Filed pursuant to Rule 424(b)(3)
Registration No. 333-271144

PROSPECTUS

8,496,560 Shares

Common Stock Offered by the Selling Stockholders

This prospectus relates to the proposed resale from time to time of up to 8,496,560 shares, or the Shares, of our common stock, par value $0.00001 per share, or the common stock, by the selling stockholders named herein, together with any additional selling stockholders listed in a prospectus supplement (together with any of such stockholders' transferees, pledgees, donees or successors).

We are registering the offer and sale of the Shares from time to time by the selling stockholders to satisfy registration rights they were granted in connection with the issuance of the Shares. We will not receive any proceeds from the sale of the Shares by the selling stockholders.

The selling stockholders may offer and sell or otherwise dispose of the Shares described in this prospectus from time to time through public or private transactions at prevailing market prices, at prices related to prevailing market prices or at privately negotiated prices. The selling stockholders will bear all underwriting fees, commissions and discounts, if any, attributable to the sales of Shares and all fees and expenses of legal counsel, accountants and other advisors for the selling stockholders, subject to certain specified exceptions. We will bear all other costs, expenses and fees in connection with the registration of the Shares. See the section titled "Plan of Distribution" for more information about how the selling stockholders may sell or dispose of its Shares.

Our common stock is listed on The Nasdaq Global Select Market under the trading symbol "TSHA." On May 1, 2023, the closing price of our common stock was $0.71 per share.

Investing in shares of our common stock involves a high degree of risk. You should review carefully the risks and uncertainties described in the section titled "Risk Factors" on page 10 of this prospectus and any similar section contained in the applicable prospectus supplement and in any free writing prospectuses we have authorized for use in connection with a specific offering, and under similar headings in the documents that are incorporated by reference into this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is May 1, 2023.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or the SEC, using a "shelf" registration process. Under this shelf process, the selling stockholders may from time to time sell the shares of common stock described in this prospectus in one or more offerings or otherwise as described under "Plan of Distribution."

This prospectus may be supplemented from time to time by one or more prospectus supplements. Such prospectus supplement may also add, update or change information contained in this prospectus. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement, you must rely on the information in the prospectus supplement. You should carefully read both this prospectus and any applicable prospectus supplement together with additional information described under the heading "Where You Can Find Additional Information" before deciding to invest in any shares being offered.

Neither we nor the selling stockholders have authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus or in any related prospectus supplement or any free writing prospectus that we have authorized. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. The Shares are not being offered in any jurisdiction where the offer is not permitted. You should not assume that the information contained in or incorporated by reference in this prospectus is accurate as of any date other than the respective dates of such document. Our business, financial condition, results of operations and prospects may have changed since those dates.

Unless otherwise stated, all references in this prospectus to "we," "us," "our," "the company," "Taysha" and "Taysha Gene Therapies," and similar designations, except where the context requires otherwise, refer collectively to Taysha Gene Therapies, Inc., together with its consolidated subsidiaries. We own various U.S. federal trademark applications and unregistered trademarks, including our company name. All other trademarks or trade names referred to in this prospectus, including any relating to a selling stockholder, are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus are referred to without the symbols ® and ™, but such references should not be construed as any indication that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus and in the documents we incorporate by reference. This summary does not contain all of the information you should consider before investing in our common stock. You should read this entire prospectus carefully, especially the risks of investing in our common stock discussed in the section titled "Risk Factors" and under similar headings in our filings with the SEC which are incorporated by reference in this prospectus, along with our consolidated financial statements and notes to those consolidated financial statements and the other information incorporated by reference in this prospectus, before making an investment decision.

Company Overview

We are a patient-centric gene therapy company focused on developing and commercializing AAV-based gene therapies for the treatment of monogenic diseases of the central nervous system, or CNS. We were founded in partnership with The University of Texas Southwestern Medical Center, or UT Southwestern, to develop and commercialize transformative gene therapy treatments. Together with UT Southwestern, we possess a portfolio of gene therapy product candidates, with exclusive options to acquire several additional development programs at no cost. By combining our management team's proven experience in gene therapy drug development and commercialization with UT Southwestern's world-class gene therapy research capabilities, we believe we have created a powerful engine to develop transformative therapies to dramatically improve patients' lives. In March 2022, we announced strategic pipeline prioritization initiatives focused on giant axonal neuropathy, or GAN, and Rett syndrome, and we have subsequently further paused substantially all other research and development activities to increase operational efficiency.

