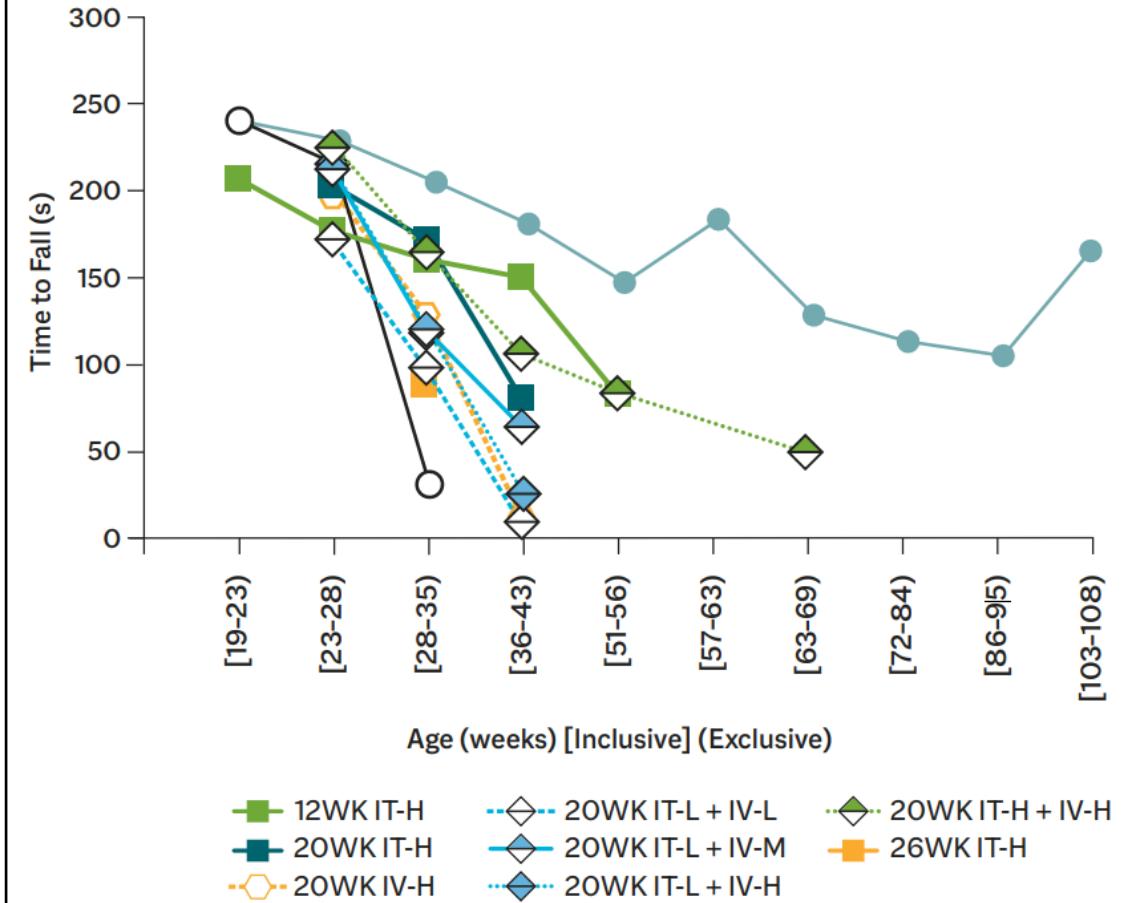
L - 7.0×10^{10} vg/mouse M - 2.2×10^{11} vg/mouse H - 7.0×10^{11} vg/mouse

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

Treated Pre-Symptom Onset



Treated Post-Symptom Onset

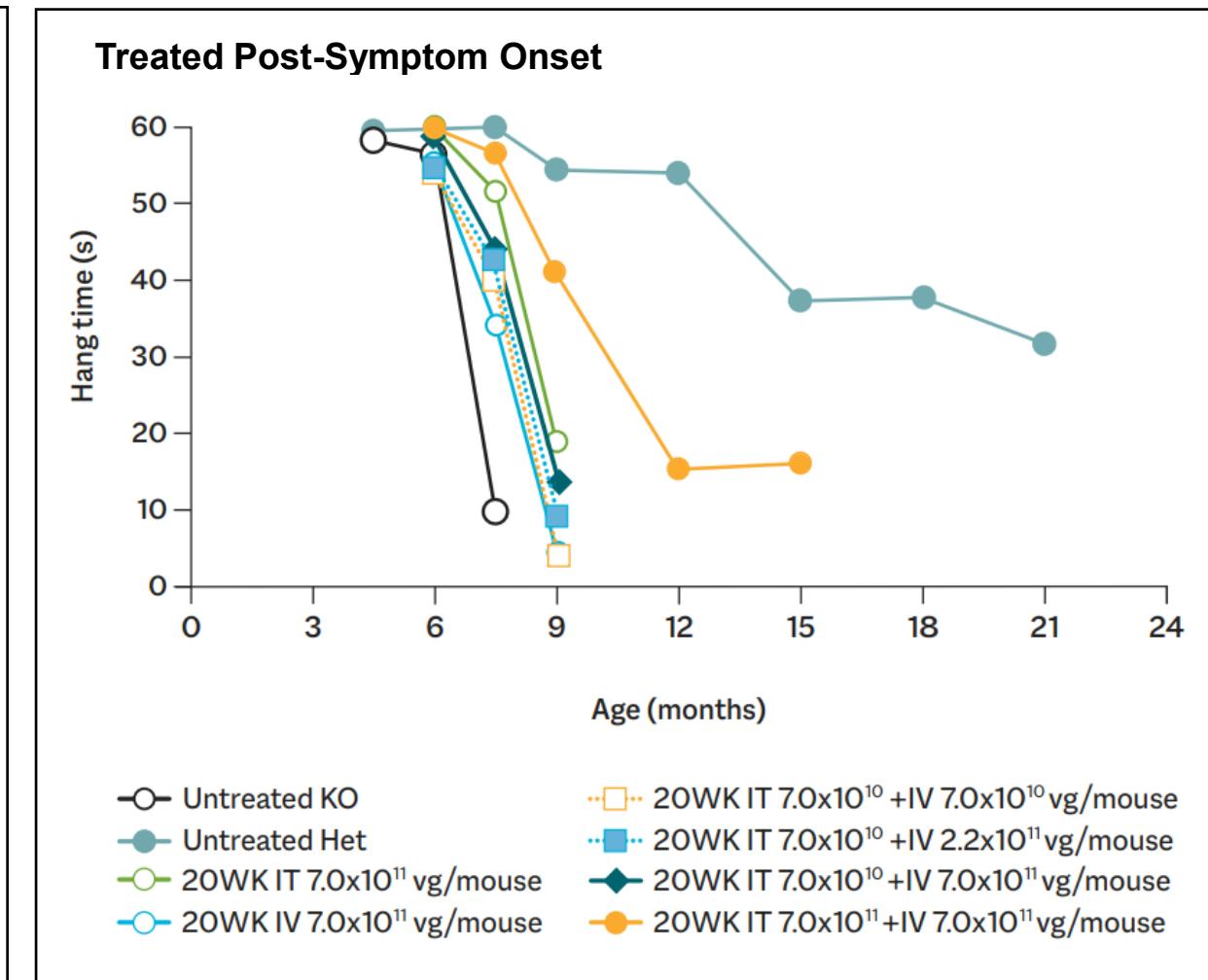
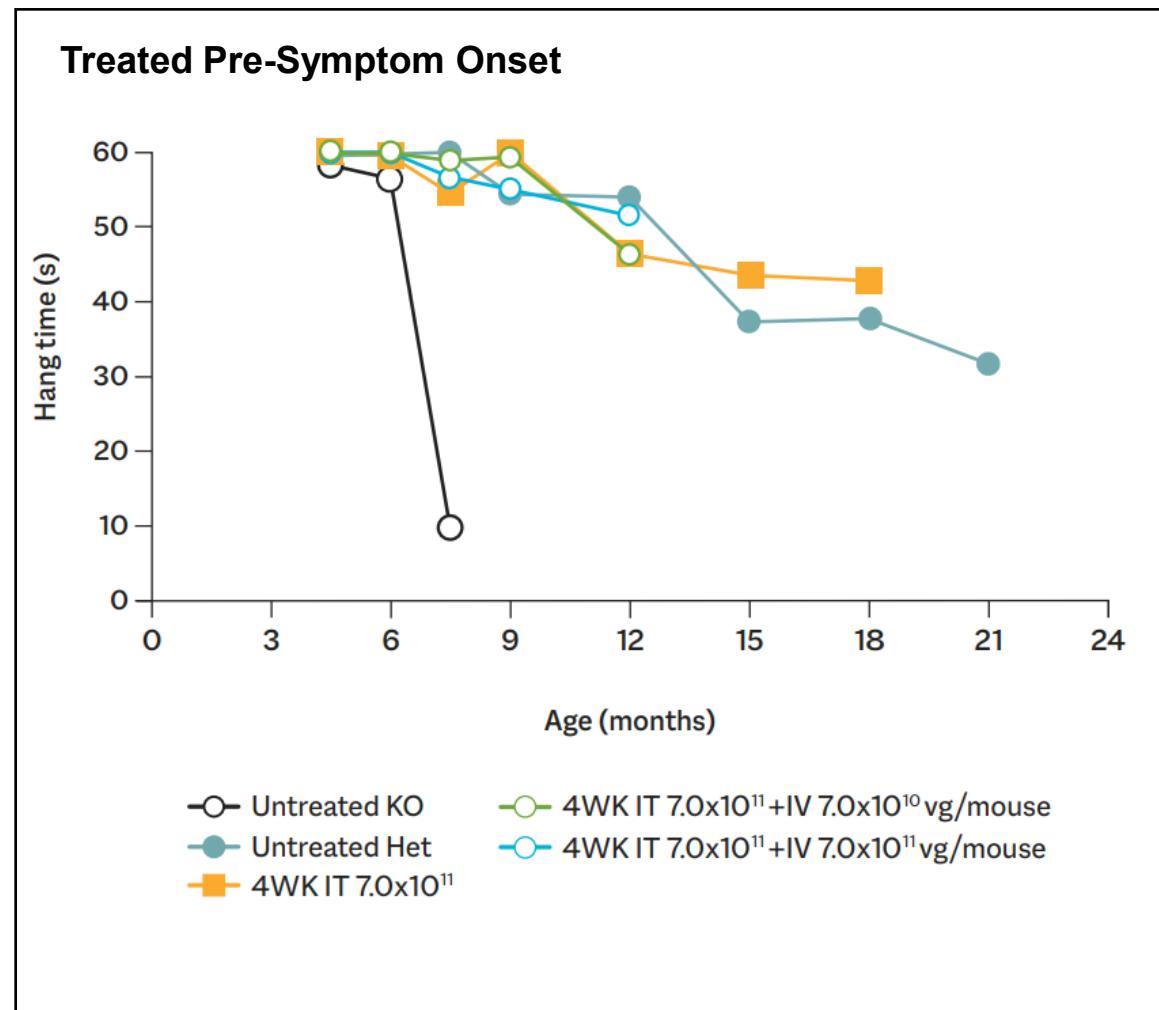


L - 7.0×10^{10} vg/mouse

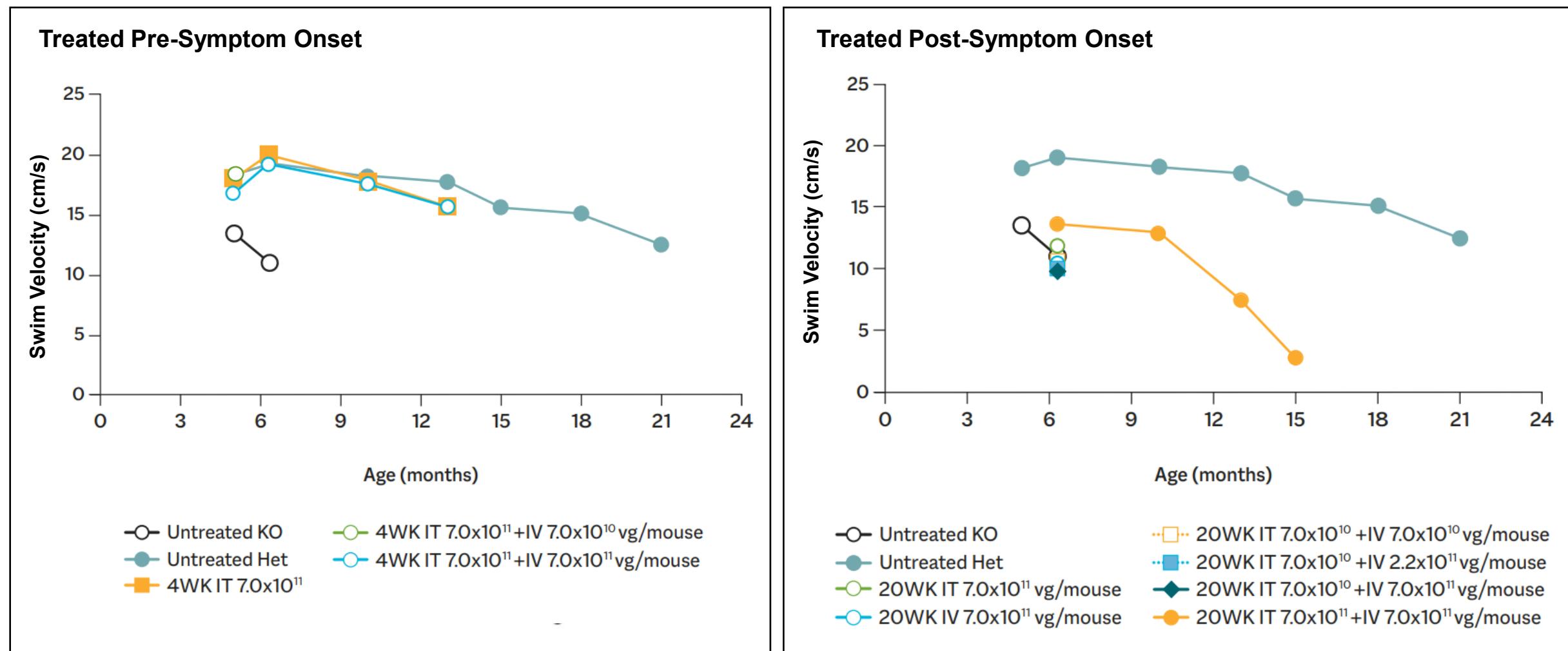
M - 2.2×10^{11} vg/mouse

H - 7.0×10^{11} vg/mouse

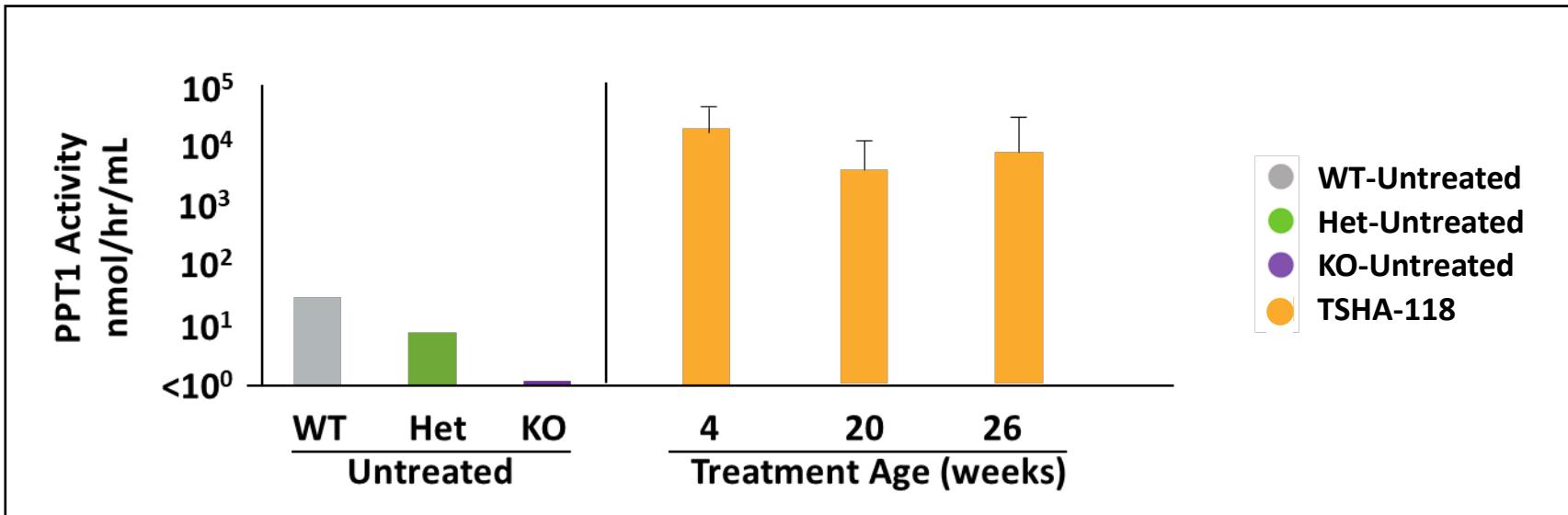
TSHA-118-treated CLN1 KO mice were evaluated for grip strength by measuring hanging time



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



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



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

Summary of 6-month toxicology safety study



Study to assess the potential toxicity and tissue biodistribution of TSHA-118 following IT and / or IV administration in wild-type Wistar Hans rats (108 male and 108 female) at 6 weeks of age



There was a wide therapeutic window with which to dose (vg/animal); IV low dose of 5.6×10^{12} , IV high dose of 2.0×10^{13} , IT low dose of 2.0×10^{11} , IT high dose of 2.0×10^{12} , and combination IV and IT high dose



The viral vector was widely distributed and detected in all tissue samples at Day 8 and Week 12



Transduction of brain, spinal cord, and other organs was evident



No toxicology findings at high dose in organs or tissues

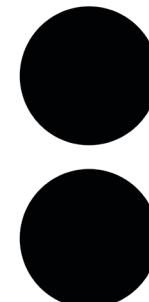
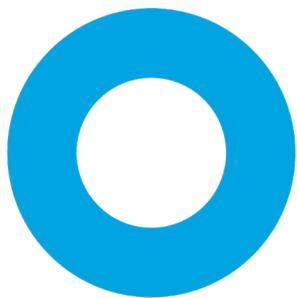


Administration of TSHA-118 was not associated with any mortality, clinical observations, body weight, or food consumption changes that were considered adverse out to 6 months post-injection



Administration of TSHA-118 resulted in supraphysiologic PPT1 enzyme activity in serum, liver, heart, brain, and spinal cord, which persisted over time

Q & A



Clinical Development Strategy



Suyash Prasad, MBBS, MSc, MRCP, MRCPCH, FFPM
Chief Medical Officer and Head of R&D

TSHA-118 program update



Advisory board March 2021



Conducted CLN1 patient focus groups in the early part of the year



Overall positive regulatory feedback with multiple key regulatory agencies



Completed cGMP drug product fill



Study design and patient feedback abstracts accepted by International Congress on Neuronal Ceroid Lipofuscinosis



Interventional protocol nearing completion

Advisory board overview



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



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



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



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

Key takeaways from Advisory board

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

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

CURIOSITY



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



Identify patient-centric endpoints and meaningful outcomes



Uncover educational gaps for families about gene therapy and clinical trials

COLLABORATION



Develop clinical trial protocols based on patient and family insights



Partner with community to raise awareness and recruit clinical trials



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

Patient / caregiver input into TSHA-118 clinical study design



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



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



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

Most challenging symptoms of CLN1 disease

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

CLN1 disease symptoms by phenotype and disease progression	Infantile CLN1 disease	Late Infantile CLN1 disease	Juvenile CLN1 disease
	<ul style="list-style-type: none">• Communication issues/ inability to speak• Seizures• Inability to sit• Inability to stand or walk• Myoclonic jerks• Irritability• Scoliosis• Chest infections• Decline in mental development/dementia	<ul style="list-style-type: none">• Communication issues / inability to speak• Seizures• Inability to sit• Inability to stand or walk	<ul style="list-style-type: none">• Communication issues / inability to speak• Vision loss• Cognitive impairment / dementia• Muscle stiffness• Hallucinations• Restlessness / sleep issues



Voices from the front line - Impact of CLN1 disease

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



Cognitive decline, mood, communication, and speech

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

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

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

Seizures

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

Motor decline

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

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

Vision

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



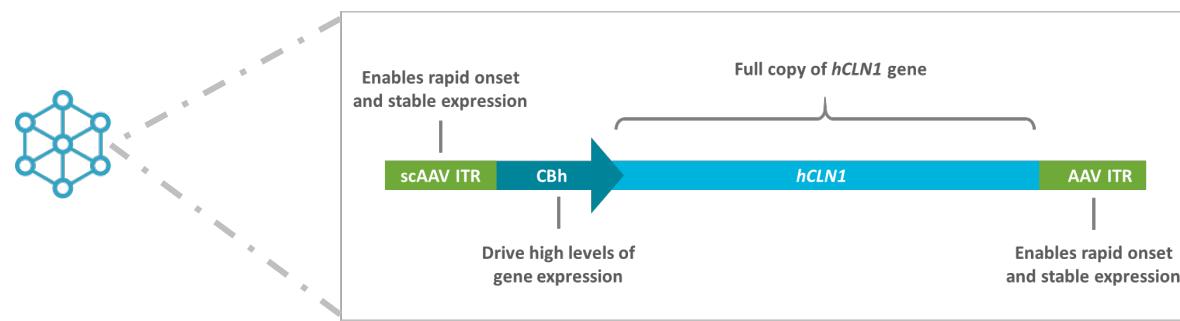
Phase 1/2 adaptive trial for TSHA-118 in CLN1

Goals and Targets of Trial

Goals

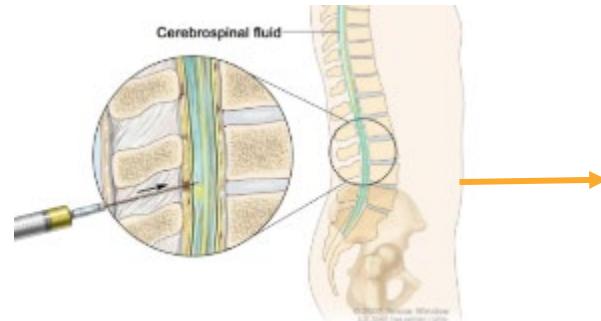
- Key biomarker endpoint – PPT1 enzyme activity in CSF and serum
- Key efficacy endpoints – Pathologic, physiologic, functional and clinical markers, UDBRS, Hamburg scale, developmental milestones, seizure activity, visual acuity

Product Details and Dose Cohorts



Route and Method of Administration

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

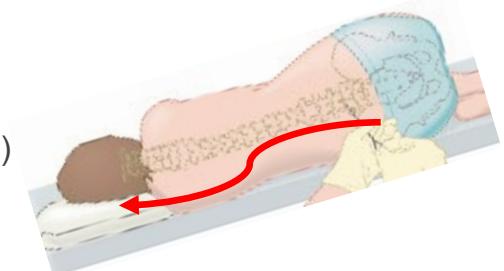


Target Recruitment

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

Dose Cohorts

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

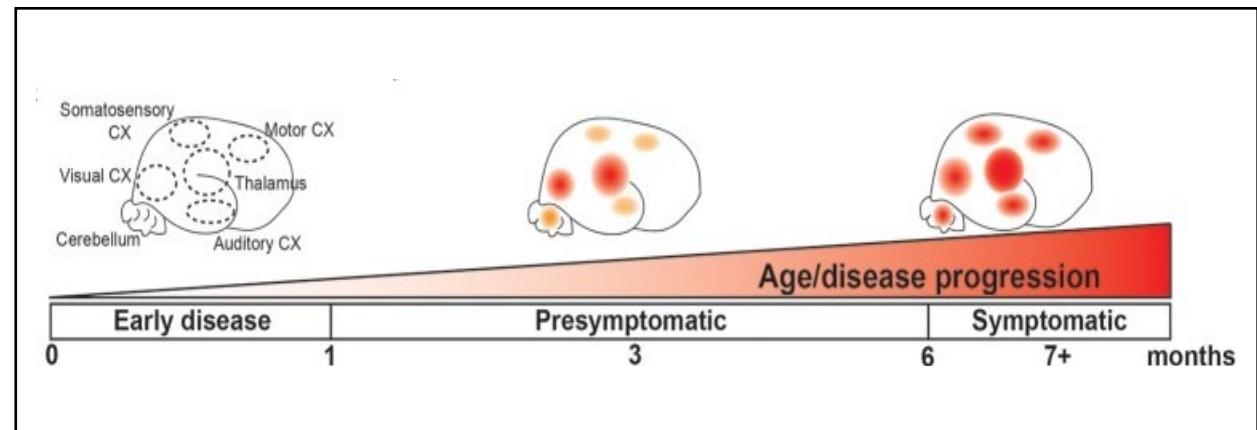


Technique to Improve Transduction

- Trendelenburg position (15-30°)
- During infusion & 1 hour post infusion

Importance of PPT1 as a biomarker for CLN1 disease

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



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

Overview of key efficacy endpoints



Biomarker: PPT1 enzyme activity in CSF and serum

- PPT1 is the underlying pathological deficit and replacement should enable removal of accumulated substrate



Unified Batten Disease Rating Scale (UBDRS) for global disease burden

- Designed to assess motor, seizures, behavioral, and functional capability in children with NCL
- Seizure type, frequency, and duration will also be assessed by UBDRS
- Precedent with other forms of Battens disease



Hamburg Scale for motor, visual, language, and seizure scores

- An established tool to capture function, rate of decline, and / or regression specific for NCLs
- Seizure scores will also be assessed by the Hamburg Scale
- Precedent with other forms of Batten disease



Bayley-III

- Cognitive Scale assesses attention to familiar and unfamiliar objects, looking for a fallen object, and pretend play
- Language Scale focuses on recognition of objects and people, following directions, and naming objects and pictures
- Motor Scale assesses gross and fine motor skills such as grasping, sitting, stacking blocks, and climbing stairs



Clinical Global Impression-Improvement (CGI-I) Scale

- A clinician-rated assessment tool used to establish global improvement or change in comparison to baseline following care, treatment, or intervention

Overview of secondary and exploratory endpoints

Disease-Specific/Global Assessments

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

Ophthalmological Assessments

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

Imaging and neurophysiology

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

Biomarkers

- Reduction in accumulation of palmitoylated substrate

Communication Assessments

- Observer Reported Communication Assessment (ORCA)

Quality of Life/Other Assessment

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

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



Ongoing collection of natural history data



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

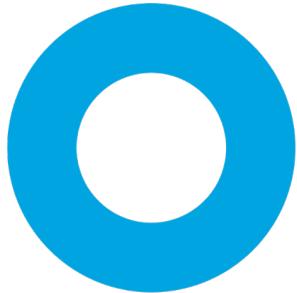


Patient finding activity in collaboration with UTSW, Rochester, Hamburg, and other potential sites and patient organizations



Site activation activities in the US and outside the US ongoing

Q & A



Closing Remarks



RA Session II

President, Founder & CEO

A decorative border consisting of a repeating pattern of vertical and horizontal lines. The lines are composed of small, colorful shapes: circles, hearts, and diamonds. The colors used include blue, orange, green, black, and white. The pattern creates a scalloped or wavy effect along the edges of the border.



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



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

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

Initiated construction of internal cGMP facility in 1H 2021

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



Thank you

A decorative border composed of various musical notes and symbols, including circles, hearts, and vertical bars, arranged in a repeating pattern.



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.



Vision

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

Strategy

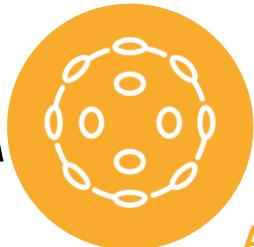
Focus on rapid clinical and commercial development by leveraging a proven capsid, manufacturing process, and delivery method

Pipeline

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

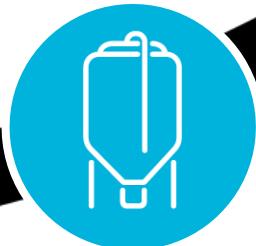
GAN program is a clear validation of the Steven Gray Lab (UTSW) and Taysha scientific approach; provides readthrough to existing pipeline

- 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)



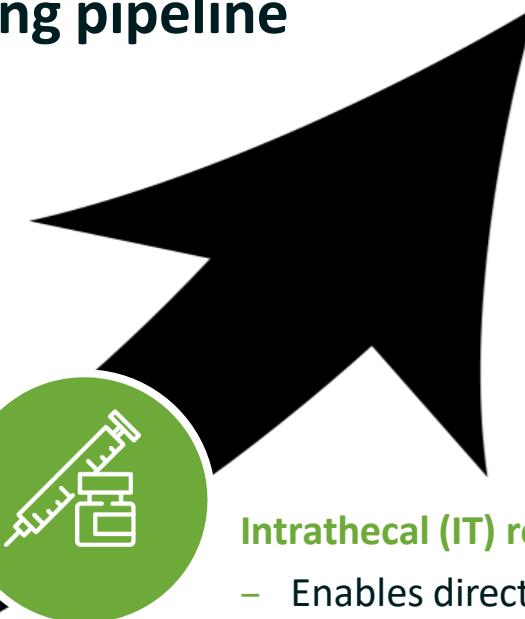
AAV9 vector for delivery of therapeutic transgene

- 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.

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 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

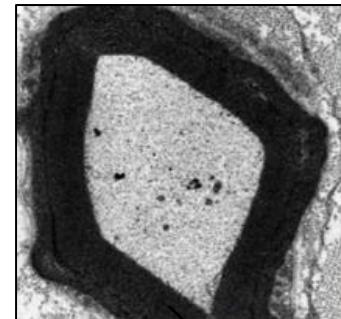
Rights acquired for \$5.5 million upfront, an aggregate of up to \$19.3 million in clinical, regulatory and commercial milestones as well as low, single-digit royalty on net sales

GAN Disease

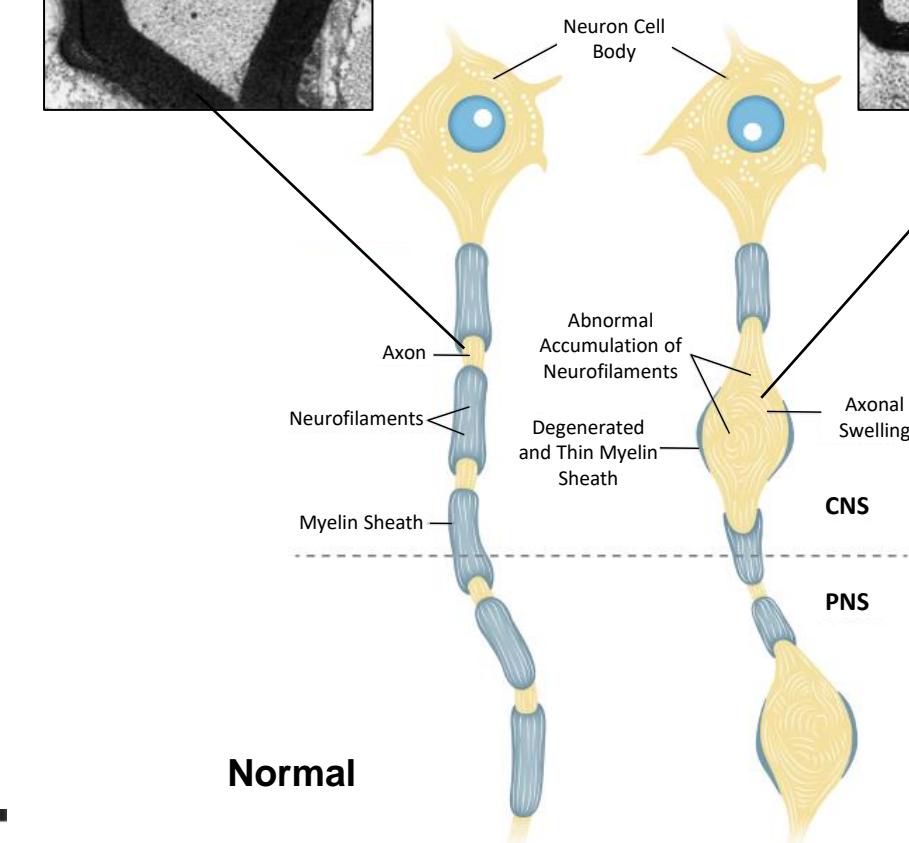
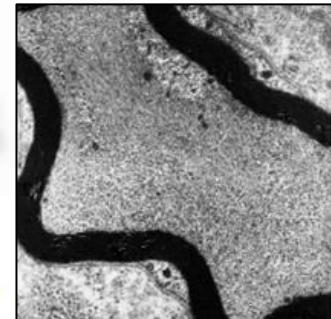
Rationale for targeting the *GAN* gene

- 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



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



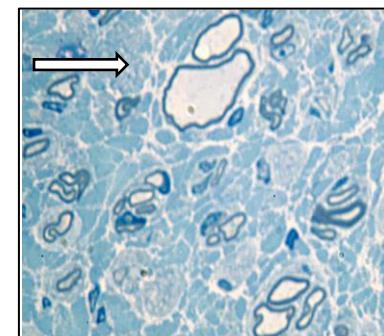
Progressive Scoliosis



Contractures



Giant Axons



Spinal Cord Atrophy

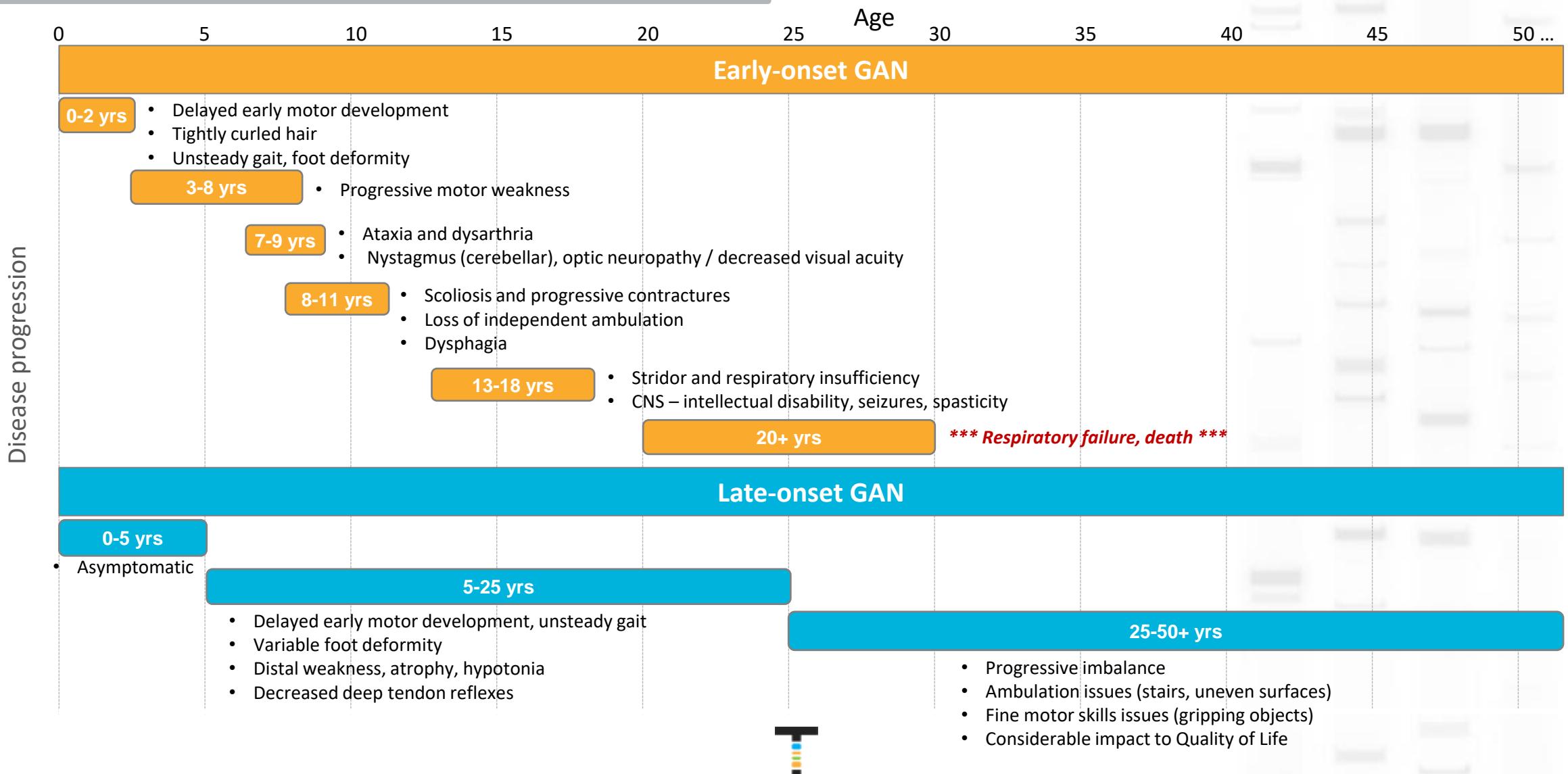


White Matter Abnormality



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



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

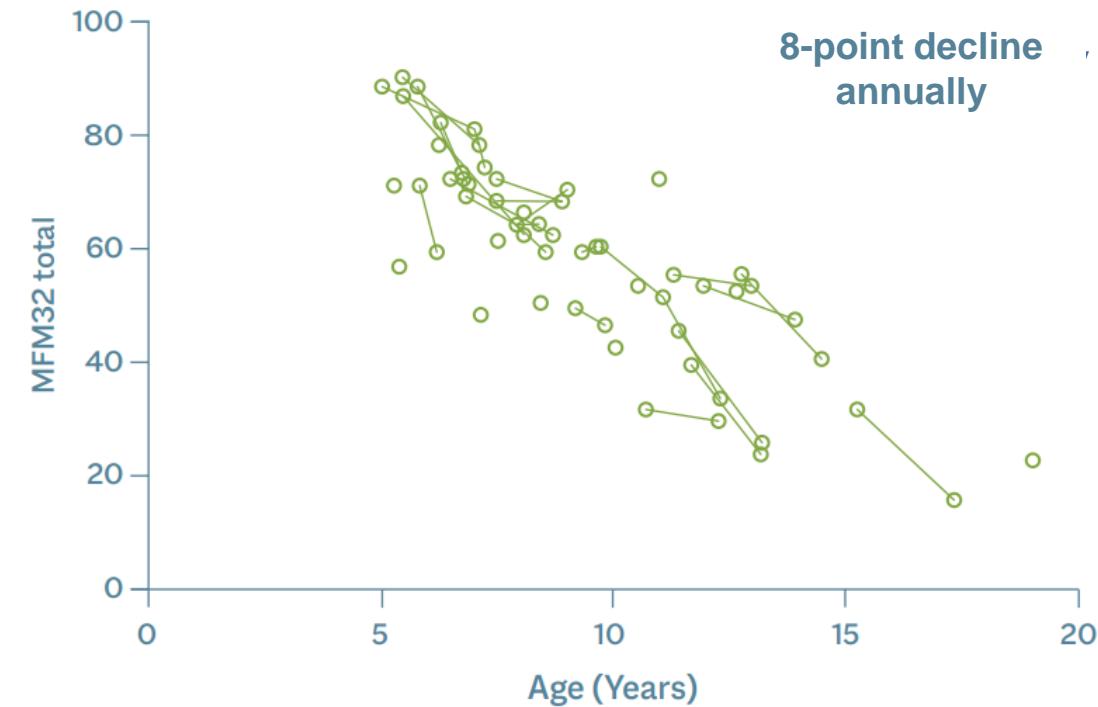
No.	Domain	Starting Position	Exercise Requested
1	D1	Supine, lower limbs half-flexed, kneecaps at zenith, and feet resting on mat	Raise the pelvis; the lumbar spine, the pelvis and the thighs are aligned and the feet slightly apart
2	D1	Supine	Without upper limb support, sits up
3	D1	Seated on the mat	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)

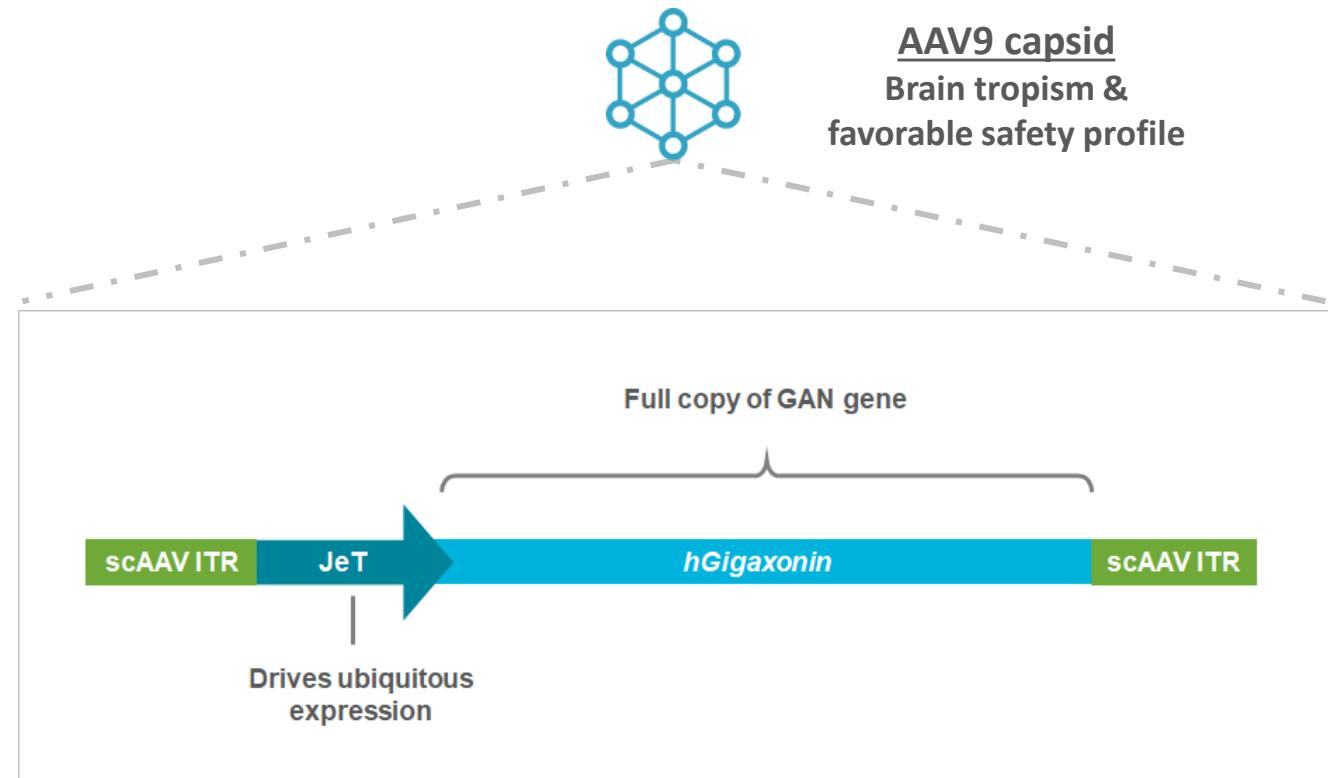


TSIA-120

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 TSIA-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



Development of Intrathecal AAV9 Gene Therapy for Giant Axonal Neuropathy

Rachel M. Bailey,¹ Diane Armao,^{2,3} Sahana Nagabhusan Kalburgi,^{1,5} and Steven J. Gray^{1,4,6}

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

Gene Therapy (2013), 1–8
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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 Nagabhusan Kalburgi, TJ McCown and RJ Jude Samulski

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

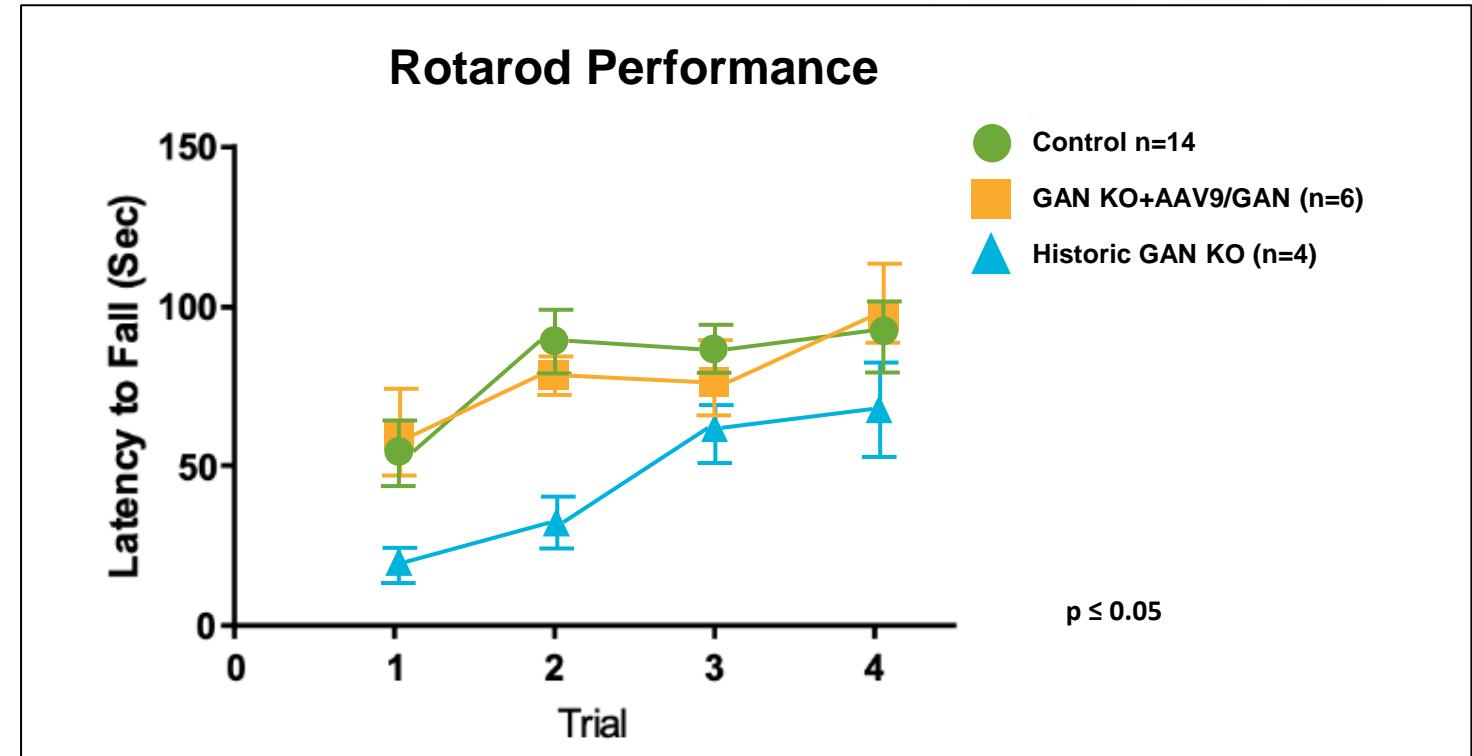
ORIGINAL ARTICLE

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

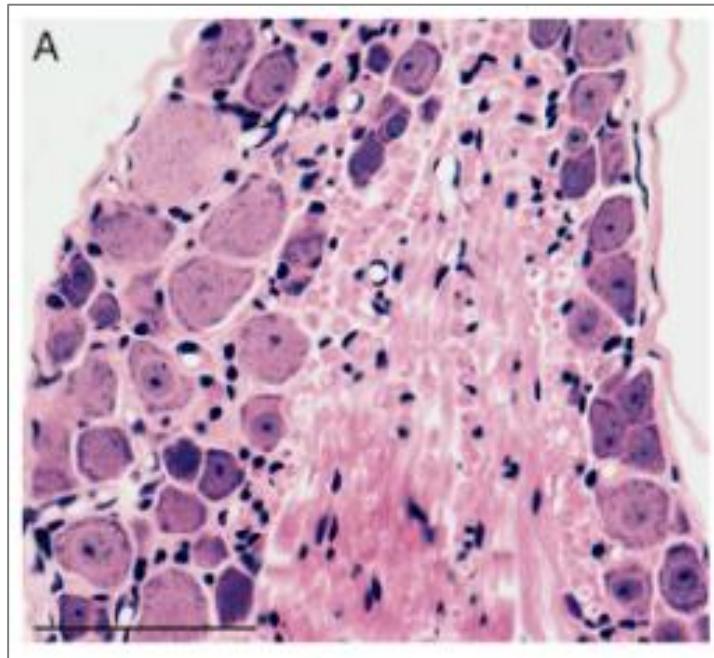
T Federici¹, JS Taub¹, GR Baum¹, SJ Gray², JC Grieger², KA Matthews¹, CR Handy¹, MA Passini³, RJ Samulski² and NM Boulis¹

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

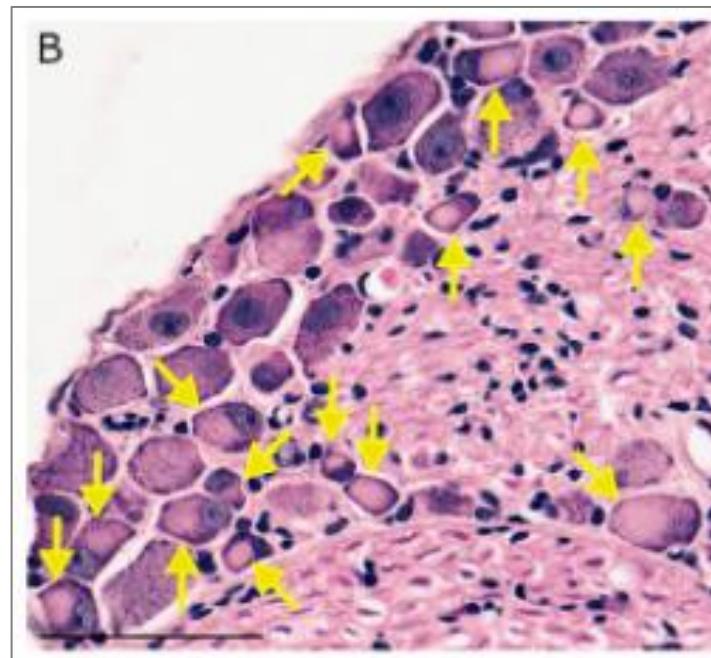
- Untreated GAN rodents performed significantly worse than heterozygous controls
- GAN rodents treated at 16 months old performed significantly better than untreated GAN rodents at 18 months old
- GAN rodents treated at 16 months old performed equivalently to heterozygous controls



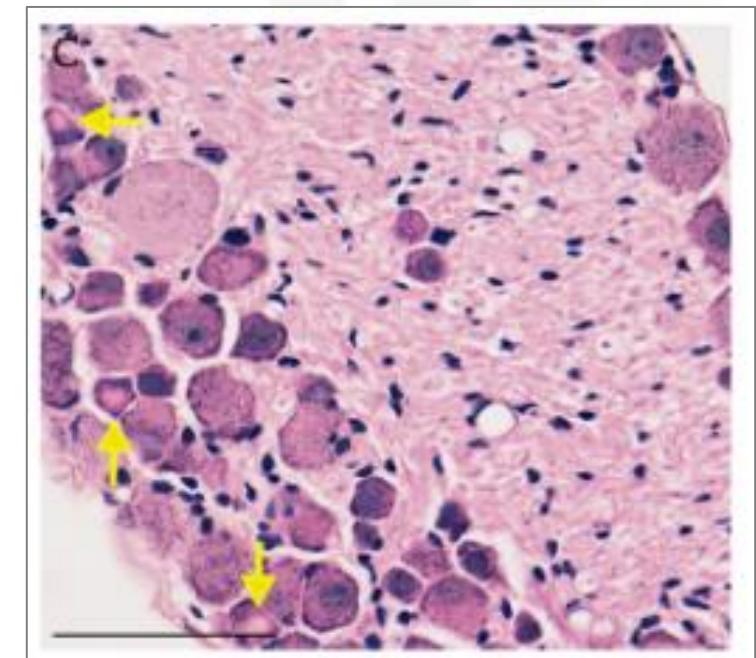
TSHA-120 improved pathology of the DRG in the GAN KO mice



Normal control



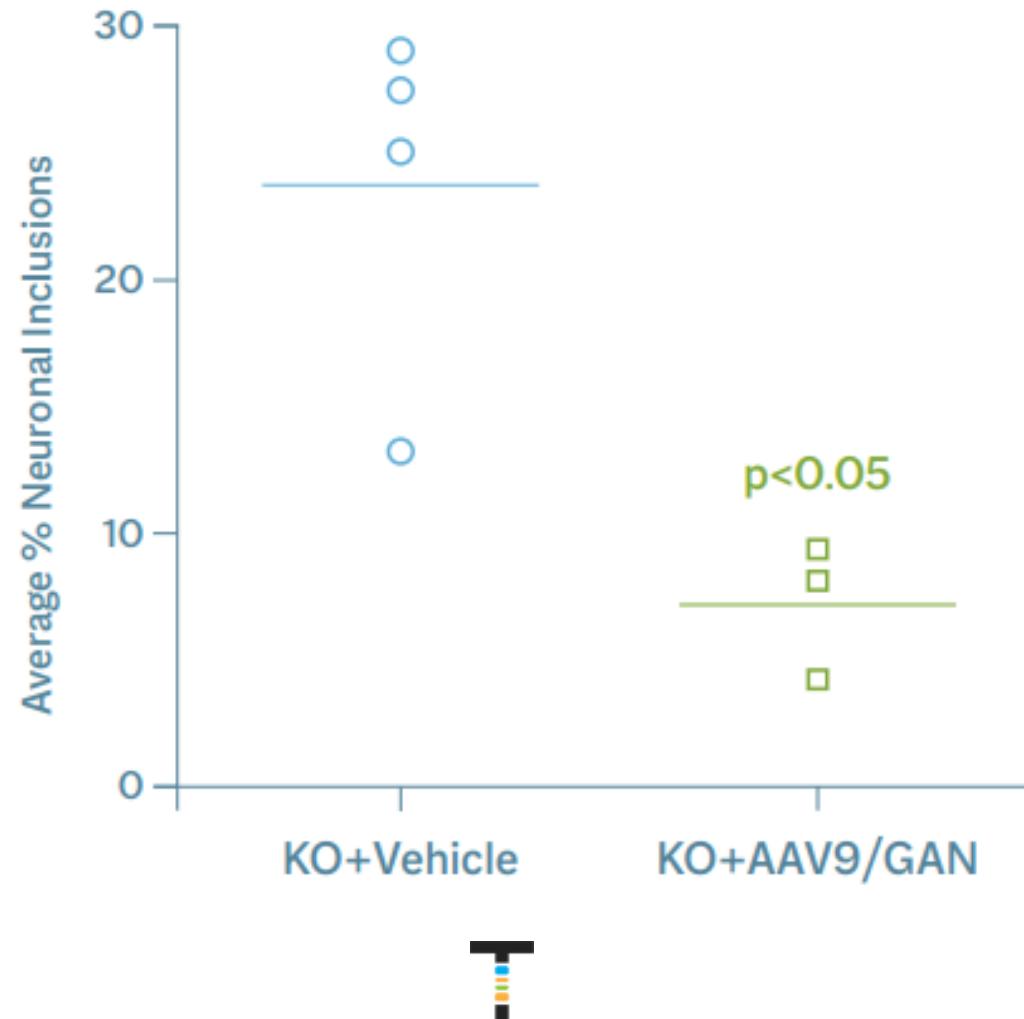
GAN KO – vehicle injected



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

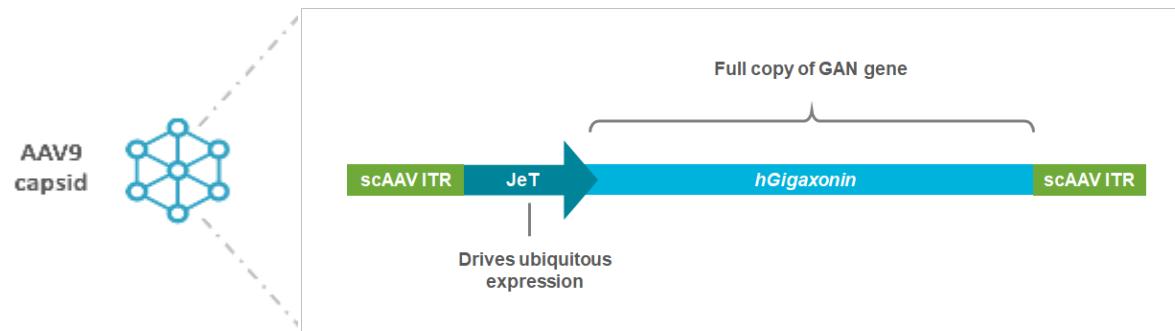
Target Recruitment

- 14 subjects injected
- > 5 years old

Target Areas to Transduce



Product Details and Dose Cohorts

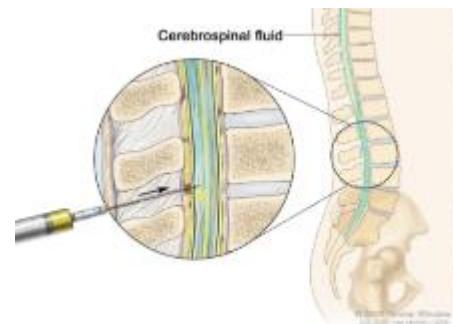


Dose Cohorts*

- | | |
|------|-------------------------------------|
| 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) |

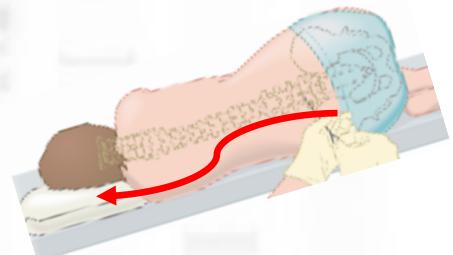
Route and Method of Administration

- 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

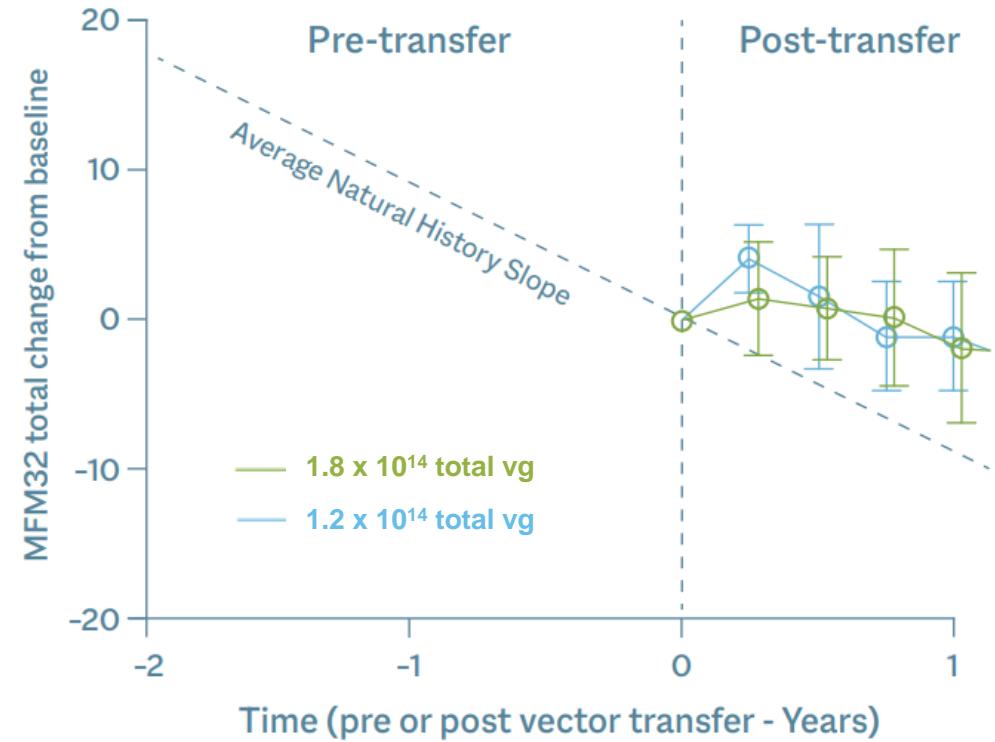


*Doses calculated by qPCR
NOTE: Subsequent slides only show data from 1.2×10^{14} vg and 1.8×10^{14} vg doses

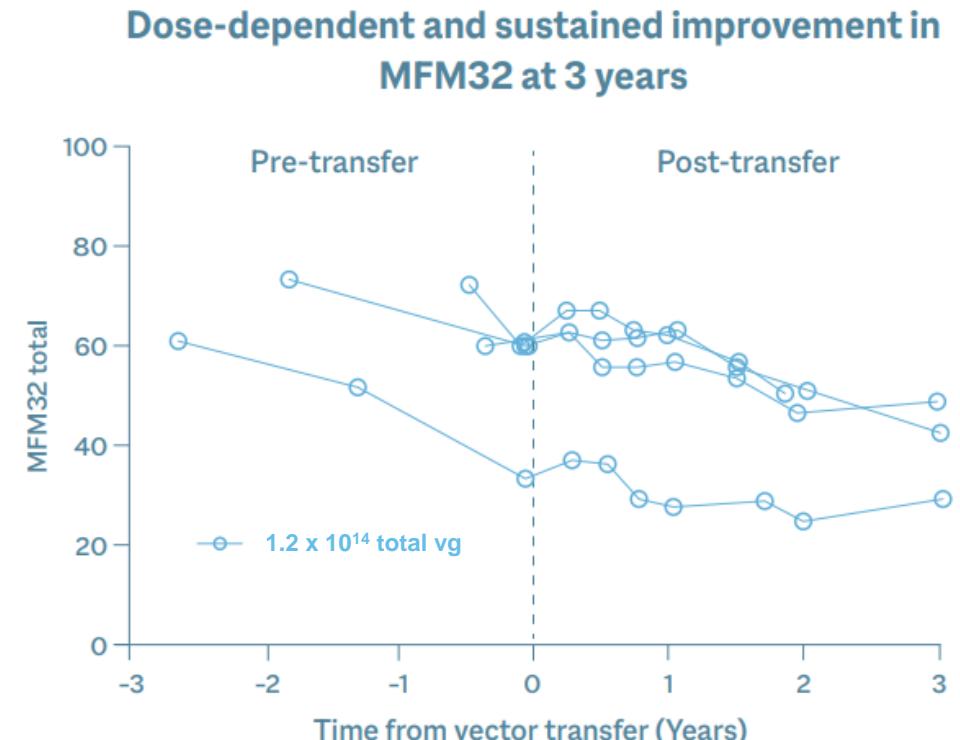
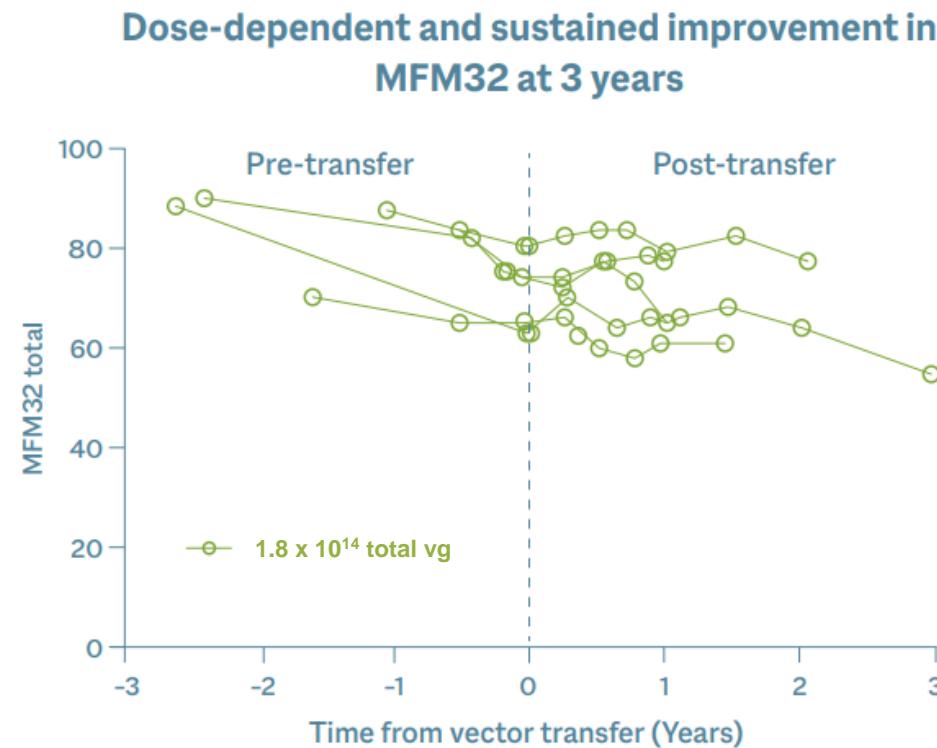
TSHA-120 achieved sustained improvement in primary efficacy endpoint and was well tolerated at multiple doses

- 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



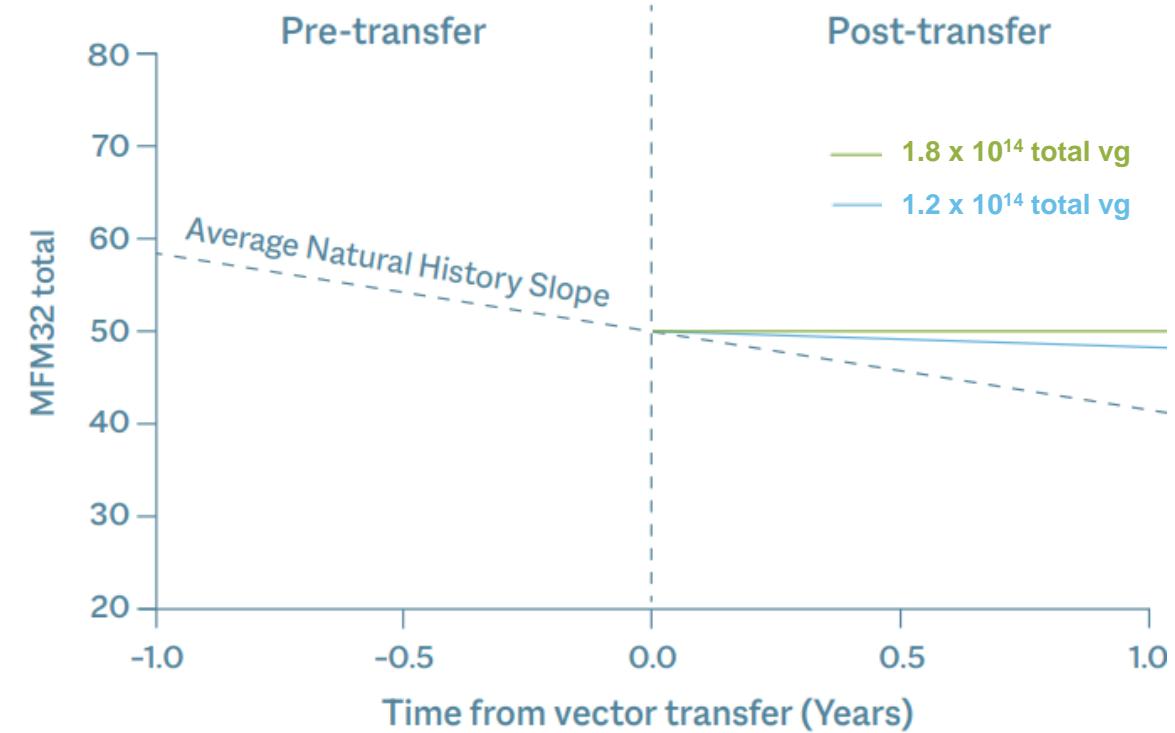
Treatment with TSHA-120 resulted in a clear arrest of disease progression at therapeutic doses and long-term durability



- 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

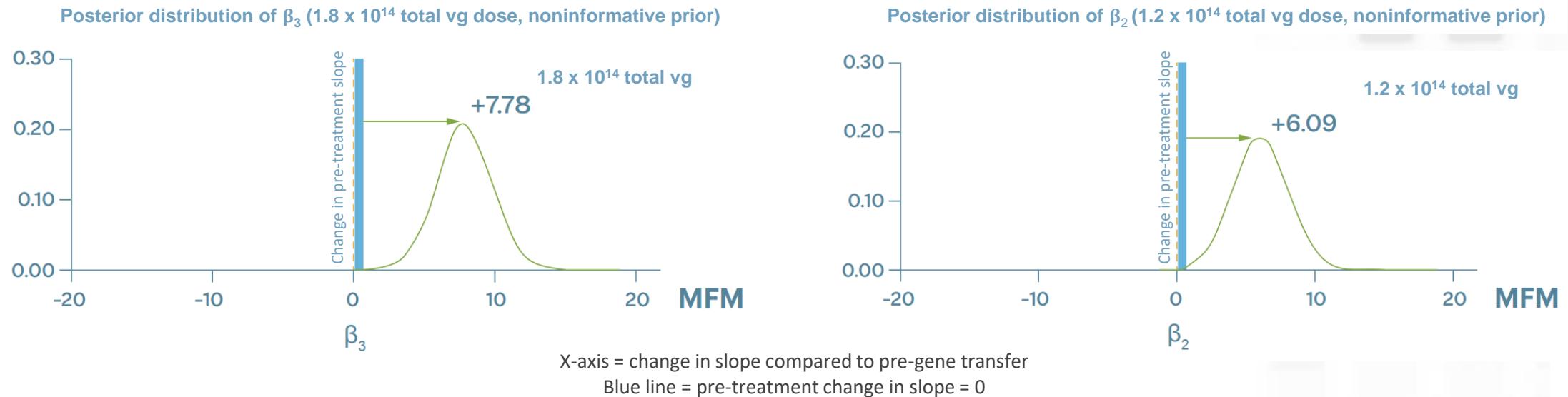


	Bayesian Analysis		Frequentist Analysis		
	Mean	Std Dev	Estimate	Std Error	p-Value
Post infusion: 1.8×10^{14} total vg	7.78	1.94	7.78	1.89	<0.001
Post infusion: 1.2×10^{14} total vg	6.09	2.11	6.07	2.05	0.004
Natural history decline	-8.19	0.74	-8.18	0.72	<0.001

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

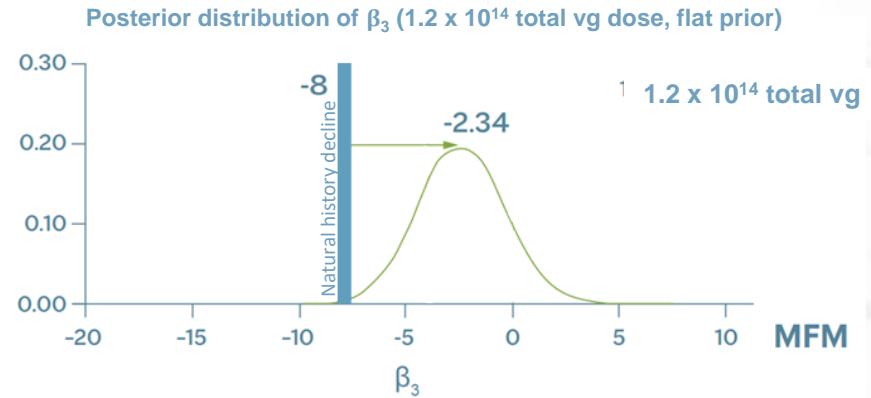
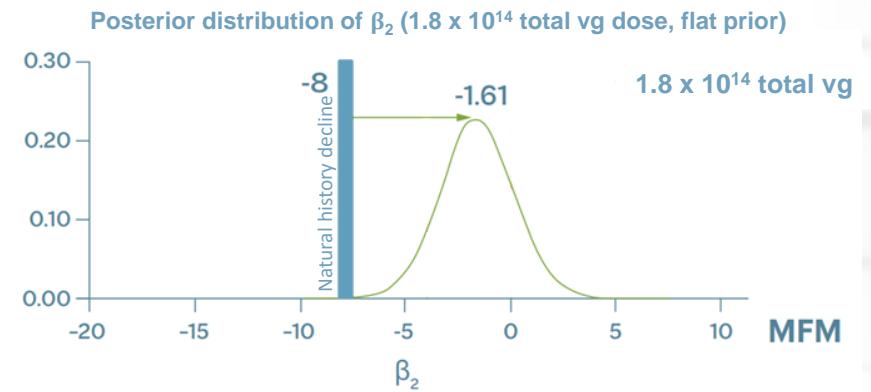


- Graphs depict treated population average annual post-treatment decline for both the 1.8×10^{14} total vg cohort and the 1.2×10^{14} total vg cohort
- 1.8×10^{14} vg halted patient pre-treatment rate of decline, avg annual slope improvement of 7.78 points
- 1.2×10^{14} vg resulted in clinically meaningful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

