

PROSPECTUS

166,663,354 Shares



Common Stock Offered by the Selling Stockholders

This prospectus relates to the proposed resale from time to time of up to 166,663,354 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), which consist of (i) 122,412,376 shares of our common stock held by the selling stockholders and (ii) 44,250,978 shares of our common stock issuable upon the exercise of outstanding pre-funded warrants, or the Pre-Funded Warrants, to purchase shares of our common stock held by certain of the selling stockholders. We will not receive any proceeds from the sale of the shares offered by this prospectus, except the exercise price of \$0.001 per share of any of the Pre-Funded Warrants exercised for cash.

The selling stockholders acquired the Shares in a private placement transaction that closed on August 16, 2023, or the Private Placement. We are filing this Registration Statement on Form S-3, of which this prospectus forms a part, to fulfill our contractual obligations with the selling stockholders to provide for the resale by the selling stockholders of the Shares. See "Selling Stockholders" beginning on page 13 of this prospectus for more information about the selling stockholders. The registration of the Shares to which this prospectus relates does not require the selling stockholders to sell any of their Shares, including any shares of common stock issuable upon the exercise of Pre-Funded Warrants.

We are not offering any Shares under this prospectus and will not receive any proceeds from the sale or other disposition of the Shares covered hereby; however, we will receive proceeds from the exercise of the Pre-Funded Warrants. See "Use of Proceeds" beginning on page 12 of this prospectus.

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 selling commissions applicable to the sales of Shares and all fees and expenses of legal counsel 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 September 8, 2023, the closing price of our common stock was \$3.64 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 9 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 September 8, 2023.

TABLE OF CONTENTS

	<u>Page</u>
ABOUT THIS PROSPECTUS	1
PROSPECTUS SUMMARY	2
THE OFFERING	8
RISK FACTORS	9
SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS	10
USE OF PROCEEDS	12
SELLING STOCKHOLDERS	13
PLAN OF DISTRIBUTION	20
LEGAL MATTERS	22
EXPERTS	22
WHERE YOU CAN FIND ADDITIONAL INFORMATION	22
INCORPORATION OF CERTAIN INFORMATION BY REFERENCE	23

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 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 3.5×10^{14} total vector genomes, or vg, (by dot blot) and 1.0×10^{14} 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 received feedback in July 2023. The FDA concluded that analytical data is sufficient to support the comparability study (comparing early clinical and pivotal lots) and pivotal lot release for use in planned clinical studies.

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 dosed the first adult patient with Rett syndrome in the first half of 2023. The independent data monitoring committee, or IDMC, meeting to review the initial safety data from the first patient took place in the early third quarter of 2023 at which time the IDMC provided clearance to dose the next patient. There have been no treatment-emergent serious adverse events as of the six-week assessment post-treatment. We will continue to report quarterly updates on available clinical data from the adult study. We submitted a clinical trial application, or CTA, to the United Kingdom's Medicines and Healthcare Products Regulatory Agency, or MHRA, for pediatric patients with Rett syndrome and submitted an IND application for pediatric patients with Rett syndrome to the FDA for TSHA-102 early in the third quarter of 2023. In August 2023, we received clearance from the FDA on our IND for TSHA-102 in pediatric patients with Rett syndrome. Additionally, in August 2023 the FDA granted Fast Track Designation to TSHA-102.

Private Placement

On August 14, 2023, we entered into a Securities Purchase Agreement, or the Purchase Agreement, with certain institutional and other accredited investors, or the Purchasers, pursuant to which we agreed to sell and issue to the Purchasers in the Private Placement (i) 122,412,376 shares of our common stock and (ii) with respect to certain Purchasers, the Pre-Funded Warrants to purchase 44,250,978 shares of common stock in lieu of shares of common stock. The purchase price per share of common stock was \$0.90 per share, or the Purchase Price, and the purchase price for the Pre-Funded Warrants was the Purchase Price minus \$0.001 per Pre-Funded Warrant. We received gross proceeds of approximately \$150.0 million from the Private Placement, before deducting fees to the placement agent and offering expenses payable by us. The closing of the Private Placement occurred on August 16, 2023.

The Pre-Funded Warrants have a per share exercise price of \$0.001, subject to proportional adjustments in the event of stock splits or combinations or similar events. The Pre-Funded Warrants will not expire until exercised in full. The Pre-Funded Warrants may not be exercised if the aggregate number of shares of common stock beneficially owned by the holder thereof immediately following such exercise would exceed a specified beneficial ownership limitation; provided, however, that a holder may increase or decrease the beneficial ownership limitation by giving 61 days' notice to us, but not to any percentage in excess of 19.99%. The Pre-Funded Warrants are further only exercisable into common stock upon the filing of a charter amendment with the Secretary of State of the State of Delaware, or the Charter Amendment, following receipt of stockholder approval of an increase in the number of authorized shares of our common stock, or the Stockholder Approval, which we will first seek to obtain at a special meeting of stockholders to be held by December 31, 2023. If we do not obtain Stockholder Approval by December 31, 2023, we are required to pay liquidated damages of 2.0% of the aggregate purchase price paid by each holder of Pre-Funded Warrants. For any subsequent failure to obtain Stockholder Approval, we are required to pay an additional 2.0% as liquidated damages.