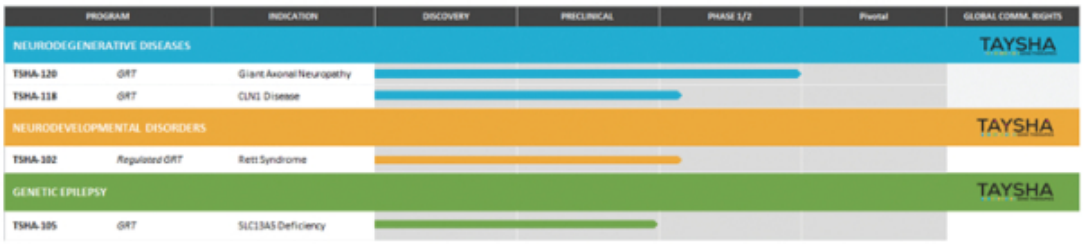
In April 2021, we acquired exclusive worldwide rights to TSHA-120, a clinical-stage, intrathecally dosed AAV9 gene therapy program for the treatment of giant axonal neuropathy, or GAN. A Phase 1/2 clinical trial of TSHA-120 is being conducted by the National Institutes of Health, or NIH, under an accepted investigational new drug application, or IND. We reported clinical safety and functional MFM32, a validated 32-item scale for motor function measurement developed for neuromuscular diseases, data from this trial for the highest dose cohort of 3.5x1014 total vg (by dot blot) and 1.0x1014 total vg (by ddPCR) in January 2022, where we saw continued clinically meaningful slowing of disease progression similar to that achieved with the lower dose cohorts, which we considered confirmatory of disease modification. We recently completed a commercially representative Good Manufacturing Practices, or GMP, batch of TSHA-120, which demonstrated that the pivotal lots from the commercial grade material were generally analytically comparable to the original clinical trial material. Release testing for this batch was completed in the fourth quarter of 2022. In September 2022, we submitted a meeting request to the U.S. Food and Drug Administration, or the FDA, and were granted a Type B end-of-Phase 2 meeting via teleconference on December 13, 2022. In January 2023, we reported feedback from the Type B end-of-Phase 2 meeting with the FDA following receipt of the formal meeting minutes. The FDA provided additional clarity for TSHA-120 where MFM32 was acknowledged as an acceptable endpoint with a recommendation to dose additional patients in a double-blind, placebo-controlled design to support a Biologics License Application, or BLA. The FDA acknowledged that our overall approach to manufacturing of commercial material was appropriate pending review of a planned Chemistry, Manufacturing and Controls, or CMC, data package for TSHA-120. Subsequently, we submitted follow up questions in response to the formal meeting minutes. The FDA clarified MFM32 as a relevant primary endpoint in the setting of a randomized, double-blind, placebo controlled trial and acknowledged Taysha's challenge in designing such study due to the ultra-rare nature of GAN. The FDA was open to acceptance of more uncertainty due to difficulty in enrolling a sufficient number of patients and regulatory flexibility in a controlled trial setting. In addition, the FDA indicated it was willing to consider alternative study designs utilizing objective measurements to demonstrate a relatively large treatment effect that is self-evident and clinically meaningful. The FDA acknowledged that the size of the safety database will be a review issue and acceptance of the existing safety data from treated patients will depend on

demonstration of product comparability. We have completed the CMC module 3 amendment submission detailing drug comparability data and are awaiting FDA feedback.

We are evaluating TSHA-102 in the REVEAL Phase 1/2 clinical trial, which is an open-label, dose escalation, randomized, multicenter study that is examining the safety and efficacy of TSHA-102 in adult female patients with Rett syndrome. We expect to dose the first adult patient with Rett syndrome in the first half of 2023 and to report initial available clinical data in the first half of 2023, with planned quarterly updates on available clinical data, primarily on safety, from the adult study thereafter. We anticipate submission of a clinical trial application, or CTA, to the United Kingdom's Medicines and Healthcare Products Regulatory Agency, or MHRA, for TSHA-102 in pediatric patients with Rett syndrome in mid-2023. We plan to submit an IND application for Rett syndrome to the FDA in the second half of 2023. We have at this time deprioritized the evaluation of our preclinical product candidates TSHA-105 for SLC13A5, TSHA-118 for CLN1 and TSHA-121 for CLN7. Although we are not currently evaluating the potential of TSHA-105, TSHA-118 and TSHA-121, we may again evaluate any of these in the future as a product candidate as a component of our pipeline expansion plans, or pursue partnerships to advance these programs.

Our Pipeline

We possess a portfolio of gene therapy product candidates for monogenic diseases of the CNS in both rare and large patient populations, with exclusive options to acquire several additional development programs at no cost. Our portfolio of gene therapy candidates targets broad neurological indications across three distinct therapeutic categories: neurodegenerative diseases, neurodevelopmental disorders and genetic epilepsies. Our current pipeline, including the stage of development of each of our product candidates, is represented in the table below:



Astellas Transactions

Option Agreement

On October 21, 2022, or the Effective Date, we entered into an Option Agreement, or the Option Agreement, with Astellas Gene Therapies, Inc. (f/k/a Audentes Therapeutics, Inc. (d/b/a Astellas Gene Therapy)), or Astellas.

Under the Option Agreement, we granted to Astellas an exclusive option to obtain an exclusive, worldwide, royalty and milestone-bearing right and license (A) to research, develop, make, have made, use, sell, offer for sale, have sold, import, export and otherwise exploit, or, collectively, Exploit, the product known, as of the Effective Date, as TSHA-120, or the 120 GAN Product, and any backup products with respect thereto for use in the treatment of GAN or any other gene therapy product for use in the treatment of GAN that is controlled by us or any of our affiliates or with respect to which we or any of our affiliates controls intellectual property rights covering the Exploitation thereof, or a GAN Product, and (B) under any intellectual property rights controlled by us or any of our affiliates with respect to such Exploitation, or the GAN Option. Subject to certain extensions, the GAN Option is exercisable from the Effective Date through a specified period of time following Astellas' receipt

of (i) the formal minutes from the Type B end-of-Phase 2 meeting between us and the FDA in response to our meeting request sent to the FDA on September 19, 2022 for the 120 GAN Product, or the Type B end-of-Phase 2 Meeting, (ii) all written feedback from the FDA with respect to the Type B end-of-Phase 2 Meeting, and (iii) all briefing documents sent by us to the FDA with respect to the Type B end-of-Phase 2 Meeting.