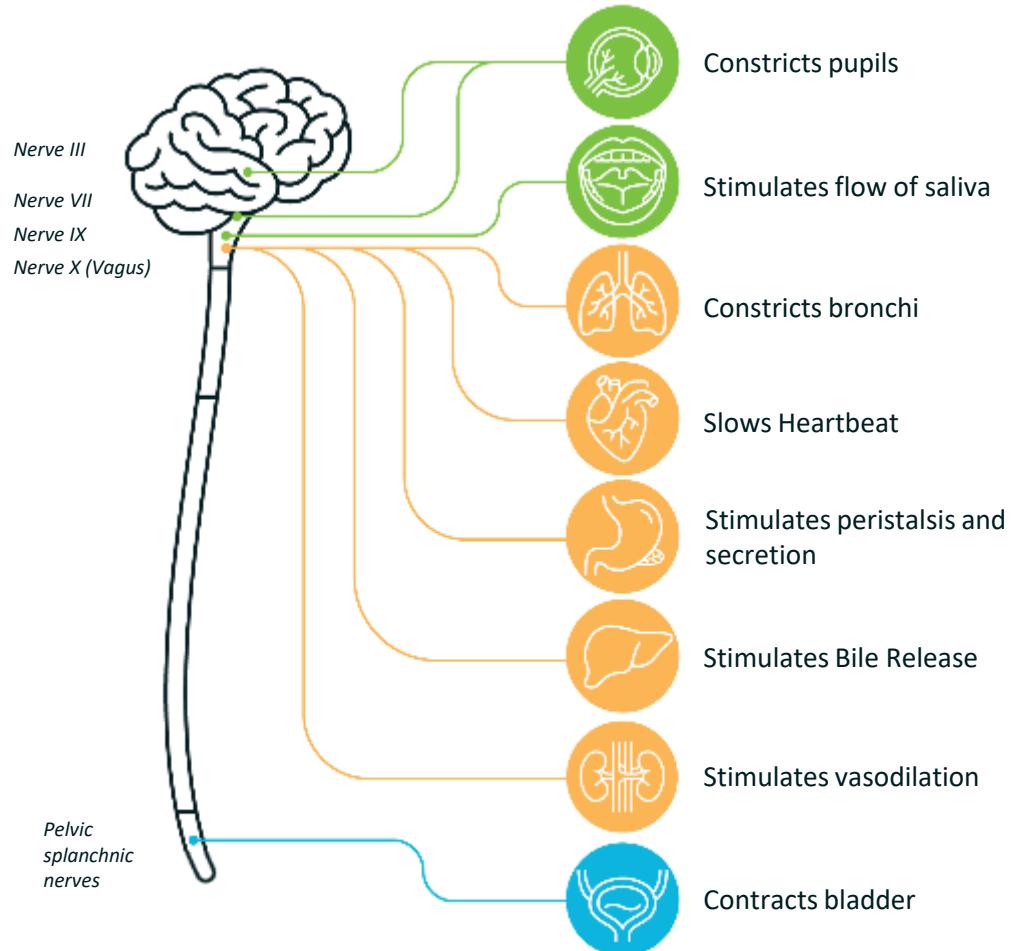
	Values = % Probability	
Change in disease progression	1.8×10^{14} total vg	1.2×10^{14} total vg
Any Slowing	99.9	99.8
Clinically meaningful slowing 50% or more	98.3	84.9

Vagus Nerve Redosing

Opportunity to achieve human POC for vagus nerve redosing

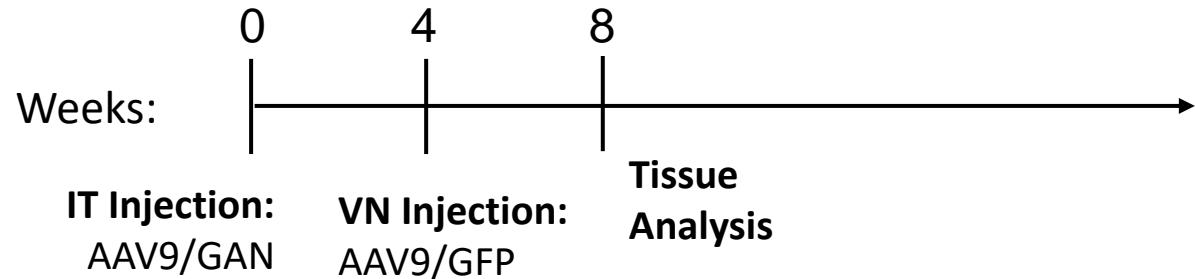
- The vagus nerve represents the main component of the autonomic nervous system
- Direct delivery to the vagus nerve may provide broad coverage of the autonomic nervous system and enable redosing by subverting the humoral immune response
- Proof-of-concept established in rodent and canine models; oral 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

Parasympathetic System

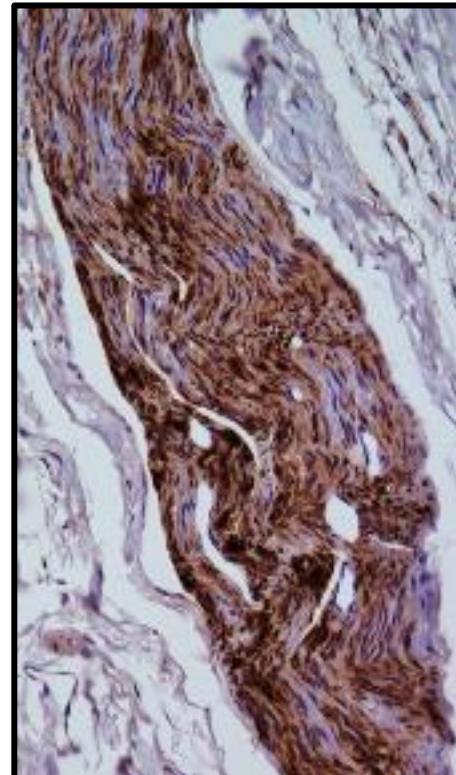


Robust expression of GFP in the vagus nerve and associated nodose ganglia in rats support redosing via vagus nerve injection

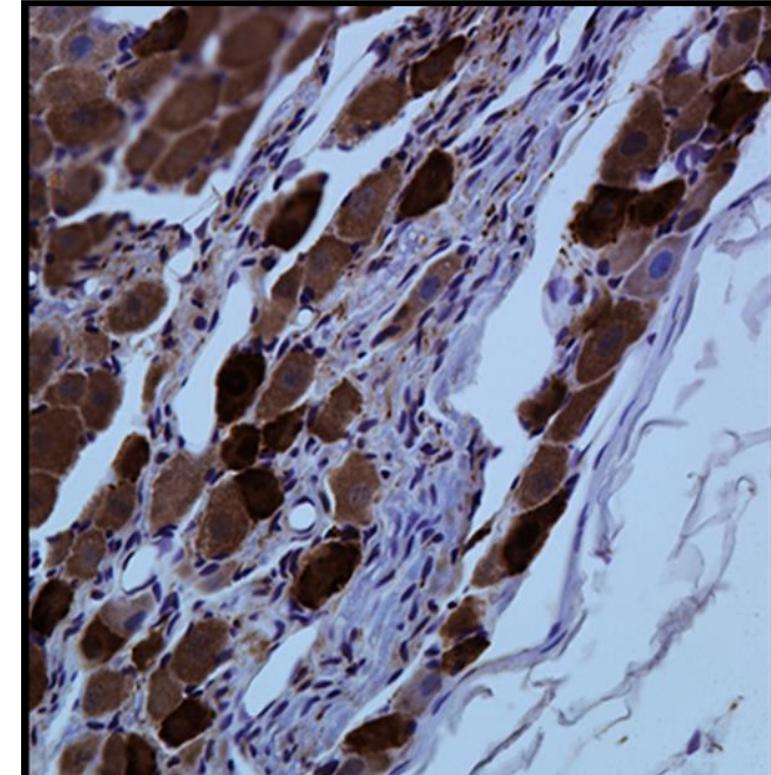
Study 1



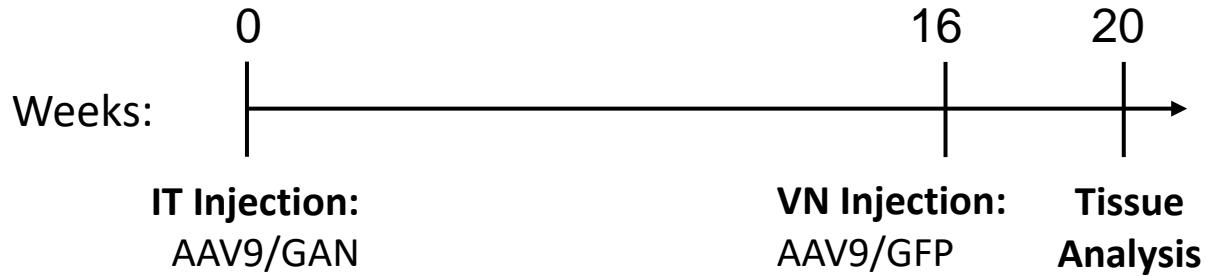
Vagus Nerve



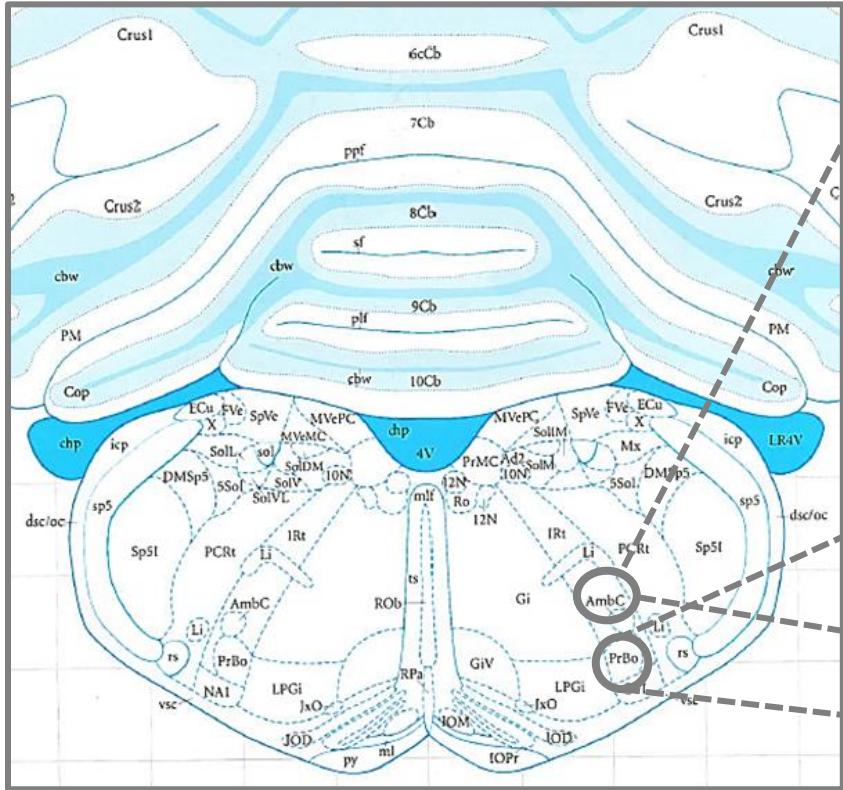
Nodose Ganglia



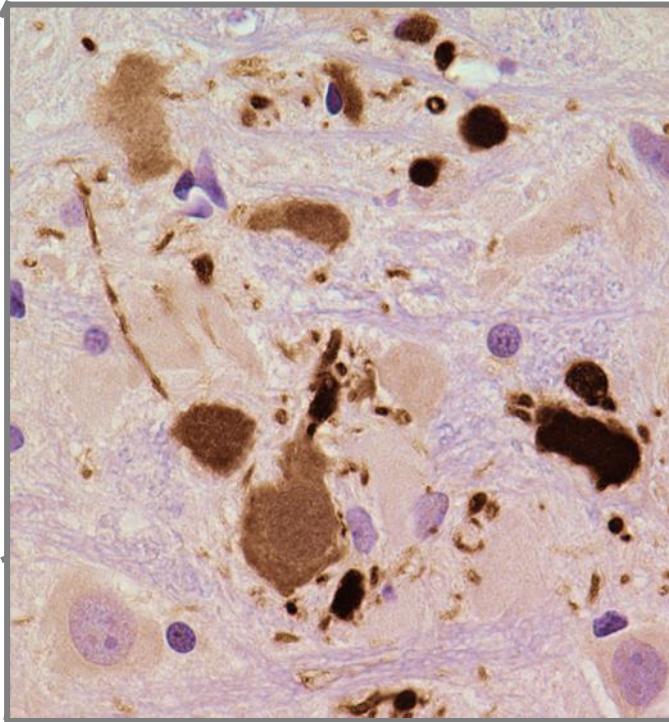
Study 2



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



Medulla

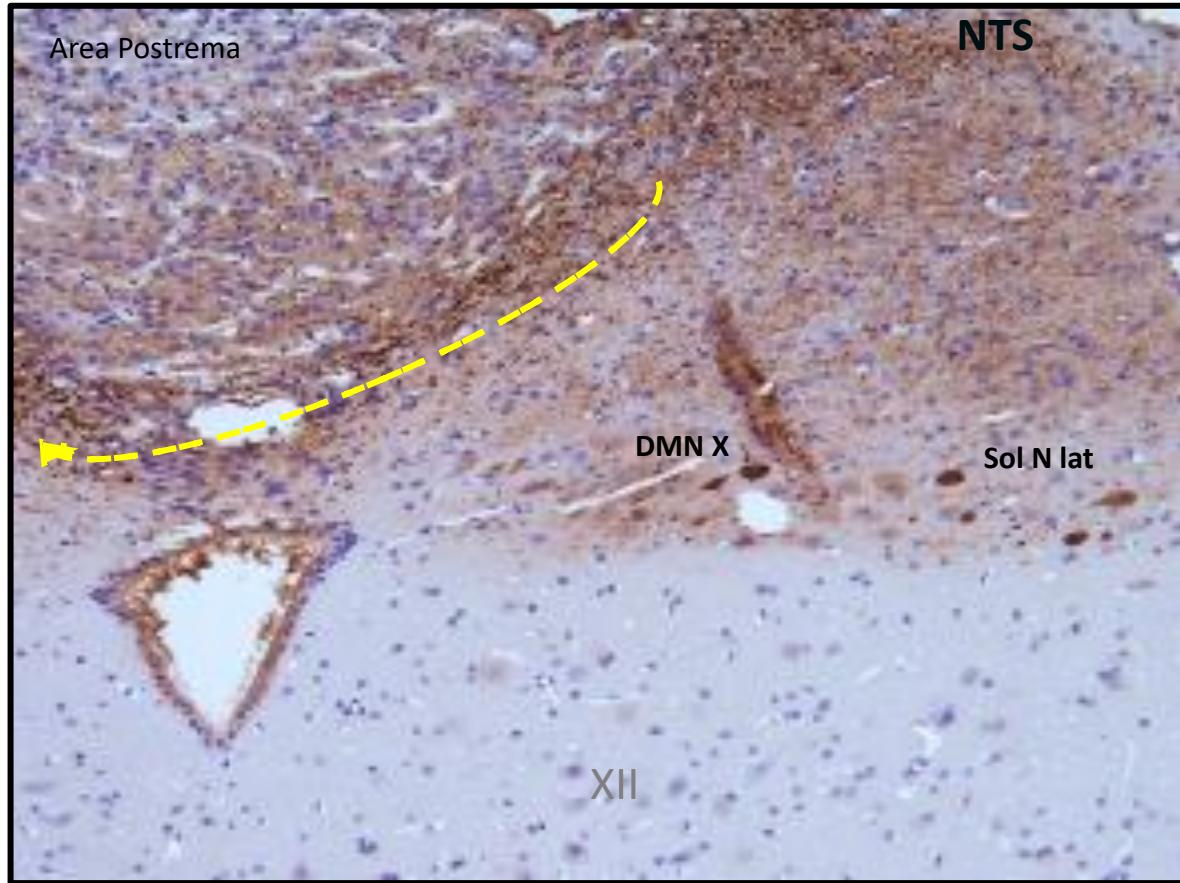


Nucleus Ambiguous

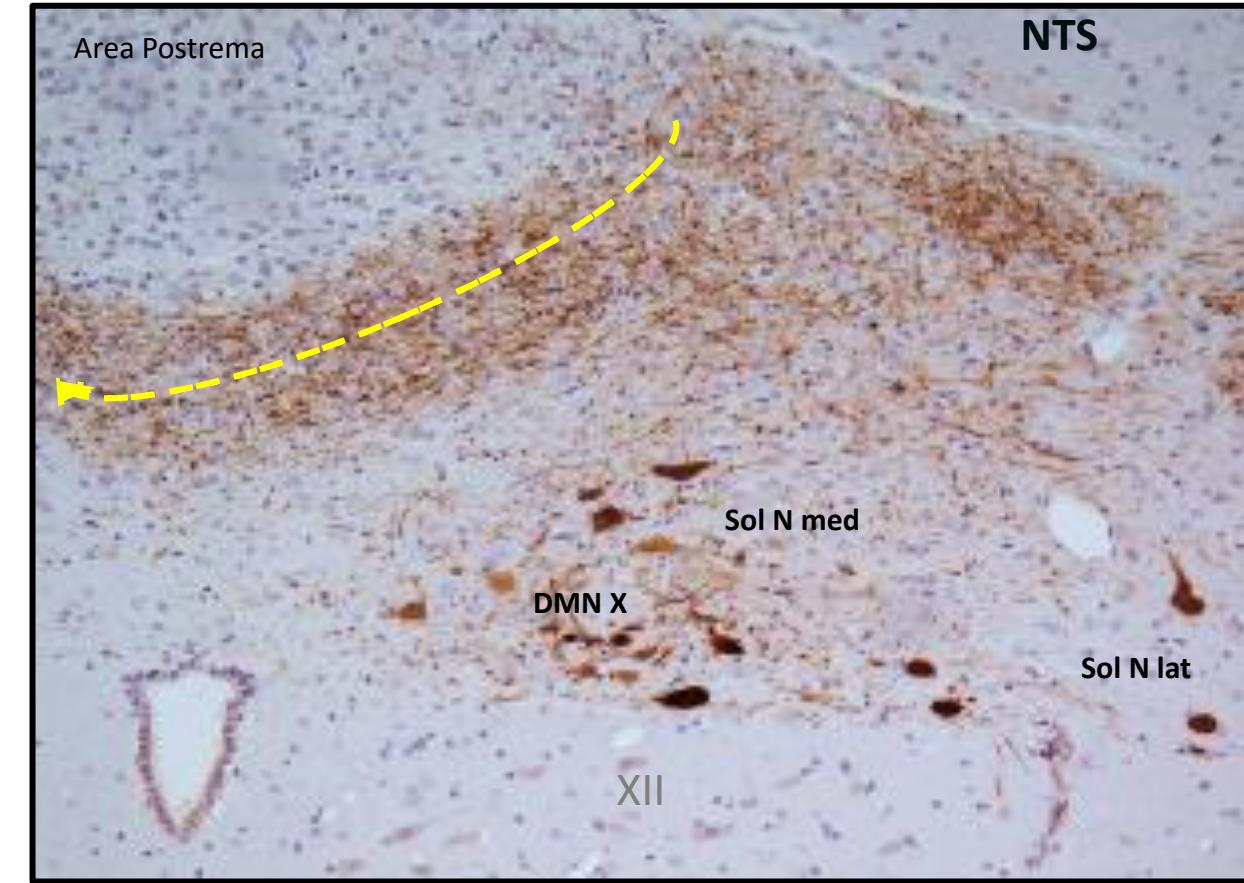


Pre-Botzinger Complex

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



*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

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



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

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

Initiated construction of internal cGMP facility in 1H 2021

**5 additional programs currently in IND-enabling studies
R&D Day in June 2021
Numerous value generating catalysts over the next 18 months**

Special Thanks



UT Southwestern
Medical Center



National Institute of
Neurological Disorders
and Stroke

Q&A

[Transcripts](#)

Taysha Gene Therapies' (TSHA) CEO RA Session II on Q1 2021 Results - Earnings Call Transcript

May 11, 2021 2:49 PM ET | **Taysha Gene Therapies, Inc. (TSHA) Stock**

**SA Transcripts**

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[▶ Play Earnings Call](#)

Taysha Gene Therapies, Inc. (NASDAQ:[TSHA](#)) Q1 2021 Earnings Conference Call May 11, 2021 8:00 AM ET

Company Participants

Kimberly Lee – Senior Vice President of Corporate Communications and Investor Relations

RA Session II – President, Founder, and Chief Executive Officer

Suyash Prasad – Chief Medical Officer and Head-R&D

Kamran Alam – Chief Financial Officer

Fred Porter – Chief Technical Officer

Conference Call Participants

Salveen Richter – Goldman Sachs

Raju Prasad – William Blair

Eun Yang – Jefferies

Operator

Welcome to the Taysha Gene Therapies First Quarter 2021 Financial Results and Corporate Update Conference Call. At this time, all participants are in a listen-only mode. Following management's prepared remarks, we will hold a brief question-and-answer session. As a reminder, this call is being recorded today, May 11, 2021.

I will now turn the call over to Dr. Kimberly Lee, Senior Vice President of Corporate Communications and Investor Relations. Please go ahead.

Kimberly Lee

Good morning, and welcome to Taysha's first quarter 2021 financial results and corporate update conference call. Joining me on today's call are RA Session II, Taysha's President, CEO and Founder; Dr. Suyash Prasad, Chief Medical Officer and Head of R&D; and Kamran Alam, Chief Financial Officer. After our formal remarks, we will conduct the question-and-answer session and instructions will follow at that time.

Earlier today, Taysha issued a press release announcing financial results for the first quarter ended March 31, 2021. A copy of this press release is available on the company's website and through our SEC filings. Please note that on today's call, we will be making forward-looking statements, including statements relating to the safety and efficacy and the therapeutic and commercial potential of our investigational drug candidates.

These statements may include the expected timing and results of clinical trials for our drug candidates and the regulatory status and market opportunities for those programs as well as Taysha's manufacturing plans. This call may also contain forward-looking statements relating to Taysha's growth and future operating results, discovery and development of drug candidates, strategic alliances and intellectual property as well as matters that are not historical fact or information.

Various risks may cause Taysha's actual results to differ materially from those stated or implied in such forward-looking statements. These risks include uncertainties related to the timing and results of clinical trials and preclinical studies of our drug candidates, our dependence upon strategic alliances and other third-party relationships, our ability to obtain patent protection for our discoveries, limitations imposed by patents owned or controlled by third parties and the requirements of substantial funding to conduct our research and development activities.

For a list and description of the risks and uncertainties that we face, please see the reports we have filed with the Securities and Exchange Commission. This conference call contains time-sensitive information that is accurate only as of the date of this live broadcast, May 11, 2021. Taysha undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call except as may be required by applicable securities laws.

With that, I'd now like to turn the call over to our President, CEO and Founder, RA Session II.

RA Session II

Thank you, Kim. Good morning, and welcome, everyone, to our first quarter corporate update and financial results conference call. As always, we hope you and your families continue to remain safe and healthy. Taysha has made great progress in the first quarter and continues to execute on its corporate initiatives. I will elaborate on some of the key achievements made thus far this year and highlight the expected milestones for the remainder of 2021. Following this, I will turn the call over to Suyash and Kamran for updates on our pipeline development and financial results, respectively.

Taysha has transformed into a pivotal stage gene therapy company with the recent acquisition of exclusive worldwide rights to a groundbreaking clinical program, TSHA-120, and AAV9 intrathecally dosed gene therapy invented by our Chief Scientific Adviser Dr. Steven Gray of UT Southwestern. The NIH is conducting an ongoing clinical trial of TSHA-120 for the treatment of giant axonal neuropathy or GAN. Notably, the GAN program is the first intrathecally dosed AAV gene therapy study in history. And as such, has had significant impact on the field.

As the program has laid the foundation for our extensive pipeline, we believe this acquisition represents a clear strategic and value-accretive opportunity that will provide read through across our entire portfolio. And inform the development of our gene therapy product candidates. We are thrilled to carry on the work done by Dr. Gray's lab and the NIH. As Suyash will discuss in more detail, TSHA-120 has a comprehensive preclinical and clinical package that we believe may support an expedited approval pathway.

The clinical data for TSHA-120 in patients with GAN are statistically significant, clinically relevant, dose-dependent and durable with a clear haul in disease progression at therapeutic doses. We are very encouraged that this represents significant value as the first potentially disease-modifying treatment for an estimated 2,400 patients living with GAN in the U.S. and in Europe alone.

As such, we intend to engage with major regulatory agencies as soon as possible and in parallel, we'll be accelerating the build-out of our commercial infrastructure to support patient identification, payer engagement and product distribution. We believe that TSHA-120, if approved, represents a near-term commercial opportunity for Taysha of more than \$2 billion. Beyond further advancing our new clinical stage programs, we continue to achieve significant progress with our preclinical programs. That we expect will provide the next wave of novel gene therapies.

We are extremely excited to announce the recent publication of new preclinical data for TSHA-102 in Rett syndrome in a highly regarded scientific journal. For the first time, we have quantitative evidence of miRARE's ability to demonstrate genotype dependent regulation of MECP2 gene expression across different brain regions in both wild-type and knockout mouse models of Rett syndrome.

Various challenges such as phenotypic variability, mosaicism, and targeting a dose-sensitive gene like MECP2 make development of a gene therapy difficult. miRARE offers a solution by allowing for the regulation of MECP2 gene expression on a cell by cell basis without causing over-expression related toxicity. Importantly, treatment with TSHA-102 and four to five week old knockout mice with Rett syndrome, resulted in a statistically significant survival extension by 56%, which is a very impressive result as these mice had meaningful accumulated disease.

In our view, the benefits in these adolescent knockout mice, should be a more translatable model of the disorder in humans. We believe these data validate our novel approach to treating Rett, help derisk the clinical program and support the advancement of TSHA-102 and into Phase 1/2 clinical trial by end of the year. We remain on track to file an IND or CTA in the second half of this year. You will hear from Suyash shortly, as he will review the robust data in greater detail. Our Chief Scientific Adviser, Dr. Steven Gray, initiated his work on miRARE and TSHA-102 in 2007. We are very pleased that his team's efforts are being realized and recognized.

Amongst other compelling preclinical data packages, we are particularly excited about TSHA-113, which has demonstrated successful AAV mediated gene knockdown, resulting in reduced TAL expression in mouse models of human tauopathies. These data may have significant implications for certain neurodegenerative diseases, including Alzheimer's disease. We are also pleased with preclinical results for TSHA-105 and SLC13A5 deficiency that demonstrate a reduction in plasma fit rate levels, normalized EEG activity and reduced number of seizures and seizure susceptibility in SLC13A5 knockout mice.

In SLC6A1 haploinsufficiency, TSHA-103 improves nesting and EEG activity in the SLC6A1 knockout mouse model and reduced spike train activity in both the SLC6A1 knockout and heterozygous mouse models. In Lafora disease, TSHA-111-LAFORIN and TSHA-111-MALIN have achieved effective knockdown of GYS1 expression in insoluble glycogen and decreased Lafora body formation in the appropriate Lafora disease mouse model.

In APBD TSHA-112 has generated significant reduction in GYS1 protein, abnormal glycogen accumulation and polyglucosan body formation in the APBD knockout mouse model. In Angelman disease, TSHA-106 increased UBE3A expression through shRNA-mediated knockdown of UBE3A-ATS, an in vitro cell line. We believe that this promising results demonstrated by our preclinical candidates validate our scientific approach and underscore our ability to drive a sustainable development engine for innovative gene therapy with the potential to impact meaningful patient population.

We are working diligently to advance our other preclinical programs in IND/CTA enabling study, and to date have already advanced six programs into IND/CTA enabling studies with an IND or CTA plan or at least one of these programs by the end of 2021. We look forward to providing further updates on our key programs at our R&D Day which will take place over two days on June 28 and 29. To support our programs, we have developed several key partnerships. Notably, we have established collaborations with Yale University, Cleveland Clinic and the UT Southwestern gene therapy program to support the creation of a novel next-generation minigene platform that is designed to overcome key challenges in gene therapy.

These minigene payloads for AAV gene therapies will be targeted for the treatment of genetic epilepsies, neuro developmental disorders and other CNS diseases. We are excited to leverage each partner's unique capabilities to expand the boundaries of AAV vector engineering and potentially open the door to treating genetic CNS diseases that have been traditionally precluded from treatment with gene therapies.

Foundational to our success is our team, which remains focused on advancing the development of our portfolio of innovative gene therapy candidates. We intend to continue this momentum by further growing our experience team. Since becoming a public company, we have expanded our team more than 10 fold and have now surpassed 120 employees. We expect to grow the team to approximately 150 employees by year end.

As noted, we are complementing the efforts of our internal team with our collaborators at UT Southwestern. With the collective expertise and dedication of these teams, our seasoned Board of Directors and independent internationally renowned scientific advisory board. We believe we are uniquely positioned to expedite the development of our gene therapy candidate and our technology platform.

I will now turn the call over to Suyash to provide a more detailed update on our R&D initiatives. Suyash, please go ahead.

Suyash Prasad

Thanks, RA. As RA mentioned, Taysha has a robust portfolio of 26 gene therapy product candidates for monogenic diseases of the CNS. Our candidates target broad therapeutic categories of immense unmet medical need, including neurodegenerative diseases, neurodevelopmental disorders and genetic epilepsies. We have recently added TSHA-120 for the treatment of giant axonal neuropathy or GAN to our pipeline, making it our most advanced program. We believe the preclinical and clinical data generated to date hold significant promise for GAN patients.

Preclinical studies have demonstrated strong proof-of-concept data for both the construct and the delivery modality. TSHA-120 performed well in preclinical studies demonstrating improved motor function and nerve pathology and long-term safety across several animal models. Preclinical data also demonstrated that TSHA-120 showed a significant improvement in the pathological appearance of the dorsal root ganglia, a key component of disease progression.

DRG inflammation is a topic that has been the focus of much discussion within gene therapy circles in recent months. This is because it has been observed as a histopathological finding in some non-human primate gene therapy studies, although the NHPs exhibited no functional compromise. Interestingly, in down and in the majority of diseases in our neurodegenerative franchise, the DRG have a significantly abnormal histological appearance and function as a consequence of underlying disease pathophysiology. Thus, it was not surprising that when treated with TSHA-120, we saw considerable improvements in the pathological appearance of the DRG in the GAN knockout mice.

We are fortunate that in addition to robust preclinical results, those considerable natural history that provides us with patient data to identify optimal marcus and endpoints for a clinical trial. To date, there are data in 45 GAN patients that demonstrate an average 8-point decline per year in the MFM32 scores that are consistent across patients of all ages. Recall that the 4-point define per year in the MFM32 is considered clinically meaningful. Notably and in line with recently published FDA guidance, regulatory agencies appreciate the availability of a well-controlled and high-quality prospective natural history study as a comparator in clinical trials for rare diseases.

In addition, we believe this natural history study provides us with a head start in identifying patients. Based on the positive preclinical results an R&D was opened, and TSHA-120 is being further evaluated in an ongoing clinical trial. The primary endpoint is to assess safety, with secondary endpoints measure of efficacy using pathologic, physiologic, functional and clinical markets. To date, 14 patients have been administered intrathecal TSHA-120 and six patients have at least three years worth of long-term follow up data. TSHA-120 has shown a dose-response relationship with the rest of disease progression at the second highest dose level, 1.8 times 10 to the 14 total VG at one-year post-treatment, affecting a statistically significant 8-point improvement on the MFM32 score, in comparison to the predicted natural history trajectory.

These results are very promising as a full point change in the MFM32 score considered clinically meaningful. Six of these patients treated at therapeutic dose levels have shown sustained dose-dependent improvements in MFM32 scores for more than three years. Long-term results demonstrated that treatment with TSHA-120 at multiple dose levels was well tolerated with no severe drug-related adverse events.

We look forward to reporting additional data later this year, including results from the highest dose cohort 3.5 times 10 to the 14 total VG. The FDA has already granted TSHA-120 orphan drug and rare pediatric disease designations, and we will continue to work closely with the regulatory authorities in the U.S. In the near-term, we expect to have discussions with the FDA and engage with other major regulatory agencies by year-end to discuss the pathway to approval for TSHA-120.

I would also like to highlight some of the promising preclinical data coming from our earlier-stage candidates that demonstrate the incredible breadth, depth and velocity of our development engine. It is important to note that there are no approved disease-modifying therapies for any of the programs in our portfolio.

With such compelling data to date for our pipeline, we are very encouraged as our gene therapy candidates could offer significant value to meaningful patient populations. We are very excited to show new preclinical data for TSHA-102 in Rett syndrome, that was recently published in brain. As RA discussed earlier, historically, it has been a challenge to find the right approach to safely regulate MECP2 expression in this disease.

The complexities are highlighted by phenotypic variability, mosaicism and the need to regulate MECP2 such that it does not cause over-expression related toxicity. Today's data give us confidence that we can achieve appropriate MECP2 expression in all cells in a genotype-dependent manner with no signs of toxicity.

With the built-in regulatory element, miRARE, TSHA-102 provided a statistically significant survival extension in knockout Rett mice by 56%, while the unregulated mini MECP2 gene transfer failed to significantly extend knockout survival at either dose tested. Additionally, the unregulated full-length MECP2 construct did not demonstrate a significant extension in survival and was associated with unacceptable toxicity profile in wild-type mice. We believe that the 56% improvement in survival in TSHA-102 treated knockout mice is extremely impressive. I see adolescent mice have accumulated significant disease.

Of note, this Rett patients do not demonstrate symptoms until about one year of age, and therefore, will not be treated until after this point, we believe these data are likely to be highly translatable to the clinical setting. In addition to survival, behavioral side effects were explored, TSHA-102 treated wild-type mice have a significantly lower mean aggregate behavioral score than those treated with unregulated full length MECP2 and then regulated mini MECP2.

Importantly, miRARE mediated genotype dependent gene regulation or shown by analyze and tissue sections from wild-type and knockout mouse treated with AAV9 vectors given intrathecally. TSHA-102 demonstrated reduced levels of MECP2 in different regions of the brain, suggesting that miRARE inhibited mean expression in a genotype dependent manner. This demonstrates that TSHA-102 achieved MECP2 expression levels with the normal physiological parameters.

In summary, these positive data demonstrated miRARE's ability to exhibit genotype dependent regulation of MECP2 gene expression across different brain regions in both wild wild-type and knockout mouse models of Rett syndrome without overexpression toxicities. We are very encouraged by these results and look forward to filing an IND or CTA in the second half of this year, followed by initiation of a Phase 1/2 trial by year-end. TSHA-102 has the potential to address a significant unmet need for an estimated 25,000 patients with Rett syndrome across the United States and in Europe.

Now I'd like to highlight some of our other preclinical programs that we have recently released data. TSHA-104, which is currently an IND/CCNA enabled studies for the treatment of SURF1-associated Leigh syndrome has demonstrated increased COX1 activity in brain and muscle and restored elevation of blood lactate on exhaustive exercise in a dose-dependent manner in SURF1 knockout mice. Dr. Qinglan Ling of UT Southwestern will be presenting these compelling data this Thursday at ASGCT. We remain on track to IND or CTA in the second half of this year.

TSHA-105, our gene therapy candidate, which is currently in IND/CCNA enabled studies for the treatment of SLC13A5 deficiency caused a significant sustained decrease of plasma citrate levels up to three months post injection compared to aged mouse wild-type controls. TSHA-105 normalized EEG brain activity, reduced the number of seizures and reduced seizure susceptibility compared to vehicle-treated controls. Dr. Rachel Bailey will be presenting these positive data this Thursday at ASGCT.

TSHA-103 is on gene therapy candidate that is an IND/CTA enabling studies for the treatment of SLC6A1 haploinsufficiency. And the SLC6A1 knockout mouse model, TSHA-103 improved nesting and EEG activity. In addition, in SLC6A1 knockout and heterozygous mouse models, TSHA-103 reduced spike train activity, which is a recording of abnormal neuronal activity associated with seizures. We believe the estimated prevalence is 17,000 patients in the U.S. and in EU.

TSHA-111-LAFORIN and TSHA-111-MALIN, our gene therapy candidates in IND/CTA enabling studies for the treatment of both subtypes of Lafora disease achieved effective knockdown of GYS1 expression in the Lafora disease, LAFORIN and MALIN mouse models, respectively. Both product candidates decreased Lafora body formation within the brain and their respected mouse models.

TSHA-112 has been tested in IND/CTA enabling studies for the treatment of adult polyglycosan body disease, or APBD. In preclinical studies, miRNA knockdown of GYS1-induced significant reductions in GYS1 mRNA, GYS1 protein, abnormal glycogen accumulation and polyglucosan bodies throughout the brain and an APBD knockout mouse model. For GM2 AB variant in preclinical studies, TSHA-119 caused a significant dose-dependent reduction of GM2 accumulation at 20 weeks in mice that were dosed intrathecally at Postnatal day one or at six weeks of age.

Long-term follow-up, which include bi-monthly behavioral as well as biochemical and histological analyses are currently ongoing. TSHA-106 is being developed for the treatment of Angelman syndrome. In vitro testing and the neuro plus cell line demonstrated consistent knockdown of UBE3A-ATS and the subsequent increase in UBE3A expression across 26 distinct shRNA candidates. Selection of a development candidate is expected by midyear, followed by interim expression and safety data from confirmatory non-human primate studies by the year-end.

TSHA-113, an AAV mediated gene knockdown construct has shown particular promise. TSHA-113 AAV9 capsid packages micro RNA shuffles are designed to target tau mRNA for all six isoforms found in the human and/or mouse brain. Treatment with TSHA-113 has shown a significant reduction in tau mRNA and protein levels while demonstrating widespread expression in neurons and GLIA. This is potentially significant implications for patients with neurodegenerative disorders characterized by deposition of abnormal tau protein in the brain, including Alzheimer's disease, MCI associated frontotemporal dementia and progressive super nuclear polio.

As you can see collectively, these preclinical data highlights our next wave of novel gene therapies, but for the potential to impact patient populations affected by significant diseases in a meaningful way. With that, we intend to file an IND/CTA for one of the following programs by the end of 2021. SLC13A5 deficiency, Lafora disease, APBD or GM2 AB variants. We also remain on track to file an IND/CTA and TSHA-102 in Rett syndrome and TSHA-104 and SURF1-associated Leigh Syndrome an IND with TSHA-101 in GM2 gangliosidosis in the U.S. during the second half of this year.

We expect to initiate the Phase 1/2 trial for TSHA-118, which is under an already open IND. We are excited to have six near-term Phase 1/2 trial initiations planned throughout our portfolio. We are making incredible progress advancing our product candidates into clinical development, and we look forward to providing additional updates at our R&D Day that will span two days in June.

We will continue to advance our pipeline by leveraging our next-generation platform technologies. As part of this initiative, we have recently established collaborations with Dr. Dennis Lal at the Genomics Institute, Cleveland Clinic, and Dr. Yang Xiaoyong at Yale University to further push the boundaries of AAV vector engineering by developing next-generation minigene Halos, this has the potential to overcome current limitations of packaging capacity, which is a critical barrier to treating genetic diseases not addressable for conventional AAV gene therapy technologies.

This may enable us to effectively treat a wider range of devastating CNS diseases, UT Southwestern will produce bio vector constructs that incorporate the minigene payloads and evaluate the constructs in both in vitro and in vivo studies. Through collective efforts of Taysha and our partners, we will continue to strive for innovations and our platform technologies that will enable us to treat a broad range of CNS diseases with novel gene therapies.

With that, I'll turn the call over to Kamran to review our financial results.

Kamran Alam

Thank you, Suyash. This morning, I will discuss key aspects of our first quarter 2021 financial results. More details could be found in our Form 10-Q, which will be filed with the SEC shortly. As indicated in our press release today, R&D expenses were \$23.9 million for the first quarter ended March 31, 2021, compared to \$5.5 million for first quarter ended March 31, 2020. The increase was primarily related to the company's development program as a result of increased manufacturing related spend, clinical and preclinical activity and headcount.

G&A expenses were \$8.2 million for the first quarter ended March 31, 2021 compared to \$0.07 million for the first quarter ended March 31, 2020. The increase was primarily due to an increase in personnel costs, resulting from increased headcount, professional services fees, and other corporate related expenses.

Net loss for the first quarter ended March 31, 2021 was \$32 million or \$0.87 per share as compared to a net loss of \$5.4 million or \$0.50 per share for the first quarter ended March 31, 2020. As of March 31, 2021, Taysha had \$228.7 million in cash and cash equivalents. We continue to expect that our working capital will be sufficient to fund our operation into 2023 inclusive of the development, regulatory and operational milestones RA and Suyash have outlined today.

And with that, I will hand the call back to RA.

RA Session II

Thanks, Kamran. We are pleased to have shared with you, our success over the first quarter. Looking ahead, we will continue to focus on rapidly advancing our pipeline with many key milestones anticipated over the next 18 months. We have made a significant transition into a pivotal stage gene therapy company with our acquisition of TSHA-120, and we expect to provide both clinical and regulatory updates by year end.

Further, we remain on track to report first in human clinical data for TSHA-101 in GM2 gangliosidosis, as well as initiate a Phase 1/2 trial of TSHA-118 and CLN1 disease that currently has an open IND. As you've heard today, we have an extensive pipeline of preclinical programs that are advancing quickly. We expect to open four INDs or CTA and have a total of five programs in clinical development, including for Rett syndrome and SURF1-associated Leigh syndrome by year end and have an additional six programs currently in IND or CTA-enabling study.

In parallel, we will continue to support our R&D initiatives by expanding our team to approximately 150 employees by year end, completing the build-out of our Dallas corporate headquarters by mid-year, as well as continuing to construction on our internal GMP manufacturing facility in Durham, North Carolina, with numerous potentially value creating near term milestones. We expect this year to continue to be a transformational period, and we look forward to providing further updates on our progress at our upcoming R&D Day event next month.

Lastly, I would like to give special thanks that the continued support and dedication of our Taysha employees, Board of Directors, scientific advisory board, collaborators, and the patients and advocates who remain our motivation every day to continue on our mission to develop curative gene therapies to eradicate devastating monogenic CNS disease.

I will now ask the operator to begin our Q&A session. Operator?

Question-and-Answer Session

Operator

We'll now begin the question-and-answer session. [Operator Instructions] The first question comes from Salveen Richter from Goldman Sachs. Please go ahead.

Salveen Richter

Good morning. Thanks for taking my questions. So one question here about – good morning. One question here about capital and resource allocation as you're running multiple trials building out a GMP facility and hiring employees. So how should we think about that over time? And secondly, with regard to the Rett program, maybe if you could touch on the registration path here and what you'd like to see from that first clinical data set to inform the pivotal program.

RA Session II

I appreciate the questions. Good morning. So I'll take the first and Suyash if you could address the question on Rett. As far as capital allocation goes, we reaffirmed our guidance this morning that we still have the capital resources to take us into 2023. As it pertains to gene therapy drug development, it's much different than kind of classic drug development from a time and cost of tests because you're not doing kind of high throughput screening, I trying to identify a target, you already know the target.

And so it's actually much more capital efficient to go after gene therapies versus other forms or other modalities. And so the way that we're thinking about this is, again, because our portfolio is appropriately staged, we have some programs that are moving into the clinic, some programs that have just hit animal proof of concept and some early discovery programs.

Most of our translational and discovery work is being done by our collaborators at UT Southwestern. And having that academic partner is a really capital efficient way to do kind of your early translational discovery work. As it pertains to the clinical development, gain, this is a pretty capital efficient modality, because the number of patients you need to actually get a signal and to achieve human proof of concept is quite small compared to some other modalities.

So again, I think, we feel very strongly about this moving five programs into clinical development this year already having a few programs in the clinic, we still feel strongly that our capital takes us into 2023. I'll stop there. And Suyash, do you want to address the question around Rett syndrome and kind of what our thoughts are on the path in the clinic and our path to approval?

Suyash Prasad

Absolutely. Thanks, RA and thanks for the question, Salveen. Yes. So for Rett syndrome, I think we've been spending a lot of time thinking about the clinical development program and the pathway to approval. And we're going to take a slightly more cautious approach for some of our other conditions such as GM2, CLN1 GAN where the diseases are a little less common and where there is an ongoing relatively high-risk of mortality quite early on.

So the way we think about Rett is that the first study of a group of two will be more of a Phase 1/2 primarily safety study with some exploration of preliminary efficacy. Following on from that, you will then perform a Phase 2/3 study, which focuses – it takes learnings from the initial Phase 1/2 study, take the learnings from that and applies it into a more expensive Phase 2/3 pivotal efficacy study.

Now with regard to the first study, the Phase 1/2 study likely we'll be do hit all older patients. As you know, FDA tends to push you away from children towards adults first and in this particular situation, we actually tend to agree with that approach. There are these risks of toxicity with over-expression of MECP2. So we just have to be quite mindful when we design this initial study. So the first study will be Phase 1/2 clinical pivotal safety, primary efficacy in the adult population in terms of endpoints will be looked at the safety aspects of safety initially. And then we'll be looking at efficacy really in three different buckets. The efficacy will be looked at, firstly with a number of the different Rett-specific clinically rated scales, for example, the Rett syndrome motor behavior assessment, the Rett syndrome behavior question are. So they are the Rett scales, we'll also be looking at seizures in some detail because children with Rett syndrome have significant seizure activity.

So we'll be looking at how frequent the seizures are, how many medications on, what triggers the seizures, how durable the seizures are and over time, hopefully will be able to see a reduction in seizure activity and bring them off medications and also see an improvement in the EEG. And then the third bucket kind of assessments will include a general multi systemic, multi-organ type aspects of Rett syndrome disease characteristics, such as the respiratory assessments, which, as you know, you have respiratory rhythm in Rett syndrome, sleep apnea issues, cardiac issues such as QT prolongation. So I think that the first, once again, will look at safety initially and some of these areas of preliminary efficacy, we will build on that and design the Phase 2/3 study subsequent to that. As we've already talked about, we'll be engaging with regulatory agencies during the course of this year to pressure test our thinking around these particular plans, and we'll be starting the clinical study towards the end of the year.

Salveen Richter

Thank you.

Operator

The next question comes from Matthew Harrison from Morgan Stanley. Please go ahead.

Unidentified Analyst

Good morning, this is Thomas on for Matthew. Can you give an update on where you are with manufacturing for the GAN program, in particular, what sort of assay work do you still need to complete? Thank you.

RA Session II

Thanks, Thomas for the question. I'll turn this question over to Fred Porter, our Chief Technical Officer on the line to talk about our manufacturing. Fred?

Fred Porter

Yes, thanks, RA. Thanks for the question, Matthew. Yes, obviously we're in the process of onboarding the GAN program. And so where we're really beginning is with the assays, reviewing the assays that were conducted by the NIH for the Phase 1, Phase 2 two clinical material, and what our intention is just try to update those methods to qualify and then validate them to prepare for a late-stage pivotal work. So, we're actively engaging on all the critical quality attributes assays with our partners to move that forward with our CDMO. In addition, we're looking very deeply into the potency assay development work, and this is something that's happening, jointly between Suyash's group and my own to move forward a potency assay very quickly to kind of synchronize a fully developed and qualified potency assay with pivotal lot manufacturing. I'm happy to answer any questions about that?

RA Session II

No, I can I add one more comment on top of Fred, and it's an important question to ask about the assay. The other assay that we're spending some time thinking about and really pulling the trigger on with some considerable effort is the – is more in the GPCR say to the DDPCR. So we get some slightly more accurate numbers in terms of titrate. So that's another arm of patent parallel with the potency of the other CMC characterization that Fred mentioned. Thank you.

Operator

[Operator Instructions] Then one, the next question comes from Raju Prasad from William Blair. Please go ahead.

Raju Prasad

Hey guys, thanks for taking a question. Congrats on the progress. I'm kind of looking down your pipeline and I see a lot of the technologies that you're de-risking from a payload perspective, the miRARE platform, the bicistronic vector, I could see follow-on indications once those technologies are derisked. But my question was more on the regulatory side. As you're kind of dealing regulators on these different indications, what types of aspects of the programs do you think will be derisked by clinical data there? Is it on endpoints and deal with endpoints with the FDA? Is it on the IT administration? Maybe some color there would be great. Thanks.

RA Session II

No, it's a great question, and it's kind of central to our scientific thesis. And really our focus on the use of validated gene therapy technology kind of coupled with very targeted novel payload design and really trying to achieve an economy to scale that really allow us to go after this kind of large portfolio of product candidates. And we're able to do that because we hold a couple of things constant. The first thing is all of our programs are AAV9, the second thing, they all use HEK293 suspension manufacturing as a platform. And the third is really around this notion of intrathecal delivery.

And this really allows us to take learnings and achieve economies of scale from one program to the next. I'll pause there, and Suyash, I'll allow you to kind of talk about maybe some of the things that we plan to discuss with regulators and how we plan to apply those learnings from one program to the next.

Suyash Prasad

Thanks, RA and thanks Raju for the question. Yes, there's lots and lots of commonalities, I think, between our programs, over and above the simple – the trifecta of comments we about AAV9, HEK239 and IT administration. There's many, many other commonalities, I think we shared and we – as a platform more than anything. Let me touch on a couple of things – I think we're going to learn a huge amount from just one program to inform the next. There's a lot of debate in the field about IT versus ICM versus ICV and several contribution between them all. I keep coming back to the perspective that IT administration works has worked for decades. I've given it myself in the world of oncology and anaesthesiology and it's worked for decades there.

When you look at the clinical data from GAN from CLN3, CLN6, and another in Zolgensma, you see it works, and it works beautifully. And I think as we continue to build our portfolio of programs, we can really I think the FDA and other regulators will just become increasingly comfortable with intrathecal administration. And there's many nuances around that, but many details. For example, we spent some time yesterday talking about a different type of think kits you might use to give intrathecal drug and the comparability – compatibility test you might need to do for some of these different methods of administration. So I think there's lots and lots of learning, in particular from GAN that will inform the rest of our portfolio.

Another piece of learning, I think that's important from GAN and as our programs progress, just on the immunosuppression regime we like to use. So the whole world of the immunology of gene therapy has evolved and evolved rapidly over the past few years, initially, people didn't get any immunological therapy and just treated liver inflammation reactively with oral prednisolone. When was decided that let's give the prednisolone first to try and prevent it. And then additional medications have been rather than added.

And we've settled very – on this very nice regime of six months of oral prednisolone plus 12 months of rapamycin and specific doses that we have a lot of experience with now and learnings from the GAN program, where a number of patients have been managed with this regime in expressive therapy very, very successfully. To the point actually, we're not seeing any evidence of any T cell-mediated information in any of the patients who received this regime from the GAN study. We're using that approach in GM2, in CLN1, in SURF1. And I think once again, we're going to build up this body of evidence for that particular regime.

I think the third thing I'll mention, and you touched on it is endpoints in the clinical trial and what we can learn from one to other. I think for a lot of our diseases, where there are these neurological features. There's a development called regression and a lack of failure to GAN milestones. And we've set on a very nice group of development to assessments the Bayley scale, the Vineland, the CHOP INTEND. And there's one or two others that are more disease specific. We know how to train the rates that do these particular assessments.

We know how to train the rates that do these particular assessments. We note of video, the assessments in a particular way, when it to upload the videos to a server, where they can then be reviewed externally by a second rater a second group of raters who are blinded to what the patients have been treated or not.

All these things had a lot of robustness to the clinical development program and learnings from one to the other. The other thing I mentioned when we were talking about Rett a few minutes ago, was just seizures how we collect seizure information, seizure activity, EEG, the medications, the patients are on, et cetera. So I think that in our discussions with the regulators, there are many, many commonalities, in particular, on the clinical development side, but I think are going to be applicable to all programs and will constitute additional learnings from one to the other. I hope that answers your question, Raju.

Raju Prasad

Yes, that's extremely helpful. Maybe just a quick follow-up on that last point. As it relates to the upcoming FDA discussions on the GAN program, how should we be looking at the results of those discussions as it relates to the potential request from the FDA. I'm thinking particularly about natural history comparator versus having to run a placebo arm or control treated arm. I mean is that something that you're looking to see kind of as to extrapolate to the rest of the pipeline? Like if they do give you a natural history comparator for pivotal, that's something that you might try for GM2 and some of the rare diseases? Or do you think that the discussions on GAN are only going to be related GAN and each individual indication will probably be a different – kind of a different kind of discussions with the agency. Thanks.

Suyash Prasad

So it's a really important point. The – how much data are already existing for a particular disease. And it's – there are certainly commonalities there from proven the program, but there are also some subtle differences, and we're doing things a little bit differently from program to program. What I will say is a higher level is some very nice guidance that was published by the FDA on gene therapy development for neurodegenerative disease and have a specific section on natural history study in historical controls.

They said very clearly, this may be appropriate for gene therapy product to treat a rare and serious neurodegenerative disease. If there's a clear unmet medical need, which is absolutely the case for most of our programs, where the inclusion of current control is not practical or ethical, which is also true, certainly for programs like GM2 or CLN1, where there is ongoing higher risk of mortality. They also talk about the disease course is well documented. And the expected treatment effect is large, it may be very, very suitable to use a natural history comparator as a control.

Now for GAN, specifically, we have 45 patients, in fact, more than that, we've presented data of 45 patients in the natural history study with data, that patients were enrollments in 2013. So it's rates of [indiscernible] (0:47:23) data on some of these patients. And we've got very, very clear indication that there's a consistent drop in the primary efficacy endpoint, the MFM32 8 points per year. I think because of that, it's also predictable. The disease course is predictable. And so for GAN, very rare disease. With – and we're seeing a very nice treatment effect in our international study. So all those things really contribute to the fact that for GAN, in particular, I think is – you don't know what the FDA you're going to say, but I think it checks all the boxes for a natural history study being an appropriate comparator.

So my guess is it's unlikely they will ask us to do any kind of more formal concurrent control. Once again, you don't know at the FDA are going to say, but it checks all the boxes from that perspective. GM2, there's a lot of already good natural history data out there in publications. And so we're making use of that CLN1, there is a prospective natural history study ongoing currently with about 40 to 50 patients in it. This is international. So we'll be using that.

So it's a little bit different from program to program. Rett syndrome, there is huge natural history databases that are available. Although for Rett, we will likely build in a concurrent control for a randomized, but non-blinded concurrent control. To add a little more robustness the clinical development plan. So let me start there. I hope I've answered your question and give us some context, but I can stop. I think we can go into more detail if you like, Raju, but most of that now.

Raju Prasad

No, that's extremely helpful. Thank you for the question.

RA Session II

Thanks, Raj.

Operator

The next question comes from Eun Yang from Jefferies. Please go ahead.

Eun Yang

Thank you. Thank you. So today, when we talk about address the patient population for your gene therapy programs, it's been kind of a focus on the U.S. and Europe. But now you look to potential approval of TSHA-120 in 2023, what are you thinking about the market opportunity outside the U.S. and Europe?

RA Session II

Thank you for the question. That's a great question. And what's interesting about rare disease commercialization is the fact that you're able to leverage a major market approval pretty much all over the world. And what I mean by that and approval in the U.S. or in the EU, you're able to initiate almost immediately reimbursed name patient program or early access programs and some of the more highly reimbursable markets where you also have an over-expression of genetic diseases. And so in some countries, like the GCC region of the Middle East, Saudi Arabia, Israel, Turkey, some of the Latin American companies – countries where reimbursement actually quite good. Brazil, Colombia, these are areas that we would actually look to commercialize post a major market approval, either under a reimbursed name patient program or early access program would have eventually you would seek a marketing approval over time.

So that's really the way that we're thinking about commercialization. We are looking globally we would most likely do this through some of your more established distribution partners. There's a number of partners, particularly in Israel, the Middle East, Turkey, Brazil that are highly skilled in achieving reimbursement for specialized products, gene therapies, high-priced products. And so we would probably most likely go this route.

We most likely would not look to out-license our product from a commercialization perspective early on, but really do our commercialization through distribution collaborations in some of these countries that I mentioned. So that's the way that we're thinking about things today. Obviously, as time goes on, you gain more information and you alter your thinking that way. But at least for now, that's the way that we're approaching our commercialization, our pre-commercialization plans.

Eun Yang

Thank you. And I have one more question on Rett syndrome program. So I'm sure that you're familiar with the Novartis program. And I don't know how much you can speak about it, but aside from your program, potentially have a better regulation of the transgene expression. Can you talk about kind of a differentiation compared to Novartis, and Novartis actively pursuing their Rett program? Thank you.

RA Session II

Thank you for the question. So what I'll just do is highlight the different – the kind of the main difference in the two approaches. And then I'll turn it over to Suyash to kind of talk about the differences in more depth. So really, the main difference in the two programs is our program, TSHA-102, is a gene therapy product, AAV9, with the self regulatory feedback we built into the transgene that caps gene expression on a cell by cell basis or as we – what was described in the paper that was recently published that has a genotypic regulation of gene expression. That's the term that we're using. Essentially, what we're doing is having a safety valve to guard against overexpression associated toxicity.

The Novartis AveXis construct is essentially self complementary AAV9 with full link MECP2 with no regulatory component. That at least is the last construct that was published that we are all publicly aware of. I'll stop there. Suyash, maybe you want to go through in a little bit more detail some of the nuances.

Suyash Prasad

Yes. Thanks, RA, and thanks for the question. I think it's an important question. As RA mentioned, the only – the major difference really is the fact that we include – we have the mini MECP2 gene, which was developed by Professor Sir Adrian Bird and very esteemed and ineligible Rett experts from Edinburgh who was actually first person to demonstrate unequivocally that Rett syndrome is a highly reversible disease.

So we use his design for the mini MECP2 gene. And then we attach this strip of micro RNA binding sites, the miRARE platform, which stands for micro RNA a responsive of auto regulatory element. So when MECP2 levels go up within the sale as a consequence of the gene therapy, the down regulatory micro RNA binding sites are triggered, they bind to this miRARE platform, which is in the untranslated region of the construct and bring down levels of MECP2, as RA suggested, acting as a safety valve.

Now we're very excited to be able to say to you that the first quantitative data demonstrating this reduction in MECP2 expression to the point where you have enough so it's efficacious, but not too much that is toxic, was published in brain, which is a very prestigious [indiscernible] (0:55:16). It went online on Friday, and we issued a press release yesterday. And I would encourage you to look at the paper, the lead author is Sara Sonet and senior authors are good friend and colleague, and our Chief Scientific Adviser, Steven Gray, there's a particular diagram in that paper, which I'd suggest you look at, which looks specifically at different levels of expression of MECP2 in different parts of the brain in different parts of the spinal cord.

And you can see very nicely that the non-miRARE construct over expresses whereas the miRARE construct expresses enough so that it is efficacious, but not toxic. So we're very excited about that fixer paper. So I think that's the main difference. The fact that we can demonstrate this – the ability to express MECP2 within these normal physiological parameters now we've shown in different parts of the brain, and we've shown it quantitatively as well.

My understanding is that Novartis is still moving forward with that program. Last I heard was the planning to move forward as an IND, but I don't know exactly where they are with that. But I think that's the main difference really between our products unless.

Eun Yang

Thank you for the details.

RA Session II

Thank you.

Operator

There are no further questions. I will now turn the call over to Mr. Session for his closing remarks.

RA Session II

So again, we appreciate everyone joining us on the call this morning. As you can see, the company has made great strides during the first quarter. And we continue to make progress throughout the rest of this year. And so we hope that you guys join us at our R&D Day, which will take place over two days in June, June 28 and June 28, and we'll provide further updates as the year goes on. Thank you for joining. Have a good day.

Operator

Ladies and gentlemen, this concludes today's presentation. Thank you once again for your participation. You may now disconnect.

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Taysha Gene Therapies, Inc. (NASDAQ:[TSHA](#)) Q3 2021 Earnings Conference Call
November 10, 2021 8:00 AM ET

Company Participants

Kimberly Lee - SVP, Corporate Communications & IR

RA Session II - President, CEO & Founder

Suyash Prasad - CMO & Head, R&D

Kamran Alam - CFO

Conference Call Participants

Joon Lee - Truist Securities

Gil Blum - Needham and Company

Laura Chico - Wedbush Securities

Elizabeth Webster - Goldman Sachs

Mike Ulz - Morgan Stanley

Kevin DeGeeter - Oppenheimer

Yun Zhong - BTIG

Kristen Kluska - Cantor Fitzgerald

Raju Prasad - William Blair

Silvan Tuerkcan - JMP Securities

Operator

Welcome to the Taysha Gene Therapies Third Quarter 2021 Financial Results and Corporate Update Conference Call. At this time, all participants are in a listen-only mode. Following management's prepared remarks; we will hold a brief question-and-answer session. As a reminder, this call is being recorded today, November 10, 2021.

I will now turn the call over to Dr. Kimberly Lee, Senior Vice President of Corporate Communications and Investor Relations. Please go ahead.

Kimberly Lee

Thank you. Good morning, and welcome to Taysha's third quarter 2021 financial results and corporate update conference call. Joining me on today's call are RA Session II, Taysha's President, CEO and Founder; Dr. Suyash Prasad, Chief Medical Officer and Head of R&D; and Kamran Alam, Chief Financial Officer. After our formal remarks, we will conduct a question-and-answer session and instructions will follow at that time.

Earlier today, Taysha issued a press release announcing financial results for the third quarter ended September 30, 2021. A copy of this press release is available on the company's website and through our SEC filings.

Please note that on today's call, we will be making forward-looking statements including statements relating to the safety and efficacy and the therapeutic and commercial potential of our investigational product candidates. These statements may include the expected timing and results of clinical trials for our product candidates. Our expectations regarding the data necessary to support regulatory approval of Taysha-120, and the regulatory status and market opportunity for those programs, as well as Taysha's manufacturing plans.

This call may also continue forward-looking statements relating to Taysha's growth and future operating results, discovering development and product candidates, strategic alliances, and intellectual property, as well as matters that are not of historical facts or information. Various risks may cause Taysha's actual results to differ materially from those stated or implied in such forward-looking statements. These risks include uncertainties related to the timing and results of clinical trials and pre-clinical studies of our product candidates are dependent upon strategic alliances and other third-party relationships, our ability to obtain patent protection for discoveries, limitations imposed by patents owned or controlled by third parties, and in requirements of substantial funding to conduct our research and development activities.

For a list and a description of the risks and uncertainties that we face, please see the reports we have filed with the Securities and Exchange Commission. This conference call contains time-sensitive information that is accurate only as of the date of this live broadcast, November 10, 2021. Taysha undertakes no obligations to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call, except as maybe required by applicable securities laws.

I'd now like to turn the call over to our President, CEO and Founder, RA Session II. RA?

RA Session II

Thank you, Kim. Good morning and welcome everyone to our third quarter financial results and corporate update conference call.

It has been a busy quarter with positive regulatory discussions for several programs, obtaining an exclusive license for the CLN7 program and collaborating with UT Southwestern on a next-generation CLN7 construct, partnering with GDX, the Hereditary Neuropathy Foundation and Charcot-Marie-Tooth Association on increasing awareness for ginixonaneuropathy and hosting investor webinars featuring disease overviews from key opinion leaders, as well as program highlights for CLN1, Rett and Angelman syndrome.

I will elaborate on some of our recent key achievements and review our expected upcoming milestones. Following this, I will turn the call over to Suyash and Kamran for updates on our pipeline developments and financial results respectively.

In October, we were pleased to announce an exclusive option from UT Southwestern to license a clinical stage CLN7 program, an AAV9 intrinsically dosed gene replacement therapy that was invented by our Chief Scientific Advisor, Dr. Steven Gray. UC Southwestern is currently running a clinical proof-of-concept trial with the first-generation construct, and we expect to have preliminary clinical data, including safety data from the first patient ever dosed intrathecally, with 1E15 total VG by the end of this year. We are collaborating with UT Southwestern to develop a next-generation construct that will provide improved potency, safety, packaging efficiency and manufacturability over the first-generation construct. Construct design is anticipated to be completed by year-end with initiation of a planned pivotal trial using the next-generation construct in 2022. With reference to human proof-of-concept data generated from the first-generation construct.

To support patient education, disease awareness, and advanced newborn screening initiatives for CLN7, we have provided a grant to Batten Hope, a leading CLN7 patient advocacy group. Currently, there are no approved treatments for this severe neurodegenerative lysosomal storage disease. And we are excited to work with UT Southwestern and support Batten Hope to further advance this promising clinical stage program.

With the addition of the CLN7 program, we expect to have five clinical stage programs by the end of this year, including ginixonaneuropathy, GM2 gangliosidosis, CLN1 and Rett syndrome.

As our programs mature, we continue to make progress on the regulatory front. This past quarter, the European Commission granted orphan drug designation for TSHA-101 for GM2, TSHA-102 for Rett syndrome, and TSHA-105 for SLC13A5-related epilepsy. Year-to-date, we have had nine regulatory interactions with multiple agencies across our portfolio and plan to submit additional request for end-of-Phase meeting for ginxonaneuropathy before the end of this year. We anticipate reporting clinical data for several programs by the end of this year.

For GAN, in September, we submitted an end-of-Phase meeting request for TSHA-120 to a major ex-U.S. regulatory agency and look forward to submitting additional requests to multiple regulatory agencies by the end of this year. In GAN, we have up to six years of longitudinal data in individual patients and collectively 55-patient years of clinical safety and efficacy data from our ongoing clinical study. We also have eight years of robust longitudinal data from a natural history study being conducted at the NIH by Dr. Carsten Bönnemann.

There has been consistency in the strength of data across multiple functional and biomarker endpoints, including the MFM32 scale, vision assessments, and nerve biopsies. We look forward to reporting clinical safety and functional MFM32 data for TSHA-120 from the high dose cohort of 3.5×10^14 total VG in December, where we believe continued clinically meaningful slowing of disease progression similar to that achieved with the lower dose cohorts would be considered confirmatory of disease modification.

For TSHA-101, the first bicistronic vector in the clinic in history, which is designed to express the subunits of HEXA enzyme in the endogenous one to one ratio. We remain on track to report preliminary clinical safety data and HEXA enzyme activity data, the plasma and CSF in December of this year. Based on natural history, 2% to 4% HEXA enzyme activity in the plasma normalizes survival and significantly improves clinical phenotype of GM2 gangliosidosis.

We anticipate preliminary clinical safety data and HEXA enzyme activity in the plasma and CSF for TSHA-101 in GM2 gangliosidosis in December from the ongoing Canadian study. We believe the HEXA enzyme activity levels of at least 5% in the plasma would be considered disease modifying based on natural history.

Regarding the safety profile, preclinical data demonstrated intrathecally delivered of TSHA-101 was safe and well-tolerated in GM2 knockout mice. Due to severity of the disease and unmet medical need, we're currently assessing the need for U.S. study to support global registration.

For our CLN7 program, we anticipate preliminary clinical data including safety data for the first patient in history to be dosed at 1E15 total VG intrathecally with the first-generation construct in December. In parallel, we expect to finalize the design of the second-generation CLN7 construct by year-end and initiate a planned pivotal clinical trial in 2022, with reference to clinical data generated by the first-generation construct.

For CLN1, the program currently has an open-IND and an additional CTA filing for TSHA-118 has been submitted. Preclinical data demonstrated that TSHA-118 was safe and well tolerated following intrathecal administration in the CLN1 knockout mice model. In preclinical models, TSHA-118-treated mice demonstrated supraphysiological levels of active PPT1 enzyme with no associated adverse effects, suggesting a wide therapeutic window for clinical dosing. We plan to initiate the clinical trial by the end of this year and expect to report preliminary clinical safety and PPT1 enzyme activity data in the first half of 2022.

For TSHA-102, in Rett syndrome, we intend to submit an IND or CTA filing in November followed by the initiation of clinical development by the end of this year. We have recently obtained preclinical data demonstrating an improvement in survival, and respiratory function as well as motor functions in relevant disease mouse models. We plan to share this data at a later date.

Notably, preliminary data from a GLP toxicology study in non-human primates demonstrated no adverse findings at the highest dose tested suggesting that the miRARE platform is successfully downregulating MECP2 expression to within normal physiological levels.

As I mentioned earlier, we will have five clinical programs by the end of this year. Many of those have been a major focus for investors given the near-term milestones. However, we wanted to highlight a few of these programs in our Investor Mini-Series, which featured key opinion leaders who provided a deep understanding of the disease and reviewed preclinical and natural history data that helped set the stage for our treatment approaches.

Leaders from patient advocacy organizations also discussed disease burden of illness from the patient and caregiver perspective and provided real world context to therapeutic endpoints and insight into how incremental improvements may lead to meaningful benefits for patients and caregivers. We hope you found these events helpful, but if you are not able to attend, the replays are available on our corporate website.

On the manufacturing front, we have completed five successful concurrent GMP manufacturing campaigns for multiple programs to-date, which are sufficient to support our planned clinical stage programs this year. We have received positive feedback from multiple regulatory agencies supporting our three pillar approach to manufacturing, which includes UT Southwestern, our CDMO partners, as well as our internal 187,000 square foot manufacturing facility located in Durham, North Carolina. We are making solid progress on the build-out of our facility. Most recently, erecting structural seal and completing subfloor piping. We remain on track to complete the facility by 2023.

Our translational and bio analytics labs will also be physically located near our manufacturing facility in Durham, to ensure a seamless communication between research and manufacturing.

Let me conclude by saying that we have accomplished much this quarter, but have more to execute on and we believe our strong balance sheet provides us with the financial and operational flexibility to achieve our numerous value-generating milestones across our programs, and importantly, a potential regulatory approval for TSHA-120 in ginixonaneuropathy. We look forward to our continued execution across our development and regulatory strategies. And we'll update you on our progress throughout the remainder of this year.

I will now turn the call over to Suyash to provide a more detailed update on our R&D initiatives. Suyash, please go ahead.

Suyash Prasad

Thanks, RA.

We continue to advance our clinical and preclinical programs as well as strengthen our pipeline with complimentary therapeutic approaches to address high unmet needs across monogenic diseases of the CNS. At the end of the year approaches, we are highly anticipating multiple data readouts across several of our lead clinical programs.

Let me start with TSHA-120, our most advanced clinical program for the treatment of ginkgoneuropathy or GAN. In December, we expect to report clinical safety and MFM32 functional data from the high dose cohort of 3.5×10^14 total VG. These data are generated by our partners and collaborators of the NINDS under the leadership of theoretical [ph] study, Carsten Bönneman. As a reminder, the clinician rated MFM32 scale as a clinically validated and accepted regulatory endpoint that assesses motor function.

To gauge with a successful outcome will look like based on the prospectively collected data on the natural history of GAN, there is a predictable decline in the MFM32 score of approximately eight points per year across all patients regardless of age. A four point change in MFM32 scale is considered clinically meaningful. To confirm modification of disease trajectory in comparison to the natural history study, we believe the high dose cohort should demonstrate continued slowing of disease progression, durability of effect and safety comparable to that which was achieved for the 1.2×10^14 and the 1.8×10^14 total VG doses.

Regarding safety recall that we have up to six years of clinical safety data demonstrates no drug-related serious adverse events, no signs of acute or subacute inflammation, no sudden sensory changes and no persistent elevation of transaminases. And also with regards to safety and preclinical studies using gangliosidosis TSHA-120 improved histopathological appearance of the dose root ganglia, which is a known complication of GAN, levered by supporting reduction in disease symptoms. We anticipate publication of the clinical data in the peer reviewed scientific journal in the near future.

In September, we submitted the scientific advice from a major ex-US regulatory agency and received a preliminary meeting date for January 2022. We anticipate submitting additional requests to multiple regulatory agencies by the end of this year.

As we think about the approval pathway for GAN in the United States, we view three possible scenarios with a potential to file for approval with the current data on hand, as the most likely scenario. Alternatively, the FDA could request, we dose a few additional patients to demonstrate the compatibility or clinical effects between clinical and commercial grade material. And lastly, the FDA may request us to perform a new clinical trial, which we view as the least likely option given the recently published guidance documents on gene therapies for neurodegenerative diseases and the extensive long-term dataset that we have in hand.

In Europe, we believe we would be able to use the current datasets upon conditional approval. We look forward to providing updates following our regulatory interactions. In the meantime, we have finalized the plan commercial grade material and have initiated the compatibility protocol to support the BLA/MAA filing.

We continue to believe the early diagnosis and treatment can dramatically improve the lives of patients with GAN. Last month, we announced the partnership with GeneDx, a global leader in genetic testing to sponsor the inclusion of a genetic marker to test the GAN and the GeneDx routine hereditary neuropathy screening panel free of charge to individuals at-risk for or suspected of having GAN. Ultimately this can help address current treatment barriers by raising disease awareness, making diagnostic tools more accessible and facilitating early intervention for patients suffering from GAN.

We are also excited to collaborate with the Hereditary Neuropathy Foundation and Charcot-Marie-Tooth Association Centers of Excellence, healthcare professionals, and patient advocacy groups to increase access to genetic testing. Collectively, our goal is to help all patients at-risk for GAN have access to genetic testing and raise awareness of opportunities to participate in clinical trials for investigational treatments to facilitate early intervention or patients suffering from GAN.

Moving to our TSHA-101 program for the treatment of GM2 gangliosidosis, we plan to report preliminary clinical safety data, and HEXA enzyme activity in plasma and CSF in December. Recall that preclinical data demonstrated intrathecal delivery of TSHA-101 was safe and well tolerated in GM2 knockout mice. Based on patient data from the natural history study demonstrate a correlation between clinical phenotype and HEXA enzyme activity, we anticipate HEXA enzyme activity levels of at least 5% in plasma to be considered disease modifying. Screening and enrollment are progressing well in our Canadian study. Due to the severity of the disease and the unmet medical need, we are currently assessing the need for U.S. trial to support a regulatory filing as you continue evaluating the fastest path to approval with regulatory agencies.

As a reminder, TSHA-101 has been granted both orphan drug designation from the FDA, and more recently from the European Commission for the treatments of GM2 gangliosidosis. TSHA-101 has also received rare pediatric disease designation from the FDA.

For CLN7 program we expect to report preliminary clinical safety data from the first patients from the clinical trial who were dosed with the first-generation construct, including the first patient in history to be dosed at 1x1015 total VG intrathecally. This will be in December. In preclinical toxicology studies safety and tolerability of intrathecal administration of the first-generation construct was demonstrated across all those levels and time points and we anticipate a similar safety profile in the clinic.

We anticipate the top colleagues and partners at UT Southwestern will dose an additional patient, with the first-generation construct before the end of the year. We are collaborating with UT Southwestern to finalize development of next-generation construct which should have improved potency, safety, packaging efficiency and manufacturability over the first-generation construct by year-end. And we plan to initiate a pivotal clinical study in 2022 using the next-generation construct with reference to the human proof-of-concept clinical data generated from the first-generation construct. Lastly, we anticipate having commercial-grade GMP material for the next-generation construct in 2022.