The Shares were not initially registered under the Securities Act. Based in part upon the representations of the Purchasers in the Purchase Agreement, we relied on the exemption afforded by Regulation D under the Securities Act, and corresponding provisions of state securities or "blue sky" laws. Each of the Purchasers represented in the Purchase Agreement that it was an "accredited investor" as defined in Regulation D of the Securities Act and that it was acquiring the securities for investment only and not with a view towards, or for resale in connection with, the public sale or distribution thereof, and appropriate legends will be affixed to the securities. The sale of the securities did not involve a public offering and was made without general solicitation or general advertising.

Under the terms of the Purchase Agreement, we agreed to prepare and file, by August 31, 2023, or the Filing Deadline, one or more registration statements with the SEC to register for resale the Shares, and to cause the applicable registration statements to become effective within a specified period after the Filing Deadline, or the Effectiveness Deadline. We also agreed to use our best efforts to keep such registration statement effective until the earlier of (i) the third anniversary of the date the initial registration statement is declared effective, or (ii) the date all Shares (assuming cashless exercise of the Pre-Funded Warrants) held by or issuable to a Holder, as defined in the Purchase Agreement, may be sold under Rule 144 without being subject to any volume, manner of sale or publicly available information requirements.

In the event the registration statement has not been filed by the Filing Deadline or has not been declared effective by the SEC by the Effectiveness Deadline, subject to certain limited exceptions, we have agreed to make pro rata payments to each Purchaser as liquidated damages in an amount equal to 1.0% of the Purchaser's Subscription Amount, as defined in the Purchase Agreement, per 20-day period or pro rata for any portion thereof for each such 20-day period during which such event continues, subject to certain caps set forth in the Purchase Agreement.

We granted the Purchasers customary indemnification rights in connection with the registration statement. The Purchasers have also granted us customary indemnification rights in connection with the registration statement.

The registration statement of which this prospectus is a part relates to the offer and resale of the Shares issued to the Purchasers pursuant to the Purchase Agreement, including the shares of our common stock issuable upon the exercise of outstanding pre-funded warrants. When we refer to the selling stockholders in this prospectus, we are referring to the Purchasers 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.

Following the closing of the Private Placement, as of August 18, 2023 we had 186,960,193 shares of common stock outstanding.

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, among others, 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.

- If we are unable to obtain Stockholder Approval for the Charter Amendment to increase the number of authorized shares of our common stock, we will be required to pay liquidated damages to holders of the Pre-Funded Warrants.

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

166,663,354 Shares (consisting of 122,412,376 outstanding shares of our common stock and 44,250,978 shares of our common stock issuable upon the exercise of the Pre-Funded Warrants).

Use of Proceeds

The selling stockholders will receive all of the proceeds from the sale of the Shares hereunder. Accordingly, we will not receive any of the proceeds from the sale of the Shares in this offering; however, we will receive proceeds from any cash exercise of the Pre-Funded Warrants. See “Use of Proceeds.”

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.

Additional Risk Related to the Private Placement

If we are unable to obtain Stockholder Approval for the Charter Amendment to increase the number of authorized shares of our common stock, we will be required to pay liquidated damages to holders of the Pre-Funded Warrants.

We are required to hold a special meeting of stockholders for the purpose of obtaining stockholder approval of the Charter Amendment to increase the number of authorized shares of our common stock no later than December 31, 2023. We have agreed to use our best efforts to obtain the Stockholder Approval and to cause our board of directors to recommend to the stockholders that they approve such matter. If the Stockholder Approval is not obtained by December 31, 2023, we are required to hold an additional stockholder meeting every three months thereafter until the Stockholder Approval is obtained.

If we do not obtain Stockholder Approval by December 31, 2023, we are required to pay liquidated damages of 2.0% of the aggregate purchase price paid by each holder of Pre-Funded Warrants. For any subsequent failure to obtain Stockholder Approval, we are required to pay an additional 2.0% of such aggregate purchase price as liquidated damages.

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 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, and 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 IND 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;
- our ability to successfully obtain the Stockholder Approval and subsequently file the Charter Amendment and the timing thereof;
- the effects of health epidemics, including the ongoing COVID-19 virus, 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 ability to establish or maintain collaborations or strategic relationships;
- our ability to identify, recruit and retain key personnel;

[Table of Contents](#)

- 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

The selling stockholders will receive all of the proceeds from the sale of the Shares hereunder. Accordingly, we will not receive any of the proceeds from the sale of the Shares in this offering; however, we will receive proceeds from any cash exercise of the Pre-Funded Warrants.