Under the Option Agreement, we also granted to Astellas an exclusive option to obtain an exclusive, worldwide, royalty and milestone-bearing right and license (A) to Exploit any Rett Product (as defined below), and (B) under any intellectual property rights controlled by us or any of our affiliates with respect to such Exploitation, or the Rett Option and together with the GAN Option, each, an Option. Subject to certain extensions, the Rett Option is exercisable from the Effective Date through a specified period of time following Astellas' receipt of (i) certain clinical data from the female pediatric trial and (ii) certain specified data with respect to TSHA-102, such period, the Rett Option Period, related to (i) the product known, as of the Effective Date, as TSHA-102 and any backup products with respect thereto for use in the treatment of Rett syndrome, and (ii) any other gene therapy product for use in the treatment of Rett syndrome that is controlled by us or any of our affiliates or with respect to which the we or any of our affiliates controls intellectual property rights covering the Exploitation thereof, or a Rett Product.

The parties have agreed that, if Astellas exercises an Option, the parties will, for a specified period, negotiate a license agreement in good faith on the terms and conditions outlined in the Option Agreement, including payments by Astellas of a to be determined upfront payment, certain to be determined milestone payments, and certain to be determined royalties on net sales of GAN Products and/or Rett Products, as applicable.

During the Rett Option Period, we have agreed to (A) not solicit or encourage any inquiries, offers or proposals for, or that could reasonably be expected to lead to, a Change of Control (as defined in the Option Agreement), or (B) otherwise initiate a process for a potential Change of Control, in each case, without first notifying Astellas and offering Astellas the opportunity to submit an offer or proposal to us for a transaction that would result in a Change of Control. If Astellas fails or declines to submit any such offer within a specified period after the receipt of such notice, we will have the ability to solicit third party bids for a Change of Control transaction. If Astellas delivers an offer to us for a transaction that would result in a Change of Control, we and Astellas will attempt to negotiate in good faith the potential terms and conditions for such potential transaction that would result in a Change of Control for a specified period, which period may be shortened or extended by mutual agreement.

As partial consideration for the rights granted to Astellas under the Option Agreement, Astellas paid us a one-time payment in the amount of $20.0 million, or the Upfront Payment. Astellas or any of its affiliates shall have the right, in its or their discretion and upon written notice to us, to offset the amount of the Upfront Payment (in whole or in part, until the full amount of the Upfront Payment has been offset) against (a) any payment(s) owed to us or any of our affiliates (or to any third party on behalf of us) under or in connection with any license agreement entered into with respect to any GAN Product or Rett Product, including, any upfront payment, milestone payment or royalties owed to us or any of our affiliates (or to any third party on our behalf) under or in connection with any such license agreement or (b) any amount owed to us or any of our affiliates in connection with a Change of Control transaction with Astellas or any of its affiliates. As further consideration for the rights granted to Astellas under the Option Agreement, we and Astellas also entered into the Astellas Securities Purchase Agreement (as defined below).

Securities Purchase Agreement

On October 21, 2022, we entered into a securities purchase agreement, or the Astellas Securities Purchase Agreement (and together with the Option Agreement, the Astellas Transactions), with Astellas, pursuant to which we agreed to issue and sell to Astellas in a private placement, or the Astellas Private Placement, an aggregate of 7,266,342 shares, or the Astellas Shares, of our common stock, for aggregate gross proceeds of approximately $30.0 million.

The shares of common stock issued by us pursuant to the Astellas Securities Purchase Agreement were not initially registered under the Securities Act of 1933, as amended, or the Securities Act. We relied on the private placement exemption from registration provided by Section 4(a)(2) of the Securities Act and by Rule 506 of Regulation D, promulgated thereunder and on similar exemptions under applicable state laws.

Pursuant to the Astellas Securities Purchase Agreement, in connection with the Astellas Private Placement, Astellas has the right to designate one individual to attend all meetings of the Board in a non-voting observer capacity.

Registration Rights Agreement

Also, on October 21, 2022, we entered into a registration rights agreement, or the Registration Rights Agreement, with Astellas, pursuant to which we agreed to register the resale of the Astellas Shares. Under the Registration Rights Agreement, we agreed to file a registration statement covering the resale of the Astellas Shares no later than April 24, 2023, or the Filing Deadline. We agreed to use reasonable best efforts to cause such registration statement to become effective as promptly as practicable after the filing thereof but in any event on or prior to the Effectiveness Deadline (as defined in the Registration Rights Agreement), and to keep such registration statement continuously effective until the earlier of (i) the date the Astellas Shares covered by such registration statement have been sold or may be resold pursuant to Rule 144 without restriction, or (ii) October 24, 2025. We have also agreed, among other things, to pay all reasonable fees and expenses (excluding any underwriters' discounts and commissions and all fees and expenses of legal counsel, accountants and other advisors for Astellas except as specifically provided in the Registration Rights Agreement) incident to the performance of or compliance with the Registration Rights Agreement by us.

We have granted Astellas customary indemnification rights in connection with the registration statement. Astellas has also granted us customary indemnification rights in connection with the registration statement.

SSI Strategy Holdings LLC Transaction

In April 2023, we entered into a securities purchase agreement, or the SSI Securities Purchase Agreement, with two affiliates of SSI Strategy Holdings LLC, or SSI, named therein, or the SSI Investors, pursuant to which we agreed to issue and sell to the SSI Investors in a private placement, or the SSI Private Placement, 705,218 shares of our common stock, or the SSI Shares, and warrants, or the SSI Warrants, to purchase an aggregate of 525,000 shares of our common stock, or the Warrant Shares. SSI provides certain consulting services to Taysha. Each SSI Warrant has an exercise price of $0.7090 per Warrant Share, which was the closing price of our common stock on the Nasdaq Global Market on April 4, 2023. The SSI Warrants issued in the SSI Private Placement provide that the holder of the SSI Warrants will not have the right to exercise any portion of its SSI Warrants until the achievement of certain clinical and regulatory milestones related to our clinical programs. The SSI Private Placement closed on April 5, 2023. Gross proceeds of the SSI Private Placement were $500,000. The shares of common stock issued by us pursuant to the SSI Securities Purchase Agreement were not initially registered under the Securities Act. We relied on the exemption from the registration requirements of the Securities Act under Section 4(a)(2) thereof.