In August, we held our first Investor Mini-Series highlighting TSHA-118 for the treatment of CLN1 disease. We were honored to have Dr. Angela Schultz, a global expert and clinical researcher who specializes in lysosomal storage disorders from the University of Medical Center, Hamburg-Eppendorf. To review the current natural history data for CLN1 disease and provide clinical insight into the use of natural history, control data in clinical trials, as well as clinical trial endpoints and design.

Dr. Steven Gray reviewed encouraging preclinical data for TSHA-118 at clinically relevant doses, demonstrating that TSHA-118 was safe and well tolerated following intrathecal administration in CLN1 knockout mice. In preclinical CLN1 models TSHA-118 treated mice demonstrated persistence super physiological levels of active PPT1 improved survival rates and sustained preservation of motor function with no associated adverse events, suggesting a wide therapeutic window for clinical dosing.

We also reviewed insights from the Scientific Advisory Board and caregiver focus groups who helps inform our clinical study design, therapeutic priorities and endpoint selection. We continue to explore the fastest pathway to approval for our CLN1 program. We have submitted a CTA filing and plan to initiate a Phase 1/2 trial by year-end.

We expect to report PPT1 biomarker data in the first half of 2022, noted that there is an increase in PPT1 activity from 0.1% to 5% would be considered positive based on the 5% to 8% range seen in adult onset patients.

In September, we hosted a Rett Investor Day highlighting our TSHA-102 program. Dr. Jeffrey Neul, an international expert in genetic neurodevelopmental disorders from Vanderbilt University Medical Center provided an overview of the natural history for Rett syndrome and clinical considerations for clinical trial design including outcome measures and biomarker selection.

Dr. Steven Gray detailed the requirements for regulated gene expression on a cell-by-cell basis to safely and effectively treat the disease. And that is exactly what our novel miRARE platform does, to regulate the degree of transgene expression based on underlying genotype on a cell-by-cell basis ensuring expression of MECP2 at the level that's improved the symptomatology of rat without causing undue adverse effects.

Importantly in preclinical animal models intrathecal myc-tagged TSHA-102 was not associated with early death and did not cause adverse behavioral side effects in wild type mice demonstrating appropriate downregulation of MECP2 protein expression. We reviewed our clinical development strategy, the recent positive regulatory feedback supporting our IND-enabled preclinical package on current dose selections. We also discussed disease specific insights from our recent discussions with Advisory Board and caregiver focus groups who provided recommendations on current clinical study design endpoints and the utility of the Rett syndrome and natural history data.

Since the Investor Day, we have recently obtained preclinical data showing improvement in survival, under respiratory and motor functions in relevant mouse models of the disease. Notably, preliminary data from a GLP toxicology study in non-human primates demonstrated no adverse findings at the highest dose tested suggesting that the miRARE platform is successfully downregulating MECP2 expression to within normal physiological levels. We plan to submit an IND/CTA for TSHA-102 this month followed by initiation of a Phase 1/2 trial by the end of this year. We anticipate preliminary clinical data by the end of 2022.

TSHA-102 has been granted rare pediatric disease designation and orphan drug designation from the FDA and more recently orphan drug designation from the European Commission.

Our most recent Investor Day focused on Angelman syndrome where we highlighted our two-pronged approach to treat this significant neurodevelopmental disorder with no approved treatments. Dr. Ben Philpot of the UNC presented the UBE3A gene replacement strategy and Dr. Ryan Butler of UT Southwestern presented the vectorized RNA mediated knockdown approach designed to unsilence the paternal copy of the UBE3A gene by targeting the antisense transcript responsible for silence in the gene. Recent publication of promising preclinical data in the Journal of Clinical Investigation Insight further detailed how our AAV-mediated UBE3A gene replacement approach recapitulates endogenous three to one isoform ratios by replacing both the short and long isoforms of UBE3A in key regions of the brain, leading to improvements in motor learning, behavior outcomes, and seizure phenotypes in mouse models of Angelman syndrome. These proof of concept preclinical data support further study of UBE3A gene replacement therapy as a potentially safe and effective treatment for Angelman syndrome. Both strategies are highly encouraging and importantly allows to target entire Angelman syndrome population positioning Taysha as a world leader in the discovery of treatments of Angelman syndrome.

As you heard this morning, we continue to progress our programs on both development and regulatory fronts and look forward to providing you updates along the way.

With that, I will turn the call over to Kamran to review our financial results. Kamran?

Kamran Alam

Thank you, Suyash.

This morning, I will discuss key aspects of our third quarter 2021 financial results. More details can be found in our Form 10-Q, which will be filed with the SEC shortly.

As indicated in our press release today, R&D expenses were \$39.5 million for the three months ended September 30, 2021, compared to \$11.1 million for the three months ended September 30, 2020. The \$28.4 million increase was primarily attributable to an increase of \$14.5 million of expenses incurred in research and development manufacturing, and other raw material purchases, which included cGMP manufacturing batches produced by Catalent and UT Southwestern.

There was an increase in employee compensation expenses of \$10.7 million, which included \$1.9 million of non-cash stock-based compensation, and \$4.9 million in third-party research and development expenses, which includes clinical trial CRO activities, GLP toxicology studies, and consulting for regulatory and clinical studies. This was partially offset by a decrease in licensing fees of \$1.7 million.

G&A expenses were \$11.2 million for the three months ended September 30, 2021, compared to a \$4.0 million for three months ended September 30, 2020. The increase of approximately \$7.2 million was primarily attributable to \$4.3 million of incremental compensation expense, which included \$1.8 million of non-cash stock-based compensation. There was an increase of \$2.9 million, mainly in professional fees related to legal, insurance, investor relations, communication, accounting, personnel recruiting, market research, and patient advocacy activities.

Net loss for the three months ended September 30, 2021, was \$51.2 million or \$1.35 per share as compared to a net loss of \$15 million or a \$1.28 per share for the three months ended September 30, 2020.

As of September 30, 2021, Taysha had \$188.8 million in cash and cash equivalent.

And with that, I will hand the call back to RA.

Suyash Prasad

I wonder if RA has dropped off for some reason. This is Suyash here.

RA Session II

My apologies. Hey, Suyash.

Suyash Prasad

Oh, my apologies. Go ahead, RA.

RA Session II

My apologies. Thank you. I was talking on mute.

So I want to thank everybody for joining the call today. We are pleased to share with you our success over the past several months. Looking ahead, we will continue our focus on advancing our pipeline expeditiously and executing on key anticipated upcoming milestones.

As a reminder, in December, we anticipate data from our highest dose cohort from our Phase 1/2 TSHA-120 study in giant axonal neuropathy; and preliminary Phase 1/2 clinical safety data and HEXA enzyme activity in the plasma and CSF for TSHA-101 in GM2 gangliosidosis. Also in December, we anticipate preliminary safety data for the first-generation construct from our CLN7 program. Lastly, by year-end, we expect to initiate a Phase 1/2 trial in CLN1 disease and Rett syndrome.

I would like to give special thanks to the continued support and dedication of our Taysha employees, Board of Directors, scientific advisory board, collaborators, and the patients and advocates who remain our motivation every day to continue our mission to develop curative gene therapies and eradicate devastating monogenic CNS disease.

I will now ask the operator to begin our Q&A session. Operator?

Question-and-Answer Session

Operator

Thank you. [Operator Instructions].

Our first question comes from the line of Joon Lee with Truist Securities. Please proceed with your question.

Joon Lee

Hi, thanks for taking our questions and congrats on the impressive accomplishment in such a short period of time. For the GM2 you seem to be implying that you may be able to submit for approval with existing data from the Canadian site. And if so, what jurisdiction do you think would be most amenable to this, and can you give us some historic proxy where something like this have happened and I have a follow-up?

RA Session II

Good morning, Joon. And thank you for the question. Maybe I'll start and then I'll pass it over to Suyash to provide his thoughts. So the current GM2 study is a global study in a sense that the clinical trial is taking place in Canada, where patients are literally coming from all over the world.

From a registration in the U.S. perspective, all you need to have is an open IND ultimately to file a BLA, and then supporting data from a robust clinical trial. And again, based on the FDA's guidance, where there is a robust natural history, a good clinical -- a good robust clinical development plan, a good endpoint that supports registration, this should not necessarily be an issue.

And so there's meaningful -- there's multiple meaningful examples of this across the rare disease spectrum. I'll turn it over to Suyash to provide a couple of examples of this. But certainly, we today feel based on the severity of the disease and the unmet medical need for the disease, and how well the program is actually enrolling; you may not necessarily do a full clinical trial in the U.S., and may just need to import one or two patients from the U.S. to be dosed. So I'll stop there, turn it over to Suyash to provide his thoughts.

Suyash Prasad

Yes, thanks, RA, and thanks for the question, Joon. And yes, we're talking through regulatory strategy on an ongoing basis. In the past four months -- four to six months, we've had nine regulatory meetings across our portfolio of programs. And these are multiple meetings with the U.S. and several other ex-U.S. agencies. So we're really getting a lot of real time information on the right approach for pathway to approval.

As RA has already said, we've been very pleased, actually, of how we've been able to identify patients for the Canadian GM2 study. There's been some delays that relates to COVID. But essentially, we've screened large numbers of patients that tell us actually, there's a large number of GM2 patients out there. Because things are going so well in Canada, we are talking about the fact, yes, perhaps we could just file ex-U.S. initially and have the IND open and then file principally with data from other countries, as opposed to from the U.S.

And as RA says it is a global study. So what I felt is if there are U.S. patients, we could actually send them to Canada for dosing. So there's multiple options here.

In terms of specific examples, and I've worked on a couple previously, in particular environment where our focus was much more on Europe initially followed by the U.S. later. I think one springs to mind I think the CLN2 Brineura program was one where the study starts in the ex-U.S. And then the filing happened in Europe prior to the U.S. from my recollection, that's true. But there are several examples why this has happened. So yes, we continue to value options. Like this, we'll open an IND in the U.S. for GM2 at some point, but things are going still well in Canada, we decided to focus our time and initiate an attention on continuing enrollment in gathering clinical data in Canada.

Joon Lee

Great. Looking forward to the data in December. And a second question and the last question, for TSHA-120 in GAN, which you have very strong data, six, eight years' worth of data. Are the materials used in the investigational study undergo the same GMP and QA process as materials you're producing in your GMP facilities? And if they are different, what would you need to do to satisfy the FDA requirements, that they are equivalent and be able to commercialize or submit for approval with existing data? Thank you.

RA Session II

Thanks Joon for the question. Great question by the way. So essentially, one of the things that we decided to do early on when we brought in the program was to make sure that we can secure a like-for-like manufacturing platform to support comparability from the clinical stage materials and the commercial grade materials.

So in order to do that, what we've decided to do was to manufacture the commercial grade material, which will ultimately support a validation run and go into the BLA and support the BLA filing and commercialization. What we've decided to do is to partner with the same CDMO partner that manufactured the original clinical grade material producing it in a like-for-like process, literally like-for-like just scaled up. So it's the same cell line. It's the same purification filtration. Literally, a same process updated for some of the recent developments for GMP manufacturing for gene therapy that the FDA likes to see.

So nothing that's out of the normal. So we feel strongly that our current dataset and our current comparability panel should support a like-for-like product, ultimately supporting a sameness argument. I'll stop there. Suyash, do you have anything to add?

Suyash Prasad

I think the only thing I'll add really, we spend a lot of time and energy very early on ensuring that we are able to characterize product in terms of contaminants in terms of collected captured ratios. We bring that learnings. We bring those learnings through to our GAN program as well. And there's a very real meaningful example where actually two weeks ago that the team were over at the CDMO part, who's manufacturing the drug for the -- manufacture the drug clinically, and will also manufacture drug through into the commercialized process. So it's Fred Porter, our Chief Technical Officer, Mish Gerhart, our Head of Regulatory and a team of about 10 people spent a full week at the facility going through all the details and looking through all the processes and ensuring that things were absolutely as pristine as possible. So we feel very confident that the clinical material -- that the material used in the clinical studies is going to be absolutely equivalent to what we're going to be using going forward in the GAN program commercially. So, yes. Great question Joon, but we're very comfortable with the approach here.

RA Session II

The only thing that I would add is that, we plan to have the commercial grade material available to support a BLA filing in the second half of next year.

Joon Lee

Got it. Well, looking forward to all the data in December, thanks for the answers. Thank you.

RA Session II

Thanks. Thanks, Joon.

Operator

Thank you. Our next question comes from the line of Gil Blum with Needham and Company. Please proceed with your question.

Gil Blum

Good morning and thank you for taking our questions. It's a bit of a follow-up on the previous discussion. So it actually makes the conceptual sense that considering you guys are using a production method commercially used to make your AAV9 that it would be translatable across your platform, but they're still variance using different genes in each program. Do you guys expect the FDA will be looking for a bridging study of any kind? I mean this is the across programs now, right. So you could have it for GAN, you could have it for CLN7, you could have it for GM2. It seems that you make really long headways with the initial studies and are looking to kind of transfer hopefully into commercial products. Thank you.

RA Session II

Hey, good morning, Gil. Thanks for the question. Maybe I'll start and then I'll allow Suyash to chime in on some of our recent discussions with regulators about kind of the -- this platform approach. What I would say is GAN is somewhat of an outlier. And what I mean by that is this was a program that essentially when we brought it in-house had five to six years of robust data basically 55 years collectively worth of safety and efficacy data with really robust product produced by a high quality kind of commercial process.

And so what we wanted to do to make sure that we had the fastest pathway to approval was basically not change anything. And this is the reason why we decided to exclusively focus on the manufacturing partner that manufactured the original clinical grade material to support our commercial grade material, which will ultimately go into the BLA. So GAN is somewhat off by its side.

Now for the rest of the portfolio, I think you're absolutely right. Our approach has always been, this is a platform and not necessarily individual product. In some cases, there's absolutely product to product variability, but essentially it's the same upstream process, the same downstream process, the same cell line, the same purification, the same bio reactors. So there's this notion around platform value. And essentially, there's a consistency around our regulatory discussions with each one of our programs. I'll stop there and let Suyash kind of talk about some of our recent regulatory interactions. It's fortunate that we've had nine regulatory actions -- interactions with multiple regulatory authorities both in the U.S. and ex-U.S., because it really gives us this deep understanding of how to augment our strategy or if our strategy is actually working. And we're pretty competent around this platform. So Suyash, maybe you want to chime in and provide some context.

Suyash Prasad

Yes. Thanks. Thanks, RA. And yes, thanks for the question, Gill. And I think RA is quite right. The GAN is a little bit of an outlier, because GAN wasn't in our hand in the earlier parts of the clinical trials and it came into our hands and so we're having to adapt somewhat, which is very appropriate. And as I say, the team visited the CDMO a couple of weeks ago. We feel very comfortable with that.

To add some color to the regulatory discussions, we have this three topics really that come up in every regulatory interaction that relate to CMC. And once again, I'll mention Fred Porter, our Chief Technology Officer who does a really a wonderful job for these regulation interactions. And the three topics that keep coming up are CMC characterization, how we characterizing the quality, the purity, the pristine of the products. The second topic is potency assays. How are you planning potency assays and at what stage are you – and how is that progressing? And the third topic is bridging studies and what type of bridging studies do we need to do? So we have a very specific approach to all those three topics. Fred talks about a very nice in the meetings and we have the regulation meeting last Friday on one of our programs, and the, topic of bridging studies came up and our approach was very well accepted by the regulator. They said, look just this all sounds fine. Just wiped it up when you follow the CTA. And what you've proposed is absolutely appropriate.

And once again, we know that for CMC methods, we have to do the right thing as early as possible. And we try as hard as we can. We're successful for the vast majority of our programs. Once again, GAN is a bit of an outlier, but the vast majority of our programs to getting commercial grade material ready, definitely by the time of the pivotal parts, when you study. For the most part before we start any clinical study at all, and ideally in the actual IND-enabling preclinical study that's really when we want to have that's our aspiration to make sure we have a commercial grade product at that early time point, does that it just makes the whole regulatory process go much smoother from a CMC perspective.

Gil Blum

Thank you for a very complete answer on this question. Maybe a quick scientific question of course GM2 program. Is there any differences between say measured and CSF guarantee you're seeing a high-level on one, different than the other or better than the other? Thank you.

RA Session II

So, Gil. It's a great question. And maybe I'll start it and will turn it over to Suyash. I think based off of the natural history; natural history for GM2 gangliosidosis is actually pretty well characterized. We have the disease that has been known for over a hundred years. And when you look at the HEXA enzyme activity level in the infantile form of the disease, and this is essentially the most severe form of the disease, these patients are essential knockouts. They have 0.1% enzyme activity. And that correlates to an early death of around three.

When just taking a patient from 0.1%, and this is enzyme activity in the plasma, let me be specific. And just taking a patient from 0.1% to 0.5% or a half a percent, you actually extend survival out to the mid-teen that goes from an infantile onset patient to a juvenile onset patient that typically come to disease in the mid-teens.

Just getting a patient to 2% to 4%. You now go from an infantile onset patient to an adult onset patient. And it normalizes lifespan just that 2% to 4%. And this again is in the plasma. And so the plasma measures of HEXA are probably the most well-known correlate to disease progression. And that's the reason why we wanted to make sure that we benchmark to that. But, but certainly you'll have different levels of HEXA activity in plasma versus CSF. I'll let Suyash go into that a little bit more in depth.

Suyash Prasad

Yes. Thanks, RA. Gil, this is a really perceptive question, because I think it's important to understand the expectations of what we're going to see from a HEXA perspective. RA is quite right. There is a lot known about HEXA that comes off GM2 gangliosidosis that's been done historically; disease was described in the late 1800s by William Tao ophthalmologist. The enzyme was identified in 1969 and there's been many, many screening programs. So we have a really good understanding of HEXA levels in the plasma.

Having said that, we wanted to not only look at the plasma levels, we also want to look at CSF levels because to us ensure simply if we're trying to transduce brain cells, we should also see an elevation of HEXA in the CSF. And we believe that that will actually reflect what's happening in the brain a little more than the plasma activity. So that's what we've accounted these days and we'll be sharing data on both towards the end of the year.

Now RA is quite correct also that once we hit 5% levels of enzyme in the serum in terms of the clinical phenotype, those are adult patients with GM2 gangliosidosis. There are some cognitive deficits and movement disorder, but they haven't generally normal lifespan. So if we change the HEXA level from less than 0.01% for an infantile to over 5%, then we anticipate that that will dramatically modify the clinical phenotype. So that's our bar.

In terms of what levels we might see in the CSF, we're assuming 5% as well, but actually, maybe less and maybe a little bit less. It's my guess that the CSF levels of HEXA may actually be a little lower than the plasma -- plasma versus HEXA. But as I say, we'll be presenting both plasma HEXA levels and CSF levels on HEXA; we've got CSF working very nicely within the preventive outdated towards the end of the year.

Operator

Thank you. Our next question comes from the line of Laura Chico with Wedbush Securities. Please proceed with your question.

Laura Chico

Hey, good morning, guys. Thanks very much for taking the questions. I just have two small ones. So first on the 120 program, could you just discuss a little bit more about the timing after the January meeting? I guess I'm just trying to better understand when we might have a little bit more clarity on the U.S. regulatory path for 120. Apologies if I missed that. And then kind of related to the earlier commentary. It sounds like the base case, we should have in our estimates is really assuming ex-U.S. regions perceived the U.S. and I just wanted to make sure that that is the kind of working base case assumption right now. Last one, just on 120 RA, I think you mentioned second half would be released with commercial grade material for 120. I just wanted to understand, are there any remaining headwinds or issues that could perhaps impact timing there? Thank you guys.

RA Session II

No, it's a great question. And thank you Laura. Maybe I'll tackle your first -- the first questions, and then I'll turn it over to Suyash to talk about our regulatory strategy.

So around manufacturability and manufacturing of the commercial grade material for ginixonaneuropathy. Right now, we actually don't foresee any headwinds that would actually limit the availability of that product in the second half of the year. We're actually fortunate; we actually did a small scale run of that, internally of that product. And it's actually a one of our best producing programs.

And so we're pretty fortunate to have that data in hand, that's at a small scale. But certainly, when we look across our portfolio and having the luxury to be able to have such a large portfolio, to reference it to, it's actually one of our best producing programs. So we're pretty excited about that being that this is going to be our first commercial campaign. So we actually don't foresee any headwinds on that. So we would reiterate that guidance of having commercial grade material available in the second half of 2022.

When you start to think about timing from an approvability perspective, I think the strategy is still the same. I think this program essentially checks all the boxes that were laid out in the draft guidance that the FDA issued in January of this year. We have six years of longitudinal individual patient data. We have dose response. We have collective 55-years of patient safety and efficacy, multiple endpoints. We have not only functional endpoints MFM32, functional endpoints around visual acuity. But we also have biopsy data. And a number of other endpoints that were collected that we'll be talking about in the publication that comes out here in the near-term.

So the way that we're looking at this is essentially, its three scenarios in the U.S., we think two of those are high probability. The first is going to be our going in strategy essentially pointing to the FDA on guidance. And this is really around using analytical comparability to support the BLA filing, essentially confirming the like-for-like material from the clinical grade material and commercial grade material.

Again, we're not changing anything. We're literally not changing anything. So there's really nothing that we could really point to other than scale. And so that would support a end of year BLA, end of 2022 BLA. They could come back and say we'd like for you to dose a few more patients. We're fortunate to have those patients identified that are currently in the natural history study. We now have a robust natural history study we reported on approximately 40 plus patients there's now over 50 patients in the natural history study that apparently being run at the NIH by our collaborator Dr. Carsten Bönnemann. And so for us to be able to roll over patients from that study to treat two to three more patients if we needed to perform some sort of clinical comparability would be something that we would be able to do relatively quickly.

And so we think the difference between doing an analytical comparability that would support a BLA filing at the end of 2022 or needing to do some clinical comparability that would be just about a six months difference. So that would probably push a BLA filing to probably mid-2023.

Europe is all by itself, right. And so Europe, the conditional approval pathway is wide open based on the guidance that the EMA is issued around conditional approval TSHA-120 checks all the boxes and that's going to be our going in discussion early in the New Year when we meet with ex-U.S. regulators really around what is the conditional approval, innovative medicine pathway that are available to us and currently that the data will support. I'll pause there. Maybe, Suyash, you want to just comment on our regulatory strategy and just the timing to get those responses back.

Suyash Prasad

Yes, I will do. And just give a bit of color, Laura, to the just some of the operational aspects of what we're trying to on the GAN program. We've got a great data package for GAN as we've already mentioned this great match race, so the dose response data clear stabilization of disease at medium low, medium high doses, and the high dose yet to come, long-term safety durability, and efficacy. And so we're really feeling confident and good about our discussions with regulators.

One of the practical challenges frankly is that the regulator is just very, very busy. In fact we're looking forward to having our 10th regulation meeting this month, but the regulator agency in question actually contacted us and said, hey, look, we're really so really busy. We're going to have to push you out to January. So this is on a different program, but it just that that very rarely happens. And so it just gives us a sense of how busy the agencies are at the moment, generally with a whole bunch of COVID stuff.

So we're putting in requests for meetings, but not actually getting the meeting for three, four, five months, down the pike. So it's a little bit of an operational challenge that frankly thoughts I've got to say, we got our first meeting on January, we'll anticipate with subsequent meetings shortly thereafter. The likelihood is for; we may also separate out really partly for the timing CMC discussions with clinical data discussions. And I think that's probably how we'll plan the cadence with some of the agencies, especially those that have more focus on CMC and this we're already touched on before the CMC is something that we want to make sure we explain our process, our situation very well. So we're planning for separate for one or two of the agencies of CMC discussions and the clinical discussions.

And the final point I'll make and all right, I was talking about this at some length in the past few days. For GAN, we've got this great efficacy data, and we talk about the efficacy data at length. We show clear disease stabilization, and dose response. One of the things we then focus on so much is the safety data, because that's actually what the regulators focus on more than anything when it comes up closer to BLA filing. And I just want to emphasize the fact that we have got years and years' worth of safety data in this program. It's very nice for me as a Head of R&D going into regulatory discussions with that duration of safety data. So usually I have six months or a year, and the regulator always turns around and says, hey, you need to study this for another year before you can file. But we have patients who were dosed in 2015. So there are patients with up to six or seven years' worth of clinical safety data. And we show just minimal issues around inflammation. There's no liver issues. There's no evidence of thrombotic microangiopathy. There's no evidence of any neuronal loss or inflammatory change in the brain that's all, no drug-related serious adverse events. It really -- we really have a very nice bucket of safety data, which I think will be very -- over the longer-term, which I think will be very much appreciated by the regulators, because as you know, the safety methods of AAV gene therapy have been discussed at some length recently. So I just want you to emphasize that in addition to the ones efficacy data we have for this program, we have some really nice long-term safety data, which I think will stand us in good stead to these regulatory discussions. So we look forward to telling you about how those go early in the New Year.

Operator

Thank you. We would just like to remind everyone to please ask one question. Thank you so much. Our next question comes from the line of Salveen Richter with Goldman Sachs. Please proceed with your question.

Q –Elizabeth Webster

Hey, good morning guys and thanks for taking our question. This is Elizabeth on for Salveen. So just two from us, and one would be you touched upon the different properties expected between the first and the next-generation construct for the CLN7 program. And maybe if you could just remind us on the specific molecular level or structural differences between the two? And then quickly on the second question just touching on patients, but first the data disclosure, given you have several data readouts towards December and then into next year. And then what venue or potential disclosure format those could take. Thank you,

RA Session II

Hey, Elizabeth. Good morning. Thank you for the question. So I'll take your first question and I'll allow Suyash to provide some insights of the second question.

On the first question around the key differences between the first-generation construct and the second-generation construct and the next-generation construct for CLN7. We haven't yet disclosed what those key molecular differences are. We do plan to disclose that upon construct design finalization, which will happen here in the next few weeks. What we know is based on some of the changes that we've made previously across our portfolio, there are changes that we can make to the construct and the sequence as well as the ITRs that will actually make the gene therapy vector more safe, make it more potent, improve on the manufacturability and allow it to actually package more efficiently in order to increase yields, once we start to get into large scale manufacturing.

So just based on our history and some of the changes that we've previously made from constructs that were coming out of our collaborators at UT Southwestern. We're going to be applying those same changes to this program. We feel pretty strongly that we would be able to still reference the clinical proof of concept data that's currently being generated from the proof of concept trial that our partners at UT Southwestern are currently running. They dose two patients. One patient has been dosed at 5E14, total VG intrathecally, and second patient has been dosed at 1E15 intrathecally total VG. And the third patient is to be dosed in December.

And so what I'll say is once that construct design is completed, which should happen here in the next few weeks and we're pretty confident of that. We'll be happy to share some of the changes that we've made in order to improve multiple aspects of the gene therapy here.

As far as your second question around data disclosure, really is -- our process is confirming our guidance today around the availability of data for our high dose cohort, which is 3.5 V to the 14 total VG for giant athermal neuropathy by the end of this year, HEXA enzyme activity in the plasma and CSF for our GM2 program by the end of this year, and preliminary clinical data from the CLN7 program by the end of this year.

As we move into 2022, you're absolutely right. The portfolio kind of played out exactly -- we're fortunate the portfolio is playing out how we would like it to in a sense where you'll kind of have this constant drumbeat of data readouts and updates as the program starts to mature. So what we've proactively said, there'll be an update for GM2 most likely in the middle of next year. There'll be an update for our CLN1 program, which will be PPT1 enzyme activity, and the CSF and in the plasma, as well as clinical safety, that'll happen in the first half of next year. There'll be an update again on our CLN7 program around functional assessments as well as clinical safety. That'll happen in the first half of next year. And then they'll also be a constant update around regulatory feedback as that comes in with -- that we hope will ultimately support a rapid path to approval for ginvixonaneuropathy and as that come in, as well as progress on our manufacturing across all front. So I think you'll actually see this constant drumbeat of high quality clinical data, both efficacy and safety starting in December of this year, and just going out to the foreseeable future.

Lastly, we plan to have our Rett syndrome, our first glimpses of Rett syndrome data available to us in at the end of next year. And I think most people understand the value creation that that program is going to generate not only because of the large patient population, but also the fact that we are essentially controlling the expression of MECP2 gene typically on a cell-by-cell basis in vivo, and not using any type of exogenous support or anything else. This is all self-contained within the construct, basically, hijacking the endogenous feedback loop of the body. And so again, that is just going to be high quality data, we were excited about some of the preliminary GLP tox data that we've gotten in our NHP studies as well as some new pharmacology data. And so we'll continue to provide updates on that as well as we get into the New Year and providing updates on enrollment.

So that's kind of how you could think about data readouts. We will be presenting data at some of the larger conferences. But as soon as those are -- those presentations are accepted. We'll be updating the Street and I would also tell you that we plan on publishing a number of papers and high quality journals, starting with *ginixonaneuropathy*, where our collaborators are putting the final touches on their definitive research paper. And hopefully, that'll be accepted here and published relatively soon.

Operator

Thank you. Our next question comes from the line of Mike Ulz with Morgan Stanley. Please proceed with your question.

Mike Ulz

Hey, guys, thanks for taking the question. Maybe a question on 120 in GAN, around the upcoming data in December for the highest dose. Maybe you can just talk about how you're thinking about stuff the dose going forward. For example, if you see in the highest dose sort of continued stability, what does that mean for you in terms of the optimal dose? Thanks.

RA Session II

Hey, good morning, Mike, and great question. I'll turn it over to Suyash. Suyash, do you want to take that question?

Suyash Prasad

Sure. Yes, so as we've already -- as you're already aware, we've got a nice dose response across the three dose groups that we've shared previously. So the 3.5E13 total VG with a low dose, which was the more the safety dose, the 1.2E14, the medium low dose and the 1.8E14 medium high dose really showed disease stabilization. So the ongoing decline of eight points per year on the MFM32 was halted with both those doses.

My guess is that the high dose is going to show at least that degree of improvement that degree of dose stabilization, which is clinically meaningful. As we know, a 4-point change in MFM32 is deemed to be a clinically meaningful change. So the fact that we improve disease by 8-points per year, which translates to 16-points over two years, 24-points over three years, is really very meaningful for these patients and families.

And if we identify patients earlier, and we treat them earlier, when they're at a higher level of functioning, that's going to be probably the most meaningful thing we can do for these patients or families.

And as you already heard on the call this morning, and we issued in press release three or four weeks ago, on our partnership with GeneDX, where we now have the mutation for GAN, the GAN mutation now on many of these hereditary neuropathy screening panels. And the costs are covered. So actually presented that the Charcot-Marie-Tooth Association meeting last weekend and talked about this screening approach. And there's a lot of excitement -- a lot of interest from patients who have different forms of axonal neuropathy that have been diagnosed as Charcot-Marie-Tooth Type 2 wanting to get screened in case they have the GAN mutation and would therefore be eligible for gene therapy construct. So identify patients earlier is going to be more critical I think than dose.

In terms of what it means if we have generally equivalent levels or generally equivalent degrees of disease stabilization going from the medium low order to the high dose. There's an argument that we should go in with the high dose that the dose we should file for an approval. There's an argument that may we go from the medium high dose the 1.8E14 total VG. Some of it will depend on safety profile. And what I will say is on the medium -- low and the medium high dose, the safety profile is very, very encouraging.

If we saw some additional safety concerns, the high dose would maybe drop down a dose of file at the 1.8E14 dose, I don't anticipate that's going to be the case actually, it's going up from the medium low -- sorry, medium high to the high. You're actually doubling the amount of drug, which for a gene therapy is not a huge jump in dose. So the actual dose we filed for and approval with I think will become a bit clearer once we share the high dose data and will become clearer when we talk to regulators.

And as you heard earlier, we'll plan on those discussions. The first one will be in January and then during the New Year, we'll have those discussions with other agencies. But my guess is it's either going to be filing on the high dose or the medium high dose that would be my guess.

Operator

Thank you. Our next question comes from the line of Kevin DeGeeter with Oppenheimer. Please proceed with your question.

Kevin DeGeeter

Hey guys, thanks for taking my questions. I mean just maybe two quick ones on GM2. Appreciate the updated perspective on how you're thinking about regulatory path, I guess, with that in mind. How many patients should we expect to see an update on in December to kind of appreciate kind of where you are from building a patient data safety base? And then as I think about duration of follow-up, from a clinical perspective, but I guess for this discussion from a regulatory perspective, what duration you'll follow-up on HEXA enzyme expression do you think you'll need to be able to gather to have robust discussions with regulators. Thanks.

RA Session II

Hey Kevin, good morning, and thanks for the question. Maybe I'll take your first question, and Suyash, if you don't mind; you could take Kevin's second question.

On the first question, what I'll say is we haven't disclosed the number of patients that will be in that update. What I will say is that Suyash and his team as well as our patient advocacy group, as well as our Med Affairs Group collectively have done a fantastic job with identifying patients globally. And this is a true global study. And so we're quite excited about that. And this is ultimately what changed our mindset really around what's the fastest pathway to approval could potentially look like. Essentially, because we were getting patients from literally all over the world and identifying patients from all over the world.

And so what I'll say is that we are on track to have that data. It'll be on multiple patients. I will say that. And what I'll also say if Suyash and his team from a screening perspective have now identified and have assessed over a double-digit worth of patients I'll say that. Again this really gives us a lot of confidence that there's a lot more patients out there that maybe the epidemiology has really led on.

And this is typically the case from a rare disease perspective. When there's a therapeutic alternative patients tend to find you. And Suyash and again the patient advocacy group and our multiple teams have done a fantastic job getting out there, finding the KOLs, having the discussion, making sure people know that this study is up and running and make sure people know that they have an ability if they're not in the territory to actually travel to the territory to be treated. And so I'll stop there. Suyash, maybe you want to address Kevin's question around just HEXA enzyme activity and duration of HEXA.

Suyash Prasad

Yes. This is a really good question, Kevin and I think that the way to think about it is take a step back and just anticipate the cadence of what might happen. So we're going to give the drug intrathecally. It travels to the brain, the caption into the brain cell, the neuron, the DNA pops out, starts producing the bi-systemic HEX alpha sub-units, beta sub-units, they combine and starts breaking down GM2 ganglioside. Now you're going to get maximal transgene expression probably three to four weeks after dosing, and then you should get maximum production of enzyme HEXA shortly thereafter.

So our guess is that at the one month time point, and we take a CSF sample at one month, we take one at three months, we take one at six months, and then we take one at 12 months for the first year. My guess is that the HEXA level in the CSF will go up at the one-month time point, but probably will not reach maximum levels, by the three-month time point, my expectation is it will reach maximum levels. In parallel with that in -- with regard to the earlier discussion we had, you will also see an elevation of HEXA levels in plasma, which is where we have more experience, but it's probably less relevant for a treatment that transduces brain cells. My guess is that you're going to see persistently elevated levels patterns, six month time point in the CSF and persistently elevated levels at the 12-month time point in the CSF.

And I don't think you're going to see any diminution activity over time. And the reason for this is that -- is that once you've trans used a brain style, it should stay trans used and still be producing transgene in perpetuity, unless there is some kind of inflammatory or immunological or disease type insult, which should -- I don't think will be the case really. So my guess is that the enzyme levels once the brain is transduced the enzyme levels and these will stay high persistently.

Now we've seen this to some degree in the mouse models where we see across a range of our programs. We can't take CSF levels from mice unfortunately of enzyme over time. But what we can do is look at plasma levels of enzyme over time, and we see them raise persistently in our chronic mouse studies over time. So my guess is we're going to see elevated levels of enzyme persistently.

Now how much enzyme -- at what persistence, what durability is required by the regulators? My guess is that if they see a nice increase, I think they're probably going to -- want to see -- we'll probably go in if we're seeing good clinical benefit at the six-month time point and persistent levels of enzyme at six-month time point, we might consider filing on that data, but in reality, the regulators usually once a year. And so my guess is it'll we will probably make a case at six months if we're seeing good clinical effect and persisting enzyme levels. But in reality, the regulators will push back in once a year, but that's my guess on how things will play back over the longer term.

Operator

Thank you. Our next question is coming from the line of Yun Zhong with BTIG. Please proceed with your question.

Yun Zhong

Hi, good morning. Thanks very much for taking the question. This is a follow-up question on the CLN7 program. Just wanted to confirm, have you had any discussion with the FDA to confirm that it will be possible to move into pivotal study, which the second-generation construct and given that there seems to be quite a lot of components you're going to change from generation one to generation two. How do you feel comfortable that some quick assays will allow you to find the optimal doses and feel comfortable still with the safety going into pivotal study? Thank you.

RA Session II

Hi, Yun. Thanks for the question. Maybe I'll start and Suyash, please chime in if you'd like to.

So what I would say there are multiple aspects that we know that we can change and maintain a certain level of functionality of the CLN7 construct, because we've done it before essentially taking programs from our collaborators, from academia and then making these subtle changes and moving that program forward into IND-enabling studies and ultimately forward into the clinic, while using the data that's been generated proof of concept data that's been generated as a basis to support clinical development.

We've actually done this multiple times across our portfolio. And these changes that we have made before will be consistent with some of the aspects that we look to change on the CLN7 program. So we think there's -- this notion of massive movements from one construct to the next is not necessarily there, right. What we do know is -- and there is multiple FDA guidance documents on how to do this, what you can do in order to reference data that's been generated essentially by another construct or similar product.

So they're clear precedent that's been set by multiple agencies around the world, both moving from animal proof-of-concept data into IND-enabling studies and ultimately into the clinic and also in the clinical setting. We've most recently seen this with one of uniQure's Gene Therapy Programs; I believe it was in hemophiliacs.

So this is a -- there has been precedent on this. And to your second question we haven't yet approached the FDA with discussions around this program. Essentially, we've had nine discussions across our portfolio. And multiple discussions planned for the New Year, and we plan to discuss this program in the New Year with the FDA around the protocol for comparability. I'll stop there. Suyash maybe you want to comment?

Suyash Prasad

Sure. And I think that the -- we've spent some considerable time talking about modifications to the construct. And I use the phrase modification, because they're relatively minor changes that we think will have some reasonable impact. And we won't go into the details of the changes that where we're proposing. But suffice it to say is optimizing the construct where we think there's going to be -- to a degree of benefit from an efficacy perspective, a benefit from a safety perspective, and a benefit from manufacturability perspective.

But we're very, very mindful, but we don't want to change it so much that it becomes a whole new package. We are very aware of what we can change and what we can't change to allow us to reference the first-generation construct from a similarity perspective with minimal bridging work. It's likely we're going to need to some bridging work in the animal. But it's likely a very simple study, perhaps a combined mouse model short duration pharmacology/toxicology study. But it's -- once again, we're planning to make minimal changes in line with our ability to reference the earlier first-generation construct.

Operator

Thank you. Our next question comes from the line of Eun Yang with Jefferies. Please proceed with your question.

Unidentified Analyst

Hi, this is Nancy [ph] on for Eun. Thanks for taking our questions. I was just curious on how is the progress on ratio of anti-capsids during the AAV9 production and what the current ratio of anti-to package capsid is, and mostly on what the range of this is between your different indications? Thank you.

RA Session II

Hi, thank you for the question. What I'll say is, and because we have such an extensive portfolio, we won't go into each one of our programs. What I'll say for our current standard is to strive for 90% full capsids, and that's kind of consistent, that's consistently our strategy across our portfolio. And sometimes we do better than that. And what I can say, for our GM2 program, we've actually gone above that -- the full ratio, that full ratio of 90%. So that's kind of what our current standard is, obviously, every program is different and so some are better producers than others. But what I will say is, we try to maintain some level of consistency in our manufacturing platform, also, ultimately to support this whole notion of platform effect. And what I'll say is we will always sacrifice yield for high quality material. And so that's probably one of the more important aspects of manufacturability to us and make sure that we're getting good, high-quality full capsids into patients, ultimately, to minimize any real safety concerns, which can be a concern that we see now, which is something that we've seen within the field. Suyash, do you want to comment?

Suyash Prasad

I'll comment. Yes, this is a really excellent question. And I think always weaving in some of what the importance here is, and it's really about the so what factor. What does the presence of anti-capsid mean? Now I've been a firm, firm believer for many years, and I think the field is moving in this direction that we have to remove as much anti-capsid as possible. A lot of manufacturers find this hard to do without sacrificing yields tremendously.

And so there's sometimes reluctance to try and remove the anti-capsid. From my perspective, looking at the patient, anti-capsid just add unnecessary borrow load, which then feeds into some of the safety issues that we've seen and people are concerned about in the AAV gene therapy space.

Now right now I've been talking about this at length and always quite as well as our intent is to have at least 90% full. We do better than that. Significantly better from that for some of our programs, which I'm very pleased about as the physician overseeing the safety of these patients. And we -- I really appreciate the fact that's RA and our full alignment, that we will sacrifice yield in order to make sure we get pristine pure highly purified product with as little anti-capsid as possible. So I think it's a really important question. We work closely with Fred, our Chief Technical Officer to try and make sure that we have very high quality products and we've got good characterization screens early on. But our intent yes is to inject patients with less than 10% and see greater than 90% for our products.

Operator

Thank you. Our next question comes from the line of Kristen Kluska with Cantor Fitzgerald. Please proceed with your question.

Kristen Kluska

Hi, good morning, everybody. Thanks for taking the questions. Just wanted to ask as you look at the clinical trials you anticipate running next year, how you're thinking about the cadence in terms of trial enrollment, given all of these different indications, have different prevalences?

RA Session II

Hey Kristen, good morning, and thank you for the question. I'll turn it over to Suyash to answer that question.

Suyash Prasad

Yes. Thank you, Kristen. Great question. It's a little different from program to program. There's a few common themes I would say. First of all, we talked a lot about our platform approach AAV9 anti-delivery HEK293, but the platform approach actually works in many other ways. One of which is frankly that the vast majority of clinicians we deal with are pediatric, metabolic or neurology experts. GM2 sale in one, sale in Southern Rett is generally looked after similar physicians. And so we a lot of the touch points in terms of finding investigators are similar. So I think that's one thing that helps us in terms of recruitment.

I think the other thing that helps us is where -- for the diseases where there are more the ultra-rare population. So we're thinking the diseases would have 1,000 patients prevalent for example. We plan to have one or two sites in the U.S. and one or two sites ex-U.S. and then transport patients from around the world to those sites. So we're focusing heavily on that, the ability to transport patients from other countries to the U.S. or to Canada or to Europe. And that's worked very well for our GM2 program. We only have one site for GM2 program currently. In Canada, we get a list of patients and the patients that have been enrolled and screened for the study come from all over the world.

It's a little different for diseases that are less rare. So disease like Rett where you're thinking 25,000 patients in the U.S. and Europe recruits and enrollment is a little different. It's a little easier, because patient -- there's more patients and they are generally tend to congregate the centers of excellence where clinicians will have 30, 40, 50 patients with Rett syndrome on their books. We have one key opinion leader, one investigator we're considering the last 200 patients with Rett syndrome. And so we can use that individual as a clinical trial. So I would ask you to roll the whole study potentially on that side. But we're going to have -- we don't want to just do a single site directed cost. There would probably be three or four sites, but I don't anticipate there being problems with enrolling some of the larger patient's populations.

And in principle, this three real approaches to finding patients for these studies and they're really led by two colleagues at Taysha, so Emily McGinnis who heads Patient Advocacy and Kome Okposo who heads Medical Affairs. And we engage with patient advocacy groups in detail and in a very sincere wholehearted way to help educate patients and families, what it means to take a gene therapy trial and that way we find patients who are interested in taking part. We work with key opinion leaders, the experts in the fields. We have them attend advisory boards. We talk to them, and that's another route of finding patients.

And then the third approach is with, on the ground, medical science layers on activity with our teams knocking on the doors of clinicians to find patient who want support. So those are really the three philosophical approaches we used to find patients. As I say, our track record thus far for GM2, we've found many, many patients that we've screened many have not been eligible, and we'll share more detail on that when we update you all with data in the clinical trial, but that's our approach and it seems to have been very successful for GM2. And so we anticipate the same approach across the rest of our programs.

Operator

Thank you. Our next question comes from the line of Raju Prasad with William Blair. Please proceed with your question.

Raju Prasad

Thanks for taking the question. Just curious to know on the GDX deal just how many patients do you anticipate finding with kind of a genetic marker. And do you have any kind of initial thoughts there? And then, second on the GM2 program, it seems like 5% is the benchmark here for biomarker, but is there any initial clinical measures that we could see moving to kind of show that there's a clinical benefit that's being changed by this increase in enzyme activity? Thanks.

RA Session II

Hi, Raj. Good morning. Thanks for the question. Maybe I'll take both questions, and then for the second question, Suyash, happy to provide some color as well. So for the first question around our collaboration with GDX, not only was it a collaboration to include giant athermal neuropathy now on their standard neuropathy panel, but it's also a collaboration that includes both the Charcot-Marie-Tooth Foundation as well as the Hereditary Neuropathy Foundation. And this was extremely important because both of those patient advocacy groups fund and partner with centers of excellence, both here in the U.S. and in Europe. And particularly for the Charcot-Marie-Tooth Association, a number of the patients that are clinically diagnosed with Charcot-Marie-Tooth have not undergone genetic screening. And based on this again, robust natural history data that our partners at the NIH and Carsten Bönnemann have been leading over the last eight years.

It was identified that this late onset phenotype ginixonaneuropathy was essentially commonly misdiagnosed as Charcot-Marie-Tooth and more particularly Charcot-Marie-Tooth Type II. We also understand that this later onset form of the disease is extremely severe and kind of debilitating, but it's not life limiting in the sense that the early onset form of the disease is where patients are essentially diagnosed at age three and either in their early teens, or I'm sorry -- in their late teens or early 20s, they succumb to the disease. Typically in the later onset form of the disease, these patients are diagnosed sometime after their fifth birthday have issues around walking, have issues around muscle strength. And essentially it's kind of one of these quality of life significant -- it kind of the significant impediment to quality of life, but they tend to live a normal life span or at the bare least into their fifth decade of life.

So what we understand is that there is just based off of the epidemiology, there's a large pool of prevalent patients in that later onset population that not that hasn't necessarily undergone a genetic test, because it's essentially when a person is diagnosed with Charcot-Marie-Tooth and particularly the Type II form, there is no genetic screening for, because there's a number of genetic mutations that were called cause this kind of umbrella diagnosis.

So we actually think that there's a large group of patients and having talked to both the CMTA foundation, as well as the Hereditary Neuropathy Foundation they both agreed that a large section of these patients are typically misdiagnosed and most likely there is a genetic underpinning of which we know a large portion up to 6%, if not more are going to be ginixonaneuropathy mutations.

So we think there's a large number of patients both in the U.S. and Europe out there. And so we're doing the work right now to kind of identify these ahead of any type of regulatory approval and eventual commercial launch.

So I'm answering your question, but not answering your question. I won't give you a specific number. But what I will say it's a large number of patients, and we will probably say, we put that number above 1,000 patients out there that are out there that we hope to, are able to identify a large number of those. Raj do you mind just reminded me of your second question.

Raju Prasad

Yes, obviously, it seems as though natural history with a 5% kind of the biomarker thresholds for GM2, just curious to know the timeline for when that may translate over into maybe early clinical measure of benefit?

RA Session II

Absolutely. Great question. Suyash, do you mind taking that?

Suyash Prasad

Sure. Yes, I just make one comment on the GAN Charcot-Marie-Tooth discussion, because I actually spoke to the Charcot-Marie-Tooth Association meeting last weekend, and sat on a panel and got to meet many patients and families. And it was clear, it's always point that the many individuals the Charcot-Marie-Tooth only have a clinical diagnosis that that, there are many adults there who were diagnosed with the disease and having that mutation analysis or genetic testing. So there's a large pool of patients, I think, who will really take advantage of this GDX partnership that we've created. And our expectation is that a significant number of patients will be found, but shouldn't that. Just based on the subjective discussions I had last weekend, I think that that seems very real and meaningful.

With regards to GM2, it's a good question, I talked to the cadence of how I expect enzyme levels to modify and improve over time. I think with the clinical improvements, I think it's going to take longer to see clinical improvements. And it may be more stabilization of disease progression than improvements. And the reason I say this is that GM2 is a very rapidly progressive, destructive disease. And what happens after physiologically is that you get the accumulation of GM2 ganglioside and the lysosomes of the cells for less and swell a rupture [indiscernible] acidic enzymatic contents, and actually cause damage to the neurons. Initially, in inflammatory process, but then it results in fibrosis, death of the neuron.

And once you've lost a neuron, you don't get it back. So I think, if a patient is significantly affected, and they've lost a lot of neurons, you're going to be able to produce the enzyme HEXA stop additional damage. And you may get some resolution of some of the inflammation that's going on in the neurons. But if you've lost neurons, you're not going to see improvement there. If we treat earlier in life, and this is why it'd be important at some point in the future to have newborn screening for this disease and then treatment before the child has had a chance to deteriorate too much. And before the neuron loss has had the chance to take hold. That will be when you start to see the best clinical improvements.

Specifically in terms of what we're collecting, or what I expect to see, we're looking at measures. We're looking at a whole host of measures. We're looking at hypertonia -- hypotonia, dysphasia, lack of head control, the Vineland Adaptive Behaviors, the bay 3 scale looking at general developments. We're looking at seizures within EGs. We're performing a communication assessment scale, the ORCA the Observer-Reported Communication Ability scale. We're looking at quality of life scales and clinical global impression scales. My guess is that by the three months or perhaps by the six months' time, but you should see some stabilization of these and maybe some improvements. Probably the earliest indicator will just be in general global clinical impression. So the CGI scale will likely be. We hope would show some improvements, and then potentially some improvement in hypertonia, see some improvements there. See some loss, some reacquisition of milestones, which will be measured by the bay 3. And I've also hope to see some diminution in seizure activity. But I'm guessing you're going to have to wait at least three months after dosing, probably six months after dosing, to see that and I think you'll see a greater improvement in the younger patients than you will in the older patients.

Operator

Thank you. Our next question comes from the line of Silvan Tuerkcan with JMP Securities. Please proceed with your question.

Silvan Tuerkcan

Yes, good morning, and thanks for taking my question. Maybe you can just give us a big picture view about your ability to manage all of these programs as the pipeline expands so rapidly, especially next year with five, six trials and regulatory discussions in detail into potential planning at the end of the year. What about your cash and manpower to maintain all of that and you expect there will be maybe some attritional, deeper prioritization or potentially some partnerships, your thoughts that will be great. Thank you.

RA Session II

Thanks, Silvan. So thanks for the question. So what I would probably say, when you start to think about the company scaling to what we hope is eventually going to be a fully integrated gene therapy company that supports not only early discovery, but also commercialization, this is exactly what we were hoping to build-out as we kind of put the blueprint of the company together and the company and quite frankly, the company is executing.

So I think the ability has just been shown the proof in the pudding in a sense, five concurrent GMP run, completed this year, non-regulatory interaction this year, good activity on the BD front, albeit a lot of those programs are coming from our Chief Scientific Adviser, Dr. Steven Gray, but they all kind of support the central thesis around intrathecal delivery, AAV9, HEK293 suspension, manufacturing, monogenic CNS disease. So you can kind of see there's a certain platform that that we're creating that essentially allows us to kind of quickly pivot from one program to the next.

As you think about scaling, the company was founded early last year, and we quickly progressed to a public company in September of last year, we just recently had our one year anniversary as a public company. We finished the year last year with one clinical stage program; we'll finish this year with five clinical stage programs. We plan to have three data readouts that we're on track and reiterating our guidance to hit those. And we have multiple programs in IND-enabling studies.

And so what I would say is the team has performed beautifully, we finished the year with -- we finished last year, so 2020 with 38 employees, we'll finish this year with close to 200 employees. And that ability to scale has really allowed us to be able to execute on really some ambitious plans. As we get into 2022, we've kind of laid out a couple of the data readouts that will be supportive of continued value-creation CLN1 enzyme activity data, Rett Syndrome, clinical safety and efficacy data at the end of next year, but also this kind of ongoing cadence of updates from our current clinical programs.

This year, I would think of it as a foundational year kind of a building year for Taysha. So 2021 really kind of laid the foundation, a lot of work happened to get us to the point to where as we move into 2022, there'll be this constant drumbeat of data, right. So we'll provide updates on ongoing updates on our current programs in ginxonaneuropathy and CLN1 in GM2 Gangliosidosis, in CLN7, and plus the newer programs that will be moving into the clinic next year. So, for us, we've shown the ability to scale, we've shown the ability to execute this year. And we'll continue to do that.

On the cash front, I think what we've reported provides us to consist keep our guidance of having cash into the second half of 2023, without the need to raise additional capital. This also gets us past some definitive regulatory readouts in our ginxonaneuropathy program, plus multiple high quality value inflection points from a clinical data perspective. So I think just across kind of all aspects of the business, I'm extremely proud of the work that the Taysha employees have undertook this year as well as our collaborators over at UT Southwestern. They're phenomenal partners to work with, but also, our collaborators on ginxonaneuropathy at the NIH have been phenomenal partners to work with and so what I see moving forward is for us to continue executing like we have. But really I think you have got to see 2021 as a foundational building year for the company and you will start to see kind of this low growth from here because we have kind of laid the foundation support what we hope to achieve moving into 2022.

Operator

Thank you. There are no further questions. I will now turn the call back over to Mr. Session for additional or closing remarks.

RA Session II

So we really appreciate everybody joining this call this morning. Again we look forward to building on the momentum that we have had in the first part of this year and continue to see you guys posted on the progress for the portfolio, from the portfolio for the remainder of the year and into 2022.

Thank you so much and you guys have a wonderful day.

Operator

Ladies and gentlemen, this concludes today's presentation. Thank you once again for your participation. You may now disconnect.

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Taysha Gene Therapies (NASDAQ:[TSHA](#)) Q4 2021 Earnings Conference Call March 31, 2022 8:00 AM ET

Company Participants

RA Session II – President, Chief Executive Officer & Founder

Kimberly Lee – Corporate Affairs Officer

Suyash Prasad – Chief Medical Officer & Head, Research & Development

Kamran Alam – Chief Financial Officer

Conference Call Participants

Elizabeth Webster – Goldman Sachs

Joon Lee – Truist Securities

Mike Ulz – Morgan Stanley

Jack Allen – Baird

Kevin DeGeeter – Oppenheimer

Gil Blum – Needham and Company

Laura Chico – Wedbush Securities

Yun Zhong – BTIG

Silvan Tuerkcan – JMP Securities

Rick Krause – Cantor Fitzgerald

Eun Yang – Jefferies

Sami Corwin – William Blair

David Hoang – SMBC

Yanan Zhu – Wells Fargo

Operator

Welcome to the Taysha Gene Therapies, Fourth Quarter and full-year 2021 financial results and corporate update. At this time, all participants are in listen-only mode. Following management's prepared remarks, we will hold a brief question-and-answer session. As a reminder this call is being recorded today March 31st, 2022. I will now turn the call over to Dr. Kimberly Lee, Chief Corporate Affairs Officer. Please go ahead.

Kimberly Lee

Good morning and welcome to Taysha's fourth quarter and full-year 2021 financial results and corporate update and conference call. Joining me on today's call our RA Session II Taysha's President, Founder, and CEO, Dr. Suyash Prasad, Chief Medical Officer and Head of R&D, and Kamran Alam, Chief Financial Officer. After our formal remarks, we will conduct a question-and-answer session. And instructions will follow at that time.

Earlier today, Taysha issued a press release announcing financial results for the fourth quarter and full-year ended December 31st, 2021. The copy of this press release is available on the company's website and through our SEC filings. Please note that on today's call, we will be making forward-looking statements, including statements relating to the safety and efficacy and the therapeutic and commercial potential of our investigational product candidates.

These statements may include the effect of timing and results of clinical trials for a product candidate. Our expectations regarding the data necessary to support regulatory approval of Taysha 120. The regulatory status and market opportunity for our clinical programs, as well as patients manufacturing plants. This call may also contain forward-looking statements relating to Taysha's growth and future operating results, discovering development and product candidates, strategic alliances, intellectual property, cash runway, and improvement limitation, and potential impacts of our strategic pipeline prioritization initiatives, as well as matters that are not of historical facts or information.

Various risks may cause actual results to differ materially from those stated or implied in such forward-looking statements. These risks include uncertainties related to the timing and results of clinical trials and preclinical studies of our product candidates are dependent upon strategic alliances and other third-party relationships. Our ability to obtain patent protection for discoveries, limitations imposed by pans owner controlled by third-parties.

And then requirement of successful funding to deduct our research and development activities. For listened description of the risks and uncertainties that we face, please see the reports we have filed with the Securities and Exchange Commission. This conference call contains time-sensitive information that is accurate only as of the date of this live broadcast, March. 31, 2022. Taysha undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call, as so as maybe required by applicable securities law. With that, I'd now like to turn the call over to our President, founder and CEO, RA Session II. RA?

RA Session II

Thank you, Kim. Good morning and welcome everyone to our call. 2021 was a year of accomplishment that included positive data from three clinical programs. Including GAN, GM2 gangliosidosis, and CLN7 disease. We are sharpening our strategic focus to prioritize key value driving registration directed programs in GAN, which has an estimated addressable patient population of 5,000 worldwide, and Rett syndrome, which affects over 350,000 patients worldwide.

To increase operational efficiency activities for other ongoing clinical programs will be minimized and all other research and development will be paused. As a result, we have reduced our workforce by approximately 35%. Our strategic pipeline prioritization, along with existing cash and financing under our current debt facility, is expected to extend cash runway into the fourth quarter of 2023. We look forward to our continued execution across our clinical and regulatory strategy.

And we'll update you on progress throughout the remainder of the year. I will now turn the call over to Suyash to provide a more detailed update on our clinical programs. Suyash, please go ahead.

Suyash Prasad

Thanks RA. Recently, we reported positive initial clinical data for GAN GM2 gangliosidosis and CLN7 disease further validating the therapeutic potential platform in multiple diseases of the central nervous system. Let's begin with Taysha 120 for the treatments of GAN. Taysha 120 is the first gene therapy to be interested equally dosed, and is this currently being evaluated as approximate groundbreaking historic dose escalation clinical trial at the NIH, under the leadership of the principal investigator, cost and dominant.

We recently reported positive clinical efficacy on safety data for the high dose cohort of 3.514 total VG, as well as long-term safety and durability data across all therapeutic doses. Treatment with Taysha 120 achieved a clinically meaningful and statistically significant slowing or halting of disease progression seen in the highest price cohort of 3.58014 total BJ on cross-sold therapeutic dose cohorts. At the highest dose, Taysha 120 demonstrated clinically meaningful and statistically significant improvements in MFM32 score by year-one compared to natural history.

Additionally, long-term durability data across all therapeutic doses demonstrated a 10-point improvement in the main change from baseline and MFM32 score by year three compared to the estimated natural history decline of 24 points. These long-term data confirmed with disease modifying effect on sustained your ability of TSHA-120. Notably, no biopsy data, pre and post-treatment with TSHA-120, provided evidence active regenerations, of fibers thereby demonstrating pathological improvement to complement the clinical benefit saying.

In addition, preservation of visual acuity as measured by the lock Moscow was observed. And this was in conjunction with improvements in retinal nerve fiber layer thickness as assessed by optical coherence tomography. So, no significant safety issues and no increase in adverse events at high doses. All adverse events relate to immunosuppression of study procedures were comparable to other Gene therapies and trends into night shop. There were no dose-limiting toxicities reported following treatment with TSHA-120.

No evidence of dorsal root ganglion inflammation, and no evidence of thrombocytopenia. Overall the states that's the most comprehensive Gene therapy dataset in GAN, offering TSHA-120 a potentially de-risk regulatory path. We believe this program currently meet the most registration requirements based on FDA and EMA's guidance for Gene therapy for neurodegenerative diseases.

We look forward to our continued discussions with major regulatory agencies on potential registration pathways for TSHA-120 and anticipate a regulatory update by mid 2022. As a reminder, TSHA-120 has already received Orphan Drugs and Rare Pediatric disease designations from the FDA. We also have partnerships in place to help raise awareness and facilitate early diagnosis of GAN.

This includes a partnership with GeneDx, the global leader in genetic testing, to include a genetic marker to test for GAN and the GeneDx routine Hereditary Neuropathy screening panel, which is free of charge to individuals at risk of, or suspected, of having GAN. It's also includes collaborations with Hereditary Neuropathy Foundation and the Charcot-Marie-Tooth Association Centers of Excellence, as well as healthcare professionals on patient advocacy groups to increase access to genetic testing. Turning to Rett syndrome, TSHA-102 is the first and only Gene therapy and clinical developments for Rett syndrome and is designed to deliver MECP2 transgene using our novel miRARE platform, or micro RNA Responsive Auto-Regulatory Element platform. This technology is exclusively licensed to Taysha and developed by Doctors [Indiscernible] and Steven Gray of UT Southwestern Medical Center. MRI is designed to provide a sophisticated regulation of transgene expression, genotypically on a cell-by-cell basis, delivering controlled expression, toxicity associated with excessive levels of MECP2.

We were very pleased to announce earlier this week, initiation of clinical development for TSHA-102 with the acceptance of our CTA by Health Canada in March. Sainte - Justine, mother and child university hospital center in Montreal, Quebec, Canada has been selected as the initial clinical sites under the direction of Dr. [Indiscernible], principal investigator. We also announced positive preclinical data that supported the CTA acceptance, including the pharmacology study and reps knockout mice assessing the efficacy of TSHA-102, and the six-month GLP toxicology study in non-human primates, exploring the budgets attributions and mechanism of action of TSHA-102.

Taysha 102 has a robust preclinical data package that supports and validates the ability of miRARE to safely regulate trends Gene expression. Data from the CTA naive and pharmacology study in last models syndrome demonstrated that miRARE regulated trends Gene expression, improved survival, respiratory function, and motor of function assessments across multiple dose levels.

A onetime intrathecal injection of Taysha 102 significantly increased survival at all dose levels with a mid to high doses improving survival across all age groups compared to vehicle treated controls. Treatment with takes you want to significantly improved body weight motor function on respiratory assessments and MECP2 knockouts mice. An additional study in the [Indiscernible] is currently ongoing with preliminary data suggesting normalization of survival.

Positive CTA enabling [Indiscernible] GLP toxicology data, non-HP reinforced Taysha launches favorable safety profile across all dose levels tested, including doses up to four fold above the Brazilians clinical stocks index. These data supported by distribution as reflected by DNA copy number in multiple areas of the brain on sections of spinal cord. Perhaps most importantly we observed correspondingly low levels of MRNI across multiple tissues.

This indicates the MRAP down regulation is appropriately minimizing a trends gene-expression from the construct in the presence of endogenous MECP2 in these wild-type NHP as expected. Let me repeat that. High levels of DNA in target tissues, meaning that there's good distribution of drug from NHP conjection. But low levels of mRNA, meaning that the down regulation by the MRAP is working well to minimize any toxicity.

Indeed, low toxicity from trenching expression was observed, which was confirmed by functional evaluations, demonstrating no detrimental change in near behavioral assessments, and histopathologic evaluations demonstrating no adverse tissue findings on necropsy. Collectively, these data further support the therapeutic potential, safety and tolerability of TSHA-102 to treat Rett syndrome across a broad dose range.

These pre -clinical safety and efficacy data will be presented at the International Rett syndrome Foundation. Rett syndrome scientific meeting taking place April 26 to 27, 2022 and Nashville, Tennessee. Currently, there are no disease modifying therapies to treat over 350,000 patients, estimated the suffer from Rett syndrome worldwide. We're excited to advance TSHA-102 as the first Gene therapy and clinical development for the treatments of this devastating neurodevelopmental disorder, and look forward to reporting preliminary Phase 1-2 clinical data by the end of the 2022.

As a reminder, TSHA-102 has been granted Rare Pediatric Disease designation and Orphan Drug designation from the FDA, and more recently Orphan Drug designation from the European Commission. For GM2 gangliosidosis, TSHA-101 is the first, and only bicistronic vector in clinical development, representing an important first for the field of Gene therapy.

Driven by the same promoter, TSHA-101 expresses both the HEXA gene, coding the alpha sub-unit, and the HEXB gene, coding for the beta sub-unit, in a one-to-one ratio, enabling the production of functional heterodimeric beta-Hexosaminidase A, and providing the ability to restore and normalize enzyme activity in GM2 gangliosidosis using one vector. We reported initial positive by-market data in January for TSHA-101, demonstrating normalization to beta sub-units of Hexosaminidase A or HEXA enzyme activity in patients with multiple forms of GM2 gangliosidosis.

We shared data for two patients, including Month 1 and Month 3 analysis for patient with Sandhoff disease, and Month 1 analysis for patient with Tay-Sachs disease. Following one particular demonstration, TSHA-101 achieved HEXA enzyme activity of a 190% of normal at Month 1, and 298% at Month 3, in Patient 1 with Sandhoff disease, representing 38-fold on 58-fold above the presumed asymptomatic level of 5% of normal identified by natural history at Month 1 and Month 3, respectively.

Patient 2 with Tay-Sachs disease, achieved HEXA enzyme activity of 25% of normal at Month 1, which represented 5-fold above the presumed asymptomatic level of 5% of normal identified by natural history. Preliminary data suggested that TSHA-101 was well-tolerated with no significant drug-related events in both patients. The unfortunate death of Patient 1 was attributed to pneumonia and pleural effusion with a concomitant hospital-acquired MRSA infection.

The independent Data Safety Monitoring Board agreed with the initial assessment from the principal investigator and confirmed that the patient's death was unrelated to study drug. patient two continues to progress well, and we're continuing to monitor patients two and three. We do not intend to perceive further enrollment in the Phase one two trial at this time due to prioritization of programs that increase operational efficiency. But we will continue to follow the patients who were previously dosed.

Well, CLN7 we reported posted preliminary clinical safety data for the first-generation construct in CLN7 investment disease from the ongoing clinical trial in collaboration of UT Southwestern Children's Health and children Medical Center Foundation. We recently dosed a fourth patient at 1E15 total VG, bringing the total to three out of the four patients dosed at 1E15 total VG, which is the highest dose ever safely administered in particularly in humans with Gene therapy.

Dose escalation from 5E14 to 1E15 total VG was supported by the data safety monitoring board. Initial data for three patients supported a favorable tolerability, on safety profile with no major adverse events across doses. Further development of sale and seven program will focus solely on the first-generation construct in collaboration with our existing partners. In 2022, we expect several potential value-creating catalysts, including regulatory feedback for TSHA-120 and GAM by mid-2022, and preliminary Phase 1-2 data for TSHA-102 and Rett syndrome by year-end.

Clinical developments of the first-generation constructs, the CLN7 remains ongoing with our existing partners. We will continue clinical development of TSHA-118 in CLN1 night in sale on one disease and expect to initiate clinical development of TSHA-105 in SLC13A5 deficiency this year. With that, I'll turn the call over to Kamran to review our financial results Kamran.

Kamran Alam

Thank you. Suyash. This morning, I will discuss key aspects of our fourth quarter and full-year ended December 31, 2021 financial results. More details can be found in our Form 10-K, which will be filed with the SEC shortly. As indicated in our press release today, recent development expenses were \$37.9 million for the three months ended December 31, 2021, compared to \$12.3 million for the same period in 2020.

Research and development expenses were \$131.9 million for the full-year ended December 31, 2021, compared to \$31.9 million for the full-year ended December 31, 2020. The \$100 million increase was primarily attributable to an increase of \$38.3 million of expenses incurred in research and development manufacturing and other raw material purchases, which included cGMP batches produced by Catalent and UT Southwestern.

We also incurred an increase in employee compensation expenses of \$32.7 million, which includes \$7.1 million of non-cash stock-based compensation, due to an increase in the employee headcount in the research and development function. We also incurred an increase of \$29 million of third-party research and development consulting fees, primarily related to GLP toxicology studies, clinical study CRO activities in consulting for regulatory and clinical studies.

In general, administrative expenses were \$11.8 million for the three months ended December 31, 2021, compared to \$6.1 million for the three months ended December 31, 2020. General and administrative expenses were \$41.3 million for the full-year ended December 31st, 2021, compared to \$11.1 million for the full-year ended December 31st, 2020. The full-year increase of approximately \$30.2 million was primarily attributable to \$16.3 million of incremental compensation expense, which included \$7.7 million of non-cash stock-based compensation due to increases in employee headcount.

We also incurred an increase of \$13.9 million in professional fees related to legal, insurance, investor relations, communications, accounting, personnel recruiting, market research, and patient efficacy activities. Net loss for the three months ended December 31st, 2021 was \$50.4 million or \$1.32 per share as compared to a net loss of \$18.3 million or a \$0.50 per share for the three months ended December 31st, 2020.

Net loss for the full-year ended December 31st, 2021 was \$174.5 million or \$4.64 per share compared to a net loss of \$60 million or \$3.40 per share for the full-year ended December 31st, 2020. As of December 31st, 2021, Taysha had \$149.1 million dollars in cash and cash equivalents. Our strategic pipeline prioritization initiatives along with existing cash and financing under the current debt facility is expected to extend cash runway into the fourth quarter of 2023. And with that, I will hand the call back to [Indiscernible].

RA Session II

Thanks, Kamran. This year we are focused on strategic pipeline prioritization initiatives for GAN and Rett syndrome. And our plan is to conduct small proof-of-concept studies in CLN1 disease and SLC13A5 deficiency. We anticipate several potentially value-creating catalysts this year, including a regulatory update for TSHA-120 in GAN by midyear, and preliminary clinical data for TSHA-102 in Rett syndrome.

I would like to give special thanks to the continued support and dedication of our Taysha employees, board of directors, scientific advisory board, collaborators, and to patients and advocates who remain our motivation everyday to continue our mission to develop curative gene therapies, to eradicate devastating monogenic CNS disease. I will now ask the Operator to begin our Q & A Session. Operator?

Question-and-Answer Session

Operator

Thank you. At this time will now be conducting a question-and-answer session. [Operator Instructions]. For participants using speaker equipment, it maybe necessary to pick up your handset before pressing the star keys. So that we may address questions for as many participants as possible, we ask you to limit yourself to one question. One moment, please while we poll for questions. Thank you. And our first question comes from the line of Salveen Richter with Goldman Sachs. Please proceed with your question.

Elizabeth Webster

All right. Good morning. This is Elizabeth on for Salveen. Just given the strong data that you had for GM2 this year, I guess, why choose to de-prioritize that program?

RA Session II

Hey, Elizabeth. Good morning. Hopefully, you can hear me okay. I think it really boils down to really focusing on a couple of key value drivers this year. Just with the uncertainty in the capital markets on a fundraising perspective, I think it was really imperative to the company in the best possible position for when Rett data will be available, as that's a pretty large opportunity. We're talking about 350,000 patients worldwide. And really the significant unmet medical need there.

What I would say is, I think there's always the opportunity to take another look at prioritization. Once we see external factors stabilized somewhat, but I think this is really -- this was extremely important to make sure where is that the company itself was put in the best possible position to preserve cash runway, but also value creation. Obviously, the focus on GAN, it's pretty evident because we're going to be embarking on regulatory pathway discussions and then, Rett is just such a large opportunity and one that we're going to be the first and only gene therapies in development where a lot of other companies haven't made at that far.

We thought it was just prudent for us to focus there. So hopefully that answers your question.

Operator

Thank you. Our next question is from the line of Joon Lee with Truist Securities.

Joon Lee

Hi, thanks for taking our questions. In addition to restructuring, would you also consider monetization of some of non-core programs via out-licensing or partnering? And then also our understanding is that the term loans from SVB is contingent upon you having three active programs. So in addition to GAN, or Rett, do you plan to have a third program still active? Thank you.

RA Session II

Good morning. Thanks for the questions. I'll take the last question first, so I think as we stated, there will be a key focus on Dan and Rett syndrome, but we're also going to be continuing development on CLN1, CLN7, and FLB 13, AE5. So in total, there's five active programs. I think what we've decided to do with essentially pause work on additional clinical programs, as well as programs moving from pre-clinical into the clinic.

And that's really where I think the prioritization came from. So we significantly meet the requirements for that long facility. And now with actually just validated, as we filed the K. Your first question around BD opportunities. I think the former head of BD in my former career, I think we were always open to having conversations around BD. I think for us, what would be important is too if we were to do a deal is to find a partner that either has an opportunity for us to reach markets that we don't necessarily have or to accelerate programs that we can not.

What I will say is there's active discussions around potentially looking at opportunities for ex-U.S. territory types of deals that could accelerate clinical development and speed-to-market and certain parts of the world. But I think this is something that will always kind of keep as dry powder. I think we will always look at raise two ways to bring in non-dilutive forms of capital. Capital while accelerating our programs. I think that's always a prudent thing to do. So really good question.

Operator

Our next question is from the line of Mike Ulz with Morgan Stanley, please proceed with your question.

Mike Ulz

Hey, guys, thanks for taking the question. Just with respect to GAN, maybe you can just give us an update on your current thinking on the path forward there in the U.S. and in the past, you'd mentioned analytic comparability as one of the potential scenarios there. And I'm just curious if you've done that analysis yet, or are you waiting to get feedback from the FDA before you move forward with that? Thanks.

RA Session II

Thanks, Mike, really good question. So really, I think it boils down to three scenarios in the United States with GAN and ex-U.S. have kind of slightly different. I think there's a clear pathway when you start to think about the EMA, which opens up the rest of the world through references the EMA, but particularly for the FDA, it boils down to three scenarios. I think two were higher probability, one is lesser profitability, but certainly could always be a route that the FDA asked you to go.

Scenario 1 would be if the FDA allows you to file with analytical comparability, essentially doing an analytical bridging study between the clinical materials and the commercial grade material. In order to, what we would say, increase the probability of success of this option. What we've decided to do with keep the manufacturer of this program at the same CDMO partner than maybe back to the clinical program we're using the same cell line same media, same downstream purification, same facility.

So these are -- essentially it's a like-for-like process and we wanted to make sure we held the thing confident because we wanted to be able to increase our probability. This is why we'd probably say would be probably not the FDA's preferred route. We haven't had that conversation with them. But if you just look at the comp and the closest comp to this would be the experience of Zolgensma.