SELLING STOCKHOLDERS

We have prepared this prospectus to allow the selling stockholders to offer and sell from time to time up to 166,663,354 shares of our common stock for their own account, consisting of (i) up to 122,412,376 shares of common stock issued to the selling stockholders and (ii) 44,250,978 shares of common stock issuable to certain of the selling stockholders upon the exercise of the Pre-Funded Warrants pursuant to the Purchase Agreement, without giving effect to any beneficial ownership limitation contained in any Pre-Funded Warrant.

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 Purchase Agreement. Under the terms of the Purchase Agreement, we agreed to prepare and file by the Filing Deadline, one or more registration statements with the SEC to register for resale the Shares, and to cause the applicable registration statements to become effective by the Effectiveness Deadline. We also agreed to use our best efforts to keep such registration statement effective until the earlier of (i) the third anniversary of the date the initial registration statement is declared effective, or (ii) the date all Shares (assuming cashless exercise of the Pre-Funded Warrants) held by or issuable to a Holder, as defined in the Purchase Agreement, may be sold under Rule 144 without being subject to any volume, manner of sale or publicly available information requirements.

The Pre-Funded Warrants may not be exercised if the aggregate number of shares of common stock beneficially owned by the holder thereof immediately following such exercise would exceed a specified beneficial ownership limitation; provided, however, that a holder may increase or decrease the beneficial ownership limitation by giving 61 days' notice to us, but not to any percentage in excess of 19.99%. The Pre-Funded Warrants are further only exercisable into common stock upon the filing of the Charter Amendment following receipt of the Stockholder Approval. We plan to hold a special meeting of stockholders seeking Stockholder Approval by December 31, 2023. Assuming we receive such Stockholder Approval, we will file the Charter Amendment promptly thereafter.

The following table sets forth, to our knowledge, information concerning the beneficial ownership of shares of our common stock by the selling stockholders as of August 18, 2023. 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 each selling stockholder 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 number of shares of common stock beneficially owned by each selling stockholder as of August 18, 2023 includes all shares of our common stock purchased by such selling stockholder in the Private Placement. Under the terms of the Pre-Funded Warrants, the Pre-Funded Warrants may not be exercised prior to the filing of the Charter Amendment following Stockholder Approval, which will not take place within 60 days of August 18, 2023; therefore, the selling stockholders do not have any beneficial ownership of the shares underlying the Pre-Funded Warrants as of August 18, 2023. The number of shares of common stock that may be offered under this prospectus, includes (x) all shares of our common stock purchased by such selling stockholder in the Private Placement and (y) all shares of our common stock underlying Pre-Funded Warrants purchased by such selling stockholder in the Private Placement without giving effect to the beneficial ownership limitation and assuming the Stockholder Approval has been obtained and the Charter Amendment has been filed. The number of shares of common stock beneficially owned by each selling stockholder following the offering assumes all of the Shares covered hereby are sold and such stockholder does not acquire beneficial ownership of any additional shares of common stock.

The percentage of shares owned before and after the offering are based on 186,960,193 shares of our common stock outstanding as of August 18, 2023, which includes the outstanding shares of common stock offered by this prospectus but does not include any shares of common stock offered by this prospectus that are issuable pursuant to the Pre-Funded Warrants, and assumes the selling stockholders dispose of all of the Shares covered by this prospectus and do 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.

Table of Contents

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.

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.

Except as otherwise noted below, the address for persons listed in the table is c/o Taysha Gene Therapies, Inc., 3000 Pegasus Park Drive, Suite 1430, Dallas, Texas 75247.