Under the SSI Securities Purchase Agreement, we agreed to file a registration statement covering the resale of the SSI Shares and Warrant Shares no later than September 25, 2023. We agreed to use reasonable best efforts to cause such registration statement to become effective as promptly as practicable after the filing thereof but in any event on or prior to the Effectiveness Deadline (as defined in the SSI Securities Purchase Agreement), and to keep such registration statement continuously effective until the earlier of (i) the date the SSI Shares and Warrant Shares covered by such registration statement have been sold or may be resold pursuant to Rule 144 without restriction, or (ii) April 5, 2026. We have also agreed, among other things, to pay all reasonable fees and expenses (excluding any underwriters' discounts and commissions and all fees and expenses of legal counsel, accountants and other advisors for SSI except as specifically provided in the SSI Securities Purchase Agreement)

incident to the performance of or compliance with the registration rights provisions of the SSI Securities Purchase Agreement by us.

The registration statement of which this prospectus is a part relates to the offer and resale of the Astellas Shares, SSI Shares and Warrant Shares. When we refer to the selling stockholders in this prospectus, we are referring to Astellas and the SSI Investors and, as applicable, any donees, pledgees, assignees, transferees or other successors-in-interest selling the Shares received after the date of this prospectus from the selling stockholders as a gift, pledge, or other non-sale related transfer.

Risks Associated with Our Business

Our business is subject to a number of risks of which you should be aware before making an investment decision. These risks are discussed more fully in the section titled "Risk Factors" immediately following this prospectus summary and under similar headings in our filings with the SEC which are incorporated by reference in this prospectus. These risks include the following:

- We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability. These factors raise substantial doubt regarding our ability to continue as a going concern.
- We will need substantial additional funding to meet our financial obligations and to pursue our business objectives. If we are unable to raise capital when needed, we could be forced to curtail our planned operations and the pursuit of our growth strategy.
- We have a limited operating history and no history of commercializing products, which may make it difficult for an investor to evaluate the success of our business to date and to assess our future viability.
- We are very early in our development efforts and all of our product candidates are in preclinical or clinical development. If we are unable to successfully develop, receive regulatory approval for and commercialize our product candidates for these or any other indications, or successfully develop any other product candidates, or experience significant delays in doing so, our business will be harmed.
- Because gene therapy is novel and the regulatory landscape that governs any product candidates we may develop is rigorous, complex, uncertain and subject to change, we cannot predict the time and cost of obtaining regulatory approval, if we receive it at all, for any product candidates we may develop.
- We intend to identify and develop novel gene therapy product candidates, which makes it difficult to predict the time, cost and potential success of product candidate development.
- The regulatory approval processes of the U.S. Food and Drug Administration, or FDA, European Medicines Agency, or the EMA, and comparable foreign authorities are lengthy, time consuming and inherently unpredictable. If we are not able to obtain required regulatory approval for our product candidates, our business will be substantially harmed.
- We have not yet completed testing of any product candidates in clinical trials. Success in preclinical studies or earlier clinical trials may not be indicative of results in future clinical trials.
- We may not be successful in our efforts to build a pipeline of additional product candidates or our next-generation platform technologies.
- Our business and operations could be adversely affected by the effects of health epidemics, including the COVID-19 pandemic.
- Gene therapies are novel, complex and difficult to manufacture. We could experience manufacturing problems that result in delays in the development or commercialization of our product candidates or otherwise harm our business.
- We and our contract manufacturers for AAV9 are subject to significant regulation with respect to manufacturing our products. The third-party manufacturing facilities on which we rely, and any

manufacturing facility that we may have in the future, may have limited capacity or fail to meet the applicable stringent regulatory requirements.

- We currently rely exclusively on our collaboration with UT Southwestern for our preclinical research and development programs, including for discovering, preclinically developing and conducting all IND-enabling studies for our lead product candidates and our near-term future pipeline. Failure or delay of UT Southwestern to fulfill all or part of its obligations to us under the agreement, a breakdown in collaboration between the parties or a complete or partial loss of this relationship would materially harm our business.
- UT Southwestern has entered into collaborations with third parties, including certain of our competitors, addressing targets and disease indications outside the scope of our collaboration. As a result, UT Southwestern may have competing interests with respect to their priorities and resources.
- Negative public opinion of gene therapy and increased regulatory scrutiny of gene therapy and genetic research may adversely impact the development or commercial success of our current and future product candidates.
- We face significant competition from other biotechnology and pharmaceutical companies, and our operating results will suffer if we fail to compete effectively.
- Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain.
- Our term loan agreement contains restrictions that potentially limit our flexibility in operating our business, and we may be required to make a prepayment or repay our outstanding indebtedness earlier than we expect.
- If we are unable to obtain or protect intellectual property rights related to any of our product candidates, we may not be able to compete effectively in our market.

Company Information

We were incorporated under the laws of the State of Texas in September 2019. In February 2020, we converted to a Delaware corporation. Our principal executive offices are located at 3000 Pegasus Park Drive, Suite 1430, Dallas, Texas 75247 and our telephone number is (214) 612-0000. Our website address is www.tayshagtx.com. The information contained on, or accessible through, our website is not incorporated by reference into this prospectus. We have included our website in this prospectus solely as an inactive textual reference.