That would more align to option two. And I would say option two is probably our base case and this is essentially what we're planning for internally. And this would be somewhat bridge between doing an analytical filing on analytical comparability and doing a new study. This is essentially where you would dose a handful of patients under the current IND and protocol using the commercial grade material.

The goal would ultimately be to propose to the FDA filing a rolling submission, essentially, following the preclinical data first. That's not changing. That's all there. Then starting to supplement the file and with the clinical data that's already been generated, which we now have seven years worth of data, safety and efficacy data. That's been generated that we've seen long-term durability dose-response, good safety, efficacy across the board.

And in supplementing that data with new data generated with the commercial grade material. What I will say is the engineering run for the commercial grade material Jeff completed, and the yields are phenomenal. And we've just kicked off our GMP run of -- for the validation batch of which is ultimately the commercial grade material that will be released in Q3. So we're actually quite excited that we've made significant progress along with our CDMO partner there.

The third scenario which we think is somewhat unlikely and would be against the FDA guidance, that they issued last year for the development of Gene therapy and neurodegenerative diseases is for them to go back and ask for an additional study. Here, the natural history is pretty well elucidated. We have three sources of comparators. Each patient in the interventional trial rolled over from the natural history study.

So that's the -- so each patient acts as their own comparator. There's also using the full cohorts, natural history cohort as a competitor. And because the natural history data was so extensive, you can actually find aged-matched controls. It was in that natural history cohort to act as a comparator. So, we're pretty fortunate that the level of robustness of the data, the long-term durability of the data, we now have pathological change, where we actually see regeneration of nerve fibers from biopsies that were taken pre and post treatment.

We feel pretty good about the dataset that we're going to go in and talk to regulators about, this should be extremely compelling. But those would be the three scenarios in the U.S. Ex-U.S., we think that lines up perfectly for the conditional approval pathway based off the dataset today, and that's going to be our conversation with the EMA regulators later this year.

Operator

Our next question is coming from the line of Jack Allen with Baird, please proceed with your question.

Jack Allen

All right. Thank you so much for taking my questions and congratulations on all progress. I guess the first one I wanted to stick in GAN and talk about TSHA-120. Maybe you can provide a little bit more context around the dating factors surrounding getting regulatory clarity here. Do you have a meeting on the calendar with FDA and any comments around when you may have clarity around the timeline in greater detail than mid-2022? And then I was just curious how the genetic testing program is going as well.

Any comments you can make around early findings from that and if you would consider presenting that data I think would be quite interesting to see a little bit more insight into epidemiology of GAN as well.

RA Session II

Thanks Jack for the question. I think the easy answer is the current guidance is for regulatory feedback is midyear 2022. So I think we're going to probably just stop at that guidance without further level of specificity. Obviously, as the agencies recover from COVID and meeting request associated with COVID approval, they're continuing to approved vaccines associated with that. Getting meetings on the both been having those meetings actually stay on the book is has been somewhat of an issue, but what I will say, I think we're comfortable with the guidance mid 2022.

And so we'll essentially stopped there with any further detail around guidance. And once we have more specificity happy to give that to you or once we have that feedback in hand, happy to give that to you. As far as the genetic testing panel, there's we've actually gone quite well and I think it's what was pretty interesting about some of the information that we've received as it's certainly. There's more patients out there than I think the epidemiology that's in the literature actually lead on just anecdotally.

And we had a pretty interesting situation where we were speaking with an investor on a Friday afternoon, we get a call on Saturday and essentially the investor's colleague next door neighbor was diagnosed with GAN. So that kind of gives you a little bit of context that I think now that the dataset is out there. And I think having the positive dataset out there and the availability of potentially of additional patients being dosed, patients tend to find you and this has just normal for rare disease and this is what we're seeing.

Operator

Our next question is coming from the line of Kevin DeGeeter with Oppenheimer.

Kevin DeGeeter

Okay. Great. Thanks for taking our questions. Maybe two-part question with regard to manufacturing. Can you provide an update as to whether this strategic refocusing has any impact on the build-out of in-house manufacturing capacity and then within the cash runway assumption, how should we think about CapEx and investment manufacturing?

RA Session II

Yeah, Kevin, thanks for the question. Obviously, manufacturing is strategically important to the company, particularly as we're embarking on to wanting a validation run for commercial grade material. Second, an extremely large indication in Rett syndrome, so what I'll say is again, manufacturing continues to stay strategically important to the company. We think it's one of the aspects that sets the company up and differentiates the company from some of our peers out there, so that continues to remain a strategic focus. As far as -- if you could remind me of your second question?

Kevin DeGeeter

[Indiscernible] Yeah, within the cash runway guidance, how should we think about maybe cumulative CapEx or some other metrics across that time frame?

RA Session II

Yes. I think, Kevin, we're not going to provide additional guidance around what we've already provided around expense management and cash management, where cash extends until Q4 of 2023. But I think, again, to just answer your question, CMC Board gene Therapy Company and they continued with our history, understanding where the bulk of the management team came from. Controlling your own destiny remains as key strategic focus of the organization. So I think that's where we'll probably stop from a guidance perspective.

Kevin DeGeeter

Thank you.

Operator

Our next question is on the line of Gil Blum with Needham and Company.

Gil Blum

Hello, everyone, can you hear me?

RA Session II

Yes, we can hear you.

Gil Blum

Okay. Maybe just kind of a general question about Rett here. So because it's a relatively larger indication, would you also expect the studies to be larger or more expensive to that account? Thank you.

RA Session II

Hi, Gil. That's a very insightful question. And I think, as you can -- the larger the opportunity, obviously, the larger the study. I'll pause and let Suyash answer, but I think the short answer to your question is yes. And I think when you start to look at the strategic prioritization, this is one of the reasons why we did -- we've done what we've done to put ourselves in the best position in order, when we have Rett data to position the organization broadly, understanding the development costs for Rett both on the clinical side but also on the CMC side are going to be quite extensive. But I'll stop there, and let Suyash chime in.

Sure, great question Gil essentially I want to say that the studies will be thing what I will say that expense the trial programs on hold is going to be bigger. Its bigger for two reasons really first of all it is still huge [Indiscernible] everybody there. This old side a little bit more, focus on the safety matters. With regards to given very active and risk of average freshly net 82 single deliveries, multiple shipment sites.

But offline as a whole with it the stocks for the traumas you will accountability to sweeten the now have nice to see K and China than which you will very excited about ready to stop basing pacings. As a whole, going to start with an adult study, primarily safety, looking at some preliminary efficacy. Absolutely dose outs went into a pediatric pills study. While the bulk of the patients with Hexa or while we think that the [Indiscernible] prices, opportunity or increasing will be, although we think all patients with Rett will improve regardless of age.

And then, shortly after that, we will also start a pediatric boy's study, which is somewhat unusual thing to do, given that there's a really small number of boys around, but the boys, you'll probably remember our stick to. So I'm very severely affected. The boss, the jump we saw in Detroit, our outlook wants to buy. So we may then maybe 200 or 300 boys in the world with it both induce some kind of rescue study there and demonstrated improvement on across low MECP2. And also worried about over expression toxicity in these boys.

It could actually quite that potential expedited part that conditions approval. So that's how we're approaching the Rett situation as a whole. The only thing that I would add to what Suyash just mentioned, when you start to think about Rett fully, not only do they offer a, an accelerated pathway to an approval just because of the nature of the phenotype.

The biology of the boy are quite similar to the biology of the animal model that we have for Rett, essentially, the industry standard animal model for Rett is the knockout mouse model, is essentially that model has no MECP2 and that's, that's basically what we're seeing to the boy in the biology for their disease and so as Suyash mentioned, there really is less of a concern around over expression, but I think when you start to look and correlate the NINDS enabling pharmacology studies one-to-one, we're seeing at multiple age groups a significant improvement across a number of post of the functional outcomes, respiratory outcomes, motor function, and a number of other functional assessments.

And again, when even those earlier in the real maze, we're seeing a normalization of survival or preliminary data suggest the normalization of survival. So this gives us a lot of confidence, the opportunity, and really our goal is to not leave a patient behind here in this population. The large indication, but just associated with the girl for talking about 350,000 patients worldwide. So it's a massive indication. But for us, I think it's more important to make sure that all patients are addressed.

Operator

Our next question comes from the line of Laura Chico with Wedbush Securities. Please proceed with your question.

Laura Chico

Hey, good morning, guys. Thanks very much for taking the question. I guess I wanted to circle back on the cash runway and with the changes. I just wanted to clarify how long the cash runway was extended and -- as it relates to the GAN program. I just want to understand the best case scenario you have around 120 and what are the options there. There are a -- but I guess, how would cash runway change if we had to go through extreme scenario where there was an additional study requested. Thanks very much.

RA Session II

Thanks, Laura. I'll pick your second question first because it's [Indiscernible]. So when you start to think about if the FDA came back with an option of doing a pivotal study in GAN just because of the patient population, it would be a pretty small study. We would essentially rollover patients that are currently in the natural history study. There is about 50 plus patients in the current natural history study, of which about 40 of them, haven't been dosed.

So the patients are there, so there is no need to go search for patients, so you wouldn't have to do some type of big patient finding opportunity. But ultimately, the cash runway would be really minimally impacted. I think when you start to think clinical development for Gene therapy trials, these trials are relatively small and the cost associated with conducting these trials are relatively small.

The big cost is associated with the production of GMP manufacturing, right? And the use of external third-parties to do that, which is what makes having your own manufacturing facility so strategically important because just, 1. Being able to get a [Indiscernible] at a high-quality manufacturer and the cost of do that are pretty high. The difference between scenario one, which would be to do analytical comparability.

The base case which would be to dose a few more patients under the current protocol with commercial grade material once it's available, and the third scenario which if you had -- if we had to do another complete study. The costs are -- I would say for scenario 2 to scenario 3 are pretty much the same. Because you already embarked on the production of GMP material that commercially validated, so your commercial grade material.

That's where the big costs are. So it really would have minimal to no impact on cash runway, the difference between, honestly, scenario 1, 2, or 3 because you're already doing the big cost impact, which is manufacturer of commercial grade GMP material. So that was your second question. Your first question was around the extension of cash runway. I think we've previously guided to cash being into the second half of 2023. We officially have been fortunate to extend cash runway by a quarter into 2025 -- into Q4 of 2023.

Operator

Our next question comes from the line of Yun Zhong with BTIG. Please proceed with your question.

Yun Zhong

Hi. Good morning. Thank you very much for taking the questions. So on the Rett syndrome, I assume it's a dose-finding study, so I was curious, how are you going to, or what kind of a markers will allow you to decide that you are getting close to the optimal dose? And also on the efficacy readout, any potential signal for efficacy? And I think we previously talked about this potential [Indiscernible] and EGP is one of them, and just curious, would that be included in the data readout by year-end any additional markers?

Suyash Prasad

Let me make a couple of comments. The two boys in the lengthened study and adults being announced at Rett. The initial stock presented is 5E14 central VG dose. And these provisions escalate up to the 1E15 central VG. Now, I think the most important thing here, is that we have an incredibly robust pre -clinical package. It's what allowed us to have a CTA open. And we've had a lot of the regulators on some of the details.

And the frequent practice behind the naval practice was designed around three studies of built-on many, many years of what the Steven Brian [Indiscernible] unit involved with. The list is both study for those [Indiscernible] perspectives of pharmacology study, which we ran in 252 mice, with [Indiscernible] well-taught mice. The 12 [Indiscernible] -- sorry, 21 [Indiscernible] hawks, and we looked at a number of different doses.

A number of different age, time points of dosing mice under the whole spectrum of parameters, all of which translate nice with the clinical, some of the optimize measures, for example, looks to getting to these mice in Portland, perform active mobile visits for breathing on a whole, such of other assessments. On that particular study, we're able to elucidate a minimally impacted dose. And then, on top of that, we also ran off toxicology studies that they will wrap and pains.

The important data was a post the end of fee base as upon distribution data. And importantly, we found with an elevated dose, all foam outsell the clinical stocking. Guys, we actually have certainly played results and toxicology with no adverse findings. And we have very high lots of DNA show good partially addition but correspondingly low levels of [Indiscernible]. The mechanistically showing that our regulations is working.

We sent the learning team for the Hong Kong study and the talks toxicology study, the Nell deliverable. This event level actually hold in regard to starting dose. And honestly its soundness, it's why we maintained and you've got to when we pick thing non-device, share any appreciable toxicity, and we expect both to be efficacious. That's how we select the base. In terms of actual measurements with, [Indiscernible] You do know, of course, that there are no official, well-known, well understood biomarkers in [Indiscernible] or in CSF.

We are looking at the [Indiscernible] biomarkers. We are looking at EEG as a potential biomarker as well and the whole [Indiscernible] the RSP, CGI, the [Indiscernible], as well as [Indiscernible] measures such as brain stem function, respiration, we'll get seizure frequency. How many seizures gotten previously, what triggers them? So, we'll really be guiding our dose selection on the [Indiscernible] of a safety signal and just in general progress with clinical perspective, on our side, EEG will be used in the [Indiscernible] biomarkers. We're not hanging any decisions around the biomarkers that's not well understood yet.

Operator

Our next question comes from the line of Silvan Tuerkcan with JMP Securities. [Indiscernible] to your question.

Silvan Tuerkcan

Good morning and congrats on all the progress. I just had two quick questions, please. Could you run me maybe in more granularity through your GAN base case in terms of getting this into commercial material into handful of patients, how much will be hand full and when could this start whether it makes sense to start right now or do you need to wait for your validation run in the third quarter to how much time to filing?

And then my second quick question would be on the CLN7 program. Now we're going ahead with a first Gene construct. Do you think that's good enough for it or you just want to get some clinical experience no matter what this program? And thank you for taking my questions.

RA Session II

Good morning. Good question. So starting with the first around, the availability of commercially -- commercial GMP material -- commercial grade GMP material on GAN. As I mentioned before, we've actually just completed our second engineering run. This was -- the first was a small-scale engineering run, at the CDMO partner that went beautifully. The second was the definitive engineering run at scale that also went extremely well.

This is -- we're actually quite fortunate. GAN and Rett are actually our two highest producing, highest yielding products. And so, one being on a pathway for regulatory discussion around what the approval pathway looks like, and the second just being a massive indication, I think this just really lines up nicely with how we're thinking about prioritizing our efforts this year. So we're actually quite excited about that.

Our GMP definitive -- the definitive GMP run for the commercial grade material just kicked off. And we expect that material to be available in Q3. This would either be the material that would support, if we're able to do analytical comparability and the agency agrees with that, that would be scenario one, which would be the best case scenario. This would be the material that would support that DLA. I still think even in the best case, it would be more of a rolling submission because they will be some still some additional work from an analytical perspective that will need to be completed.

From a base case, which we consider scenario two, kind of the base case. You would still need this material to be released in order to commence dosing a few more patients under the current protocol. And so what you would do for scenario one, scenario two, and scenario three really are -- really the same activities. You need commercial grade material, you're going to either under scenario two or three, you need a dose additional patients with commercial grade material.

Under scenario one, you need the commercial grade material in order to support the BLA, in order to eventually commercialize the product. So all the activities are the same, but from a timing perspective, we expect that material to be released into three of this year. But as I mentioned, the two engineering runs, small-scale and large-scale engineering runs kicked off and completed quite nicely and we've recently kicked off the commercial grade GMP run. So we're pretty excited about the progress there hence the [Indiscernible].

Operator

Our next question is from the line of Kristen Kluska with Cantor, please proceed with your question.

Rick Krause

Good morning. This is Rick on for Kristen. Thank you for taking our question. In terms of the prioritize programs announced today, could you please talk a little bit about the potential for grants or other non - dilutive funding opportunities around these implications. For example, we understand that federal funding bill was recently passed supporting funding for Rett syndrome research. Thank you.

RA Session II

Now, it's a really good question. I think for Rett obviously ready GAN are squarely within the activities that we have for a ties and that's where the bulk of our R&D investments are going. But certainly we always look for additional opportunities for non - dilutive financing, either that's to grants, government grants, advocacy grants. We've done in our history, we've yet having spoken a lot about them. But what we've done in the past, it collaborate very closely with average groups where they funded a lot of the early group of concept work.

And we've kind of taken a program over once we've gotten to a definitive animal proof-of-concept in order to do the IND, enabling tox studies in the IND, enabling pharmacology studies in kind of when the big dollars that you need associated with GMP [Indiscernible] before you go into a clinical trials. So these things are, are always top-of-mind and in our history, I think we've, we always look for ways to bring in non - dilutive forms of financing, particularly even more importance.

In a situation where the market it from a macro perspective is a little bit uncertain [Indiscernible] political down sector and a number of other issues that are macro, that aren't specific to the company. Including looking at potential business development opportunities, particularly Rett programs that we see broad therapeutic potential, but unfortunately debts having hit our level of prioritization. Now again, we always have the opportunity to revisit that, if and when situations change.

But today, where I would say for clarity, the company has focused on the guidance that we've given you guys today. So that's just -- that's where we are, but I think to your question, we always look for non - dilutive ways along with our partner that advocacy -- along with our partners at UT Southwestern for non - dilutive funding. I just wanted to answer Silvan's second question and apologize, Silvan, for skipping over at around CLN7.

To clarify the CLN7 programs has actually gone quite well. As Suyash mentioned, we've recently dose the fourth patient, which is the third patient dose that one each of the 15, which is the highest dose ever given [Indiscernible] in a Gene therapy trial. Patient safety was reported at Wellness symposium earlier this year. This pace has continued to do well. And, ultimately, I think you guys have heard me say this before, if it's not broke, don't fix it.

And so we're going to continue to focus solely on the first generation construct. Because ultimately that's going to allow for faster pathway to registration. So that's really what's led us there, but future development will be focused solely on the first generation construct. Thank you both for the questions.

Operator

Thank you. Our next question is from the line of Eun Yang with Jefferies, please proceed with your question.

Eun Yang

Thank you for taking my question. And so I have a question on GAN. So for the -- toward the end of last year, you mentioned that -- I think the -- you're meeting with the ex-regulatory -- ex-U.S. regulatory agencies scheduled in January. So have you met with them? I know you are not going to provide an update on till later this year, but want to -- just wanted to check if you have a met with them? And also in the U.S., you talked about 3 scenarios for some time. It sounds like option 2 could have been a likely option when you meet with the FDA.

Before it is option 2, what would it be the timing for [Indiscernible] filing? I think a in the past, you mentioned them around me to 2023. So want to get your updated view on that. And lastly, RA, you mentioned that your cash runway has been increased the by one quarter. So should we really think about the reduction in work force by 35% leave to one quarter extension in the cash runway? Thank you.

RA Session II

Thanks for your questions. So starting with your first question around regulatory, we have previously guided that we did conduct a meeting in late January within ex-U.S. regulatory authority around scientific advice for our GAN program. We're still awaiting formal meeting minutes from that program or from that meeting. And once we have all of the formal meeting minutes, both from this regulatory meeting as well as the regulatory meetings that will be scheduled with the U.S. agency and other agencies, we'll make sure to summarize those and provide that guidance and update that guidance once we have the formal feedback but it would just be premature for me to speak kind of outside of school about meeting minutes.

Certainly the tone was a good meeting. It was a long meeting and they were quite interested. The data obviously, as we laid it out, is compelling. But again, I want to make sure that we have final meeting minutes in hand before we provide any additional feedback on that. Around GAN specifically, I think you're absolutely right. We've kind of coalesced around scenario two as a base case and that's kind of the case that we are planning for internally.

What I would say is the difference between scenario two, dosing the patient under -- a handful of patients under the current protocol and scenario three, is doing a second study, it's probably six to eight months. There's not much of a gap really between either one of those scenarios. The reason for that is because all the patients are identifying, you're not going out to have to identify Jason.

This would essentially be a rollover from the natural history study, as I mentioned, there is already 50 plus patients in the natural history study of which only 14 of those patients have been dosed. So you can think about 40 or so of those patients haven't been dosed and we continue as I mentioned, to identify patients on an ongoing basis quite successfully. So from a goal with perspective, we really won't have an issue from timing around enrollment.

More so the timing is associated with the availability of commercial grade material, and then as I mentioned, that material would be available in Q3. So if you would take scenario two, which is very similar to the Zolgensma scenario from our previous life, where essentially the FDA approved Zolgensma on the basis of the original nationwide children's study. And then, those original phasings.

And I think it was close to about ten phasings that were dosed in that study. They didn't allow AveXis Novartis at the time to supplement the dataset with data from the pivotal study with their commercial material that will be delivered from Libertyville, which was the commercial manufacturing facility located up in Chicago. And so this would essentially be the pathway that we're considering as the best case because it's the best comp that we have out there.

This is a rare pediatric life-threatening neurodegenerative disease, where there's no therapeutic alternatives. In the case of Zolgensma, there was actually a therapeutic alternative and an approval ahead of that in Spinraza. In the case of [Indiscernible] neurolopathy, there's nothing. And so certainly in our conversations with advocacy, and our conversations with KOL, we pressure-tested our thinking and maybe you think this would be the optimal approach to potentially go into.

Now we're going to go in and do our best to convince the agency around some area one, but I think realistically, I think what we're going to do as planned for a mid -- somewhat of a mid-case, which would be scenario two. That would allow us to either initiate a rolling submission at the end of this year or the beginning of next year. And ultimately lead to an approval either late -- and when I say late, into the year 2023 or early 2020 in the U.S. Obviously, the pathway in Europe is quite different.

We feel strongly that we meet the guidance around the conditional approval pathway. And that's going to be our going in conversation with the EMA regulators. It's really how to accelerate registration option for this program under the conditional approval pathway. And so that's going to be our goal. And so we want to be in the position. If the regulators agree, which, again, with the dataset that we have in hand, we think there is a strong possibility to initiate a rolling submission by the end of this year.

Operator

Thank you. Our next question is from the line of Sami Corwin with William Blair.

Sami Corwin

Hey guys, thanks for taking my question. For the Rett study, will there be different outcome measures for patients depending on their age or disease stage? And then, can we expect any data this year from these CLN1 or CLN7 clinical trials? Thanks.

RA Session II

Hey, Sami. Good morning. Thanks for the question. Could you repeat your first question? I'm sorry, we couldn't hear you.

Sami Corwin

Will there be different outcome measures for patients in the Rett trial depending on their disease stage?

RA Session II

It's a really good question. Suyash, do you want to tackle that personally?

Suyash Prasad

Yes. In general. Yes and no. [Indiscernible] We're going to be looking at similar work buckets of [Indiscernible] measurements, regardless of [Indiscernible]. We'll be looking at specific [Indiscernible] that RSP do, such as the meds behavior assessment, [Indiscernible] practice scale. We'll be looking at certain seizure measurements, EEGs, for example, and [Indiscernible]. We'll be looking for [Indiscernible] assessments that restrict the stress index, sleep apnea, etc. Communication assessments, the [Indiscernible] assessments, plus a whole host of different biomarkers, which

Operator

Thank you. Our next question is from the line of David Hoang with SMBC.

David Hoang

Hey, thanks for providing the update and taking my questions. So I just had a few -- again, going back to the base case for GAN and the regulatory path there, do you have any sense about how many additional patients FDA might ask you to dose? And then in terms of the follow-up on those patients, do you know who received the commercial grade material. What do you exactly need to report? Is it just safety and PK data or do you need to follow them and get some efficacy data as well?

RA Session II

I think it's a really good question. And David, unfortunately, you guys cut out a little bit, so we'll go back and answer Sandy's question after we answer your question, David, but your question was really I think it boils down to what do you think you'll need to show from an efficacy perspective. Around the commercial grade material and how long do you think the follow up would be around what you would need in order to prove comparability.

What I'll tell you the best tramp and that's again would be in Zolgensma. Zolgensma, the FDA allowed us previously to use the intend as a really nice biomarker around activity in comparability between the original clinical trial material and the commercial grade material. Because the top [Indiscernible] actually pretty went up a went up pretty uniformly within the first 30 days across call pace and but you know, if you are getting really good cut target engagement.

I don't think that's too dissimilar here where we're using the MFM32, which is similar in a sense size, the chop in ten for older patients. And I think when you look across the entire dataset, you do see a really nice kind of stabilization and improvement in disease as compared to the natural history quite shortly thereafter dosing. And so I think using our previous experience in Zolgensma, I don't think that that is far removed.

Now, what I will say, this is speculation because we haven't had the discussion, directly to what they're going to ask for. And certainly we're going to do what they ask us to do. But I think what well ultimately do is lean on the [Indiscernible] database that we

Operator

Please, standby. We'll resume with your answer in a moment, Mr. Juan. Our speakers here. You may continue with your answer. It was with Mr. Juan. Please stand by, we will resume our question-and-answer session momentarily. Thank you. Please stand by everyone, our question-and-answer session will resume momentarily, thank you. Ladies and gentlemen thank you're standing by, we will resume our question-and-answer session momentarily, please remain on the line. Thank you.

RA Session II

We're already in session. We're just dialing in.

Operator

We can hear you now. Please continue.

RA Session II

It's a Gene therapy call. Operator? So we're going to give us another go. We just dialed in, gets let us know when we dial out and we did have the bone line available and we'll just have a bone around them. Can we go out again?

Operator

I can hear you. You can be heard into the conference again now, where we still have Mr. Hong on the line with this first question.

RA Session II

Perfect, perfect. David, sorry about this. We're just having some technical issues in the room. But to your question, I was just basically correlating our experience with Zolgensma and the approval pathway, Zolgensma and what the FDA assets to do. As we compare to trying to use that experience for kid. So the question was really around, what would the extent of the follow-up, the extent of the follow-up, in the Zolgensma was really using the Chopping 10 as they compare at former comparator or clinical comparability of the commercial grade material.

And so we're fortunate to have a similar assessment in that [Indiscernible], which is essentially the Chopping 10 for the older kids. And what we're seeing is pretty early a nice separation between patients that are in the interventional trial compared to the natural history study. And so for us, we think that that could be a useful example and competitor to provide to the FDA, because you actually see a nice separation relatively quickly.

What I'll also say is when you start to look at the long-term safety and durability, the patient that we have the most efficacy data on received the lowest middle dose, with the dose of 1.2 E^14 and and I think these patients, if they didn't receive the intervention, we would have probably succumb. Because where this patient started was actually one of the lower scores on the MFM32. And we did essentially seeing a real nice stabilization disease now going out five years.

So I think with that totality of data, along with the pathology data from the biopsies, along that having a validated instrument that's been used in regulatory approvals before in MFM32, I think we have a really compelling argument to be able to go in and -- basically suit them for the minimum amount of follow-up if possible, really just to validate that we have active drug. That could be somewhere between [Indiscernible].

Operator

Ladies and gentlemen, please stand by while we switch speakers ' lines. Speakers, please continue with your second line.

David Hoang

Hi, guys.

Operator

Please go ahead, you're on your second line. I'm going to disconnect. I'm hearing feedback on the another line. May I disconnect at this time?

RA Session II

We have to disconnect the other line. Yeah. And so, I think I answered the question ultimately. I think I was just providing some additional commentary. So I think I answered David 's question. And then -- and again, sorry for the technical difficulties there.

Operator

Thank you. Please standby while we resume with the line of Sami Corwin. Sami, please go ahead.

Sami Corwin

Hey guys. Yeah. I think you were just going to answer my question on, if you can expect any data from CLN1 or CLN7.

RA Session II

Thanks, Sami. Yes. So we've already presented data earlier this year on the CLN7 program. That was on the first three patients that were dosed. The first being 5B to the 4T, the next two that were presented was at the 1/8 to the 15 dose. And we -- and we've mentioned that an additional patient was treated at 1A to the 15. And so we've already reported data on that program, and we could follow those patients. On CLN7, what we've decided to do is not guide to the availability of clinical data, but to say that we continue.

We're morphing this program into -- and limiting enrollment to a proof-of-concept study. A little bit different of a strategy from a fast pathway to registration type of strategy, and so we'll guide to data later this year on the CLN1 program.

Operator

Thank you our final question comes from the line of Yanan Zhu with Wells Fargo, please proceed with your question.

Yanan Zhu

Thanks for taking my question and congrats on the initiation for the Rett syndrome program can have a trial. So my first -- my question is on the GAN programs data because I think RA you mentioned about H-matched control. I think so far the MFM32 data you presented is mainly the overall natural history control cohort. So I was wondering what does the H-matched controls look like? Because I think you mentioned you have enough patient data there to do the specific age match.

And also it that part of the conversation or package with your [Indiscernible]. Thank you.

RA Session II

Hey Yanan, thanks for the question. So essentially what I'll say is those analysis are ongoing, but I think what's important here, we have previously showed data that from the previous doses of patients pre -treatment decline and their post-treatment stabilization. That's data that we actually shared last year when we acquired the program. The data that we shared this year was essentially a comparison from the full cohort of natural history that basically shows an 8.07 decline compared to the cohorts experience.

Depending on that particular dose cohort, that's the data that we've shared recently. And now the analysis around age-matched controls, which is a little bit more extensive, is ongoing, but I think you're absolutely right. This just lends itself to the robustness of the data itself. The fact of the matter is that we have access to natural history data that offers three levels of control is extremely -- it's extremely compelling.

So when you start to look at the dataset that we're going to go in and have conversations with the regulators, you'll have natural history data, there's three levels of control. Biopsy data, functional data, across a number of meaningful clinical functions, including MFM32, including visual acuity, pathology data from the biopsy, but also retinal nerve fiber thickness data, as well as a whole host of sensory endpoints that we haven't presented to the street yet.

We feel, honestly, I think if you would ask Suyash and I'm only answering this because of the technical difficulties that we had. If you asked Suyash. He would probably tell you that he's never gone into a conversation with a regulator with this wealth of data before. And I think this gives us a lot of confidence around the conversation with regulators. And so that's essentially what I'll say.

The level of comparison from the natural history, the wealth of endpoints that were collected, the pathology data that we have in hand and what that shows really lends itself, and it is why we feel so confident about our conversations, and to be quite honest, why we made the decision around prioritization today.

Operator

Thank you. At this time, we've reached the end of the question-and-answer session and I'll now turn the call over to [Indiscernible] for closing remarks.

RA Session II

Yes. Thank you Operator, and first and foremost, we just want to apologize for any other technical difficulties. I think we got through probably about 80% of the questions before that started to kick in. So hopefully, our colleagues from the analyst community found this helpful, as well as the broader community. But we really appreciate you guys joining us this morning.

I think the way we're thinking about 2022 is a year of focus, is a year of operational efficiency, and it's a transformational year as we potentially transition the company from now, and I say this every year which is actually quite nice, now from a clinical stage company to a late-stage clinical company into a registration company preparing for our first commercial launch, and so that is an important level of transition.

Obviously, we're doing this in uncertain times from a capital markets perspective, but I think the changes that we've made today and announced today has really set the company up to be in the best possible position for when we have both data in hand from our Rett syndrome program and feedback from regulators around organic program and it put us, again, in a position of strength. We really want to thank you guys for joining us today and hope you all have a wonderful day and a wonderful rest of the week, so thank you.

Operator

Thank you, everyone who joined us today. This will conclude today's conference call and webcast. You may now disconnect your lines this time. We thank you for your participation.

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Taysha Gene Therapies, Inc. (NASDAQ:[TSHA](#)) Q1 2022 Earnings Conference Call May 16, 2022 8:00 AM ET

Company Participants

Kimberly Lee - Chief Corporate Affairs Officer

RA Session II - President, Founder, and Chief Executive Officer

Suyash Prasad - Chief Medical Officer and Head, R&D

Kamran Alam - Chief Financial Officer

Conference Call Participants

Gil Blum - Needham & Company

Elizabeth Webster - Goldman Sachs

Kevin DeGeeter - Oppenheimer & Company

Jack Allen - Baird

Yun Zhong - BTIG

Laura Chico - Wedbush Securities

Yanan Zhu - Wells Fargo

Operator

Good morning. Welcome to Taysha Gene Therapies' First Quarter 2022 Financial Results and Corporate Update Conference Call. At this time, all participants are in listen-only mode. Following management's prepared remarks, we will hold a brief question-and-answer session. As a reminder, this call is being recorded today May 16, 2022. I will now turn the call over to Dr. Kimberly Lee, Chief Corporate Affairs Officer. Please go ahead.

Kimberly Lee

Good morning and welcome to Taysha's first quarter 2022 financial results and corporate update conference call. Joining me on today's call are RA Session II, Taysha's President, Founder, and CEO; Dr. Suyash Prasad, Chief Medical Officer and Head of R&D; and Kamran Alam, Chief Financial Officer. After our formal remarks, we will conduct a question-and-answer session and instructions will follow at that time.

Earlier today, Taysha issued a press release announcing financial results for the first quarter ended March 31, 2021. A copy of this press release is available on the company's website and through our SEC filings. Please note that on today's call we will be making forward-looking statements, including statements relating to the safety and efficacy and the therapeutic and commercial potential of our investigational product candidates. These statements may include the expected timing and results of clinical trials for a product candidate. Our expectations regarding the data necessary to support regulatory approval of TSHA-120 and the regulatory status and market opportunity for those programs as well as Taysha's manufacturing plans. This call may also contain forward-looking statements relating to Taysha's growth and future operating results, discovering development and product candidates, strategic alliances and intellectual property as well as matters that are not of historical facts or information.

Various risks may cause Taysha's actual results to differ materially from those stated or implied in such forward-looking statements. These risks include uncertainties related to the timing and results of clinical trials and preclinical studies of our product candidates are dependent upon strategic alliances and other third-party relationships, our ability to obtain patent protection for discoveries, limitations imposed by patents owned or controlled by third-parties, and the requirements of successful funding to conduct our research and development activities. For a list and description of the risks and uncertainties that we face, please see the reports we have filed with the Securities and Exchange Commission. This conference call contains time-sensitive information that is accurate only as of today of this live broadcast, May 16, 2022. Taysha undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call, except as maybe required by applicable securities law.

I would now like to turn the call over to our President, Founder and CEO, RA Session II. RA?

RA Session II

Thank you, Kim. Good morning and welcome everyone to our first quarter 2022 financial results and corporate update conference call. Since our last update, we have continued to advance our core development programs, with particular focus on giant axonal neuropathy or GAN and Rett syndrome. In March, we were pleased to initiate clinical development of TSHA-102, under a CTA approved by Health Canada for the first and only gene therapy in clinical development for Rett, which affects over 350,000 patients worldwide. We look forward to reporting preliminary Phase 1/2 clinical safety and efficacy data by year end.

We were also pleased to recently receive orphan drug designation for TSHA-120 for giant axonal neuropathy from the European Commission further highlighting the unmet need for treatment options in GAN and the potential of TSHA-120 to provide a disease modifying treatment for these patients. We look forward to providing a regulatory update by mid-2022. As we look ahead, we remain focused on executing on our strategic pipeline prioritization initiatives and expect our current capital resources along with full access to our existing term loan facility to fund operating expenses and capital requirements into the fourth quarter of 2023.

I will now turn the call over to Suyash to provide a more detailed update on our clinical programs. Suyash, please go ahead.

Suyash Prasad

Thanks, RA. As RA noted, we have made significant recent progress and its launch in our clinical programs for GAN and Rett syndrome and expect exciting milestones throughout the remainder of the year.

I will begin with Rett syndrome. TSHA-102 is a transgene for MECP2, which is a protein essential for neuronal development and function. The challenge in gene replacement therapy of MECP2 is finding the appropriate balance of sufficient physiological expression to correct the deficiency, whilst also avoiding overexpression and the associated toxicity. To do this, TSHA-102 regulates the expression of MECP2 using the novel microRNA responsive auto-regulatory elements platform known as miRARE that is exclusively licensed to Taysha and developed by Drs. Sarah Sinnett and Steven Gray of UT Southwestern Medical Center. miRARE provides sophisticated regulation of transgene expression on a cell-by-cell basis ensuring controlled expression that avoids excessive levels of MECP2.

We recently initiated clinical development of TSHA-102 under an approved CTA by Health Canada. In further support of this promising program, we presented positive IND CTA enabling preclinical data at the International Rett Syndrome Foundation Scientific Conference and ASCEND Rett Syndrome National Patient Advocacy Summit. These data supported the CTA acceptance, including a pharmacology study in Rett knockout mice, assessing the efficacy of TSHA-102 and a 6-month GLP toxicology study in non-human primates exploring the safety by distribution and mechanism of action of TSHA-102. Collectively, these preclinical results confirm the ability of TSHA-102 to regulate transgene expressions within appropriate physiological levels.

This week, we will have a prevalence of the 25th Annual Meeting of the American Society of Gene & Cell Therapy, or ASGCT, while we will be presenting the safety and by distribution data in NHPs as well as safety data in rats. These presentations will further support the ability of our miRARE platform to control gene expression and address the challenge of ensuring appropriate levels of microbial expression that have limited effective therapeutic development with other gene replacement strategies.

As RA indicated, there are over 350,000 patients estimated to suffer from Rett syndrome worldwide, spanning patients as young as 6 months into adulthood. Currently, there are no disease-modifying therapies to treat this devastating condition. We are excited to advance TSHA-102 in the REVEAL Phase 1/2 clinical trial as the first gene therapy in clinical development for Rett syndrome. But REVEAL study is an open label dose escalation randomized multi-center study that will examine the safety and efficacy of TSHA-102 in adult female patients with Rett syndrome. Up to 18 patients will be enrolled. In the first cohort, a single 5E14 total vg dose of TSHA-102 will be given intrathecally.

The second cohort will be given a 1E15 total vg dose of TSHA-102. Key assessments will include Rett-specific kind of global assessments, quality of life, biomarkers and neurophysiology and imaging assessments. Sainte-Justine Mother and Child University Hospital Center in Montreal, Quebec, Canada has been selected as the initial clinical trial site under the direction of Dr. Elsa Rossignol, Assistant Professor, Neuroscience and Pediatrics and Principal Investigator. We look forward to reporting preliminary first-in-human data by the end of 2022. TSHA-102 has been granted rare pediatric disease designation and orphan drug designation from the FDA and more recently orphan drug designation from the European Commission.

Turning to TSHA-120 for the treatment of GAN, earlier this year, we reported positive clinical efficacy and safety data for the high dose cohort of 3.5E14 total vg delivered intrathecally as well as long-term safety and durability across all therapeutic doses. Treatment with TSHA-120 achieved a clinically meaningful or statistically significant slowing or halting of disease progression across all therapeutic dose cohorts that was further confirmed by long-term data demonstrating sustained durability.

Notably, nerve biopsy data provided new evidence for active regeneration of nerve fibers following treatment with TSHA-120. In addition, we observed preservation of visual acuity as measured by the LogMAR scale and optical coherence tomography. There were no significant safety issues, no increase in adverse events at high doses and no dose limiting toxicities. All adverse events related to immunosuppression or study procedures were comparable to other gene therapies and transient in nature. Lastly, there is no evidence of dorsal root ganglion inflammation or thrombocytopenia. We recently completed a commercially representative GMP batch for TSHA-120 and release testing for this batch is currently underway.

Also in April, TSHA-120 received orphan drug designation from the European Commission further supporting a large unmet need for treatment options in GAN and potentially expedited support in regulatory approval. As a reminder, TSHA-120 previously received orphan drug on rare pediatric disease designations from the FDA. Partnerships with genetics testing leader, GeneDx, to sponsor the inclusion of a genetic marker for GAN testing and the GeneDx routine hereditary neuropathy screening panel free of charge are ongoing as well as a collaboration with a hereditary neuropathy foundation and the Charcot-Marie-Tooth Association Centers of Excellence healthcare professionals and patient advocacy groups to help raise awareness on the early diagnosis of GAN.

We remain well positioned to further advance TSHA-120 through regulatory approval and believe the comprehensive gene therapy dataset generates the data in GAN offers TSHA-120 a potentially derisk regulatory path that meets most registration requirements of the FDA and EMA. We look forward to our continued discussions with major regulatory agencies on potential registration pathways for TSHA-120 and anticipate providing a regulator update by mid-2022.

At the upcoming ASGCT meeting, Dr. Rachel Bailey, Assistant Professor in the Department of Pediatrics at UTSW will be presenting data on vagus nerve delivery of TSHA-120 to treat the autonomic nervous system dysfunction in GAN. There will also be other presentations on some of our earlier stage programs, including preclinical data in tauopathy, Prader-Willi syndrome and Angelman syndrome. There will also be a symposium on innovative approaches and translational strategies in gene therapy development.

In addition to expected regulatory fever for TSHA-120 in GAN by mid-2022 and first in human preliminary Phase 1/2 safety and efficacy data for TSHA-102 in Rett syndrome by year end, we remain focused on continued clinical development of the first generation construct for CLN7 disease in partnership with UT Southwestern and under the leadership of Dr. Ben Greenberg, Vice Chair of Clinical and Translational Research and Principal Investigator during the course of 2022. Clinical development of TSHA-118 in CLN-1 disease also remains ongoing and we intend to initiate clinical development for our small proof-of-concept study for TSHA-105 and SLC13A5 deficiency.

With that, I will turn the call over to Kamran to review our financial results. Kamran?

Kamran Alam

Thank you, Suyash. This morning, I will discuss key aspects of our financial results for the first quarter ended on March 31, 2022. More details can be found in our Form 10-Q, which will be filed with the SEC shortly.

As indicated in our press release today, research and development expenses were \$37.8 million for the 3 months ended March 31, 2022 compared to \$23.9 million for the 3 months ended March 31, 2021. The \$13.9 million increase was primarily attributable to an increase of \$9.3 million in employee compensation, which included \$2.2 million of severance and one-time termination costs in connection with the strategic reprioritization of programs completed in March 2022 and \$1 million of non-cash stock-based compensation.

Additionally, in the 3 months ended March 31, 2022, we incurred an increase of \$2.9 million of expenses in research and development, manufacturing and other raw material purchases. We also incurred an increase of \$1.7 million in third-party research and development consulting fees primarily related to GLP toxicology studies and clinical study activities.

General and administrative expenses were \$11.5 million for the 3 months ended March 31, 2022 compared to \$8.2 million for the 3 months ended March 31, 2021. The increase of approximately \$3.3 million was primarily attributable to \$2.9 million of incremental compensation expense, which included \$0.4 million of severance and one-time termination costs and \$0.7 million of non-cash stock-based compensation. We also incurred an increase of \$0.4 million in professional fees related to insurance, Investor Relations, communications, accounting and market research.

Net loss for the 3 months ended March 31, 2022 was \$50.1 million or \$1.31 per share as compared to a net loss of \$32 million or \$0.87 per share for the 3 months ended March 31, 2021. As of March 31, 2022, Taysha had \$96.6 million in cash and cash equivalents. This cash balance excludes \$12 million in gross proceeds generated from the sale of common shares under our existing at-the-market facility or ATM in April. Current cash and cash equivalents along with full access to our existing term loan facility, is expected to fund operating expenses and capital requirements into the fourth quarter of 2023.

And with that, I will hand the call back to RA.

RA Session II

Thanks, Kamran. Our focus for 2022 continues to be on executing across our core development programs. And I am extremely proud of our team's progress and accomplishments this quarter. We continue to maintain a strong cash position that should provide runway into the fourth quarter of 2023. We would like to thank our Taysha employees, Board of Directors, Scientific Advisory Board, collaborators and the patients and advocates for their ongoing support of our mission to develop curative gene therapies to eradicate devastating monogenic CNS disease.

I will now ask the operator to begin our Q&A session. Operator?

Question-and-Answer Session

Operator

Thank you. [Operator Instructions] Our first question comes from the line of Joon Lee of Truist Securities. Please proceed with your question.

Unidentified Analyst

Hi, good morning and thank you for taking my question. This is [indiscernible] on for Joon. So what is the probability by which you think FDA might ask you to have efficacy data on new patients using commercial grade material and how long would you take – would you think it takes to provide such data? Thank you.

RA Session II

Hey, good morning [indiscernible]. Thank you for the question. I think we have gone through this, when we actually presented the definitive dataset earlier this year really around kind of the current scenarios and how we look at them. We essentially cut them in two parts, one being ex-U.S., one being the U.S., particularly for the FDA, that breaks down to about three scenarios, the first being able to immediately file off the data that we have generated thus far. Again, we have reported data from all therapeutic dose cohorts, including the high dose of 3.5v to the 14 earlier this year, where we really see really nice efficacy and safety durability. And now we have really nice pathological data with the biopsy showing nerve fiber regeneration, which essentially we view as a game changer. And so we are pretty excited about this dataset, not only because we show clinical, but – we show really nice clinical data, but also safety and efficacy data, but also really the biopsy data and the natural history, which essentially has been going on for close to 10 years. And each patient rolling over from their natural history study provides three levels of control. The patient has a comparison between their own pre-treatment and post-treatment performance, because of such a large natural history study over 50 patients at this point, we are able to show age matched controls and then you are able to compare the entire cohort to a patient's performance. So we are really excited again about the breadth of this data.

As I mentioned, our base case is most likely that the FDA would ask you to dose a few more patients using the commercial grade material. And this is a similar pathway of what they asked [indiscernible] during the registration of zolgensma. Most likely it would be what we would consider a handful of patients, somewhere between probably 3 to 5 patients. Those patients are already identified. So from a timing perspective, this would shorten any type of recruitment effort to get these patients into the study, because essentially they would rollover from the natural history study. So these patients are already identified and our partners at the NIH is under the leadership of Carsten Bönnemann who have done a fantastic job keeping that steady moving and the wealth of data that we have generated from that study. So, we really see the difference between filing immediately based off the current dataset and dosing a few more patients. We are probably looking at about a 6-month time difference. It's not a huge time difference, because again, we don't have to go out and identify patients, those patients are already identified. And so we think by dosing a few more patients that would probably set us up for an approval towards the end of 2023. This is again the FDA scenario. The EMA are going in position is that we meet all the requirements for conditional approval and the hope is to initiate MAA filing by the end of the year.

We would also ask just shifting focus back to the FDA. Based off the current dataset, we would ask the FDA as a default to initiate a rolling submission based off of the data that we've generated. The preclinical data won't change. The clinical dataset is it would be near final if they asked us to dose a few more patients. So, we would be able to start the review of the current dataset. And obviously, we would have completed the release testing and the analytical panel for our commercial grade material, which we have already completed the manufacturer of this currently undergoing release testing when we are quite excited about not only the yields, but also the product purity from that run. So that's kind of our going in strategy. We are going to go in and ask for approval based off the current dataset, but our base case would be dosing a few more patients that would immediately rollover from the NIH natural history study. And so this is something that we have previously stated before and it continues to be our base case.

Operator

Thank you. Our next question comes from line of Gil Blum with Needham & Company. Please proceed with your question.

Gil Blum

Good morning and thanks for taking our question. We have another quick one on TSHA-120. So what more is there to do on your commercial grade product, what more things do you need to do there? And maybe you can give us an idea of how many patients can be treated with this batch? Thank you.

RA Session II

Yes. It's actually a really good question, Gil. Thanks. Thanks for asking. And I will start and Suyash please chime in, if you would like. But essentially, there is not much more to do on this commercial grade material. We initiated the manufacturing run rolling this year. We have now completed that manufacturing run. It was quite successful both from a yield perspective and a purity perspective. The current analytics that we run around comparability to the original clinical material are spot on and those tests continue to be ongoing. The team – Suyash's team, along with Fred's team are continuing to work on key assays, key release assays that will support the BLA, including the definitive potency assay, which the team has made significant progress on, which I am quite pleased about. And just to give you an idea, on just the yields from this run, the team has done just a fantastic job around manufacturability. And depending on the dose and I will just go with a high dose of 3.5v to the 14. We are over 50 patients worth of drug. And so that gives you an idea around just one the strength of our platform. This is using our HEK293 suspension triple plasmid transfection platform that we use across the entire portfolio, but also just really the strength of the team that we have in CMC. So I couldn't be even more proud. So what we will do is the – this run will continue to go undergo release testing, stability testing and whatnot. And the team will continue to gather data to support the BLA, but really this – the progress that the team has made in this manufacturer of this commercial grade material has gone. It's gotten even better as we could imagine. So I will stop there. Suyash, do you have anything to add?

Suyash Prasad

No, I think I would just echo the fact that the batches made, there was plenty of product majors or high yielding run and release testing is underway looking at the characterization of the product and it's all looking very promising thus far. RA is quite correct, the only thing we are doing is outstanding is to finalize the potency assay. And just to remind you, potency assay essentially exists to demonstrate that the molecule that we are administering closely mimics and what's effectively in the clinical settings it does in the lab setting and every lot needs to be tested, there is predefined acceptance character that need to be met. And the FDA and the regulators are pretty keen to ensure obviously the product we make on an ongoing basis is consistent and highly appropriate level of quality. And as RA said, we have made a lot of progress in finalizing that potency assay. So, everything is looking great. We are release testing is of the way and the drug is going to be available to pre-treating patients imminently.

Operator

Thank you. Our next question comes from the line of Salveen Richter with Goldman Sachs. Please proceed with your question.

Elizabeth Webster

Hey, good morning, guys and thank you for taking our question. This is Elizabeth on for Salveen. Maybe just switching over to Rett, if you could comment on the nature of the first clinical data we expect to see and how many patients we can expect to see data from? And then a second one from us are, what kind of assumptions have been baked into the 4Q '23 cash runway guidance? Thank you.

Suyash Prasad

Sure. Let me take the question about the clinical trial, then Kamran and RA can handle the second question. So with regard to the Rett clinical trial, this is a trial in adult females with Rett syndrome. To remind you, we just felt given – just given the concerns about potential overexpression, which we show with actually downregulate very nicely in our RMHP data, we still wanted to be a little bit conservative. And so we are starting off in adults and the plan will be to move into children, pediatric females with a Rett at some point thereafter and then we want to plan a small study in boys, the very rare population of boys with Rett shortly thereafter. Now, in terms of expectations with regard to what we are going to have coming out of the clinical trial data of the adult study, which we anticipate sharing data from by the end of the year, the likelihood is going to be safety data and to have some preliminary efficacy data, we are not sure at the moment. We will, as is the case for these first enhanced studies with these innovative products, they have to target those things. We can't go several patients all at once. We have to dose one patient, leave with a period of time and then dose the second patient after a DMC review and then leave with a period of time for dosing the next patients. So my guess is going to be a small number of patients safety data by the end of this year potentially some preliminary efficacy data if we are starting to see some early signs of that, but I think that's why we are focusing on clinical trial at the moment. With regard to the assumptions, I'll let RA and Kamran take that question.

Kamran Alam

Sure and thanks, Liz for the question. I was actually talking on mute. So just to reiterate what Suyash mentioned, we are quite excited about the Rett data, the preclinical datasets that supports the CTA, and again, are really excited about what this means to the Rett community being the first and only gene therapy, actually in clinical development for Rett syndrome. And I think just to echo what Suyash mentioned, it will really be on the totality of data, the amount of endpoints that are being collected are immense. Both from physician reported Rett syndrome outcomes, patient reported outcomes, respiratory measures, obviously, some neurodevelopmental measures as well as movement. So it's really going to be a whole host of endpoints that will share including safety and safety is going to be probably one of the most important ones because there's always this notion around overexpression and the data from our NHP study or NHP talks study not only demonstrated the safety of our construct at four – doses up to fourfold above what the starting dose will be in the clinical setting, but also proof of mechanism the ability to down regulate the expression of MECP2 in the presence of wild type in the presence of wild type MECP2 and so again, for us, it's quite exciting. But certainly, this is one of the reasons why we decided to start into adults. So I would probably characterize it. Similarly the way that Suyash did and it'll be on the totality of data, it'll be safety with some preliminary efficacy in there.

From an assumption perspective on cash runway, the way that we're thinking about this is we have with the full drawdown of our current term loan facility from Silicon Valley Bank, we have the ability to be able to extend runway into Q4 of 2023. With our – along with our existing cash, and that's kind of the assumption, the base case assumption that's gone in as you are aware, we executed on a pipeline parameterization exercise earlier this year, which we announced this our yearend earnings call, which also included a risk of 35%. And essentially, kind of right sizing based off of a clear focus on two key programs. And that's our Rett syndrome program. And our ginixonaneuropathy program, which we're both quite excited about. And then taking two of the additional clinical development assets and moving those from more of a registration director trial to more of a proof of – kind of small proof of concept studies that being CLN1, and then SLC13A5. What I would also say though, is again, I'm quite, I'm quite excited about the progress that the team has made just in this short period of time. And really, the ability to be able to get through this prioritization analysis and kind of report focus accompany. And still execute is just been something that I've been immensely proud of. It's not easy for anyone out there, in biotech, and particularly in gene therapy, but the team is really nose to the grind and executing. And so for us, all of this has been baked into our cash analysis, and we continue to look at ways to augment and extend runway.

Operator

Thank you. Our next question comes from line of Kevin DeGeeter with Oppenheimer & Company. Please proceed with your question.

Kevin DeGeeter

Hey, great, thanks for taking our questions. Just on again regulatory update, RA, can you comment on your confidence sort of that, that mid 2022 update timeline? I guess sort of underlying this question is, is it reasonable to conclude they've had the necessary meetings with FDA and other regulatory agencies are waiting for feedback at this point? Are there kind of open scheduling components that could impact that timeline and cause some uncertainty that?

RA Session II

Yes, thanks, Kevin, for the question. Good morning. So I think we're competent and reiterating that guidance around that the mid 2022. From a regulatory feedback perspective, again, I think, most people go in to have conversations with the FDA, and the EMA in a COVID environment and other regulatory agencies in a COVID environment. Obviously, there's been some flux, there's been a little bit of flux in scheduling. But with that being said, we're quite excited in the promise of the dataset that we've presented thus far, the reproducibility of that data, and the fact of the matter that's a product is not only efficacious, but durable and safe at multiple doses, including a really robust natural history study. And now, a really now the beginnings of what would be a really nice data package from a Module Three perspective from a CMC comparability. So we're going to go in with that dataset. And obviously, our goal and strategy is to be able to file off of the current dataset and as the default base case, we essentially default to being prepared to dose a few more patients with the commercial grade material. So we are reiterating that guidance. We've done that in our communications and I look forward to updating you guys here closer to the – to later this year, but again, mid-year 2022 is our guidance around having that feedback in here.

Operator

Thank you. Our next question comes from the line of Jack Allen with Baird. Please proceed with your question.

Jack Allen

Hi, thank you so much for taking the questions and congratulations on all progress. I wanted to shift gears back to Rett really briefly and talk about the dose there. I know you mentioned that you're starting at 5E14 total VG and then moving up to 1E15. And that, I guess the preclinical package showed safety at 4x the first dose, I was just curious was there a dose in the preclinical package where you did see tolerability issues and how much coverage do you think you have to dose escalate as we move through the study based on the existing preclinical package?

RA Session II

Thanks, Jack. Great question and good morning. I'll turn it over to Suyash to answer that question.

Suyash Prasad

Yes, hi, Jack. Thanks for the question. So it's a really important question. The those select for the clinical trial for a gene therapy study, getting the dose Rett the first time is really important, because you've got to make sure you give enough drug to make sure the drugs are effective, but also make sure that there's no safety or tolerability issues, because once you've given gene therapy, drugs, you can't take it away again. So it's a really critical decision that needs to be made. And in particular, for Rett, where there is this risk of over expression toxicity. So you have to get the amount of protein being produced appropriate within the appropriate physiological limits enough to make sure you're having efficacy, but not so much protein that it causes toxic side effects. Because of that, we actually did a very, very disciplined preclinical package, which included a mouse pharmacology study. So a mouse model pharmacology study, we did a Rett toxicology study, we did an NHP toxicology study, all of the studies were very extensive and very comprehensive. The mouse study was over 250 mice, the Rett study was over 120 rats, NHP study was 24 NHPs. And the mouse pharmacology study is where you look for a dose that's going to be efficacious. And we're able to – we were able to identify that very clearly in terms of demonstrating enough drug causing an improvement in survival, motor assessments, respiratory assessments and other assessments. So the 5V14 total VG dose is above that level. And then on the other end, both in the Rett talks, and the NHP tops, we tested doses up to an equivalent of 2V15 total VG human equivalents that's fourfold over the starting dose. And to answer your question, specifically, there was no adverse events of any note at the 2V15 dose. So, it's possible we could go even higher with that. But we didn't test higher than that, because we didn't think there would be a need to go higher than 2V15, simply because we saw efficacy at a much lower amount in the naive and pharmacology study. And I think it was that combination of studies that really persuaded Health Canada to allow the CTA to be opened. And I think there is one other important piece around this NHP study that is really, really important. And I will actually be discussing this at a poster presentation at ASGCT, I think it's tomorrow, tomorrow, Wednesday – it's Tuesday, actually, yes, presenting it Tuesday. I have actually presented state of the big Rett syndrome, scientific conference that's organized by the ISRA, about three or four weeks ago. And the NHP tox does three things, it shows a full absence of any kind of toxic effects, which is important for fourfold higher clinical dose, it also shows really excellent biodistribution from an intrathecal dose throughout the brain and the spinal cord. So, you are getting back to copy numbers in a very nice range, one to two copies particular genome in different parts of the brain, and the spinal cord, in the ganglia and the

peripheral nervous system. And it also shows correspondingly low levels of RNA. And don't forget, these are wild type NHPs. So, what that means is you are getting great delivery of drug into the brain and spinal cord, but actually very high down-regulation, meaning not much RNA being produced, which is appropriate given this a wild type animal. So, that NHP study shows safety, it shows biodistribution, but importantly, mechanism of action. And so I will be going through that data in more detail the ASGCT meeting tomorrow. So, that group of studies together, was really very persuasive to Health Canada till last week in the CTA.

Operator

Thank you. Our next question comes from the line of Yun Zhong with BTIG. Please proceed with your question.

Yun Zhong

Hi. Thank you very much for taking the question. This is actually a follow-up question on just what you said, just now Suyash. So, on Rett syndrome, has anyone looked at comparability between non-human primates and human patients in terms of biodistribution? And also given that this is not cross correction to be expected? So, are there any data to suggest the transduction efficiency, or do you have an estimate on how many cells will need to be transduced to see reasonable efficacy?

Suyash Prasad

Two very good questions. So, the first question was about the translatability of NHP biodistribution to human. It's a good question. No one has done it specifically in Rett. What we have done is we have shown very nice biodistribution with our Rett program with an intrathecal dose into an NHP, which is of course smaller than the human being. But the anatomy is very similar. And it's probably the best corollary looking at blood sugar in any animal model to the human. And we get really nice biodistribution throughout the brain and the spinal cord with the intrathecal dose of injection. Now, in the human setting, the only way to really ascertain biodistribution is in a sad situation if the patient was to pass away and to look at DNA and RNA, and protein in that individual. And that did happen very early on in one of the GAN patients. One of the low dose GAN patients who sadly passed away through progression of disease, this data has been presented by Carson Palmer and Steven Gray at the ASGCT meeting a few years ago. And they showed that with an intrathecal dose of AAV9 gene therapy for GAN. You actually got nice biodistribution, although it's a low level, but it was a low dose throughout all target organs, tissues. And the other thing I will say from what we learned from the GAN program, and don't forget GAN AAV9 is HEK293, and intrathecally delivered, so lots of similarities to the Rett program. The other thing I will say about GAN is, is that we have demonstrated more recently in our January presentation that we see improvements in the peripheral nerves, in the nerve biopsies. Now, these are nerve biopsies that are performed in the radial superficial nerve, which is a nerve in the wrist. And what this means is that drug is getting down into the peripheral nerve system, down to the wrist, from an intrathecal dose of injection. So, for those reasons, we are confident that intrathecal dose of drug will actually deliver drug in the Rett syndrome very nicely to all the tissues that needs to be transfused which are brain in particular and the spinal cord and brainstem. That's answer of the first question. The second question you had was about, what proportion of cells need to be transduced. And it's difficult to know, but we certainly believe that, with this 50-50 ratio of mosaics versus, versus non-mosaics – sorry, wild type versus null cells in the mosaic setting, we certainly know that if we transduce some of the cells, you are going to get some clinical benefit. And the likelihood is, the more cells that are now being transduced, the better clinical benefit you get. So, our approach, once again, is to give a high dose of drug intrathecally to enhance biodistribution. And we know we have confidence, that giving high doses of drug, you still see a nice down-regulation of the protein being produced, which for the wild type cells. So, once again, we don't know exactly how many cells need to be transduced. But I think a small number will give you

some benefit. A large number may give more benefits. But we are quite confident giving high doses to enhanced biodistribution, because we see our down-regulation package working nicely. Hopefully, that answers your question, Yun?

RA Session II

The only thing that I would add, Suyash, to what you mentioned are just two examples. I would say, the preclinical data set that we have been able to generate, particularly the NHP data set really gives us the opportunity to maximize transduction efficiency. And Suyash mentioned this before, I just wanted to reiterate this. The fact of the matter is that we didn't see – we didn't observe tox at any dose that was actually given including to 2E15. You always have the ability to be able to increase dose to really maximize transduction efficiency and to be able to get really nice biodistribution. We see nice biodistribution at the levels that we are starting at. But again, if we wanted to be able to maximize that, we obviously have the ability to be able to go higher. The second point that I just wanted to make and I think it's something that does get overlooked is a nice correlation to our CLN7 study, which is being done under a collaboration with our partners at UT Southwestern. This is again a membrane bound protein similar to MECP2. So, it's not – there is no cross correction here. And we have shown the ability to be able to dose patients up to 1E15 and to be able to do that successfully and safely. So, some of that early preliminary data was presented at World Symposium earlier this year and since that data has been presented, there has been an additional patient that has been dosed at the high dose which is 1E15. So, again, I think I like to remind the field around the number of firsts that's really come out of this collaboration with Taysha and UT Southwestern, where you have the first centrifugally dose gene therapy in history. That's our giant axonal neuropathy study, the first gene therapy in development for Rett syndrome. You now have the first gene therapy with the self regulatory feedback loop in clinical development to control expression on a cell-by-cell basis. The first to be able to dose intrathecally at 1E15 and to be able to do that safely and to demonstrate safety of an AAV9 construct, so just in the short period of time that the company has been in existence. There has been a number of firsts that have been generated. And it's something that I am very proud of, and I always remind our employees to be proud of the number of firsts for the field of gene therapy that's been generated by the company and our partners like UT Southwestern.

Operator

Thank you. Our next question comes from a line of Laura Chico with Wedbush Securities. Please proceed with your question.

Laura Chico

Hey. Good morning, guys. Thanks for taking the question. I wanted to circle back with regards to the spend, I am wondering if you can offer a little bit more clarity on perhaps the breakdown between R&D and G&A. And RA, I think you made an earlier comment too, about kind of exploring additional channels for monetization, just wondering if you could kind of expand on that a little bit. Thanks guys.

RA Session II

Sure. Thanks Laura. Good morning. So, I will start with your last question first, really around just ways that we are thinking about extending cash runway. Obviously, having business development opportunities continue to remain an opportunity for us to be able to go and bring in non-dilutive forms of capital. What I would say to that is that, we are constantly looking at potential strategic collaborations with parties, whether those are regional collaborations or collaboration around specific assets. But it's something that we consistently look at, and we have been fortunate to essentially get a lot of calls, after we have made our announcement at the year-end earnings call. And so, we continued to explore those as a potential way of bringing in non-dilutive capital. What I would also say is, again, we look very carefully around which programs that would continue in, and what the company would actually focus on from a clinical development perspective. And essentially, what we decided to do is once for programs that have hit proof-of-concept, we have essentially ceased with those and for – again, for the ones that are currently in clinical development, and haven't yet hit proof-of-concept. We will continue to move forward with those until we hit that milestone, particularly with a focus on CLN1 and SLC13A5, going away from that registration – speed to registration pathway, which is going to be a lot more expensive, from a CMC perspective and a clinical development perspective, and really just begin continuing to validate the platform from a proof-of-concept perspective. And then still focus with our two lead programs on the fastest pathway to approval. And that's our giant axonal neuropathy in our Rett syndrome program, which we continue to be all-in on, but still doing from a totality of our portfolio, really looking with an eye to preserve cash and long-term runway and so that's the way that that we are kind of looking at looking at this. I think, again, as I mentioned earlier, we executed on a strategic pipeline prioritization earlier this year, which is starting to play out where essentially we pause, work on a lot of our preclinical programs, and essentially kind of begin reconstituted a number of our clinical programs continuing to move them forward done for an effort to preserve cash runway and I think you will start to see R&D expense, come down over the next few quarters and start to get to a certain run way as we get into the second half of the year, that we will be able to hold constant ways to augment that. Obviously, if there is a turnaround in the capital markets, we should be able to go in and raise capital through our currently available ATM, which we have already done. Since our year-end earnings call, we have been able to successfully draw down some capital from that ATM that extended cash runway and we will continue to be strategic in the way that we look at that. But I would probably say non-dilutive forms of capital, our current term loan facility, which again allows us to have cash into

Q4 2023 and then obviously, the ability to be able to tap our ATM, which we have already done. I think all of those things being consistent are ways that we would look to extend runway. Maybe, Kamran, you would want to comment on just the breakdown between R&D and G&A.

Kamran Alam

Yes. Sure. Happy to. Thanks RA and thanks for the question, Laura. So, over 75% of our operating expenses are R&D related. And as RA mentioned, because of their strategic pipeline prioritization efforts, we will be able to reduce that R&D expense burn significantly over the next coming quarters as a result of pausing research and development activities on our preclinical programs, as well as significant reduction in our CMC expenses. Ultimately, as a reminder, we conducted six GMP batches last year, some of which were completed in Q1 of this year in terms of product release. And we are only doing GMP manufacturing on our GAN program this year. So, you can expect a significant reduction in our CMC expense year-over-year and in subsequent quarters as a result. So, again, a lot of a lot of nice work to really focus our resources and our efforts primarily on of course, GAN.

RA Session II

Thanks Kamran.

Operator

Thank you. Our next question comes from line of Yanan Zhu with Wells Fargo. Please proceed with your question.

Yanan Zhu

Hi. Thanks for taking my questions. A couple on the Rett syndrome clinical trial, what is the waiting period for safety observation, once patient one is dosed? And how could – how would you ascertain whether there is MECP2 overexpression associated toxicity given that the MECP2 duplication syndrome share a lot of the same manifestations with Rett syndrome? Thank you.

RA Session II

Hi Yanan. Good morning. I will turn that question over to Suyash to provide some context. Suyash?

Suyash Prasad

Sure. So, the staggering specifically is eight weeks. So, after patient is dosed for a review of the eight week time point, and discussions with DMC will then show with the absence of any safety issues, we will then go ahead and dose the next patient. But that's between patients one or two as time progresses, the staggering changes in the clinical trial course. And we do less staggering as the study progresses. Specifically, with regard to signs of over-expression toxicity, it's a good question. And it's one we have discussed at length, both with regulators and with key opinion leaders. And the bottom line is that most patients, in fact, all patients in the adult study, certainly unlike in the pediatric study will be in the Phase 3 of Rett syndrome, i.e., they are stable and not declining. You may recollect that there is four phases to the clinical progress of patients with Rett. The first is where they get the diagnosis. The Phase 2 is when there is a rapid decline in functionality. Phase 3 is when they are in a stable phase by a state with a very complex level of functioning. And then there can be a phase for years, sometimes decades, and then they end up into a deterioration phase. To all patients who have struggled in the Phase 3, i.e., they are stable. So, what we are looking for clinically is any kind of deterioration, okay, because there is such a poor state, they have been stable for a while. If there is any deterioration seen in terms of Rett syndrome type behaviors or other neurological features, it's likely to be due to over-expression than a progression of Rett syndrome. Now, will we miss a definite, no, we wouldn't, because we can't biopsie the brain tissue, of course, in the clinical trial in patients. But the way we are observing specifically MECP2 over especially toxicity is by looking for a change in the mental status and the change of neurological status, and your behavioral status, and central nervous system, peripheral nervous system, deterioration after dosing with a gene therapy, because that's unlikely be due to progression of Rett is likely to be due to over a special toxicity of MECP2. Having several of that, we anticipate that's highly unlikely given NHP tox data and our rat tox data where we gave very high doses of the drug fourfold of the present clinical dose, and so no toxicity even at that high level.

RA Session II

Thanks Suyash.

Operator

Thank you. Ladies and gentlemen, we have come to the end of our time allowed for questions. I will turn the floor back to Mr. Session for any final comments.

RA Session II

Thank you, operator. And again, thank you for everybody for joining our Q1 call today. As we iterated earlier, the company has performed quite nicely coming out of Q1 and our strategic pipeline prioritization, also refocus on continuing to move forward our GAN program, our Rett program, from a speed to registration aspect, and then morphing some of our earlier clinical programs to more proof-of-concept studies. I couldn't be prouder of the execution of the team. I couldn't be prouder of the focus of the team and we continue to invite you guys to follow the progress that the company continues to make strides later this year. With that, I wish you guys a wonderful week, many of us will be at ASGCT. So, I would ask you guys to come by and say hi. And I look forward to seeing many of you there. With that, we will end today's call. Thank you.

Operator

Thank you. This concludes today's conference. You may disconnect your lines at this time. Thank you for your participation.

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Taysha Gene Therapies, Inc. (NASDAQ:[TSHA](#)) Q2 2021 Earnings Conference Call
August 16, 2021 8:00 AM ET

Company Participants

Kimberly Lee - Senior Vice President, Corporate Communications and Investor Relations

RA Session II - President, Chief Executive Officer and Founder

Suyash Prasad - Chief Medical Officer and Head, R&D

Kamran Alam - Chief Financial Officer

Conference Call Participants

Elizabeth Webster - Goldman Sachs

Joon Lee - Truist Securities

Laura Chico - Wedbush Securities

Gil Blum - Needham & Company

Eun Yang - Jefferies

Raju Prasad - William Blair

Yun Zhong - BTIG

Mike Ulz - Morgan Stanley

Kristen Kluska - Cantor Fitzgerald

Operator

Welcome to the Taysha Gene Therapies Second Quarter 2021 Financial Results and Corporate Update Conference Call. [Operator Instructions] As a reminder, this call is being recorded today, August 16, 2021. I will now turn the call over to Dr. Kimberly Lee, Senior Vice President of Corporate Communications and Investor Relations. Please go ahead.

Kimberly Lee

Good morning, and welcome to Taysha's second quarter 2021 financial results and corporate update conference call. Joining me on today's call are RA Session II, Taysha's President, CEO and Founder; Dr. Suyash Prasad, Chief Medical Officer and Head of R&D; and Kamran Alam, Chief Financial Officer. After our formal remarks, we will conduct a question-and-answer session and instructions will follow at that time.

Earlier today, Taysha issued a press release announcing financial results for the second quarter ended June 30, 2021. A copy of this press release is available on the company's website and through our SEC filings. Please note that on today's call, we will be making forward-looking statements including statements relating to the safety and efficacy and the therapeutic and commercial potential of our investigational drug candidates. These statements may include the expected timing and results of clinical trials for our drug candidates and the regulatory status and market opportunity for those programs as well as patient manufacturing plans.

This call may also contain forward-looking statements relating to Taysha's growth and future operating results, discovery and development of drug candidates, strategic alliances and intellectual property as well as matters that are not historical facts or information. Various risks may cause Taysha's actual results to differ materially from those stated or implied in such forward-looking statements. These risks include uncertainties related to the timing and results of clinical trials and preclinical studies of our drug candidates or dependence upon the strategic alliances and other third-party relationships; our ability to obtain patent protection for our discoveries, limitations imposed by patents owned or controlled by third-parties and the requirements of substantial funding to conduct our research and development activities. For a list and a description of the risks and uncertainties that we face, please see the reports we have filed with the Securities and Exchange Commission.

This conference call contains time-sensitive information that is accurate only as of the date of this live broadcast, August 16, 2021. Taysha undertakes no obligations to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call, except as maybe required by applicable securities laws.

With that, I'd now like to turn the call over to our President, CEO and Founder, RA Session II.

RA Session II

Thank you, Kim. Good morning and welcome everyone to our second quarter financial results and corporate update conference call. Taysha continues to make significant progress on several key clinical, manufacturing and strategic corporate initiatives, which were highlighted at our recent R&D and Manufacturing Investor Day as well as our recent press release announcing our non-dilutive financing with Silicon Valley Bank. I will elaborate on some of our recent key achievements and review the expected milestones for the remainder of 2021. Following this, I will turn the call over to Suyash and Kamran for updates on our pipeline developments and financial results respectively.

At our R&D Day held in June, we presented positive data on a number of our key development programs. These data included Phase 1/2 visual acuity data for TSHA-120 in patients with ginkgonaneuropathy or GAN, genotypic-specific MECP2 expression data for TSHA-120 in Rett syndrome, natural history data in GM2 gangliosidosis, preclinical data for TSHA-118 in CLN1, natural history data in CLN1 disease, along with clinical patient phenotype data and SURF1-associated Leigh syndrome.

We also disclosed the positive effects of TSHA-105 on seizures and associated deaths in SLC13A5 knockout mice, the effects of TSHA-103 on abnormal EEG activity in SLC6A1, knockout and heterozygous mouse models and preclinical data for TSHA-112 in APBD and TSHA-111-LAFORIN and TSHA-111-MALIN in Lafora disease.

Lastly, we disclosed the effects that TSHA-113 on tau expression in MAPT-associated tauopathy and our two novel approaches for the treatment of Angelman syndrome. Suyash will review these pipeline developments shortly. Part of our success relies on robust, sustainable and high-quality manufacturing to support our portfolio and we are pleased to announce that we have achieved several successful GMP runs that further support our 5 planned Phase 1/2 clinical trials and numerous IND/CTA-enabling studies. In July, we held a Manufacturing Day to highlight how our flexible and scalable approach, which seamlessly integrates R&D and manufacturing de-risked our overall portfolio and supports consistent delivery of high-quality clinical material across our broad pipeline.

Our three-pillar approach to manufacturing includes dedicated capacity at UT Southwestern, a collaboration with Paradigm, a subsidiary of Catalent and the development of our internal manufacturing facility. We continue to make progress on the construction of our multi-product facility in Durham, North Carolina, which will have 2,000 liters of capacity. Additionally, the capacity at UT Southwestern is expected to increase from 500-liter to 700-liter scale by the end of the year, which will continue to support our IND-enabling and early clinical trial efforts and ensure high quality, efficient and accessible production for our pipeline.