Name of Selling Stockholder	Beneficial Ownership Prior to this Offering		Number of Shares Being Offered ⁽²⁾	Beneficial Ownership After this Offering ⁽¹⁾	
	Number of Shares	Percentage of Outstanding Common Stock		Number of Shares	Percentage of Outstanding Common Stock
Entities affiliated with FMR LLC ⁽³⁾	27,969,982	14.96%	26,826,688	1,143,294	*
Entities affiliated with Paul B. Manning ⁽⁴⁾	23,476,333	12.55%	16,466,667	7,009,666	3.03%
RA Capital Healthcare Fund, L.P. ⁽⁵⁾	18,472,503	9.88%	61,111,110	—	—
Entities affiliated with RTW Investments, LP ⁽⁶⁾	16,893,185	9.04%	18,505,556	—	—
Entities affiliated with Venrock ⁽⁷⁾	14,444,444	7.73%	14,444,444	—	—
TCG Crossover Fund I, LP ⁽⁸⁾	11,111,111	5.94%	11,111,111	—	—
Entities affiliated with Acuta ⁽⁹⁾	3,826,285	2.05%	3,333,333	492,952	*
Invus Public Equities, L.P. ⁽¹⁰⁾	3,663,104	1.96%	2,222,222	1,440,882	*
Kynam Global Healthcare Master Fund LP ⁽¹¹⁾	2,880,333	1.54%	2,880,333	—	—
Octagon Investments Master Fund LP ⁽¹²⁾	2,777,778	1.49%	2,777,778	—	—
Entities affiliated with John A. Stalfort III ⁽¹³⁾	1,933,671	1.03%	827,778	1,105,893	*
GordonMD Long Biased Master Fund LP ⁽¹⁴⁾	1,666,667	*	1,666,667	—	—
Entities affiliated with Sean P. Nolan ⁽¹⁵⁾	1,598,715	*	444,444	1,154,271	*
Entities affiliated with SSI Strategy Holdings LLC ⁽¹⁶⁾	1,460,774	*	555,556	905,218	*
Entities affiliated with Crestline ⁽¹⁷⁾	453,000	*	453,000	—	—
Entities affiliated with John D. Carr ⁽¹⁸⁾	1,167,111	*	1,111,111	56,000	*
B Group Capital LLC ⁽¹⁹⁾	992,056	*	555,556	436,500	*
Jayson Rieger ⁽²⁰⁾	689,432	*	272,222	417,210	*
Entities affiliated with Steven M. Goldman ⁽²¹⁾	468,889	*	388,889	80,000	*
Adam Burke ⁽²²⁾	270,108	*	138,889	131,219	*
Entities affiliated with Don Mosman ⁽²³⁾	196,556	*	105,556	91,000	*
Peter R. Taylor Irrevocable Trust ⁽²⁴⁾	194,444	*	194,444	—	—
Phillip Donenberg ⁽²⁵⁾	185,425	*	111,111	74,314	*
David Zawitz ⁽²⁶⁾	128,472	*	72,222	56,250	*
Tom Selinger ⁽²⁷⁾	66,262	*	55,556	10,706	*
Joseph Pedersen ⁽²⁸⁾	33,504	*	11,111	22,393	*
Jeffrey Kopocis ⁽²⁹⁾	26,705	*	16,667	10,038	*
David Glover ⁽³⁰⁾	18,875	*	3,333	15,542	*

* Represents beneficial ownership of less than 1%

Table of Contents

- (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 without giving effect to the beneficial ownership limitation in the Pre-Funded Warrants and assuming the Stockholder Approval has been obtained and the Charter Amendment has been filed.
- (3) “Beneficial Ownership Prior to this Offering” consists of (i) 15,715,577 shares of common stock issued in the Private Placement to Fidelity Select Portfolios: Biotechnology Portfolio, or Fidelity Biotechnology Portfolio, (ii) 811,647 shares of common stock held by Fidelity Biotechnology Portfolio prior to the Private Placement, (iii) 936,201 shares of common stock issued in the Private Placement to Fidelity Mt. Vernon Street Trust: Fidelity Series Growth Company Fund, or Fidelity Series Growth Company Fund, (iv) 3,547,617 shares of common stock issued in the Private Placement to Fidelity Mt. Vernon Street Trust: Fidelity Growth Company Fund, or Fidelity Growth Company Fund, (v) 5,095,775 shares of common stock issued in the Private Placement to Fidelity Growth Company Commingled Pool, (vi) 155,468 shares of common stock held by Fidelity Growth Company Commingled Pool prior to the Private Placement, (vii) 1,531,518 shares of common stock issued in the Private Placement to Fidelity Mt. Vernon Street Trust: Fidelity Growth Company K6 Fund, or Fidelity Growth Company K6 Fund, and (viii) 176,179 shares of common stock held by Fidelity Growth Company K6 Fund prior to the Private Placement. Fidelity Biotechnology Portfolio, Fidelity Series Growth Company Fund, Fidelity Growth Company Fund, Fidelity Growth Company Commingled Pool, and Fidelity Growth Company K6 Fund are managed by direct or indirect subsidiaries of FMR LLC. Abigail P. Johnson is a director, the chairman and the chief executive officer of FMR LLC. Members of the Johnson family, including Abigail P. Johnson, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders’ voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders’ voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC. Neither FMR LLC nor Abigail P. Johnson has the sole power to vote or direct the voting of the shares owned directly by the various investment companies registered under the Investment Company Act, or the Fidelity Funds, advised by Fidelity Management & Research Company LLC, or FMR Co. LLC, a wholly owned subsidiary of FMR LLC, which power resides with the Fidelity Funds’ Boards of Trustees. FMR Co. LLC carries out the voting of the shares under written guidelines established by the Fidelity Funds’ Boards of Trustees. The address of the principal place of business of these persons, funds and accounts is 245 Summer Street, Boston, MA 02210.
- (4) “Beneficial Ownership Prior to this Offering” consists of (i) 16,466,667 shares of common stock issued in the Private Placement to the Paul B. Manning Revocable Trust dated May 10, 2020, or the PBM Revocable Trust, (ii) 4,837,407 shares of common stock held by the PBM 2023 Grantor Retained Annuity Trust, or the PBM Annuity Trust, prior to the Private Placement; (iii) 2,091,704 shares of common stock held by BKB Growth Investments, LLC, or BKB, prior to the Private Placement, (iv) 22,000 shares of common stock held by BKB G2 Investments, LLC, or BKB2, prior to the Private Placement, and (v) 58,555 shares of common stock issuable upon the exercise of options held by Paul B. Manning that are exercisable within 60 days of August 18, 2023. Mr. Manning is the trustee of the PBM Revocable Trust and has sole voting and dispositive power over the shares held by the PBM Revocable Trust. Mr. Manning is trustee of the PBM Annuity Trust and has sole voting and dispositive power over the shares held by the PBM Annuity Trust. Mr. Manning is co-manager of Tiger Lily Capital, LLC, the manager of BKB and BKB2 and has shared voting and dispositive power over the shares held by BKB and BKB2. The address of the principal place of business of each of these persons and entities is 200 Garrett Street, Suite S, Charlottesville, VA 22902.
- (5) “Beneficial Ownership Prior to this Offering” consists of 18,472,503 shares of common stock issued in the Private Placement to RA Capital Healthcare Fund, L.P. Such amount does not include 42,638,607 shares of common stock issuable upon exercise of a Pre-Funded Warrant purchased by RA Capital Healthcare Fund, L.P. in the Private Placement. The Pre-Funded Warrants may not be exercised until the filing of the Charter