Implications of Being an Emerging Growth Company and a Smaller Reporting Company

We qualify as an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For so long as we remain an emerging growth company, we may take advantage of relief from certain reporting requirements and other burdens that are otherwise applicable generally to public companies. These provisions include:

- reduced obligations with respect to financial data, including only being required to present two years of audited financial statements, in addition to any required unaudited interim financial statements with correspondingly reduced “Management’s Discussion and Analysis of Financial Condition and Results of Operations” disclosure;
- an exception from compliance with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended;
- reduced disclosure about our executive compensation arrangements in our periodic reports, proxy statements and registration statements;

- exemptions from the requirements of holding non-binding advisory votes on executive compensation or golden parachute arrangements; and
- an exemption from compliance with the requirements of the Public Company Accounting Oversight Board regarding the communication of critical audit matters in the auditor's report on financial statements.

We may take advantage of these provisions until we no longer qualify as an emerging growth company. We will cease to qualify as an emerging growth company on the date that is the earliest of: (i) December 31, 2025, (ii) the last day of the fiscal year in which we have more than $1.235 billion in total annual gross revenues, (iii) the date on which we are deemed to be a "large accelerated filer" under the rules of the SEC, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, or (iv) the date on which we have issued more than $1.0 billion of non-convertible debt over the prior three-year period. We may choose to take advantage of some but not all of these reduced reporting burdens. We have taken advantage of certain reduced reporting requirements in this prospectus. Accordingly, the information contained herein may be different than you might obtain from other public companies in which you hold equity interests.

In addition, under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have elected to take advantage of the extended transition period to comply with new or revised accounting standards and to adopt certain of the reduced disclosure requirements available to emerging growth companies. As a result of the accounting standards election, we will not be subject to the same implementation timing for new or revised accounting standards as other public companies that are not emerging growth companies, which may make comparison of our financials to those of other public companies more difficult. As a result of these elections, the information that we provide in this prospectus may be different than the information you may receive from other public companies in which you hold equity interests. In addition, it is possible that some investors will find our common stock less attractive as a result of these elections, which may result in a less active trading market for our common stock and higher volatility in our share price.

We are also a "smaller reporting company," meaning that the market value of our shares held by non-affiliates is less than $700 million and our annual revenue was less than $100 million during the most recently completed fiscal year. We may continue to be a smaller reporting company if either (i) the market value of our shares held by non-affiliates is less than $250 million or (ii) our annual revenue was less than $100 million during the most recently completed fiscal year and the market value of our shares held by non-affiliates is less than $700 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company, we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

THE OFFERING	
Common Stock Offered by the Selling Stockholders	8,496,560 shares.
Use of Proceeds	We will not receive any of the proceeds from the sale of the Shares in this offering. The selling stockholders will receive all of the proceeds from the sale of the Shares hereunder.
Risk Factors	An investment in our common stock involves a high degree of risk. See the information contained in or incorporated by reference in the section titled “Risk Factors” and under similar headings in the other documents that are incorporated by reference herein, as well as the other information included in or incorporated by reference in this prospectus.
Nasdaq Global Select Market Symbol	Our common stock is listed on The Nasdaq Global Select Market under the symbol “TSHA.”

RISK FACTORS

An investment in our common stock involves a high degree of risk. Prior to making a decision about investing in our common stock, you should consider carefully the specific risk factors discussed in the sections titled “Risk Factors” contained in our most recent Annual Report on Form 10-K, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus in their entirety, together with other information in this prospectus, the documents incorporated by reference, any prospectus supplement and any free writing prospectus that we may authorize. These risks and uncertainties are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us, or that we currently view as immaterial, may also impair our business. If any of the risks or uncertainties described in our SEC filings or any additional risks and uncertainties actually occur, our business, financial condition, results of operations and cash flow could be materially and adversely affected. In that case, the trading price of our common stock could decline and you might lose all or part of your investment.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference herein contain forward-looking statements. These are based on our management's current beliefs, expectations and assumptions about future events, conditions and results and on information currently available to us. Discussions containing these forward-looking statements may be found, among other places, in the sections entitled "Business," "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" contained in the documents incorporated by reference herein.

Any statements in this prospectus, or incorporated herein, about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and are forward-looking statements. Within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, these forward-looking statements include statements regarding:

- our ability to continue as a going concern;
- the timing, progress and results of our preclinical studies and clinical trials of our product candidates, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available and our research and development programs;
- the timing of our planned Investigational New Drug and Clinical Trial Agreement submissions, initiation of clinical trials and timing of expected clinical results for TSHA-102 for Rett, TSHA-120 for GAN and any other current and future product candidates that we advance;
- the timing of any submission of filings for regulatory approval of, and our ability to obtain and maintain regulatory approvals for, our current and future product candidates;
- the outbreak of the novel strain of coronavirus disease, COVID-19, which could adversely impact our business, including our preclinical studies, clinical supply and clinical trials;
- our ability to identify patients with the diseases treated by our product candidates, and to enroll patients in trials;
- our expectations regarding the size of the patient populations, market acceptance and opportunity for and clinical utility of our product candidates, if approved for commercial use;
- our manufacturing capabilities and strategy, including the scalability and commercial viability of our manufacturing methods and processes;
- our expectations regarding the scope of any approved indication for, TSHA-102, TSHA-120 or any other current or future product candidate that we advance;
- our ability to successfully commercialize our product candidates;
- our ability to leverage our platform, including our next-generation technologies, to identify and develop future product candidates;
- our estimates of our expenses, ongoing losses, future revenue, capital requirements and our need for or ability to obtain additional funding before we can expect to generate any revenue from product sales;
- our ability to establish or maintain collaborations or strategic relationships;
- our ability to identify, recruit and retain key personnel;
- our reliance upon intellectual property licensed from third parties and our ability to obtain such licenses on commercially reasonable terms or at all;
- our ability to protect and enforce our intellectual property position for our product candidates, and the scope of such protection;