In order to further our mission in the development of novel gene therapies for the treatment of monogenic diseases of the CNS, we recently became a founding member of the newly formed rare disease company coalition, a first-of-its-kind alignment of life science companies committed to discovering, developing and delivering rare disease treatment. We look forward to working together to expedite the delivery of our transformative therapies to the millions of patients with rare diseases. In the second half of this year, we expect numerous value-creating preclinical, clinical and regulatory milestones. Recently, we have had a number of meetings with multiple regulatory agencies regarding our Rett syndrome, GM2 gangliosidosis and CLN1 disease programs as we prepare for IND/CTA submission.

I am pleased to share that we have received positive feedback from these agencies that paved the way for multiple anticipated IND/CTA filings in the second half of this year. For TSHA-120, our pivotal stage product candidate and GAN, we anticipate data from the high-dose cohort in the second half of this year and expect to provide a regulatory update by year end. For GM2 gangliosidosis, we remain on track to report first-in-human safety and HEXA biomarker data in the second half of this year. For our CLN1 program, which currently has an open IND, we anticipate dosing of the first patient in our Phase 1/2 trial in the second half of this year. Collectively, by year end, we anticipate that we will have 5 programs in clinical development.

The rapid advancement of our numerous candidates will not be possible without the support of our dedicated and talented team. We recently appointed Mary Newman as Chief Development Officer. She was a former Senior Vice President of Regulatory Affairs at Astellas Gene Therapies, formerly Audentes and brings over 30 years of experience in translational development, program management and regulatory affairs. At Taysha, we now have 155 employees in addition to 70 colleagues at UT Southwestern across multiple functional areas, including discovery, translational development, GMP manufacturing and clinical care.

The collective expertise and dedication across these teams, including our seasoned Board of Directors and independent internationally renowned Scientific Advisory Board, uniquely positions the expedited development of our gene therapy candidates and our technology platform. We have ambitious corporate objectives planned over the next 12 to 18 months. And we are very pleased to have recently entered into a non-dilutive term loan agreement with Silicon Valley Bank that provides Taysha with up to \$100 million in non-dilutive financing at an attractive iterate that lowers our overall cost of capital, bolsters our cash position, and provides additional financial and operational flexibility.

We believe full drawdown of this funding will extend our cash runway to support key value-creating milestones, including the release of Phase 1/2 data from the highest dose cohort in GAN and Phase 1/2 data in GM2 gangliosidosis, CLN1 disease and Rett syndrome and importantly, a potential regulatory approval for TSHA-120 in GAN without the need for additional financing. We look forward to updating you on our continued progress throughout the remainder of the year, including at our upcoming virtual investor mini series for our CLN1, Rett syndrome and Angelman syndrome programs, where we will feature presentations from key opinion leaders and highlight progress made to-date.

I will now turn the call over to Suyash to provide a more detailed update on our R&D initiatives. Suyash, please go ahead.

Suyash Prasad

Thanks, RA. We have made significant progress in the second quarter and continue to achieve important clinical advancements that further support a potential regulatory approval of our most advanced program, TSHA-120, which holds significant promise for patients with giant athermal neuropathy, or GAN. At our R&D Day, in addition to the compelling clinical data demonstrating halting of disease progression as assessed by the well-validated and established motor assessment tool, the MFM32, we presented new visual acuity data from the ongoing Phase 1/2 trial investigating TSHA-120 in patients with GAN. In children and adolescents with GAN, there is an ongoing and progressive deterioration in vision towards blindness, which is understandably one of the most challenging and upsetting symptoms from the perspective of the patient and family.

With this new data, we were able to demonstrate a dose-dependent trend towards stabilization of visual acuity, i.e., the ability of AAV9 gene therapy to preserve visual function, which otherwise would be lost. We also discussed in depth the natural history data in GAN that was published in the highly regarded neurology journal, Brain earlier this summer. As a reminder, all GAN natural history data was generated and supported by the National Institute of Neurological Disorders and Stroke, or NINDS under the leadership of the principal investigator, Carsten Bönneman. Included in the publication was the largest cohort of genetically confirmed patients with early and late onset forms of GAN. This large cross-sectional analysis highlighted clinical differences between patients with early onset versus late onset GAN based on performance on the MFM32, a validated and well-known scale to measure strength and motor function as well as other functional motor scales and disease markers. Additionally, a robust assessment of many clinically relevant outcome measures for GAN was performed, including motor, sensory, respiratory, neurophysiologic, MRI and biopsy assessments. Moreover, this was the first clinical study ever to formally and comprehensively evaluate autonomic nervous system dysfunction in a cohort of individuals with GAN.

Overall, this natural history study has been instrumental in clinical trial design for the ongoing Phase 1/2 trial and the data included in the Brain publication will serve as baseline data for the natural history comparator arm to the interventional study. As already noted, we remain on track to report clinical data from the highest dose cohort from this ongoing Phase 1/2 trial in the second half of this year and to provide a regulatory update on the program by year end. We have also made significant progress across our preclinical programs. Positive preclinical data for TSHA-102 and Rett syndrome was published also in the Journal of Brain that provided quantitative evidence of MIRA's ability to exhibit genotype dependent regulation of MECP2 gene expression on a cell-by-cell basis across different regions of the brain in both wild-type and knockout mouse models of Rett syndrome. We recently have productive and collaborative pre-IND CTA discussions with several key regulatory agencies and received positive feedback that support our anticipated IND/CTA submission in the second half of this year.

In GM2 gangliosidosis, we were able to discuss in detail at our R&D Day had the existing and in-depth natural history data on this condition informs us about disease progression and in particular motor development delays. We believe these data help provide a comparator for ongoing and future interventional trials. We continue to expect preliminary safety and biomarker data in the Queens University Phase 1/2 trial for TSHA-101 in the second half of this year. Specifically, we will be disclosing HEXA enzyme activity in serum and CSF and expect that 5% HEXA enzyme activity will be considered a positive result. In the U.S., we had a productive and informative meeting with the FDA. We remain on track to initiate a Phase 1/2 trial in the second half of this year.

Moving on to our CLN1 program, additional preclinical data for TSHA-118 were presented at R&D Day, which was demonstrated sustained preservation of motor function and rescue with higher doses of TSHA-118 and earlier intervention in CLN1 knockout mice. There are two ongoing natural history studies assessing CLN disease, which will help further our understanding of the disease, inform on our clinical trial design and serve as comparative data in a future trial for TSHA-118. These two studies include a prospective observational study assessing the natural history of CLN diseases and the retrospective and the prospective study to characterize the age-at-onset of major symptoms and the relationship between age and severity.

TSHA-118 currently has an open IND. We recently have very productive and collaborative meetings with several key regulatory agencies and positive feedback that support dosing of the first patient, which we anticipate should occur in the second half of this year. TSHA-118 has been granted orphan drug designation, rare pediatric disease designation and fast track designation from the FDA and orphan medicinal product designation from the EMA for the treatment of CLN1 disease.

For TSHA-104 in SURF1-associated Leigh syndrome, we announced at R&D Day, new data demonstrating that only a small increase in COX-1 activity can significantly improve the clinical phenotype in these patients, further supporting our SURF1 gene replacement strategy with TSHA-104. Reduced tox activity also correlated with disease worsening in patient fibroblasts, further supporting the impact of COX activity on disease outcomes. This phenomenon draws correlations to other diseases that we are targeting, including GM2 and CLN1, while small increases in activity can have a pronounced physiological impact.

We plan to file an IND/CTA for TSHA-104 in the second half of this year. Additionally, a natural history study that is part of our clinical development program is expected to enroll its first patient. This study will follow patients for initial period of time prior to enrollment into the interventional trial. At our R&D Day, Dr. Rachel Bailey, Assistant Professor in the Department of Pediatrics at UT Southwestern, presented positive preclinical data for TSHA-105 in SRC39 deficiency that demonstrated improvement of EEG activity and reduction in seizures and associated deaths in SLC13A5 knockout mice.

We continue to advance TSHA-105 towards the clinic and expect that patients currently enroll in an ongoing prospective natural history study would be available to enter our clinical trial. We are currently considering an open label randomized dose escalation Phase 1/2 trial to examine the safety, tolerability and preliminary efficacy of TSHA-105 in the treatment of SLC13A5 deficiency. Biomarkers include citrate levels in the plasma, urine and CSF.

Moving on to TSHA-103 in SLC6A1 haploinsufficiency disorder at our R&D Day, Dr. Kim Goodspeed, Assistant Professor in the Department of Pediatrics, Neurology and Psychiatry at UT Southwestern and Dr. Steven Gray, Associate Professor in the Department of Pediatrics at UT Southwestern and Chief Scientific Advisor at Taysha, highlighted the nature of the disease and the positive preclinical data to-date. In SLC6A1 knockout and heterozygous mouse models, CNS administration of TSHA-103 rescued abnormal seizure activity, notably recently obtained positive data demonstrating rescue or functional measures such as nesting, open field activity, hind limb clasping and latency to fall from the rotarod.

We are now evaluating dose and age response and finalizing the dose from our preclinical pharmacology experiments. We are also developing an interventional trial protocol. In APBD and Lafora, Dr. Berge Minassian, Division Chief of Pediatric Neurology at UT Southwestern and Chief Medical Advisor at Taysha provided an in-depth discussion about the nature of both diseases at our R&D Day and highlighted positive preclinical data that supports advancement of these programs. Specifically, TSHA-112 reduced GYS1 expression in the APBD knockout model, which resulted in decreased polyglucosan body formation in mice brain. TSHA-111-LAFORIN and TSHA-111-MALIN reduced GYS1 expression in the LAFORIN and MALIN knockout models, which resulted in decreased Lafora body formation in mice brain. We continue to make good progress on both programs and are currently developing an interventional trial protocol. Preclinical data for TSHA-113 in tauopathies presented at R&D Day demonstrated significant reduction in tau mRNA and protein levels, validating the potential use of AAV-mediated gene silencing to achieve lifelong reduction of tau protein levels and supporting further preclinical development for the treatment of tauopathies.

Lastly, we were very excited to highlight at our R&D Day on novel approaches to treat Angelman syndrome. We are targeting the entire Angelman syndrome population via knockdown of UBE3A-ATS to unsilenced the paternal allele and also using a gene replacement strategy on UBE3A to mimic the maternal UBE3A allele expression. We have shown compelling fluorescence images of the cerebellum that demonstrates UBE3A expression following administration of TSHA-106, our short hairpin RNA candidates. As you can see, our robust portfolio of clinical and preclinical candidates continues to advance expeditiously. And as RA noted, we have a number of clinical and regulatory catalysts expected in the second half of the year. We will continue to provide updates on our programs throughout the year.

With that, I will turn the call over to Kamran to review our financial results.

Kamran Alam

Thank you, Suyash. This morning, I will discuss our recent non-dilutive financing and key aspects of our second quarter 2021 financial results. More details can be found in our Form 10-Q, which will be filed with the SEC shortly. We recently secured a non-dilutive term loan financing for up to \$100 million from Silicon Valley Bank, or SVB, with \$40 million available at closing, of which Taysha has drawn \$30 million. We have the option to drawdown the remaining tranches subject to certain conditions. The interest rate is the greater of 7% or the Wall Street Journal prime rate plus 3.75% and there are no financial covenants or warrants associated with this financing. We believe that full drawdown of this funding will extend our cash runway through multiple key value-creating milestones, including a potential regulatory approval of TSHA-120 in GAN without the need for additional financing.

Moving on, as indicated in our press release today, R&D expenses were \$30.6 million for the 3 months ended June 30, 2021 compared to \$3.1 million for the 3 months ended June 30, 2020. The \$27.5 million increase was primarily attributable to an increase of \$10.3 million of expenses incurred in research and development, manufacturing and other raw material purchases, which included CGMP batches produced by Catalent and UT Southwestern. We incurred an increase in employee compensation expenses of \$8.5 million, which included \$2.2 million of non-cash stock-based compensation and \$8.7 million in third-party research and development expenses, which includes clinical trial CRO activities, GLP toxicology studies and consulting for regulatory and clinical studies.

G&A expenses were \$10.1 million for the second quarter ended June 30, 2021 compared to \$0.9 million for the second quarter ended June 30, 2020. The increase was primarily attributable to incremental compensation expense, which included non-cash stock-based compensation and additional consulting and professional fees. Net loss for the second quarter ended June 30, 2021 was \$40.9 million or \$1.09 per share as compared to a net loss of \$21.2 million or \$1.95 per share for the second quarter ended June 30, 2020. As of June 30, 2021, Taysha had \$197.4 million in cash and cash equivalents. This does not include funds from the recently announced debt financing.

And with that, I will hand the call back to RA.

RA Session II

Thanks, Kamran. We are pleased to have shared with you our success over the second quarter. Looking ahead, we will continue our focus on advancing our pipeline expeditiously and executing on key anticipated milestones in the second half of 2021. We reiterate guidance for the expected clinical, regulatory and preclinical milestones in the second half of 2021, including reporting data from the highest dose cohort from the Phase 1/2 TSHA-120 study in GAN, providing a regulatory update for the GAN program, reporting preliminary Phase 1/2 safety and biomarker data for TSHA-101 in GM2 gangliosidosis and initiating Phase 1/2 trials in CLN1 disease, Rett syndrome and SURF1-associated Leigh syndrome.

I would like to give special thanks to the continued support and dedication of our Taysha employees, Board of Directors, Scientific Advisory Board, collaborators, UT Southwestern and the patients and advocates who remain our motivation everyday to continue our mission to develop curative gene therapies.

I will now ask the operator to begin our Q&A session. Operator?

Question-and-Answer Session

Operator

Thank you. [Operator Instructions] Our first question comes from the line of Salveen Richter with Goldman Sachs. Please proceed with your question.

Elizabeth Webster

Hey good morning guys and thank you for taking our question. This is Elizabeth on for Salveen. Just wanted to ask if you could provide a little bit more color on the nature of the pre-IND and CTA positive feedback you have gotten from regulatory agencies? And then just I guess more broadly, what are some of the venues that Taysha could present the data into – in the second half of 2021 and just Taysha's approach to data releases on the forward?

RA Session II

Sure. Thanks, Elizabeth and good morning. What I will do is I will take the first question and then – I am sorry, I will take the second question and then we will throw the first question to Suyash to give some color around some of our recent discussions with regulators. Essentially, our approach to releasing data is either going to be primarily through press release and/or doing an investor call. As you recall, we have done a number of kind of these mini Investor Days over the last few months. First is our R&D Day. The second was the Manufacturing Day. We have the CLN1 Investor Day coming up here in the next few weeks and that will be followed by our Rett syndrome Investor Day and then our Angelman Investor Day. And so depending on the timing of when the data is going to be available to release. We are either going to do it through a press release, which you would obviously press release it anyway, but to provide some additional color we may do a call around that as well, so more to come, but certainly exciting times for the second half of the year. Suyash, maybe you want to provide just some general color around some of our regulatory interactions over the last few months, primarily the number of interactions that we have had over the last few months.

Suyash Prasad

Yes, thanks RA and thanks for the question, Elizabeth. We have had a very, very hectic schedule of regulatory activity over the past few months and that was purposeful. As you know, with our approach to regulatory engagement, we are filing in multiple jurisdictions for each of our programs. So we have probably had close to 10 regulatory interactions which included the FDA and several other countries. And in general, they have been very, very good. The tone has been collegial. We have been able to answer all their questions. There has been very few surprises along the way. I think it would be fair to say that the actual discussions themselves, we focused on a few topics of note, and I'll bucket them to three categories. One is CMC and a large part of that is potency acid testing. And once again, we have a very similar approach across our programs. We have a very disciplined way of looking at potency. We start all the word early. So that discussion goes well and there is no general surprises there. On the non-clinical side, we have a very robust package of toxicology across all our programs, which include a combination of mouse chronic tox rate 6-month tox and NHP tox, which could be 3 to 6 months. And in general, most of the agency is very favorable there. There is a few slight differences in what the expectations are, i.e., some agencies want a little more in terms of species and duration of time and some agencies want a little bit less. And as we all know, the FDA tends to be a little more conservative. But once again, our plans are very robust and comprehensive. So the multiple agencies are generally very favorable for those. And the third bucket of question usually tends to be around clinical sub-design and endpoints. And once again, we've had – we give a lot of thought to our end points we've in feedback from patients and families, feedback from key opinion leaders, and we write the protocol in a very disciplined way. We make sure that the majority of our developmental progression assessments are videos and that adds on to a robustness to the studies. And so once again, those discussions go well also. So lots of interactions, lots of very good interactions, and we have a few more yet to come. But I would say that there is been really very little surprises and the engagement has been collegial and very positive thus far. In fact, one of the agencies have said to us at the last meeting. What we're looking forward to seeing you next time. So I think that's really just signifies the tone of the conversations.

Elizabeth Webster

Great. Thank you so much.

Operator

Thank you. Our next question comes from the line of Joon Lee with Truist Securities. Please proceed with your question.

Joon Lee

Hi, thanks for taking our question and for the update. So the Rett syndrome, which is a relatively larger indication and a really interesting one, you guided to clinical data by year-end '22, but no mention of any biomarker data released in the press release. Are you skipping – are you planning to skip the biomarker data disclosure altogether in favor of the initial clinical data? This one just stood out to us given the planned biomarker data disclosures for the other programs. And also, is your micro active response element, something that is patented? Or is this more of a protected by in-house know-how. And I have a quick follow-up after that. Thank you.

Suyash Prasad

Sure. Well, I can take the question on the biomarker data and then RA can talk about the IP. With regards to the biomarker data, it's a great question, Joon. I really wish we had a good biomarker for Rett syndrome, many, many scientists and expert clinician physician sciences have been looking for a biomarker for this particular disease. But sadly, there isn't a good blood-based biomarker or a good CSF biomarker. I think with regard to biomarkers, the best biomarker that we have, which is not very good, is probably EEG. The EEGs of children with the retro abnormal, and it's possible that we will see a modification in the EEG as an early Rett on the biomarker of activity of the drug.

But it's not really a very good, very established, very robust, well-accepted biomarker, which is why we don't specifically guide that biomarker day. But if something looks interesting early we will plan to share it. I mean I think the best hope for Rett is really to see what we see from a safety perspective and then from a efficacy perspective thereafter. We are, however, collecting blood and CSF and performing full metabolomics and proteomics analyses. So something does crop up as an interesting useful biomarker, then we will see it there. I don't hold much hope for that, frankly, because many, many experts have been looking for biomarker for a long time. So ultimately, we do – we are guiding to enrolling the study start in the study by the end of this year and clinical data by the end of 2022. And I'll hand over to RA now for the IP question.

RA Session II

Sure. Thanks, Suyash. And Joon, thanks for the question. Good morning. So our MI rare platform is covered by strong intellectual property. We're pretty excited about that and the broad applicability of the platform to not only show genotypic MECP2 expression on a cell-by-cell basis but also the ability to exploit this platform for other indications where there may be a dose sensitive nature to the protein. And so there is a really nice correlation to this in a lot of other disease areas, Fragile X being one of them, Angelman being another, Pitt-Hopkins, FOXG1. So there is a number of these where you have the potential to either use the exact same microRNA binding sites to build into another transgene or to pick a new subset of microRNA binding sites to – depending on the disease itself. So we're actually pretty excited about it. I think it is something that significantly differentiates our approach to others. And if you recall, our approach to gene therapy is really to use validated gene therapy technology, coupled with very targeted payload design. So the validated piece, AAV9 intrathecal delivery HEK293 suspension but really innovate around payloads and am I rare being an important piece of that. And so as we continue to build out the data set in other disease areas, obviously, we will continue to expand our IP estate around that.

Joon Lee

Excellent. Thank you. And just a quick follow-up for all your programs, given they all use the AAV9 vector, are your starting doses for all the other programs comparable? And is your dose escalation strategy also comparable between programs? Thank you.

RA Session II

Really, really, good question. And I think it speaks to this platform approach. And again, our approach to using kind of this validated technology and using that and exploring that in multiple indications. Suyash, maybe you want to give some thoughts there.

Suyash Prasad

Sure, I can. It's a very good question. And in general, I would say, yes, we are approaching the first dose for each patient in each program. We're ending up in a relatively similar ballpark of around 5E14 total vg, which as you know, is a high dose being direct brain and spinal cord with a low dose in terms of systemic exposure for compressed to systemic drugs which are dosed vg for [indiscernible]. What I would – where I would say the programs differ a little bit is how aggressively we can accelerate or escalate the doses thereafter. And it depends on a couple of things really. The most important thing it depends on is the therapeutic window that we have. And for several of our programs, we actually have a very broad therapeutic in window, for example, CLN1 or GM2 where you have a secreted enzyme, so where you actually can – a little bit of bit of enzyme goes a long way. But on the converse side, actually overproducing enzyme in supraphysiological quantities actually has no impact as detrimental whatsoever. So for those programs, we can accelerate and escalate the dose in quite rapidly. But then there are programs such as Rett where, as you know, there is a relatively narrow therapeutic window, and we have to be a little bit more cautious in accelerating or escalating the dose, despite the fact that we have the MRI platform, which self regulates the proportion of MECP2 that's being produced for Rett. So I would say that we generally start in the same ballpark, but then as we escalate the dose is higher, we do that in a slightly different rate dependent on the therapeutic window we have for each program.

Joon Lee

Thank you.

RA Session II

Thanks, Joon.

Operator

Thank you. Our next question comes from the line of Laura Chico with Wedbush Securities. Please proceed with your question.

Laura Chico

Good morning guys. Thanks very much for taking the question. My first one, I was just wondering if you could spend a minute on the loan agreement and perhaps why you think this makes sense now? And just wanted to clarify, how does that change the cash runway estimates? And then my follow-up, just around expectations for the 35E14 dose in GAN. You'd already seem to have an effect at the lower doses. So just trying to understand which doses or dose would be advanced commercially? Thanks very much.

RA Session II

Hi, Laura. Good morning. And what I'll do is I'll take the first question around the non-dilutive financing and then Suyash, we will turn it over to you for GAN around dosing. So the way that we think about this and kind of from a timing perspective, we felt really strongly that we had the opportunity in an environment where the cost of capital is at historically low rates, the ability to add this finance. And particularly, we're in a situation where the equity capital markets are somewhat volatile and not necessarily accurately valuing innovative gene therapy companies. And because we have such a robust portfolio, a number of programs in the clinic, a number of data readouts here to come later this year and kind of for the foreseeable future and even the opportunity to – the opportunity to reach a GAN approval without the need for additional financing, we thought this was as good a time as any to bring on this non-dilutive capital. I think a couple of things that we talked about is – the terms of this deal were quite attractive. We talked about a 7% interest rate which is a historically low interest rate. We talked about no financial covenants, no warrant coverage. This is about a clean deal as you can get in a single partner to be able to do this with and one that has the credibility, I think, of the name that goes along with it in Silicon Valley Bank. And so for us, it's all about optionality. It's all about being able to move things best-in-class forward and not necessarily have to slow anything down or make any particular trade-offs as we get into the next year. And because we can't predict what's going to happen in the equity capital markets, we thought this was just a wonderful opportunity to be able to add some additional dry powder to the tank. That's literally it. And we were pretty excited about, again, being able to announce this deal partnering with SVB and being able to get into the second half of this year with multiple data readouts. We're talking about GAN high dose data, regulatory feedback around registration pathway on GAN, GM2 gangliosidosis, safety and biomarker data, CLN1 first patient dosed Rett syndrome open clinical trial, right? Just more of these and more of these to come, so I'll pause there and turn it over to Suyash and Suyash, maybe you want to talk about the 1.8E to the 14 total vg dose versus the 35E14 total vg dose.

Suyash Prasad

Absolutely. Thanks for the question, Laura. Yes, you're right. As the 1.8E14 dose looks very, very, very, very good. We see clear stabilization of disease progression at that dose. We have patients out just quite some contributable time at that dose, so showing sustainability of effect and that improvement is clinically relevant clinically meaningful. – i.e., it halts the 8-point decline in the MFM32 scale, which translates to an 8-point improvement every year, 16 points over 2 years, etcetera. And also when you run the basin analysis and we have these slides in our in our corporate debt. We know that that 1.8E14 dose patient who is dosed will have a 98.1% chance of a clinically meaningful improvement. So it's a really solid dose, and the drug would frankly be approvable on that dose. What I will say is that when Carsten Bönnemann and the NIH, and this is a study that's been run at NIH. And for several years, has been run very, very nicely. Carsten initially set out to other dose response to be going all the way up to 35E14 total vg. Now three patients have actually been dosed at a higher dose, and we will have data to share on the 1-year time put on those three patients in the second half of this year. And my guess is that those patients will either show at least the same as the medium high dose of the 1.8E14 or be slightly better. And for these children with this relentlessly progressive neurological deterioration towards death, you have to give them every best chance of having the most significant clinical benefit. What I will say is that as we approach our regulatory meetings towards the end of this year, we have this really wonderful data package. We will have the 3E14 dose as part of the package. And as you know, we have this great natural history study. We have dose responsiveness. We have clear stabilization of the disease at the medium high dose. I expect there will be at least the same in the high dose. We have long-term safety, long-term efficacy long-term durability. So I am looking forward to having those decisions with the regulators. But in terms of commercializing, I think likely it will be the 2.5E14 dose. But as I said, the 1.8E14 would probably be more than up as well. Let me stop there. Thank you.

Laura Chico

Thank you.

Operator

Thank you. Our next question comes from the line of Gil Blum with Needham & Company. Please proceed with your question.

Gil Blum

Good morning everyone and thanks for taking our question. So do you guys have any thoughts on the recent lifting of the Zolgensma clinical hold on the IT administration? And do you think this is just a change in the way the FDA views the risk benefit for IT AAV gene therapy? And I have a follow-up.

RA Session II

Hey, Gil. Good morning. Maybe I'll start, and Suyash, please provide some additional comments. I think for us, we were really excited to actually see that news come out about a week or so ago that not only did the FDA lift the clinical hold on the IT formulation for Zolgensma, but also the fact that Novartis we're going to be conducting a Phase 3 study in the Type 2 and 3 patient population. And again, I think we've seen the data from the original study where Zolgensma demonstrated a significant improvement in the Hammersmith essentially twofold over what would be considered clinically meaningful that was sustained, safe and effective in the patients that were treated with the intrathecal dose. And so we were quite excited by that. We felt like the clinical data, both from an efficacy perspective, but also from a safety perspective supports it. And again, when you think about the totality of data, particularly around the combination of AAV9 and enterthecally, we think, again, this is an extremely effective way and route of administration to be able to deliver directly to the CSF. This has been demonstrated in our very own genome neuropathy study but also in the Amicus CLN6 trial, which has had phenomenal data. Their recent CLN3 studies and then again, we talk about Zolgensma. And so from a regulatory perspective, I believe the clinical hold was lifted based on some NHP toxicology data that the agency asked Novartis to conduct and so I think, again, the fact of the matter that they conducted those additional toxicology results, the fact that Zolgensma has now been in well over 100 sorry, 1,400 patients globally, I think, really speaks to the safety and efficacy of using AAV9 as a gene therapy approach for the treatment of monogenic CNS diseases. And so again, I think this kind of mirrors some of the recent feedback we've gotten from the agency, where they have taken a very pragmatic approach to your toxicology package and then the fact that we go in with three species of tax in most cases, this dovetails nicely with what they are looking for. I'll stop there. Suyash, I know you probably have some additional comments.

Suyash Prasad

Sure. Thanks, RA, and thanks, Gil, for the question. I think that we've had 1 year, 1.5 years where the FDA has seeming to have been clamping down with clinical holds. Both for safety matters and for CMC-related issues in the AAV gene therapy space. I do wonder if that's changing now. Actually, we have the Zolgensma hold lifting recently. And this morning, we also announced the lifting of the hold once again, AAV9 gene therapy for Danon the Rocket Pharmaceuticals program. So I wonder if there is been a bit of a shift in the perspective of the FDA and they are just getting a little more comfortable spending less time on COVID and more time on gene therapy now. I think specifically with our Zolgensma product, it's definitely transferable to the wider wider AAV9 space. It's good news for AAV9. As already mentioned, the clinical data from that intrathecal study in a strong trial was actually very, very positive. We saw clinically meaningful effects on the Hammersmith scale, which is a scale that's used for slightly older children and the CHOP-INTEND because obviously, you're going into SMA Type 2 and Type 3. And the doses are in the E14 ranges. So once again, you can learn a lot quite translatable to our programs as well. The issues have been for safety that's now listed with the NHP study. Our approach to toxicology, as I've already mentioned, is very robust. And thus far, in our discussions with the FDA, they have been very accepting for an acceptable for it. So I'm hoping this is shifting the FDA's paradigm a little bit. But the fact that Zolgensma off clinical hold was good news for AAV as was the lifting of the hole for Danon disease this morning as well.

Gil Blum

Alright, thank you for all the color. And could you maybe give us an idea of the number of patients that you can currently treat with the GMP runs that you've conducted? Would these be sufficient for your initial clinical studies and the programs that you mentioned?

RA Session II

No, it's a really good question, Gil, and we appreciate it, and that's absolutely correct, when we go in and we do a GMP run, not only are we doing GMP runs for our IND-enabling tox package, but we're also doing GMP runs for the entire cohort of a clinical trial because what we want to do is make sure that there is consistency between material giving to the same patient in a particular indication and not necessarily adding any unnecessary variability into a clinical trial by having a certain set of patients treated with one GMP run and then having another set of patients treated with another GMP run. And so what we can do is because of our capacity, we do have the ability to be able to manufacture GMP material for an entire dosing cohort within a clinical trial. So we're pretty excited about that. Not only do we have that material, but we also have material left over for routines to make sure that we could do any type of needed analytical comparability between any type of preclinical material that we also keep and kind of put in the freezer to make sure there is always the ability to go back and do analytical comparability or any recharacterization that would be potentially needed to support a regulatory filing.

Gil Blum

Great. Thank you for taking our question and congrats on the progress.

RA Session II

Awesome. Thanks, Gil.

Operator

Thank you. Our next question comes from the line Eun Yang with Jefferies. Please proceed with your question.

Eun Yang

Thank you. I have a couple of questions regarding 120 on the clinical and regulatory update that we are expecting by end of this year. So will the highest core high-dose core data come out before the regulatory update? So that's the first question. And second question is, so you're going to be requesting on end of phase meeting with the FDA and engage you with AAV by year-end. So do you think you would have an update from the regulatory agency discussions or is it possible that you could request a meeting and waiting for the meeting to happen potentially early next year? Thank you.

RA Session II

Good morning. And it's great to hear from you, and thank you for your questions. So I'll take both of these. So from a disclosure perspective, I think it's likely that we would share the high-dose data cohort before we would disclose any particular feedback from any regulatory agency discussions that we plan to have here in the second half of the year. So that is the cadence from a timing perspective. The goal is to have feedback by the end of the year and not request the meeting by the end of the year. So we will be putting in those submissions. Those meeting submissions here in the next month or so in order to ensure that we will have feedback depending on the workload of the agency, obviously, it's up to them when they grant you a meeting and with COVID. What we've tried to do is to request those meetings early because we know that, in some cases, those meetings can be a little bit delayed. And so we're going to take a similar approach here from a GAN perspective, particularly in the U.S. where we're going to put in the meeting request in time to receive feedback here by the end of the year. In Europe, particularly with MHRA, from a scientific advice perspective, EMA from a scientific advice perspective, those meetings are a little bit more straightforward, to be quite honest. And those agencies have been granting meetings and somewhat of a normal time period, particularly MHRA, you're able to get a face-to-face meeting with them relatively efficiently. So that's the way that we're going to approach regulatory interactions here in the second half of the year. And hopefully, we will have that feedback in time in order to provide an update to the Street by the end of this year. But certainly, that's our going-in approach.

Eun Yang

Okay, thank you for the clarity. And I have one quick question on the financials. So in second quarter, R&D, you have around \$10 million in R&D manufacturing and other raw material purchases. So going forward, the third quarter, I mean, second half of this year, should we assume that R&D increases quarter-over-quarter would they be more normalized from second – the first quarter run rate? Or with all the clinical programs are advancing. And would you expect R&D to increase from the second from the second quarter run rate? Thank you.

RA Session II

Really, really good question. I'll start and Kamran, maybe you want to provide some additional color. I think as we discussed, we've had a number of GMP manufacturing campaigns to support multiple clinical trial starts here in the first half of this year, particularly in the second quarter, and those were being conducted in collaboration with our partners over at Catalent. And again, the goal was to have high quality, robust material that we had a high degree of confidence in that would be able to treat our patients effectively. With the portfolio as large as ours in kind of the way that the programs are kind of running from a cadence perspective, we expect to have a number of new programs move into the clinical development next year as well as a number of programs that are currently in IND/CTA enabling studies that will be moving into – that will be moving into clinical development as we get into 2022. And so I think you will see some level of consistency and normalization. But with the breadth of the portfolio that we have, there will certainly be some growth. I will stop there, Kamran, maybe you want to provide some additional color.

Kamran Alam

Yes. Thanks, RA and thanks for the question, Eun. So ultimately, as we continue down the clinical trial initiation, numerous programs in our portfolio, you can expect to see some additional clinical trial expenses getting incurred in second half of this year and into 2022 as well.

Eun Yang

Okay. Thank you very much.

RA Session II

Thank you.

Operator

Thank you. Our next question comes from the line of Raju Prasad with William Blair. Please proceed with your question.

Raju Prasad

Thanks for taking the question. I kind of just want to understand how the kind of commercial scale-up and identification of patients is going, maybe particularly in 120, a lot of questions that we get are kind of related to how big that market opportunity is. So, maybe if you could just talk about the number of kind of prevalent patients that you have identified and how you are kind of looking at building up the commercial scale up? And then I got another follow-up.

RA Session II

It's a really good question and good morning Raj. And so the way that we are thinking about patient identification, we are actually being quite pragmatic, particularly today. So, not only have we brought on our Head of – our Chief Commercial Officer, who led the commercialization of Zolgensma and when he joined Taysha, he was actually the U.S. General Manager for Zolgensma. We have also brought on the leadership team below him, our VP of Marketing who was the VP of Marketing on the Zolgensma program, our Head of Payer Engagement who also led that effort on the Zolgensma program as well as our Head of Product Distribution, who also led that program in Zolgensma. So first and foremost, it was about bringing on people that knew exactly what they were talking about. That was kind of the first and foremost thing that was important to us. From a patient identification perspective, what we have done is we partnered not only with Invitae to a previously announced partnership, which we are continually expanding on. We have also recently partnered with GDX particularly around patient identification ex-U.S. And what we know about this population is that this is really a prevalent population split into two segments; early onset GAN and late-onset GAN. Early onset GAN being kind of the more progressive form of the disease that typically progresses to death around late-teens to early-20 and then late onset GAN that typically presents in kind of the teenage years and has a significant quality of life impact, but typically doesn't progress to death. And these patients tend to live into their fifth decade of life, albeit it's a pretty compromised quality of light. And so the majority – the split between those two populations is about 25%, 75%, 25% being to the early onset GAN, 75% being in the late onset GAN. And because that's the larger population and those patients tend not to progress as quickly where we are really able to build up a fairly large prevalent population. So, when you think about this, this is a real prevalent opportunity. The incidence of these – the incidents here would be relatively small. We are talking in the U.S. somewhere around 30 or so – or U.S. and Europe, somewhere around 30 or so patients. But the prevalent population is actually quite big. And the late onset patients are all identified, but they haven't been genotyped. And I think that's the important piece, and this is what we are going to be doing with gene DX is really going out partnering with the CMT Foundation. So, we are working through our partnership discussions right now with the CMT Foundation really around genotyping, all the CMT2 patients that are currently in their network of clinics. And they have done a fantastic job with a number of validated clinical sites throughout the U.S. and Europe. And the way you think of that CMT, the way you would think about the GAN population or the late onset GAN population that is in that CMT group is there is about 4 million births in the

U.S. per year. The CMT incidence is about one in 2,200 or 2,200 patients, of which type two is about 17% of that. And then around 6%, it could even be higher, we have seen in some literature. But the number that we actually use for our 2,400 patients is around 3%. But the literature goes and is fully disclosed that 6%. We want to be a little bit more conservative. But up to 6% of CMT type two population has a confirmed GAN mutation. We have actually seen literature like I said, that gets into the double-digits. But this is ultimately how we back calculate our epidemiology and get to the numbers, the 2,400. Likely, the number is a lot higher in Europe – in U.S. and Europe, it's probably closer to about 3,000 to 3,500, but we wanted to be conservative with our estimates. Hopefully, that helps.

Raju Prasad

Great. Thanks. And then with the FDA panel coming up next month, obviously, we have seen some clinical holds come off with Zolgensma as well as Rocket's Danon disease program this morning. I just wanted to kind of get your thoughts on how to look at how are you guys looking at that that panel moving forward?

RA Session II

Awesome. Suyash, maybe do you want to take that question?

Suyash Prasad

Sure. Yes. Thanks for the question, Raju. I think, yes, it's going to be interesting. I am looking forward to seeing the panel, actually in seeing how the discussion goes. The way the FDA have structured the panel looking at five specific areas. They look for integration and oncogenicity risks, toxicity, thrombotic microangiopathy tissues and the nonclinical front of toxicity especially related to DRG and then clinical finds on neurotoxicity that based on brain MRI findings. So, I think we are actually just looking forward to listening and learning. All those five areas that if they are talking about, we have given us some considerable thought to and have mitigated against them, both by looking at them, looking for some of these issues, specifically in our preclinical work. For example, we look at DRGs in all of our preclinical NHP studies now. And thus far, we haven't seen any signs of DRG inflammation. And not just looking at things from the nonclinical perspective, but you also build in appropriate mitigations into the clinical trial design as well, i.e. we built in monitoring to local hepatotoxicity tissues. We have built in clinical monitoring to look at platelet counts, which gives a clue to early issues with thrombotic microangiopathy. We look at – we actually have – it's been an interesting discussion with the regulators just in general about how to monitor for DRG inflammation over – in the clinical trial. And essentially, we come up with a good plan that the regulator has been very acceptable of, which is looking at reflex testing periodically at each visit. So specifically, the six reflexes in the body, ankle, knee, etcetera. And also nerve conduction studies at baseline and the three-month period to the first year thereafter. So, we have been giving this a lot of thought. I am not expecting to hear anything at this meeting that's a big surprise to us. I am hoping to learn more that I am hoping to go into more detail around the mechanism of what's happening. And I am also hoping that they take the safety issues that they are thinking about considering and they look at it from the context of the balance of risks and benefits in the patients because once again, for the patient communities that we are trying to serve, these are children who have demonstrating will offer the rapid progression towards that. And in that context, some minor safety issue should not be – should not preclude a charter being included in the clinical trial or being dosed.

RA Session II

Suyash, maybe you want to just comment on some of the recent NHP data that we have obtained in our GAN program because I think this kind of plays into just kind of what's going on in the field.

Suyash Prasad

Sure. And yes, it's a good reminder. Alright. Thank you. Yes, we recently conducted another study in the – for our GAN program, specifically in NHP study that looked at our re-dosing approach. But as part of that assessment, we actually gave a clinically meaningful dose of GAN factor and re-dose these NHPs, re-dosed some of these NHPs eight weeks subsequent to dosing. And we took on all the NHPs, those that received both one dose and those that had received two doses. And we looked very carefully of any signs of toxicity or inflammation in the new property. And with a specific focus, of course, there is lots of interest in the DRG and spinal cord and neuronal tissue. So, no evidence whatsoever of any kind of information in any of the samples we took. So, from our perspective, it was very reassuring and it's specifically a vector is already in the clinic at the moment for us.

Raju Prasad

Great. Thanks.

RA Session II

Thanks Raju.

Operator

Thank you. Our next question comes from the line of Yun Zhong with BTIG. Please proceed with your question.

Yun Zhong

Hi. Thanks very much for taking my questions. So, first question on GM2 program. Do you expect the biomarker data to include substrate reduction? And how long do you think the patient will need to be followed for you to see any signals suggesting clinical efficacy, please?

RA Session II

Thank you. Good morning. And maybe I will take the first question and Suyash can take the second. From a data disclosure perspective, what we are expecting to disclose will be safety data from the Queens Phase 1/2 study as well as HEXA enzyme activity data from the CSF. Those will be the two measurements that we will be disclosing and then in subsequent disclosures that we have moved into the first half of 2022 and then later in 2022, we will be providing some additional disclosures around other key aspects of the disease. But for the second half of this year, those will be the two markers that we will be providing feedback on. Suyash, maybe you want to take on second question around the – your second question around kind of timing of when you would see kind of clinical impact.

Suyash Prasad

Sure. Thanks Yun, for the question. I think it's an important question, just the cadence of events, what's going to happen after we dose a patient with GM2, what's the normal course, what's the expected course of events. So, RA is quite correct and that the biomarker data we will be showing will be HEXA levels in the CSF and in the blood. You asked specifically about GM2 ganglioside reduction. We are, of course, measuring that. My guess is that will take a little bit longer than the HEXA to change. And so that will be – there is also a late disclosure. And in terms of clinical improvement, my hope is that I anticipate – if you think about the cadence of events, you dose a patient, you should get much more transient expression, maybe three weeks after dosing. So, I guess by the first month, you should be seeing a nice increase in the HEXA activity. And then by three months after initial dose, it should be maximal. My guess is that the clinical stabilization, you wouldn't start to see until about three months. I would hope to see the beginnings of some change in clinical progress by about three months. It may take even longer, it may be six months. But my guess is that treatment will start seeing the signs of [indiscernible].

Yun Zhong

Okay. And then on the Rett syndrome program, do you have a target range that you hope to see that the gene transiting expression will fall into that range or would you just rely on the self-regulatory mechanism of the technology to look more on the clinical kind of the end point, please?

Suyash Prasad

Yes, this...

RA Session II

Another good question – go ahead Suyash. Go ahead please.

Suyash Prasad

Well, I will start – alright you jump in if I miss anything out. It's a really good question Yun. And it's been – we have had a number of advisory boards for Rett, and we have asked everybody the same question, what is the – what is our range of MECP2 expression, is it – do we need to get exactly 100%, is it between 80% and 120%, what's the upper limit? We know that 200% is too much because you get degradation, but there is 150% levels okay. And none of the clinicians can answer that. What I will say is that in the animal studies, when you hit about 150%, that was a MECP2, you are starting to see some kind of deterioration. But our intent is to try and keep the level of MECP2 generally physiological, i.e., about normal, being a little bit more conservative. The way Steve Gray has designed the microRNA binding sites. They just they run a little bit lower, lower than 100%, so between 90% and 100% levels of expression. Now of course, we can't measure MECP2 expression in a chart because in order to do that, you would have to buy up to the brain and look at levels of MECP2 expression. So, it's technically possible, but ethically, you wouldn't be able to obviously take that biopsy except, of course, in the unfortunate penicillins to die would perform an autopsy and get the data in that way. But we wouldn't be able to measure MECP2 expression in the clinical setting in the vast majority of cases. And so we are going to be relying in particular on clinical treatment. But the target is going to be physiological levels, which the self-regulatory feedback loop is able to obtain very, very nicely.

Yun Zhong

Great. Thank you.

RA Session II

Thank you.

Operator

Thank you. Our next question comes from the line of Mike Ulz with Morgan Stanley.
Please proceed with your question.

Mike Ulz

Hi guys. Thanks for taking the question. Just for the GM2 program, you are on track to give an update sort of later this year. But assuming you get positive results there, are you planning to advance a single dose into the Phase 1/2 U.S. study or might you decide to advance multiple doses there? And then secondly, do you need to make any process modifications to the material you plan to use in the U.S. study versus the material that you are currently using in the Queens study? Thanks.

RA Session II

Hi Mike. Thanks for the question. I will take the second question and Suyash maybe you want to talk about dosing. But to your second question, the material that we produce for the Canadian study is made in the exact same facility with the exact same process that the U.S. clinical trial material is being manufactured with. So, that will be the exact same like-for-like material with the same analytics, same product characterization, same release testing. So, we are pretty fortunate for that. And the reason why we do that is to make sure that if we do see a remarkable result that we are able to take that to regulators and then start to have discussions around regulatory pathway relatively quickly versus having to go back and do some type of process development change. So, that – so, to your original question, that's the exact identical material from the same facility, same process. Suyash, maybe you want to just talk about dosing.

Suyash Prasad

Sure. Yes. Thanks for the question, Mike. And the good thing about GM2 is one of the programs that has this very wide therapeutic window that I have already touched on i.e., you don't need much to get a significant improvement. We are seeing 5% levels of enzyme will be more than enough to result in dramatic improvement. And I would say this based on the current data that exists that show that infants for the disease have less than 0.1% activity of HEXA. When you go up to about 2% to 3%, i.e. the adult forms of the disease, they actually have a normal life span by that. So, if you are hitting 5%, then more likely, that will be enough to give you quite a dramatic clinical improvement. So, you don't need much to get to a level that results in considerable clinical improvement. On the other end, you can actually express the enzyme super physiologically, and we have seen this in our toxin pharmacology, preclinical work. And it's a very safe enzyme. So, you can actually express it super physiologically on the other end. And there are no adverse consequences there. So, we have a very broad therapeutic window. Now to give you some context, 14 total VG is a high dose being given intrathecally, but it's a relatively low dose in comparison to systemic administered gene therapies. So, we actually think that we are likely to have quite a significant benefit with our 5e14 dose. Now if we are seeing a good benefit in that 5e14 dose from a biomarker perspective and more important from a clinical perspective, we will probably just go ahead with the 5e14 dose in the U.S. study and file on that data. If indeed, we think there is room for improvement. We have absolutely the opportunity to go higher if we need to. My guess is we would probably go from a 5e14 to 1e15 total VG. So, we have that possibility of doing that. The study designed for the U.S. is not fully finalized yet, and I think it's fair that we are going to learn a little bit from the Canadian study before we actually finalize the design of the U.S. study. But 5e14 I think is likely to be good enough. But if there is any potential room for improvement, we absolutely haven't scoped to go to the 1e15 dose.

Mike Ulz

Great. Thank you.

RA Session II

Thanks Mike.

Operator

Thank you. Our last question comes from the line of Kristen Kluska with Cantor Fitzgerald. Please proceed with your question.

Kristen Kluska

Hi, good morning. Thanks so much for taking my question. For the GAN program, could you please discuss what you hope to see on some of the assessments beyond MFM32, including muscle strength and brain imaging, especially in light of the understandings and the correlation that were reported with MFM32, including in the recent Brain publication? And I guess, specifically, what signals would help you further validate that the gene therapy is slowing down the disease progression? Thank you.

RA Session II

Hi Kristen. Good morning. Suyash, I will turn it over to you. I think probably some of the best data that we have is something that we just recently shared, particularly around visual acuity. I think that particular end point is going to be extremely clinically meaningful to patients because it's such a quality of life endpoint. And Suyash maybe touch on that and then some of the other endpoints that Kristen discussed.

Suyash Prasad

Sure. Thanks for the question, Kristen. And I could probably spend a good 10 minutes or 15 minutes talking about this. There is such a wealth of data being collected in this NIH study is really remarkable. So, we have seen the MFM32, which is – I always describe it as CHOP INTEND for older children. You have got three domains looking at central strength, proximal muscle strength of arms, shoulders and hips and distal strength, fingers and toes. And we see clear stabilization of disease at the medium, low and the medium high dose in this progression. MFM32 drops by eight points a year in kids with GAN. This is a clinically significant decline every year. Four points to forget is deemed to be clinically meaningful. And we showed clear stabilization of disease at that medium, low and the medium-high dose. In conjunction with that, as RA has mentioned, we have now presented some data on vision and visual acuity. And specifically, we look at something called the LogMAR. And this is a bit like the snow and chart. When you get to the opposition, you sit there and you read the letters off the wall. The LogMAR does this within a more rigorous kind of research-focused manner. And what we have seen in patients that have been treated, we have seen a dose response difference in stabilization of LogMAR. So, children who have GAN, their vision deteriorates over time. And it's one of the most significant, most worrisome clinical effects. I think one of the things that parents worry about so much the fact that child loses their ability to see because more than anything it means they stop being able to communicate in the same way as that also moves the ability to articulate words and hear, for example. So, it's very troubling from a patient and family perspective. And what we see, and there is a nice slide in our corporate deck now, you see that a lot loss going about 0.3 when you need glasses, score of about 0.6 is when you have significant visual deterioration when you are hitting about 1.3, that's when you are legally registered as being blind. After the vast majority of patients, apart from one outlier in our data set, the LogMAR scale deters over time and progresses towards blindness. When you treat you actually halt the decline. So, it's similar to the MFM32 where visual acute is declining, you treat and then suddenly it stabilizes out at the level of function. So, you are preserving vision for the duration in these children. Certainly, we have seen a significant duration of visual preservation in this particular study. So, vision is key. In terms of other endpoints, we are looking at neuropathy type scores and looking at sensation. My guess is that sensation is going to improve or stabilize, but it's one of those parameters that's quite hard to measure. You also alluded to muscle strength. My guess is that muscle strength will also improve already stabilized the ongoing deterioration in myometry will stabilize. And I think that's also true for some of the other major assessments such as the time

tell me to walk test, they [indiscernible] etcetera. And Carsten and the team were also looking at respiratory muscle strength, and I anticipate once again that the forced vital capacity will stabilize, the way the MFM stabilizes out. And I say these things with confidence because all of these assessments are highly, highly correlated in the natural history study in the brain paper that you mentioned earlier. Now in addition to the clinical measures, we are also doing a number of tests in the study as well. So, we are performing nerve conduction studies i.e., looking at electrophysiology, looking at MRI scans. And also importantly, we are performing biopsies in these patients, too. I am looking forward to seeing how the days will pan out, but my guess is the vast majority will reflect in there, what we have seen is the MFM32.

Kristen Kluska

Great. Thank you for taking my question.

RA Session II

Thanks Kristen.

Operator

Thank you. Ladies and gentlemen, that concludes our question-and-answer session. I will turn the floor back to Mr. Session for any final comments.

RA Session II

Thank you, operator, and thanks, everyone, for joining the call today. We look forward to building on the momentum ahead until the end of this year, and we will continue to keep you updated on our progress throughout the remainder of this year. Operator, we will turn it back over to you.

Operator

Thank you. And this concludes today's conference. You may disconnect your lines at this time. Thank you for your participation.

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Taysha Gene Therapies, Inc. (NASDAQ:[TSHA](#)) Q2 2022 Results Conference Call
August 11, 2022 8:00 AM ET

Company Participants

Dr. Kimberly Lee - Chief Corporate Affairs Officer

RA Session - President, Founder, and Chief Executive Officer

Dr. Suyash Prasad - Chief Medical Officer and Head, R&D

Kamran Alam - Chief Financial Officer

Dr. Frederick Porter - Chief Technical Officer

Conference Call Participants

Joon Lee - Jo Securities

Gil Blum - Needham & Company

Mike Ulz - Morgan Stanley

Eun Yang - Jefferies

Jack Allen - Baird

Yun Zhong - BTIG

Sami Corwin - William Blair

Rick Miller - Cantor Fitzgerald

Operator

Greetings. Welcome to the Taysha Gene Therapies Second Quarter 2022 Financial Results and Corporate Update Conference Call. At this time, all participants are in listen-only mode. Following management's prepared remarks, we will hold a brief question-and-answer session. As a reminder, this call is being recorded today, August 11, 2022.

I'll now turn the call over to Dr. Kimberly Lee, Chief Corporate Affairs Officer. Please go ahead.

Dr. Kimberly Lee

Good morning, and welcome to Taysha's Second Quarter 2022 Financial Results and Corporate Update Conference Call. Joining me on today's call are RA Session, II Taysha's President, Founder and CEO; Dr. Frederick Porter, Chief Technical Officer; Dr. Suyash Prasad, Chief Medical Officer and Head of R&D; and Kamran Alam, Chief Financial Officer.

After our formal remarks, we will conduct a question-and-answer session and instructions will follow at that time. Earlier today, Taysha issued a press release announcing financial results for the second quarter ending June 30, 2022. A copy of this press release is available on the company's website and through our SEC filings.

Please note that on today's call, we will be making forward-looking statements, including statements relating to the safety and efficacy and the therapeutic and commercial potential of our investigational product candidates. These statements may include the expected timing and results of clinical trials for our product candidates, our expectations regarding the data necessary to support regulatory approval of TSHA-120 and the regulatory status and market opportunity for those programs as well as Taysha's manufacturing plans.

This call may also contain forward-looking statements relating to Taysha's growth and future operating results, discovery and development of product candidates, strategic alliances and intellectual property, as well as matters that are not of historical facts or information. Various risks may cause Taysha's actual results to differ materially from those stated or implied in such forward-looking statements.

These risks include the uncertainties related to the timing and results of clinical trials and preclinical studies of our product candidates, or dependence upon strategic alliances and other third-party relationships, our ability to obtain patent protection for discoveries, limitations imposed by patents owned or controlled by third parties and the requirements of substantial funding to conduct our research and development activities. For a list in description of the risks and uncertainties that we face, please see the reports we have filed with the Securities and Exchange Commission.

This conference call contains time-sensitive information that is accurate only as of the date of this live broadcast, August 11, 2022. Taysha undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call, except as may be required by applicable securities law. I would now like to turn the call over to our President, Founder and CEO, RA Session II. RA?

RA Session

Thank you, Kim. Good morning, and welcome, everyone, to our 2022 Second Quarter Financial Results and Corporate Update Conference Call. We continue to execute on the advancement of our core clinical programs and are excited to announce important data from our Giant Axonal Neuropathy, or GAN program and Rett Syndrome program. These data include stabilization and recovery of sensory nerve conduction in patients with GAN following treatment with TSHA-120 despite expectations of a rapid and irreversible decline in sensory function in untreated patients observed in natural history.

Importantly, the measure of sensory nerve conduction represent a definitive clinical end point. In addition, we now have positive analytical comparability data demonstrating that our commercial grade and clinical trial material are functionally indistinguishable across all key quality attributes. Frederick Porter, our Chief Technical Officer, will provide more details shortly.

On the regulatory front, we had positive discussions with the U.K.'s Medicines and Healthcare Products Regulatory Agency, or MHRA, and received feedback that we believe support our regulatory strategy. With full comparability data in hand, in conjunction with additional clinical data plus feedback from the MHRA, we believe this provides the most robust package to support our ongoing regulatory engagement. We expect to provide additional regulatory feedback, including from the FDA by the end of this year.

For Rett Syndrome, we are highly encouraged by late-breaking neonatal data in preclinical mouse models, demonstrating new normalization of survival and normalization of behavior. As you will hear from Suyash shortly, we believe the totality of preclinical data generated to date, by TSHA-102 is a comprehensive data set in Rett Syndrome that further supports earlier treatment and clinical advancement of this promising product candidate. We look forward to reporting preliminary Phase I/II clinical data in adult females with Rett Syndrome by the end of this year.

Now I'll turn the call over to Fred to discuss updates on our comparability data for TSHA-120 again. Fred?

Dr. Frederick Porter

Thanks, RA, and good morning, everyone. In the next few slides, I'll review our manufacturing progress for the GAN program and our comparability package that supports the transition to our final commercial manufacturing process.

Next slide. Our manufacturing development program for TSHA-120 was kicked off in mid-2021, one we initiated our partnership with our CDMO partner to deliver our commercial-ready manufacturing process. We've rapidly executed several tech transfer runs leading up to production of our 500-litre pivotal batch in April of this year. In parallel, we progressed several key analytical development efforts internally to deliver a comprehensive data package to support product release and comparability in line with agency guidance for pivotal stage programs.

Next slide. Our commercial grade manufacturing run was highly productive, yielding over 200 vials of finished drug product filled into 2 separate lots that are currently undergoing release testing. After inspection and testing, over 50 patient doses are available for clinical use. In addition to supporting the ongoing clinical study, these lots were enrolled in a comprehensive stability study to provide critical shelf-life data in support of our BLA filing. The 500-litre production also represents our final commercial scale, which aligns with our commercial projections. We believe this high-yielding process supports a favorable cost of goods and ensures us that we will be able to meet commercial demand with a reasonable number of batches annually.

Next slide. In considering the analytical panel for product release and comparability, there are 4 key areas of importance for gene therapies, strength, purity, potency and safety. These important attributes have informed the panel of assays that were in the process of validating at our CDMO partner to support both product release and comparability. The analytical method selected aligned with agency expectations in terms of accuracy, precision and robustness for measuring each product attribute.

Next slide. In order to assess comparability of our clinical trial material and the newly manufactured material from our commercial manufacturing process, we've applied this panel of release assays for side-by-side testing with our comprehensive assay panel. Shown here are 8 of the most critical attributes that reflect on the purity, potency and safety of our product.

First, all results demonstrated that both clinical trial material and commercial grade material are a high purity and lack significant levels of host cell or process contaminants such as protein and DNA or aggregated species. Vector purity was in excess of 95% for all 3 lots, and host cell protein contamination was below detection. Aggregation of all lots was also very low. Both cell and plasma DNA contamination are also important attributes to discuss with regulatory agencies since carryover represents a theoretical immunogenicity or oncogenicity risk.

Residual plasma and wholesale DNA were similar for all lots indicating a consistent product profile for both lines. Empty capsids are a key attribute for AAV vectors since empty capsids can stimulate immune responses to the vector and reduce potency. All 3 lots were highly enriched in full particles and meet recent FDA draft guidance in terms of analytical methodologies and present full capsids.

Finally, potency of AAV vectors is a key measure that is intended to correlate with clinical efficacy. We developed several product-specific potency assays to measure functional activity of our product, which is reported relative to a reference standard. These assays recapitulate the biological activity of TSHA-120 where the AAV transduction process of cell entry, DNA and packaging, gene transcription and translation occur in an immortalized mammalian cell line.

Functional activity is measured by quantitation of TSHA-120 transgene RNA levels or gigaxinin protein expression as 2 independent and complementary readouts. We observed good agreement with both methodologies and the activity of all 3 GMP lots against our reference, which gives us confidence that the lots are of high and comparable activity.

Overall, these results support our view that our early clinical trial material and commercial-grade material are biochemically and biophysically similar and should perform identically in a clinical study. We plan to present these final study results with additional regulatory agencies and anticipate regulatory feedback by the end of this year.

Next slide. Recently, regulators have encouraged sponsors to conduct deeper analysis of product contaminants not covered by standard release assays to better assess product safety and comparability. To comply with this guidance, we have added PacBio next-generation sequencing to our product characterization panel to better understand the nucleic acid composition of our products.

This method not only allows us to identify the source of nucleic acid, but also the fragment size, sequence variability, which also need to be considered when assessing AAV safety and efficacy. Our analysis of clinical trial material and commercial-grade pivotal batches demonstrates that the source and composition of transgene and contaminating host and plasma DNA is nearly identical and provides further support that the nature of our product is unchanged between our early clinical and commercial-grade batches.

Next slide. In summary, we have successfully executed 6 batches of TSHA-120, our pivotal 500-litre scale GMP batch was productive, yielding over 5 -- excuse me, 50 doses for the high-dose cohort, which positions us for future BLA-enabling activities and commercial production.

Importantly, our comprehensive comparability analysis demonstrated that the clinical grade material and commercial-grade material are nearly identical by key critical quality attribute measures, including next-generation sequencing analysis. We've also made rapid progress developing a product-specific potency method, which is on track for validation and product release, which aligns with regulatory expectations. We feel this progress supports a strong regulatory package that we will discuss with additional regulatory agencies this year, including the FDA. I'll now turn over the call to Suyash to discuss additional program updates for GAN. Suyash?

Dr. Suyash Prasad

Thank you, Fred, and good morning, everyone. As RA noted earlier, we continue to make notable progress in advancing our clinical programs for GAN and Rett Syndrome and expect exciting milestones throughout the remainder of the year.

I'll begin with recent updates on TSHA-120 for GAN. Building on the positive clinical efficacy and safety data and long-term durability data that we reported earlier this year, we are pleased to report new nerve conduction study data for TSHA-120 in GAN. We are grateful to our partners of the NINDS for leading the GAN natural history study and the interventional trial under the leadership of Dr. Carsten Bonnemann, principal investigator at the NIH.

Next slide. Nerve conduction studies are a neurophysiological measure and the specific measure of relevance to GAN is the sensory nerve action potential or SNAP which is considered a definitive clinical endpoint. The test is performed by applying an electrical stimulus to the sensory nerve fibers and recording the actual potential at a point further along the nerve. There are 3 main parameters. The first is the amplitude of the action potential, which is the peak-to-baseline measurement and functional significance is that this is related to the number of axons in a nerve.

With axonal degeneration neuropathies, the primary feature is a markedly reduced sensory nerve action potential or SNAP amplitude. The next parameter is latency, which is the time from stimulus to an initial electrical deflection. This can be compromised in the demyelinated neuropathies. Lastly, conduction velocity is the speed with which the electrical signal travels down the nerve. This can be affected by axonal loss, but more so with demyelination.

The NIH natural history study suggest rapid and irreversible decline in centric function early in life in patients with GAN. SNAPs are within the normal range early in life and then undergo a rapid reduction in SNAP amplitude around the age of symptom presentation. This graph depicts the median SNAP amplitude per age for the natural history population in the NIH study. The horizontal black line represents the lower limit of normal.

As you can see, the youngest chart on this graph is approximately 2 years of age and as a SNAP well within the normal range. As children reached the ages of 3 or 4 years, which is the usual age of symptom presentation, the SNAP deteriorates markedly. You may recall that the initial symptomatology in the 3- to 4-year old includes unsteadiness and a wide-based gate, reflecting the fact that they lose the ability to feel the ground beneath their feet.

It is, therefore, unsurprising that the nerve conduction studies reflect this symptomatology. The first green line depicts the fact that every patient with GAN has an abnormally low SNAP amplitude by the age of 4 years, reflective of compromised sensory neural function. The second green line indicates that 100% of patients have a fully absent snap by the age of 9 years, which will be considered to be irreversible.

Next slide. This image is the same data as the previous slide, but with a line of best fit added to demonstrate the rapid decline in SNAP attitude from normal to absent at an early age. Next slide. Of the patients treated in the efficacy dose onto the study, 42% or 5 of 12 patients had a positive SNAP past the age of 9 years and of the last patient visit, which is remarkable considering that none of the natural history of patients had a positive snap past the age of 9 years. The specific values for the 5 patients in question are shown in the graph on the right, where one of the patients demonstrated near-complete recovery and continued on an upward trajectory from a baseline of 0 at the time of treatment.

Next slide. Many of the patients who were dosed in the interventional trial had an absent SNAP response and would not be expected to recover. From this graph, you can see that 100% of patients treated with TSHA-120, who had a positive sensor response initially maintained a positive response after treatment rather than continuing to decline to 0 as would normally be expected. Once SNAP reaches 0, sensory function is considered non-recoverable. Notably, 100% of these patients, which is 3 of 3, have a positive value at baseline and maintained a positive SNAP at the last study visit. The longest span is 3 years to date and the patients continue to maintain an upward trajectory.

Next slide, please. These 5 graphs demonstrate individually plotted patient SNAP changes from baseline and importantly, includes the patient running data from the natural history study. There is continuing improvement in SNAP amplitude from either a declining snap or an absent snap. Importantly, and remarkably, 2 patients had a SNAP amplitude that had been absent for over a year in the natural history study and after dosing, demonstrated consistent and sustained improvement. This recovery of function in a neurophysiological measure that is definitive and consistent over time is contrary to natural history and exciting to see.

Next slide. Earlier this year, we shared positive pathology data from nerve biopsies which confirmed the fact treatment with TSHA-120 can stimulate active regeneration of axons. We now have the entire data set demonstrating 100% of TSHA-120 treated patients had regenerative nerve clusters present 1 year after treatment in the biopsies. Peripheral nerve biopsies were obtained at baseline and a 1-year post gene therapy transfer and superficial and radial sensory nerve. Analysis of 11 of 11 evaluable samples completed to date, consistently demonstrates an increase in the number of regenerative clusters at year 1 compared to baseline. The remaining 2 samples were unable to be assessed due to biopsy limitations.

Collectively, these data confirm the presence of regenerating node clusters, suggesting active regeneration of nerve fibers and improvement in disease pathology. This, coupled with the nerve conduction study data provides evidence that the peripheral nervous system can not only respond to treatment, but actually improve as opposed to just stabilize. Here, we have included a representative patient case study showing the superficial radial sensory nerve at baseline and 1 year post treatment with TSHA-120.

At baseline on the left, the arrow identifies a giant degenerating Axon and the star identifies a regenerating cluster. On the right is what the nerve looks like 1 year after treatment. The yellow arrows are indicating regenerative clusters, which as you can see, are notable in number. This pathology data and the neurophysiology are suggestive of recovery of neuronal tissue after administration of TSHA-120 and such endpoints, given their unbiased and definitive nature are often viewed favorably by regulatory agencies.

Next slide. We believe our GAN program includes a comprehensive set of evidence generated across diverse disease manifestations, supporting a robust clinical package. These include MFM32 motor function assessment of TSHA-120 treatment demonstrating clinically meaningful slowing of disease progression across all therapeutic dose cohorts compared to natural history decline with a durability of effect. Electrophysiologic nerve conduction studies provided definitive clinical endpoint and support recoverability, stabilization and, in some cases, improvement in sensory response in patients treated with TSHA-120.

Nerve biopsy histopathology confirmed that treatment with TSHA-120 detected the presence of regenerative nerve clusters suggestive of active regeneration of nerve fibers. Pathological biomarker measurements of rectal nerve fiber layer thickness as assessed by optical coherence tomography, demonstrated stabilization and prevention of the visual loss following TSHA-120 treatment. Visual acuity, as assessed by LogMAR also stabilized after treatment. And lastly, we heard from Fred earlier about how an extensive panel of release assays demonstrated that the clinical and commercial-grade material were comparable across key quality attributes and confirmed by next-generation sequencing.

Next slide, please. Now let's review the MHRA regulatory feedback we have received to date for our GAN program and discuss how this feedback supports our continued regulatory discussions. We believe this initial feedback, coupled with the CMC comparability data that Fred discussed, positions us well to further advance TSHA-120 through regulatory approval.

Next slide. A number of recent product approvals and positive regulatory opinions for therapies targeting rare CNS indications and indeed non-CNS gene therapies, especially in the context of unmet clinical need, points to flexibility in the current environment from a regulatory filing perspective. This includes a number of agreements from regulatory agencies for the use of accelerated or conditional pathways to approval. Some examples include EliCell with treatment of cerebral leukodystrophy, or STARZ, the treatment of AADC deficiency, SRP-9001 for Duchenne muscular dystrophy and tofersen SOD1-ALS.

Next slide. Our discussions with the MHRA have been collegial, collaborative and helpful. The MHRA agreed with our commercial manufacturing and release testing strategy, including potency assays. They recommended dosing a few patients with commercial-grade material, which will be released in September 2022. And lastly, it was supportive of our proposal to perform validation work, including patient and family feedback, which is ongoing on the MFM32 as a key clinical end point. We believe this positive feedback from the MHRA in conjunction with the totality of preclinical data generated to date for TSHA-120 represents a robust package supporting additional discussions with regulatory agencies. We expect additional regulatory feedback, including from the FDA by year-end.

Next slide. We continue to work with regulatory agencies with the goal of achieving conditional approval in Europe and accelerated approval in the United States based on EMA and FDA industry guidance for gene therapies in neurodegenerative diseases. Based on key registrational requirements from regulatory agencies, including the FDA and EMA, we have outlined some possible scenarios for approval. With the EMA, we believe there is potential to file for conditional approval based on current data set for EMA guidance documents. For the FDA, the first scenario was immediate filing for approval based on the current data set and comparability.

Alternatively, we may need to dose a few more patients to demonstrate comparability of clinical effect between clinical and commercial-grade material, which is a similar approval pathway for Zolgensma in spinal muscular atrophy. The last scenario is to perform a new pivotal trial, which we think is unlikely, given the recently published FDA guidance document on gene therapies for neurodegenerative diseases and the extensive long-term safety and efficacy data set available. MHRA feedback further aligns us with scenario 2, which is our base case. We expect to have additional regulatory guidance, including the FDA by year-end. As a reminder, TSHA-120 previously received orphan drug and rare pediatric disease designations from the FDA.

Next slide. Now let's turn to the late-breaking preclinical data we reported today for TSHA-102 in Rett Syndrome. Next slide. As a reminder, Rett Syndrome is an X-linked neurodevelopmental disorder that is characterized by mutations in MECP2, a protein essential for neuronal and synaptic function in the brain. Female heterozygous patients with Rett syndrome are Mosaic carriers of normal and mutated MECP2. The challenge in gene replacement therapy of MECP2 is finding the appropriate balance of sufficient physiological expression to correct the deficiency whilst also avoiding overexpression and the associated toxicity. The estimated prevalence of Rett Syndrome is 350,000 patients worldwide with an instance of 1 in 10,000 female births worldwide.

Next slide. Because of this spectrum and risk of toxicity, development of a gene therapy for Rett Syndrome requires a regulated expression of MECP2. Previous MECP2 gene therapy approaches, of course, dose-dependent side effects after intra-CSF administration in wild-type and Rett Syndrome knockout mice. We have developed a novel mRNA responsive target sequence called miRARE to regulate the expression of the MECP2 transgene and prevent the risk of overexpression toxicity. We believe our approach provides a superior therapeutic profile to that of unregulated MECP2 gene replacement.

Next slide. TSHA-102 regulates expression of MECP2 is a novel microRNA responsive auto-regulatory element platform, known as miRARE that is exclusively licensed to Taysha developed by Dr. Sara Sinnott and Stephen Gray of UT Southwestern Medical Center. miRARE provides sophisticated regulation of transgene expression, genotypically on a cell-by-cell basis, ensuring controlled expression that avoids excessive levels. miRARE is a targeted panel for endogenous microRNAs, which regulate MECP2 expression.

In the presence of high levels of intracellular MECP2, endogenous down regulatory micro RNAs are secreted as part of the cell's normal feedback inhibitory process. Which then bind the miRARE platform on the construct and reduce output and expression of MECP2 from the construct. This ensures that intracellular levels of MECP2 whether in a wild-type cell or a mutated cell and immune mosaic patient stay within appropriate physiological levels.

Next slide. Today, we are excited to share near normalization of survival in neonatal mass bonds of Rett Syndrome following Taysha administration. Survival was significantly extended in MECP2 knockout male mice following a single CSF injection after day 2 of TSHA-102 at 8.8 E10 VG per mouse, which is the human equivalent dose of 2.86 E14 total VG and a little lower than planned for the human clinical trial. Preliminary data demonstrated approximately 70% of the treated knockout males survived study conclusion at 34 weeks of age versus 9 weeks in vehicle-treated mice. All cohorts, including vehicle were sacrificed to 34 weeks.

Next slide. We then looked at the Bird score, which is a composite measure of 6 different phenotypic abilities that relates to Rett syndrome. These include breathing, gate, general condition, high blend classing, mobility and tremor. Over the course of the study, TSHA-102 appeared to normalize behavior, as assessed by the Bird score.

Next slide. The totality of preclinical data generates the date for TSHA-102 represents the most robust package supporting Rett syndrome clinical advancement for gene therapy. I've just reviewed the recent preclinical study in neonatal Rett knockout mice, demonstrating near normalization of survival, normalization of body weight and normalization of behavior as assessed by bird score. We have previously discussed the pharmacology data demonstrating significant improvement in survival, body weight, motor function and respiratory health across treatment ages in knockout mouse models and while we were able to ascertain a minimally effective dose.

We've also previously discussed toxicology data supporting a favorable safety profile of TSHA-102 in Sprague Dawley wild-type rats up to a 6-month time point and the human equivalent doses fourfold over the clinical starting dose. The nerve conduction studies performed remains the normal range for all groups at all time points, signifying no evidence of dose or ganglia inflammatory change. And lastly, toxicology data supporting TSHA-102 was well tolerated at human equivalent doses of up to 2 E15 total VG and demonstrated abroad by distribution to brain, spinal cord and systemically in non-human primates.

Perhaps most importantly, the toxicology studies have demonstrated that the down regulatory miRARE platform is working well and that there was minimal expression of MECP2 in a wild-type cell with normal preexisting levels of MECP2. These 4 preclinical studies together represent a comprehensive and robust package supporting the clinical advancement of TSHA-102 for Rett syndrome.

Next slide. Our first-in-human Phase I/II study of TSHA-102 for Rett syndrome, also known as the REVEAL study is ongoing. Centas you've seen a mother and child University Hospital Center in Montreal, Quebec, Canada is the initial clinical site for the study, which is under the direction of principal investigator, Dr. Elsa Rossinyol. Target recruitment is up to 18 adult females. It has a 3+3 study design with 3 randomly selected delayed treatment control participants in each dose cohort, and each cohort may be expanded with up to 3 additional participants.

Next slide. We look forward to preliminary Phase I/II clinical safety and efficacy data in adult females by year-end 2022. We have completed GMP manufacturing for Rett using our commercial process. And lastly, a study the pediatric female rep population and the rescue study in rep males are planned for 2023. As a reminder, TSHA-102 has been granted rare pediatric disease designation and orphan drug designation from the FDA and more recently orphan drug designation from the European Commission. With that, I'll turn the call over to Kamran to review our financial results. Kamran?

Kamran Alam

Thank you, Suyash. This morning, I will discuss key aspects of our financial results for the second quarter ended June 30, 2022. More details can be found in our Form 10-Q, which will be filed with the SEC shortly.

Next slide. As indicated in our press release today, research and development expenses were \$23.1 million for the 3 months ended June 30, 2022, compared to \$30.6 million for the 3 months ended June 30, 2021. The \$7.5 million decrease was primarily attributable to a decrease of \$3.8 million in third-party R&D primarily related to GLP toxicology studies, a decrease of \$3.2 million in R&D manufacturing costs and lower employee compensation expenses of \$0.5 million.