Table of Contents

Amendment following receipt of the Stockholder Approval or if the aggregate number of shares of common stock beneficially owned by entities affiliated with RA Capital Healthcare Fund, L.P. immediately following such exercise would exceed 9.99% of the total number of shares of our common stock then issued and outstanding after giving effect to such exercise. RA Capital Management, L.P. is the investment manager for RA Capital Healthcare Fund, L.P. The general partner of RA Capital Management, L.P. is RA Capital Management GP, LLC, of which Peter Kolchinsky and Rajeev Shah are the managing members. Each of Mr. Kolchinsky and Mr. Shah may be deemed to have voting and investment power over the securities held by RA Capital Healthcare Fund, L.P. The principal business address of these persons and entities is 200 Berkeley Street, 18th Floor, Boston, MA 02116.

- (6) “Beneficial Ownership Prior to this Offering” consists of (i) 9,683,503 shares of common stock issued to RTW Master Fund, Ltd. in the Private Placement, (ii) 6,826,919 shares of common stock issued to RTW Innovation Master Fund, Ltd. in the Private Placement, and (iii) 382,763 shares of common stock issued to RTW Biotech Opportunities Fund, Ltd. in the Private Placement. Such amounts do not include 924,243, 651,596, and 36,532 shares of common stock issuable upon exercise of Pre-Funded Warrants purchased by RTW Master Fund, Ltd., RTW Innovation Master Fund, Ltd. and RTW Biotech Opportunities Fund, Ltd. or, collectively, the RTW Funds, respectively, in the Private Placement. The Pre-Funded Warrants may not be exercised until the filing of the Charter Amendment following receipt of the Stockholder Approval or if the aggregate number of shares of common stock beneficially owned by entities affiliated with RTW Investments, LP, or RTW, immediately following such exercise would exceed 9.99% of the total number of shares of our common stock then issued and outstanding after giving effect to such exercise. RTW, in its capacity as the investment manager of the RTW Funds, has the power to vote and the power to direct the disposition of the shares held by the RTW Funds. Accordingly, RTW may be deemed to be the beneficial owner of such securities. Roderick Wong, M.D., as the Managing Partner of RTW, has the power to direct the vote and disposition of the securities held by RTW. Dr. Wong disclaims beneficial ownership of the shares held by the RTW Funds, except to the extent of his pecuniary interest therein. The address and principal office of RTW Investments, LP is 40 10th Avenue, Floor 7, New York, NY 10014, and the address of Dr. Wong and each of the RTW Funds is c/o RTW Investments, LP, 40 10th Avenue, Floor 7, New York, NY 10014.
- (7) “Beneficial Ownership Prior to this Offering” consists of (i) 10,267,111 shares of common stock issued in the Private Placement to Venrock Healthcare Capital Partners EG, L.P., or VHCP EG, (ii) 3,797,444 shares of common stock issued in the Private Placement to Venrock Healthcare Capital Partners III, L.P., or VHCP III and (iii) 379,889 shares of common stock issued in the Private Placement to VHCP Co-Investment Holdings III, LLC, or VHCP Co-III. VHCP Management III, LLC, or VHCPM is the sole general partner of VHCP III and the sole manager of VHCP Co-III. VHCP Management EG, LLC, or VHCPM EG, is the sole general partner of VHCP EG. Dr. Bong Koh and Nimish Shah share the power to vote and dispose of the securities held by VHCPM and VHCPM EG. The principal business address of these persons and entities is 7 Bryant Park, 23rd Floor, New York, NY 10018.
- (8) “Beneficial Ownership Prior to this Offering” consists of 11,111,111 shares of common stock issued in the Private Placement to TCG Crossover Fund I, LP. TCG Crossover GP I, LLC is the general partner of TCG Crossover Fund I, LP and Chen Yu is the sole managing member of TCG Crossover GP I, LLC and holds voting and dispositive power with respect to these securities. The principal business address of these persons and entities is 705 High Street, Palo Alto, CA 94301.
- (9) “Beneficial Ownership Prior to this Offering” consists of (i) 500,000 shares of common stock issued to Acuta Opportunity Fund, LP in the Private Placement, (ii) 73,943 shares of common stock held by Acuta Opportunity Fund, LP prior to the Private Placement, (iii) 2,833,333 shares of common stock issued to Acuta Capital Fund, LP in the Private Placement, and (iv) 419,009 shares of common stock held by Acuta Capital Fund, LP prior to the Private Placement. Anupam Dalal, M.D. as chief investment officer of Acuta Opportunity Fund, LP and Acuta Capital Fund, LP has the power to vote and dispose of the securities held by the funds. The principal business address of these persons and entities is 255 Shoreline Drive, Suite 515, Redwood City, CA 94065.
- (10) “Beneficial Ownership Prior to this Offering” consists of (i) 2,222,222 shares of common stock issued in the Private Placement and (ii) 1,440,882 shares of common stock held prior to the Private Placement. Invus Public Equities Advisors, LLC, or Invus PE Advisors, controls Invus Public Equities, L.P., or Invus PE, as