- our ability to comply with the terms of our term loan agreement;
- our financial performance;
- our competitive position and the development of and projections relating to our competitors or our industry;
- our estimates regarding future revenue, expenses and needs for additional financing;
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act; and
- other risks and uncertainties, including those listed under the caption “Risk Factors” in our most recent Annual Report on Form 10-K and other filings we make with the SEC.

In some cases, you can identify forward-looking statements by the words “may,” “might,” “can,” “will,” “to be,” “could,” “would,” “should,” “expect,” “intend,” “plan,” “objective,” “anticipate,” “believe,” “estimate,” “predict,” “project,” “potential,” “likely,” “continue” and “ongoing,” or the negative of these terms, or other comparable terminology intended to identify statements about the future, although not all forward-looking statements contain these words. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements.

You should refer to the “Risk Factors” section below and contained in any applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus, for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. Given these risks, uncertainties and other factors, many of which are beyond our control, we cannot assure you that the forward-looking statements in this prospectus will prove to be accurate, and you should not place undue reliance on these forward-looking statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to revise any forward-looking statements to reflect events or developments occurring after the date of this prospectus, even if new information becomes available in the future.

USE OF PROCEEDS

We will not receive any of the proceeds from the sale of the Shares in this offering. The selling stockholders will receive all of the proceeds from the sale of the Shares hereunder.

SELLING STOCKHOLDERS

We have prepared this prospectus to allow the selling stockholders to offer and sell from time to time up to 8,496,560 shares of our common stock for their own account, consisting of (i) up to 7,266,342 shares of common stock issued to Astellas in the Astellas Private Placement, (ii) up to 705,218 shares of common stock issued to SSI in the SSI Private Placement, and (ii) 525,000 shares issuable upon the exercise of the SSI Warrants.

We are registering the offer and sale of the Shares to satisfy certain registration obligations that we granted the selling stockholders in connection with the purchase of the Shares pursuant to the Astellas Securities Purchase Agreement and the SSI Securities Purchase Agreement.

Pursuant to the Registration Rights Agreement, with respect to the Astellas Shares, we have agreed to prepare and file with the SEC such amendments and supplements to this prospectus, and the registration statement of which this prospectus forms a part, used in connection therewith as may be necessary to keep such registration statement continuously effective and free from any material misstatement or omission to state a material fact therein until the earlier of (i) the date the Astellas Shares covered by such registration statement have been sold or may be resold pursuant to Rule 144 without restriction, or (ii) October 24, 2025. We have also agreed, among other things, to pay all reasonable fees and expenses (excluding any underwriters' discounts and commissions and all fees and expenses of legal counsel, accountants and other advisors for Astellas except as specifically provided in the Registration Rights Agreement) incident to the performance of or compliance with the Registration Rights Agreement by us.

Pursuant to the SSI Securities Purchase Agreement, with respect to the SSI Shares and Warrant Shares, we have agreed to prepare and file with the SEC such amendments and supplements to this prospectus, and the registration statement of which this prospectus forms a part, used in connection therewith as may be necessary to keep such registration statement continuously effective until the earlier of (i) the date the SSI Shares and Warrant Shares covered by such registration statement have been sold or may be resold pursuant to Rule 144 without restriction, or (ii) April 5, 2026. We have also agreed, among other things, to pay all reasonable fees and expenses (excluding any underwriters' discounts and commissions and all fees and expenses of legal counsel, accountants and other advisors for SSI except as specifically provided in the SSI Securities Purchase Agreement) incident to the performance of or compliance with the registration rights provisions of the SSI Securities Purchase Agreement by us.

The following table sets forth (i) the name of each selling stockholder, (ii) the number of shares of common stock beneficially owned by each selling stockholder, (iii) the number of shares of common stock that may be offered under this prospectus and (iv) the number of shares of common stock beneficially owned by each selling stockholder assuming all of the shares covered hereby are sold.

Beneficial ownership is determined in accordance with the rules of the SEC, and includes voting or investment power with respect to our common stock. Except as indicated by the footnotes below, we believe, based on the information furnished to us, that the selling stockholders named in the table below has sole voting and investment power with respect to all shares of common stock that they beneficially own, subject to applicable community property laws.

The selling stockholders may sell some, all or none of the Shares offered by this prospectus from time to time. We do not know how long the selling stockholders will hold the Shares covered hereby before selling them and we currently have no agreements, arrangements or understandings with the selling stockholders regarding the sale or other disposition of any Shares. The information set forth in the table below is based on 64,178,567 shares of our common stock outstanding as of April 5, 2023 and assumes the selling stockholders dispose of all of the Shares covered by this prospectus and does not acquire beneficial ownership of any additional shares of common stock. The registration of the Shares does not necessarily mean that the selling stockholders will sell all or any portion of the Shares covered by this prospectus.

As used in this prospectus, the term "selling stockholders" includes the selling stockholders listed in the table below, together with any additional selling stockholders listed in a prospectus supplement, and their donees, pledgees, assignees, transferees, distributees and successors-in-interest that receive Shares in any non-sale transfer after the date of this prospectus.