General and administrative expenses were \$9.9 million for the 3 months ended June 30, 2022, compared to \$10.1 million for the 3 months ended June 30, 2021. The decrease of approximately \$0.2 million was primarily attributable to a decrease of \$1.1 million in professional fees related to market research, recruiting, accounting and patient advocacy activities. This was partially offset by \$0.9 million of incremental employee compensation expenses.

Net loss for the 3 months ended June 30, 2022, with \$33.9 million or \$0.84 per share as compared to a net loss of \$40.9 million or \$1.09 per share for the 3 months ended June 30, 2021. As of June 30, 2022, the company had cash and cash equivalents of \$66.2 million compared to \$149.1 million on December 31, 2021. Taysha continues to expect that its current cash and cash equivalents in addition to full access to existing term loan facility, is sufficient to fund operating expenses into the fourth quarter of 2023. And with that, I will hand the call back to RA.

RA Session

Thanks, Kamran. We remain focused on achieving our anticipated near-term milestones in 2022 and building long-term value. Our programs in GAN and Rett syndrome continue to advance and demonstrate exciting disease-modifying potential as further supported by the new clinical nerve conduction data in GAN and neonatal preclinical data in Rett syndrome presented today. As we look ahead, we expect a regulatory update for our GAN program and preliminary Phase I/II data for TSHA-102 in adult females with Rett syndrome by year-end.

I will now ask the operator to begin our Q&A session. Operator?

Question-and-Answer Session

Operator

Thank you and at this time, we'll be conducting a question-and-answer session. [Operator Instruction] And our first question comes from the line of Joon Lee with Jo Securities. Please proceed with your question.

Joon Lee

Good morning, thanks for taking questions. My name is Joon. I'm just wondering, have there been any discussions with the FDA on regulatory lamina for 120, just thinking mostly in terms of the 3 scenarios that you've previously laid out on whether or not the FDA might have to redose patients with GMP material. Also, if such discussions have occurred, will the safety data be sufficient? Or has the FDA made or indicated additional need for efficacy biomarker or clinical data? Thank you.

RA Session

Good morning. Maybe I'll start and then I'll turn it over to Suyash to provide some additional insight. Where we guided you this morning was that we'll have some additional feedback from regulatory agencies, including the FDA by the end of the year. I think the regulatory feedback that we've noted from MHRA kind of aligns ourselves with what we consider scenario 2, which is the need to dose additional patients using the commercial material. You know, we kind of see that as our base case, and that's what we've been planning for.

The good thing about that is the patients are already identified. They're currently in our natural history study. And what we would do is just roll over patients from the natural history study into the current ongoing trial. We would do that once our GMP material is actually fully released, which should happen here in the next few weeks, which we're quite excited about. And the fact that, as we've noted on the call that the original clinical trial material and the new commercial grade material are virtually identical, as all key quality metrics. So I think when you look at all of those things in consideration, I think that lines up nicely for how we're planning to move forward, which we consider scenario 2 is probably the most likely case. That would be the need to dose a few more patients using the commercial material.

I think ultimately, our discussion with the agencies will really be about how to accelerate whatever the potential filing would be. And I think the use of a rolling submission would be something that I think we would be more encouraged to ask the agencies about. I think this environment, what we're seeing from a regulatory perspective is a good environment, particularly for gene therapy and CNS therapy. The agency has shown significant flexibility. And I think we've listed off a number of those examples, both the FDA and EMA. So we feel pretty good about our approach.

Keep in mind, we've now shown you data across multiple functional endpoints; We've now shown new data across pathological endpoints; We've now shown you data across definitive end points that include that, again, our hard endpoints, right, that don't include any type of proceeds bias. So with all of that totality of data, coupled with the comparability data that we now have in hand, we feel pretty good about our discussions moving forward with the agencies. So I'll pause there to Suyash -- Suyash, do you have anything to add or we could move on.

Dr. Suyash Prasad

I think you said it all, all right.

RA Session

Perfect.

Joon Lee

Thank you, and then if I could just ask the yield of the 50 doses that you've already manufactured, will that support the highest dose that was tested in clinical trials for all 50 of the doses that are ready to go? Thank you.

RA Session

The answer to that is yes. That 50 doses at the high dose, which is 3.5 E to the 14.

Operator

And our next question comes from the line of Gil Blum with Needham & Company. Please proceed with your question.

Gil Blum

So just a question to clarify and make sure that I fully understand this. The additional regulatory feedback that we will be getting by year-end 2022, is this a change from previous estimates?

RA Session

So thanks, Gil, for the question and good morning. So our previous guidance was that we would have regulatory feedback by year-end. We didn't disclose from what agency we would have that feedback from. So essentially, the feedback that we provided on the call today is in line with our previous guidance. What we've decided to do because of the success of our commercial-grade manufacturing line and the comparability data that we've generated from that, including potency assays, including release assays as well as the additional clinical trial data that we showed you guys today. What we decided to do was essentially hold the submission to the FDA until we had a fully robust baked CMC package. We now have that.

I think you would probably consider that package extremely comprehensive again, across all the clinical endpoints that we've shown you. But more importantly, I think the CMC data, which is really where I think the crux of the conversation was going to be. The fact that we're seeing virtually identical material across a number of key attributes, including next-generation sequencing, I think it's going to be extremely compelling to the agency. So we wanted to make sure we actually had that data in hand as the manufacturing run got underway, and we saw the progress that it was making and the good progress that it was making, we decided to hold that.

And so now we'll be submitting that full data package to additional regulatory agencies including the FDA. And so we expect that to provide the FDA the information to be able to provide clear guidance around what the registration pathway would look like. And for us, we think that aligns with probably most likely scenario 2. The use of the accelerated pathway, but the need to dose a few patients using that material, which is actually released in September. So this all lines up nicely and it's pretty consistent with what we said when we talk about what a potential launch date could be.

Gil Blum

Okay. And maybe a question on SNAP. How it's established was SNAP as a surrogate endpoint for function and GAN. I mean it is very -- it is remarkable to see something going from zero to something, but just to help us understand the functional benefits.

RA Session

No, absolutely. Suyash, do you want to answer that and I can provide some comments after.

Dr. Suyash Prasad

Sure. Oh yeah hi Gil, I think that this is really the first ever time SNAP amplitude data, SNAP data in general has been presented or published for a large body of patients with GAN. And it is quite remarkable. It's quite -- what is notable here is the consistency of what you see in the natural history and how it mirrors clinical progress of these patients. You saw in the earlier image that around the age of 2, the SNAPS are well within the normal range, and they rapidly decline from the age of about two and a half to 3 to the point where by the age of four every child has an abnormal SNAP. By the age of 9, everyone has an absent SNAP. And what I would say is that this kind of pattern is quite consistent with other axonal neuropathies, another similar hereditary centermost neuropathies where you do see the nerve conduction studies being affected quite dramatically.

What I think is important with GAN is the fact that it really mirrors what's happening clinically and correlates very nicely. We've talked before about how patients with this disease generally is symptom free in the first few months of life. They may have slightly delayed motor milestones around the age of 2, 2.5, these children present with unsteadiness and a wide-based gate and a high stepping gate because they can't feel the ground beneath their feet. And this is exactly what these conduction studies are demonstrating.

I think one point I will make is that what you're looking -- and I tried to get into this in the presentation, there are 3 frames you'll look out with a nerve conduction study -- amplitude, which is the height of the electrical deflection; Latency, which is how quickly the electrical stimulation takes to start; And velocity, which is the actual speed down the actual nerve. And neuro really in that earlier times were used in the demyelinating disorder multiple sclerosis, where you tended to see more effects on latency and more effects on velocity. However, for these axonal neuropathies, where you're losing axonal amplitude as the key parameter and you can see how it correlates very nice in the natural industry.

But more importantly, actually, clearly stabilizes or even improves -- and you're right to the fact that a handful of patients improved from 0 and are still continuing on an upward trajectory -- is very impressive and is also reflected in what I shared in the biopsy data you saw an increasing presence of regenerating the clusters.

Let me stop there. I could go on even longer, but let me stop there.

RA Session

The only thing that I would add -- and thanks, yes, the only thing that I would add to what Suyash mentioned is, I think it's important to note that MFM32 is a definitive clinical endpoint. Essentially, it's a hard endpoint, and it's functional. And I think when you look at that in correlation of what Suyash mentioned around how it correlates to MFM32, how it correlates to biopsy data, how it correlates to the LogMAR data that we've shown before, I really start to think all these things are moving the exact same way. You really start to put together a really nice clinical package. And really, you have to look at the totality of the data set that's all moving the exact same way. So we feel really good about this. And again, having this data in hand allows us to just have even more robust engagement with regulatory agencies around the most accelerated pathway.

Gil Blum

Thank you. That was very helpful. And then last one on Rett. What would you need to dose male rescue study? That's -- the timing there seems pretty important. But if you can and that...

RA Session

It's a really good question. Suyash, maybe you just want to comment on kind of the phenotype of the males and how they correlate to the knockout animal and then maybe go deeper into Gil's question.

Dr. Suyash Prasad

Sure. Yes. So the important thing here is that the males are knockouts. And for an X-linked disease, this means that they have no MECP2 whatsoever. In contrast to the females where the females are mosaics and half of themselves have normal levels of P2 or the other half have mutated or absent that P2. And so in the clinical setting, the males actually are more severely affected. And the vast majority in the human situation actually die in utero. A handful survive and lots of life through early infancy and may die in the first few months of life or sometimes to live up to the age of 2 or 3. And then so come usually to due to respiratory infection or some respiratory compromise. So it's a very, very severe form of Rett.

And there aren't many of these patients, the male, knockout males that survived perhaps 200 in the world. So -- and they've also been a fairly, I guess, a forgotten group and the Rett patient community are actually very pleased that's part of our clinical development program, which, as we alluded to earlier in the call, we're starting in Q4s initially during the course of 2023, we'll start a pediatric girl study, and then we'll also do a pediatric boys study, a rescue study. And the Rett patient community are very happy that we're actually addressing this kind of underserved population. Specifically on your question around GoSkill, it's a really interesting question. On the one hand, there's an argument to go with a higher dose because these boys -- the high dose starting our pediatric -- our girls study, which is starting at 5 E14 total VG.

And from our previous pharmacology mass oncology study, we ascertained the minimally effective dose was around 3 E14 total VG. So we're actually going in above that for the 5 E14 total VG. There's not going to go slightly higher in the males, but actually, our time is to stop the same dose. That 5 E14 total VG and the pediatric boys study that I think will be quite significant in improving that phenotype. Likely, we will go to a second dose of a 1 E15 as well.

Gil Blum

All right. Thank you for taking our questions. Good luck. Thank you.

Operator

[Operator Instructions] Our next question comes from the line of Salveen Richter with Goldman Sachs. Please proceed with your question.

Unidentified Analyst

Hi thanks for taking our question and congrats on the progress. This is Tommy on for Salveen. We had a follow-up on the SNAP question. Could you help us gauge the expected consistency in SNAP across treated patients? For example, if there's characteristics at baseline that might impact the response after treatment. And on the MHRA feedback, how many patients do you think will need to be dosed with the commercial-grade material? And how does this affect the time line? Thank you.

RA Session

Thanks for the question. I'll turn it over to Suyash, maybe I'll provide some additional comments once he's done. Suyash?

Dr. Suyash Prasad

Sure. Yeah. I mean the stats, it's an interesting question. We -- it's hard to know exactly what characteristics of the patients would predict a good response. And it's also hard to know simply because there are not that many patient numbers that have been dosed to be able to ascertain that with that degree of accuracy. What I would say is that the suggestion it makes full sense is that the earlier you treat, the more likely you are to have a response, the younger patient you treat, the more likely you are to have a response.

And also, I think importantly, and this makes perfect sense is that if you -- if you can treat before the SNAP is lost or is absent, you're more likely to see an improvement in the -- in this hard endpoint and more likely to see a functional improvement as well. Having said that, very surprisingly, and we were very pleased to see that in a number of patients who actually had an absence of that and an absence of that for a period of time, we actually saw improvements in the nerve conduction SNAP amplitude that continued on lower trajectory.

With regards to the MHRA, yes, we -- this is -- this was one of the questions that we talked about in detail. It was clear that they wanted us to dose more patients. And this is in line with our thesis of option 2, i.e., a handful more patients with clinical trial material. We tried in our discussion, and it was a very collegial, fruitful, long, in-depth discussion across all aspects of the program. I mean was there was over 2 hours, we talked about the preclinical data, the clinical data in depth. And there's a lot of in-depth discussion on the CMC piece as well. But they would not really be held to a specific number. They essentially said a handful of patients for a period of time for us to come back with a proposal.

So what we decided to do, and our previous thoughts have always been, it's probably going to be about 3 to 5 patients for about 6 months. So our thinking was less also continue with other agencies and also got the feedback from all agencies we've come up with a proposal on the specific number of patients. But my guess, as I say, is it's going to be around about 3 to 5 patients for about 6 months.

RA Session

Thank you for the question.

Operator

Our next question comes from the line of Mike Ulz with Morgan Stanley. Please proceed with your question.

Mike Ulz

Just on GAN, you mentioned doing some additional validation work on the MSM32 endpoint. Can you just give us a sense of your plans there and maybe how long that validation work might take? Thanks.

RA Session

Thanks, Mike. One comment I'll make before I turn it over to Suyash is that, that validation work has actually been ongoing for quite some time. So we feel pretty good about the timeline there. And the fact that MFM32 has been used as a regulatorily accepted endpoint in a number of neuromuscular diseases. So we also feel good about that there. The particular work on GAN, I'll turn it over to Suyash to discuss further.

Dr. Suyash Prasad

Sure. Thanks. And thanks for the question, Mike. So the -- RA's quite correct, MFM32 is actually validated the pediatric neuromuscular disease in general and has been used several times previously as in supporting evidence in regulatory discussions before. Having said that, it's always best to do a formal validation as far as you can for the specific disease in question. So the plan has always been for us to formally validate the MFM32 for Giant Axonal Neuropathy. And we actually talked about this with the MHRA, and they were very open to and accepted and pleased that we've actually started this work.

Now there are 3 pieces to this work. The first is to any kind of validation work. The first is a general qualitative feedback that solicited from patients and families and clinicians and PTs and OTs in a structured interview setting. And that work has been completed. And actually, we're just in the process of writing up that work, and we'll be submitting that for publication. I'm guessing about 6 to 8 weeks' time. So you'll be able to see that work in detail in the future. The second piece is to take all that information and run it through a specific -- there's a way of analyzing this qualitative semi-structured interview data, and this process is for content validation. So that that'll be the next step.

And then once we've done the content validation, there's another whole additional process to the psychometric validation where we take all the natural history study data, and we take all the data from the interventional study, looked at how the MFM correlates with other aspects of other endpoints, other aspects of the disease and also with the qualitative information that we picked up in the qualitative interviews and in the content validation piece, and then we do a formal sacramental validation. That will get risk numbers of package will usually publish this work and it will end up being quite a significant report that goes in with the actual BLA filing and other regulatory interactions.

In terms of timing, the process, it can take -- it can usually take quite a long time, 12 to 18 months to do it properly. Having said that, because we have this large natural history study with 50 patients worth of data, all of them have done the MFM, this truncate the time line somewhat. So it's probably going to be, I guess, a 9 to 12-month process from now.

Operator

Our next question comes from the line of Eun Yang with Jefferies. Please proceed with your question.

Eun Yang

Thank you very much for squeezing me. I have one question and one -- another very quick question. So first question is for the Rett Syndrome data that we are expecting, you started the study in Canada probably only second quarter. So how many patient data are we going to be seeing? So that's question number one. And second question is kind of a quick question. So in the past, you consistently said that scenario number two is the most likely regulatory outcome, with that, you anticipated a potential launch by end of 2023 in the U.S. So is this still on track? Thank you.

RA Session

Good morning, Eun, and thanks for the question. Maybe I'll take the question and if Suyash had anything to add, I'll turn it over to him. But on your first question, we typically haven't commented on how many patients worth of the data that we provide in any of our other indications or data update. So I think we're going to remain consistent with that operating procedure. What we will guide to is that you will have data in Rett Syndrome by the end of the year -- patient data in Rett Syndrome by the end of the year that we'll disclose to The Street. So we're staying consistent with that guidance.

Your second question around kind of what we've got into in the past from a timing perspective, again, I think again, I think we're staying relatively consistent. I think the initial regulatory feedback that we've received aligns itself with scenario two. I think some of the recent discussions that have happened in other indications and other companies with both the FDA and the EMA, is showing a nice flexibility around the use of the accelerated approval pathway.

I think the way that our comparability protocol has played itself out as well as the commercial yields or the yields that we've gotten from our commercial launch, all support this notion of being ready to file a BLA as soon as possible. And so ultimately, I think we're still on that same time period. I think what I've guided in the past is always by the end of 2023 or early 2024 from a commercial launch perspective, and I think we're still on that time period.

Ultimately, this is going to be a discussion point for the regulators, but certainly the preclinical data is all completed. The majority of the preclinical data has been published for quite some time. We now have a strong CMC comparability package that basically shows that our material from the clinical trial and our commercial-grade material are virtually identical by a number of key attributes. And we now have significant clinical data across multiple functional pathological hard endpoints coupled with biopsy.

I think when you look at that, it's probably one of the most robust packages from a rare disease perspective. And so we feel pretty good about it and the fact that all the data is moving the exact same way. So what I'll say is I think we're consistent with that timing. Previously, I think I've always guided to by the end of the year, the end of 2023 or early 2024. And so I think we're still within that time.

Operator

Our next question comes from the line of Jack Allen with Baird. Please proceed with your question.

Jack Allen

Hi. Thank you so much for taking the questions, and congratulations on all the progress. Just two quick ones. One's really quite straightforward. I guess I'll start with that.

Do you have a meeting with the FDA on the books for the second half of this year as you look to gain that guidance in GAN? And then I just wanted to ask on the SNAP results on GAN. Any comments you can make with regard to the doses those patients received and a dose-dependency you saw on the SNAP results would be great. Thank you so much.

RA Session

Hey, Jack. So to your first question, I don't think we would guide to whether we had a meeting or have a meeting on the books. I think what we are confirming is that we will have feedback from the FDA around the regulatory pathway by the end of the year.

We feel pretty good about that guidance. And I think that is not only the FDA, but that will be also other regulatory agencies. We would be able to provide a pretty robust update on that by the end of the year. So we're staying with that guidance.

But I do think the data that we've shown you guys this morning, more particularly the comparability data that Fred and his team have done a great job being able to generate, is really what the key outstanding question, I think probably more so from the analyst community. But also the fact that are you able to produce at commercial scale identical product in order to get those same clinical results, right? And again, I think the approach to that Fred had taken has just been phenomenal. And the team has done a great job in generating these results, not only across a bunch of key attributes, but also being able to confirm it by next-generation sequencing. And I think that's a very important point as well, that we're basically seeing identical product.

I look back at the old Zolgensma pathway back in the day when we were having these similar discussions around the clinical trial material generated at Nationwide and then eventually what became the commercial material that was generated at the Libertyville facility. It literally was night and day. It was night and day to what we're actually seeing and what Fred's team has been able to do. So we feel pretty good about going into those meetings, having solved the big question. That's always been the big question.

Also, around potency assay, and Fred and his team along with Suyash and his team now generated a matrix of potency assays across again, a number of key quality attributes that we feel extremely good about that are functional in nature and reproducible. And we've now finished that work in-house and have tech transferred that work out to a CRO. So again, everything is moving exactly the way that we'd like it in order to hit the timelines that I just laid out. So we feel pretty good about that.

So hopefully that answers your first question. Jack, could you repeat your second question?

Jack Allen

Yep. Thank you so much for the call on the first question. That does a great job of answering that. The second question is really briefly, any comments you can make around dose dependence of the SNAP result. I realize there's a limited cohort there, but I'd love to hear about what doses those patients received.

RA Session

No, it's actually a really good question. Suyash, do you want to comment there?

Dr. Suyash Prasad

Sure. Yeah. It's essentially in keeping with what we saw across the other endpoints. So you'll recall there's four different dose cohorts in the study. The initial dose, 3.5E13 is more of a safety dose that generally didn't show much efficacy. It was detectable, even though some families said that there's some qualitative improvements.

Cohort two was a 1.2E14. Cohort three, 1.8E14. And cohort four was a 3.5E14 total VG. And those three upper doses are clustered quite close together. I think if we designed the study now, we would actually not have full dose cohorts and we would have -- or probably two dose cohorts. We'd have a bigger range between the two.

And what I would say is that across all the endpoints, the data from those test scores two, three, and four were generally pretty comparable. And that was also true for the SNAP. We saw nothing for the very low dose cohort, but we saw improvements in the higher dose cohorts. It is a suggestion that you're teasing out a bit more of a dose response over the SNAP. There's a suggestion that the highest dose is getting a little bit more in the way of improvements on the amplitude than cohorts two or three.

But in general, cohorts two, three, and four all results in good improvements, both in SNAP and in the presence of regions with no clusters.

Operator

Our next question comes from the line of Yun Zhong with BTIG. Please proceed with your question.

Yun Zhong

Hi. Thank you very much for taking the question. So I wanted to confirm that the feedback that you received from MHRA does not change your confidence that you will be able to file based on available data when you talk to the EMA and also want to confirm that by year end when you provide feedback, would that feedback include EMA feedback as well? Because EMA sometimes can be less flexible in terms of clinical endpoint versus surrogate endpoint that you talked on the call. Thank you very much.

RA Session

Thanks, Yun. Maybe I'll start and then I could turn it over to Suyash that -- to provide an update. I think from your second question, I think the EMA actually is a little bit -- I think it may be opposite of your assessment. They've actually shown quite a bit of flexibility, particularly around the use of their conditional approval pathway as well as this notion around the totality of data.

What I would also say is the fact that there's no surrogate endpoints here. I think what's interesting is, we have multiple functional endpoints. We have now shown you guys a definitive hard endpoint. We now have shown you guys data around visual acuity and the stabilization of visual acuity, the stabilization in the loss of retinal nerve fiber thickness.

We've now shown you guys biopsy data that correlates to all the functional outcomes. And couple that with again, the comparability data that we've laid out. So we feel pretty good about going into those discussions with a very robust package.

And just on top of that, I think most important, the safety across let's call it seven years. This was the first intrathecally dosed gene therapy trial in history. So we now have seven years' worth of safety data. And the safety has been consistent. And this drug seems to be extremely well tolerated in the clinical setting.

And so for us, we feel again, really, really good about it. I think to your first question around will that update by the end of the year include feedback specifically from the EMA, what I will say is we will have feedback from multiple regulatory agencies, including the FDA, by the end of the year. We do plan to engage the EMA within that time period as well. Yun, did that answer your question?

Yun Zhong

Yes, it did. Thank you very much.

Operator

Our next question comes from the line of Sami Corwin with William Blair. Please proceed with your question.

Sami Corwin

Hi, guys. Congrats on the progress, and thanks for taking my question. Do you think these additional patients you're going to dose -- the additional GAN patients you're going to dose will also satisfy the FDA if they wanted additional patients just as clinical material? And then can you just broadly speak about how dosing in the Rett trial is going?

RA Session

So to answer your second question first, we typically don't guide around first patient dosed or ongoing dosing of patients. We just remain consistent with that and just reiterate the guidance that you will have preliminary clinical data -- patient data by the end of the year in Rett, we're pretty confident with that.

I think most important was the late-breaking pre-clinical data that we showed you guys today, which just, in my opinion, was extremely remarkable in a disease like Rett and in extremely severe mouse model, which is the male knockout model where we saw near normalization of survival and actually never got to a median survival throughout the life of -- throughout the conduct of the study, it was just extremely encouraging and for me just reinforces the need to keep moving this program forward quickly. But also the ability to be able to get down into that pediatric growth population, which are the most affected patients, but also those pediatric boys, that the fact that we're able to see the results not only consistent from a survival perspective, but also from a behavior, being able to normalize behavior as assessed by the Bird score, being able to normalize body weight.

I think taking that data and the neonatal model also correlates to what we've shown you from that large pharmacology study that we presented. We presented this data at ASCPT where, again, we saw improvement in survival, motor function, behavior, but also respiratory function, which was quite remarkable. So for us, we think that again, the totality of data, both efficacy and safety with this program kind of put this program in rarefied air to be quite honest and just really encourages us to move quickly in order to get to those pediatric girls as well as that rescue boy study and to do it urgently for patients. So that's the -- that's our question on Rett.

And could you just repeat your question on GAN?

Sami Corwin

Yeah. Do you think these additional GAN patients you plan on dosing in September once the clinical trial material -- or sorry, once the commercial materials release, do you think that quantity of patients and duration of follow-up will also satisfy the FDA if they wanted additional patients dosed?

RA Session

Sure. I'll start and I'll let Suyash take over. I think that's exactly what our plan calls for, is alignment around patient numbers. I think what we had always planned to do was to proactively dose patients, right? As soon as the commercial material is available, which should be here in the next few weeks, we expect this material to be fully released with all the comparability work completed.

We plan on initiating patient dosing where these patients are essentially already identified. We've had a protocol amendment that went through about four or five months ago, if not longer, that allows us to dose down to age three to actually start dosing younger patients. So it's always been our intent to continue dosing patients, but I would say to get alignment between all regulatory agencies, particularly around the number, but also the duration I think is extremely important. But I think consistent with what these agencies have shown recently, which again, gives us a high degree of confidence, I think the plan that Suyash laid out, which is what we are internally planning for three to five patients for about six months of follow-up, I think should be sufficient.

But again, we really do need to have that conversation with regulators. I'll stop there. Suyash, do you have anything to add?

Dr. Suyash Prasad

Not really to add, but just to emphasize the fact that we'll look at all the regulatory agency feedback in totality and conduct the study on an ongoing basis in order to meet all the needs. And my guess is, yes, it'll be three to five patients, six months' worth of data. And that should meet the needs of the MHRA, the EMA, the FDA, and any other agency we're in discussions with.

RA Session

The only thing that I would add to Suyash's point is that, again, this timing is consistent with what we've kind of laid out. I think what the big piece and what the seminal ask for us will be is the fact that if we can initiate a rolling submission. Because again the CMC data, the comparability, the probability data is kind of all completed, the potency assay is completed, that work is being tech transferred right now. When you start to think about the majority of the clinical data, it's been ongoing for seven years and both from a safety and efficacy perspective across multiple endpoints. Natural history data has been ongoing for two years before that, right? So we're approaching almost ten years of natural history data. So it's a big wealth of data. It's a big wealth of data in a relatively small population, which I think we are quite encouraged about. But certainly, the FDA needs some time and other agencies will need some time to go through it.

So we feel really strongly about this approach around a rolling submission in the use of an accelerated pathway. So that's ultimately going to be our act.

Operator

And our last question comes from the line of Kristen Kluska with Cantor Fitzgerald. Please proceed with your question.

Rick Miller

Good morning. This is Rick on for Kristen. Thank you for taking our question. Just a question on the individual patient SNAP data.

It looks like patient A appeared to show little change from baseline. Could you talk about how you're thinking about the specific case and what it might be telling us potentially about baseline characteristics or time of dosing? Thanks.

RA Session

Thanks for the question. I think what's probably more important is how you relate this toward the natural history and the fact that this patient actually has a positive SNAP three years after dosing, which I think is extremely important. When you look at -- when you contrast this with natural history, virtually every patient in the natural history cohort at this particular time point and this would be consistent with patient A would have zero SNAP. So the fact that we're actually seeing stability in a positive response is extremely remarkable.

So what I would say is it's a small dataset, but even with patient A doing stability in a positive way that's durable is extremely important, particularly in the context of a relentlessly progressive neurodegenerative disease, essentially. So this is consistent with what we're seeing in the biopsies. But this is in total contrast to what you would see in the natural history. I'll pause there.

Suyash, do you have anything to add?

Dr. Suyash Prasad

I hear what you're saying. I mean, patient A on its own is actually what we were hoping to see. We would have been very pleased if all patients stabilized because this is a child. If you look at that based on what the dose there, that scores about six microvolts and that is well below the normal limit and -- from the actual history data is on a very rapid downward trajectory.

So that's -- that would have disappeared probably six months after that time of dosing if they hadn't been dosed. And we saw stabilization. And that's what we're hoping to see. The only reason it doesn't look so good is because the other patients are actually doing so much better.

So, yeah, we were happy with that. We were very happy with our patients' performance, especially in comparison to the natural history, but simply because most of the other patients did significantly better. And once again, just to emphasize the fact that to go from a zero SNAP, if you look at patient B and you look at patient D, those patients had zero SNAP amplitude for well over a year. And for them to improve and for patient B in particular to be close to normal of the three and a half year time period, and still on an upward trajectory is really very significant and you would not expect to see this in a neurodegenerative disease. So it's very powerful data.

Operator

And we have reached the end of the question-and-answer session. I'll now turn the call back over to Mr. RA Session for closing remarks.

RA Session

Thank you, operator. And again, I think we've been quite excited about the progress that the company has made across our core programs in Giant Axonal Neuropathy, Rett Syndrome. I think we will remain focused on these two key programs, moving these programs forward, particularly in the case of TSHA-120 GAN towards an accelerated regulatory pathway. We'll provide guidance and feedback from regulatory agencies by the end of the year, including from the FDA.

But we're quite excited with the data that we've shown you guys today. I think, again, for us, this allows us the opportunity to have the most robust package and robust discussion with these agencies really around the totality of the data set that all is moving the exact same way. I think the data that our CMC group, led by Fred Porter, our Chief Technical Officer, presented today again shows the fact that we're getting almost virtually indistinguishable drug from our clinical trial material to our commercial scalable process. Again, continue to support this notion around like-for-like material.

And then turning to our Rett Syndrome program, we feel extremely encouraged by the late-breaking preclinical data that we've shown you guys today, which is showing near normalization of survival in a very severe mouse model. And again, we look forward to reporting preliminary clinical data by the end of the year from our ongoing Phase 1 last two studies. So I wish you guys a wonderful rest of the week, a wonderful day, and we look forward to connecting here in the near future.

Operator

And this concludes today's conference, and you may disconnect your lines at this time.
Thank you for your participation.

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Taysha Gene Therapies, Inc. (NASDAQ:[TSHA](#)) Q1 2023 Earnings Conference Call May 11, 2023 4:30 PM ET

Company Participants

Hayleigh Collins - Director and Head of Corporate Communications

Sean Nolan - CEO

Sukumar Nagendran - President and Head of Research and Development

Salman Bhai - Assistant Professor of Neurology at UT

Kamran Alam - CFO

Conference Call Participants

Abigail Gray - Baird

Gil Blum - Needham & Co.**Operator**

Thank you for standing by. This is the conference operator. Welcome to the Taysha Gene Therapies First Quarter 2023 Earnings Conference Call. As a reminder, all participants are in listen-only mode and the conference is being recorded. After the presentation, there'll be an opportunity to ask questions. [Operator Instructions]

I would now like to turn the conference over to Hayleigh Collins, Director, Head of Corporate Communications. Please go ahead.

Hayleigh Collins

Thank you. Good afternoon and welcome to Taysha's first quarter 2023 financial results and corporate update conference call. Earlier today Taysha issued a press release announcing financial results for the first quarter 2023. A copy of this press release is available on the Company's website and through our SEC filings.

Joining me on today's call are Sean Nolan, Taysha's CEO, Sukumar Nagendran, President and Head of Research & Development; Kamran Alam, Chief Financial Officer and Salman Bhai, Assistant Professor of Neurology at UT, Southwestern. We will hold a question-and-answer session following our prepared remarks.

Please note that on today's call, we will be making forward-looking statements, including statements relating to the existing clinical data for TSHA-120 the therapeutic and commercial potential of TSHA-120 and TSHA-102. These statements may include expected timing and results of clinical trials of our product candidates and other clinical and regulatory plans and the market opportunity for those programs.

This call may also contain forward-looking statements relating to Taysha's growth, forecasted cash runway and future operating results, discovery and development of product candidates, strategic alliances and intellectual property, as well as matters that are not of historical facts or information. Various risks may cause Taysha's actual results to differ materially from those stated or implied in such forward-looking statements.

These risks include uncertainties related to the timing and results of clinical trials of, and regulatory interactions for our product candidates, our dependence upon strategic alliances and other third-party relationships, our ability to obtain patent protection for our discoveries, limitations imposed by patents owned or controlled by third parties and the requirements of substantial funding to conduct our research and development activities.

For a list and description of the risks and uncertainties that we face, please see the reports we have filed with the Securities and Exchange Commission including our Annual Report on Form 10-K for the year ended December 31, 2022. The conference call contains time-sensitive information that is accurate only as of the date of this live broadcast, May 11, 2023.

Taysha undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call, except as may be required by applicable securities law.

With that, I would now like to turn the call over to our CEO, Sean Nolan.

Sean Nolan

Thank you, Hayleigh, and welcome, everyone to our 2023 first quarter financial results and corporate update conference call. Today, I will begin with a brief corporate update. Then Dr. Sukumar Nagendran, President and Head of R&D of Taysha will provide an update on our clinical development programs along with our collaborator, Dr. Salman Bhai, Assistant Professor of Neurology at UT Southwestern. Kamran Alam, our Chief Financial Officer will then follow-up with a financial update before I provide closing remarks and open the call up for questions.

We've made significant progress across to lead programs in Rett syndrome and giant axonal neuropathy this year, and remain on track to deliver on multiple key milestones, including the generation of first-in-human clinical data for TSHA-102 in adult patients with Rett syndrome, the submission of a CTA to the MHRA to initiate expansion of TSHA-102 in pediatric patients, the submission of an IND application to the FDA for TSHA-102, and obtaining further clarity from the FDA on the regulatory path forward for TSHA-120 in GAN.

Screening is completed and the dosing of our first potential patient with TSHA-102 in the Phase 1/2 REVEAL trial in adult Rett syndrome is scheduled for the second quarter of this year. For our GAN program, the new comprehensive analyses of the totality of the data for TSHA-120 continues to be encouraging and includes compelling findings that offer potential to further support a regulatory path forward.

I want to highlight that much of the data presentation plan for the FDA will be new to the agency. And we will work to contextualize the data in a manner that clearly elucidates the potential for meaningful benefit to patients. We plan to submit the meeting request this quarter and expect the formal meeting to occur in the third quarter of this year.

In the near-term, we look forward to hosting an R&D day in June, where we will provide an overview of the GAN disease state and share these new clinical data analyses. Additionally, we plan to provide an update on our Rett program. Suku and Salman will discuss this in more detail shortly.

At the upcoming ASGCT conference, new preclinical data supporting TSHA-102 and the miRARE technology in Rett syndrome will be presented as part of a poster presentation. We remain focused on achieving the anticipated near-term milestones for Rett syndrome and GAN programs and continue to work towards our mission of bringing transformational new treatments to patients with these devastating neurodegenerative diseases.

I will now turn the call over to Suku to provide a more in depth discussion of our clinical programs in Rett syndrome, and GAN. Suku?

Sukumar Nagendran

Thank you, Sean, and good afternoon, everyone. First, I will start with an update on TSHA-102, our gene therapy program in development for the treatment of Rett syndrome. As a reminder, TSHA-102 utilizes an innovative miRNA-Responsive Auto-Regulatory Element or miRARE platform to regulate the cellular expression of MECP2 at the upcoming ASGCT Conference. We are excited to present new preclinical data that we believe supports the potential for TSHA-102 and the miRARE technology as part of a poster presentation on May 19.

For our Phase 1/2 REVEAL study in adult patients with Rett syndrome. We have completed screening and scheduled the dosing for the first potential patient. We expect the dosing to take place in the second quarter of 2023. We plan to report initial available clinical data, which will be primarily on safety in the second quarter of the year at our upcoming R&D Day.

In the second half of the year, we plan to continue dosing adult patients with Rett syndrome in our REVEAL trial and provide quarterly updates on available clinical data thereafter. We receive feedback from Health Canada on our protocol amendment to expand enrollment eligibility to subject 15 years or older in the REVEAL trial, which suggests that Health Canada support the expansion following initial efficacy and safety data from adult patients.

We plan to submit a CTA to the U.K. MHRA, for TSHA-102 in mid-2023 to enable the initiation of a pediatric Rett syndrome study. We also have an IND application submission to the U.S. FDA plan in the second half of the year to further expand our clinical study footprint with TSHA-102.

Now let's turn to TSHA-120 for the treatment of GAN, an ultra-rare neurodegenerative indication that no approved treatments or established regulatory pathway. As Sean mentioned, we are currently completing a comprehensive review of data from the ongoing natural history and interventional trial that includes functional, biological and electrophysiological assessments.

We plan to seek a formal meeting with the FDA to discuss a new analysis that FDA has not seen and regulatory path forward for TSHA-120. As a reminder, early analysis based on MFM32, the primary efficacy scale discussed at the FDA Type B end of Phase 2 meeting demonstrated clinically meaningful slowing of disease progression in patients with GAN following treatment with TSHA-120 across the therapeutic dose cohorts.

Importantly, long-term analyses points to sustain durability and the ability of TSHA-120 to prevent nerve degeneration, generate nerve fiber and preserve visual acuity, which are significant findings for patients affected by neuro-degeneration. Importantly, over six point [ph] years of long-term clinical safety data, supports a well-tolerated safety profile with no major drug related events.

The FDA stated that MFM32 can be a relevant primary endpoint in the setting of a randomized double-blind controlled trial and acknowledged Taysha's challenge in executing and enrolling such a study design due to the ultra-rare nature of GAN. As such, the FDA indicated that it is open to regulatory flexibility in a controlled trial setting and is willing to consider alternative study designs utilizing objective measurements to demonstrate a relatively large treatment effect that is self-evident and clinically meaningful.

Our comprehensive analyses of the totality of data from the ongoing natural history and interventional trial, which will inform our plans for future interactions with the FDA continues to be encouraging and includes compelling new findings with potential to further support the regulatory path forward.

I will now turn the call over to our collaborator Dr. Salman Bhai from UT Southwestern, who will provide a high level overview of some of our initial analysis of the data for TSHA-120 in GAN and the clinical relevance to the disease state. Salman?

Salman Bhai

Thank you, Suku and hello everyone. My name is Dr. Salman Bhai and I'm an Assistant Professor of Neurology at UT, Southwestern. I earned my Medical Degree and completed my Neurology Clinical Training at Harvard Medical School, with specialization in neuromuscular disorders. As a practicing neuromuscular neurologist, I'm keenly aware of the devastation that GAN causes, not only to patients, but also to their families.

I've been working closely with Taysha on the development of the TSHA-120 program for over a year and a half, and then energized by the opportunity to help bring a potentially transformational treatment to the GAN community. I've been heavily involved in the ongoing comprehensive analyses of the totality of data, and I've been working collaboratively with the team to identify new data findings.

Based on the GAN clinical phenotype and pathophysiology, we're building a clinical narrative around the data to support our regulatory path forward for TSHA-120. I'm pleased to provide an update on the compelling findings from our ongoing data analyses. One goal of evaluating the totality of the data for TSHA-120 is to determine whether we can identify potential objective measurements that demonstrate a clinically meaningful treatment effect.

For context, I think it's important to understand that GAN, clinically manifest with marked in coordination, ataxia. Due to both severe central and peripheral nervous system degeneration, which lead to significant disability and early mortality caused by respiratory failure. There is no approved treatment for this ultra-rare fatal disease. We have access to the largest natural history database of GAN to-date through the NIH.

As a result of our analyses of these data, we have a clear understanding of how to measure meaningful treatment effect for these patients. I'm a neurologist. So of course, let's start with the neuroanatomy. We know their central and peripheral nervous system degeneration with GAN. Specifically, this involves the cerebellum, long tracks and sensory and motor nerves. Clinically, these anatomical localizations translate to severe in coordination, which is ataxia, and weakness.

Patients struggle with simple tasks like picking up objects and feeding themselves. How can we measure this, the integration of the central nervous system and the peripheral nervous system pathologies. We believe we have a comprehensive scale that we prospectively collected in the natural history and interventional patients. The modified Friedreich ataxia rating scale or mFARS, which was recently used as the primary outcome measure for drug approval for Friedreich ataxia.

This scale is based on functional and objective measures within the neurologic exam. Focusing on ataxia, a key driver of disability in GAN patients as a whole, we can prospectively measure the integration of the central and peripheral nervous systems using mFARS. We can then capture several objective peripheral nervous system data points, including nerve conduction studies, myometry and nerve pathology.

We have scientific evidence of TSHA-120, leading to peripheral nerve regeneration in some patients, meaning nerves or growing back. Nerve conduction studies indicate sensory nerves recover responses that were absent prior to treatment, a key finding that was truly unexpected, and to my knowledge has never been demonstrated previously in GAN patients. We also see an increase in regenerative clusters on nerve biopsy. This is direct electrophysiological and biological evidence of nerve regeneration.

In neurodegenerative disease, the peripheral nervous system data is key because recovery of sensory nerves directly impacts patients' performance on mFARS, providing links between objective biologic data and a clinical rating scale. Importantly, by developing a disease progression model through Bayesian analysis, based on the natural history data, we show that the progression of mFARS in GAN is predictable, monotonic and homogenous across patients.

Thus, we can use this model to determine treatment effect. Preliminary determinations of treatment effect size relative to the disease progression model as measured by mFARS and with multiple peripheral nervous system endpoints show disease slowing. Let me repeat, we have direct central nervous system and peripheral nervous system outcome measures, and clinical and biological objective data that show positive disease modification with TSHA-120 in an ultra-rare, fatal neurodegenerative disorder that has no approved treatment.

The restoration of sensory nerve responses on nerve conduction studies and positive impact on other clinically relevant endpoints show the potential for even greater clinical impact in this neurodegenerative disorder, if treated at an earlier stage of disease with TSHA-120. I believe these data have the potential to provide objective measurements that demonstrate clinically meaningful treatment effects.

We are truly, truly inspired by these patients and their caregivers. We are hopeful that we can bring a potentially transformational treatment to the GAN community, and we look forward to working collaboratively with the FDA through our anticipated future discussions.

With that, I'll now turn the call back to Suku.

Sukumar Nagendran

Thank you, Salman. As you can see, we have compelling findings that we expect to submit as a part of a former meeting request to the FDA in the second quarter of this year. These data will inform our discussions with the FDA regarding alternative study designs, additional objective measures and ultimately a regulatory path forward. We anticipate a formal meeting to occur in the third quarter of 2023.

Importantly, administration of TSHA-120 also shows a translational or correlation between preclinical and clinical studies with TSHA-120, GAN knockout mice show improved dorsal root ganglia pathology and motor function, both of which translate to our human studies with improved sensory nerve integrity and sensory nerve action potentials better known as SNAP as detected by nerve conduction studies and biopsy analysis and improvement or stabilization in strength.

We saw similar clinical translational impact with spinal muscular atrophy and the SMN delta 7 mouse models which were developed Zolgensma at AveXis which showed improvement of stabilization, motor function and strength after treatment with gene therapy. That for congruency seen in human studies as well.

In June, we are excited to host a Virtual R&D Day where we will detail this new analysis and review therapeutic potential in the context of the GAN disease state, as well as provide an update on our Rett syndrome program, including new preclinical data for TSHA-102, in Rett syndrome being presented at the upcoming ASGCT Annual Meeting and available clinical data from Phase 1/2 to REVEAL trial in adults.

Lastly, with respect to manufacturing, we have completed the CMC module 3 amendment submission detailing our commercial process product manufacturing, and drug comparability analysis, and are waiting feedback from the FDA. We continue to believe in the transformative potential of TSHA-120 and look forward to having a collaborative dialogue with the FDA regarding the potential registrational path to bring TSHA-120 to patients with GAN who to reiterate have no approved treatments.

I will now turn the call over to Kamran to discuss financials. Kamran?

Kamran Alam

Thank you, Suku. Research and development expenses were \$12.5 million for the three months ended March 31, 2023, compared to \$38.2 million for three months ended March 31, 2022. The \$25.7 million decrease was due to reduce research and development compensation as a result of lower headcount of \$10.7 million. The decrease was also due to reduce manufacturing and other raw material purchases of \$7.1 million.

We also incurred \$6.4 million reduced expense and non-clinical studies related to translational and toxicology studies, and \$1.5 million lower expense in other research and development activities.

General and administrative expenses were \$8.8 million for three months ended March 31, 2023, compared to \$11.5 million for three months ended March 31 2022. The decrease of \$2.7 million was due to reduce general and administrative compensation as a result of lower headcount and reduced consulting and professional fees.

Net loss for the three months ended March 31, 2023 was \$17.6 million, or \$0.28 per share, as compared to a net loss of \$50.3 million, or \$1.32 per share for three months ended March 31, 2022. The net loss for the three months ended March 31, 2023 was partially offset by revenue of \$4.7 million recognized related to the Astellas transaction.

As of March 31, 2023 Taysha had \$63.4 million in cash and cash equivalents. Taysha continues to expect that its current cash resources will support plant operating expenses and capital requirements into the first quarter of 2024.

I will now turn the call back over to Sean for his closing remarks. Sean?

Sean Nolan

Thank you, Kamran. We believe that the clinical and preclinical data generated to-date across our Rett syndrome and GAN programs reinforce our gene therapy approach and the therapeutic potential for our innovative programs to address severe unmet needs and monogenic central nervous system disease. In the year ahead, we are focused on executing across our near-term milestones in our Rett syndrome and GAN programs.

In the second quarter of this year, we look forward to dosing the first potential adult patient with Rett syndrome, and reporting initial clinical safety data for TSHA-102. We are excited to host an R&D Day in June to review the analysis of the totality of the data for TSHA-120. That will inform our regulatory path forward for TSHA-120 as well as provide an update on our Rett syndrome program. We look forward to providing further updates on our programs throughout the year.

With that, I will now ask the operator to begin Q&A. Operator?

Question-and-Answer Session

Operator

Thank you. [Operator Instructions] The first question comes from Yanan Zhu with Wells Fargo Securities. Please go ahead.

Unidentified Analyst

Hi thanks, for taking our question. This is Juan Hang [ph] for Yanan, and congrats on the progress. So first on the GAN program. So - thanks for the color on the new analysis. I wonder if the patient data will be compared to their own control, like pretreatment progression or be compared to the natural history? And I wonder if there is a bar clear bar on what levels of change from those readout clinically meaningful?

Thank you.

Sean Nolan

Thank you for the question. I would ask Suku to take that first and feel free to add on Salman?

Sukumar Nagendran

Yes. So I will answer the question based on how I understood it. And if I do not place, you know, clarify your question. So the analysis that it's still ongoing, we do plan to compare each patient to their own pretreatment status as well based on the natural history that has been collected by the NIH. But we also have the option of looking at the broader data set in the natural history database where there were 52 patients with a mix of all types of GAN, which include classic GAN, and non-classic GAN.

And I would remind you that in these two types of GAN, the root cause of the disease is the same, hence the gene therapy, and its findings, I think will lead to hopefully a very productive discussion with the FDA if and when we get that meeting. I hope that answers the core of your question was there a second part to your question that I may have missed?

Unidentified Analyst

Yes, thank you, for the color on that. The second part is - for those readout, is there a clear bar on what levels of change clinical meaningful?

Salman Bhai

Great question. It's important to understand clinically, what's not only important for the patients, but also for the families. Right, a simple number on mFARS that changes doesn't necessarily mean it's important to the patient. And that's why we work closely with patients and have interview with families to identify what's most important from them.

As a clinician, it's important for me to understand that patients enjoy independence and we're looking at our data to correlate objective biologic data with functional clinical outcome measures to define how that link is there and what it means for patients. When we have that data in totality, we are seeing positive trends. But of course, this is preliminary. We also use data from other diseases that have ataxia and peripheral nervous system disease to come up with congruence.

As you know, this is an ultra-rare disease. So to clearly identify clinical meaningfulness for this disease alone is difficult and perhaps impossible. However, if we correlate it to other diseases and other clinical syndromes related to this, we can come up with very good proxies that would give a reasonable answer for what patients think is important.

Unidentified Analyst

Got it. Thank you so much.

Operator

The next question comes from Jack Allen with Baird. Please go ahead.

Abigail Gray

Hi, this is Abby Gray on for Jack Allen. Thank you for taking our question. Recently, we've seen the FDA leadership make what appears to be a significant push to pursue the accelerated approval pathways for gene therapies, I guess, namely Starpeta's product in DMD. And we realize that you're still discussing the regulatory pathway for GAN?

So we're hoping you could provide some color surrounding the correlations you're seeing between functional endpoints such as the MFM32 score and the more objective biomarker endpoints such as the retinal thickness or retinal vein thickness and nerve biopsy results?

Sean Nolan

Excellent question, right when we take a look at functional clinical measures, of course, there's an issue with sometimes there's bias or effort dependent, and that's where we turn to biology. And that's in the biology. That's where the question of accelerated approval can come in. So specifically, if we're looking at sensory nerve action potentials, for example, something that we're seeing recover that was not previously there.

Well, that feeds into the feedback into your coordination for mFARS and motor function as well. If you have deafferentation have your muscles, meaning you can't feel where your muscles are, your strength will decrease. And so having these kinds of markers correlate to clinical measures is important. We take it a step further, because sensory nerve action potentials are electrophysiology.

We had nerve biopsies that show axonal regeneration preliminarily, as we evaluate this data, we can also look for giant axons decreasing, and that gets closer and closer to the biology. So, we can then tie and correlate that biology, from histology, to clinical data to functional outcome measures and have a very clear trajectory of what's happening to the patient. Does that answer your question or Suku go ahead?

Sukumar Nagendran

Can I add a little bit also - little bit of more information, which I think is relevant? As Dr. Salman Bhai walked you through - when you step back and look at GAN, obviously, it's an ultra-rare disease, there's no therapeutic option available, obviously, neither intervention where the benefit outweighs the risk and in our assessment using the predefined efficacy endpoints for the protocol in the interventional study, looking at the model that we've generated, looking at the progression of the disease, looking at post-doc analysis.

What we're seeing collectively at this point in time is a trend when it comes to functional, physiological, biological electrophysiological, and human potential radiologic impact of the intrathecal gene therapy that affects the broad spectrum of the disease in the central nervous system and the peripheral nervous system in a clinically meaningful way.

So hopefully, once you complete the analysis, and we go to the FDA and receive that meeting, we can make our case for an appropriate regulatory path, which may hopefully result in approval sooner rather than later.

Abigail Gray

Wonderful, thank you so much.

Sukumar Nagendran

Thank you.

Operator

The next question comes from Kristen Kluska with Cantor Fitzgerald. Please go ahead.

Unidentified Analyst

Hi, this is Rick on for Kristen, thank you for taking our question. Just ask about maybe you could add a little bit more color on the preclinical Rett syndrome data guided for ASGCT this month. How can we kind of put this into context as it relates to other data, other preclinical data we've seen from the program and what should we be expecting there?

Sukumar Nagendran

No, that's a great question. So let me start by saying I'm very excited about the ASGCT data with the caveat that I can't speak about it in great detail, because it's embargoed. So the date I think is in our press release, but it's on the Friday let's see that's next Friday, which is the 19th between 12 to 2 is when the information will be presented in front of the poster. So if someone is there, hopefully you all will go review it.

What is frustrating about gene therapy, and you know, I've been in drug development for a very long time, but it's very rare unusual, where I see preclinical data translate directly into the clinic in the human. I saw this in the SMA program when I was CMO, Chief Medical Officer of AveXis. I did comment that we are seeing this with GAN now where the preclinical data appears to translate into the human based on the 14 patients we have dosed.

And what I would state is that the Rett preclinical data that's being presented at ASGCT next week is very interesting, but the details as you decipher them, I think will hopefully show that we have a very good construct with the miRARE technology that hopefully is validated in this preclinical data that will be presented next week.

And to go beyond that, I'm also hoping that once we start dosing patients, both adults and hopefully children, that all this preclinical work that has been done in these different rodent models and other models will now translate almost one-to-one in the human and hopefully create an SMA like situation and zolgensma.

So again, to tie this back together, I'm sincerely hoping that the preclinical data presented next week at Rett, which I think I hope you'll find impactful will translate into the human and give us hope that we have something clinically meaningful in this gene therapy product.

Unidentified Analyst

Thank you.

Operator

[Operator Instructions] The next question comes from Joon Lee with Truist Securities. Please go ahead.

Unidentified Analyst

Hi, good afternoon, this is Mary on for Joon. So given the ultra-rare situation for GAN, is it at all feasible to do double-blind placebo controlled trial or not and also for objective measures like mFARS? Is there the aim for getting a statistically significant change for this measure? And is that again, given the ultra-rare situation is that possible or not? Thank you.

Salman Bhai

Excellent question. When we think about ultra-rare diseases like this, first, we come into a question of what's the practicality of doing an RCT in a blinded fashion with the placebo control. I think with this disease, that's not possible. We simply don't have enough patients to power a study to find statistical significance. And that's why we're using our data to look at patients as own control as well as natural history to serve as a control right with this disease.

When we have natural history as a control, it serves as a powerful comparator arm now that we have several other patients within the natural history to compare to the intervention, we can determine treatment effect and find statistical significance. mFARS, as you mentioned, is objective. It's of course, the neurologic exam, which I love. So that adds some objectivity to it. And we're able to detect changes, especially when we use the disease progression model to show differences.

The next step is to find clinical meaningfulness in our data. And that's our hope, with the biology, the histology, the electrophysiology to the clinical impact right it's quite widespread over the central and peripheral nervous system. And we're able to detect those changes, Suku?

Sukumar Nagendran

Yes Salman and one more thing I have to emphasize is the NIH has generated the largest natural history database that exists in the world for GAN. That's point one. Number two is the interventional data that we have is also the largest for a disease, like GAN. The third thing that Denihan and we've discovered in the natural history study is that all these patients have ataxia, and therefore makes them far as an appropriate clinical measure to see the efficacy of the product, right Salman?

Salman Bhai

Yes, yes, the neuroanatomy fits perfectly what we're seeing in patients and 100% have ataxia. So why not measure that, and why not use biologic measures to show that correlation between biology to function.

Sean Nolan

Yes, this is Sean, maybe just to add, one other point is that the FDA asked for a double-blind placebo controlled trial in the context of MFM being the primary endpoint, because they thought it was effort based. And when we asked them for clarification around that, they did come back and acknowledge that in this type of a disease state with an ultra-orphan population, you could not feasibly conduct that study.

But they also then went on to say, and reinforce published guidance that a well-controlled trial that has - clinically meaningful endpoints that are objective would be considered, and hopefully what you're getting a flavor for here, and that the doctor bias providing additional color on is that, as we've interrogated the database, and as Suku said, it's the largest database in the world, for GAN, we're seeing across multiple clinical domains that affect both the CNS and the PNS.

What we think is clinically meaningful impact on objective endpoints that are unequivocally objective. And so that's why we're so confident or I should say, encouraged by the data that we're generating thus far. And we look forward to, showing it in much more detail at the upcoming R&D Day.

Salman Bhai

Can I add a point to that too, with the natural history data, what's crucial for this model, which we've shown is that it's homogeneous, it's predictable and based off those reasons, we can now use that model to compare to our intervention patients.

Unidentified Analyst

Awesome. So if I made like, I reformulate the question and ask it a different way, if mFARS was the primary objective from the beginning, would that trial data so far make it convincing for FDA to have, to approve?

Salman Bhai

Awesome question, right. In hindsight, when we take a look at this data, right, it's clear, we look at the neuroanatomy. It's quite clear. But with an ultra-rare disease like this, it's always a struggle, right? What's the initial hypothesis? And what are we getting? So if we were to go back and make that the primary, of course, right, this is a disease that has ataxia on 100% of patients, and those are the findings that we're seeing that we believe to be clinically meaningful.

Sean Nolan

And I would add one more thing to what Dr. May just said is that these patients who were treated were 6 years and older. So the disease had already progressed somewhat given it was neurodegenerative. And given that we saw 6 or more patients having restoration of snap or center innovation potential and other measures of electrophysiology that could potentially translate into a clinically meaningful effect that could be far greater if not treated much earlier given that the neodegeneration may have not progressed as much.

Obviously, to caveat it by saying we haven't studied cellenthant 6 years away, and we have great interest to see if we can have that kind of significant impact in younger patients as well. So collectively, we are very encouraged with the data that we are seeing and looking forward to meeting with the FDA and talk with them.

Operator

[Operator Instructions] The next question comes from Gil Blum with Needham & Co. Please go ahead.

Gil Blum

Maybe a good place to start is just to help me understand the order of events. So you're having your R&D event ahead of an FDA meeting in the third quarter. Why not the other way around?

Sean Nolan

So that's a good question. So keep in mind, though, that we are putting the meeting request in the second quarter, and there is going to be a certain time lag before we actually get the meeting, hopefully. But at the same time, we are generating significant amounts of data from prespecified endpoints post our analysis and the model that Dr. Bay was talking about that we think are truly clinically relevant.

And there is significant interest from many who would like to understand not only the impact of our intrathecal gene therapy on this specific ultra-rare disease to understand benefit over risk but there's also significant interest in trying to understand the clinical platform, what kind of impact would it have across a broad aspect of neurodegenerative and neuro-developmental disorders.

And I would again remind you that if you look at the SMA program with Georgens, the IV formulation had a significant impact in SMA Type 1 and some other subtypes as well. But recently in Novartis released more data with the intrathecal approach where they have a significant clinical impact in SMA Type 2, Type 3, and Type 4 as well.

So this platform, I think, being proven over time will give us hopefully a simple route of administration, which is through lumber puncture that could address many complex disorders of the central nervous system. So due to the significant interest, we think it's appropriate to have this R&D meeting towards the end of June so that we can talk about some of our findings that I think will be hopefully significantly relevant to the patients in question.

Sukumar Nagendran

I think the other thing to add to that is that in a perfect world, there would be a scientific conference that lines up with us, and that would have been the preferable way to disclose things. But in all candor, we stepped through this analysis, not knowing exactly what the outcomes are going to be. And at this point, we're very encouraged by what we're seeing.

And you hopefully can tell from the way we're coming across on the call that we feel this is very compelling. And so we felt that was the best way to disclose it, explain how we were going to move things forward with the agency and highlight our rationale and then provide the data that, in our view, justifies our conviction with the program.

Gil Blum

Okay. That's fair. And bear with me here for a second because this is a little complicated. So Sarepta is on top of minds of everyone. And I'll venture to say that the reason the FDA was okay with Sarepta submitting on an external control for a functional measure is just because they have a random study right behind it.

And that's basically the key difficulty, right? And if you're doing an open-label study for a functional endpoint, the training aspect of it, right, that's what the FDA does not like. And that gets me to my actual question. Is mFARS more objective?

Salman Bhai

As a neurologist, of course. I would say that it is. So for example, if you hold your arms out in front of you if you happen to have a headset on and you take your right pointer finger and touch your nose, there's a little bit of jitter there. Not to most people, that might not be much. But to me, I can pick that up. Now if you have even more jitter, I can pick that up further and start to objectify what your exam findings look like.

And so that's mFARS. So not only are there objective pieces from the neurologic exam there that I can point towards and say, this has intra and interrater reliability, but there's also objective measures that then back that up. So if I was a bad neurologist and not diagnosing correctly, I have objective measures there to help support that. But mFARS as far as I would argue, has objective measures within that.

Gil Blum

Okay. Because in my opinion, I think I might go to the heart of the matter because it's really obvious that the FDA doesn't like external controls when it comes to things that can be trained in an open-label study.

Sean Nolan

And also like the Reata product that was approved with mFARS.

Sukumar Nagendran

Exactly. But there is a history on the regulatory side that sometimes it's just impractical to ask for randomized fiscal control trials and perfection when it comes to clinical trial design. But when there is no therapeutic option available and these kind of studies, especially in ultra-disease show clinical benefit, I think that it becomes a negotiation between the regulatory agencies and the sponsor in making sure the product is appropriately made available to the patient community in question.

And I would go even further to state that Peter Marks and colleagues have been out there, obviously, encouraging a serious discussion between the agency SBIR and the sponsor of this kind of ultra-rare disease program in having some flexibility if the benefit for is the risk, and there's no other therapeutic option available to the patient community, such as in GAN, which is an ultra-rare disease.

If you meet these patients and see and see what happens to them, I think that pathway is now open for us to appropriately position our data, talk to the FDA and show them that we ourselves are convinced. And hopefully, we can convince them that it's an appropriate product for approval such that patients can use the gene therapy product.

Sean Nolan

And I think one other thing to add that we would simply be that in addition to mFARS, what we're trying to do is also demonstrate multiple endpoints that are objective. And I don't want to talk about Snap or EIM, CMA, and MRIs, right? So could just show that no matter where you're kind of cutting the bread, you're getting an effect in all these domains that can only be attributable to the drug.

And I think with the model that we've got put together, we have a very scientifically driven, data-driven control that we can point to, and this highlights the effectiveness across all these different domains. So put very simply, we're not hanging our hat on any one thing. It is the totality of the data.

Gil Blum

Okay thank you taking our question and again congrats on the progress.

Sean Nolan

Thank you.

Operator

[Operator Instructions] This concludes the question-and-answer session. I would like to turn the conference back over to Mr. Sean Nolan for any closing remarks. Please go ahead.

Sean Nolan

Thank you, operator, and thanks to all of you for joining us on the call this afternoon. Have a great rest of your day. Take care.

Operator

This concludes today's conference call. You may disconnect your lines. Thank you for participating, and have a pleasant day.

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Taysha Gene Therapies, Inc. (NASDAQ:[TSHA](#)) Q3 2022 Results Earnings Conference Call November 8, 2022 8:00 AM ET

Company Participants

Kimberly Lee - Chief Corporate Affairs Officer

RA Session - President, Founder and Chief Executive Officer

Suyash Prasad - Chief Medical Officer and Head of Research and Development

Kamran Alam - Chief Financial Officer

Fred Porter - Chief Technical Officer

Conference Call Participants

Gil Blum - Needham & Company, LLC

Geulah Livshits - Chardan

Mehdi Goudarzi - Truist Securities

Michael Ulz - Morgan Stanley

David Hoang - SMBC Nikko

Benjamin Paluch - Robert W. Baird

Yanan Zhu - Wells Fargo

Tiffany Marchell - William Blair

Whitney Ijem - Canaccord Genuity

Operator

Thank you for standing by. Welcome to Taysha Gene Therapies Third Quarter 2022 Financial Results and Corporate Update Conference Call. At this time, all participants are in listen-only mode. Following management's prepared remarks, we will hold a brief question-and-answer session. As a reminder, this call is being recorded today, November 8, 2022.

I will now turn the call over to Dr. Kimberly Lee, Chief Corporate Affairs Officer. Please go ahead.

Kimberly Lee

Good morning, and welcome to Taysha's third quarter 2022 financial results and corporate update conference call. Joining me on today's call are RA Session, II Taysha's President, Founder and CEO; Dr. Suyash Prasad, Chief Medical Officer and Head of R&D; and Kamran Alam, Chief Financial Officer. After our formal remarks, we will conduct a question-and-answer session and instructions will follow at that time.

Earlier today, Taysha issued a press release announcing financial results for the second quarter ending September 30, 2022. A copy of this press release is available on the company's website and through our SEC filings.

Please note that, on today's call, we will be making forward-looking statements, including statements relating to the safety and efficacy and the therapeutic and commercial potential of our investigational product candidates, as well as the strategic investment by Astellas, including the potential for Astellas to exercise any other options we granted to them. This call may also contain forward-looking statements relating to Taysha's growth and future operating results, discovery and development of product candidates, strategic alliances and intellectual property, as well as matters that are not of historical facts or information. Various risks may cause Taysha's actual results to differ materially from those stated or implied in such forward-looking statements.

These risks include uncertainties related to the timing and results of clinical trials and preclinical studies of our product candidates or dependence upon strategic alliances and other third-party relationships, our ability to obtain patent protection for our discoveries, limitations imposed by patents owned or controlled by third parties and the requirements of substantial funding to conduct our research and development activities. For a list and description of the risks and uncertainties that we face, please see the reports we have filed with the Securities and Exchange Commission.

This conference call contains time-sensitive information that is accurate only as of the date of this live broadcast, November 8, 2022. Taysha undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call, except as may be required by applicable securities law.

I would now like to turn the call over to our President, Founder and CEO, RA Session II. RA?

RA Session

Thank you, Kim. Good morning and welcome everyone to our 2022 third quarter financial results and corporate update conference call.

I am very proud of what the company has accomplished in the past few months. The strategic investment from Astellas and the successfully completed public follow on offering have strengthened our balance sheet and extended our cash runway into the first quarter of 2024. We are excited about the recent strategic investment from Astellas to support the development of TSHA-120 for giant axonal neuropathy or GAN and TSHA-102 for Rett syndrome.

The partnership with Astellas underscores the therapeutic and market opportunity of these two programs, and importantly, further validates our scientific approach of combining established gene therapy technology with innovative targeted payload design.

Under the terms of the agreement, Astellas will make a \$50 million investment in Taysha, in exchange for 15% of Taysha's outstanding shares pre follow-on financing, as well as an exclusive option to license the worldwide development, manufacturing and commercial rights to TSHA-120 in GAN for a period of time after receipt of the formal Type B end of Phase 2 meeting minutes from the FDA.

Astellas will also receive an exclusive option to license the worldwide development, manufacturing and commercial rights to TSHA-102 in Rett syndrome for a period of time after we provide a fellow access to certain clinical data from the planned Rett female pediatric study.

Astellas will also receive a right of first offer related to a change in control of Taysha for a period of time after receipt of the Rett clinical data package. To further strategically align the two companies, Astellas will also receive one board observer seat on the Taysha board of directors, enabling us to leverage Astellas' clinical and commercial expertise. The economics associated with the potential licenses will be negotiated by both companies at a later date should Astellas decide to exercise any of its options.

Next slide. We believe we have selected the best possible partner in Astellas, a premier biopharmaceutical company that has built global R&D, manufacturing and commercialization capabilities. Astellas is a dedicated leader in the field of gene therapy, with large scale, fully integrated, in-house GMP manufacturing.

Building upon Astellas' acquisition of Audentes, this partnership fits strategically within their long term vision of expanding its gene therapy capabilities and enhancing focus on genetic regulation to ultimately bring new transformative gene therapies for serious genetic diseases with limited treatment options.

We believe Astellas' clinical development and commercialization experience, combined with Taysha's capabilities and know-how in gene therapy, will help us achieve our shared objectives. We look forward to this partnership and the potential to bring life-changing treatments to patients around the world.

In 2023, we expect to provide an update on the regulatory pathway for TSHA-120 in GAN in January, following our Type 2 end of Phase 2 meeting with the FDA. In addition, we intend to disclose preliminary clinical data for TSHA-102 from the first cohort of adult patients with Rett syndrome, and initiate a Phase 1/2 clinical study for TSHA-102 in female pediatric patients with Rett syndrome in the first half of 2023.

I will now turn the call over to Suyash to discuss our clinical programs. Suyash?

Suyash Prasad

Thank you, RA. And good morning, everyone. Our two lead clinical programs have generated a significant amount of compelling evidence and have exciting upcoming milestones that could support their potential to make lifechanging impacts for patients worldwide.

I'll begin with a recent update on TSHA-120 for GAN. Our GAN program includes a comprehensive and robust clinical package that is supported by evidence generated across multiple clinical, functional, neurophysiological, and pathological endpoints.

These include the MFM32 motor function assessment, demonstrating clinically meaningful slowing of disease progression across all therapeutic dose cohorts compared to natural history decline, with a durability of effect observed up to five years post dosing.

The progressive loss of visual acuity towards blindness, as assessed by LogMAR, stabilized after treatment with TSHA-120. This was supported by the findings in retinal nerve fiber layer thickness, or RNFL, as assessed by optical coherence tomography, which demonstrated stabilization and prevention of further retinal tissue loss following TSHA-120 treatment.

Electrophysiologic nerve conduction studies that support recoverability, stabilization and, in some cases, improvement in sensory response in patients treated with TSHA-120.

Nerve biopsies confirmed that treatment with TSHA-120 result in active regeneration of nerve fibers. And lastly, CMC comparability testing validated that our clinical and commercial grade material are comparable via our release assays and next generation sequencing.

We have a Type B end of Phase 2 meeting scheduled with the FDA via teleconference on December 13, which will enable us to have discussions regarding a pathway to a BLA filing. We expect receipt of the formal meeting minutes by mid-January, at which time we will provide an update.

Next slide, please. We continue to work with regulatory agencies with the goal of achieving conditional approval in Europe and accelerated approval in the United States based on EMA and FDA industry guidance for gene therapies in neurodegenerative diseases.

Based on key registrational requirements from regulatory agencies, including the FDA and the EMA, we have outlined some possible scenarios for approval. In Europe, we believe there's potential to follow conditional approval based on current data set for EMA guidance documents. In the US, the first scenario is immediate filing for approval based on the current data set and comparability.

The second scenario, which we view as our base case, sees us dosing a few more patients to demonstrate comparability of clinical effects between clinical and commercial grade material, which was a similar approval pathway for Zolgensma in spinal muscular atrophy.

The last scenario is to initiate a new pivotal trial, which we think is unlikely, given the published final guidance document on human gene therapies for neurodegenerative diseases and extensive long term safety and efficacy datasets available.

Next slide please. Let's move on now to TSHA-102, the first and only gene therapy in clinical development for Rett syndrome. TSHA-102 utilizes the novel and micro RNA, or mRNA, responsive autoregulatory element platform to regulate trans gene expression phenotypically on a cell by cell basis. The totality of preclinical data generated to date for TSHA-102 represents the most robust data package supporting the clinical advancement of a gene therapy in Rett syndrome. This includes preclinical data and neonatal Rett knockout mice demonstrating near normalization of survival, normalization of body weight and normalization of behavior as assessed by the Bird Score.

Pharmacology data demonstrated significant improvement in survival, body weight, motor function and respiratory health across treatment ages in Rett knockout mice. Toxicology data supported a favorable safety profile of TSHA-102 in wild type rats up to doses fourfold over the clinical starting dose.

Nerve conduction studies remained at the normal range, signifying no evidence of dorsal root ganglia inflammation or other neuropathic deterioration. And lastly, toxicology data in non-human primates demonstrated that all doses studied are well tolerated, while showing broad biodistribution to the brain and spinal cord.

Importantly, NHP studies demonstrated that the down regulatory miRARE platform worked well with low levels of RNA and minimal expression of MECP2 in wild type cells, which have normal pre-existing levels of MECP2. These four preclinical studies together represent a comprehensive and robust package supporting the clinical advancement of TSHA-102 For Rett syndrome.

Our first-in-human Phase 1/2 trial of TSHA-102 for Rett syndrome, also known as the REVEAL study is ongoing. Considering our partnership with Astellas and our intent to provide them with a more comprehensive dataset, we now expect to report preliminary clinical safety and efficacy data from the entire first cohort that includes up to six adult patients with Rett syndrome in the first half of 2023. Also in the first half of 2023, we intend to initiate a female pediatric study in Rett syndrome.

As a reminder, TSHA-102 has received orphan drug and rare pediatric disease designations from the FDA and has been granted orphan drug designation from the European Commission.

In summary, we believe we have a compelling and robust clinical package for TSHA-120 in GAN and preclinical package for TSHA-102 in Rett syndrome. We are extremely excited about the strategic investment and support from Astellas, and look forward to providing additional updates in the first half of 2023 for our two lead clinical programs.

With that, I'll turn the call over to Kamran to review our financial results. Kamran?

Kamran Alam

Thank you, Suyash. This morning, I will discuss key aspects of our financial results for the third quarter ended September 30 2022. More details can be found in our Form 10-Q, which will be filed with the SEC shortly.

As indicated in our press release today, research and development expenses were \$16.4 million for the three months ended September 30, 2022 compared to \$39.5 million for the three months ended September 30, 2021. The \$23.1 million decrease was due to a reduction of \$11.7 million in research and development, GMP, manufacturing and other raw material purchases. Additionally, we incurred \$6.7 million less expense in third-party research and development consulting fees, primarily related to non-clinical GLP toxicology studies and a decrease of \$4.7 million in employee compensation expenses.

General and administrative expenses were \$8.7 million for the three months ended September 30, 2022 compared to \$11.2 million for three months ended September 30, 2021. The decrease of approximately \$2.5 million was primarily due to a reduction of \$1.3 million in professional fees related to pre-commercialization, recruiting and patient advocacy activities. Additionally, compensation expense decreased by \$1.2 million compared to the same period in 2021.

Net loss for the three months ended September 30, 2022 was \$26.3 million or \$0.64 per share as compared to a net loss of \$51.2 million or \$1.35 per share for the three months ended September 30, 2021.

As of September 30, 2022, the company had cash and cash equivalents of \$34.3 million, which does not include the recent \$50 million strategic investment from Astellas or the net proceeds of \$25.6 million generated from the follow-on offering closed in October 2022. We expected that the existing cash and cash equivalents, along with the investment from Astellas and the net proceeds received from the public offering, will enable funding of operating expenses and capital requirements into the first quarter of 2024.

And with that, I'll hand the call back to RA.

RA Session

The next 6 to 12 months will be a busy time for Taysha. On December 13, we're scheduled to have a teleconference with the FDA to discuss the pathway to a BLA filing for TSHA-120 in GAN. We expect to provide a regulatory update on the program once we receive the final meeting minutes from the FDA, likely in mid-January of 2023.

In the first half of 2023, we anticipate clinical data for TSHA-102 from the entire first cohort of adult patients with Rett syndrome, and intend to initiate a female pediatric study in Rett syndrome. We look forward to providing updates on our progress throughout the year.

Question-and-Answer Session

Operator

[Operator Instructions]. Our first question is from Gil Blum with Needham & Company.

Gil Blum

Maybe one on Astellas here. Can you remind us if Astellas has experience in manufacturing of AAV9 ACE genetic medicine? I can't remember exactly what the Audentes vector was.

RA Session

Maybe I'll start out and I'll turn it over to Fred because he's had an extensive experience with the gene therapy manufacturing group over at Audentes and actually took a tour of the new manufacturing site in Sanford.

So, the original Astellas programs in Pompe and X tubular myopathy, those AAV8 programs, not AAV9 programs. But what I will say is the manufacturing is nearly identical. They're using HEK-293, triple plasma transfection and suspension, just like we are. And as we were actually building our facility that we now paused, the layout was almost identical. And so, we feel like there's a significant opportunity to be able to leverage that asset as the collaboration moves forward.