its general partner and accordingly, may be deemed to beneficially own the shares of common stock held by Invus PE. The Geneva branch of Artal International S.C.A., or Artal International, controls Invus PE Advisors, as its managing member and accordingly, may be deemed to beneficially own the shares of common stock held by Invus PE. Artal International Management S.A., or Artal International Management, as the managing partner of Artal International, controls Artal International and accordingly, may be deemed to beneficially own the shares of common stock that Artal International may be deemed to beneficially own. Artal Group S.A., or Artal Group, as the sole stockholder of Artal International Management, controls Artal International Management and accordingly, may be deemed to beneficially own the shares of common stock that Artal International Management may be deemed to beneficially own. Westend S.A., or Westend, as the parent company of Artal Group, controls Artal Group and accordingly, may be deemed to beneficially own the shares of common stock that Artal Group may be deemed to beneficially own. Stichting Administratiekantoor Westend, or the Stichting, as majority shareholder of Westend, controls Westend and accordingly, may be deemed to beneficially own the shares of common stock that Westend may be deemed to beneficially own. Mr. Amaury Wittouck, as the sole member of the board of the Stichting, controls the Stichting and accordingly, may be deemed to beneficially own the shares of common stock that the Stichting may be deemed to beneficially own. The principal business address for Invus PE and Invus PE Advisors is 750 Lexington Avenue, 30th Floor, New York, NY 10022. The principal business address for Artal International, Artal International Management, Artal Group, Westend and Mr. Wittouck is Valley Park, 44, Rue de la Vallée, L-2661, Luxembourg. The principal business address for the Stichting is Claude Debussylaan, 46, 1082 MD Amsterdam, The Netherlands.

- (11) “Beneficial Ownership Prior to this Offering” consists of 2,880,333 shares of common stock issued in the Private Placement. Yue Tang as the managing member of Kynam Global Healthcare Master Fund LP, or Kynam, has the power to vote and dispose of the securities held by Kynam. The principal business address of these persons and entities is 221 Elm Rd., Princeton NJ, 08540.
- (12) “Beneficial Ownership Prior to this Offering” consists of 2,777,778 shares of common stock issued in the Private Placement. Octagon Investments GP, LLC is the general partner of Octagon Investments Master Fund LP. Ting Jia as managing member of Octagon Investments GP, LLC has the power to vote and dispose of the securities held by Octagon Investments Master Fund LP. The principal business address of these persons and entities is 654 Madison Avenue, 21st Floor, New York, NY 10065.
- (13) “Beneficial Ownership Prior to this Offering” consists of (i) 438,889 shares of common stock issued in the Private Placement to John A. Stalfort III, (ii) 610,492 shares of common stock held by John A. Stalfort III prior to the Private Placement, (iii) 388,889 shares of common stock issued in the Private Placement to the John A. Stalfort III 2018 Irrevocable Trust, or the Stalfort Trust, and (iv) 495,401 shares of common stock held by the Stalfort Trust prior to the Private Placement. Gineane Holly Stalfort as trustee of the Stalfort Trust has the power to vote and dispose of the securities held by the Stalfort Trust.
- (14) “Beneficial Ownership Prior to this Offering” consists of 1,666,667 shares of common stock issued in the Private Placement. GordonMD Global Investments LP is the investment manager of GordonMD Long Biased Master Fund LP. Craig D. Gordon, M.D. as chief executive officer has the power to vote and dispose of the securities held by Gordon MD Long Biased Master Fund LP. The principal business address of these persons and entities is 9460 Wilshire Blvd., Suite 420, Beverly Hills, California 90212.
- (15) “Beneficial Ownership Prior to this Offering” consists of (i) 444,444 shares of common stock issued to Nolan Capital LLC in the Private Placement, (ii) 1,091,101 shares of common stock held by Nolan Capital LLC prior to the Private Placement, (iii) 1,170 shares of common stock held by Sean P. Nolan prior to the Private Placement, and (iv) 62,000 shares of common stock issuable upon the exercise of options held by Sean P. Nolan that are exercisable within 60 days of August 18, 2023. Sean P. Nolan is the President of Nolan Capital LLC and has shared voting and dispositive power with respect to the shares held by Nolan Capital LLC.
- (16) “Beneficial Ownership Prior to this Offering” consists of (i) 277,778 shares of common stock issued in the Private Placement to SSI Strategy Sidecar 1, LLC, which is wholly owned by SSI Strategy Holdings LLC, (ii) 277,778 shares of common stock issued in the Private Placement to SSI Strategy Sidecar 2, LLC, which is wholly owned by SSI Strategy Holdings, LLC, (iii) 352,609 shares of common stock held by SSI Strategy Sidecar 1, LLC prior to the Private Placement, (iv) 352,609 shares of common stock held by SSI Strategy