	Beneficial Ownership Prior to this Offering			Beneficial Ownership After this Offering[1]	
Name of Selling Stockholder	Number of Shares	Percentage of Outstanding Common Stock	Number of Shares Being Offered[2]	Number of Shares	Percent of Outstanding Common Stock
Astellas[3]	7,266,342	11.3%	7,266,342	—	— %
SSI Investors[4]	817,718	*	1,230,218	—	— %

* Represents beneficial ownership of less than 1%

(1) Assumes each selling stockholder sells the maximum number of shares of our common stock possible in this offering.

(2) Represents all of the shares of our common stock that the selling stockholders may offer and sell from time to time under this prospectus.

(3) The shares reported under "Beneficial Ownership Prior to this Offering" consists of 7,266,342 shares of our common stock purchased by Astellas in the Astellas Private Placement. Astellas shares voting and investment power with respect to all shares of common stock it beneficially owns with Astellas Pharma Inc., a company organized under the laws of Japan, and Astellas US Holding, Inc., a company incorporated under the laws of the State of Delaware. The address of the principal business office of Astellas is 225 Gateway Boulevard, South San Francisco, CA 94080. The address of the principal business office of Astellas Pharma Inc. is 2-5-1, Nihonbashi-Honcho, Chuo-Ku, Tokyo 103-8411, Japan. The address of the principal business office of Astellas US Holding, Inc. is 1 Astellas Way, Northbrook, IL 60062.

(4) In accordance with Rule 13d-3(d), the shares reported under "Beneficial Ownership Prior to this Offering" consists of (1) 352,609 shares of our common stock purchased in the SSI Private Placement by SSI Strategy Sidecar 1, LLC, which is wholly owned by SSI Strategy Holdings LLC, (2) 352,609 shares of our common stock purchased in the SSI Private Placement by SSI Strategy Sidecar 2, LLC, which is wholly owned by SSI Strategy Holdings, LLC, (3) 56,250 Warrant Shares held by SSI Strategy Sidecar 1, LLC issuable upon the exercise of common stock warrants exercisable within 60 days of April 5, 2023, and (4) 56,250 Warrant Shares held by SSI Strategy Sidecar 2, LLC issuable upon the exercise of common stock warrants exercisable within 60 days of April 5, 2023. The share numbers do not reflect 206,250 Warrant Shares and 206,250 Warrant Shares held by SSI Strategy Sidecar 1, LLC and SSI Strategy Sidecar 2, LLC, respectively. The holder of the SSI Warrants will not have the right to exercise any portion of its SSI Warrants until the achievement of certain clinical and regulatory milestones related to our clinical programs. Amulet Capital Fund II, L.P. has the power to appoint a majority of the Board of Managers of SSI Strategy Holdings LLC. Amulet Capital Fund II, L.P. is controlled by Amulet Capital Fund II GP, L.P. Amulet Capital Fund II GP, L.P. is controlled by Ramsey Frank and Jay Rose, and as such could be deemed to share voting control and investment power over the shares that may be deemed to be beneficially owned by SSI Strategy Sidecar 1, LLC and SSI Strategy Sidecar 2, LLC. The address for SSI Strategy Sidecar 1, LLC and SSI Strategy Sidecar 2, LLC is 9 Campus Drive, Suite 103, Parsippany, NJ 07054. The address of Amulet Capital Fund II, L.P., Amulet Capital Fund II GP, L.P., Ramsey Frank and Jay Rose is 1 Lafayette Place, Suite 301, Greenwich, CT 06830.

Relationships with Selling Stockholders

As discussed in greater detail under the section titled "Prospectus Summary—Astellas Transactions," in October 2022, we entered into the Astellas Transactions, pursuant to which we sold and issued 7,266,342 shares of our common stock to Astellas. We also entered into the Registration Rights Agreement with Astellas, pursuant to which we agreed to file a registration statement with the SEC to cover the resale by Astellas of the Astellas Shares. Pursuant to the Astellas Securities Purchase Agreement, in connection with the Astellas Private Placement, Astellas has the right to designate one individual to attend all meetings of the Board in a non-voting observer capacity.

As discussed in greater detail under the section titled "Prospectus Summary—SSI Strategy Holdings LLC Transaction, we entered into the SSI Purchase Agreement, pursuant to which we sold and issued 705,218 shares of our common stock and warrants to purchase 525,000 shares of our common stock to the SSI Investors. SSI provides certain consulting services to Taysha.

PLAN OF DISTRIBUTION

The selling stockholders, which as used herein includes donees, pledgees, transferees or other successors-in-interest selling shares of common stock previously issued or interests in shares of common stock received after the date of this prospectus from a selling stockholder as a gift, pledge, partnership distribution or other transfer, may, from time to time, sell, transfer or otherwise dispose of any or all of their shares of common stock or interests in shares of common stock on any stock exchange, market or trading facility on which the shares are traded or in private transactions. The selling stockholders may sell their shares of our common stock pursuant to this prospectus at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale, or at negotiated prices.

The selling stockholders may use any one or more of the following methods when disposing of shares or interests therein:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- one or more underwritten offerings;
- block trades in which the broker-dealer will attempt to sell the shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- short sales;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;
- broker-dealers may agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share;
- a combination of any such methods of sale; and
- any other method permitted pursuant to applicable law.

The selling stockholders may, from time to time, pledge or grant a security interest in some or all of the shares of common stock owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the shares of common stock, from time to time, under this prospectus, or under an amendment to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act amending the list of selling stockholders to include the pledgee, transferee or other successors in interest as selling stockholders under this prospectus. The selling stockholders also may transfer the shares of common stock in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus.