I'll pause there. Fred, maybe you want to give some insight?

Fred Porter

I certainly agree with you. I think while Astellas' main experiences in AAV8, the platform manufacturing approach that Astellas is taking and we are developing at Taysha are really complementary. It's our intention that, as we move forward our programs, that it's really our know-how that will follow these programs through in partnership with Astellas or independently. So, I think it's still again very well suited to a collaboration.

Operator

The next question is from Eun Yang with Jefferies.

Unidentified Participant

This is Matt Chandler [ph] on for Eun Yang. Just want to know, with Astellas' option for TSHA-120 available for a period of time following the receipt of those minutes, are there any specified outcomes from the end of that Phase 2 meeting or that Type 2 meeting with the FDA for Astellas to opt in, or are you expecting anything there?

RA Session

What we've shared with Astellas is the full dataset from that study as presented to the FDA, and we've also shared with them the range of possible outcomes that we've laid out for you guys and what we kind of consider the base case, that being to dose a few more patients, let's call it, three to five for somewhat of a period of time, hopefully, around six months or less in order to kind of demonstrate clinical comparability. And that's something that we've been consistent with in our communication with them.

One thing I will say is I can't speak for Astellas and how they would make their decision, but this is the way that we frame the conversation with Astellas and they're fully aware and understand how either one of those scenarios could play out.

I think what's most important to them is the fact that this is a severe neurodegenerative disease with no treatment alternatives, the fact that the data set here is as robust as it possibly can get for a gene therapy asset. Also, the fact that we have not only long term safety, but long term durability, long term efficacy, functional endpoints, pathological endpoints, and really one that I think leads itself ultimately to a high probability of success and eventual approval. So, I think that's the way that they're framing it versus one particular outcome or another. But, again, I think that's probably a better question posed to Astellas, but the way that I've laid it out to you today is the way that we've framed it for them.

Operator

The next question is from Geulah Livshits with Chardan.

Geulah Livshits

I'm wondering if you could give some color on how a potential registrational trial design would be similar or different from the ongoing Phase 1 or 2 in Rett syndrome in terms of the control group, patient types and endpoints. And if you have a an understanding of, among the several functional outcome buckets, if there are any particular ones that carry more weight in the eyes of regulators or experts in the space.

RA Session

I'll turn that question over to Suyash to discuss how we're thinking about a pivotal design for Rett syndrome. Suyash?

Suyash Prasad

I think it's an interesting one. We actually know we're moving forward to the adult study. Currently, this clinical trial is ongoing, and we intend to strive for the pediatric study in the first half of next year. I think a registration labeling study will really focus on the pediatric population more than anything. I think this is the key population that is of interest. But that also will be applicable to the wider population because we do feel the gene therapy will be applicable to all populations across the age spectrum in Rett syndrome.

In terms of differences between registration enabling pediatric study and an adult study, the buckets are the same. The buckets of assessments are the same, i.e. one big bucket is looking at seizures, how frequent are the seizures, how severe are they, how long are they, and how we reduce the burden there. Another bucket is looking at specific Rett type behavioral assessments, such as the Rett Syndrome Hand Function Scale, the Rett Syndrome Behavior Questionnaire, and there's two or three others that we include in with the adults study and the pediatric study.

Another big bucket is looking at autonomic features of disease, i.e. the respiratory outcomes, which we've demonstrated very clearly, an improvement in the animal studies in which we know from a patient family perspective is incredibly distressing to both adults with the disease and children with the disease.

We're also looking at communication capability as a bucket and also a mix of different biomarkers, whether exploratory CSF or blood-based biomarkers or EEG neurophysiological biomarkers. So the buckets are the same from the adults to the children. Some of the specific assessments are a little bit different, i.e. there are some specific assessments that are more relevant for children and for adults.

One example would be the baby's developmental assessment, which looks at development progression across early childhood. So, that's a scale that will be included within the actual pediatric study that is not in the adult study. So I think there's a lot we can learn from the adult study, the move into the pediatric study.

I do think that the likelihood is that registration enabling study – and we're looking a long way out now here. Our registration enabling study will most likely be in the pediatric population. But the buckets of endpoints are generally the same. I'll stop there.

Operator

The next question is from Joon Lee with Truist Securities.

Mehdi Goudarzi

This is Mehdi on for Joon. Congrats on the quarter and the deal with Astellas. So, about the buffering capacity of the miRARE system, what is the range of tolerated viral copy numbers per cell? And basically, what is the expected translatability of the outcomes from adult patients to pediatrics? Would the same dosing be used in this group?

RA Session

I'll ask Suyash to answer the question. Suyash, just to clarify, I think the question was, is there a limit in cell copy number or kind of genomes per cell in the miRARE platform and how that actually responds would be the first question. The second question would just be the translatability from a dose perspective from the adult population into the pediatric study?

Suyash Prasad

The first question is a really interesting one. The way the construct was designed, it was over-engineered. So there are six micro RNA binding sites in the actual construct itself, plus an additional three in the untranslated region of the construct. These are binding sites to down regulatory micro RNA.

Now, you only need one, to be frank, to be able to keep the level of MECP2 within the appropriate physiological range. But because of this issue of maybe ACE targeting two, three or four copies, Steve Gray, our Chief Scientific Adviser, in partnership with Sarah Sinnett built in kind of an overabundance of these down regulatory micro RNA binding sites in order to make sure we really are truly going to make sure that we do not over express any MECP2.

Now, the exact number of genome copies, we don't know that. What we do know from the toxicology studies is that we've given a fourfold dose over the initial starting dose. The initial stuff, there's 5E14 total vg. And in both NHPs and in rats, over a three and six month period, we gave three doses in both toxicology dose, all the way up to 2E15 human equivalent. And so, we know that sort of fourfold overdosing of the initial clinical starting dose, you actually see minimal adverse – or, well, no adverse toxicological findings. And we know that there's high numbers of gene copies getting to the cells with an intrathecal dose of that high. So we have absolute confidence that going into the 5E14 level in the humans, which is far below the highest dose given the toxicology studies, is not going to result in overexpression. I hope that answered your first question.

The second question about dose translatability from children to adults or from adults down to children, in this case, it's very interesting. Most of the time, when you give a drug systemically, i.e. into a vein, you dose on a vg per kilos basis. So, for example, a six year old boy will generally weigh 20 kilos. So, if you're giving, I don't know, 1E14 vg per kilo, you multiply that by the 20 kilos that he weighs, and obviously, a larger boy or girl, a 12 year old who may weighed 30, 35 kilos, an adult may weigh 60, 70 kilos, so you multiply that number and you do the dose translatability on the weight. It's different for a CNS delivered drug, an intrathecally delivered drug because you're giving the gene therapy – it's a very limited space.

And the other thing that's different is that, as children develop from babies through toddlerhood into teenage years, their organs all grow at different rates, and the organ that grows the fastest, almost the biggest in proportion to the rest of the body is the brain. And so, dose translatability is only really an issue between the ages of zero and four. Once a child hits four years of age, the CSF volume and brain volume are pretty similar to adults. And so, we've done a lot of animal modeling and we've done a lot of looking at the literature, and we've got an approach for kind of moderating the pediatric and the adult doses. And after the age of about four years of age, we give every patient, whether they're a child or an adult, the same dose. Below the age of four, we ratio the dose down dependent on both the CSF volume and the brain volume. And we've got a very thoughtful way of doing this, and it's been discussed with the FDA and other regulators. So, they're very much in agreement.

But as I say, I think the vast majority of patients who will be enrolling in the pediatric study will probably be over the age of three or four. And it's likely we're not going to change that dose, therefore, because the size of a three or four year old, by the time a child reaches three or four years of age, they've reached the brain size of an adult. So, it's likely to be – the way the current pediatric protocol is designed, it's going to be as the same 5E14 total vg starting dose.

Sorry, there were too long answers. But hopefully I gave you comprehensive answers to your questions.

Operator

The next question is from Salveen Richter with Goldman Sachs.

Unidentified Participant

This is Mason [ph] on for Salveen. Along the endpoints that are given for the first clinical data in Rett, what's your view on the bar for success and what threshold you would view as clinically meaningful?

RA Session

Maybe I'll just give a start and then we'll turn it over to Suyash to give kind of a more detailed answer. I think the way that we've looked at these initial clinical studies is certainly safety is going to be extremely important and more so important in the Rett population.

The way that the construct is designed, and Suyash went into this in great detail, is to really make sure that patients get to a level of MECP2 that they need and actually to see not only a significant improvement across kind of the spectrum of disease, but also make sure that we're able to do that safely in the presence of wild type MECP2. And keep in mind these patients with Rett syndrome are mosaics, meaning 50% of their cells are normal and 50% of their cells are kind of [indiscernible] or not producing MECP2.

And to also give you a little bit further detail in the disease is too much MECP2 is toxic. And so, the way that the construct was designed is to express the level of MECP2 that's needed in a genotypic manner on a cell by cell basis. And so, most importantly, confirmation that the construct is doing that. The way that it's been proven in the animal models, both the knockout mouse, the Rett, as well as in the NHP, is going to be extremely important.

And I think as we look across the spectrum of disease from an efficacy perspective, in the initial study, it's really going to be the totality of data across the spectrum. And Suyash laid out some of those key endpoints that we'll be looking at.

But for us, it's kind of holistically the study – safety, making sure that the down regulatory micro RNA construct is working well, and then the totality of efficacy.

I'll pause there, but, Suyash, maybe you have something to add.

Suyash Prasad

I could add a little bit more color. Everything you say is absolutely accurate. And thanks for the question. It's exactly the right question to be asking.

First and foremost, we've got to clear the bar of safety, as RA says. Secondly, we are expecting to, and hoping to, see preliminary efficacy. What I will say, to set expectation is that, when you look at adults versus children, we expect the children to do better than the adults from an efficacy perspective. And we say that for two reasons.

First of all, in general, treating a developing brain seems to result in better clinical outcomes, and also functional outcomes in animal studies than an adult brain. And also, from our animal studies where we did a very large pharmacology study looking at dosing, many different ages of Rett knockout mice, and it was clear that the younger mice performed better than the older mice. So, that's one thing. One important point I'll make.

But I think, from a clinical meaningfulness perspective, we spend a lot of time talking to patients and families. And it's clear that subtle improvements, some of which if they're translates in the adults, from the animals to the humans, will be beneficial. For example, we've already mentioned the autonomic dysfunction, this breathing dysrhythmia that both children and adults with the Rett have, and it's due to autonomic dysfunction in the brain, when they have these alternating periods of very rapid breathing, which is correlated with high levels of anxiety, and then hypoxic excess, where they don't breathe at all for a while and start to go a little blue and cyanosed, and this causes incredible stress to the family. So, anything that can help moderate even that dysfunctional rhythm in a subtle way, and which we saw significant improvement in the animal models, I think will be clinically meaningful to the patients and the families.

In addition, if we can reduce the seizure burden at all, or even bring in some functionality, a modicum of functionality in hand function, for example, all these things will be clinically meaningful. But I think another way to look at it is we're looking at many, many different outcome measures because this is a global neurological developmental disease, and even the subtle change across several different outcome measures will be very, very impactful to the patients and the families.

Operator

The next question is from Mike Ulz with Morgan Stanley.

Michael Ulz

Just given the importance of the pediatric Rett data to the Astellas decision, can you maybe comment on what the trigger is to starting the pediatric study in the first half of 2023. Just curious if you're looking to the adult study in terms of a certain number of patients or certain level of follow-up prior to deciding to start the pediatric study.

RA Session

Maybe I'll just start. And maybe I'll just take that question in the interest of time. I think, ultimately, the main trigger for starting that pediatric study is really getting some level of patient experience and follow up in the adult study. And for us, we don't think that that's a large number of patients. But we do want to make sure that that level of experience is going to be for multiple months of follow-up. And really, for us, it's a safety issue. We want to make sure that that down regulatory micro RNA, those binding sites and that construct, the miRARE platform, is doing exactly the way that we designed it and the way that it's performed in the preclinical studies. That's essentially what we're looking for.

What I'll also say, for the pediatric study, is the pediatric study is going to be a global study. The goal is to do this study in multiple countries around the world. And for us, it's really going to be around laying out kind of the right sequence of filings of both CTAs and then the IND in the United States will also kind of play a role for the way that different sites come online.

But for us, really, the main kind of gateway to us is just getting some level of follow-up. And we've kind of detailed this internally and we haven't disclosed this to the Street. But some level of follow up for multiple months from a few patients in the adult study would give us the confidence to include that into the data package for the pediatric study. And so, we're well on our way to doing that. And we feel good about the guidance that we've laid out with initiating that study in the first half of next year. So we're really excited about it. And the fact that this is a population with significant unmet medical need. There's a large number of patients out there, so recruitment should not be an issue.

The Rett advocacy group puts the prevalence of Rett worldwide at somewhere around 350,000 patients worldwide. We've calculated in the US and Europe somewhere between around 25,000 to 35,000 patients, just in those two geographies. So, the issue around enrollment is a non-issue. It's really for us to make sure that we're getting meaningful data from both the adult study as a gateway into the pediatric population.

Operator

The next question is from David Hoang with SMBC.

Michael Ulz

I just had one. In the case of Rett syndrome, if you were to get MECP2 overexpression to a toxic level with the construct, can you just give us an idea about what that toxicity might look like based on your animal studies? And then how quickly and definitively would it manifest?

RA Session

Maybe I'll start and then I'll turn it over to Suyash. So, we didn't see that in our animal studies. And again, I think Suyash laid out kind of the extensive package that we put forward to both the regulators up in Canada that we'll be putting into the follow-on CTAs and INDs to expand the study geographically. But, for us, I think what we saw was the fact that we were able to dose up to really high doses and we've kind of stopped at fourfold over what the human equivalent starting dose would be at 2E15. We just didn't go above that because we would never be dosing theoretically above that level. But we didn't see any type of toxic effects. I think what we can probably do and have Suyash answer the question, theoretically, of what you would see. And this is really informed by the experience of MECP2 duplication, most likely.

Suyash, do you want to kind of comment there?

Suyash Prasad

Yeah, I will just reemphasize that we gave very high doses in the toxicology study and saw no evidence of any toxicity due to overexpression. And in fact, measured in all the tissues in the animals, DNA, RNA, and protein, we've got high levels of DNA, meaning we're getting good distribution of TSHA-102 into all the tissues in the NHP, but very low levels of RNA, and correspondingly low levels of MECP2, meaning the down regulatory system is working well.

Having said that, it's a very good question to ask. Just in case you see some kind of neurological toxicity that's totally not predicted, what might that look like? And in theory, there's two ways of really drawing that parallel. The first is by looking at what's happened in the clinical situation. And the second is looking at the animal situation. So, in the clinical situation, there is a condition known as MECP2 duplication syndrome, where children inherit two copies of the MECP2 genes. So, they have double the amount of MECP2 and they have associated neurobehavioral and neurological issues related to that.

And in fact, it doesn't look that different to Rett syndrome. These are children who – it's actually a little more severe than Rett and the symptoms come on a little earlier. But basically, you see a whole host of evidence of developmental regression, a lack of milestones, you get seizures, problems with autonomic nervous system dysfunction as well.

So, from a clinical perspective, you see neurological and neurobehavioral outcomes that are global in nature. And that's also true for the animal situation where you encourage overexpression of MECP2. In a mouse model, for example, you will see significant neurobehavioral toxicity and also a drop in survival.

Once again, I emphasize these are highly theoretical. We've not seen anything of that nature whatsoever in our rat or toxicology studies, even when we've been giving very high doses.

Operator

The next question is from Jack Allen with Baird.

Benjamin Paluch

This is Benjamin Paluch calling in from Jack Allen. How quickly could you begin dosing patients with a commercial product of TSHA-120? And will the commercial product require a new IND?

RA Session

Maybe I'll start and we can turn it over to Suyash to kind of talk about the regulatory pathway. So, as we've disclosed, we plan to have a teleconference with the FDA on December 13. This was a Type B end of Phase 2 meeting. And the goal of this meeting is really to lay out in detail the regulatory pathway to approval.

What we've also disclosed is significant clinical safety and efficacy data across a number of meaningful functional pathological endpoints, as well as really nice safety over the history of the study. And the study has been ongoing. Keep in mind, this is the first intrathecally dosed gene therapy study in history. The study was initiated in 2015. So we're going on the seventh year of the study. And there was a run in study, a natural history run-in study that initiated two years before that in 2013 that all patients that were dosed in the interventional trial rolled over from.

So, we really have nice levels of control and comparison from kind of a pre-treatment experience and a post treatment experience. And so, we're going to be going in and discussing the totality of the dataset, as well as the manufacturing overview of the clinical trial material and the commercial material with the FDA. And we've presented data on the commercial grade material by all of our key quality attributes and release assays, as well as the next generation sequencing. The product is biologically indistinguishable. And we're really excited about the work that Fred and his team performed on the commercial product. So, that product is available and ready to go.

What we would do is we're taking the full comp analytical comparability dataset, including the validated potency assay to the FDA for our meeting in December, along with all the clinical data that we've laid out before, and we're putting that in front of the FDA to really ask the question that are we ready for prime time? We think that we are based off of their recent guidance that was finalized about a week or two ago, which is the development of gene therapy for neurodegenerative diseases. Our program across both the CMC section, across the clinical section, checks all the boxes. And it's really to kind of outline the path forward to approval. That's really going to be the key question.

So I think any time after that meeting, we're ready to go to dose additional patients, if that is the need, but that may not necessarily be the need, but we'll have to just wait. We'll have to wait on that conversation with the FDA in order to inform you guys further.

What we would go back to as our base case is kind of scenario two, which means we would need some level of minimum clinical comparability, call it, three patients for six months in order to demonstrate clinical comparability.

The goal is to file some sort of rolling submission as we're generating that data because, keep in mind, the CMC data's not changing, the clinical data, for the most part, is not changing and, certainly, the preclinical data is not changing. And there's a lot of data to put forward in a submission. So we'll inform you guys more post that meeting sometime in January when we have those official meeting minutes in hand. But our base case is kind of providing some level of clinical comparability, most likely three to five patients six months, in that range.

Operator

The next question is Yanan Zhu with Wells Fargo.

Yanan Zhu

On the Rett syndrome, could you talk about, from this panel of endpoints, which might be the earliest from which you can expect to see signals? And also, is the adult study a three plus three design, in that you have the opportunity to expand the treatment cohort, should you see any safety events? And lastly, is there a pre-specified duration at which point the delayed treatment patients are supposed to be crossed over to treatment?

RA Session

Unfortunately, we're only going to be able to take a couple of those questions. Probably I'll do the first when we talk about the design of the study. And I just want to keep in mind, the design as a study for the first cohort is up to six patients, somewhere between three to six patients will be included in that first cohort to just be clear. And that would be patients on treated drug as well as the delayed treatment patients.

On your first question, I think it was more so around what do we hope to see first from an efficacy perspective in the adult patients that would give us confidence that that would translate into the rest of the population? And so, for that question, Suyash, I'll turn it over to you. But maybe it's helped informed by what we saw in the animal studies.

Suyash Prasad

Yeah. Just to clarify, Yanan, the way the protocol is designed, RA is quite correct that we're having up to six patients in the cohort. However, there is a proviso to extend that further, if indeed there is some kind of adverse event that's seen, which, as you know, is a relatively common proviso in most of these Phase 1/2 clinical trials. So, that proviso is there as part of the adaptive study design.

In terms of endpoints that might improve, I think that it's an interesting one. I think for the animal studies, what we expect to improve quickly is the breathing dysfunction that I've already mentioned previously. There are these alternating patterns of rapid and shallow breathing. And in our animal studies, we saw that improve relatively quickly. So that's one possibility, although, frankly, we'll wait and see what happens. But we assume that's one of the changes that may happen relatively quickly.

The other point I will make is that, the other precedent is in the – if you look at the Acadia trofinetide study where they use an analogue of IGF-1 to try and encourage the growth of synapses in the brain, which are missing in Rett syndrome, as you know, they saw changes in the Clinical Global Impression of severity scale and in the RSBQ, which is a caregiver rated Rett syndrome general development questionnaire. And both of those showed improvements relatively quickly. Within about four to five weeks, you can see the separation from placebo. So, I would say what we'd be looking for are the physiological changes in breathing and some of the global Rett syndrome behaviors improving within a few weeks after dosing.

What I will say, as a comparison to the Acadia trofinetide data is that – don't forget, for the gene therapy, we've got to about two or three weeks to get maximal transgene expression. So it may not be quite as rapid as an IGF-1 analog being dosed, but I still think it's going to be – we're going to see potential signs within a matter of weeks.

Operator

Next question is from Sami Corwin with William Blair.

Tiffany Marchell

This is Tiffany on for Sami. For the GAN 120 program, in sort of your base case scenario outcome for the FDA meeting, with dose more patients for comparability, can you provide any color on maybe how quickly you might feel enroll these patients? Have already been identified? And also, like, what sort of range of follow-up could you imagine you might reasonably need to demonstrate comparability? And just as a quick second, do you still have any plans for filing MMA (sic) [MAA] with the EU? Thanks,

RA Session

I could probably answer this relatively quickly. So, the way that we're thinking about TSHA-120 in GAN and kind of what the next stage of development would actually look like, these patients, essentially from the interventional study, have all rolled over from the natural history study. And so, we've dosed 14 patients to date. 12 of those patients in the therapeutic doses and all of those patients rolled over from the natural history study.

So, what's really nice is, you actually have call it one to two, even three years of pre-treatment experience or kind of natural history decline and you're able to compare that with the post treatment intervention and kind of this ongoing stabilization in disease, which was really clear across a number of the key endpoints, not only clinically meaningful, but statistically significant. We're talking about the MFM32, we're talking about visual acuity, we're talking about retinal nerve fiber thickness.

What's also really interesting is the fact that we have biopsies, and this is really kudos to the NIH and the fact that they just designed a very robust study and the fact that they were able to take biopsies pre and post. So, pre dosing and then after dosing up to one year. And we see the – clearly see in a statistically significant manner, the regeneration of nerve clusters and kind of this act of regeneration, which is really exciting.

So, again, functional endpoints, pathological endpoints. We feel really good about the data set and you couple that with the fact that we have commercial scale material that's biologically indistinguishable from our clinical trial material.

So, again, I think all things considered, we feel pretty good going into that meeting, and about proposing what an accelerated pathway could look like to approval. Patients have been identified because, keep in mind, we've only dosed 14 patients over the history of the study. And there's around 50 plus patients in the natural history data set right now. And so, essentially, we could roll patients over from that natural history study into the clinical trial in order to meet whatever the requirement the FDA has laid out for us in order to generate the data needed for regulatory filing.

We'll know more here relatively quickly. The meeting is in December. We'll get the meeting minutes in January. And we'll provide that guidance. But I think if you look at the recent finalized guidance that the FDA has laid out around the development of gene therapy for neurodegenerative diseases and you look over this program, both from a safety and efficacy perspective, as well as the natural history perspective, the program checks all the boxes. Hopefully, that answers your question in the US.

In Europe, it is absolutely our intention to eventually file an MAA in Europe. We do think that pathway will be further – that pathway will be further clarified based on our conversations with the FDA because whatever you would do in the US, you would want to also have that agreement with the regulators in Europe. So, you're only doing it once in order to support that MAA. But we see the pathways on almost a parallel, kind of parallel path. But we would certainly want to make sure whatever we would need to do that would support registration in the US, that would also be an agreement that we could get with Europe.

Operator

The next question is from Whitney Ijem with Canaccord Genuity.

Whitney Ijem

A follow-up on the Rett study update in the first half of next year. I guess, can you talk about what you mean when you say complete cohort that we'll be getting? Or is there a specific amount of follow-up you're waiting for in all of the patients? Or are we waiting for early data from the delayed treatment controls or just kind of help us understand what you mean when you say complete cohort?

RA Session

What I will just reiterate is the fact that first cohort is up to six patients, most likely somewhere between three to six patients. And what we're trying to make sure is that we have enough patients and enough robust follow-up from those patients in order to inform the initiation of the pediatric study. That's really what we're trying to define here. And that's kind of how we see complete. And that's somewhat of a subjective answer. But the way that we're looking at this is three to four patients, including a delayed treatment patients that could act as kind of a real time level of control.

Keep in mind, the natural history in Rett syndrome is probably some of the most well characterized natural history data out of any disease. And the patient advocacy groups who lead the way here have done a fantastic job. So, you also have that dataset to compare to.

But really, for us, it's getting to three to six patients, including a delayed treatment patient, enough data, enough follow up in order to inform the initiation of the pediatric study. And for us, we feel like we'll have enough comfort for that to file the INDs and CTAs for the pediatric study to initiate that study in the first half of next year.

Operator

That's all the time we have for questions. I'll turn the call back over to Mr. Session for closing remarks.

RA Session

Thank you, operator. And again, I'd just thank everybody for joining the call this morning. It's been a quite interesting quarter for Taysha and the company. I couldn't be prouder of the way that the company has responded. It's a very tough market. And I think we could all agree it's quite an interesting market. And we've been into this cycle for over a year now, almost two years. And I just couldn't be prouder of the resilience of the employees of Taysha, the resilience of the patient community, the fact that they supported us, been with us, encouraged us, and we really want to thank them.

And so, I think we're starting to now see the tide turn. We're starting to see that Taysha spirit rise and we're really excited about the next few months and what that has to offer for Taysha, starting with the Type B end of Phase 2 meeting we'll have in December with the FDA. We're quite excited to go into that meeting and to get those meeting minutes to be able to share early next year as well as continued generation of data in our Rett syndrome program and the initiation of the pediatric study in the first half of next year.

And what we're also excited is to now be able to share this with the wonderful partner in Astellas, one that has a real commitment to patients, but a commitment to gene therapy, the modality and also innovative medicines, and so we're really excited to be embarking on this new journey with our partners Astellas and look forward to a very fruitful partnership with them.

With that, I wish you guys a wonderful day. Go vote. Go vote. Go vote. And we'll talk to you guys soon. Thanks.

Operator

Ladies and gentlemen, this concludes today's presentation. Thank you once again for your participation. You may now disconnect.

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Taysha Gene Therapies, Inc. (NASDAQ:[TSHA](#)) Q3 2023 Results Conference Call
November 14, 2023 4:30 PM ET

Company Participants

Hayleigh Collins - Director and Head of Corporate Communications

Sean Nolan - Chief Executive Officer

Sukumar Nagendran - President and Head of Research and Development

Kamran Alam - Chief Financial Officer

Conference Call Participants

Whitney Ijem - Canaccord Genuity

Kristen Kluska - Cantor Fitzgerald

Salveen Richter - Goldman Sachs

Gil Blum - Needham & Co

Yanan Zhu - Wells Fargo Securities

Jack Allen - Baird

Joon Lee - Truist Securities

Silvan Tuerkcan - JMP Securities

Operator

Good afternoon and welcome to the Taysha Gene Therapies Third Quarter 2023 Earnings Call. At this time, all participants are in a listen-only mode. A question-and-answer will follow the formal presentation. [Operator Instructions] Please note that this call is being recorded.

I would now like to turn the call over to Hayleigh Collins, Director, Head of Corporate Communications and Investor Relations. Thank you and you may proceed, Hayleigh.

Hayleigh Collins

Thank you. Good afternoon and welcome to Taysha's third quarter 2023 financial results and corporate update conference call. Earlier today, Taysha issued a press release announcing financial results for the third quarter 2023. A copy of this press release is available on the Company's website and through our SEC filings.

Joining me on today's call are Sean Nolan, Taysha's CEO; Sukumar Nagendran, President and Head of R&A; Kamran Alam, Chief Financial Officer. We will hold a question-and-answer session following our prepared remarks.

Please note that on today's call, we will be making forward-looking statements including statements relating to the therapeutic and commercial potential of TSHA-102 including the reproducibility and durability of any favorable results initially seen in our first and second patients dosed in the REVEAL trial and including our preclinical product candidates to positively impact quality of life and alter the course of disease in the patients we seek to treat in our research, development and regulatory plans for our product candidates.

These statements may include the expected timing and results of clinical trials for our product candidates and other clinical and regulatory plans, and the market opportunity for those programs. This call may also contain forward-looking statements relating to Taysha's growth, forecasted cash runway in future operating results, discovery and development of product candidates, strategic alliances and intellectual property, as well as matters that are not historical facts or information.

Various risks may Taysha's actual results to differ materially from those stated or implied in such forward-looking statements. These risks include uncertainties related to the timing and results of clinical trials and regulatory interactions for our product candidates are dependents upon strategic alliances and other third party relationships, our ability to obtain patent protection for our discoveries, limitations imposed by patents owned or controlled by third parties, and the requirements of substantial funding to conduct our research and development activities.

For a list and description of the risks and uncertainties that we face, please see the reports that we have filed with Securities and Exchange Commission, including our annual report on Form 10-K for the year ended December 31, 2022, and our quarterly report on Form 10-Q for the quarter ended September 30, 2023 that we filed today.

The conference call contains time-sensitive information that is accurate only as of the date of this live broadcast, November 14, 2023. Taysha undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call, except as may be required by applicable securities laws.

With that, I would now like to turn the call over to our CEO, Sean Nolan.

Sean Nolan

Thank you, Hayleigh, and welcome everyone to our 2023 third quarter financial results and corporate update conference call. Today, I will begin with a brief update on our corporate and clinical activities. Then Dr. Sukumar Nagendran, President and head of R&D of Taysha will provide an update on the clinical development of our TSHA-102 program. Kamran Alam, our Chief Financial Officer, will follow up with a financial update and I will provide closing remarks and open the call up for questions.

This quarter, we continue to advance the clinical development of our lead gene therapy program in Rett syndrome, including generating new clinical data in our adult trial in Canada and further engaging in regulatory discussions on our planned pediatric trials in the United States and United Kingdom. As a reminder, the REVEAL Phase 1/2 adult trial is a first in human study that was designed primarily to evaluate safety.

Recall, when we initiated the REVEAL trial in Canada, there was low expectation of efficacy for the stage 4 adult population among the KOLs in the Rett syndrome community, due to the advanced and relentless progression of the disease. The focus was placed primarily on safety. Therefore, it was very exciting when we announced the encouraging initial impact that TSHA-102 appeared to have across multiple clinical domains in the first adult patient treated.

Today, we are pleased to share that as of the week 12 assessment, patient one has demonstrated a sustained response and key efficacy measures and new improvements in several areas, including hand function, which is a hallmark manifestation of Rett syndrome. Additionally, the second adult patient treated also demonstrated a consistent early response across multiple clinical domains four weeks following treatment. The two patients have quite different genetic mutations, with the first patient's MECP2 mutation manifesting in a more severe disease phenotype than the second patient's mutation.

Interestingly, while baseline characteristics and related assessments are very different between the two patients, for example, patient one was completely non-ambulatory and patient two could walk with prompting. Both patients demonstrated an improvement across key clinical domains and presented similarly in a number of efficacy measures as early as were weeks four following treatment. The principal investigator observed that both patients demonstrated improvements across clinical domains, including autonomic function, socialization, and gross and fine motor skills with sustained and new improvements in the first patient at 12 weeks, and initial improvements in the second patient four weeks following treatment.

We believe these early improvements in both patients, coupled with the sustained response through week 12 in the first patient, support the transformational potential of TSHA-102 across multiple genotypes of Rett syndrome and further validate our construct. Suku will discuss the clinical observations and data in more detail. In addition to the positive clinical outcomes data, we are encouraged by the initial safety profile of TSHA-102. The data from the first adult patient showed TSHA-102 was well-tolerated with no treatment emergent serious adverse events, as of the 20-week assessment, and initial data from the second patient showed that TSHA-102 was well tolerated with no treatment emergent serious adverse events as of a six-week assessment.

The Independent Data Monitoring Committee or IDMC recently convened to review the initial clinical data from the second patient dose with TSHA-102 following the patient's required 42 day evaluation period, as well as the 20-week clinical data from the first patient. Based on the encouraging clinical data, the IDMC recommended the continuation of the REVEAL Phase 1/2 adult trial, and provided clearance to dose the third patient in the first cohort evaluating the low dose of TSHA-102.

Looking ahead, we remain focused on further exploring the initial therapeutic potential of TSHA-102 across different ages and geographies. We expect to dose the third adult patient and complete dosing in the low dose cohort in either the fourth quarter of 2023 or the first quarter of 2024. Expansion of the TSHA-102 into earlier stages of the disease remains on track with dosing of the first pediatric patient in our planned U.S. trial anticipated in the first quarter of 2024. Additionally, we expect to receive a response from the UK MHRA on our clinical trial application submission for TSHA-102 in pediatric patients with Rett Syndrome by the end of this year.

We recently entered into a loan and security agreement with Trinity Capital that includes no financial covenants or warrants and terminated our existing loan and security agreement with Silicon Valley Bank. This has extended our cash runway by one quarter into 2026, which will further support the clinical development of TSHA-102. Cameron will provide more details on the agreement. With the extension of our runway and encouraging clinical data in TSHA-102, we believe we are well positioned to execute across our key value creating milestones. Moving forward, we plan to continue to advance TSHA-102 program in an effort to bring a potentially transformational treatment to patients living with this devastating disease.

I will now turn the call over to Suku to provide a more in-depth discussion on our clinical program in Rett syndrome.

Suku?

Sukumar Nagendran

Thank you, Sean, and good afternoon everyone. I'm pleased to provide an update on our TSHA-102 gene therapy program in clinical evaluation for the treatment of Rett syndrome. As a reminder, TSHA-102 utilizes a novel MRI technology designed to mediate MECP2 expression in the central nervous system on a cell by cell basis to mitigate risk of over expression the X chromosomal inactivation and silencing of MECP2 expression that occurs randomly with Rett syndrome results in a mixture of cells that are either deficient in or express MECP2 normally. The heterogeneity in MECP2 expression is what makes Rett syndrome challenging with traditional small molecule and simple gene therapy approaches, but we believe our novel MRI technology can appropriately address this challenge and provide therapeutic benefit.

TSHA-102 is currently being investigated in the ongoing REVEAL Phase 1/2 adult trial of first in human open label, randomized dose escalation and dose expansion study, evaluating the safety and preliminary efficacy of TSHA-102 in adult females with Rett syndrome due to me P2, loss of function mutation. The trial, which was designed primarily as a safety study, is also measuring pre-specified efficacy measures. All efficacy data being collected in this Phase 1/2 trial is hypothesis generating as we continue to generate longer term data across more patients and cohorts, these measures will further inform our thinking relative to optimal primary endpoint selection for registration study purposes.

To date, two adult patients have been dosed with TSHA-102 in the first cohort evaluating the low dose. We are highly encouraged by the early safety and efficacy data seen in both adult patients. Importantly, we believe these data which have been reviewed by the IDMC, reinforce the transformational potential of TSHA-102. TSHA-102 was generally well tolerated with no treatment emergency areas, adverse events as of 20 week post-treatment assessment for the first patient and the six week assessment for the second patient.

In terms of efficacy data, as Sean referenced earlier, it is important to understand that we did not expect to see meaningful efficacy data in adults with Rett syndrome, particularly in patients with the most advanced stage of disease due to the severity and progressive nature of Rett Syndrome. However, based on the clinical data from two adult patients in the low dose cohort, we are seeing clear signs of improvement across multiple domains following treatment with TSHA-102, including autonomic function, socialization, as well as growth and fine motor skills. To provide you with a clear and collective picture, let's begin with an overview of the baseline status of the two patients prior to treatment with TSHA-102.

Both patients had been diagnosed with stage four Rett syndrome, the late motor deterioration stage, which is the most advanced stage of the disease. However, the patients possess different genetic backgrounds and mutation types in their MECP2 gene, which manifest in dramatically different phenotypes and clinical severity. Studies have confirmed that MECP2 mutation type is a reliable predictor of Rett syndrome disease severity with most severe mutations, correlating to greater motor dysfunction, loss of ambulation, and a higher prevalence of scoliosis.

Patient one, a 20-year old female has a large deletion within her MECP2 gene that manifests as a highly severe phenotype. The patient's severity is evident by her clinical presentation at baseline. Prior to treatment, she was in a constant state of hypertonia with complete loss of ambulation and was wheelchair bound. She had lost the ability to sit or stand by eight years old. Additionally, the patient had limited body movement, required constant back support, and had lost fine and gross motor function early in childhood. She had very little hand function with essentially no function of a non-dominant hand. She experienced frequent apnea and hyperventilation episodes and had a history of seizures.

The patient's level of severity is reflected in her baseline scores across efficacy measures, including clinical global impression severity of CGIS, which is a 7 point scale that rates the severity of the participant's illness relative to the clinician's experience with participants who have the same diagnosis. At baseline, the patient's CGI score was 6 indicating severely ill. In contrast, the second patient, a 21-year old female, had a missense mutation in 2 gene that manifests in a milder phenotype. The patient presented with a milder form of disease, which is reflected in a clinical presentation at baseline.

Prior to treatment, she had only past partial loss of ambulation and could walk with prompting, but she experienced progressive kyphosis and bradykinesia impacting her gait and balance. Hand stereotypical appeared at three years old and she mostly held her hands firmly together. Her ability to reach and grasp objects was weak. Additionally, the patient experienced frequent hyperventilation episodes and had a history of frequent seizures. Her level of severity is reflected in her baseline scores across efficacy measures. A baseline CGIS score was 4 indicating moderately ill. The key takeaway is that there are phenotypic differences between the two stage 4 patients, which are correlated to their genetic status.

Importantly, we are seeing a consistent pattern of improvement across pre-clinical domains and efficacy measures in both adult patients following treatment with TSHA-102, despite the differences in their genetic status and severity. Based on clinical observations by the principal investigator both patients demonstrated improvements across multiple clinical domains impacting activities of daily living, including autonomic function, socialization, and growth, and fine motor skills following treatment with TSHA-102.

Specifically, 12 weeks following treatment, the first patient demonstrated sustained a new-improvements from a initial four and six week assessment in multiple clinical domains including fine motor and hand function with the gained ability to grasp objects with her non-dominant hand and transfer them to her dominant hand for the first time since infancy. She was also able to open her hands and dissociate her fingers with the gained ability to stretch her nose and touch a screen.

Progressive loss of hand function is a hallmark characteristic of Rett syndrome and a key area of concern for caregivers that impact a patient's ability to communicate and impedes daily activities, which ultimately limits independence. These new improvements in hand function 12 weeks following treatment, which are not observed in the natural history of Rett syndrome, are very encouraging and support the potential of TSHA-102 to bring meaningful therapeutic benefit to patients and caregivers.

Further, the patients achieved additional gross motor improvements since her initial six week assessment. When she had gained the ability to sit unassisted for three minutes for the first time in over a decade but at week 12, the patient improved the ability to sit unassisted with caregivers reporting her ability to sit up to 15 minutes, and she demonstrated restored movement in her legs. The second patient also demonstrated clinical improvements following treatment specifically, she demonstrated gross motor improvements four weeks following treatment.

Her posture, gait and stability improved, resulting in straight posture and smoother movements when walking. Her fine motor skills also improved. Following treatment, specifically, her hand stereotypies, which are repetitive purposeless hand movements and a diagnostic hallmark of red syndrome improved for the first time since regression at age three. Based on the principle investigator's observations, the patient displayed less forceful hand running, and hands were often open and relaxed at week four, providing new opportunities for fine motor skill learning.

Following treatment, both patients demonstrated improved socialization with increased interest in social communication and activities and improved autonomic function with improved breathing patterns and reduced breathing dysrhythmias, including less breath holding spells and infrequent hyperventilation. The first patient also demonstrated a sustained improvement in sleep quality and duration at week 12. Overall, both patients also demonstrated improvements across key efficacy measures following treatment TSHA-102, which reinforce these clinical observations by the principal investigator.

Let's begin now with an update on the efficacy measures from the first patient. The first patient demonstrated sustained a new improvement across key efficacy measures through week 12. Specifically, she had sustained improvement from the initial four week assessment in clinical global impression improvement of CGI Clinical global impression severity of CGIS and Rett syndrome behavior questionnaire or RSVQ.

CGI is a clinician reported 7 point assessment of overall improvement following treatment adapted to Rett syndrome that accounts for key aspects of the disease. A sustained score of two indicating much improved was reported at week 12, which is consistent with the score reported at the week four assessment. Additionally, the patient demonstrated a sustained 1 point improvement from the baseline score of six indicating severely ill to a score of five indicating markedly ill at CGIS at week 12, which is consistent with the week four score.

In RSBQ, which is a fortified item questionnaire that assesses Rett syndrome characteristics, the patient demonstrated a sustained 22 point total score improvement from the baseline score of 52 to a score of 30 at week 12. The score was driven by improvements in hand behaviors, nighttime behaviors, breathing problems and facial expressions.

Importantly, the first patient also demonstrated new improvements from the initial four-week assessment in the revised Motor Behavior Assessment or RMBA, parental global impressions improvement of PGI-I and Rett syndrome hand function scales or RSHFS. The RMBA, which is a 24question clinician reported scale measuring disease behaviors of Rett syndrome demonstrated a total score improvement of 6 points from the baseline score of 43 to a score of 37 at week 12. The score was driven by improvements in motor dysfunction and social skills.

PGI-I is a caregiver reported assessment of overall improvement following treatment that uses 7 point scale. A score of two indicating much improved was reported at week 12. The RSHFS is a clinician reported outcome of hand function in patients with Rett syndrome, which is evaluated by an experienced independent physical therapist who codes the demonstrated hand function in each video at one of four levels, ranging from no active grasping of any objects to independent grasping.

The highest score that can be achieved is a four. The first patient demonstrated a significant improvement in RSHFS at 11 weeks following treatment. At week 11, although there were no changes from the baseline score of three indicating the ability to hold an object factor two seconds in a dominant hand, she was able to increase the number of objects held from one to two. Additionally, she gained from basic grasping ability in a non-dominant hand.

At baseline, she could not hold any objects with a non-dominant hand, and at week 11 the score of three was demonstrated indicating the ability to hold an object for at least two seconds. She also demonstrated the ability to hold two different objects in a non-dominant hand at week 11. Again, it's very important to note that hand function improvements are not observed in the natural history of Rett syndrome. Now let's discuss the efficacy data from the second patient.

Recall, the second patient had a baseline CGIS severe score of four indicating moderately ill versus the baseline CGIS score of 6 indicating severe ill for patient one. The second patient demonstrated an improvement four weeks post-treatment in CGI-I, PGI-I, RSBQ, and RMBA, a score of three indicating minimally improved was reported at week four in both CGI-I and PGI-I for patient two, the patient demonstrated a four-point improvement in the RSBQ total score from a baseline score of 37 to a score of 33 at week four. As a comparison, the first patient's RSBQ total score was 30 at week 12. The second patient's score was driven by improvements in body rocking facial expressions, walking, standing, and breathing abnormalities.

Additionally, she demonstrated a 7 point improvement in the RMBA total score from the baseline score of 38 to a score of 31 at week four, which was driven by improvements in social skills and respiratory behaviors, including less frequent hyperventilating and breath holding. There were no changes for weeks post treatment in CGIS and RSHFS in the second patient. However, the principal investigator noted improved hand stereotypies, which are not measured in the RSHFS for the first time since regression at age three, and the patient displayed less forceful handling with more open and relaxed hands. We will continue to monitor the patient's progress over time.

More details on the available data can be found in our form 10-Q for the quarter ended September 30, 2023, filed with the SEC. The first patient severity and genetic background suggests that she has less residual MECP2 at baseline and therefore it is reasonable that the treatment effect would be of greater magnitude than the treatment effect observed in the second patient with mild disease. However, while the two patients presented with very different clinical features at baseline, both patients responded in a clinically meaningful manner and presented similarly in a number of key efficacy measures at the week four post-treatment assessment.

The critical takeaway is that the following treatment with TSHA-102, there were early improvements observed across consistent clinical domains and key efficacy measures in the two stage four adult patients with different genetic mutations, severity and phenotypic expression, which is encouraging and may allow us to address an unmet medical need for patients with Rett syndrome across multiple genotypes. Collectively, these improvements coupled with the new and sustained response through week 12 in the first patient supports the transformative potential of TSHA-102 across multiple genotypes of Rett syndrome. We continue to look for consistent patterns of improvement as we dose more patients and evaluate the clinical impact of TSHA-102 in our adult trial.

Looking ahead, we expect to dose the third adult patient and complete dosing in the low dose cohort in either the fourth quarter of 2023 or first quarter of 2024. We intend to provide further updates on available clinical data from the low dose cohort in the REVEAL Phase 1/2 adult trial in the first quarter of 2024. Our efforts to expand the clinical evaluation to pediatric patients with early stages of disease progression remain underway. We are focused on clinical trial initiation activities for our U.S. pediatric Rett Syndrome trial and anticipate dosing the first pediatric patient in the first quarter of 2024.

As a reminder, Part A of a dose finding study will focus on identifying the maximum administered dose and maximum tolerated dose in pediatric girls five to eight years of age with Rett syndrome. Data from Part A will be assessed by the regulatory agencies and the IDMC to determine final key elements of Part B or Phase 2 of the study such as hierarchy of efficacy, endpoint and study duration. Part B will evaluate TSHA-102 in 2H cohorts and expanded 5 to 8H cohort with 1, 2, 1 randomization of randomized treat cohort or delay treatment cohort and a cohort for three to five years of age.

We expect to receive feedback from the UK MHRA on our submitted clinical trial application for the proposed pediatric study by the end of this year, which will further inform program timelines in the UK. As a reminder, there are no approved disease-modifying therapies currently available that treat the genetic root cause of Rett syndrome. There is high unmet need with Rett syndrome caused by a pathogenic likely pathogenic MECP2 mutation afflicting between 15,000 and 20,000 patients in the US, EU, and UK, and a high burden of care associated with it.

TSHA-102 recently received fast track designation and has already received orphan drug and rare pediatric disease designation from the U.S. FDA and has been granted often drug designation from the European Commission for the treatment of Rett syndrome. Overall, we're highly encouraged by the early efficacy and safety data in the first two adult patients and look forward to sharing additional progress.

I will now turn the call over to Kamran to discuss our financial results.

Kamran?

Kamran Alam

Thank you, Suku. Research and development expenses were \$11.8 million for the three month ended September 30, 2023 compared to \$16.8 million for the three month ended September 30, 2022. The net change was due to a \$9.3 million decrease due to lower compensation expense as a result of reduced headcount, lower licensing milestone fees, fewer manufacturing batches, and fewer raw material purchases. This was partially offset by a \$4.3 million increase in activity surrounding ongoing clinical trial efforts and the Rett syndrome REVEAL adult and pediatric studies.

General and administrative expenses were \$8.6 million for the three months ended September 30, 2023 compared to \$8.7 million for the three months ended September 30, 2022. The decrease of \$0.1 million was due to reduced compensation expense due to lower head count of \$2 million and reduced consulting and professional fees of \$0.7 million, partially offset by \$2.6 million issuance costs allocated to the liability classified pre-funded warrant issued in connection with the private placement financing completed in August, 2023.

Net loss for the three months ended September, 2023 was \$117.1 million or \$0.93 per share as compared to a net loss of \$26.5 million or \$0.65 per share for the three months ended September 30, 2022 due to a \$100.5 million non-cash expense recorded in Q3 2023 from a change in the fair value of warrant liability from pre-funded warrants in connection with the private placement financing completed in August 2023.

As of September 30, 2023, the Company had cash and cash equivalent of \$164.3 million. The Company expects that its existing cash and cash equivalent will fund operating expenses and capital requirements into 2026. Taysha entered into a loan and security agreement with Trinity Capital on November 13th and terminated its existing loan and security agreement with Silicon Valley Bank. As Sean noted, our cash runway now extends into 2026 as a result of this agreement and there are no financial covenants or warrants associated with the loan and security agreement.

I'll now turn the call back over to Sean for his closing remarks. Sean?

Sean Nolan

Thank you, Cameron. We are highly encouraged by the clinical data observed in TSHA-102 program to date, the initial safety profile of TSHA-102, and the early and consistent pattern of improvement in observed across clinical domains in both adult patients with very different genetic mutation severity, coupled with the sustained response through week 12 for the first patient is encouraging.

We believe the data presented today further validates the therapeutic potential of TSHA-102 for patients and families living with Rett syndrome. We remain focused on our key upcoming milestones as we approach 2024, including dosing additional patients in the REVEAL adult trial in both low and high dose cohorts and expanding our clinical footprint into pediatric patients in the U.S. and UK.

With that, I will now ask the operator to begin our Q&A session. Operator?

Question-and-Answer Session

Operator

[Operator Instructions] The first question comes from Whitney Ijem from Canaccord Genuity. Please proceed with your question, Whitney.

Whitney Ijem

First question from me, again, great data. Just curious though, in terms of the RSVQ, it looked like in the first patient it increased slightly from week 8 to week 12. Sorry if I missed it, but can you provide any more color, I guess, on which domains in particular changed over that timeframe?

Sean Nolan

Whitney, I can turn it over to Suku, but I think, the main domains where there were changed were in breathing socialization and gross and fine motor skills. Would you -- is there anything that you would add to that Suku?

Sukumar Nagendran

No, Sean, I mean, as you pointed out, those were the domains that actually improved and I think what is interesting to note is that it also correlates with some of the clinical observations that are obvious that have been evaluated by the PI as well as evaluated when it comes to the broad application of CGI and CGIS. So, it's an interesting correlation and given that patient one month's much sicker than patient two, you also see the significant change there in the RSVQ that is maintained from 4 weeks to 12 weeks post-treatment.

Whitney Ijem

And then just does. And then just kind of a broader question, how are you guys thinking about these two patients from a proof-of-concept perspective for the miRARE tech? I guess kind of what else or what else in terms of data or patients, patient number or follow-up would you be looking for to kind of consider this technology de-risked? And can you remind us how you're thinking about additional indications where it might make sense?

Sean Nolan

Sure. Well, I'll go first and certainly open up the Suku, if he has additional comments. But I would say, you know, what's encouraging to us about, you know, proof of concept with the miRARE technology is that the first patient had significantly severe disease at baseline, right? I mean, the CGIS was at 6. So you would infer from that that she's got a relatively low level of endogenous MECP2 and yet preliminarily with through we week 12, we're seeing encouraging response across clinical domains.

And then you juxtapose that with patient two. So keep in mind that that phenotype from patient one is based on a significant deletion genetically. Patient two had a missense mutation resulting in a much less severe manifestation of the disease. So you would think she probably is generating more endogenous MECP2 than patient one. And yet, we through week, let's see, week six, haven't seen any safety concerns with that particular patient.

So in a way, Whitney, I think with the first two patients seen, you're seeing very, very different genotypes corresponding phenotypes and levels of endogenous MECP2 and you're seeing consistent response across clinical domains, and there appears to be a promising safety profile. So, I would say these first two patients are good indicators of the potential safety of the miRARE technology.

Sukumar Nagendran

And what I would add to what you just said, Sean, in very simple terms, is given that there were two different genotypes with different phenotype representations that fit into the classification of classic Rett syndrome, it is reassuring to see that our gene therapy actually worked quite effectively in both patients. And as we continue to accumulate more data and accumulate different genotypes that present as classic Rett syndrome, it'll also give us the confidence that this gene therapy will be applicable to the broader Rett syndrome patient population as a whole.

And the second piece of the puzzle is, as you pointed out or you asked, miRARE technology is critical to maintain a very tight control of MECP2 protein levels in the nucleus. And I think based on the clinical improvements that appear to happen very quickly post gene therapy, given that our product has self-complimented technology as well, that changes have been noted in a positive manner by the PI within one to two weeks post dosing. And this is also reassuring because it enables us to see clinical improvements, which also precede the need for the biomarkers, as such to measure response, which is sometimes what you need in other products, because they take much longer to act.

Operator

The next question comes from Kristen Kluska from Cantor Fitzgerald. Please proceed with your question, Kristen.

Kristen Kluska

Let me also add my congratulations that a second patient exceeded the expectations here. With this particular readout, you commented a lot about the cardiac and some of the respiratory items. And I wanted to see if you can kind of give us a context about the importance of some of these measures. From our understanding is with this disorder, about a quarter of the patient's due experience, a sudden death as a result of complications from these matters.

Sukumar Nagendran

Yes, let me address that because that's a very important question. So, Rett syndrome patients typically do have autonomic dysfunction. And when you think of autonomic dysfunction, it's usually a respiratory abnormalities i.e., they have episodes of apnea where they have breath holding spells followed by significant hyperventilation. That's one. Second, they have a history of seizures depending on which part of the brain, the foresight exists. They also have significant sleep abnormalities at times where they cannot fall asleep, cannot stay asleep, may have also sleep terrors, and they also have GI dysfunction usually I think it's more constipation than diarrhea.

So, these are pretty standard when it comes to Rett syndrome patients. And what we highlighted in patient one and patient two is that our gene therapy, once dose within a week or two, had significant positive impact on these respiratory abnormalities. So, there was significant reduction in these apnea spell as well as hyperventilation episodes. We did not really talk about cardiac abnormalities because these patients did not have any cardiac abnormalities in rhythm or any concerns on the EKGs done. So, those are not clinically appropriate at this point in time for an efficacy measure of a clinical evaluation with our gene therapy.

Kristen Kluska

Okay, thanks. And then looking at the two different phenotypes here, do you think that the scales and the specific anecdotes shared today weigh differently across the different types? Or is it more important you think to just focus on the bigger picture? So I guess while, all of these endpoints you shared are important, I guess the question I'm trying to ask is if any of them are particularly weighed more for each of the different phenotype shared. Thanks again.

Sukumar Nagendran

Yes, let me take that question, that's another very important question because when you look at Rett syndrome patients, you have to break them down into what is their clinical abnormalities that they present with, what are the autonomic dysfunction abnormalities they present with and then these scales that we refer to CGI-I, CGI-S, RSBQ, R-MBA and the hand function scales. I would really focus on the clinical impact of our gene therapy.

Because, for example, if you looked at patient one and patient two, even though their phenotypes are different, they both had developmental milestone abnormalities, meaning patient one was unable to sit, I think after the age of seven or eight. Patient two had difficulties in walking in an appropriate maintenance of gait and posture, probably after the age of 10. These patients also have difficulty with sometimes tracking objects with their eyes. Most of them do have significant hand function abnormalities and stereotypic movements, and they also have difficulties with social interaction and many of them have cognitive challenges.

So clinically, those are components that we have to focus on. And we did highlight that our gene therapy in both patient one and two did have impact on some of these aspects of the disease. We've also highlighted the impact on the autonomic dysfunction and then the scales that you refer to really the numbers on the scales and the degree of change on these scales actually depend on how severe the phenotype is. The more severe the phenotype, the higher the RSBQ and the RMB scores can be.

And then post-treatment, if the therapeutic is efficacious then you'll see a relative change in the number and you will see that even in RSBQ for the second patient, the numbers are much lower because the patient overall has a much milder phenotype. So, you have to keep that relative aspect in mind and look at the broader clinical impact of the product because clinical transformation impact, I think, is far more important from a clinical management and regulatory review standpoint sometimes than a certain scales. And I'll leave it at that for now.

Operator

The next question comes from Salveen Richter from Goldman Sachs.

Unidentified Analyst

This is Elizabeth on for sine. Congratulations on the data. I was hoping you could provide additional color on the seizure activity in the seizure diary. Specifically what was the baseline seizure rate for each patient prior to steroid treatment and what's being observed now? And then also for the second patient, if you could provide some color on how quickly improvements were observed. I know for the first patient, those were observed quite soon after treatment. So any color there would be helpful.

Sean Nolan

Yes. So, that's a very important question that you ask because, so I'm going to try and walk you through first patient and second patient because there are lots of clinical aspects to the seizure history in both patients. So patient one, stage four 20 year old female, right, with severe Rett syndrome had four to five seizures per quarter before the gene therapy was given. The first six weeks post gene therapy there were no reported seizures in the seizure diary nor in the EEG that was reviewed by the PI.

After week six, what was noticed is, this patient is on prednisolone and sirolimus and sirolimus actually works on the liver and inhibits the cytochrome P450 system, which results in Dilantin levels dropping significantly. So what happened after week six up to now is that the Dilantin levels dropped to below 50, which is very low, and therefore there was some breakthrough seizures in this patient. From what I recall, I think this patient had about seven seizures during the period following the six weeks post-treatment.

Now, it is also of interest to note before the gene therapy was given, whenever this patient one had seizures, usually it was when the Dilantin levels were below 100, but I think usually above 50. So I would say that even though this patient had breakthrough seizures six weeks post-gene therapy, this happened when the Dilantin levels were below 50. And therefore, I think the gene therapy still had a protective effect, but the Dilantin levels got way too low to which allowed for breakthrough seizures. So that is patient one, and the patient is doing well. Patient...

Sukumar Nagendran

Yes. So just to try to hit a punch line on that question, Elizabeth, I would say pre and post treatment through week 20 the seizure rates are comparable. His pre-treatment, the patient generally experienced seizures if she had dilantin levels below a 100. And now what it is looking like post-treatment is that the seizures occur when she's less than 50 so at a much lower amount of Dilantin.

Sukumar Nagendran

Yes. Thank you, Sean, for clarifying that. And then patient two had roughly four seizures per month, which is 12 seizures, I guess every quarter. Following gene therapy treatment with our product, this patient had one breakthrough seizure up to week six, if I recall on day 13th. But that was it, just one seizure. So, that is a good signal that our gene therapy is most likely having impact on seizure incidence in this patient as well. So, that's the update on the seizure question for you. Thank you.

Unidentified Analyst

Super helpful. And then just on the second question of the rapidity of response observed in the second patient.

Sukumar Nagendran

Yes. So, that's another important question. So just again to go back to the technology, your product has a self-complementary DNA. So once it's given into the central CSF and gets into the central nervous system, the episode is formed within 48 hours and we think starts producing the MECP1 protein. And the principal investigator has noted that clinical impact appears to be noted within seven to 10 days initially post the gene therapy being given via lumbar puncture. And this includes impact on some motor function as well as reducing some of the autonomic abnormalities. So we are pleased to see that and we hope that will continue because that will hopefully give some of these patients rapid relief of their serious symptomology.

Operator

Thank you. The next question comes from Gil Blum from Needham & Co. Please proceed with your question.

Gil Blum

Allow me to have my congratulations. It's actually rather impressive. So one thing I do want to understand about some of these metrics, could there be a ceiling effect, I mean, specifically talking about RSBQ, we're kind of seeing a leveling around 30. I'm not super familiar with the scale, but is that a possibility?

Sean Nolan

A ceiling effect?

Sukumar Nagendran

Yes, sorry, go ahead, Sean.

Sean Nolan

Well, what I would say to that, Gil, is a non-clinician would be -- I think we have to take into account the stage of the disease, the age of the patients and the dose that we're in at this particular point in time in the study all have to be considered into whether or not there's a ceiling being demonstrated. We are right now landing in some similar spots to your point, and it's still a little early in the assessment, but with that, I'll defer to Suku on the clinical question.

Sukumar Nagendran

No, that's an important question that I think we are still struggling to assess, because keep in mind that both these patients were adults, right? So they were 20 and 21 year old females where we frankly did not expect to see much effect. And the most severe the patient, the higher, I assume the RSBQ score should be given that there are 45 items in that scale, and 38 of them are used to maximize the score of up to a 90. And also keep in mind the -- it is very important to understand who actually does the assessment. It's usually done by the parents or the caregivers over a period of time. So they have to reflect on how the patient or their child is doing over a course of a week or so. So there can be some variability in the score being assessed as well.

And then finally, as far as there being a ceiling effect, I think what we are observing with the gene therapy is the more sicker the patient, the higher the score and the greater the drop. While the patient is not as sick, the drop may not be as significant because they're starting at a much lower baseline. I think I can probably answer your question once you dose a few more patients and we have a little more data. And then the other thing to keep in mind with RSBQ is that the questions you have to actually look at the questions being asked because some of the questions have been designed to evaluate the disease process that worsens over time. RSBQ frankly was not developed to evaluate the therapeutic intervention.

Now, the caveat is for phenotype did use RSBQ combined with CGI-I for a combined endpoint to get their approval. And if you look at the 17 to 20 year old group that for phenotype study that drop in the RSBQ only 2 points. So I guess in relative terms, even though I don't like doing cross study comparisons, our first patient showed a 22 and a 23 point drop and the second patient who has much milder disease at a 4 point drop.

Gil Blum

The severity was...

Sean Nolan

And the severity, that's right.

Gil Blum

And I agree this is very early. This is more for educational purposes. My second question, so kind of as a segue in a hypothetical adult study, would it be beneficial to look at patients with more severe disease just to increase the signal to noise?

Sean Nolan

Yes, you're saying, basically enrich the study with more severe patients to show a bigger effect. You know what's interesting, Gil, when you look at the phenotype data, they generated their P-value difference essentially off the severe patients. But there really wasn't much effect in CGI-I or RSVQ and mild to moderate. So your point's a good one. I think, what's exciting us and we have to see more patients, I think to get to a more definitive answer.

But what we liked about this was the fact that the genotypes were so different and the corresponding phenotypes were so different, yet we're still seeing response is very encouraging that, again, the population that could be treatable here continues to remain significant. So I would say, to reaffirm Suku's point, let's see some more patients, let's get to the high dose as well. And that'll certainly inform how we think about Part B endpoints and trial design.

Operator

The next question comes from Yanan Zhu from Wells Fargo Securities. Please proceed with your question.

Yanan Zhu

So, I have a question on R-MBA and I think, if I heard this correctly, I think the patient number two's R-MBA improvement is roughly 7 points. And that sounds like, that's as big as patient number one's 12 week improvement and much bigger and bigger than patient number one four week improvement. If you comment on why despite of the milder disease in this patient R-MBA improvement appears to be quite striking? And if you can provide the baseline R-MBA score for this patient that would be great. And I have a maybe one or two follow ups.

Sean Nolan

So, the baseline scores to your point were for patient one was 43, for patient two is 38, and then at week four for patient two is 31, week four for patient one was 48, and now at week 12 patient one's at 37. So, there's been a 6 point drop in patient one over 12 weeks and a 7 point drop in patient two over four weeks.

And then, I'll turn it over to Suku to try to get at the rest of your question. What was driving this?

Sukumar Nagendran

Right. So that's an important question because R-MBA is a clinician assessment of the patient as well, and it has five components and I think goes up to a score of as you can see on the scale. The first patient who was much sicker, these R-MBA score was influenced by anxiety, right, and fear and also increased paroxysm, right, which shifted the score in a manner that didn't show improvement.

But actually, when we talked to some of the experts, the understanding was that increased muscle function in the face included the maceta muscles where there bruxism is actually positive. But in the assessment of these questions that were set up, as I said, they were arranged and designed to actually show disease worsening, not necessarily a therapeutic response. And to my knowledge, R-MBA has never been validated to evaluate a therapeutic intervention.

In patient two though, given that this patient had much milder disease, the change I think is positive because this patient already did not have some of the previous abnormalities of severe patients such as patient one hand. And therefore, the questions asked in the R-MBA didn't cloud the actual assessment. So, I guess my point again is that you need to really understand what the questions are within some of these measures to make sense of the eventual numbers. And Kamran, do you want to comment on that or?

Kamran Alam

So, in terms of provide the motor behavior assessment some of the improvements were in social skills and respiratory behavior.

Sukumar Nagendran

So, I guess if I can add one punctuate that point though, what I would also say is that the clinical assessments of each of these patients, especially hopefully for a transformative therapy, will significantly overcome sometimes the need for these skills that mostly have not been validated for therapeutic intervention and assessment.

Yanan Zhu

Thank you, and then -- I'm sorry, my follow up is that for the 4 point improvement RSBQ, which sounded like similar to Treg phenotype, what Treg phenotype can achieve, but it is also on the other hand, sounds like the patient had many improvements clinically. Could you comment on what could the improve the nature of the improvement differ in what you saw in this patient compared with if this patient had been treated with Treg phenotype for example? And maybe lastly, about patient number three, I was just wondering, have you identified that patient, if so, how severe that patient is? Thank you.

Sean Nolan

I would say, with the Treg phenotype piece of the question, when you look at patients that had moderate or mild disease, the impact on RSBQ was 1. So in this particular circumstance, you would definitely grade this person out as a mild or moderate and the impact that we demonstrated was 4 on that particular scale. And as we said, it was driven primarily by the breathing, the socialization and the gross and fine motor skills.

So, it's very consistent with the feedback that that's being put forward by the physician and her assessments and observations by the parents and their assessments and observations. And where she's landing is 33, which is in the same ballpark at week 12 is where the first patient is landing, which is at 30. So, it looks like we're getting a very nice response from her.

And again, I think the Suku's point, the scales I think to me are becoming. It's good to see correlation that the scales are moving in the right direction along with what's being observed clinically. And we're seeing a lot of congruence across clinical domains, which I think is a testament to the product getting to where it needs to be levels of MECP2 being put forward into a more therapeutic area and which is why we're seeing some comprehensive behavior across the table.

As it relates to patient number three, I would say that we have identified the next adult patient. She has not yet gone through screening and there's a couple things at play which is why we modified the guidance to Q4 this year. Q1 next year dosing is that it's final stages of an LAR process, which we've talked about in the past, which we don't have absolute line of sight to, so we know it should be in that window.

And within the institution there's windows of time given the holidays and what have you -- where the patient can slot in. So, it is still possible this year could be Q1 next year. We'll keep you apprised on that, but we do not know any baseline characteristics at this particular juncture. We just do know that it would be a stage four patient.

Operator

The next question comes from Jack Allen from Baird. Please proceed with your question, Jack.

Jack Allen

I was hoping you could provide some more context around the steroid regimen that's given post dose here and how the results from patient one or shaping up in the context of the steroid taper? So, what degree of confidence do you have that these results are different from potential? Any potential impact that could be due to steroids in the short term post gene therapy?

Sean Nolan

Yes, so for this protocol, all patients who are over the age of 18 will be started on prednisolone, 1 milligram per kilogram from day minus seven. And that will be continued out to 16 weeks and then it'll be tapered off over a certain number of weeks down to 0.5 milligrams a kilogram and then 0.25. These patients also get sirolimus at a much lower dose than what's used for transplant based on the body surface area. Also starting around day minus seven and runs, if I recall, 36 weeks and then it's tapered after that. We've looked extensively into the literature, we've talked to all the experts who treat Rett syndrome and they've all said that both prednisone and sirolimus no way or form impacts the clinical progression of the disease. Some people have actually done some experiments too, and they say there is no impact and therefore any improvement seen with the disease is actually due to the gene therapy that has been given.

Jack Allen

And then just as it relates to the sirolimus dosing and the potential implications that had on the seizures the patient two, have you given any consideration to modifying that dosing moving forward?

Sukumar Nagendran

Yes, we've actually have started looking into it, but the issue is sirolimus with prednisolone and we have some experience now with the GAN program where we showed that patients could be dosed regardless of the seropositivity to AAV9 antibodies, which is actually very helpful, especially given that our gene therapy is working in adult patients as well, where there is a higher seropositivity.

But we have to balance that, as you said, with the type of anti-seizure medicine being used, especially if levels do drop significantly like what happened with Dilantin. So I guess the bigger question is, if -- are there other medicines that we can try, which are not processed in a way through the liver and impacted negatively by sirolimus. So I think that's something that we have to continue to assess for now.

Sean Nolan

Yes, I would just add to that, Jack, that it was patient one that was on the Dilantin. And the other thing, at least based on her history, is she's tried multiple products to control the seizures, and Dilantin was the only one that appeared to work. So, it may be a bit of a unique circumstance. We'll just have to see and monitor carefully as we proceed in the study.

Operator

Thank you. The next question comes from Joon Lee from Truist Securities. Please proceed with your question.

Unidentified Analyst

Congrats on the data and thanks for taking our question. This is Mandy for Joon. So you have a closed direct competitor in gene therapy or Rett syndrome from Neurogen NGN-401. Could you please elaborate on anything specifics in your program that could be viewed as a strong differentiator of your program? I mean from construct, design, route of administration those levels because the capsid seems to be the same. And I have a second question, which is related to TSHA-120 in GAN. So are there -- what's the latest there? Is there any takers or are there any negotiations going on for this program? Thank you.

Sean Nolan

Thanks, Joon. Well let's, let's start with the GAN question. I would just say there's not a lot to comment on specifically. We are in the process that we've outlined of stepping through strategic alternatives, and I wouldn't want to comment on anything until it's actually been resolved. So stay tuned on that one, but nothing to report specifically. As it relates to Neurogen, I guess a couple things I could say high level would be -- you're correct that both constructs use AAV9 as the capsid. But that's where the similarities end.

So number one, we have a mini gene. They have a full-length gene. Promoters are slightly different. I think that a key aspect is really the regulatory element, miRARE that we have versus the exact technology that they have. So, the way I would describe our construct is that, it's able to take into account and read the endogenous levels of MECP2 in each cell that it goes into. And based on the level of endogenous MECP2, it will either create exogenous MECP2 or not.

And so I think that's the distinguishing feature where our understanding of the exact technology is that essentially regulates itself. It is not taking into account the endogenous levels of MECP2. So potentially, there could be additional risk for over expression with that construct. I mean, we'll find out in the clinical setting. But that's a key area of differentiation. I would also just note that we're going through intrathecal delivery versus the ICV route that the Neurogen team is embarking upon there.

So, there's a lot of differences. I can't comment anymore on the Neurogen program. I'm not aware of anything specific. But I would just say at this particular point in time, we're quite pleased with what we're seeing in our construct. And I would just go back to the first question that Whitney asked. And proof of concept with our construct with these two very different phenotypes and genotypes is encouraging, right?

We saw a very severe patient that would arguably have very low levels of MECP2, and we're seeing a nice response. And in a patient with a less severe mutation, where you would expect her to be producing significantly more MECP2, we're seeing response coupled with the fact that we're not seeing any signs of over expression. So hopefully that gets at your question, Jim.

Operator

[Operator Instructions] The next question comes from Silvan Tuerkcan from JMP Securities. Please proceed with your question.

Silvan Tuerkcan

Thank you very much for taking my questions and congratulations on the great update here. Just considering this is one single trial site and one investigator, can you just comment on the objectivity and variability of especially autonomic function measures? I would assume that they're measured by some sort of scale a device. How does the breathing pattern, how is it measured, how does it improve? And also the sleep quality and duration. I think that's a very important measure here.

Sean Nolan

Yes, I would just say that there's a lot of -- both of those functions are measured via different scales and by different people. Some of them are going to be measured like the CGI-I as an example, the R-MBA, that's going to be measured by the clinician. That's her clinical observations of what's happening during a clinical assessment. Whereas with the RSVQ or the PGI, that's going to be caregiver administered, and they're going to log that in and demonstrate what they're seeing there. And then we do have examples like when we look at motor function like the hand function is a good example, right? That's being videotaped and sent to an independent party to review and score that.

So Suku, I'll turn it over to you to add more color.

Sukumar Nagendran

And also I think your question was with reference to autonomic abnormalities, right, seen in these patients. So, I'll break this down for you. So remember, in these adult patients who've been referred into this single center in Montreal, they do have physicians who've been taking care of them now for a very long time, so you have the medical history that allow as documents, the abnormalities seen, whether it's in sleep, seizure history, respiratory abnormalities or GI function.

Also, when it comes to sleep, usually these patients also have sleep lab evaluations whenever appropriate and possible that documents the abnormalities that are observed. When it comes to seizures that are usually seizure diaries, parental diaries, and also EEG activities that have been measured that give you some sense of how often these seizures happen. And then when it comes to GI dysfunction, it depends on clinical reports, but also sometimes you do mobility studies in these patients, that may give you a good sense how abnormal GI function could be.

So those are the general parameters that are used to make these assessments. And then the PI obviously does the assessments based on past history and then post-treatment evaluation for the protocol. And then finally, some of these questionnaires scales that Sean was referring to may have subtle questions or obvious questions that give you some hint of is, are there continued sleep abnormalities, are there continued demo motor dysfunction, are there continued respiratory abnormalities, et cetera. So it's a collective assessment of each patient over time.

Silvan Tuerkcan

And just regarding the dosing of the -- not the third patient, but then at the higher, going to the higher dose, is there another DSMB meeting required to switch the higher dose post dosing of the third patient? Thank you so much.

Sukumar Nagendran

Yes. Once the third patient is dosed, you wait six weeks and then you collect the data, clean the database, and then you have to meet with the IDMC or DSMB before you go to the higher dose cohort of 1E15.

Operator

The next question comes from Eun Yang from Jefferies. Please proceed with your question.

And it seems like we no longer have Eun connected on the line, and at this time there are no further questions in the queue.

Ladies and gentlemen, we have reached the end of the question-and-answer session, and I'd like to turn the call back to Sean Nolan for closing remarks.

Thank you, Sean.

Sean Nolan

Just want to thank everyone for attending the call. We appreciate the questions and look forward to speaking again soon.

Take care.

Operator

Thank you. Ladies and gentlemen, that does conclude today's conference. Thank you very much for joining us. You may now disconnect your lines.

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Taysha Gene Therapies, Inc. (NASDAQ:[TSHA](#)) Q4 2022 Earnings Conference Call
March 28, 2023 4:30 PM ET

Company Participants

Hayleigh Collins - Director and Head of Corporate Communications

Sean Nolan - Chief Executive Officer

Sukumar Nagendran - President and Head of Research and Development

Kamran Alam - Chief Financial Officer

Conference Call Participants

Whitney Ijem - Canaccord Genuity

Jack Allen - Robert W. Baird & Co.

Silvan Tuerkcan - JMP Securities

Yun Zhong - BTIG

David Hoang - SMBC Nikko Securities

Joon Lee - Truist Securities

Operator

Greetings, and welcome to the Taysha Gene Therapies Fourth Quarter and Full-Year 2022 Earnings Call. At this time, all participants are in a listen-only mode. A brief question-and-answer session will follow the formal presentation. [Operator Instructions] As a reminder, this conference is being recorded.