Table of Contents

Sidecar 2, LLC prior to the Private Placement, (v) 100,000 shares issuable upon the exercise of common stock warrants held by SSI Strategy Sidecar 1, LLC exercisable within 60 days of August 18, 2023, and (vi) 100,000 shares issuable upon the exercise of common stock warrants held by SSI Strategy Sidecar 2, LLC exercisable within 60 days of August 18, 2023. The share numbers do not reflect 162,500 shares underlying outstanding warrants to purchase common stock and 162,500 shares underlying outstanding warrants to purchase common stock held by SSI Strategy Sidecar 1, LLC and SSI Strategy Sidecar 2, LLC, respectively, which had not vested as of August 18, 2023. The warrants vest and become exercisable upon 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 of common stock 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.

- (17) “Beneficial Ownership Prior to this Offering” consists of (i) 316,000 shares of common stock issued in the Private Placement to Crestline Summit Master, SPC – Peak SP, or Crestline Peak SP, and (ii) 137,000 shares of common stock issued in the Private Placement to Crestline Summit Master, SPC – Crestline Summit APEX SP, or Crestline Summit APEX SP and together with Crestline Peak SP the Crestline entities. Melinda Lilly as the managing director of the Crestline entities has the power to vote and dispose of the securities held by the Crestline entities. The principal business address of these persons and entities is 201 Main Street 1100, Fort Worth, TX 76102.
- (18) “Beneficial Ownership Prior to this Offering” consists of (i) 1,111,111 shares of common stock issued in the Private Placement to Carr Family, LLC and (ii) 56,000 shares of common stock held by John D. Carr prior to the Private Placement. John D. Carr as the manager of Carr Family, LLC has the power to vote and dispose of the securities held by Carr Family, LLC. The principal business address of these persons and entities is 1020 Harris Street, Charlottesville, VA 22903.
- (19) “Beneficial Ownership Prior to this Offering” consists of (i) 555,556 shares of common stock issued in the Private Placement and (ii) 436,500 shares of common stock held prior to the Private Placement. Branden B. Muhl as the manager of B Group Capital LLC has the power to vote and dispose of the securities held by B Group Capital LLC. The principal business address of these persons and entities is 2900 McKinnon St. Suite 1101, Dallas, TX 75201.
- (20) “Beneficial Ownership Prior to this Offering” consists of (i) 272,222 shares of common stock issued in the Private Placement and (ii) 417,210 shares of common stock held prior to the Private Placement.
- (21) “Beneficial Ownership Prior to this Offering” consists of (i) 277,778 shares of common stock issued in the Private Placement to the Steven M. Goldman Family LLC, (ii) 15,000 shares of common stock held by the Steven M. Goldman Family LLC prior to the Private Placement, (iii) 111,111 shares of common stock issued in the Private Placement to Steven M. Goldman and (iv) 65,000 shares of common stock held by Steven M. Goldman prior to the Private Placement. Steven M. Goldman as managing member of the Steven M. Goldman Family LLC has the power to vote and dispose of the securities held by the Steven M. Goldman Family LLC.
- (22) “Beneficial Ownership Prior to this Offering” consists of (i) 138,889 shares of common stock issued in the Private Placement and (ii) 131,219 shares of common stock held prior to the Private Placement.
- (23) “Beneficial Ownership Prior to this Offering” consists of (i) 55,556 shares of common stock issued to The Don and Jenna Mosman Revocable Living Trust, or the Mosman Trust, in the Private Placement (ii) 91,000 shares of common stock held by the Mosman Trust prior to the Private Placement, and (iii) 50,000 shares of common stock issued to Donald E. Mosman, Jr. in the Private Placement. Donald E. Mosman, Jr. as manager of the Trust has the power to vote and dispose of the securities held by the Mosman Trust.
- (24) “Beneficial Ownership Prior to this Offering” consists of 194,444 shares of common stock issued in the Private Placement. Peter R. Taylor as trustee of the Peter R. Taylor Irrevocable Trust has the power to vote and dispose of the securities held by the Peter R. Taylor Irrevocable Trust.