In connection with the sale of our common stock or interests therein, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the common stock in the course of hedging the positions they assume. The selling stockholders may also sell shares of our common stock short and deliver these securities to close out their short positions, or loan or pledge the common stock to broker-dealers that in turn may sell these securities. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction).

The aggregate proceeds to the selling stockholders from the sale of the common stock offered by them will be the purchase price of the common stock less discounts or commissions, if any. Each of the selling stockholders reserves the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of common stock to be made directly or through agents. We will not receive any of the proceeds from this offering.

The selling stockholders and any underwriters, broker-dealers or agents that participate in the sale of the common stock or interests therein may be "underwriters" within the meaning of Section 2(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of the shares may be underwriting discounts and commissions under the Securities Act. Selling stockholders who are "underwriters" within the meaning of Section 2(11) of the Securities Act will be subject to the prospectus delivery requirements of the Securities Act.

To the extent required, the shares of our common stock to be sold, the names of the selling stockholders, the respective purchase prices and public offering prices, the names of any agents, dealer or underwriter, any applicable commissions or discounts with respect to a particular offer will be set forth in an accompanying prospectus supplement or, if appropriate, a post-effective amendment to the registration statement that includes this prospectus.

In order to comply with the securities laws of some states, if applicable, the common stock may be sold in these jurisdictions only through registered or licensed brokers or dealers. In addition, in some states the common stock may not be sold unless it has been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

We have advised the selling stockholders that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares in the market and to the activities of the selling stockholders and their affiliates. In addition, we will make copies of this prospectus (as it may be supplemented or amended from time to time) available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act. We or the selling stockholders may indemnify any broker-dealer that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act.

We have agreed to indemnify the selling stockholders against liabilities, including liabilities under the Securities Act and state securities laws, relating to the registration of the shares offered by this prospectus.

We have agreed with the selling stockholders to keep the registration statement of which this prospectus forms a part effective until such time as the shares offered by the selling stockholders have been effectively registered under the Securities Act and disposed of in accordance with such registration statement, the shares offered by the selling stockholders have been disposed of pursuant to Rule 144 under the Securities Act or the shares offered by the selling stockholders may be resold pursuant to Rule 144 without volume or manner-of-sale restrictions.

LEGAL MATTERS

Cooley LLP, New York, New York, will pass upon the validity of the shares of common stock offered hereby. As of the date of this prospectus, GC&H Investments, LLC, an entity consisting of current and former partners and associates of Cooley LLP, beneficially holds an aggregate of 16,021 shares of our common stock.

EXPERTS

The financial statements incorporated in this prospectus by reference from the Company's Annual Report on Form 10-K have been audited by Deloitte & Touche LLP, an independent registered public accounting firm, as stated in their report, which is incorporated herein by reference. Such financial statements have been so incorporated in reliance upon the report of such firm given upon their authority as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

This prospectus is part of a registration statement we filed with the SEC. This prospectus does not contain all of the information set forth in the registration statement and the exhibits to the registration statement. For further information with respect to us and the securities we are offering under this prospectus, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. You should rely only on the information contained in this prospectus or incorporated by reference in this prospectus. We have not authorized anyone else to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus is accurate as of any date other than the date on the front page of this prospectus, regardless of the time of delivery of this prospectus or any sale of the securities offered by this prospectus.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. The SEC maintains a website at www.sec.gov that contains reports, proxy and information statements, and other information regarding issuers, such as us, that file electronically with the SEC.

Copies of certain information filed by us with the SEC are also available on our website at www.tayshagtx.com. Information contained in or accessible through our website does not constitute a part of this prospectus and is not incorporated by reference in this prospectus. We have included our website address as an inactive textual reference only.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The SEC file number for the documents incorporated by reference in this prospectus is 001-39536. The documents incorporated by reference into this prospectus contain important information that you should read about us.

The following documents are incorporated by reference into this document:

- our Annual Report on Form 10-K for the year ended December 31, 2022, filed with the SEC on March 28, 2023, and as amended on Form 10-K/A filed with the SEC on April 27, 2023;
- our Current Reports on Form 8-K/A filed with the SEC on January 6, 2023 and March 8, 2023 and our Current Reports on Form 8-K filed with the SEC on January 19, 2023, January 31, 2023, March 28, 2023 and April 27, 2023 (to the extent the information in such reports is filed and not furnished); and
- the description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on September 18, 2020, including any amendments or reports filed for the purposes of updating this description.

We also incorporate by reference into this prospectus all documents (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items) that are filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (i) after the date of the initial filing of the registration statement of which this prospectus forms a part and prior to effectiveness of the registration statement, or (ii) after the date of this prospectus but prior to the termination of the offering. These documents include periodic reports, such as Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as well as proxy statements.

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered, without charge upon written or oral request, a copy of any or all of the documents that are incorporated by reference into this prospectus but not delivered with the prospectus, including exhibits that are specifically incorporated by reference into such documents. You should direct any requests for documents to Taysha Gene Therapies, Inc., Attn: Corporate Secretary, 3000 Pegasus Park Drive, Suite 1430, Dallas, Texas 75247, and our telephone number is (214) 612-0000.

Any statement contained in this prospectus or contained in a document incorporated or deemed to be incorporated by reference into this prospectus will be deemed to be modified or superseded to the extent that a statement contained in this prospectus or any subsequently filed supplement to this prospectus, or document deemed to be incorporated by reference into this prospectus, modifies or supersedes such statement.

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8,496,560 Shares

Common Stock

PROSPECTUS