It is now my pleasure to introduce your host, Hayleigh Collins, Director and Head of Corporate Communications. Thank you, Ms. Collins. You may begin.

Hayleigh Collins

Thank you. Good afternoon, and welcome to Taysha's fourth quarter and full-year 2022 financial results and corporate update conference call. I'm Hayleigh Collins, Taysha's recently appointed Director and Head of Corporate Communications. I will also be overseeing Investor Relations activities. Ever in corporate communications experience in rare diseases having previously served in a similar role at Jaguar Gene Therapy. I'm excited to join Taysha at this pivotal time and look forward to working with the team to help bring potentially life-changing therapies to patients with rare diseases with high unmet medical needs.

Earlier today, Taysha issued a press release announcing financial results for the fourth quarter and full-year 2022. A copy of this press release is available on the Company's website and through our SEC filings. Joining me on today's call are Sean Nolan, Taysha's CEO, Sukumar Nagendran, President and Head of R&D and Kamran Alam, Chief Financial Officer. We will hold a question-and-answer session following our prepared remarks.

Please note that on today's call, we will be making forward-looking statements, including statements relating to the existing clinical data for TSHA-120 and the therapeutic and commercial potential of TSHA-120 and TSHA-102. These statements may include expected timing and results of clinical trials of our product candidates and other clinical and regulatory plans and the market opportunity for those programs. This call may also contain forward-looking statements relating to Taysha's growth, forecasted cash runway and future operating results, discovery and development of product candidates, strategic alliances and intellectual property, as well as matters that are not of historical facts or information. Various risks may cause Taysha's actual results to differ materially from those stated or implied in such forward-looking statements.

These risks include uncertainties related to the timing and results of clinical trials of, and regulatory interactions for our product candidates, our dependence upon strategic alliances and other third-party relationships, our ability to obtain patent protection for our discoveries, limitations imposed by patents owned or controlled by third parties and the requirements of substantial funding to conduct our research and development activities. For a list and description of the risks and uncertainties that we face, please see the reports that we have filed with the Securities and Exchange Commission including our Annual Report on Form 10-K for the year ended December 31, 2022.

This conference call contains time-sensitive information that is accurate only as of the date of this live broadcast, March 28, 2023. Taysha undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date of this conference call, except as may be required by applicable securities law.

With that, I would now like to turn the call over to our CEO, Sean Nolan.

Sean Nolan

Thank you, Hayleigh, and welcome, everyone to our 2022 fourth quarter and full-year financial results and corporate update conference call. Today, I will begin providing a brief corporate outlook for 2023. Then Suku Nagendran, President and Head of R&D of Taysha will provide an update on our clinical development programs followed by a financial update from Kamran Alam, our Chief Financial Officer. I will then provide closing remarks before opening the call up for questions.

The actions taken earlier this year to improve execution and expedite progress with our two lead clinical programs in Rett syndrome and GAN are having a positive effect. For TSHA-102 in Rett syndrome, we remain on track to execute across our timelines for both initial available safety data and regulatory submissions this year and our ongoing Phase I/II REVEAL adult study. Suku will provide further details here shortly.

For TSHA-120 in GAN, an ultra-rare disease with no currently approved treatments. We recently received constructive feedback from the FDA regarding our follow-up questions to the Type B end-of-Phase II meeting. We are completing a comprehensive review of the data from the ongoing natural history and interventional trial including functional, biological and electrophysiological assessments. The preliminary analysis appears encouraging and we believe there are some compelling new findings that we intend to share with the FDA to further discuss a potential regulatory path forward. Again, Suku will discuss this in further detail shortly.

In the year ahead, we remain focused on achieving the anticipated near-term milestones in our Rett syndrome and GAN programs and continue to work towards our mission of bringing transformational new treatments to patients with these devastating neurodegenerative diseases.

I will now turn the call over to Suku to provide a more in-depth discussion of our Rett syndrome and GAN programs. Suku?

Sukumar Nagendran

Thank you, Sean, and good afternoon, everyone. First, I will start with an update on TSHA-102, our gene therapy program for the treatment of Rett syndrome. As a reminder, TSHA-102 utilizes an innovative miRNA-Responsive Auto-Regulatory Element or miRARE platform designed to regulate the cellular expression of MECP2 for the treatment of Rett syndrome.

TSHA-102 has received orphan drug and rare pediatric disease designations from the FDA and has been granted orphan drug designation from the European Commission. In our REVEAL Phase I/II trial in adult patients with Rett syndrome, we recently initiated screening for the first potential patient and we anticipate dosing the first patient in the first half of the year. We remain on track to report initial available clinical data, primarily on safety, for TSHA-102 in the first half of 2023 and plan to provide quarterly update on available clinical data thereafter.

Importantly, we recently submitted a protocol amendment to allow patients as young as 15 years old to be included in the study, which we believe will further expedite enrollment. In the second half of the year, we intend to continue dosing patients with Rett syndrome in our REVEAL trial. For our study in pediatric patients with Rett syndrome, we plan to submit a CTA to the UK MHRA for TSHA-102 in mid-2023. We also have an IND application submission to U.S. FDA planned in the second half of the year.

Now let's turn to TSHA-120 for the treatment of GAN, which to reiterate is an ultra-rare neurodegenerative indication with no approved treatments or established regulatory pathway. TSHA-120 has received orphan drug and rare pediatric disease designations from the FDA and has been granted orphan drug designation from the European Commission.

In regards to manufacturing, we recently submitted a CMC module 3 amendment submission to the FDA detailing our commercial process product manufacturing and drug comparability analysis. As Sean mentioned, we also received feedback from the FDA in response to our follow-up questions to the formal Type B end-of-Phase II meeting minutes. The FDA clarified MFM32, the primary efficacy scale discussed at the FDA Type B end-of-Phase II meeting, as a relevant primary endpoint only in the setting of a randomized double blind controlled trial, while also acknowledging Taysha's challenge in executing and enrolling such a study design due to the ultra-rare nature of GAN.

As such, the FDA is open to regulatory flexibility in a controlled trial setting and is willing to consider alternative study designs utilizing objective measurements to demonstrate a relatively large treatment effect that is self-evident and clinically meaningful. We are completing a comprehensive review of data from the ongoing natural history and interventional trial including functional, biological and electrophysiological assessments, which will inform our plans for future interactions with the FDA.

The ongoing analysis include functional assessments of MFM32 and Ataxia as progressive gait and limb ataxia, is a common clinical manifestation observed in patients with GAN that often leads to loss of ambulation by the second decade. Additionally, we continue to analyze functional and structural aspects of the retina and optic nerve given that GAN patients experience deterioration of visual acuity and optic nerve degeneration over time.

We are also conducting several objective biological and electrophysiological assessments including sensory nerve action potential, nerve and skin biopsies, ganglion cell and retinal nerve fiber layer thickness, brain and spine MRI images and muscle responses to nerve activation to determine whether there is a relatively large treatment effect that is self-evident and clinically meaningful.

We intend to continue a collaborative dialogue with the FDA regarding the potential registrational path to bring TSHA-120 patients with GAN who reiterate have no approved treatments or established regulatory pathway. We plan to submit a formal meeting request to the agency in the second quarter of 2023 to further discuss the potential regulatory pathway forward for this ultra-rare disease.

I will now turn the call over to Kamran to discuss financials. Kamran?

Kamran Alam

Thank you, Suku. Research and development expenses were \$13.9 million for the three months ended December 31, 2022, compared to \$37.9 million for the three months ended December 31, 2021. Research and development expenses were \$91.2 million for the full-year ended December 31, 2022, compared to \$131.9 million for the full-year ended December 31, 2021. The \$40.7 million decrease was primarily attributable to a decrease of \$20.3 million in research and development manufacturing and other raw material purchases and a \$9 million decrease in license fees.

The decrease in research and development expenses for the year ended December 31, 2022 was also attributable to a \$12 million decrease in third-party research and development fees, mainly related to non-clinical and toxicology studies and a \$4.7 million decrease in compensation expense as a result of lower headcount. Overall, lower research and development expenses for the year ended December 31, 2022 were partially offset by higher clinical trial expenses of \$2.4 million and higher severance expense of \$2.9 million in 2022.

General and administrative expenses were \$7.3 million for the three months ended December 31, 2022, compared to \$11.8 million for the three months ended December 31, 2021. General and administrative expenses were \$37.4 million for the year ended December 31, 2022, compared to \$41.3 million for the year ended December 31, 2021. The decrease of approximately \$3.9 million was primarily attributable to \$5 million of lower consulting professional fees and reduced compensation expenses driven by lower headcount in 2022. Lower general and administrative expenses were partially offset by \$1.1 million of severance expense.

Net loss for the three months ended December 31, 2022 was \$55.7 million, or \$0.99 per share, as compared to a net loss of \$50.4 million, or \$1.32 per share, for the three months ended December 31, 2021. In November 2022, we recorded a \$36.4 million non-cash, non-recurring impairment charge related to the North Carolina manufacturing facility. Currently, we are in the process of actively looking for buyers for the North Carolina manufacturing facility.

The net loss for the three months ended December 31, 2022 was partially offset by revenue of \$2.5 million recognized related to the Astellas Transactions. Net loss for the full-year ended December 31, 2022 was \$166 million or \$3.78 per share, as compared to a net loss of \$174.5 million, or \$4.64 per share, for the full-year ended December 31, 2021.

As of December 31, 2022, Taysha had \$87.9 million in cash and cash equivalents. The company continues to expect that its current cash resources will support planned operating expenses and capital requirements into the first quarter of 2024.

I will now return the call back over to Sean for his closing remarks. Sean?

Sean Nolan

Thank you, Kamran. I am pleased with the progress we have made with our two lead programs during the first few months of 2023, including initiating screening of the first potential patient in the adult Rett study and submitting a protocol amendment that should further expedite patient enrollment. For GAN, we are encouraged by the constructive feedback received from the FDA and the preliminary assessment of the comprehensive data analysis to support a formal meeting request in the second quarter to further discuss the potential regulatory path forward. Our focus throughout this year will be on the execution and delivering across our planned milestones for Rett syndrome and GAN programs. We look forward to providing further updates throughout 2023.

With that, I will now ask the operator to begin our Q&A session. Operator?

Question-and-Answer Session

Operator

Thank you. We will now be conducting a question-and-answer session. [Operator Instructions] Thank you. And our first question is from Yanan Zhu with Wells Fargo Securities. Please proceed with your question.

Unidentified Analyst

Hi. Thanks for taking our question. This is [Quan] on for Yanan. So my question is on the Rett syndrome program, so given that acadia's DAYBUE is now approved for Rett syndrome patients aged five to 20, how would that affect your clinical study count in enrollment, particularly for the UK study? And do you need to include DAYBUE into your trial design? Thank you.

Sean Nolan

Thank you very much for the question. We've [indiscernible] thought in our planning and I'd like to ask Suku to provide some perspective on that. Suku?

Sukumar Nagendran

Yes. Thanks, Sean. This is an important question that you asked because I think getting a product approved for a terrible disease like Rett, I think, is very important for the whole disease state and the patient population. What I would also identify is that by having trofinetide approved, it also increases the awareness of the disease state amongst the physician and patients communities, which could potentially increase the number of accessible prevalent patients and also result in, I think, some serious discussion at the state and federal level when it comes to newborn screening, which could further increase the number of patients available from an incident standpoint. So what I'm saying is collectively this could be a real plus for the whole disease community, but also for sponsors like us who are doing interventional trials.

Now to address your question about whether – once you have an approved product like trofinetide, where the mechanism of action obviously is very different from our product TSHA-102, which addresses the root cause of the disease, we would ideally like to treat patients that are treatment naive such that we can optimize and show the FDA and other regulatory authorities and the patient communities and the healthcare providers who treat this disease that this – our product will have significant impact on clinical progression of disease.

Now that is the hope, but the caveat is as you ask, if there is an approved product, there is always possibility that we may have to have a arm which has a combination product evaluation as well, and that is something we would be happy to discuss further with the regulators and take it on a case-by-case basis. But my team is already considering this in the protocol designs for the future. Sean, anything else you'd like to add?

Sean Nolan

The only other thing I would add is, is that, given the half life of the product and some of the adverse event profile, there's opportunity for patients that take the drug may not be able to stay on it. So you've got a pool of, call it, non-treated patients that you could potentially access. And we experienced with Zolgensma study is that even with the addition of SPINRAZA, patients would be willing to either wait or wash out from taking those other medicines. So we'll certainly keep an active eye on the impact that trofinetide is having. We've given it a great deal of consideration into our scenario planning for clinical trial designs and we remain confident that we'll be able to enroll patients in the U.S. and in other geographies including Canada and the UK. So thank you.

Sukumar Nagendran

And Sean, if I can add one more point. Also, if you look at the trofinetide label, the discontinuation rates in the trials are very high due to GI symptoms and I've forgotten the exact numbers, but you may have to look that up. I think it was anywhere from, I don't know, 70% to even 90% in some of the trials. So that may have significant impact on more patients being available even though this product is available for patients with Rett syndrome.

Unidentified Analyst

Got it. Very clear. Thank you.

Operator

Thank you. Our next question is from Whitney Ijem with Canaccord. Please proceed with your question.

Whitney Ijem

Thanks for taking the question. So for GAN, you kind of listed out a lot of additional endpoints, functionally biomarker, et cetera that you're looking at. And I'm just curious, are those things that were selected all the way along hadn't been analyzed or focused on, or are those things that you are calling patients back in now to look at and will be comparing to natural history? And then part two of my one question is, is the goal there to kind of continue the dialogue with the FDA, use that data to potentially support filing or use that data to design another study?

Sean Nolan

So I'll take a first hand of that, Suku, and feel free to opine. I wanted to answer the first part of your question. This is data that's existing in the database. So these are patients – remember there's been 12 patients that have been treated. We've got the natural history before they were treated, and then all the study visits over the course of time in some cases many, many years and there are a multitude of assessments that were done. And what Suku's team has been doing is, is comprehensively and systematically going through all of that data to fully assess it and to see if there are additional data points that can or metrics that can augment and further demonstrate the clinically meaningful effect and the objective measurement effect of the treatment on these patients suffering from GAN.

And to answer your second question, I'll turn it over to Suku. The idea would be that we would submit a formal meeting request this quarter – the second quarter to dialogue with the FDA about this data and we will put forward after we fully have analyzed this – our view on what we think is the appropriate pathway forward. And that could very well be trying to seek approval with the existing data. So we haven't made a final determination yet, but we're encouraged by the data that we've gathered thus far and how it's starting to line up. Suku, what would you add or clarify to what I said?

Sukumar Nagendran

Yes, Sean. Thank you. So as you highlighted, it's an ultra-rare disease with no available treatment, very small patient population, and the patients are treated – in general, they were more than six years of age. So what we've observed is a slowing of disease as we've all previously talked about when it comes to MFM32. And as Sean pointed out, there were many efficacy endpoints in the protocol that the NIH designed, and it's that dataset that we are looking at when it comes to functional, biological and electrophysiological endpoints. But we're also doing some modeling work, and we think that comprehensive data analysis should give us enough information to go back to the FDA and request a meeting in the second quarter of this year for further discussion on what is the best path forward in a dataset that we think could really make a difference in these patient's lives, especially given it's an ultra-rare disease with no other treatments available. So cautiously optimistic as we collect all the data work with the NIH, and then go to the FDA hopefully and hopefully move this program forward. Thanks for the question.

Whitney Ijem

Thank you.

Operator

Thank you. Our next question is from Jack Allen with Baird. Please proceed with your question.

Jack Allen

Great. Thank you so much for taking the question. I'm going to stick with GAN here. And I was wondering if you could provide an update as to where things sit as it relates to the Astellas option for GAN, how are you thinking about the ex-U.S. opportunity? And then what's the turnaround time for the meeting request and who have you been meeting with specifically at the FDA? I'd love to get any insights there. It does sound like Peter Marks is quite optimistic about accelerated approvals based on a recent medical meeting that you are speaking at?

Sean Nolan

Yes. I'll take a stab at this, and Suku, please jump in. I think to answer your last question first, in terms of who from the FDA is going to be there, it's premature for us to say. We could not definitively make a statement relative to that. We'll do everything we can to make sure that the package that we put together is as compelling as possible based on both the natural history and the interventional data. And your point about Peter Marks is, is a good one. I mean, obviously we're headquartered in Dallas. The MDA Conference was in Dallas. There was a lot of buzz about some of the comments that he has made about how to deal with ultra orphan diseases. And obviously we feel like this one fits the bill tremendously. And that flexibility may lend itself well to the program, but we also understand we have to make that case.

There's new leadership there now with Celia Witten taking over, and it'll – like, we're all watching to see what will happen. And hopefully, we can get some additional flexibility as Peter's kind of outlined in many of his public remarks over the course of time. Suku, do you mind taking on the other two questions from Jack? And Jack you might want to just, if you're on the line...

Sukumar Nagendran

Jack, can you repeat the question because there is a lot of question that you asked.

Jack Allen

Yes. Thanks so much, and I apologize. I know we're still limited to one. But the other questions I had were surrounding the Astellas option. Where does that fit or where does that fit as it relates to GAN? And then maybe if you could just touch on the ex-U.S. path forward for GAN and how you're thinking about potentially following in Europe, I would think? Thanks so much.

Sukumar Nagendran

Sean, do you want me to take that or would you like to take that?

Sean Nolan

Yes, I'll take it. On the ex-U.S. piece, Jack, we're not – we are focused right now on the U.S., so we have not had additional interactions with anyone overseas since the initial discussions. And we want to focus on all of our efforts, energy and resources right now on the U.S. As it relates to the Astellas option that is, we really haven't provided too much detail about that. But what I would say is that, we're still in a window where Astellas has the option and the time to evaluate whether or not they want to opt-in. I think it stands to reason that they would likely make a decision after we have this upcoming FDA meeting that we're planning to have. So we're planning to submit the meeting request in the second quarter. Hopefully, mid-ish year we have that actual meeting. And again, I can't speak for Astellas, but I would say around that time is when they would have the information to make a more fulsome decision on whether or not they want to opt-in on the program. So it's still a very active opt-in.

Sukumar Nagendran

And Jack, you have one more question on the regulatory turnaround times. As you know, it depends on the type of meeting we request, right? Whether it's a Type A, B, C, or D. And I think that's the decision we'll have to make, and that'll impact the turnaround times. Some as you know, could be 30 days or anywhere from 30 to 75 days depending on the type of meeting requested from the FDA, so...

Jack Allen

Great. Thank you so much. I appreciate you taking the questions.

Sukumar Nagendran

Yes. Thanks.

Operator

Thank you. Our next question is from Gil Blum with Needham & Company. Please proceed with your question.

Unidentified Analyst

Hi. This is Rohit on for Gil. Thanks for taking our questions. Can you just talk about the ex-U.S. market for TSHA-102, and would you be open to partnering the program? Thanks.

Sean Nolan

Well, I would say that the opportunity is significant, right? I think when we talk about the factors, there's approximately 25,000 patients in the U.S. and EU combined. So the opportunity over there is significant. There's good infrastructure over there in terms of clinical study sites, treatment centers, the patients are well identified. So we're encouraged by the opportunity over there. It's one of the reasons we've focused our clinical efforts in submitting that CTA mid-year into the UK.

Just trying to think of the second part of the question. Well, the partnering aspect, I would say that that's something that we would potentially consider. I think you always have to look at all options, your current capital situation and make a determination on resource wise and otherwise, is it better to partner that or to better to keep it to yourself. Right now, the plans are for us and we have the funding this year to execute the trial as we've outlined it, the plan trial, I should say. So it's an option that we have, should we decide to pursue that.

Unidentified Analyst

Thank you.

Operator

Thank you. Our next question is from Silvan Tuerkcan with JMP Securities. Please proceed with your question.

Silvan Tuerkcan

Yes. Thank you. Thanks for taking my questions. Just to come back to GAN, I think the last time the FDA attempted you a modest or I don't remember exactly the wording, effect on the primary endpoint and that's why they wanted maybe a controlled trial. But I mean, obviously those are just words. And so how do we know now that they're open to a strong efficacy measure that you have met the bar with these additional endpoints. Could you stack them together to show a strong outcome here with the data at hand or how do you imagine this will play out? Thank you.

Sean Nolan

Well, I would say first of all that what the FDA said at the meeting minutes, the initial meeting minutes was very focused on MFM32 because that's where the majority of the discussion happened. That was the primary endpoint, that was the focus of the company. And so all of their comments were generally around that particular endpoint where they basically said, because they believe it's subjective, you need to have a double blind randomized controlled trial. So when we went back to them and we asked the subsequent questions, I would say that the new news is that they restated their review on MFM32, but then they said that they're willing to evaluate alternative trial designs that are controlled and a control can be natural history as you know, that have endpoints that are clinically meaningful and essentially objective.

And so that is a, I would call it a door that was – a new door open there opportunity wise that makes a lot of sense to us so that it's incumbent upon us to determine what do we think is the data that would justify and address those two aspects, what is clinically meaningful and what is objective. And so with that, I'll turn it over to Suku to just give you a flavor of the comprehensiveness and the totality of data that we're looking at and why we're encouraged. Suku?

Sukumar Nagendran

Yes. Thanks, Sean. So your question is an important one. So let me start by saying again, I think somebody earlier asked about Peter Marks and the FDAs position when it comes to [CNS] ultra-rare disease, where there is no treatment available. So I think those remarks at the MDA were very important and hopefully we'll have some strategic impact on any sponsor that's dealing with an ultra-rare disease GAN or otherwise.

Now, as Sean pointed out, as we continue our in-depth detailed analysis, the big question here is it's not just a MFM32. There are multiple other efficacy endpoints. And the question is, will our intrathecal gene therapy actually show broad clinical impact, some or most of which could be collectively considered clinically significant, whether it's really in a very large way or even in a moderate fashion in our ultra-rare disease that allows us to make a case in behalf of patients and as the sponsor for potential accelerated approval or an approval that is acceptable such that we can make this medicine available to the patient community.

And as Sean pointed out, it's the collective birth of data I think that could eventually make the case for this therapy for further review at the FDA and for us to make the case for the submission of a meeting with the FDA in the second quarter. So I hope you understand what I'm trying to explain. It's not just MFM32. There are multiple other endpoints that I think that we've observed with the help of the NIH and other experts that are presenting this ultra-rare disease called GAN, that our product may have clinical impact. And I think that collective case is what may give strength to the potential review and approval of the product. So take you, and I'm keeping my fingers crossed, that's what we can do for this patient community. Thank you.

Silvan Tuerkcan

Great. Thank you very much.

Operator

Thank you. Our next question is from Yun Zhong with BTIG. Please proceed with your question.

Yun Zhong

Hi. Thank you very much for taking the question. So my question is on the Rett syndrome program. And so the change in the patient age to treat patient as young as 15 years old. In addition to helping patient enrollment maybe, do you have any other goals that you would like to achieve in terms of treatment outcome analysis and the initial data? Would that be safety only or will you be able to provide any additional information?

Sean Nolan

Suku, would you like to take this question, please?

Sukumar Nagendran

Yes, Sean, I will. Absolutely. So this is another very important question. So there was a very important clinical reason that my team and obviously as a sponsor, we decided to submit this updated version for amendment to Health Canada because by dropping the age to 15, and we do have pre-clinical data and other data that supports us doing this, it enables us to treat a younger group of patients, which we think in this neurodevelopmental disorder may allow us to have greater impact over time. So the question on the table is, a) by dropping the age and having certain endpoints in our efficacy measures and also evaluating safety, will we not only have access hopefully to more patients, given that it's now a larger patient pool, but could we also show greater clinical impact that goes beyond safety in a much shorter timeframe?

So the question is, when you treat adult patients who have more mature disease or more progressive disease over the age of 18, will it take much longer for any product to have impact versus once you drop the age, could you have much greater clinical efficacy impact. So our hope, even though the initial dataset that we'll accumulate over time will be safety data. The big question on the table is will we also show greater clinical efficacy impact? And my hope as a clinician is that is what we will also see, which will allow us to show the strength of our gene therapy intervention for Rett syndrome, which as you know, is a terrible disease by treating the root cause of the disease. So that is our hope, and I hope that answers your question.

Yun Zhong

Okay. Great. Thank you.

Operator

[Operator Instructions] Our next question is from David Hoang with SMBC. Please proceed with your question.

David Hoang

Thanks for the update and taking my question. I had one question just with GAN. Have you consider – are you formally considering accelerated approval pathway there? Is that something given the endpoints and the data that you are now reviewing? Do you think that path would be available to pursue? And if so why or if not, why not?

Sean Nolan

Suku, would you please take that question?

Sukumar Nagendran

Yes, Sean. I can only give you my opinion based on the data that I've seen in our overall regulatory discussions, right. So obviously, what we can do is look at our dataset, see if the broad impact of our product gene therapy is truly clinically meaningful, and then ask for the meeting with the FDA. And absolutely, if we believe our product is truly making a difference in this ultra-rare disease, while there's no treatment option available, I would absolutely love to ask for the FDA to consider our product for accelerated approval such that we can make the medicine available to patients. But the caveat is this, right. So this I have to be very clear on is we have to have a collective dataset that truly enables us to make a convincing case with the FDA that this gene therapy qualifies for accelerated approval. So that is what we are hoping for, and that is the plan when we submit our request for an FDA review once we do complete our full analysis, okay. So I hope that helps, and I don't know Sean, if you wish to add anything more to what I said?

Sean Nolan

Yes. Look, the only thing I would add to that is when you think about some of the remarks from what Dr. Peter Mark said has said multiple times publicly, and you think about the disease state of GAN and a product that could merit an accelerated rule. It certainly fits the bill. We don't want to get ahead of ourselves at all, and we don't want to prejudge final data. I would just say that based on the preliminary assessment, we're encouraged about the package that we can put together and we will certainly make the most aggressive presentation we can based on data to four patients, and to get down this product as soon as possible, given that there's nothing available to particular point in time. So if we're convinced the data is compelling and meets the bar, you would push hard for something like that. Thanks for the question.

Operator

Thank you. Our next question is from Joon Lee with Truist Securities. Please proceed with your question.

Joon Lee

Hi. Thanks for the update. When you say in your press release that the FDA is open to regulatory flexibility in a “controlled trial settings”, does that necessarily refer to placebo controlled trial setting or can that include some other controlled setting? And it's the latter, what could it be?

Sean Nolan

Well, I'll give you my answer to that and Suku, please opine. But when you look at FDA guidance and you look at accelerated approval, there's generally a consideration of a controlled trial. And that controlled trial is one of the designations would be as an example, natural history. So I think there's a distinction between a controlled trial and a double blind placebo controlled trial. And the language written in the responses that we got from the FDA are clear on those. When they were talking about MFM32, they were talking about a double blind placebo controlled trial, when they were talking about alternate trial designs that met the bar of clinically meaningful and objective end points, they talked about a controlled trial. So I think they're speaking to the letter of the guidance, but Suku, I would ask you for further clarification on that.

Sukumar Nagendran

Yes. Thanks, Sean. So given that it's an ultra-rare disease, doing a placebo controlled trial, I don't think it will be practical and could take forever. So if there are alternative study design, necessary or have to be discussed, the simplest would be to dose a few more patients where you already have pre-treatment natural history for comparison. So with that caveat, our hope is that the collective dataset that we submit to the FDA will qualify for a serious review and potential appropriate approval if the FDA thinks that's the best way path forward for the patient community. So I would leave it at that. And Sean, is there any other question you wish me to address? So hopefully, we addressed the question that was asked.

Sean Nolan

No, I think you did.

Sukumar Nagendran

Okay. Thank you.

Joon Lee

Thanks.

Operator

There are no further questions at this time. I would like to turn the floor back over to Sean Nolan for closing comments.

Sean Nolan

Thank you, everyone for their time and interest in what we're trying to accomplish here at Taysha. I'm very pleased that the progress we've made in the short time period in 2023, we've got a long way to go, we are working hard, and we look forward to sharing future updates with you in the coming months. Thank you all and have a good night.

Operator

This concludes today's teleconference. You may disconnect your lines at this time.
Thank you for your participation.

- Read more current TSHA [analysis and news](#)

- View all [earnings call transcripts](#)

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Taysha: The FDA Just Stuck A Major Blow To Their Plans

Feb. 06, 2023 8:00 AM ET | **Taysha Gene Therapies, Inc. (TSHA) Stock** | ALPMF, ALPMY | 2 Likes



Avisol Capital Partners

Investing Group Leader

Summary

- Taysha has a good chance of scoring with the GAN indication.
- Astellas may license this program if that happens.
- However, the FDA's request for more patients is a critical problem.
- We are Avisol Capital Partners, a team of medical/biotech experts and finance professionals. We lead the investing group [Total Pharma Tracker](#), where we aim to make the science of biopharma investing easily understandable to regular investors.



janiecbras

Since its IPO in September 2020, Taysha Gene Therapies (NASDAQ:[TSHA](#)) stock price has been on a consistent decline. Starting out at \$20, it went up to \$35 for a brief spell, but it has been downhill ever since. The stock currently trades at \$1.5, and even a major collaboration with Astellas ([OTCPK:ALPMF](#)) has not helped.

Taysha's pipeline looks like this:



Taysha pipeline (Taysha website)

So they have three clinical stage candidates, TSHA-120, TSHA-118 and TSHA-102.

A brief overview of the company would go like this: launched in 2020 to develop monogenic gene therapies for CNS diseases. First proof of concept (preclinical) data from a program in Angelman Syndrome, which does not seem to be on the current pipeline any longer. First clinical (?) safety data from a program in CLN7 disease, a form of Batten Disease, which, again, does not seem to be on the pipeline anymore, although there's a program in CLN1 disease, which is another genetic subtype of Batten Disease. Then in January 2022, the first real data - from the high dose cohort for TSHA-120 in giant axonal neuropathy, or GAN. The data showed marked improvements across all dose cohorts at various time durations. Key [data](#):

- The high dose cohort of 3.5×10^{14} total vg led to a 5-point improvement in the change in the rate of decline in MFM32 score by year 1, compared to natural history decline of 8 points, the company said. 32-item Motor Function Measure (MFM32) is a key measure used to assess the functional abilities of patients with neuromuscular diseases.
- Across all therapeutic dose cohorts, there was a 7-point improvement in the rate of decline in MFM32 score by year 1, compared to natural history decline of 8 points.
- By year 3, the mean change in MFM32 was a 10-point improvement for all therapeutic dose cohorts, compared to the estimated natural history decline of 24 points.

There are 5000 patients in the company's addressable markets (according to [orphanet](#), to date 50 families have been identified, although the number should be substantially more). This is a terrible pediatric, hereditary disease where patients become wheelchair-bound in the second decade of their lives, and "typically die in the third decade from respiratory failure." There are no approved treatments. There has not even ever been any other trial run by the industry outside of this one - [here](#).

Taysha, earlier in preclinical studies, also showed positive [data](#) for this indication:

Treatment with AAV/JeT-GAN restored the normal configuration of IFs [intermediate filaments] in patient fibroblasts within days in cell culture and by 4 weeks in GAN KO mice.

While there are risks associated with the AAV9 vector, and the market is really small and largely undiagnosed, this data is a proof of concept for the whole Taysha platform. This is what caused Astellas to take an interest in Taysha - not just the GAN indication alone, but the platform itself was partly validated by this early data.

Taysha's other clinical stage program is for Rett Syndrome. A phase 1/2 trial is ongoing for TSHA-102.

Astellas paid \$50mn to pick up a 15% stake in TSHA stock. In exchange, Astellas received an option to license these two gene therapies after end of phase 2 meeting minutes have been received from the FDA (for GAN), and the company provides Astellas access to certain clinical data from the female pediatric study (for Rett). As the company mentions:

Regulatory update for TSHA-120 in GAN following receipt of formal meeting minutes from the Type B end-of-Phase 2 meeting with FDA expected in mid-January 2023

This is then a major catalyst for this small company because once they get positive feedback from the FDA, Astellas may decide to license the program for an upfront fee, plus milestones and royalties. This will be a major deal here for TSHA.

Astellas also received one seat on Taysha's board of directors. If Astellas decided to exercise its option, there will be a separate and hopefully larger agreement and payments.

Update after the FDA minutes

As I was preparing this report, [the FDA came back](#) with a request to Taysha to dose more patients to support a marketing application for TSHA-120. The FDA suggested a placebo-controlled, double-blinded design for these extra patients. The company has requested more clarity from the FDA on the design and data requirements for approval. This has led to a selloff in the stock, and a restructuring effort at Taysha. Astellas may not opt in to the program now, as well. On the positive side, the FDA has agreed to MFM32 as an acceptable endpoint for the trial.

Financials

TSHA is a microcap with a market cap of \$109mn and a cash reserve of \$34mn. On top of that, Astellas invested \$50mn. Immediately after the Astellas investment, TSHA ran a \$28mn offering. They should have approximately \$90mn at this moment. Research and development expenses were \$16.4 million for the three months ended September 30, 2022, while general and administrative expenses were \$8.7 million. That leaves them with a cash runway till the first quarter of 2024. Now with the added expense of more patients in the trial, the funds may not last long.

In December, TSHA brought in Chair of the Board of Directors, Sean P. Nolan, as the new CEO. Mr Nolan was the CEO of gene therapy company AveXis before it was bought out by Novartis.

Bottomline

TSHA is trading at 52-week lows. They will now need a new trial before they can submit a BLA, which will drain resources and time. My opinion before the FDA's response was that this was a risky stock but maybe worth a small investment given the decent GAN data. The data is still good, and they do have some cash. However, this is now an even riskier investment, even with the Astellas interest and the GAN data.

Editor's Note: This article discusses one or more securities that do not trade on a major U.S. exchange. Please be aware of the risks associated with these stocks.

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Home > Stock Ideas > IPO Analysis > Healthcare

Taysha Gene Therapies Seeks \$125 Million IPO For Ambitious Pipeline

Sep. 17, 2020 3:17 PM ET | **Taysha Gene Therapies, Inc. (TSHA) Stock** | SIOX, AZN, AZNCF... |

8 Comments | 2 Likes



Donovan Jones

Investing Group Leader

Summary

- Taysha Gene Therapies has filed proposed terms for a \$125 million IPO.
- The firm is developing gene therapies for various neurodegenerative and other monogenic disease candidates.
- TSHA is still at a preclinical stage of development for its entire pipeline and the IPO isn't cheap, so may be more suited to long-term hold institutional investors.
- I'm Donovan Jones, a software and IPO specialist analyzing technology companies. I also run the investing group [IPO Edge](#) with exclusive analysis of the U.S. IPO market.

Quick Take

Taysha Gene Therapies (NASDAQ:[TSHA](#)) has filed to raise \$125 million in an IPO of its common stock, according to an S-1 [registration statement](#).

The company is developing genetic therapy treatments for various neurodegenerative diseases and other disorders.

TSHA is still at a preclinical stage and the IPO is priced above the typical range for clinical stage biopharma IPOs, so it may be more suited to long-term hold institutional investors.

Company & Technology

Dallas, Texas-based Taysha was founded to advance its pipeline of various gene AAV (adeno-associated virus delivered) therapy candidates for neurodegenerative diseases, neurological disorders and genetic epilepsies.

Management is headed by president and Chief Executive Officer Mr. RA Session II, who has been with the firm since the firm's founding and was previously Chief Business Officer of the gene therapy subsidiaries of BridgeBio Pharma ([BBIO](#)).

Below is a brief overview video of Tay-Sachs Disease:



Source: [healthery](#)

The firm's lead candidate is TSHA-101 and is being developed for the treatment of GM2 gangliosidosis, or Tay-Sachs [disease](#). Management expects to begin Phase 1 trials in Canada by the end of 2020. The company also expects to submit INDs for four programs to the US FDA by the end of 2021.

Below is the current status of the company's drug development pipeline:



*Option rights

** Taysha has exclusive options to acquire an additional four programs from UT Southwestern

GRT: Gene replacement therapy; mRNA: microRNA; shRNA: short hairpin RNA

Source: Company S-1 Filing

Investors in the firm have invested at least \$18 million and include PBM Capital Group, UT Southwestern and FMR LLC (Fidelity Management).

Market & Competition

According to a 2020 market [research report](#) by Data Bridge Market Research, the market for GM2 ganglioside diseases, of which Tay-Sachs is one form, is approximately one incidence for every 320,000 live births.

This represents a forecast CAGR (Compound Annual Growth Rate) of 5%, the disease is a rare disease. However, it is growing due to family history being an indicator of potential heritability.

Key elements driving this expected growth are the emergence of new drugs to treat complications from the disease group.

However, the market suffers from restraints due to 'limited operating revenue opportunities for research and development of targeted therapies...and low healthcare budgets in developing countries.

Major competitive vendors that provide or are developing treatments include:

- Axovant Sciences ([AXGT](#))

- Amicus ([FOLD](#))
- Recursion Pharmaceuticals
- IntraBio
- Johnson & Johnson ([JNJ](#))
- Pfizer ([PFE](#))
- Eli Lilly & Company ([LLY](#))
- Bristol-Myers Squibb ([BMY](#))
- AstraZeneca ([AZN](#))
- Novartis ([NVS](#))

Financial Status

Taysha's recent financial results are typical of a development stage biopharma in that they feature no revenue and material R&D and G&A expenses associated with its development activities.

Below are the company's financial results since September 20, 2019:

	Period from September 20, 2019 (date of inception) through December 31, 2019	Six Months Ended June 30, 2020
Statement of Operations Data: (in thousands, except share and per share data)		
Operating expenses:		
Research and development	\$ 987	\$ 8,576
General and administrative	128	1,018
Total operating expenses	<u>1,115</u>	<u>9,594</u>
Loss from operations	(1,115)	(9,594)
Other expense:		
Change in fair value of preferred stock tranche liability	—	(17,030)
Interest expense	—	(27)
Total other expense	<u>—</u>	<u>(17,057)</u>
Net loss	\$ (1,115)	\$ (26,651)
Net loss per common share, basic and diluted	\$ (0.13)	\$ (2.67)
Weighted-average common shares outstanding, basic and diluted	<u>8,834,951</u>	<u>10,000,000</u>
Pro forma net loss per common share, basic and diluted (unaudited)(1)		\$ (1.91)
Weighted-average shares outstanding used in computing pro forma net loss per share (unaudited)(1)		<u>13,924,176</u>

Source: Company registration statement

As of June 30, 2020, the company had \$11.2 million in cash and \$20.1 million in total liabilities. (Unaudited, interim)

IPO Details

Taysha intends to raise \$125 million in gross proceeds from an IPO of its common stock, selling 6.6 million shares at a proposed midpoint price of \$19.00 per share.

No existing shareholders have indicated an interest to purchase shares at the IPO price, a common feature of life science IPOs.

Assuming a successful IPO, the company's enterprise value at IPO would approximate \$662.7 million, excluding the effects of underwriter over-allotment options.

Management says it will use the net proceeds from the IPO to advance its monogenic gene therapy pipeline and for general corporate purposes.

The firm's presentation of the company roadshow is [available here](#).

Listed bookrunners of the IPO are Goldman Sachs, Morgan Stanley, Jefferies, and Chardan.

Commentary

Taysha is seeking public capital market investment to advance its large gene therapy pipeline through trials.

The firm's lead candidate hasn't entered Phase 1 safety trials yet and its first four programs won't likely enter trials in the U.S. until 2022.

The market opportunities for the monogenic treatment of various rare diseases are significant but difficult to quantify for such a large cohort of treatment programs.

The firm has disclosed no research or commercial collaborations with major pharma firms, so is pursuing a go-it-alone approach at this time.

The company's investor syndicate includes Fidelity Management Research, but no notable life science venture capital firms.

As to valuation, management is asking IPO investors to pay an enterprise value of \$662 million, well above the typical range for even a clinical stage firm, much less a still preclinical firm such as Taysha.

Given the company's preclinical stage of development and high valuation, the IPO appears to be more suited to long-term hold institutional firms.

Expected IPO Pricing Date: September 23, 2020.

Editor's Note: This article discusses one or more securities that do not trade on a major U.S. exchange. Please be aware of the risks associated with these stocks.



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This article was written by



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He also leads the investing group [IPO Edge](#) which offers actionable information on potential growth stocks through IPO filings, a database of U.S. IPOs, and a guide to investing to walk you through the entire IPO lifecycle. [Learn more.](#)

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Taysha Gene Therapies Gets A 'Thumbs Up'

Mar. 07, 2022 1:50 PM ET | **Taysha Gene Therapies, Inc. (TSHA) Stock** | 12 Comments | 4 Likes



Bret Jensen

Investing Group Leader

Summary

- Shares of biopharmaceutical concern Taysha Gene Therapies, Inc. (TSHA) have lost over 70% of their value from their \$20 IPO priced in September 2020.
- The company has an essentially no-cost discovery pipeline from an arrangement with the UT Southwestern Medical Center, allowing it to focus its efforts on clinical advancement.
- With as many as 27 gene-therapy shots on goal (four in the clinic) for primarily rare and untreated CNS diseases, Taysha merited a deep dive.
- A full investment analysis follows in the paragraphs below.
- I am Bret Jensen, an analyst with years of experience in the biotech sector. I lead the investing group [The Biotech Forum](#) where we focus on proprietary, breaking research on biotech and biopharma stocks.



janiecbros/E+ via Getty Images

"When your past shows up to haunt you, make sure it comes after supper so it doesn't ruin your whole day." - Jay Wickre

Today, we provide an in-depth look at a small developmental name with an amazing amount of 'shots on goal', strong analyst support and a very cheap valuation after the sector's decline. A full analysis follows below.



TSHA - Stock Chart (Seeking Alpha)

Company Overview:

Taysha Gene Therapies, Inc. (NASDAQ:TSHA) is a Dallas-based clinical-stage biopharmaceutical concern focused on the development of adeno-associated virus (AAV)-based gene therapies for the treatment of monogenic diseases of the central nervous system (CNS). The company has four assets in the clinic and one more whose entry is imminent, as well as 22 other discovered compounds in its pipeline. Taysha was formed in 2019 in conjunction with the University of Texas Southwestern Medical Center and went public in September 2020, raising net proceeds of \$165.9 million at \$20 per share. Its stock trades just below \$6.00 a share, equating to a market cap of approximately \$220 million.

UT Southwestern Partnership

The company's relationship with UT Southwestern provides that the latter conducts discovery and preclinical research and manufacture AAV vectors for use in both preclinical and clinical trials. Taysha is responsible for clinical advancement of the assets, as well as commercialization, which is covered by a worldwide royalty-free license. Their pipeline consists of intrathecally (directly into cerebrospinal fluid) administered gene therapies that attack neurogenerative and neurodevelopmental disorders, as well as genetic epilepsies. This relationship came courtesy of RA Session II, who is both the President & CEO of Taysha and Entrepreneur-in-Residence at UT Southwestern. The former owns 9.4 million shares of TSHA while the latter received 2.2 million shares (20% ownership pre-IPO) for providing the development pipeline milestone and royalty fee. Curiously, UT Southwestern has since shed its position from 2.18 million shares (at the time of the IPO) to 1.15 million shares.

Session II and many members of Taysha came from AveXis, a gene therapy concern that was purchased by **Novartis (NVS)** for \$8.7 billion in 2018. AveXis developed what would become Zolgensma (onasemnogene abeparvovec), a gene therapy for the treatment of spinal muscle atrophy - the first-ever approved for a rare genetic disease. Taysha and Novartis are members of the Bespoke Gene Therapy Consortium, a \$76 million initiative of the FDA and National Institutes of Health to speed up gene therapy development for ~7,000 rare diseases.

Pipeline:

Despite its relationship with UT Southwestern, which was leveraged to raise pre-IPO and IPO capital, Taysha's three most advanced clinical assets have been purchased from other entities.

Unparalleled gene therapy pipeline focused exclusively on monogenic CNS disorders



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

4

TSHA - Pipeline (September Company Presentation)

TSHA-120. Of its clinical candidates, TSHA-120 jumped the line when its commercial rights were acquired mid-clinical (Phase 1/2) trial in April 2021. It was under evaluation for the treatment of giant axonal neuropathy (GAN), a rare autosomal disease characterized by abnormally large axons, a consequence of mutations in the GAN gene. The affected axons do not effectively transmit nerve signals resulting in atrophy of the spinal cord and progressive degeneration of motor skills. The more prevalent early-onset GAN is characterized by tight, curly hair in the first two years of life, loss of independent ambulation by age 11, and death before 30.

The study was conducted by the National Institutes of Health in collaboration with advocacy group Hannah's Hope Fund, but was essentially UT Southwestern's first foray into intrathecally administered AAV therapies and laid the foundation for Taysha. For \$5.5 million upfront plus potential milestones of \$19.3 million and low single-digit royalties to Hannah's, Taysha acquired the worldwide rights to its now lead therapy.

Most recently updated in January 2022, results from the study have been encouraging. Patients in the highest dose cohort (3.5×10^{14} total vg; n=3) registered a five-point improvement in the rate of decline versus a natural history decline of eight points at year 1 (p=0.04) as measured by MFM32 (32-item motor function measure). Across all dose cohorts, TSHA-120 demonstrated a seven-point improvement in mean change in MFM32 at year 1 compared to natural history (n=12, p<0.001). Furthermore, the duration of effect of once-administered TSHA-120 was observed three years post dosing. Based on this small-cohort analysis which contains 53 patient years of data, Taysha expects to engage the FDA and EMA in 2022 with a path towards a possible BLA filing at YE22 without an additional trial. A worse-case scenario involves another trial. A middle ground involves dosing a few more patients, which would push a filing into mid-2023. The company's lead candidate has already received rare pediatric disease and orphan drug designations from the FDA for a GAN indication with ~2,500 patients in the U.S. and EU, no standard of care, and an estimated \$2 billion global market opportunity.

TSHA-101. Taysha's second-most advanced asset is TSHA-101, which is being investigated for the treatment of GM2 gangliosidosis, a group of dreadful disorders caused by the accumulation of lipid components of cell membranes (gangliosides), particularly the plasma membranes of neurons. The buildup results in rapid neurodegeneration and death for most by the age of five for those afflicted with the most prevalent infantile form. The accumulation of gangliosides is due to a deficiency of the Hex A enzyme, which is responsible for their breakdown. GM2 gangliosidosis, comprised of Tay-Sachs and Sandhoff diseases, afflicts ~500 patients across the U.S. and EU.

From a single capsid, the TSHA-101 construct is designed to express the HEXA and HEXB genes - which encode for subunits of the Hex A enzyme - making it the first bicistronic gene therapy under clinical evaluation. Taysha in-licensed the therapy from Queen's University in Canada, which is conducting a Phase 1/2 trial to assess it in the treatment of both Tay-Sachs (HEXA) and Sandhoff (HEXB) diseases.

Initial returns were especially encouraging for the one Sandhoff infant, who was dosed in early September 2021, demonstrating Hex A enzyme activity 190% of normal at month 1 and 288% of normal by month 3. Considering natural history data show Sandhoff patients with activity levels at 5% of normal, this was a significant development. Very unfortunately, the patient died on January 14, 2022 due to pneumonia, which the principal investigator deemed treatment unrelated. A final determination by the Data and Safety Monitoring Board is expected shortly.

The other patient (Tay-Sachs) demonstrated enzyme activity 25% of normal at month 1, which was still five times greater than typical symptomatic Tay-Sachs patients and conducive with longer life expectancies.

Despite the setback, a third patient is now undergoing treatment and evaluation with a fourth in screening. Taysha now expects to piggyback onto this study with a protocol amendment to expand enrolment from four to 15 patients with the trial becoming registrational. TSHA-101 has received orphan drug and rare pediatric disease designations from the FDA and orphan drug status from the EU for the treatment of GM2 gangliosidosis.

The company in-licensed TSHA-101 for \$3 million upfront with potential milestones of \$20 million and low single-digit royalties.

TSHA-118 preclinical studies to date

#	Study Scope (ID)	Model System	Age at dosing	Route of Administration & Dose (vg/animal)	Major Findings
1	Proof of Concept; (UNC-2014-001)	PPT1 ^{-/-} mice	1, 4, 12, 20, 26 weeks	IT: 7.0x10 ¹⁰ , 2.2x10 ¹¹ , 7.0x10 ¹¹	<ul style="list-style-type: none"> Elevated levels of active PPT1 in serum Significant survival benefit and functional improvements Rescue of behavioral deficits
2	Safety and Efficacy (UNC-2015-001)	PPT1 ^{-/-} and PPT1 ^{+/+} mice	P0 – P2	IV: 2.8x10 ¹¹	<ul style="list-style-type: none"> Significant survival benefit: median life-span 21 months in treated mice vs. 8.3 months in untreated mice
3	Efficacy of Combination IT and IV Dosing; (UNC-2016-001)	PPT1 ^{-/-} mice	20 weeks	IT: 7.0x10 ¹⁰ , 7.0x10 ¹¹ IV: 7.0x10 ¹¹ IT: 7.0x10 ¹⁰ , 7.0x10 ¹¹ each in combination with IV: 7.0x10 ¹⁰ , 2.2x10 ¹¹ , or 7x10 ¹¹	<ul style="list-style-type: none"> Dose-dependent survival benefit and improvements in function Single routes and lower doses provided some benefit Maximum benefit with high IT plus high IV dose at this stage of disease (i.e. - 20 week old mice)
4	Efficacy of Combination IT and IV Dosing; (UNC-2017-001)	PPT1 ^{-/-} mice	4 weeks	IT: 7.0x10 ¹¹ IT: 7.0x10 ¹¹ in combination with IV: 7.0x10 ¹⁰ or 7.0x10 ¹¹	<ul style="list-style-type: none"> Testing up to 12 months demonstrated survival or behavioral benefits for the combination treatment similar to IT dose alone, which had a median lifespan of 18.7 months
5	Biodistribution and PPT1 Activity Comparison; (UNC-2017-002)	C57B1/6 mice & Fischer rats	Mouse: 9 wks Rat: 11 wks	IT Mouse: 9.1x10 ¹¹ IT Rat: 3.64x10 ¹²	<ul style="list-style-type: none"> Maximum dose IT injection of TSHA-118 in wild-type rats and mice resulted in similar levels of vector biodistribution and PPT1 enzyme activity in serum and most tissues of both Cross-species comparison supports the dosing rationale of 5.0x10¹⁴ total vg and 1x10¹⁵ total vg for human trial
6	Toxicology Study in Rat; (MPI-2389-010)	Wistar Hans rats	6 weeks	IT: 2.0x10 ¹¹ , 2.0x10 ¹² IV: 5.6x10 ¹² , 2.0x10 ¹³ IT: 2.0x10 ¹² in combination with IV: 2.0x10 ¹³	<ul style="list-style-type: none"> Administration of TSHA-118 was not associated with any mortality, clinical observations, bodyweight, or food consumption changes

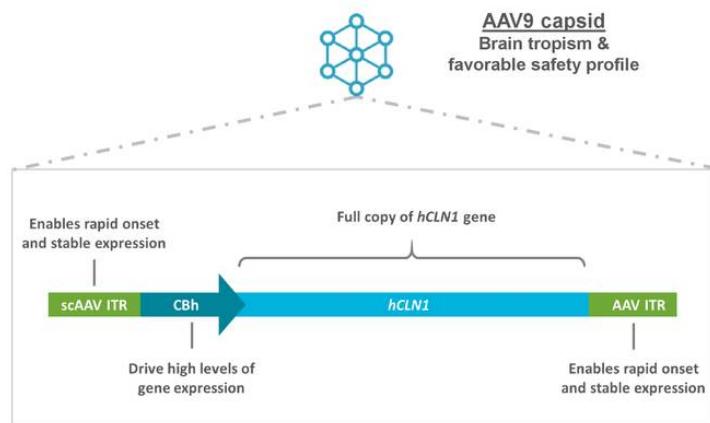
Taking these nonclinical studies into consideration, there is support for 5.0x10¹⁴ total vg and 1.0x10¹⁵ total vg dosing in human trials

TSHA - 118 Studies (September Company Presentation)

TSHA-118. The company's third clinical asset (TSHA-118) was acquired from **Abeona Therapeutics (ABEO)** in August 2020. In return for \$3 million upfront, potential milestones of \$56 million, and high-single-digit royalties, Taysha received a prospective treatment for CLN1 disease, one of a family of neuronal ceroid lipofuscinoses (genetic lysosomal storage diseases). The CLN1 gene encodes a glycoprotein involved in the degradation of a certain lipid-modified protein (PPT1). A mutation to this gene leads to an accumulation of PPT1 and ultimately neuronal cell death, triggering rapid deterioration of speech and motor skills, visual failure, and in the infantile-onset form, death by seven years of age. There are ~1,000 patients afflicted with this form of Batten disease between the U.S. and EU. Approximately 60% of patients have infantile-onset CLN1 with PPT1 enzyme activity of ~0.1%; the other three forms have higher degrees with adult-onset CLN1 activity at 5% to 8%. Higher enzyme activity correlates with a longer and more normal lifespan.

CLN1 disease is a severe neurodegenerative lysosomal storage disease

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



T

51

CLN1 Disease (September Company Presentation)

This gene replacement therapy just entered the clinic in December 2021, undergoing assessment in a single-arm Phase 1/2 trial with preliminary safety and efficacy data expected in 1H22. Taysha is hoping for at least 5% PPT1 enzyme activity, which should be life-extending.

TSHA-121. Along the lines of CLN1, the company has a construct (TSHA-121) that is undergoing Phase 1 study for the treatment of CLN7 disease, another CNS childhood malady with a global population of 4,000. Preliminary efficacy results are to be presented on February 9, 2022 at the 18th Annual WORLDSymposium.

Taysha also anticipates gene therapy asset TSHA-102 for Rett Syndrome, also procured from Abeona on somewhat similar terms as TSHA-118, to enter the clinic shortly.

Balance Sheet & Analyst Commentary:

With what will likely become many clinical programs with small or extremely small patient populations, Taysha held unrestricted cash of \$188.8 million and a \$30 million term loan as of September 30, 2021 with an additional \$30 million draw remaining on the facility (subject to certain conditions). It should be enough liquidity to get the company into 2H23.

With a promising and largely untapped approach to therapy - only a handful of gene therapies have been approved for the ~7,000 recognized rare diseases - it is not surprising to see the Street unanimously bullish on Taysha's prospects. Ten buy and four outperforms ratings and a twelve-month price target north of \$40.00 a share.

Paul B. Manning, who is the CEO of PBM Group, a private equity concern that was behind Taysha's speedy capital raises and entrance into the public markets - as well as a beneficial owner - has used the weakness in shares of TSHA to add over 400,000 to his position so far in 2022. Two directors also added just over \$100,000 in aggregate to their holdings in early February.

Verdict:

Simply put, there are just too many shots on goal here to not justify a valuation higher than the current approximate \$40 million market cap after subtracting net cash. If management's confidence in its ability to leverage its current TSHA-120 dataset for a YE22 BLA submission is prescient, a potentially \$2 billion market opportunity would open for a company with a ~\$300 million valuation. With 26 candidates in tow, TSHA deserves at least a small holding in a well-diversified biotech portfolio.

"Depending on the reality one must face, one may prefer to opt for illusion." - Judith Guest

Bret Jensen is the Founder of and authors articles for the Biotech Forum, Busted IPO Forum, and Insiders Forum

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Bret leads the investing group [The Biotech Forum](#), in which he and his team offer a model portfolio with their favorite 12-20 high upside biotech stocks, live chat to discuss trade ideas, and weekly research and option trades. The group also provides market commentary and a portfolio update every weekend. [Learn more.](#)

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Taysha Gene Therapies: Astellas Throws Lifeline For First Dibs On Rett And GAN Programs

Nov. 17, 2022 6:04 PM ET | **Taysha Gene Therapies, Inc. (TSHA) Stock** | 7 Comments | 1 Like



Jonathan Faison

Investing Group Leader

Summary

- Shares have fallen by 85% since Sept 2020 IPO as cash resources dwindled to \$34M as of last month.
- Company was forced to cut 35% of workforce, stop construction of its cGMP manufacturing facility and focus on two lead clinical candidates.
- Astellas, after seeing all available internal information and data, threw Taysha a \$50M lifeline (\$20M payment & \$30M investment for 15% stake).
- Bear thesis includes safety/tolerability concerns (Novartis discontinued its Rett program last year), negative FDA feedback for GAN and additional financing needs in 2023.
- TSHA is a Speculative Buy. I see pathway to value creation via adult Rett data for full cohort of patients 1H 23 along with progress for pediatric cohort to follow.
- I am Jonathan Faison, a biotech investor with over 15 years of experience. I lead the biotech investing group [ROTY Biotech Community](#), a group of dedicated investors who are passionate about sharing biotech ideas.



Artur Plawgo

Shares of Taysha Gene Therapies (NASDAQ:[TSHA](#)) have fallen by 85% since the September 2020 IPO was priced at \$20. Performance is an even more brutal -88% since my [initial article](#) was published in April 2021 (talk about poor timing).

The company surely suffered during these past couple years, a product of both the overall macro picture as well as biotech bear market and management missteps. Unfortunately, this was a good example of a leadership team that bit off more than it could chew (failing to adequately take heed of cash burn and resources as they sought to build out a 187,000 square foot cGMP manufacturing facility and progress a broad portfolio of CNS gene therapy programs).

To be fair, in the March quarterly report, Founder and CEO RA Session II took the right steps when he announced a workforce reduction of 35% along with narrowing of focus to both GAN and Rett syndrome programs. Research and development expenses tripling to \$37.9M was clearly not sustainable in light of the depressed state of the sector as well as the company's dwindling cash resources.

While highly aware of the significant risks (especially safety) involved in the gene therapy field, after the Astellas collaboration news I chose to reenter the stock ahead of 1H 23 Rett data updates.

Chart



FinViz

Figure 1: TSHA daily chart (Source: Finviz)

When looking at charts, clarity often comes from taking a look at distinct time frames in order to determine important technical levels and get a feel for what's going on. In the daily chart above, we can see shares steadily fall from the \$10 level to a low of \$1 as the company struggled to stay afloat (even proposing a share offering in September only to decide against it, perhaps due to lack of demand or in light of deal discussions with Astellas). Share price briefly jumped to the \$3 level on news of the Astellas partnership, only to pull back closer to \$2 on news of a \$30M secondary offering to follow. My current take is that risk-tolerant investors interested in this name should accumulate dips in the near term (below the \$3 level).

Overview

Founded in 2020 with headquarters in Texas (115 employees), Taysha Gene Therapies currently sports enterprise value of ~\$50M and estimated Q3 cash position of ~\$110M (if current secondary offering is successful) providing them operational runway into 1H 2024. Per filing prospectus, there were ~41M shares outstanding as of June 30 (excluding 7.2M shares from recent Astellas private placement and shares to be issued in current secondary offering).

Taysha is utilizing a specific validated gene therapy technology (AAV9) that's proven its efficacy, safety and durability in multiple diseases via peer data. AAV9 is coupled with novel targeted payload design and intended to address a range of monogenic CNS disorders. Again, after cutting costs, the company is mainly focusing on just the GAN and Rett syndrome programs. They do intend to conduct small proof-of-concept studies in CLN1 disease and SLC13A5 deficiency. Another benefit is highly scalable manufacturing (keep in mind they paused or cancelled construction of a new 187,000 square foot cGMP facility in North Carolina as part of cost cuts).

Founding collaboration is with UT Southwestern Gene Therapy program, as Dr. Steven Gray headed the first intrathecal dosed gene therapy candidate. This collaboration gives Taysha access to scale and expertise across their gene therapy portfolio. Intrathecal delivery (injection in spinal canal) is the chosen route of delivery as doctors have given intrathecal medicine for decades in outpatient setting across multiple modalities - it allows them to target the CNS broadly and avoid neutralizing antibodies by starting on the right side of the blood brain barrier. Management refers to multiple studies run by the likes of AveXis in SMA, Amicus, and the list goes on regarding validation of this approach and technology. Taysha utilizes highly scalable HEK293 manufacturing process with excellent yield (provides right balance between scalability, yield and risk, safe and effective across multiple serotypes in clinic to date, feel strongly does not come with inherent toxicities that come with other systems).

Lead GAN program originated from Chief Scientific Officer Steven Gray's lab and is the first intrathecally dosed gene therapy study in history. As for opportunity in GAN, there are around 2400 prevalent patients in US + EU (\$500M to \$1B potential peak sales). GAN is an ideal target for the company's approach because it is a small gene that fits well into AAV9 capsid, has high transduction at target organ and there's evidence that low level expression of gigaxonin may restore function in humans. This construct is clearly a model for other candidates in pipeline to treat additional CNS diseases. A rare inherited genetic disorder, GAN patients are typically symptomatic before the age of 5.



Comprehensive set of evidence generated across disease manifestations support a robust clinical package

Assessment	Type	Findings
MFM32	Motor Function	<ul style="list-style-type: none"> TSHA-120 demonstrated clinically meaningful slowing of disease progression across all therapeutic dose cohorts compared to natural history decline Durability of effect observed up to 6 years post dosing
Nerve Conduction	Electrophysiologic	<ul style="list-style-type: none"> TSHA-120 patients demonstrated recoverability, stabilization, and improvement in sensory response
Histopathology	Nerve Biopsy	<ul style="list-style-type: none"> TSHA-120 treated patients demonstrated histopathological presence of regenerative nerve clusters suggesting active regeneration of nerve fibers
Retinal nerve fiber layer (RNFL)	Biomarker measuring thickness	<ul style="list-style-type: none"> TSHA-120 stabilized RNFL preventing further progression of axonal loss
LogMar	Visual Acuity	<ul style="list-style-type: none"> Treated patients with TSHA-120 stabilized visual acuity compared to pre-treatment decline
Comparability	CMC	<ul style="list-style-type: none"> Commercial grade material comparable to clinical grade via release assay panel

Corporate Slides

Figure 2: TSHA-120 GAN program summary (Source: *Updated slides*)

As for primary clinical measure, the MFM32 is a validated quantitative scale (motor function measure with four-point change considered to be clinically meaningful including for other indications like DMD, SMA, cerebral palsy, etc). In this 32-item scale, a higher score is better, and for frame of reference, natural history study for GAN shows an 8-point decline annually (in 45 patients, age 3 to 21 years old). MFM32 will be the primary endpoint for a confirmatory trial. Safety and efficacy results here are promising, especially two highest doses which showed meaningful slowing of disease progression along with dose dependent effect (statistically significant). Highest dose of TSHA-120 resulted in an 8-point improvement vs. historical control, with 6-point improvement occurring at second-highest dose (keep in mind 4-point change is considered meaningful). TSHA-120 was considered well tolerated and six patients have been followed for more than three years (seeing sustained dose dependent improvements in MFM32 scores). Further analysis shows nearly 100% probability of clinically meaningful slowing of disease progression compared to natural history.

As for TSHA-102 for Rett syndrome, this is one of the most common genetic causes of intellectual disabilities in women. Rett is caused in most cases by loss of function mutations in the MECP2 gene. MECP protein is essential to neuronal and somatic function in the brain. For effective treatment, MECP2 expression needs to be titrated to correct the MECP2 deficiency while avoiding adverse effects associated with having too much MECP2. Regulation of MECP2 to appropriate levels needs to occur on a cell by cell basis, thus a proprietary method of transgene regulation was developed called miRARE (miRNA targeting panel that binds to endogenous downregulatory microRNAs that are activated in presence of high levels of MECP2). Preclinical studies for TSHA-102 showed favorable tolerability and increased survival in knockout mouse model. The estimated prevalence of Rett syndrome is 25,000 patients in the US and EU.

Astellas Deal and Pipeline Update

On Oct. 21, the company entered into an Option Agreement with Astellas Gene Therapy, granting them an exclusive option to obtain an exclusive, worldwide, royalty and milestone-bearing right and license to both the GAN and Rett Programs.

GAN option is exercisable anytime from the present through receipt of the formal minutes from Type B end of phase 2 meeting between Taysha and the FDA (formal communication on the outcome of this meeting expected in January 2023).

As for the Rett option, it can be exercised anytime through receipt of clinical data from the female pediatric trial.

Totality of preclinical data generated to date represents most robust package supporting Rett syndrome clinical development

TSHA-102
Rett Syndrome

Study Scope	Species	Findings
Neonatal (n=49)	Mouse	<ul style="list-style-type: none"> Near normalization of survival in neonatal knockout Rett mice Normalization of body weight Normalization of behavior as assessed by Bird Score
Pharmacology (n=252)	Mouse	<ul style="list-style-type: none"> Significant improvement in survival, body weight, motor function and respiratory health across treatment ages in Rett knockout mouse model
Toxicology (n=160)	Rat	<ul style="list-style-type: none"> Favorable safety profile of TSHA-102 in Sprague Dawley rats up to 3.85E12 vg/animal up to the 26-week time point Nerve conduction studies remained in normal range for all groups at all timepoints Motor nerve conduction studies remained normal even at high dose
Toxicology (n=24)	NHP	<ul style="list-style-type: none"> Doses of up to 2.31E14 vg/animal (HED 2.0E15) were well tolerated with broad biodistribution to brain, spinal cord in NHPs

Corporate Slides

Figure 3: TSHA-102 Rett program summary (Source: [Updated slides](#))

Provisions of this collaboration are quite interesting, as terms of license agreement have not been negotiated yet and this will occur after receipt of FDA minutes or Rett data. During the Rett Option period, Taysha agreed not to solicit offers or proposals from other companies (seems like Astellas wants to lock this up) and terms include a "Change of Control" clause giving Astellas the right of first proposal for any potential buyout or transaction.

In return, Astellas paid them \$20M upfront payment and purchased \$30M of stock (over 7.2M shares) via private placement.

As for the associated clinical update, Taysha notes that the Type B meeting for GAN program has been scheduled for Dec. 13 with the FDA and so receipt of formal meeting minutes are expected in mid-January.

With respect to TSHA-102 for the treatment of Rett syndrome, originally the company was going to report early phase 1/2 data at the end of this year (just safety). However, after this deal with Astellas, they now expect to report preliminary safety and efficacy clinical data from the first cohort of adult patients 1H 23. They also plan to initiate the female pediatric clinical study 1H 23.

Detailed breakdown of finances states that they had just \$34.3M of cash as of Sept. 30 (quite desperate considering Q2 net loss was ~\$33M). However, this does not include \$50M payment from Astellas as well as the expected \$30M of proceeds from secondary offering that followed. Interestingly enough, the filing for the secondary offering shows that insider Paul Manning/PBM Capital has indicated desire to purchase up to \$5M of shares in the financing.

From are my notes from the associated call:

- \$30M investment was made by Astellas for 15% of outstanding shares (implies \$200M valuation). This was confusing in the initial press release, where investors and all news sources cited a \$50M investment. However, the deal format entails a \$20M payment and \$30M investment via private placement.
- Astellas receives certain rights to change of control until after Rett data (whether Astellas wants to license the two candidates or outright buyout the company, they are able to counter should another pharma make an offer).
- Regarding Rett syndrome program, which is what most attracted Astellas, toxicology data showed favorable safety at up to 4x higher dose in NHP (non-human primates) than starting dose in humans. Also, there was no evidence of dorsal root ganglia inflammation. NHP data at all doses studied showed the gene therapy candidate was well tolerated with broad biodistribution.
- The effect on Rett knockout mice up to 20 days post birth (50% through their normal life span) was striking. In some cases they allowed mice to mature to a level of adulthood (accumulating significant level of disease burden) before intervening with treatment. Yet, they still saw improvements across multiple parameters in survival, respiratory function and motor function.
- I'm a fan of the phase 1 trial design, as I think it's unethical for any patient to not receive treatment. Six adult Rett patients are being enrolled and randomized to treatment with TSHA-102 or delayed treatment control (three patients on drug, three patients with delayed treatment). This way, the study will be more robust and allow them to compare treated patient to non-treated.
- Capital injection is meant to allow them get to meaningful data sets in Rett adult AND pediatric patients.

- The deal came out of conversations over the past four to five months with Astellas.
- If all goes well with GAN regulatory-wise, they could commercialize it in 2024.
- Astellas had access to "all available data" that Taysha was in possession of to make this decision (sounds to me like they saw initial human data).

Q3 Update

For Q3, cash position of \$34M (+ \$50M from Astellas and \$25.6M from secondary offering= \$109M total) is still insufficient compared to net loss of \$26M. However, it's much better than teetering on the brink of bankruptcy, which is where the company was previously. Research and development expenses were sliced by more than half to \$16.4M, while G&A fell to \$8.7M. Management is guiding for operational runway into Q1 2024, but I expect another financing by mid 2023 after Rett data update.

\$28M secondary offering was priced at \$2/share (14M shares), which was very disappointing given the prior runup. I definitely jumped the gun here in terms of pulling the trigger versus even showing a day or two more of patience, but that error/lack of prudence is on me and me alone.

On the bright side, Director of the Board Paul Manning bought ~\$3M worth in the offering and now owns nearly 7M shares or 11.2% of the company.

They continue to guide for TSHA-102 data update in first cohort of Rett syndrome adult patients 1H 23 (initiation of female pediatric cohort around the same time frame). This language sounds increasingly confident, as prior pediatric cohort was only going to be started if adult data was good.

Regulatory update for TSHA-120 in GAN is expected mid-January 2023 (devil's advocate is that despite the strong data, FDA asks for more info on CMC or even more clinical data). We will see.

As for the conference call and Q&A, here are a few nuggets:

- In regard to pivotal trial design for Rett syndrome, it seems too early to ask. However, management states that this would focus on pediatric population as this is the key population of interest (also applicable to wider population). Assessments are similar such as looking at frequency of seizures, how severe and how long they

are. Another bucket is respiratory outcomes which they demonstrated improvements very clearly in animal models. They also look at communication ability, behavioral scale, biomarkers, EEG, etc. Buckets are same from adults to children, but specific assessments are a bit different.

- With regard to safety, toxicology studies showed they gave 4-fold dose over the initial starting dose ($5e14$ total vg) in both NHPs and rats over three- and six-month period (all the way up to $2e15$ equivalent). 4-fold dosing of initial clinical starting dose they saw no adverse toxicological findings. Thus, they have absolute confidence in $5e14$ level in humans will not result in overexpression of MECP2 (key concern).
- Vast majority of patients enrolled in pediatric study will be over the age of three or four (won't need to change dose because size of child's brain has reached size of adult's). Again, $5e14$ starting dose in both.
- As for bar for success in clinical data, safety will be extremely important (construct is designed to make sure patients get the level of MECP2 they need, to see significant improvement across spectrum of disease and doing that safely in the presence of wild-type MECP2). 50% of these patients' cells are normal, 50% are null or not producing MECP2. Too much MECP2 is toxic, so the construct is designed to express the needed level of MECP2 on a genotypic cell-by-cell basis. Totality of data will be important in terms of efficacy and they're expecting preliminary efficacy. They expect children to do better than adults because treating developing brain results in better outcomes in animal studies than adult brain. Also, animal studies across many different ages of mice showed it was clear the younger mice did better than the older ones. Autonomic dysfunction (rapid breathing, hypoxic excess go blue because not breathing) is one key area that if moderated by treatment would be clinically meaningful for patients and families. If they can reduce seizure burden or bring modicum of functionality to hand function, these are additional examples of things that are meaningful. This is a global, neurological developmental disease so they are looking at a wide variety of measures.
- Pediatric study will be a global study in multiple countries around the world. Gateway for moving into pediatric study is getting some level of follow up for

multiple months in adult study to give them confidence to include in data package for pediatric trial.

- Rett advocacy group puts worldwide prevalence at ~350,000 patients and recruiting for such a study should not be a problem per management. Company calculated 25,000 to 35,000 in US and EU alone.
- Analysts asked what toxic adverse events would look like due to MECP2 overexpression in humans, but management reminds him that they did not see this in animal studies at very high doses.
- Initial adult data would be in three to five patients to give them confidence to move forward into children. Natural history in Rett syndrome is some of the most well-characterized out of any disease. For them, it's getting to three to six patients including delayed treatment patient.
- For GAN program (the most advanced asset), their intention is to file an MAA in Europe and they believe current data package checks all the boxes regarding FDA guidance for gene therapies in neurodegenerative diseases. However, to my eyes playing devil's advocate, they still don't sound overly confident here (perhaps FDA requests more information, more data implying delays, etc).

Final Thoughts

To conclude, listening to the Astellas deal conference call twice (along with referring to my prior notes) convinced me to hop on for a pilot position with a view toward Rett data updates 1H 23 along with progression into the pediatric clinical study. The Rett patient community currently has nothing else out there for them after Novartis' gene therapy program was discontinued last year ([see their reaction](#)) and so I'm (not only as an investor) rooting for results (here or elsewhere) that bring them hope.

For readers who are interested in the story and have done their due diligence, TSHA is a Speculative Buy and I suggest accumulating dips below \$3. A conservative strategy could be to purchase half of desired exposure presently, then wait for Type B meeting notes in January for the GAN program before considering further action.

One risk that comes to mind is additional dilution in 2023 (they only have runway to Q4 2023 or 1H 2024 at latest, which also depends on the success of current secondary offering where pricing or demand could be weak in the worst-case scenario). Safety/tolerability issues including patient deaths or Grade 4 adverse events that unfavorably skew risk/benefit of gene therapy treatments has always been a key concern for this area of biotechnology (just look at Audentes Therapeutics/Astellas' XLMTM program [still on clinical hold](#)). Disappointing data in Rett would weigh very heavily on shares, as despite promising long-term results for GAN I don't think the market will give much credit to the latter until approval. Regarding GAN Type B meeting with the FDA, it's clear the company is hoping for a win with green light to proceed for regulatory filing. The FDA lately has been quite amenable to rare diseases where nothing is approved, such as recent green light to Relyvrio's recent approval in ALS changing the fortunes of Amylyx ([AMLY](#)). However, playing devil's advocate, the FDA could request a pivotal study be run first instead of as a confirmatory trial. Other issues could also arise, such as if they have questions on the material used in clinical study vs. that intended for commercial launch (bridging study). One final risk, as alluded to above, is that current secondary offering fails (insufficient demand) or is priced at unfavorable levels (causing share price to fall further).

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 [Manzil](#) • Jun. 19, 2019 2:46 PM

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