[Table of Contents](#)

- (25) “Beneficial Ownership Prior to this Offering” consists of (i) 111,111 shares of common stock issued in the Private Placement, (ii) 3,000 shares of common stock held prior to the Private Placement, and (iii) 71,314 shares of common stock issuable upon the exercise of options that are exercisable within 60 days of August 18, 2023.
- (26) “Beneficial Ownership Prior to this Offering” consists of (i) 72,222 shares of common stock issued in the Private Placement and (ii) 56,250 shares of common stock held prior to the Private Placement.
- (27) “Beneficial Ownership Prior to this Offering” consists of (i) 55,556 shares of common stock issued in the Private Placement and (ii) 10,706 shares of common stock held prior to the Private Placement.
- (28) “Beneficial Ownership Prior to this Offering” consists of (i) 11,111 shares of common stock issued in the Private Placement and (ii) 22,393 shares of common stock held prior to the Private Placement.
- (29) “Beneficial Ownership Prior to this Offering” consists of (i) 16,667 shares of common stock issued in the Private Placement and (ii) 10,038 shares of common stock held prior to the Private Placement.
- (30) “Beneficial Ownership Prior to this Offering” consists of (i) 3,333 shares of common stock issued in the Private Placement and (ii) 15,542 shares of common stock held prior to the Private Placement.

Relationships with Selling Stockholders

Each of the selling stockholders has not had any material relationship with the registrant or any of its predecessors or affiliates, within the past three years, except as hereinafter described. As discussed in greater detail above under the section titled “Prospectus Summary—Private Placement,” in August 2023, we entered into the Purchase Agreement with the selling stockholders, pursuant to which we sold and issued shares of our common stock and Pre-Funded Warrants to purchase our common stock. The Purchase Agreement includes certain registration rights, pursuant to which we agreed to prepare and file, by the Filing Deadline, one or more registration statements with the SEC to register for resale the common stock issued under the Purchase Agreement and the shares of common stock issuable upon exercise of the Pre-Funded Warrants issued pursuant to the Purchase Agreement, and to cause the applicable registration statements to become effective by the Effectiveness Deadline.

The Selling Stockholders include several of our officers and directors, or affiliates thereof, and 5% or greater stockholders.

Sean P. Nolan, the President of Nolan Capital, LLC, has served as our Chief Executive Officer since December 2022 and as Chairman of our Board since March 2020.

Paul B. Manning, the trustee of The Paul B. Manning Revocable Trust, is a beneficial owner of more than 5% of our common stock. Mr. Manning served as a member of our Board from March 2020 to June 2023. He has served as a board observer since June 2023.

Phillip Donenberg has served as a member of our Board since August 2020.

John A. (Sean) Stalfort III has served as a member of our Board since June 2023.

FMR LLC is, and prior to the Private Placement was, a beneficial owner of more than 5% of our common stock.

PLAN OF DISTRIBUTION

The selling stockholders, which as used herein includes donees, pledgees, transferees or other successors-in-interest selling shares of common stock 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, donees 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).

[Table of Contents](#)

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(a)(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(a)(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 use our best efforts to cause the registration statement of which this prospectus is a part to remain continuously effective until the earlier of (1) the third anniversary of the date the registration statement of which this prospectus is a part is declared effective or (2) the date on which all of the Shares may be sold without restriction pursuant to Rule 144 of the Securities Act.

LEGAL MATTERS

Cooley LLP, Washington, D.C., 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 of Taysha Gene Therapies, Inc. incorporated in this prospectus by reference from the Annual Report on Form 10-K have been audited by Deloitte & Touche LLP, an independent registered public accounting firm, as stated in their report. 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, as amended on [Form 10-K/A](#) filed with the SEC on April 27, 2023;
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2023 and June 30, 2023 filed with the SEC on [May 11, 2023](#) and [August 14, 2023](#), respectively;
- 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](#), [April 27, 2023](#), [May 19, 2023](#), [June 5, 2023](#), [June 6, 2023](#), [June 22, 2023](#), [June 23, 2023](#), [August 4, 2023](#), [August 14, 2023](#), [August 24, 2023](#) and [August 29, 2023](#) (each 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.

166,663,354 Shares



Common Stock

PROSPECTUS
